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MINIMALNO INVAZIVNE METODE ZA LEČENJE TIROIDNIH NODUSA I KARCINOMA

Apstrakt: Nodusi u štitnoj žlezdi su prisutni kod otprilike polovine populacije. Oko 5% svih nodula je maligno. Minimalno invazivne metode za lečenje tiroidnih nodusa (TN) postaju značajna alternativa hirurgiji.

Perkutana ablacija etanolom (PAE) je efikasna u lečenju cisti štitne žlezde i metastaza tiroidnog karcinoma u limfne čvorove vrata. Perkutana laserska abolacija (PLA) značajno smanjuje veličinu nodula i poboljšava subjektivne simptome. Komplikacije terapije primenom PEA su retke, prolazne i blage. Radiofrekventna ablacija (RFA) je efikasna za lečenje nodusa svih veličina i sastava. Komplikacije RFA su retke i prolazne. Mikrotalasna ablacija je efikasna u lečenju nodusa štitne žlezde a komplikacije su retke. Fokusirani ultrazvuk velike snage (FUVS) je transkutana metoda. Efikasan je u lečenju nodusa štitne žlezde, a komplikacije su retke. Grejvsova hipertireoza je takođe lečena primenom FUVS. Metode termoablacije (TA) postaju sve popularnije, pa je 2020. Evropsko udruženje za štitnu žlezdu objavilo vodiče kliničke prakse za upotrebu termoablacije kod benignih nodusa štitne žlezde.

Metaanaliza je pokazala da se recidivi niskorizičnog papilarnog mikrokarcinoma posle lečenja TA retko javljaju i da su komplikacije lečenja retke. Zbog toga su Evropsko udruženje za štitnu žlezdu i Evropsko društvo za kardiovaskularnu i interventnu radiologiju objavili vodič kliničke prakse za upotrebu minimalno invazivnih metoda za lečenje malignih lezija štitne žlezde.

Upotreba minimalno invazivnih metoda lečenja tiroidnih nodusa i karcinoma će se proširiti i postati deo rutinske kliničke prakse.

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Nodusi štitne žlezde spadaju u najčešće poremećaje kod ljudi. Palpacija se detektuju u oko 10% populacije, ali autopsija i ultrazvuk štitne žlezde kod oko 50% populacije. Nodusi štitne žleze se češće nalaze kod žena neko kod muškaraca, a njihova učestalost raste sa starenjem. Oko 5% svih nodusa je maligno (1,2). Od sredine 1990-ih prevalencija tiroidnog karcinoma se povećava (3).

Nodusi štitne žlezde predstavljaju značajno opterećenje za zdravstveni sistem. U Francuskoj je za četiri godine obavljeno 35.367 operacija štitne žlezde. Od toga je 58% operacija bilo zbog benignih nodusa i strume i 17 % zbog karcinoma (4). U Nemačkoj je u periodu od aprila 2017. do jula 2018. godine obavljeno 12.888 operacija štitne žlezde zbog benignih bolesti (5). Zbog toga su razvijene alternativne metode za lečenje nodusa štitne žlezde: perkutana ablacija etanolom (PAE), metode termoablacije (TA) i metode krioablacije. Krioablacija je metoda koja obećava ali su iskustva sa ovom metodom relativno mala.

PAE se koristi još od devedesetih godina prošlog veka. Crille je 1966. opisao aspiraciju ciste štitne žlezde (6). Upotrebu etanola za sklerozaciju ciste štitne žlezde je objavio Rozman 1989. godine (7). Livraghi je 1990. opisao upotrebu PAE za lečenje autonomnih nodusa štitne žlezde (8). U Srbiji je Anđelković uspešno koristio PAE za lečenje autonomnih nodusa štitne žlezde (9). Bennedbk i Hegedüs su sproveli randomizovano, dvostruko slepo istraživanje i dokazali efikasnost PAE u lečenju cista štitne žlezde (10). PAE je uspešno korišćena za lečenje metastaza tiroidnog karcinoma u limfne čvorove vrata (11–13). U lečenju cističnih nodusa štitne žlezde PAE je podjednako uspešna, ima isti stepen komplikacija kao RFA (14, 15).

PLA je metoda u kojoj se laserski zrak koristi za zagrevanje tkiva. Randomizovana studija sa kontrolnom grupom je pokazala da upotreba PLA značajno smanjuje veličinu nodusa štitne žlezde i poboljšava subjektivne simptome (16). Dalje studije potvrdile su superiornost PLA nad lečenjem tiroidnih nodusa levotiroksinom (17). Nedavna metaanaliza ukazala je na efikasnost PLA tokom 36 meseci praćenja (18). Nepovoljni efekti PLA su retki, prolazni i blagi (19).

RFA je efikasna u lečenju nodusa svih veličina i sastava (tkivnih, delimično cističnih i cističnih) (20). Studija u kojoj su oboleli praćeni preko pet godina je dokazala dugoročnu efikasnost RFA u lečenju nodusa štitne žlezde (21). Efikasnost RFA potvrđena je metaanalizom Čana (22). Druga metaanaliza pokazala je da RFA tretman značajno poboljšava kompresivne i kozmetičke simptome (18). Komplikacije RFA su retke i prolazne (23).

Mikrotalasna ablacija je još jedna od metoda termalne ablacije koja se koristi za lečenje nodusa štitne žlezde. Efikasna je u lečenju nodusa štitne žlezde, a ozbiljne komplikacije su veoma retke (24, 25).

Fokusirani ultrazvuk velike snage (FUVS) je elegantna metoda lečenja štitnih žlezda. Ovo je transkutan metod i veoma je jednostavan za upotrebu. Operater samo treba da locira nodus i označi ga na ekranu (26). Efikasan je i u lečenju nodusa štitne

žlezde, a komplikacije su retke (27–29). Međutim, postoji inverzna korelacija između veličine čvora pre ablacije i procentualnog smanjenja volumena (30). Grejvsova hipertireoza je takođe FUVS. U studiji pacijenata sa recidivima Grejvsove hipertireoze 59% lečenih osoba bilo je u remisiji 24 meseca po završetku terapije (31). Nažalost, kod lečenja fa FUVS postoji problem bola, a zbog toga i pitanje da li je sedacija ili anestezija neophodna tokom FUVS tretmana (32, 33).

Kako metode TA postaju sve popularnije u 2020. godini, Evropsko udruženje za štitnu žlezdu objavilo je vodič kliničke prakse za lečenje benignih nodusa štitaste žlezde minimalno invazivnim metodama (34). Glavne preporuke su sledeće:

- Preporuka 1: Kod odraslih pacijenata sa benignim nodusima štitaste žlezde koji izazivaju simptome pritiska i/ili kozmetičke probleme i odbijaju operativno lečenje, termalna ablacija pod vizualnom je ekonomski isplativa intervencija niskog rizika u poređenju sa operativnim lečenjem ili praćenjem.
- Preporuka 2: Upotreba termalne ablacije za lečenje asimptomatskih promena se ne preporučuje.
- Preporuka 9: Na osnovu direktnih poređenja i ravnoteže između efikasnosti i neželjenih efekata, perkutana laserska ablacija i radiofrekventna ablacija se preporučuju kao oblici lečenja prvog reda.
- Preporuka 12: Kod polinodozne strume, zbog nedostatka dokaza o efikasnosti i očekivane potrebe za ponavljanjem lečenja, metode termoablacije treba ograničiti na pacijente sa dobro definisanim dominantnim čvorom ili one koji nisu kandidati za tiroidnu hirurgiju ili lečenje radioaktivnim jodom.
- Preporuka 13: Metode termoablacije se ne preporučuju kao prva linija terapije cistične ili dominantno cistične noduse štitne žlezde, jer su skuplje i kompleksnije od ablacije etanolom.
- Preporuka 15: Metode termoablacije se ne preporučuju za lečenje velikih autonomnih funkcionalnih nodusa, jer se retko uspostavi normalna tiroidna funkcija. Metode termoablacije treba koristiti samo kod pacijenata koji odbijaju ili nisu kandidati za RAI terapiju ili operaciju.
- Preporuka 16: Metode termoablacije treba uzeti u obzir kod mladih pacijenata sa malim autonomnim funkcionalnim nodusom i nepotpunom supresijom okolnog tiroidnog tkiva, jer postoji veća verovatnoća normalizacije funkcije štitne žlezde i prednosti izbegavanja radioaktivnosti i kasnijeg rizika od hipotireoze.

Nedavna metaanaliza aktivnog nadzora niskorizičnih papilarnih karcinoma pokazala je da se rast tumorskih čvorova definisan kao povećan prečnika za više od 3 mm nalazi u samo 4,4% (95% intervala poverenja [CI] 3,2–5,8%) obolelih. Metastaze u limfnim čvorovima vrata nalaze se samo u 1,0% (95% CI 0.7–1.4%) obolelih (35).

Petogodišnje praćenje obolelih od papilarnog mikrokarcinoma niskog rizika pokazalo je potpun nestanak tumora posle lečenja TA (36). Druga studija, koja je obuhvatila 154 pacijenta sa papilarnim mikrokarcinomom niskog rizika, pokazala je potpuni nestanak tumora kod 93,7% pacijenata sa tumorom manjim od 0,5 cm u prečniku i kod 85,4% pacijenata sa tumorom većim od 0,5 cm u prečniku. Međutim, potpuna regresija tumora je opisana kod svih 54 pacijenta praćenih više od četiri godine (37). Metaanaliza je pokazala da su recidivi komplikacije posle lečenja papilarnog mikrokarcinoma niskog rizika primenom TA veoma retki (38).

S obzirom na to da su se metode TA pokazale prihvatljivim za lečenje niskorizičnih papilarnih karcinoma, Evropsko udruženje za štitnu žlezdu i Evropsko društvo za kardiovaskularnu i interventnu radiologiju su objavili vodič kliničke prakse za upotrebu minimalno invazivnih metoda za lečenje malignih lezija štitne žlezde (39). Glavne preporuke su sledeće:

- Preporuka 1: Treba razmotriti upotrebu minimalno invazivnih metoda u multimodalnom pristupu pacijentima sa rakom štitne žlezde.
- Preporuka 5: Treba razmotriti upotrebu metoda TA za pacijente sa niskorizičnim papilarnim mikrokarcinomom štitne žlezde, uglavnom kod pacijenata sa visokim hirurškim rizikom, kod pacijenata kod kojih se očekuje da će imati kratak životni vek, kod pacijenata sa komorbiditetima, ili kod obolelih koji ne žele operativno lečenje ili aktivni nadzor.
- Preporuka 6: Obavestiti pacijente sa slučajno otkrivenim papilarnim mikrokarcinomom štitne žlezde koji su pogodni za aktivan nadzor. O mogućnostima lečenja TA kao alternativi operativnom lečenju ili aktivnom nadzoru.
- Preporuka 9: PAE i FUVS ne treba koristiti za lečenje papilarnog mikrokarcinoma štitne žlezde, zbog nedostatka dokaza i tehničkih ograničenja.
- Preporuka 10: Razmotriti minimalno invazivno lečenje u palijativne svrhe, preferencijalno u kontekstu multimodalnog pristupa, kod pacijenata sa primarnim karcinomom štitne žlezde, isključujući niskorizični papilarni mikrokarcinom štitne žlezde.
- Preporuka 11: Treba razmotriti minimalno invazivno lečenje kao alternativnu opciju hirurške disekcije vrata kod pacijenata sa metastazama u limfnim čvorovima vrata i rezistencijom na terapiju radioaktivnim jodom, koji imaju visok operativni rizik ili odbijaju dalje lečenje.
- Preporuka 12: Pre započinjanja minimalno invazivnog lečenjaneophodno je potvrditi dijagnozu karcinoma štitne žlezde biopsijom finom iglom ili core biopsijom.
- Preporuka 14: Treba razmisliti o minimalno invazivnom lečenju u palijativne svrhe kod recidiva diferentovanog karcinoma štitne žlezde sa raširenim metastazama u limfnim žlezdama vrata, centralnom lokacijom, dokazanom

vezivanju radioaktivnog joda i kliničkim i histološkim faktorima koji ukazuju na agresivnu bolest.

Upotreba minimalno invazivnih metoda lečenja tiroidnih nodusa i karcinoma će se proširiti i postati deo rutinske kliničke prakse.

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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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