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## IMAGE-GUIDED METHODS IN THE TREATMENT OF THYROID NODULES AND CANCER

**Abstract:** Thyroid nodules (TN) are present in about half of the population. About 5% of all nodules are malignant. Image-guided methods for the treatment of TN are becoming a significant alternative to surgery.

Percutaneous ethanol ablation (PEA) is effective in the treatment of thyroid cysts, and neck lymph node metastases. Percutaneous laser ablation (PLA) significantly reduces the size of the nodules and improves subjective symptoms. The adverse effects of PEA are rare, transitory, and mild. Radiofrequency ablation (RFA) is effective for nodules of all sizes and compositions. The major complications of RFA are rare and transient. Microwave ablation is also effective in the treatment of thyroid nodules with rare major complications. High-intensity focused ultrasound (HIFU) is a transcutaneous method. It is effective in the treatment of thyroid nodules, and complications are rare. Graves' hyperthyroidism was also treated with HIFU. As thermal ablation (TA) methods are becoming more popular in 2020, the European Thyroid Association published clinical practice guidelines for the use of image-guided ablation in benign thyroid nodules.

A meta-analysis showed that low-risk papillary thyroid microcarcinoma recurrences after TA treatment are rare, as are complications. As the TA methods are acceptable for the treatment of the low-risk papillary thyroid carcinoma European Thyroid Association and Cardiovascular and Interventional Radiological Society of Europe issued clinical practice guidelines for the use of minimally invasive treatments in malignant thyroid lesions.

Image-guided treatments for thyroid nodules and cancer are here to stay. Their use will expand and become part of routine clinical practice.

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Thyroid nodules are among the most common disorders in humans. Palpation detects thyroid nodules in approximately 10% of the population, but autopsy and ultrasound find nodules in approximately 50% of the population. Nodules are more common in women than in men, and their prevalence increases with age. About 5% of all nodules are malignant (1, 2). Since mid-1990, there has been an increase in the prevalence of thyroid cancer (3).

Thyroid nodules present a significant burden on the health system. In France, for four years, 35367 thyroid surgeries were performed. Fifty-eight percent of the surgeries were performed for nodules and goitres and 17% for cancer (4). In Germany, in the period from April 2017 to July 2018, 12888 thyroid surgeries were performed for benign diseases (5). Therefore, alternative methods for the treatment of thyroid nodules were developed: ethanol ablation, thermal ablation and cryoablation methods were developed. Cryoablation is a promising method, but at this time, there is limited experience with this method.

Percutaneous ethanol ablation (PEA) has been used since the nineties. In 1966 Crille reported thyroid cyst aspiration (6). The use of ethanol for the sclerosation of thyroid cysts was described by Rozman in 1989 (7). Livraghi used PEA to treat autonomous thyroid nodules also in 1990 (8). In Serbia, Anđelković reported successful treatment of autonomous thyroid nodules using PEA (9). Bennedbk and Hegedüs conducted a randomized double-blind trial and demonstrated the efficacy of PEA in the treatment of thyroid cysts (10). Interestingly, PEA was used successfully to treat neck lymph node metastases (11–13). Compared to radiofrequency ablation (RFA), PEA has the same success rate and complication in the treatment of cystic thyroid nodules (14, 15).

Percutaneous laser ablation (PLA) is a method in which a laser beam is used to heat tissue. A randomized control study showed that the use of PLA significantly reduces nodule size and improves subjective symptoms (16). Further studies confirmed the superiority of PLA over levothyroxine treatment (17). A recent meta-analysis proved the efficacy of PLA during 36 months of follow-up (18). PLA adverse effects are rare, transitory, and generally mild (19).

Radiofrequency ablation (RFA) is also used. Its effectiveness is proven for nodules of all sizes and different compositions (solid, semi-cystic and cystic) (20). The 5-year follow-up proved the long-term efficacy of RFA in the treatment of thyroid nodules (21). The efficacy of RFA was confirmed by a meta-analysis by Chan (22). Another meta-analysis showed that RFA treatment significantly improves compressive symptoms and cosmetic outcomes (18). The major complications of RFA are rare and transient (23).

Microwave ablation (MWA) is another method of thermal ablation of thyroid nodules. It is also effective in the treatment of thyroid nodules with rare major complications (24, 25).

High-intensity focused ultrasound (HIFU) is an elegant method of treating thyroid nodules. This is a transcutaneous method and is very simple to use. The operator just needs to locate the nodule and mark it on a screen (26). It is also effective in the treatment of thyroid nodules, and complications are rare (27–29). However, there is an inverse correlation between preablative nodular volume and percentage volume shrinking (30). Graves' hyperthyroidism was also treated with HIFU. In the study of patients with recurrent thyroid disease, 24 months remission rate was 59% (31). Still, there is a problem of pain and whether sedation or anaesthesia is necessary during HIFU treatment (32, 33).

As thermal ablation methods are becoming more popular in 2020, the European Thyroid Association published clinical practice guidelines for the use of image-guided ablation in benign thyroid nodules (34). The main recommendations are as follows:

- Recommendation 1: In adult patients with benign thyroid nodules that cause pressure symptoms and/or cosmetic concerns and decline surgery, image-guided thermal ablation (TA) should be considered as a cost- and risk-effective alternative option to surgical treatment or observation alone.
- Recommendation 2: We recommend against the use of TA for asymptomatic lesions.
- Recommendation 9: Based on direct comparison studies, and balance between efficacy and side effects, PLA and RFA are recommended as the first-line TA treatment modalities.
- Recommendation 12: In multinodular goitres, due to lack of evidence of efficacy and the expected need for repeat treatment, TA should be restricted to patients with a well-defined dominant nodule or those who are not candidates for thyroid surgery or radioactive iodine treatment, as a palliative therapy option.
- Recommendation 13: Because of higher cost and complexity, as compared to aspiration and EA, TA procedures are not recommended as a first-line treatment for pure or dominantly cystic thyroid lesions.
- Recommendation 15: We recommend against TA as the first-line treatment for large autonomous functions thyroid nodules (AFTN); due to the low rate of restoration of normal thyroid function, TA should be considered only for patients who decline or are not candidates for RAI therapy or surgery.
- Recommendation 16: TA should be considered in young patients with small AFTN and incomplete suppression of perinodular thyroid tissue due to the higher probability of normalization of thyroid function and the advantage of avoiding irradiation and restricting the risk of late hypothyroidism.

A recent meta-analysis of active surveillance of low-risk papillary carcinoma found that tumour nodule growth defined as increased diameter by more than 3 mm

occurred in only 4.4% (95% confidence interval [CI] 3.2–5.8%) of the patients. The rate of cervical lymph node metastasis was 1.0% (95% CI 0.7–1.4%) (35). Five-year follow-ups of patients with low-risk papillary thyroid microcarcinoma showed complete resolution of the lesion (36). Another study that included 154 patients with low-risk papillary thyroid microcarcinoma showed complete disappearance of tumor in 93.7% of patients with a tumor less than 0.5 cm in diameter and 85.4% of patients with a tumor greater than 0.5 cm in diameter. However, complete disappearance of the tumor occurred in all 54 patients followed for more than four years (37). A meta-analysis showed that low-risk papillary thyroid microcarcinoma recurrences after thermal ablation treatment are very rare, as are the major complications (38).

As the thermal ablation methods seem to be acceptable for the treatment of the low-risk papillary thyroid carcinoma European Thyroid Association and Cardiovascular and Interventional Radiological Society of Europe issued clinical practice guidelines for the use of minimally invasive treatments in malignant thyroid lesions (39). The main recommendations are as follows:

- Recommendation 1: Consider the use of image-guided minimally invasive treatments in the multimodal approach to patients with thyroid cancer.
- Recommendation 5: Consider the use of image-guided thermal ablation for patients with low-risk papillary thyroid microcarcinoma, mainly if the patient is at surgical risk, is expected to have a short life expectancy, has comorbidities that need to be prioritized before thyroid surgery, or is unwilling to undergo surgery or active surveillance.
- Recommendation 6: Inform patients with incidentally discovered papillary thyroid microcarcinoma who are suitable for active surveillance about thermal ablation as a therapeutic alternative to immediate surgery or active surveillance.
- Recommendation 9: Abstain from using PEA and HIFU for papillary thyroid microcarcinoma treatment, due to insufficient evidence and technical limitations.
- Recommendation 10: Consider minimally invasive treatment for palliative purposes, preferentially in the context of a multimodality approach, in patients with primary thyroid cancer, other than low-risk papillary thyroid microcarcinoma.
- Recommendation 11: Consider minimally invasive treatment as an alternative option to surgical neck dissection in patients with radioiodine refractory cervical recurrences who are at surgical risk or decline further surgery.
- Recommendation 12: Confirm the diagnosis of differentiated thyroid carcinoma recurrence by fine-needle aspiration or core-needle biopsy before minimally invasive treatment.

- Recommendation 14: Consider minimally invasive treatment only for palliative purposes in differentiated thyroid cancer recurrences with extensive lymph node involvement, central location, evidence of radioiodine uptake, and clinical and histological factors suggestive of aggressive disease.

Therefore, image-guided treatments for thyroid nodules and cancer are here to stay. The use of these methods will expand, and the price will decrease, making these methods available and part of routine clinical practice.

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