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Ultrasound-guided percutaneous laser ablation for papillary thyroid microcarcinoma: a literature review

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Abstract

The incidence of papillary thyroid microcarcinoma has been increasing worldwide. However, the optimal management strategy remains a topic of discussion and varies from an active follow-up to a thyroidectomy. New thermoablation techniques for selected cases seem to be sufficiently effective but minimally invasive. One of the newest thermoablation methods is ultrasound-guided percutaneous laser ablation. There are already some data showing promising results of this method in the management of papillary thyroid microcarcinomas. In this article, we review recent papers and conclude on the current status of the ultrasound-guided percutaneous laser ablation technique for the management of papillary thyroid microcarcinomas. **(Endokrynol Pol 2023; 74 (2): 128–134)**

Key words: *ultrasound therapy; thyroid microcarcinoma; PTMC; percutaneous laser ablation; laser ablation; OR and LA*

Introduction

Thyroid cancer is the most common malignancy of the endocrine system. The morbidity of endocrine cancer has increased over the past few decades, primarily due to the raised incidence of papillary thyroid microcarcinoma (PTMC) [1, 2]. PTMC is a frequent papillary thyroid carcinoma (PTC) measuring less than 10 mm in diameter [2, 3]. Due to the development of diagnostic technologies, such as high-definition ultrasound, ultrasound elastography, fine-needle aspiration (FNA) biopsy, and core-needle aspiration (CNA) biopsy, more patients were diagnosed with incidental PTC, and PTMC accounts for 87% of these PTC cases. The prognosis of PTMC is usually good [4]. Only a minority of cases develop aggressive behaviour with either lymph node or distant metastases. Usually, lobectomy or thyroidectomy is chosen for effective treatment of PTMC, but sometimes it is not suitable for patients who refuse surgical treatment or patients at high surgical risk because of old age and comorbidities [1, 5]. In these cases, minimally invasive procedures have already been recommended for the treatment and control of PTMC recurrences [1, 2, 6]. Ultrasound (US)-guided percutaneous procedures, such as ethanol ablation (EA), percutaneous laser ablation (PLA), microwave ablation (MWA), and radiofrequency ablation (RFA), were suggested as an alternative to open PTMC surgery for high-risk patients because of good long-term results [2, 3]. Using US-guided PLA, a very small percentage of cases show aggressive behaviour with either lymph node or distant metastases during long-term follow-up [5]. This method was recommended by the European Thyroid Association and the American Association of Clinical Endocrinologists in the 2010 Thyroid Nodule Guidelines and the 2020 European Thyroid Association Clinical Practice Guideline as an effective treatment alternative in benign thyroid nodules, based on a clinically significant decrease in nodule volume and the amelioration of local symptoms, safety, and clinical efficacy. PLA is also recommended for patients who decline surgery or are at surgical risk. [7]

In this review, we focus on US-guided PLA for PTMC treatment.

Literature search and inclusion criteria

Two authors independently searched the electronic databases of Cochrane Library, Embase, Central, and PubMed up to December 2021. The following

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keywords were included in various combinations: "Ultrasound Therapy", "Thyroid Microcarcinoma" OR "PTMC", "Percutaneous Laser Ablation" OR "Laser Ablation" OR "LA". Before inclusion, all articles were assessed individually.

Patients

All patients signed an informed consent document before the US-guided PLA procedure. For the retrospective study, approval was given by the hospital ethics committee [1, 2, 6]. The inclusion criteria for patients were as follows: (1) single lesion with a maximum diameter of 10 mm, (2) cytological diagnosis showing unifocal PTMC, (3) solid lesion without coarse calcification (the maximum dimension of a strong echo with acoustic shadow > 2 mm), (4) no contact between lesion and thyroid capsule or its disruption, (5) no tumour invasion to other organs such as the trachea, common carotid artery, or oesophagus, and (6) patients unsuited or unwilling to undergo surgery because of high-risk, old age, or other reasons. The exclusion criteria were as follows: (1) cytologic diagnosis showing other types of thyroid malignancies such as medullary carcinoma, (2) clinically apparent multicentricity, (3) multiple lesions or single lesion larger than 10 mm in maximum diameter, (4) lesion with cystic components, (5) lesion located in the isthmus or invading into the thyroid capsule, common carotid artery, or trachea, (6) ultrasound or other image studies showing cervical or distant metastasis, and (7) calcifications in the nodes more than 2 mm in diameter [1, 2, 6].

Among 5 articles included in this review, 2 articles were from Italy [5, 8] and 3 from China [1, 2, 6]. The efficacy of ultrasound-guided laser ablation for papillary thyroid microcarcinoma is demonstrated in Table 1 and Table 2.

Pre-PLA evaluation

Before each PLA procedure, all patients underwent an ultrasound examination to determine the size of the nodule [6]. Patients were evaluated with a real-time ultrasound equipped with a 13-MHz linear probe and a built-in neodymium yttrium-aluminium-garnet (Nd-YAG) laser device [1]. Before each PLA session, the size, volume, location, ultrasonic characteristics, and internal vascularity of the nodules, and the presence of abnormal lymph nodes in the neck were carefully evaluated. All nodules were measured in 3 orthogonal diameters: length, width, and thickness. The following equation was used to calculate the volume:

$$V = \varpi \times a \times b \times c / 6$$

Table 1. *Summary of post-ablation follow-up in diameter (months) out of 5 different research papers. It includes the diameter of papillary thyroid microcarcinoma before the percutaneous laser ablation (PLA) and from 10–20 minutes to 42 months after the procedure*

No.	Year	Author	Pre-ablation	10–20 minutes	30 minutes	1 hour	7 days	1M	3M	6M	12M	18M	24M	30M	36M	42M
1	2011	Papini et al.	8	No data	No data	No data	No data	Missing data	No data	No data	Missing data	No data	Missing data	No data	No data	No data
2	2013	Valcavi et al.	9 ± 1	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
3	2017	Zhou et al.	4.8 ± 1.2	No data	No data	14.6 ± 2.5	15.0 ± 3.3	11.2 ± 2.9	8.1 ± 2.3	5.4 ± 1.4	2.6 ± 1.9	2.0 ± 1.8	0	No data	No data	No data
4	2018	Zhang et al.	4.6 ± 1.5	13.7 ± 2.3	No data	14.1 ± 2.4	14.6 ± 2.7	No data	No data	No data	No data	No data	No data	No data	No data	0.6 ± 1.3
5	2019	Ji et al.	5.1 ± 3.4	No data	12.9 ± 4.1	No data	No data	14.7 ± 4.5	7.9 ± 3.6	4.8 ± 2.7	2.3 ± 1.4	1.7 ± 0.7	1.1 ± 0.6	No data	No data	No data

Table 2. *Summary of post ablation follow-up volume (months or percentage (the average volume reduction rates of the tumour)) out of five different research papers*

No.	Year	Author	Pre-ablation	10–20 minutes	30 minutes	1 hour	7 days	1M	3M	6M	12M	18M	24M	30M	36M	42M
1	2011	Papini et al.	205.1	No data	No data	No data	No data	Missing data	No data	No data	Missing data	No data	Missing data	No data	No data	No data
2	2013	Valcavi et al.	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
3	2017	Zhou et al.	43.7 ± 37.8	No data	No data	566.8 ± 267	1098.2 ± 51	259.8 ± 149	87.1 ± 69.2	33.8 ± 24.3	9.1 ± 13.5	4.5 ± 5.7	0	No data	No data	No data
4	2018	Zhang et al.	41.0 ± 40.4	435 ± 234.9	No data	517.6 ± 262	1062 ± 490	–11.3%	–3.3%	2.2%	44.70%	88.5%	95.3%	96.8%	100%	100%
5	2019	Ji et al.	52.8 ± 30.6	No data	726.5 ± 187.2	No data	No data	258.1 ± 97	102.7 ± 39.5	44.7 ± 24.3	10.2 ± 8.7	5.7 ± 6.5	2.1 ± 1.3	No data	No data	No data

where V is the volume, a the length of the tumour, and b and c are the other 2 perpendicular diameters [2, 6]. The mean volume increasing multiplier (MVIM) was calculated as follows:

$$MVIM = (V2 - V1)/V1 \times 100\%$$

where $V2$ represents the postoperative volume, and $V1$ represents the preoperative volume [1].

PLA procedure

During the PLA procedure, the patients lay on an operating table in the supine position with the neck extended [2, 3, 6]. Under sterile conditions, 2% lidocaine was usually used for local anaesthesia [1, 2, 5, 6]. There were some cases where general anaesthesia was performed [8]. To protect vital organs (trachea, recurrent laryngeal nerve common carotid artery, and oesophagus) from thermal damage, a hydro dissection solution of 2% lidocaine and 0.9% sodium chloride solution (1:8 dilution) was injected into the surrounding thyroid capsule to achieve a "liquid isolating zone" [2]. During the injection, talking to the patient is recommended to monitor the status of phonation [6]. After anaesthesia, a 21-gauge guide needle percutaneously penetrated the target lesion under real-time ultrasound guidance, and then the core needle was withdrawn. After the correct positioning of the needle, a 300-μm plane-cut optic fibre was inserted through the sheath of the 21-gauge needle into the same position. Then the introduction needle was withdrawn approximately 5 mm, exposing the tip of the fibre in direct contact with the tumour. The optic fibre was connected to a continuous-wave Nd:YAG laser source operating at 1.064 μm with an optical beam-splitting device [1, 2]. Continuous expansion of a strong gas echo area around the fibre head indicated the release of the energy. The ablation was stopped once the lesion was completely covered [1]. Then laser ablations were performed with an output power of 3 W or 4 W, using an appropriate exposure time to ablate an area a few millimetres larger than the original lesion [6]. The total energy delivered during PLA might ranged from 989.4 ± 417.6 J to 3600 J [1, 5]. Contrast-enhanced ultrasound (CEUS) was performed immediately after the ablation to evaluate the perfusion property of the ablated area. [6] When the thyroid contrast agent filling completely covered the defect area, and the filling exceeded the edge of the primary lesion by 1-2 mm, the lesion was considered completely ablated [1]. According to some authors' experience, the standard time to complete LA is 10 mins [8].

Post-PLA observation

Patients were closely monitored for 60 min after PLA for possible complications such as haematoma, voice change, tracheal injury, and oesophageal perforation. Neck compression was administered for 20-30 min to avoid bleeding [6]. Local therapy evaluation was conducted with conventional US, CEUS, and US-guided free-needle aspiration biopsy (FNAB). Conventional US examinations were usually performed at one hour, 7 days, and 1, 3, and 6 months after the PLA procedure and every 6 months after that. The complications, size, and volume of the ablated area and the development of recurrent and metastatic tumours are evaluated during follow-ups. CEUS is performed at 10–20 min and 7 days after the PLA procedure. The extent of the ablation zone's lack of enhancement is evaluated during CEUS examination to confirm that more extensive necrosis is achieved than the nodule pre-operation [2]. The ablation is considered successful if in all imaging findings the following conditions are met: (1) no contrast enhancement is detected around or within the lesion; (2) the margin of the ablated area is seen to be clear and smooth; and (3) the ablated area extends beyond the tumour border [2]. US-guided FNAB of the ablated area and the surrounding thyroid parenchyma is performed at 1, 6, and 12 months after PLA if the ablated zone persists. US-guided FNAB can also be performed if suspicious metastatic lymph nodes are found in the neck [2, 6].

Lab work is also performed. Thyroid-related hormone levels are measured, including TSH, FT3, and FT4. Patients are re-examined monthly if thyroid-related hormone levels are abnormal [1].

Results

We summed up several authors' results of PLA treatment. The procedure was well tolerated and without any significant or permanent side effects. No local infection, neck haematoma, or dysphonia were registered [2, 6]. Also, none of the authors in their research mentioned that the laryngeal nerve was damaged during the LA procedure. There were only a few cases in which thyroid hormone levels were abnormal, TSH levels were increased, and FT3 and FT4 levels were slightly decreased during the first and second months post-PLA. However, these abnormalities recovered

Table 3. *Parameters of ablation. It consists of the mean total energy delivery, the active time, the power, and the length of wave during percutaneous laser ablation (PLA)*

No	Year	Country	Author	Age	Female	Male	Power [W]	Time [s]	Joule of energy	Wave length [nm]
1	2011	Italy	Papini et al.	81	1	0	3	600	3600	No data
2	2013	Italy	Valcavi et al.	52.3 ± 9.3	3	0	3	600	1800	1064
3	2017	China	Zhou et al.	16-69	17	13	3-4	274 ± 57	1097 ± 229	1064
4	2018	China	Zhang et al.	42.5 ± 12.3	41	23	3-4	271.6 ± 86.7	994 ± 310	1064
5	2019	China	Ji et al.	43.9 ± 17.6	25	12	3-4	165.9 ± 92.8	989.4 ± 417	1064

Table 4. *General data in different studies. It consists of the laser device used for percutaneous laser ablation (PLA), needle type, duration of follow-up period, number of incomplete ablations and recurrences, complications, and frequency of scar-like areas*

No	Year	Country	Author	Laser device	Needle	Follow-up	Incomplete ablation	Recurrent	Complications	Scar like areas
1	2011	Italy	Papini et al.	Nd-YAG	21 G	24	0	0	No complications	Missing data
2	2013	Italy	Valcavi et al.	No data	21 G	No data	0	0	Not mentioned	No data
3	2017	China	Zhou et al.	Nd-YAG	21 G	13.2 (12–24)	1	0	No serious complications	66.7%
4	2018	China	Zhang et al.	Nd-YAG	21 G	25.7 ± 8.2	2	1	No complications	20.3%
5	2019	China	Ji et al.	Nd-YAG	21 G	16.5 ± 6.9	8	1	No serious complications	64.9%

Nd-YAG — neodymium yttrium-aluminium-garnet

spontaneously 3 months later [1]. No changes in renal and liver function were registered [5]. For all PLA procedures, a Nd-YAG laser source was used operating at 1064 μm. The mean total energy delivery during PLA ranged from 400 J to 1750 J (Tab. 3 and 4). The active time during PLA ranged from 150 s to 600 s. The maximum follow-up period lasted 42 months. A few patients required a second ablation procedure due to incomplete ablation, as shown by CEUS. Some authors mention that no contrast agent perfusion was found in the ablation area [1, 2]. The range of thermal damage was slightly more extensive than the ablated tumour and included an approximately 2–3-mm rim of normal tissue around the tumour that faded away at the border of the cavitation [6, 8].

Right after PLA, internal echoes of the tumours in all cases changed from hypoechoic to hyperechoic on greyscale images due to gas formation during the ablation. The original tumour disappeared and was replaced by a well-defined hypoechoic area with a strip of high echo in the centre one hour after the procedure [2, 5, 6]. CEUS detected no vascular signals in the ablated zones. If the conventional ultrasound showed a hypoechoic area inside the tumour or residual enhancement was seen inside the lesion during CEUS, incomplete ablation was strongly implied [6].

The greyscale of the ultrasonic appearance of the ablated area after one week was almost the same as at one hour after the PLA procedure. However, the mean values of maximum diameter and volume on the seventh day after PLA were larger than pre-treatment [6]. The necrotic areas had extended beyond the tumour borders, and the margins of the ablated areas were clear and smooth, as shown on CEUS [2]. The size of the ablated area started to slowly decrease after the seventh day of follow-up [6]. According to Zhang L. et al., among 64 patients who participated in the PLA treatment, 51 (79.7%) ablation zones completely disappeared after 42 months of follow-up, and 13 (20.3%) ablation zones remained as scar-like lesions. Inflammatory cells, and necrotic and carbonized tissue without any viable neoplastic cells were shown in US-guided FNAB of the ablated zones at 1, 6, and 12 months of follow-up. No regrowth of treated lesions was found on conventional ultrasound examination [2, 6]. However, few cases of suspicious metastatic lymph nodes were detected in the neck, and the patients received open surgical treatment [1, 2].

Discussion

The extensive use of cervical ultrasonic examination and US-guided FNAB has resulted in an increasing number of cases of incidentally discovered PTMCs. Over the years, there have been many discussions about the treatment of papillary thyroid microcarcinoma. Previously prevailing treatment methods for PTMC were total or lobular surgical resection, endoscopic thyroidectomy, I^{131} treatment, or even surveillance [1]. According to the 2009 American Thyroid Association Guidelines, the initial surgical procedure should be a near-total or total thyroidectomy for patients with thyroid cancer larger than 1 cm in diameter [8]. However, this does not reflect recommendations in 2015 American Thyroid Association Management Guidelines — for patients with thyroid cancer > 1 cm and < 4 cm without extrathyroidal extension and without clinical evidence of any lymph node metastases (cN0) the initial surgical procedure can be either a bilateral procedure (near-total or total thyroidectomy) or a unilateral procedure (lobectomy) [7]. However, PTMC is a specific subgroup of PTC and is defined by the WHO as having the largest dimension of 1 cm or less and usually with a good prognosis [9]. Some patients are unwilling to have surgical treatment because of increased surgical risk due to age and relevant comorbidities, postoperative pain, or cosmetic concerns [2, 5, 6]. This has led to the development of new follow-up strategies and minimally invasive treatment of PTMC. A few years ago, ultrasound-controlled ablation therapies received much attention concerning PTMC [6]. According to the research, US-guided PLA seems to encounter the fewest complications of all US-guided technologies [3]. The technique used for PLA is minimally invasive and effective and does not leave scars on the neck [1]. Also, the PLA procedure is well tolerated compared with total or lobular thyroidectomy, it is safe and inexpensive, and does not require hospitalization [6, 8]. Minimally invasive ablation of PTMCs that appear unifocal and isolated to the thyroid gland at US examination may be used to decrease the risk of the tumour growing locally or of extra-glandular spread in elderly patients or patients with relevant comorbidities, who are not candidates for surgical resection. After PLA, patients can be followed up with clinical and US evaluations once a year and chest computed tomography (CT) scan every 2 years [5].

Some authors suggest percutaneous ethanol injection for PTMC treatment, but thermal ablation is more likely to lead to nodular degeneration and necrosis than ethanol [7]. Percutaneous ethanol injection has also been suggested to treat metastasis in cervical lymph nodes. The procedure is effective and safe as reported, but ethanol can be randomly spread in the tissue, and the area of coagulative necrosis cannot be precisely predicted. Also, alcohol can seep into the cervical tissues, which can cause neck pain, laryngeal nerve

damage, and posttreatment fibrosis. For this reason, thermal ablation seems to be more suitable for PTMC treatment because of the predictable and well-defined area of necrosis close to vital structures [5].

The main goal of the PLA procedure is to destroy the tumour by inserting an applicator directly into the tumour and inducing coagulation necrosis by locally raising the temperature. It is essential to make sure that the ablation is complete as soon as possible after the treatment, so that any residual viable tumour tissue can be retreated promptly to obtain an excellent local therapeutic effect [2]. Imaging plays the most crucial role in real-time confirmation of the successful ablation. There are a few essential imaging findings: (1) no contrast enhancement can be detected within or around the tumour; (2) the margin of the ablated area must be clear and smooth; and (3) the ablated area should extend beyond the tumour border. Imaging findings can be revealed by conventional ultrasound and CEUS. CEUS is superior to conventional US. CEUS is a contrast harmonic imaging method that allows the description of focal lesions by evaluating their micro-vascularization with second-generation contrast material [2].

The definitive confirmation of the therapeutic effect is histological evaluation. Immunohistochemical methods depend on the binding between an antigen and its specific primary antibody. If the laser energy has destroyed the antigen of the tissue, the primary antibody cannot recognize its epitope and the immunohistochemical staining is negative. The cell can lose its vitality if the denaturation of the proteins and the damage of the epitopes are widespread all over the cell. This can be called histologically confirmed irreversible cellular damage [8].

The complication rate during ablation relates to the location of the lesion [1]. For a successful PLA procedure, the injection of hydro-dissection solution and US monitoring or CEUS are recommended. Also, it is recommended that conversation be maintained with the patient while performing PLA to detect any voice changes [6]. Due to the protective effect of the hydro-dissection solution between the mass and the expected location of the recurrent laryngeal nerve or other vital organs, complications and side effects are minimal. There is no report on laryngeal nerve damage or any serious complications after the PLA procedure. The most frequent side effects reported are pain and regional discomfort. However, that could be explained by parenchymal oedema and thermal damage of the thyroid capsule [6]. One of the most common complications after open surgical treatment is hypothyroidism, which is observed in about 75% of patients after thyroid lobectomy. This is due to the removal of a large amount of normal gland tissue, and it might result in a decrease in endogenous hormone secretion. In contrast, hypothyroidism is not common after the PLA procedure. According to the research of Ji et al., only one out of 37 patients was found to have hypothyroidism during the first and second months post-PLA, and this patient recovered spontaneously after 3 months post-PLA.

In most of the studies, several limitations should be mentioned: (1) the follow-up period was relatively short, and long-term outcome was not inevitable; (2) multifocality and micrometastases could not be detected without histological examination even when US examination showed that the tumours were completely ablated; (3) using FNAB before PLA might have led to false-positive or false-negative results, so repeated aspiration biopsy is recommended for the patients with any inconsistency between clinical findings and cytological results for PTMC also in patients with suspicious findings on the US; and (4) it is challenging to predict tumour aggressiveness even though many molecular studies have addressed this [1, 6, 8].

Conclusions

According to the current literature, percutaneous LA is a safe and feasible alternative to surgical treatment for complete PTMC destruction in selected cases. LA allows the procedure to be performed for high-risk patients without any severe complications. Supposedly, LA may become a primary choice for PTMC treatment, but more prospective studies are still needed to confirm the long-term oncological results of PLA compared to surgical treatment.

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