2022 Expert consensus on the use of laser ablation for papillary thyroid microcarcinoma

Lu Zhang*, Wei Zhou*, Jian Qiao Zhou, Qian Shi, Teresa Rago, Giovanni Gambelunghe, Da Zhong Zou, Jun Gu, Man Lu, Fen Chen, Jie Ren, Wen Cheng, Ping Zhou, Stefano Spiezia, Enrico Papini and Wei Wei Zhan

*Department of Ultrasound, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; bDepartment of Endocrinology and Metabolism, Regina Apostolorum Hospital, Rome, Italy; cDepartment of Ultrasound, The Seventh People’s Hospital, Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China; dEndocrinology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; eDepartment of Ultrasound, The Affiliated Jinying Hospital of South-East University Medical College, Jiangsu, China; fDepartment of Ultrasound, The Affiliated Suzhou Hospital of Nanjing Medical University, Jiangsu, China; gDepartment of Ultrasound, Sichuan Provincial People’s Hospital, Sichuan, China; hDepartment of Ultrasound, The First Affiliated Hospital of Zhejiang Chinese Medical University, Zhejiang, China; iDepartment of Ultrasound, The Third Affiliated Hospital of Sun Yat-sen University, Guangdong, China; jDepartment of Ultrasound, Harbin Medical University Cancer Hospital, Heilongjiang, China; kDepartment of Ultrasound, The Third Xiangya Hospital of Central South University, Hunan, China; lDepartment of Endocrinology and Ultrasound-Guided Surgery, Ospedale del Mare, Naples, Italy

ABSTRACT

Objective: With the aim of standardizing and improving the use of ultrasound-guided PLA on PTMC, a panel of experts from China and Italy, jointly issued this expert consensus on the clinical use of PLA for low-risk PTMC.

Methods: This expert consensus was developed by Chinese and Italian experts who have specific competence and expertise in this area. An evidence-based approach combining the knowledge and practical experience of the panelists was utilized.

Results: Twenty-six expert consensus recommendations were developed, spanning topics including the indications and contraindications of PLA for PTMC, physician training, preoperative preparation of patients, intraoperative technical procedures, possible complications, efficacy assessment, follow-up strategy, the approach to new PTMC and metastatic lymph nodes after treatment, thyroid-stimulating hormone inhibition therapy, and quality control of the entire procedure.

Conclusion: We summarized practical recommendations about standardized and improved PLA treatment for PTMC.

1. Introduction

Over 90% of thyroid malignancies are papillary carcinoma [1], with about 50% of these papillary thyroid microcarcinoma (PTMC) [2]. Due to the indolent nature of PTMC, traditional surgical treatment is not appropriate for all patients due to the risks of complications, surgical scar, loss of thyroid function, and adverse impact on quality of life are taken into account [3–5]. For these reasons, active surveillance (AS) has been proposed as an alternative strategy to surgery for patients with low-risk PTMC [6,7]. However, there are substantial drawbacks of AS, including the need for life-long ultrasound (US) follow-up and increased patient anxiety due to the awareness of disease persistence. For PTMC patients who refuse surgery but do not agree to AS, nonsurgical thermal ablation (TA) treatments are increasingly proposed [8]. Currently, TA of benign and malignant thyroid lesions may be performed by percutaneous laser ablation (PLA), microwave ablation (MWA), radiofrequency ablation (RFA), or high-intensity-focused ultrasound ablation (HIFU) [9–11].

TA by PLA for PTMC was first performed in 2011 in an elderly patient with multiple organ dysfunction in Italy [12]. This feasibility study was followed by several trials on PLA for solitary PTMC [13,14], demonstrating that PLA is an effective and minimally invasive treatment. The advantages of laser ablation are the small size (21 gauge) and the flexibility of the introducer needle, which can navigate the fiber into the target lesion. These characteristics allow easy insertion of the ablation device with no need for skin incision,
and minimal damage to the thyroid [15,16]. Presently, PLA can be defined as an appropriate minimally invasive treatment for thyroid lesions due to its safety, minimal trauma, rapid postoperative recovery, limited impact on thyroid function, and low recurrence rate in long-term follow-up [14,17,18].

With the aim of standardizing and improving treatment for PTMC, a panel of experts from China and Italy, jointly issued this expert consensus on the clinical use of PLA for low-risk PTMC.

2. Methodology

Under the auspices of the Ultrasound Department of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, a panel of 16 experts from China and Italy with a declared interest in the field of PLA was created. A consensus meeting, the China–Italian Expert Consensus Conference on Laser Ablation for PTMC, was held online on 18 December 2021. PUBMED, MEDLINE, and Web of Science electronic databases were searched to identify publications on PLA and other techniques for thyroid nodules published between 2000 and 2022. Published papers with full or abstract results were included, as were relevant preclinical studies. Based on these data and clinical practice experience, the experts came to a consensus on recommendations for PLA treatment of PTMC in clinical practice.

The selection and quality evaluation of the selected studies were carried out simultaneously. The Evidence Level and Recommendation Grading System were developed based on a review of existing guidelines and other grading systems [19,20] (Tables 1 and 2). Study design and quality (risk of bias) are the primary factors considered for level of evidence. For recommendation grading, we considered the quality of evidence, clinical benefit and harm, cost, patient preference, and value.

3. Consensus recommendations

The panel of 16 experts reached consensus on PLA treatment of PTMC in clinical practice, resulting in a total of 26 recommendations (Table 3).

4. Introduction to laser ablation

High-power semiconductor lasers can be used for laser surgery and tumor ablation. PLA uses a Nd:YAG laser source, which operates with a forward and progressive mode of action. The output laser has a wavelength of 1064 nm, which has strong penetration into tissues and can be used for thermal ablation. The light is transmitted through optical fibers, usually composed of materials such as quartz. In recent years, with improved precision of optical fiber manufacturing, the process of cutting and polishing the light output end of the optical fiber allows front-side irradiation in a ring format. This can also be achieved by adding a lens cap. Recently, a new technology called Orblaze™ has been embedded in a 1064-nm laser diode, and in animal models the induced tissue lesion has an almost-spherical shape, which could more precisely necrotize neoplastic lesions [21].

The thermal effect of the laser arises from absorption of photon energy released from the optical fiber tip by tissue molecules, and conversion to kinetic energy. This causes an increase in local temperature resulting in irreversible damage to the cells around the optical fiber tip. When coagulation necrosis occurs locally, the spread of laser energy is slowed. Once the energy threshold is broken through, the ablated area advances progressively forward due to the cavitation and coagulation process of the surrounding tissue, linked to the temperature–time exposure. The expansion of the ablation volume correlates with the increase in laser energy, but the necrotic area does not increase significantly when the total energy exceeds 1800 J, meaning that laser ablation is relatively accurate and controllable.

Key question 1: What are the technical characteristics of PLA in the treatment of PTMC?

Compared with other thermal ablation techniques, PLA has several advantages:

1. Accuracy: The range of necrotic tissue caused by different output powers and energy is relatively stable, and the maximum range of a single point-shaped fiber laser ablation is an approximate 16–18 mm × 8–10 mm ellipsoid. The size of introducer needle is 21 G, so it can accurately puncture a small lesion and maintain its position in the target tumor during the ablation process.
2. High temperature: Without a cold circulation system, the temperature in the tumor’s center continues to rise over time. The temperature can reach 200 °C, rendering the central tissue vaporized and carbonized. Notably, while the immediate area reaches very high temperatures, the temperature rapidly drops in the surrounding tissue.
3. Safety: The maximum lateral ablation size of PLA is only 4–5 mm, so the lateral heat diffusion can be accurately controlled. Even if the side of the fiber is close to the large blood vessels, trachea wall, or recurrent laryngeal nerve, the likelihood of damage is very low. Therefore, PLA is suitable for tumors close to critical structures. PLA has minimal heat conduction along the needle, and if the fiber tip is positioned properly, burning of the skin or muscle is rare. As the size of introducer needle is just 21 G and the diameter of the fiber is only 300 μm, the risk of bleeding is small. If a large blood vessel is punctured, the bleeding can be controlled by local compression. No electric current is used, so PLA can also be performed in patients with pace-makers.

Expert Recommendation 1: PLA is specifically indicated for thermal ablation of small PTMC due to its accuracy, thorough tumor inactivation, and safety. Recommendation strength: strong recommendation; moderate quality evidence.
Table 1. Level of evidence.

| Level of evidence | Description of supporting evidence | Interpretation |
|-------------------|-----------------------------------|----------------|
| High quality      | RCT without important limitations or overwhelming evidence from observational studies | Can apply to most patients in most circumstances without reservation |
| Moderate quality  | RCT with important limitations or strong evidence from observational studies | Can apply to most patients in most circumstances without reservation |
| Low quality       | Observational studies/case studies | May change when higher-quality evidence becomes available |
| Insufficient      | Evidence is conflicting, of poor quality, or lacking | Insufficient evidence to recommend for or against |

RCT: randomized controlled trial.

Table 2. Grading of recommendations.

| Recommendation | Clarity of risk/benefit | Quality of evidence |
|----------------|-------------------------|---------------------|
| Strong recommendation | Benefits clearly outweigh harms and burdens, or vice versa. | High/moderate |
| Weak recommendation | Benefits closely balanced with harms and burdens. | High/moderate/low |
| No recommendation | Balance of benefits and risks cannot be determined. | Insufficient |

Table 3. Recommendations.

| Figure | Recommendation content | Recommendation strength |
|--------|-------------------------|-------------------------|
| 1      | PLA is specifically indicated for thermal ablation of small PTMC due to its accuracy, thorough tumor inactivation, and safety. | Strong recommendation; moderate quality evidence |
| 2      | PLA is indicated for biopsy-proven PTMC without evidence of extrathyroidal spread at clinical and sonographic examination. | Strong recommendation; moderate quality evidence |
| 3      | PLA is not recommended for PTMC with suspicious extrathyroidal spread, metastasis, and other uncontrolled situations that limit the expected lifespan of the patient. | Strong recommendation; moderate quality evidence |
| 4      | PLA is also indicated for PTMC with isolated BRAF mutation at molecular analysis. PLA is not indicated in the presence of TERT promotor mutation or other aggressive mutations. | No recommendation; insufficient evidence |
| 5      | A training period undertaken in centers with specific expertise as well as initial tutorial assistance are essential for operators performing thermal ablation treatment. | Weak recommendation; low quality evidence |
| 6      | A multidisciplinary team including a member with specific interventional expertise should assess the feasibility of PLA based on all the relevant clinical, laboratory and imaging data and the patient’s preference. | Strong recommendation; moderate quality evidence |
| 7      | The patient must be fully informed about the procedure methods, the expected outcomes, risks, and post-treatment follow-up. The informed consent form should be signed before treatment. | Strong recommendation; high quality evidence |
| 8      | Local anesthesia is suggested before PLA. Conscious sedation or general anesthesia may be considered in selected cases. | Strong recommendation; low quality evidence |
| 9      | Hydrodissection is recommended before PLA for PTMC that is close to the thyroid capsule, recurrent laryngeal nerve or other vital structures to reduce the risk of thermal injury. | Strong recommendation; low quality evidence |
| 10     | At the beginning of the procedure, a higher power (4.5–5.5 W) can be used until tissue gasification, then a lower power (3.0–3.5 W) can be used for the remainder of treatment. | No recommendation; insufficient evidence |
| 11     | PLA has a forward and progressive mode of action. Therefore, the tip of the optical fiber should be placed at the proximal end of the PTMC so that the necrotic area can completely cover the lesion. | Strong recommendation; moderate quality evidence |
| 12     | PLA treatment should be planned on the basis of the size, position, and depth of the PTMC. The final margin of coagulative necrosis should exceed the PTMC by at least 2 mm. | Weak recommendation; low quality evidence |
| 13     | For a small PTMC (≤5 mm), single-fiber fixed ablation can achieve complete ablation of the target lesion. | Weak recommendation; moderate quality evidence |
| 14     | The recommended method of optical fiber insertion may be either through the thyroid isthmus or along the longitudinal axis of the PTMC. | Weak recommendation; low quality evidence |
| 15     | For larger PTMCs (6–10 mm), the use of two fibers for combined ablation should be considered. Single-fiber multi-point superimposed ablation (i.e., the pull-back technique) may also be used. | Weak recommendation; low quality evidence |
| 16     | CEUS evaluation should be performed at the end of treatment to assess the completeness of the ablation, and the nonperfusion zone should exceed the margins of PTMC by 2 mm. | Weak recommendation; low quality evidence |
| 17     | When vagal hyperactivity occurs during PLA treatment, the ablation should be stopped and the vital signs of the patient should be monitored. Ablation may be restarted after the patient’s condition stabilizes. | Strong recommendation; low quality evidence |
| 18     | Postoperative local pain usually resolves spontaneously. The administration of analgesic or corticosteroid medications should be considered for persistent pain. | Strong recommendation; low quality evidence |

(continued)
5. Indications and contraindications

Key question 2: In which situations is PLA indicated for PTMC treatment?

1. Biopsy-proven PTMC with evidence of a single lesion on US imaging;
2. A distance greater than 1–2 mm from the margin of PTMC to the thyroid capsule;
3. No evidence of cervical lymph node metastasis and distant metastasis on imaging.

On the premise that the patient meets the above criteria, is fully informed of the possible complications and risks of the procedure [22], and has provided informed consent, the patient can be treated with PLA.

The recurrent laryngeal nerve mostly travels outside the dorsal medial capsule of the thyroid, so if the margin of PTMC is more than 1–2 mm away from the dorsal medial capsule, the hydrodissection technique can significantly reduce the risk of recurrent laryngeal nerve injury. For PTMC with a distance to the dorsal medial capsule less than 1–2 mm, the decision to perform PLA treatment should be determined by the operator based on their own experience.

Whether PLA can be used to treat multifocal PTMC according to PLA indications for single-focal PTMC remains controversial, and should be decided after considering the patient’s preferences, the characteristics of the lesions, and the risk of PLA.

Expert recommendation 2: PLA is indicated for biopsy-proven PTMC without evidence of extrathyroidal spread at clinical and sonographic examination. Recommendation strength: strong recommendation; moderate quality evidence.

Key question 3: What are the contraindications of PLA treatment for PTMC?

1. Presence of biopsy-proven cervical lymph node metastasis from PTMC;
2. Extrathyroidal invasion into the muscle or cervical vital structures;
3. Severe clotting disorder;
4. Inability of the patient to cooperate during the treatment;
5. Limited neck extension that prevents an appropriate puncture path.

For PTMC patients with systemic diseases who are at surgical risk, a multidisciplinary evaluation is needed to provide appropriate consideration of the benefits and risks of treatment. PLA treatment is not recommended for PTMC patients with life-threatening comorbidities and an expected limited life span.

Expert Recommendation 3: PLA is not recommended for PTMC with suspicious extrathyroidal spread, metastasis, and other conditions that limit the expected lifespan of the patient. Recommendation strength: strong recommendation; moderate quality evidence.

Key question 4: Can molecular markers be used to assess the aggressiveness of PTMC?

The BRAF mutation is reported in 69% of patients with PTMC [23]. As the majority of PTMCs with BRAF mutation...
demonstrate a favorable prognosis, an isolated BRAF mutation in cytological samples cannot be used as a prognostic marker to guide the treatment of PTMC patients. Conversely, the coexistence of TERT promoter and BRAF mutations is associated with a more aggressive behavior with greater relapse and increased mortality [24,25]. Therefore, the tests for both TERT promoter and BRAF mutations should be recommended when available.

**Expert Recommendation 4:** PLA is also indicated for PTMC with isolated BRAF mutation at molecular analysis. PLA is not indicated in the presence of TERT promoter mutation or other aggressive mutations. **Recommendation strength: no recommendation; insufficient evidence.**

### 6. Pre-ablation preparation

**Key question 5:** What are the training requirements for doctors intending to perform tumor ablation?

1. If local health authorities have professional qualification requirements for performing thermal ablation, PLA can be performed only after the requested qualification(s).
2. Operators should have participated in several laser ablation sessions and subsequently have passed a dedicated examination. For physicians with protracted experience in US examinations and US-guided fine-needle aspiration (FNA), the training can be expedited in the presence of an expert tutor.

**Expert Recommendation 5:** A training period undertaken in centers with specific expertise as well as initial tutorial assistance are essential for operators performing thermal ablation treatment. **Recommendation strength: weak recommendation; low quality evidence.**

**Key question 6:** What clinical, laboratory and imaging evaluations should be requested before PLA is performed?

1. Detailed medical history including current medical therapy, allergies, high blood pressure, diabetes, and any cardiovascular, brain, liver, lung or kidney diseases. Any underlying disease(s) should be effectively controlled before laser ablation. If the patient is receiving oral anticoagulants, discontinuation is recommended if their condition permits [26];
2. Comprehensive evaluation of platelets count, coagulation and anticoagulation indicators;
3. Preoperative confirmation of malignancy with FNA or core-needle biopsy (CNB) is mandatory [11,18];
4. Complete blood count, viral serum indicators, complete thyroid function, calcitonin, electrocardiogram, laryngoscopy, and conventional US should be performed. Contrast-enhanced ultrasound (CEUS) should be performed only in selected cases according to local experience [11,18].

**Expert Recommendation 6:** A multidisciplinary team including a member with specific interventional expertise should assess the feasibility of PLA based on all relevant clinical, laboratory and imaging data and the patient’s preference. **Recommendation strength: strong recommendation; moderate quality evidence.**

**Key question 7:** What information should be provided to gain informed consent?

Before PLA, the patient should be fully informed of the following information orally and in writing, and should sign an informed consent form [9]:

1. Anesthesia, treatment plan, and expected outcomes;
2. Methods of patient cooperation during PLA treatment;
3. Level of discomfort that the patient may experience during and after ablation, and how to manage this;
4. Potential complications that may occur during and after the ablation, as well as the respective treatment measures;
5. Methods and duration of follow-up after PLA treatment;
6. The risk of tumor recurrence, occurrence of new PTMC and lymph node metastasis, and the possibility of repeated PLA or surgical treatment.

**Expert Recommendation 7:** The patient must be fully informed about the procedure’s methods, the expected outcomes, risks, and post-treatment follow-up. The informed consent form should be signed before treatment. **Recommendation strength: strong recommendation; high quality evidence.**

### 7. Intraoperative operation

**Key question 8:** How can pain be managed during PLA treatment?

PLA allows precise targeting because of the highly concentrated heat and the predictable size of ablation. If the nodules are close to the thyroid capsule, heat reaches the capsule during thermal ablation by diffusion, and the patient will complain of neck pain radiating to the jaw, head, or ears. In this situation, 1–2% lidocaine can be used before PLA to relieve pain in the skin, subcutaneous tissue, and thyroid capsule.

Local anesthesia is preferred because it is easy to operate and keeps the patient awake. If complications such as drug allergy, pain, or recurrent laryngeal nerve injury occur during the procedure, the patient may immediately vocalize their complaint, and serious complications may be prevented. However, in specific clinical conditions or institutions, local nerve block, conscious sedation, and general anesthesia can be also employed with the help of an anesthetist.

**Expert Recommendation 8:** Local anesthesia is suggested before PLA. Conscious sedation or general anesthesia may be considered in selected cases. **Recommendation strength: strong recommendation; low quality evidence.**

**Key question 9:** How is hydrodissection for PLA treatment performed?

Due to the presence of critical structures (trachea, large vessels, esophagus, and nerves) close to the thyroid gland, heat diffusion during the ablation procedure may cause intraoperative pain, postoperative discomfort, and potential complications. Hydrodissection before treatment can prevent...
cervical pain and protect surrounding tissues from thermal damage. When the nodule is close to the capsule, 0.9% saline or 5% glucose solution can be injected outside the thyroid capsule to form a ‘liquid isolation zone’. However, as the operation progresses, the liquid will be rapidly absorbed.

The following techniques can be used to prevent the rapid dispersion of fluid: (1) using a neck indwelling needle with a slow and continuous perfusion; (2) shortening the operation time; (3) fixing the fiber introducer needle inside the nodule before performing hydrodissection.

Special attention should be paid to protect the recurrent laryngeal nerve in the ‘dangerous triangle’, which lies behind the capsule of the thyroid gland. If it is impossible to completely separate the thyroid capsule from the recurrent laryngeal nerve, the lateral energy should be strictly controlled and the patient’s voice should be repeatedly checked.

**Expert Recommendation 9:** Hydrodissection is recommended before PLA for PTMC that is close to the thyroid capsule, recurrent laryngeal nerve or other vital structures to reduce the risk of thermal injury. **Recommendation strength: strong recommendation; low quality evidence.**

**Key question 10:** What power output and energy delivery should be used?

The ablation volume of a single optical fiber is generally stable. As the power and energy increase, the laser ablation range gradually increases. A near-linear relationship exists between ablation volume and energy input up to an energy delivery of 1800 J, but any further energy delivery above this results in a limited increase of the ablation volume. Based on experimental data with fixed treatment parameters (5 W output, 1800 J delivery), there is a highly predictable ablation range of 10–13 mm forward, 4–5 mm backward, and 4–5 mm lateral. For nodules with a hard texture and a background of Hashimoto’s thyroiditis, a high power (4.5–5.5 W) can be used to break through the hard area at the beginning of the procedure. When the gasification area starts to move forward, the output power can be lowered to 3.0–3.5 W to achieve an appropriate ablation area for moving forward slowly and safely.

**Expert Recommendation 10:** At the beginning of the procedure, a higher power (4.5–5.5 W) can be used until tissue gasification occurs, then a lower power (3.0–3.5 W) can be used for the remainder of the treatment. **Recommendation strength: no recommendation; insufficient evidence.**

**Key question 11:** What are the key points of using optical fiber in PLA ablation of PTMC?

As PLA has a forward and progressive mode of action, a fixed position ablation is usually used. The introducer needle is placed in the proximal part of the lesion and retracted after the insertion of the optical fiber, so that the tip of the optical fiber is placed at the proximal end of the nodule. If necessary, a puncture rack can also be used. This special guide system contains an array of entry angles, and multiple puncture tracks may be attached to linear probes. These devices are useful for multi-point, multi-layer ablation of large lesions or lesions in critical sites. When the nodule is near the trachea or ‘dangerous triangle’, in addition to hydrodissection, the direction of needle entry should be nearly parallel to the medial capsule of the thyroid, and the long axis of the ablated zone should not intersect with the predicted course of the recurrent laryngeal nerve.

The necrotic area should completely cover and exceed the margins of the PTMC by at least 2 mm. For a small nodule (≤5 mm), fixed ablation with a single fiber can generally achieve complete ablation. For a larger lesion (6–10 mm), it is difficult to achieve complete ablation by fixed positioning of a single fiber. The following modalities provide a wider range of ablation: (1) multi-fiber combined ablation, whereby two needles are placed with a spacing of approximately 5 mm; (2) single-fiber multi-point superimposed ablation, whereby the optical fiber is pulled back from the introducer needle to adjust the position after one part of the nodule is completely ablated, and the optical fiber is re-inserted into a different part of the nodule.

**Expert Recommendation 11:** PLA has a forward and progressive mode of action. Therefore, the tip of the optical fiber should be placed at the proximal end of the PTMC so that the necrotic area can completely cover the lesion. **Recommendation strength: strong recommendation; moderate quality evidence.**

**Expert Recommendation 12:** PLA treatment should be planned on the basis of the size, position, and depth of the PTMC. The final margin of coagulative necrosis should exceed the PTMC by at least 2 mm. **Recommendation strength: weak recommendation; moderate quality evidence.**

**Expert Recommendation 13:** For a small PTMC (≤5 mm), single-fiber fixed ablation can achieve complete ablation of the target lesion. **Recommendation strength: weak recommendation; moderate quality evidence.**

**Expert Recommendation 14:** The recommended method of optical fiber insertion may be either through the thyroid isthmus or along the longitudinal axis of the PTMC. **Recommendation strength: weak recommendation; low quality evidence.**

**Expert Recommendation 15:** For larger PTMCs (6–10 mm), the use of two fibers for combined ablation should be considered. Single-fiber multi-point superimposed ablation (i.e., the pull-back technique) may also be used. **Recommendation strength: weak recommendation; low quality evidence.**

**Key question 12:** How do you know when ablation coverage is complete?

Compared with other thermal ablation technologies, PLA has a smaller ablation range and more predictable heat diffusion. The temperature in the central part of the ablation area continuously rises due to the absence of cold fluid circulation, but because the gasification dissipates slowly, it is difficult to immediately assess the ablation volume with conventional US examination. The ablation process may be stopped when the strong echo area generated by gasification exceeds the edge of the lesion. CEUS should be used to precisely define the ablation area. If the nonperfusion area exceeds the PTMC margin by 2 mm, the ablation range is considered sufficient. Otherwise, a further ablation procedure should be performed.
Expert Recommendation 16: CEUS evaluation should be performed at the end of treatment to assess the completeness of the ablation, and the nonperfusion zone should exceed the margins of the PTMC by 2 mm. Recommendation strength: weak recommendation; low quality evidence.

Key question 13: How should vagal hyperactivity be managed during PLA?

Vasovagal reflex syncope during ablation is usually caused by anxiety or local pain. When the systolic blood pressure drops to 80 mmHg, unconsciousness may occur. The treatment measures are as follows: (1) stop PLA treatment, place the patient in the supine position, elevate lower limbs, administer intravenous saline infusion and mask oxygen (6–10 L/min), and monitor ECG, blood pressure, and oxygen saturation; (2) if the patient does not respond to the above treatment, atropine (0.5–1.0 mg) should immediately be given by slow intravenous injection, and this may be repeated after 3–5 min according to patient’s condition.

Expert Recommendation 17: When vagal hyperactivity occurs during PLA treatment, the ablation should be stopped and the vital signs of the patient should be monitored. Ablation may be restarted after the patient’s condition stabilizes. Recommendation strength: strong recommendation; low quality evidence.

8. Post-ablation management

Key question 14: What complications may occur after PLA and how should these be managed?

Potential complications after PLA include cervical pain, local bleeding, thyroid function abnormality, infection and recurrent laryngeal nerve injury. In general, their incidence is low and they are rarely serious.

1. Severe pain is a minor complication of thermal ablation, with an incidence of 3.2% [27]. It generally occurs when heat is transmitted to the thyroid capsule, which causes cervical pain that radiates to ears, jaw, and back. In most patients, the pain is immediately relieved as soon as laser firing stops. To prevent pain during ablation, the tip of laser fiber should be placed at a safe distance from the thyroid capsule and insulating fluid can also be injected. Persistent pain is rare and managed with oral analgesics. For severe pain, analgesic or corticosteroid medications should be given after the exclusion of injury to the surrounding organs.

Expert Recommendation 18: Postoperative local pain usually resolves spontaneously. The administration of analgesic or corticosteroid medications should be considered for persistent pain. Recommendation strength: strong recommendation; low quality evidence.

2. Local hemorrhage can usually be controlled by applying pressure to the cervical region for a few minutes. The hemorrhage may then be assessed by CEUS or US. In exceedingly rare cases of persistent bleeding, hemostatic drugs may be administered intravenously, and a surgical consult should be requested [28]. The hematoma is usually absorbed within 1 week after ablation.

Expert Recommendation 19: In the event of local hemorrhage, local pressure should be applied until the bleeding stops. Surgical consultation is needed in case of severe bleeding. Recommendation strength: strong recommendation; low quality evidence.

3. Abnormal thyroid function is a minor complication after PLA. A transient increase of serum anti-thyroid antibodies and thyroglobulin levels may be observed. Delayed transient hyperthyroidism or hypothyroidism is rare and generally self-limiting [28]. If hyperthyroidism occurs, the majority of patients will spontaneously recover by avoiding iodine in their diet. Severe hyperthyroidism is treated using oral antithyroid drugs. If thyroid hormone surge occurs, levothyroxine tablets can be taken orally. Thyroid function should be monitored regularly in these patients, with dosage adjusted accordingly.

Expert Recommendation 20: Abnormal thyroid function is rare after PLA for PTMC and usually recovers spontaneously. Persistent functional abnormalities should be treated using established methods. Recommendation strength: weak recommendation; low quality evidence.

4. Infection is a rare complication after PLA. Antipyretics and broad-spectrum antibiotics should be given if the patient has a persistent temperature above 38°C. If a local abscess occurs, accurate cleaning and drainage of the wound under US monitoring are needed to prevent the risk of cellulitis and upper mediastinum involvement.

Expert Recommendation 21: In the rare event of local severe infection, the wound should be cleaned and drained, and systemic antibiotics should be administered. Recommendation strength: strong recommendation; low quality evidence.

5. Injury of the recurrent laryngeal nerve is a rare complication with an incidence of approximately 0.7% [27]. The main manifestations are an abrupt hoarseness during PLA, and coughing when drinking. The majority of symptoms are self-limiting due to recovery of ipsilateral nerve and compensation of the contralateral nerve. Minor thermal stimulation to the recurrent laryngeal nerve can also result in the above symptoms, but they may spontaneously disappear within a few hours. To prevent recurrent nerve injury, the relationship between the target area of ablation and the recurrent laryngeal nerve should be carefully evaluated before PLA, and the range of ablation should be precisely controlled. Corticosteroids may be used to reduce nerve edema immediately after PLA; neurotrophic drugs can be also used. The vast majority of patients recover within a few weeks to several months.
Expert Recommendation 22: The majority of symptoms arising from laryngeal nerve injury spontaneously disappear due to recovery of the ipsilateral nerve and compensation of the contralateral nerve. Corticosteroids and neurotrophic drugs can be considered in severe cases. Recommendation strength: strong recommendation; low quality evidence.

6. Other complications: (1) The incidence of skin burn is very low. In the case of accidental damage to the skin, topical antibiotic ointment should be applied. (2) Tracheal perforation is an exceedingly rare but serious complication that requires surgical repair [29].

Key question 15: What is the recommended follow-up strategy after PLA?

After PLA, follow-up visits are recommended at 1 week, 1 month, 3 months, 6 months, and every 6–12 months thereafter. CEUS is indicated for assessing the area of ablation within 2 h and 1 week after PLA, while US examination and thyroid function assessment should be performed at each time point. Gray-scale US can be used to assess the reduction rate, changes of the ablated lesion, and occurrence of new neoplastic foci or metastatic lymph nodes.

Expert Recommendation 23: After PLA, long-term follow-up is needed to evaluate the completeness of ablation and to rule out local regrowth, new PTMC occurrence and cervical recurrence. Recommendation strength: strong recommendation; high quality evidence.

Key question 16: Is a biopsy of the ablated area recommended after PLA?

In the first case of PLA for PTMC, performed by Papini in 2011, FNA and CNB performed at 1 month and 12 months after PLA showed that necrotic substances and inflammatory cells, but not tumor cells, were found in the ablation area [12]. FNA has also been used by others to determine whether there are viable tumor cells in the ablation site at 1, 6, and 12 months after PLA [18,30]. However, coagulative necrosis caused by thermal ablation may reduce the diagnostic accuracy of FNA in the ablation area [31]. Compared with FNA, CNB is reported to have a higher diagnostic accuracy and a lower rate of inadequate samples [32,33]. However, currently, it is not routinely used after thermal ablation [19,34].

Expert Recommendation 24: FNA should be performed if regrowth of the ablated zone is observed. In the case of incomplete PTMC ablation or biopsy-proven regrowth of the tumor, a second PLA procedure or surgery should be offered. Recommendation strength: strong recommendation; moderate quality evidence.

Key question 17: How should the occurrence of suspicious cervical lymph nodes during follow-up be managed?

The sensitivity, specificity, and accuracy of ultrasonography in the diagnosis of metastatic lymph nodes are 33%, 93%, and 69% for the central compartment, and 70%, 84%, and 88% for the cervical lateral compartment [35]. As preoperative assessment of lymph node metastasis may underestimate their presence, particularly in the central compartment, the diagnosis of metastatic lymph nodes may occur after ablation [9,14,36–38]. Although the probability of recurrence after thermal ablation is low, FNA assessment should be performed for any suspicious cervical lymph node detected by US after PLA. Long-term follow-up is required after PLA, and surgical treatment or re-ablation can be performed for newly discovered, biopsy-proven, metastatic lymph nodes. Risk factors for cervical lymph node metastasis include a maximum diameter of PTMC >6–7 mm, age <45 years, male sex, extra thyroidal growth, multifocality, and location in the lower third of thyroid gland [39,40].

Expert Recommendation 25: Surgery is recommended when a biopsy-proven lymph node metastasis is detected during follow-up. PLA can be considered as an alternative option for patients with small recurrences after treatment who refuse or are not suitable for surgical treatment. Recommendation strength: no recommendation; insufficient evidence.

Key question 18: Is thyroid-stimulating hormone (TSH) suppression therapy required after PLA?

Because the area of tissue destruction after PLA treatment is relatively small, thyroid function is almost completely preserved. Considering that TSH may stimulate differentiated thyroid cancer cells proliferation, oral L-T4 may be appropriate for TSH suppression therapy, taking into account the conditions of treatment, and the patient’s preference, age, and previous disease. If TSH can be maintained in the range of 0.5–2 mU/L without oral administration of levothyroxine, TSH inhibition therapy is not required. If the TSH level exceeds 2 mU/L, treatment can be performed as appropriate. The 2015 guidelines from the American Thyroid Association discuss drug intervention for TSH suppression in low-risk patients in more detail [19]. Due to the increased risk for atrial fibrillation, cardiovascular and all-cause mortality, and osteoporosis in elderly patients, TSH suppression treatment should be cautiously considered and TSH level should not be lower than 0.1 mU/L [41–43].

Expert Recommendation 26: For patients with no abnormal thyroid function and TSH <2 mU/L after PLA, TSH inhibition is not routinely recommended. If TSH reaches >2 mU/L, levothyroxine can be administered as appropriate. Recommendation strength: no recommendation; insufficient evidence.

9. Quality control

This expert consensus includes a brief introduction to PLA, indications and contraindications of the use of this procedure for PTMC, the need for physician training and qualification, the requirements for informed consent, the intraoperative technical procedures, the efficacy assessment, the potential intra- and post-procedural complications and their management measures, and the approaches to recurrent PTMC and metastatic lymph nodes.

To improve the efficacy and safety of this treatment, it is necessary to standardize the PLA procedures and follow-up. Quality control implementation may decrease the number of repeated examinations and re-treatments, save medical
resources, and ensure the long-term effectiveness of treatment and follow-up. Quality control should include:

1. A defined minimal threshold of PLA treatments per year that is associated with adequate operation proficiency and treatment quality.
2. Standardization of the records that document cases of PTMC treated with PLA;
3. A video recording or the final images of the ablation site as a reference during follow-up and for retrospective data analysis;
4. Networking with surgical centers and hospital emergency response teams for an interdisciplinary approach to PTMC and timely management of intra-operative and postoperative complications;
5. An annual summary report of the outcomes of PLA-treated PTMC.

Disclosure statement
No potential conflict of interest was reported by the author(s).

Funding
The author(s) reported there is no funding associated with the work featured in this article.

ORCID
Jian Qiao Zhou  http://orcid.org/0000-0002-0964-8407
Man Lu  http://orcid.org/0000-0002-3455-834X

References
[1] Rossi ED, Pantanowitz L, Hornick JL. A worldwide journey of thyroid cancer incidence centred on tumour histology. Lancet Diabetes Endocrinol. 2021;9(4):193–194.
[2] Shafique K, LiVolsi VA, Montone K, et al. Papillary thyroid microcarcinoma: reclassification to non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): a retrospective clinicopathologic study. Endocr Pathol. 2018;29(4):339–345.
[3] Yamamoto Y, Maeda T, Izumi K, et al. Occult papillary carcinoma of the thyroid. A study of 408 autopsy cases. Cancer. 1990;65(5):1173–1179.
[4] Lang W, Borrusch H, Bauer L. Occult carcinomas of the thyroid. Evaluation of 1,020 sequential autopsies. Am J Clin Pathol. 1988;90(1):72–76.
[5] Harach HR, Franssila KO, Wasenius VM. Occult papillary carcinoma of the thyroid. A “normal” finding in Finland. A systematic autopsy study. Cancer. 1985;56(3):531–538.
[6] Ito Y, Miyachi A, Kihara M, et al. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. Thyroid. 2014;24(1):27–34.
[7] Ito Y, Uruno T, Nakano K, et al. An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. Thyroid. 2003;13(4):381–387.
[8] Tufano RP, Pace-Asciak P, Russell JO, et al. Update of radiofrequency ablation for treating benign and malignant thyroid nodules. The future is now. Front Endocrinol (Lausanne). 2021;12:698689.
[9] Papini E, Monpeyssen H, Frasoldati A, et al. 2020 European thyroid association clinical practice guideline for the use of image-guided ablation in benign thyroid nodules. Eur Thyroid J. 2020;9(4):172–185.
[10] Mauri G, Hegedus L, Bandula S, et al. European Thyroid Association and Cardiovascular and Interventional Radiological Society of Europe 2021 clinical practice guideline for the use of minimally invasive treatments in malignant thyroid lesions. Eur Thyroid J. 2021;10(3):185–197.
[11] Xu D, Ge M, Yang A, et al. Expert consensus workshop report: guidelines for thermal ablation of thyroid tumors (2019 edition). J Cancer Res Ther. 2020;16(5):960–966.
[12] Papini E, Guglielmi R, Gharib H, et al. Ultrasound-guided laser ablation of incidental papillary thyroid microcarcinoma: a potential therapeutic approach in patients at surgical risk. Thyroid. 2011;21(8):917–920.
[13] Valcavi R, Piana S, Bortolani GS, et al. Ultrasound-guided percutaneous laser ablation of papillary thyroid microcarcinoma: a feasibility study on three cases with pathological and immunohistochemical evaluation. Thyroid. 2013;23(12):1578–1582.
[14] Kim HJ, Chung SM, Kim H, et al. Long-term efficacy of ultrasound-guided laser ablation for papillary thyroid microcarcinoma: results of a 10-year retrospective study. Thyroid. 2021;31(11):1723–1729.
[15] Gambelunghe G, Stefanetti E, Avena N, et al. Percutaneous ultrasound-guided laser ablation of benign thyroid nodules: results of 10-year follow-up in 171 patients. J Endocr Soc. 2021;5(7):bva081.
[16] Mauri G, Nicolas L, Della Vigna P, et al. Percutaneous laser ablation for benign and malignant thyroid diseases. Ultrasonography. 2019;38(1):25–36.
[17] Peng K, Zhou P, Liu W. Long-term efficacy of ultrasound-guided percutaneous laser ablation for low-risk papillary thyroid microcarcinoma: a 5-year follow-up study. Biomed Res Int. 2021;2021:6616826.
[18] Zhang L, Zhou W, Zhan W, et al. Percutaneous laser ablation of unifocal papillary thyroid microcarcinoma: utility of conventional ultrasound and contrast-enhanced ultrasound in assessing local therapeutic response. World J Surg. 2018;42(8):2476–2484.
[19] Haugen BR, Alexander EE, Bible KC, et al. 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26(1):1–133.
[20] Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol. 2013;66(7):719–725.
[21] Ridouani F, Tuttle RM, Ghosn M, et al. Ultrasound-guided percutaneous laser ablation of the thyroid gland in a swine model: comparison of ablation parameters and ablation zone dimensions. Cardiovasc Interv Radiol. 2021;44(11):1798–1806.
[22] Pacella CM, Mauri G, Achille G, et al. Outcomes and risk factors for complications of laser ablation for thyroid nodules: a multicenter study on 1531 patients. J Clin Endocrinol Metab. 2015;100(10):3903–3910.
[23] Cohen Y, Xing M, Mambo E, et al. BRAF mutation in papillary thyroid carcinomas. J Clin Endocrinol Metab. 2014;99(5):E754–E765.
[24] Melo M, da Rocha AG, Vinagre J, et al. TERT promoter mutations are a major indicator of poor outcome in differentiated thyroid carcinomas. J Clin Endocrinol Metab. 2014;99(5):E754–E765.
[25] Xing M, Liu R, Liu X, et al. BRAF V600E and TERT promoter mutations cooperatively identify the most aggressive papillary thyroid cancer with highest recurrence. J Clin Oncol. 2014;32(25):2718–2726.
[26] Lee SY, Savides TJ. Management of anticoagulation before and after gastrointestinal endoscopy. Am J Gastroenterol. 2010;105(3):703–725.
[27] Choi Y, Jung SL. Efficacy and safety of thermal ablation techniques for the treatment of primary papillary thyroid
microcarcinoma: a systematic review and meta-analysis. Thyroid. 2020;30(5):720–731.

[28] Valcavi R, Riganti F, Bertani A, et al. Percutaneous laser ablation of cold benign thyroid nodules: a 3-year follow-up study in 122 patients. Thyroid. 2010;20(11):1253–1261.

[29] Di Rienzo G, Surrente C, Lopez C, et al. Tracheal laceration after laser ablation of nodular goitre. Interact Cardiovasc Thorac Surg. 2012;14(1):115–116.

[30] Zhou W, Jiang S, Zhan W, et al. Ultrasound-guided percutaneous laser ablation of unifocal T1N0M0 papillary thyroid microcarcinoma: preliminary results. Eur Radiol. 2017;27(7):2934–2940.

[31] Chu KF, Dupuy DE. Thermal ablation of tumours: biological mechanisms and advances in therapy. Nat Rev Cancer. 2014;14(3):199–208.

[32] Chung SR, Baek JH, Choi YJ, et al. The role of core needle biopsy for the evaluation of thyroid nodules with suspicious ultrasound features. Korean J Radiol. 2019;20(1):158–165.

[33] Chung SR, Suh CH, Baek JH, et al. The role of core needle biopsy in the diagnosis of initially detected thyroid nodules: a systematic review and meta-analysis. Eur Radiol. 2018;28(11):4909–4918.

[34] Na DG, Baek JH, Jung SL, et al. Core needle biopsy of the thyroid: 2016 consensus statement and recommendations from Korean Society of Thyroid Radiology. Korean J Radiol. 2017;18(1):217–237.

[35] Zhao H, Li H. Meta-analysis of ultrasound for cervical lymph nodes in papillary thyroid cancer: diagnosis of central and lateral compartment nodal metastases. Eur J Radiol. 2019;112:14–21.

[36] Cho SJ, Baek SM, Na DG, et al. Five-year follow-up results of thermal ablation for low-risk papillary thyroid microcarcinomas: systematic review and meta-analysis. Eur Radiol. 2021;31(9):6446–6456.

[37] Yan L, Lan Y, Xiao J, et al. Long-term outcomes of radiofrequency ablation for unifocal low-risk papillary thyroid microcarcinoma: a large cohort study of 414 patients. Eur Radiol. 2021;31(2):685–694.

[38] Li J, Liu Y, Liu J, et al. A comparative study of short-term efficacy and safety for thyroid micropapillary carcinoma patients after microwave ablation or surgery. Int J Hyperthermia. 2019;36(1):640–646.

[39] Zhang L, Wei WJ, Ji QH, et al. Risk factors for neck nodal metastasis in papillary thyroid microcarcinoma: a study of 1066 patients. J Clin Endocrinol Metab. 2012;97(4):1250–1257.

[40] Lee KJ, Cho YJ, Kim SJ, et al. Analysis of the clinicopathologic features of papillary thyroid microcarcinoma based on 7-mm tumor size. World J Surg. 2011;35(2):318–323.

[41] Wang LY, Smith AW, Palmer FL, et al. Thrytropin suppression increases the risk of osteoporosis without decreasing recurrence in ATA low- and intermediate-risk patients with differentiated thyroid carcinoma. Thyroid. 2015;25(3):300–307.

[42] Pajamäki N, Metso S, Hakala T, et al. Long-term cardiovascular morbidity and mortality in patients treated for differentiated thyroid cancer. Clin Endocrinol (Oxf). 2018;88(2):303–310.

[43] Savin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med. 1994;331(19):1249–1252.