NEW PERSPECTIVES IN SURGERY AND ONCOLOGY OF PAPILLARY THYROID CANCER

PhD thesis

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Content

Abbreviations

TOETVA- transoral endoscopic thyroidectomy vestibular approach

ABBA- axillary bilateral breast apprach

BABA- bilateral axillary breast approach

ATA- American Thyroid Association

ETE - extrathyroidal extension

FNAB- fine needle aspiration biopsy

SCM- sternocleidomastoid muscle

Tg-thyreoglobulin

MEN- multiple endocrine neoplasia

DTC- differentiated thyroid cancer

PTC- papillary thyroid cancer

FTC- follicular thyroid cancer

CEA-carcinoembryonic antigen

RAI- radioiodine

NIS- natrium-iodide symorter

FT3- free triiodothyronine

FT4- free thyroxine

hNIS- human natrium-iodide transporter

SPECT- single photon emission computer tomography

TSH- thyroid stimulating hormone

rhTSH-recombinant human thyroid stimulating hormone (Thyrogene)

PD-L1- programmed death-ligand1

NSCLC- non-small cell lung cancer

HNSCC- head and neck sqamous cell carcinoma

FDA- Food and Drug Administation

1. Introduction

In thyroid surgery, achieving a cosmetically pleasing scar has become a crucial aspect, as neck scars are usually noticeable. To improve patient satisfaction, smaller incisions are now being utilized. Over recent decades, new endoscopic techniques have been introduced using breast or axillary approaches, although the cosmetic outcome remains unsatisfactory.

In recent years, progress has been made with the development of the transoral endoscopic thyroidectomy vestibular approach (TOETVA). This approach is appropriate for patients with small thyroid carcinomas without extrathyroidal extension, benign nodules up to 4-5 cm, as well as for parathyroid adenomas and follicular lesions (Anuwong et al., 2016). However, metastatic thyroid diseases and large substernal goiters should still be treated with conventional open surgery.

Darker skin types are more prone to issues like keloids or other scarring issues. The renowned surgeon, Kocher, was the first to opt for horizontal scars instead of vertical ones to improve their cosmetic appearance (Wilhelm T et al., 2012, O'Connell DA et al., 2008). For young women from Far-Eastern countries, neck scars are synonymous with death and can negatively impact their lives, further intensified by keloids and other scarring (Choi Y et al., 2014).

This problematic scarring led surgeons to devise a new technique without scars. While there were several attempts to remove the thyroid from the axillary or areolar region, these methods took longer and still resulted in scar formation (Christakis et al., 2014).

The optimal solution thus far is TOETVA, which leaves no visible scarring on the skin. However, this novel procedure is only suitable for small thyroid cancers without extrathyroidal extension (Anuwong et al., 2018).

Differentiated thyroid carcinoma, specifically papillary, accounts for approximately 90% of new cases of thyroid cancer in iodine-sufficient regions globally.

This is the most prevalent thyroid malignancy, but it also has a generally favorable prognosis, with over
90% survival rates after 10 years of treatment (Kitahara et al., 2022).
Total thyroidectomy is commonly accepted as the preferred procedure for all metastatic thyroid carcinomas.

Papillary thyroid carcinoma, constituting 75% of all thyroid malignancies and over 90% of differentiated thyroid cancers, is the most frequently-occurring type of thyroid cancer. Despite the tumor's slow growth and positive prognosis, managing locoregional recurrence remains a significant challenge. Consequently, lymph node surgery emerges as a crucial consideration in treating papillary thyroid carcinoma (Miccioli et al., 2017).

Clinically noticeable lymph node metastasis is found in approximately 15% to 30% of patients. Reports show that unnoticed metastasis can go up to 90%. Half of the clinically node-negative patients might develop lymph node metastasis. Furthermore, lymph node metastasis occurs in 15% to 50% of patients suffering from papillary thyroid microcarcinoma, a condition wherein a papillary thyroid carcinoma is 10mm or less in diameter (Kitahara et al., 2022).

Follicular thyroid cancer, constituting 10–15% of all thyroid cancers, is the second most common type. Also known as follicular carcinoma, it is recognized as a "well-differentiated" thyroid cancer, similar to papillary thyroid cancer. However, it typically exhibits a greater degree of aggression, it occurs predominantly in a slightly older demographic, and it is less frequently seen in children. Unlike papillary thyroid cancer, follicular thyroid cancer rarely arises post-radiation exposure.

The fatality rate tied to follicular thyroid cancer often depends on the extent of vascular invasion, a characteristic trait of this type of cancer. This trait leads to distant metastasis, which is more common than in papillary thyroid cancer (Grebe et al., 1995). Even when the cancer remains small within the thyroid, there's potential for distant spread, affecting the lungs, bones, brain, liver, bladder, and skin. Unlike papillary cancer, instances of lymph node involvement are far less common in follicular thyroid cancer, estimated at only 8–10%.

Hürthle cell thyroid cancer is a rare and aggressive form of the disease, varying greatly in its ease of cure(Chen et al., 1996). Medullary thyroid cancer, frequently

sporadic in nature, also occurs as part of an inherited disease known as multiple endocrine neoplasia (MEN) in about 25% of cases.

Unlike more common types of thyroid cancers such as papillary and follicular, medullary thyroid cancer originates from the thyroid's
parafollicular C cells. With medullary cancer, the standard treatment is a thyroidectomy. compared to papillary cancer, it also necessitates prophylactic central neck dissection due to significantly elevated calcitonin and CEA levels (Pelizzo et al., 2023). Despite the crucial impact of surgery in medullary thyroid cancer treatment, a positive FNAB identifying tumor foci is insufficient for diagnosis on its own-- elevated levels of calcitonin and CEA are also required.

Metastatic DTC cases should be treated in centers where all personnel and instrumental conditions are optimal. In cases of DTC with extrathyroidal extension, male gender, and older age are predisposing factors contributing to disease recurrence in the presence of nodal metastases. However, studies have shown that lymph node metastases decrease survival rates, with this effect being more pronounced among elderly patients.

Lymph node metastases are predominantly found in the central neck, with the gland's lymphatic drainage followed by venous drainage (Mao et al., 2020). The anticipated lymphatic drainage pattern of thyroid carcinoma is a central cervical (level VI) metastasis, followed by lateral cervical (levels II through V) compartment metastasis. The tumor's location within the thyroid gland can influence the metastasis site.

Tumors located in the isthmus, middle, and lower parts of the gland predominantly metastasize to the central nodes, while tumors in other gland sections usually metastasize to ipsilateral lateral regions (Randolph et al., 2012). The most common cervical lymph node classification system, recommended by the American Joint Committee on Cancer and the American Academy of Otolaryngology and Head and Neck Surgery, delineates the central compartment as level VI lymph nodes, and the lateral compartment as levels II through V.

Dissection, the process of removing lymph nodes, involves excising both the lymph nodes and soft tissues extending from the lateral wall of the carotid sheath to the trapezius muscle, and from the subclavian vein to the hypoglossal nerve. The procedure

typically involves removing levels II, III, IV, and V. In cases with evident metastatic disease at level VI, this level can also be excised.

The “berry picking” procedure, which only removes suspicious and enlarged lymph nodes, is generally deemed inadequate (Robbins et al., 2002).

The neck has six anatomical levels, which are used to stage and plan treatment for thyroid and other head and neck cancers.

Level I: submental and submandibular

- superiorly: mylohyoid muscle and mandible
- inferiorly: inferior border of the hyoid bone
- anteriorly: platysma muscle
- posteriorly: posterior border of the submandibular gland
- There are two sublevels: level Ia (submental nodes): anteromedial between the anterior bellies of both digastric muscles; level Ib (submandibular nodes): posterolateral to the anterior belly of the digastric muscles.

Level II: upper internal jugular (deep cervical) chain

- superiorly: base of the skull at the jugular fossa
- inferiorly: inferior border of the hyoid bone
- anteriorly: posterior border of the submandibular gland
- posterolaterally: posterior border of the sternocleidomastoid muscle
- medially: medial border of the internal carotid artery
- There are two sublevels: level IIa: inseparable from or anterior to the posterior edge of the internal jugular vein; includes jugulodigastric nodal group; level IIb: posterior to and separable by a fat plane from the internal jugular vein.

Level III: middle internal jugular (deep cervical) chain

- superiorly: inferior border of the hyoid bone
- inferiorly: inferior border of the cricoid cartilage
- anteriorly: anterior border of the sternocleidomastoid muscle
- posterolaterally: posterior border of the sternocleidomastoid muscle
- medially: medial border of the common carotid artery

Level IV: lower internal jugular (deep cervical) chain

- superiorly: inferior border of the cricoid cartilage
- inferiorly: level of the clavicle
- anteriorly: anterior border of the sternocleidomastoid muscle
- posterolaterally: oblique line drawn through the posterolateral edge of the sternocleidomastoid muscle and the lateral edge of the anterior scalene muscle
- medially: medial border of the common carotid artery
- includes medial supraclavicular nodes including Virchow node

Level V: posterior triangle

- superiorly: skull base at the apex of the convergence of sternocleidomastoid and trapezius muscles
- inferiorly: level of the clavicle
- anteromedially: posterior border of the sternocleidomastoid muscle
- posterolaterally: anterior border of the trapezius muscle
- There are two sublevels: level Va: superior half, superior to inferior border of the cricoid cartilage (posterior to levels II and III); includes spinal accessory nerve; level Vb: inferior half, inferior to inferior border of the cricoid cartilage (posterior to level IV); includes lateral supraclavicular nodes.

Level VI: central (anterior) compartment

- superiorly: inferior border of hyoid bone
- inferiorly: superior border of manubrium (suprasternal notch)
- anteriorly: platysma muscle
- posteriorly: trachea (medially) and prevertebral space (laterally)
- laterally: medial borders of both common carotid arteries (medial to levels III and IV) includes anterior jugular, pretracheal, paratracheal, prelaryngeal (Delphian), and perithyroidal nodes

Level VII refers to the upper mediastinal region, an extension of the paratracheal chain that lies beneath the suprasternal notch and above the trachea. This area is typically accessed not by a head, neck, or thyroid surgeon, but by a thoracic surgeon.

All higher levels ultimately drain to the jugular nodes on their respective sides, then to the right lymphatic duct or the thoracic duct on the left. One critical aspect of thyroid surgery is to securely ligate the lymphatic vessels to prevent lymphatic leakage, which could lead to serious complications that are difficult to manage.

In metastatic DTC patients, level I does not factor into a neck dissection since metastasis does not occur in this region. It is relevant in cases of squamous cell carcinoma of the head and neck, which can also metastasize to level I nodes.

Surgeons should have a thorough knowledge of neck anatomy to successfully perform thyroid surgery and prevent potential intraoperative and postoperative complications.

Sosa et al. (YEAR) suggested that the complications arising during surgery can often be attributed to medium and low-volume surgeons. This implies that these surgeons may lack the frequency of practice required to manage complex scenarios, leading to a higher incidence of recurrent laryngeal nerve palsy and postoperative hypoparathyroidism. In fact, low-volume surgeons, performing fewer than 25 thyroidectomies a year, are found to be responsible for 81% of such complications (Abdalgadir et al., 2017).

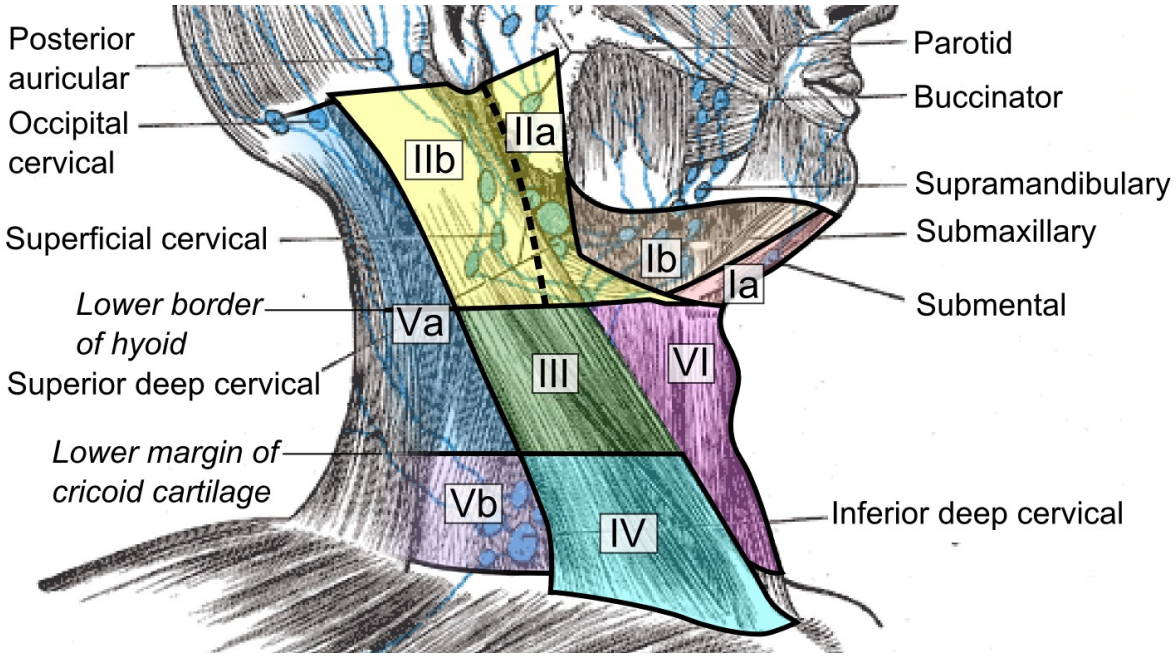


Figure 1. Levels of the neck lymph nodes , antomical boundaries are allocated "Mikael Häggström, M.D. via Wikimedia Commons" (https://upload.wikimedia.org/wikipedia/commons/4/45/Cervical_lymph_nodes_and_levels.svg) https://commons.wikimedia.org/wiki/File:Cervical_lymph_nodes_and_levels.svg, Cervical lymph nodes and levels

Iodine is an essential constituent of the thyroid hormones, key factors for human development and physiology during intrauterine and postnatal development. Active iodide transport into the thyroid epithelial cells is mediated by the Na^+/I^- symporter (NIS). Radioiodine based diagnosis and therapy of thyroid diseases has been applied since 1940 (Seid et al., 1946, Borges et al.,2021) but NIS was the only first cloned in 1996 in the laboratory of Nancy Carrasco. (35,Dai et al.,1996, De La Vieja et al.,2000,Dohan et al.,2003, Levy et al.,1997) NIS is a plasma membrane glycoprotein, and NIS secondary structure model with 13 transmembrane segments has been proposed based on experimental data. (Levy et al.,1996, Revera et al.,2017, Eskandari et al.,1997)

NIS couples the inward translocation of Na down its electrochemical gradient to the simultaneous inward “uphill” translocation of I against its electrochemical gradient.

The Na^+ gradient that provides the driving force for cellular I^- uptake is maintained by the Na^+/K^+ ATPase. Two Na^+ are transported per each I^-. In the thyroid, both NIS and Na^+/K^+ ATPase are located on the basolateral surface of the thyroid follicular cells, facing the blood supply. (Revera et al.,2017, Eskandari et al.,1997,Paroder et al.2011)

TSH and I^- are the two main factors that regulates thyroidal I transport: TSH stimulates it and I decreases it. Hence TSH stimulation and I depletion are the two most important modulators routinely used to optimize radioiodine treatment of metastatic thyroid carcinoma. (Eskandari et al.,1997,Paroder et al.2011, Tacebay et al.,2000)

NIS – mediated radioiodine therapy of thyroid cancer is the oldest routinely applied molecular targeted radiotherapy available today. Nowadays the NIS gene is one of the most promising candidates for gene therapy applications being both a therapeutic and a reporter gene. (Tacebay et al.,2000, Doha net al., 2004, Ferreira et al., 2005)

A major drawback of available traditional cytotoxic anticancer therapies is that they are not selective for cancer cells. They have significantly toxicity against normal cells as well. Therefore, the ultimate aim of any new anticancer therapy is to achieve selective destruction of cancerous tissue with minimal harm to healthy cells.

One of the most promising approaches to accomplishing this is targeted radiation therapy. The radiation therapy is a prime example of targeted radioiodine therapy via selectively expressed plasma membrane transporters. (Ferreira et al.,2005, Spitzweg et al.,2021, Maysor et al., 2021)

Radioiodine therapy has been employed with great success for over 60 years to destroy thyroid cancer remnants and/or metastases after thyroid surgery. The presence of NIS in thyroid cancer cells ensures that administered radioiodine is selectively accumulated in these cells, thus causing little damage to other cells and only minimal side effects. Thus far, radioiodine therapy has been viewed as applicable only to thyroid cancer. NIS can concentrate various radionuclides in target cells and can facilitate exciting application of NIS including diagnostic and /or therapeutic gene. (Wapnir et al., 2003, Niccola et al., 2015) Recent observations have raised the possibility to applying radioiodine therapy to breast cancer and other cancers by introducing NIS into tumour via viral vectors or upregulating the tumors' endogenous NIS expression if present. The

NIS as a transgene can thus do image guided radiotherapy, monitoring of gene and vector biodistribution and evaluate trafficking of therapeutic cells.

Potential limitation of ectopic (extrathyroidal) NIS expression is that extrathyroidal tissues do not allow organification of iodide. Therefore the accumulation of iodine is the sum of cellular uptake and efflux, largely dependent on the plasma availability (absorption and clearance) of the tracer. (Niccola et al., 2015, Martin et al., 2019, Dohan et al., 2001, Altorjay et al., 2007, Portulano et al.,2014)

NIS is a master molecule of I metabolism. NIS has been shown in rodents to be responsible for iodine absorption from the intestine. (Dohan et al., 2001, Altorjay et al.,2007)

Some of the absorbed iodine gets organified in the thyroid. Iodine is secreted by NIS in the salivary glands and in the stomach into the gastrointestinal lumen and again absorbed via NIS in the small intestine. Iodine is finally excreted through the kidney by glomerular filtration. (Levy et al.,1996, Reverea et al., 2017)

Polarized expression of NIS in the epithelial cells results in vertical transepithelial transport of I^-.

At all cellular level NIS expression is polarized, it is located to the basolateral plasma membrane in all tissue where it is expressed, except in the enterocytes of the small intestine, where NIS is confined to the apical membrane. (Wapnir et al.,2003,Niccola et al.,2016) Basolaterally , the localized NIS transports I^- into the lumen, which is in contrast to apically localized NIS translocates I^- from lumen surrounded by the cells. Interestingly, NIS is regulated differently in each of these tissues. Current apical expression of NIS in the epithelium of the small intestine has been demonstrated only in rodents. (Altorjay et al. 2007)

Natrium/sodium iodide transporter (NIS) is a plasma membrane glycoprotein that couples the inward translocation of Na^+ down its electrochemical gradient to the simultaneous inward "uphill" translocation of I^- against its electrochemical gradient. NIS-mediated radioiodine therapy of thyroid cancer is the first and most successful molecular targeted radiotherapy available today. (Dohan et al.,2001) Radioiodine uptake is decreased in thyroid cancer, because of absent NIS expression or impaired plasma targeting of NIS.(Portulano et al.,2014)

About 90 % of thyroid cancers are originate from follicular cells as differentiated thyroid cancer (DTC) , 90% of DTC is papillary thyroid cancer (PTC, and110 % is follicular thyroid cancer (FTC). (Fagin et al.,2016) The standard of care for localized or locally advanced PTC is surgery followed by radioiodine (RAI) ablation and thyroid stimulating hormone suppression therapy. In contrast, recurrent and/or metastatic papillary thyroid cancer, especially if it loses its radioiodine accumulation capacity during dedifferentiation and progress, can be an untreatable disease. The 5-year survival rate in localized cases is 98%, but with metastasis, the rate decreases to 55,5%. With radioiodine (RAI)-accumulating persistent thyroid cancer, the 10-year survival rate is 29%, but in cases of lost RAI accumulation, it is only 10%. (Weitzman et al., 2019) Progression of metastatic disease can be delayed with repeated radioiodine therapy, but over time the tumor dedifferentiates and loses its ability to accumulate radioiodine.

RAI accumulation in thyroid cancer cells is mediated by the Na^+/I^- symporter (NIS). NIS is a plasma membrane glycoprotein that couples the inward translocation of Na^+ down its electrochemical gradient to the simultaneous inward "uphill" translocation of I^- against its electrochemical gradient. NIS-mediated RAI therapy for thyroid cancer is the first and most successful molecular targeted radiotherapy that is currently available. (Dohan et al., 2003) In lack of NIS expression or impaired plasma targeting of NIS, RAI uptake may be decreased or absent in thyroid cancer. (Dohan et al., 2001)

The prognosis for patients with iodine-refractory thyroid carcinoma is poor, and the average survival time is 3-5 years. The treatment of RAI refracted metastatic disease is challenging, multikinase inhibitors (sorafenib, leenvatinib) can be administered to slow down disease progression. RAI refractoriness (lack of RAI accumulation) of metastatic PTC is caused by a decrease in NIS expression or impaired plasma-membrane targeting of the transporter. Understanding the pathomechanism of iodine uptake disorder in thyroid cancer could open up the possibility of reinduction of RAI uptake.(Yu et al., 2023)

There are several ongoing clinical trials with mitogen-activated protein kinase (MAPK) inhibitors (selumetinib, dabrafenib, and trametinib) to reinduce RAI uptake in RAI-refractory thyroid cancer. (Yu et al., 2023)

Programmed cell death ligand (PD-L1) an immune checkpoint molecule one of the most important target of FDA and EMA approved cancer immunotherapy.

PD-L1 a membrane bound protein, member of the immune globulin superfamily. It contains an N terminal part facing extracellularly, a transmembrane domain, and a short carboxy terminal facing intracellularly (Kornepati et al., 2022) PD-L1 expressed on the cell surface of cancer cells binds to PD-1 (programmed death1) on effector T cells and inhibits their anticancer effect. In cancer immunotherapy administered Anti-PD-L1 and/or anti- PD-1 antibodies inhibit PD-L1 – PD-1 interaction, and reactivates anticancer T effector functions. This so called „cell-extrinsic" PD-L1-PD-1 interaction inducing PD-1 downstream signaling leading to T cell inactivation is well described.

Recently discovered "cell-intrinsic" PDL1 signaling is mostly PD1 independent, and in cancer cells modulate proliferation, survival, signaling, gene expression …etc. (Kornepati et al., 2022). Also anti-PDL1 antibodies interacting with PD-L1 on the cancer cell surface could induce PD-L1 intrinsic signaling.

The more dedifferentiated thyroid carcinomas are, the more frequently they express the "immune-hijacking" molecule PD-L1 on their surfaces. At the same time, iodine uptake by differentiated thyroid carcinoma is reduced due to impaired NIS expression or plasma membrane targeting, and tumor cells become RAI refractory during further dedifferentiation and no longer take up RAI. Thyroid cancer dedifferentiation leads to high PD-L1 expression and absent RAI uptake. While several publications have reported on the separate and distinct expression of NIS or PD-L1 in thyroid cancer, to date, no studies have examined simultaneous expression of NIS and PD-L1 in the same tumor samples.

2.**Objectives**

We aimed to examine the surgical results of patients who underwent the TOETVA procedure, as well as the outcomes of metastatic papillary thyroid cancer patients who underwent open surgery at the National Institute of Oncology between 2013-2018. The Head and Neck Multidisciplinary Cancer Center, the leading thyroid center in Hungary, conducts an average of 600–700 thyroid surgeries annually.

Thyroid is the most frequent target of autoimmune pathology. Immune thyroiditis, one of the most often experienced adverse effect of cancer immunotherapy with immune checkpoint inhibitor antibodies. While there is a lot of knowledge accumulating on thyroid autoimmunity, there is very few known about the immuno-editing process during the course of thyroid cancer.

The aim of our study was to follow the distribution of radioiodine in the human body by whole body SPECT (single photon emission computer tomography) imaging and correlate this with NIS immunhistochemistry in radioiodine accumulating human tissues.

We were particularly interested to evaluate NIS expression in human small intestinal epithelium as well as to understand its possible role in I^- absorption, and recirculation. The low mutational burden of differentiated thyroid cancer it is hypothesized to confer low immunogenicity, but the high prevalence of thyroid autoimmunity, seem to be contradictory, and raises questions about the real immunogenicity of thyroid cancer. There are only a handful of studies that have evaluated immunotherapy in DTC in humans. And consequently there are no predictive biomarkers which can be used to indicate immunotherapy in DTC. Iodine supply has a significant impact on all kind of thyroid pathologies. Most published studies on the expression of PD-L1, presence of CD8+T lymphocytes in thyroid cancer were reported from geographical areas with high iodine intake. In contrast, in Hungary iodine intake is low, this could also affect the immuno-editing process of thyroid cancer.

We had also interest to investigate and correlate PD-L1 and NIS expression in lymph node metastatic PTC tumor samples and correlate these to the size, multifocality, metastatic nature, and iodide accumulating ability (plasma membrane expression of NIS) of the DTC.

3.Materials and Methods

Between June 2018 and October 2021, a total of 12 patients with thyroid cancer or nodules, measuring between 1 and 5 cm, underwent TOETVA surgery at the National Institute of Oncology. We performed lobectomies on 11 patients, and one underwent an isthmusectomy. Patients must be nasotracheally intubated for this process, positioning their heads in a hyperextended position on an inflatable pillow under the shoulders. The method was modified as described below.

The anesthetist, who is experienced in TOETVA anesthesia, performed gentle hydrodissection on our last four patients. This involved infiltrating the thyroid capsule with lidocaine and saline under ultrasound guidance. We injected a virtual space between the thyroid's true capsule and pseudo-capsule with 20 mL of a 0.5% lidocaine solution containing adrenaline, also under ultrasound guidance. This technique, along with injecting the Erb point - a pivotal step in thyroid operations conducted under regional anesthesia by our team - is a unique approach used exclusively by us in TOETVA surgery. It also involves performing external hydrodissection of the thyroid's pseudo-capsule (Figure 2.).

Figure 2. Infiltration of thyroid's pseudocaspule

A: trachea

B: thyroid lobe

C: local anesthetica

D: needle

E: SCM muscle

Patients are administered 1.2 g of intravenous Amoxicillin Clavulanic acid for antibiotic prevention. We prepare three oral vestibule incisions for the trocars, adhering to the standard practice of avoiding the mental nerve. The middle incision made above the frenulum is intended for the 1cm optic trocar; the other two 5-mm incisions on both sides are for the instruments. The mouth is rinsed with 0.2% chlorhexidine before the procedure.

The subplatysmal plane is hydrodissected using a Veress needle, and 30–50 ml of a saline solution, which includes 1mg of adrenaline in 500 ml saline, is used. After the optic trocar is inserted, the lower border is the jugulum, and the lateral border is the sternocleidomastoid (SCM) muscle. Carbon dioxide (CO_2) is used for insufflation, maintained at 6 Hgmm.

Figure 3. Location of the endoscopic ports

The side ports are inserted under visual guidance, using general laparoscopic equipment designed for abdominal procedures. The cranio-caudal view facilitates the identification of the recurrent laryngeal nerve. Once the operative field is clear, the next step is to carefully separate the thyroid lobe from its bed. Key aspects of the operation include identifying and preserving the parathyroid glands and the recurrent laryngeal nerves. Preoperative hydrodissection allows for easier dissection and provides an avascular plane that aids in identifying vessels and nerves. The thyroid lobe is then transported to the neck using an endobag. Lastly, 3/0 Monocryl sutures are used to close the vestible wounds.

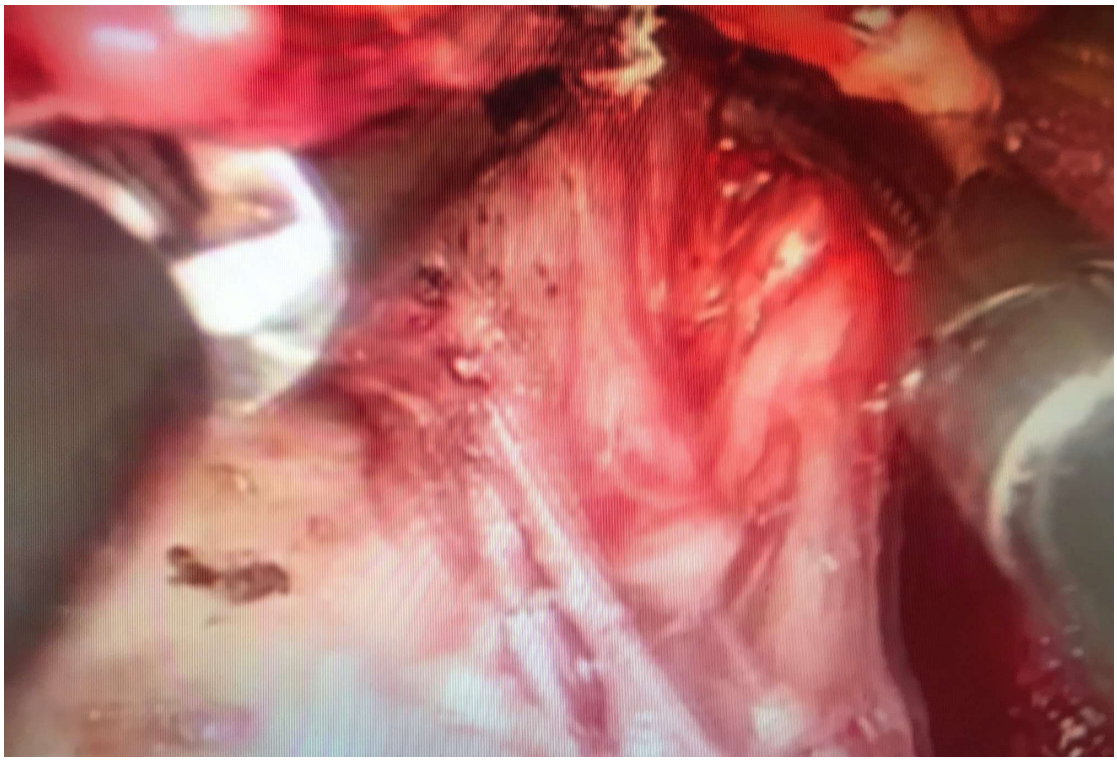


Figure 4. Identification and ligation of the right superoir thyroid vessels with ultrasonic device

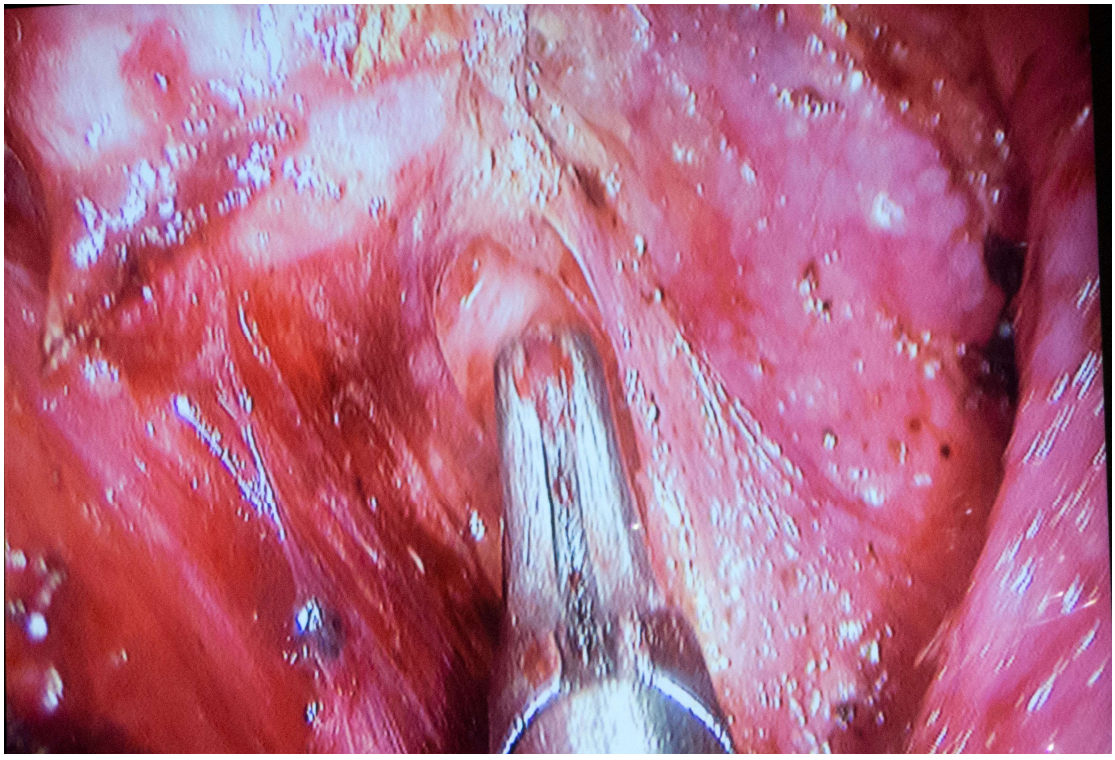


Figure 5. Identification of the right recurrent laryngeal nerve

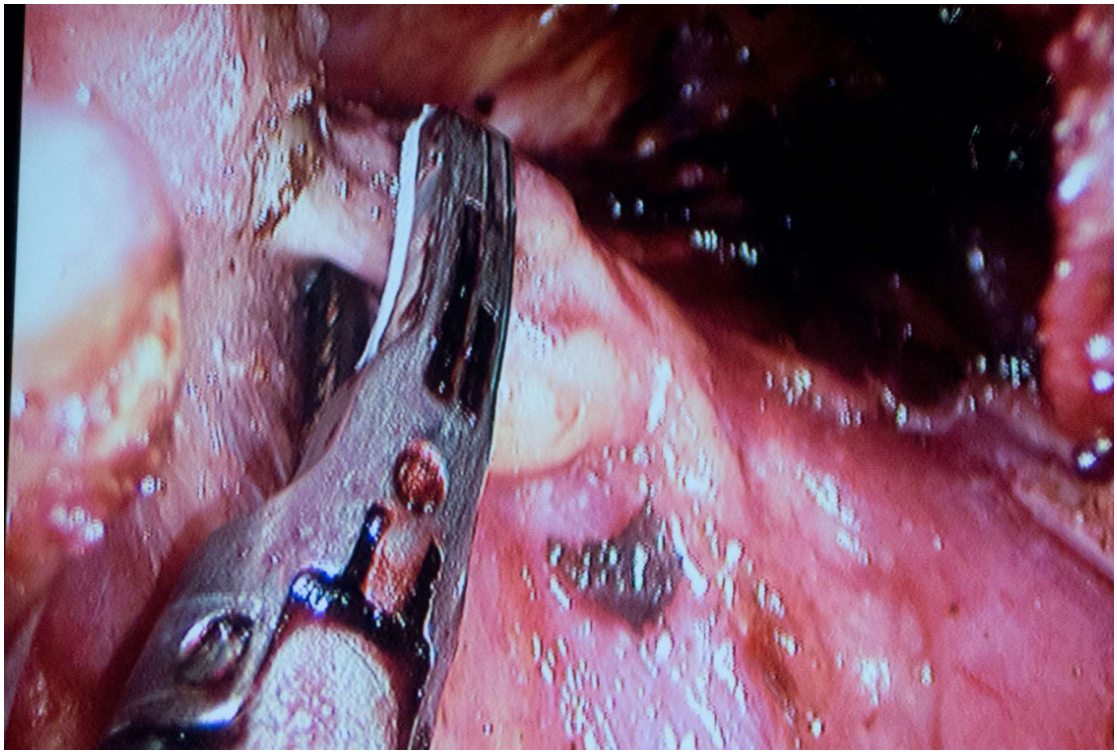


Figure 6. Ligation of the inferior thyroid vessels with ultráson device, identification of right lower parathyroid gland

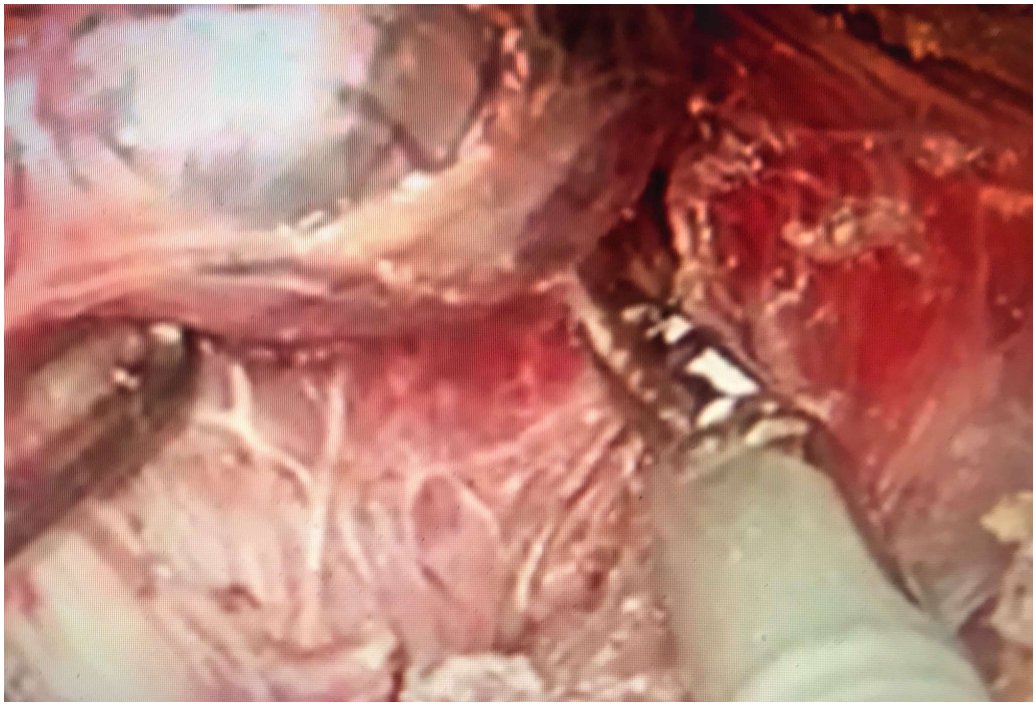


Figure 7. Blunt dissection of the right thyroid lobe from its bed

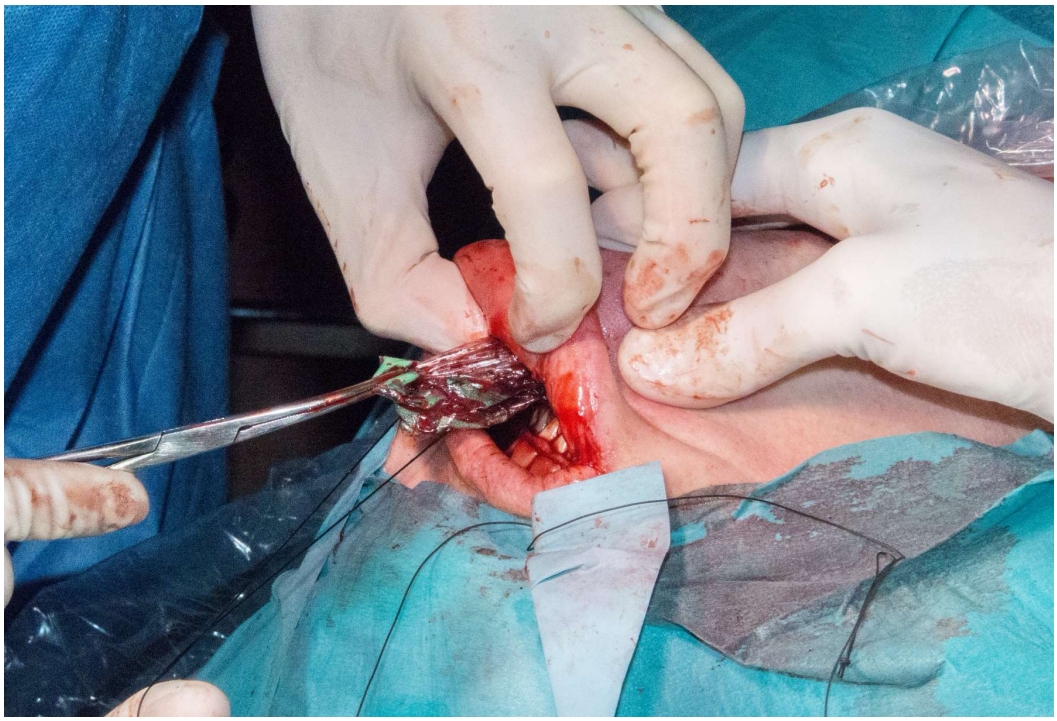
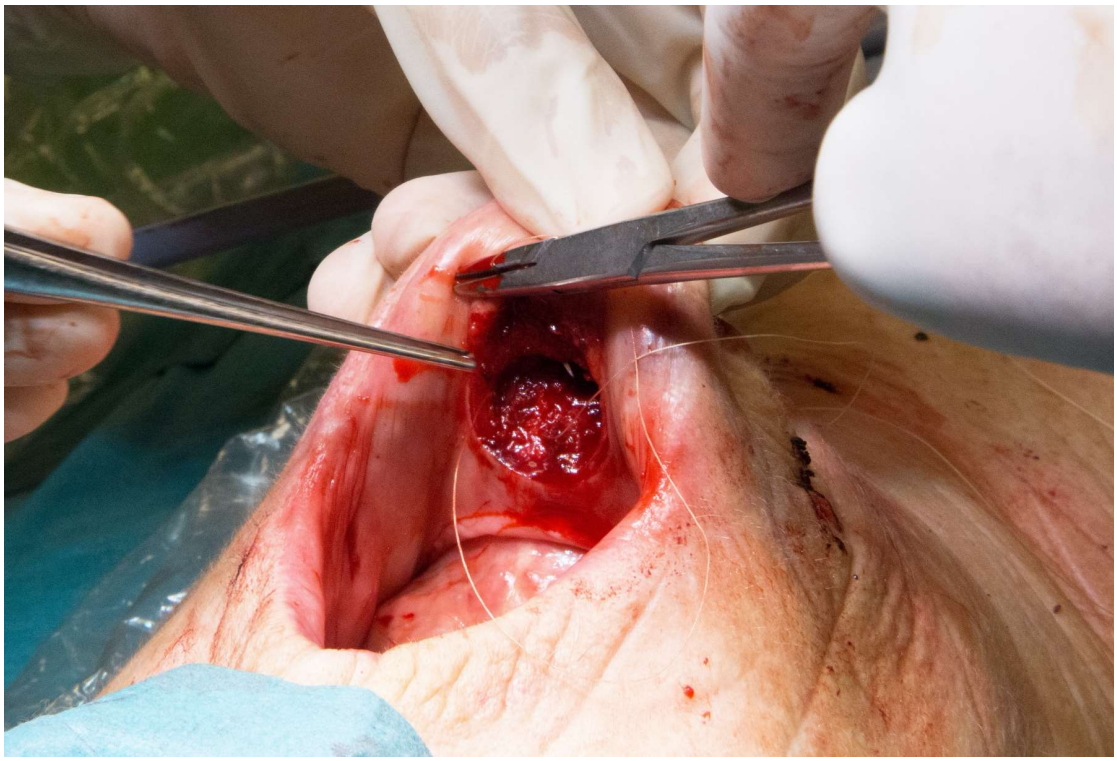


Figure 8. Pulling out the right thyroid gland through the tunnel



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igure 9. Closing the wound with 3/0 absorbable suture in 2 layer

The side ports are inserted under visual guidance, using general laparoscopic equipment designed for abdominal procedures. The cranio-caudal view facilitates the identification of the recurrent laryngeal nerve. Once the operative field is clear, the next step is to carefully separate the thyroid lobe from its bed. Key aspects of the operation include identifying and preserving the parathyroid glands and the recurrent laryngeal nerves. Preoperative hydrodissection allows for easier dissection and provides an avascular plane that aids in identifying vessels and nerves. The thyroid lobe is then transported to the neck using an endobag. Lastly, 3/0 Monocryl sutures are used to close the vestible wounds.

TOETVA (transoral endoscopic thyroidectomy vestibular approach) is a proper procedure for T1-2 thyroid cancers without extrathyroidal extension (ETE), or cysts (not larger then 5-6 cm), thyroid adenomas, parathyroid adenomas are suitable for TOETVA procedure. Contraindication can be substernal extension or larger tumors with ETE. (Anuwong et al., 2016)

In the Head and Neck Multidisciplinary Cancer Center of the National Institute of Oncology we examined and analyzed the operations and those results of 130 metastatic papillary thyroid cancer patients operated by the same 2 surgeon (a senior and a junior thyroid surgeon).

Both of them are high volume surgeons with a thyroid operation number over 300/year. Preoperative imaging and FNAB were carried out before the operation in every case. Regarding the metastatic lymph nodes, thyroidectomy was performed in all cases. According to the ATA guidelines (2015), NCCN guidelines (2019) lymph node dissections were performed after biopsy proven. (Haugen et al., 2016, Haddad et al., 2022)

Patients' clinical records were reviewed from 2013 to 2018 for those that underwent total thyroidectomy with central lymphadenectomy, supplemented with or without lateral lymphadenectomy. These patients had preoperative cytological evidence of differentiated thyroid cancer and biopsy-confirmed lymph node metastasis.

We identified 130 patients with papillary thyroid cancer and lymph node metastasis in our retrospective study.

All patients underwent the surgery with the same two practiced neck endocrine surgeons. Diagnostic conclusions of differentiated thyroid cancer were obtained preoperatively via ultrasound (US) - guided fine-needle aspiration biopsy (FNAB). The preoperative preparation incorporated measurements of free thyroid hormone (FT3, FT4), thyrotropin (TSH), thyroglobulin (Tg), and anti-thyroglobulin antibody (TgAb). A meticulous ultrasonographic neck scan was also performed. Ultrasound proved highly effective for diagnosing thyroid conditions, offering near-100% accuracy when supplemented with FNAB and serum Tg tests. Additional imaging studies were utilized if local or distant metastasis was suspected. All patients underwent routine pre- and postoperative laryngoscopy. We recorded demographics and postoperative complications, inclusive of transient or continuous hypoparathyroidism, vocal cord paralysis, and local and distant recurrence detected during postoperative monitoring. Hypocalcemia, defined as less than 2.1 mmol/l (normal range being 2.15–2.65 mmol/l), was considered lingering if it lasted more than 6 months.

Biochemical assays

FT3, FT4, Tg,TgAb, and TSH were determined by automatic ultrasensitive immunochemical assays (Liaison XL).

Surgery

The procedures performed were total thyroidectomy, paratracheal lymph node dissection, and lateral neck dissection for cases with confirmed lateral metastasis. Recurrent laryngeal nerves were consistently identified and exposed until their insertion in the larynx. Additionally, parathyroid glands were identified and preserved. We performed muscular autoimplantation into the sternocleidomastoid muscle if parathyroid glands appeared devascularized or were accidentally removed. Serum calcium levels were tested on the first day after surgery. If a patient’s serum calcium level was low, we began administering oral or, in specific cases, intravenous calcium and vitamin D supplement

Radioiodine ablation

RAI is used to eliminate the normal thyroid remnant and irradiate small neoplastic cell clusters, thereby reducing recurrence risk. Post-surgery, all patients underwent

adjuvant radioiodine ablation with iodine^{131} (131I). The criteria for postoperative 131I treatment, beyond lymph node involvement, included extracapsular thyroid invasion or locoregional extension, an unfavorable histological subtype, and vascular or lymphatic invasion, particularly with diameters >1 cm. To ensure adequate endogenous TSH levels (>30 mU/mL), which enhances radioiodine uptake, patients discontinued L-T4 replacement 3–4 weeks before radioiodine treatment; when withdrawal from L-T4 was not suitable, TSH stimulation was achieved with Recombinant Human Thyrotropin (rhTSH, Thyrogen) following standard protocols. A whole-body scan was performed 4–7 days post-radioiodine treatment.

Follow-up

Patients underwent neck ultrasounds and serum Tg and TgAb level checks every 6 months as part of their ongoing L-thyroxine treatment. A serum Tg level of ≤ 0.2 ng/mL was classified as undetectable. To monitor for potential recurrence in patients believed to be disease-free, Tg detection methods were used. In patients that tested positive for TgAb, whole-body 131I scanning after rhTSH stimulation and neck ultrasound were employed. The median follow-up duration was 47 months, with a range from 0 to 196 months.

Statistical analysis

The Mann-Whitney U-test (Statistica 12.5, StatSoft, Tulsa, OK, USA) was employed to examine the correlations between factors such as capsular, lymph node and vascular invasion, Hashimoto status, LND and sex, with tumor size, metastatic lymph nodes and age. The log-rank test was utilized to compare overall survival rates based on the aforementioned factors, along with pathology and laterality. Lastly, the Cox regression method was implemented to investigate the impact of tumor size, the number of lymph nodes, metastatic lymph nodes and age on survival in thyroid cancer surgical treatment.

NIS polarized expression was studied in I^--accumulating tissues via immunohistochemistry using a polyclonal Ab against the C terminal end of hNIS.

Radioiodine distribution in human body was evaluated on rutine planar whole body imaging after I-131 therapeutic administration in patients underwent thyroidectomy for cancer. Post-therapeutic whole body scan is rutinely performed, one representative image is shown in Figure 1.

A whole-body scanner was used to image whole-body distribution. In the case of I-131, a high-energy collimator (up to 450 keV) was used with a scanning speed of 12 cm/min and a window setting of 364 keV ±15%. Counts were obtained from the regions of interest over the whole body and the thyroid in anterior and posterior images.

Geometric averages for anterior and posterior counts were used. The counts were calibrated to the counts at time $t < 60$ min before any voiding.

Immunohistochemistry

The immunohistochemistry examinations were carried out paraffin embedded tissues. HNIS polarized expression was studied in I^- accumulating tissues by immunohistochemistry using a polyclonal Ab against the C terminal end of hNIS. (Levy et al., 1997,) HNIS immunohistochemistry was performed as previously described. Briefly: Five micron sections were cut from surgical blocks of I^- accumulating tissues; thyroid, salivary gland, stomach, small intestine. All slides were deparaffinated, rehydrated and subjected to antigen retrieval. Endogenous peroxidase activity and biotin activity was blocked using commercial blocking system (Ventana). Sections were stained using anti-hNIS rabbit polyclonal antibody (1ug/ul, in 1:4000 dilution) directed against the C terminus (generous gift from Dr Nancy Carrasco) using commercial immunohistochemistry kit (Ventana). All slides were counterstained with hematoxylin.

The local Institutional Review Board of the National Institute of Oncology reviewed and approved the retrospective immunohistochemistry examination of paraffin embedded samples of 89 randomly selected regional lymph node metastatic papillary thyroid cancer patients operated in the National Institute of Oncology between 2013 and 2018.

Five-micron sections were cut from surgical paraffin blocks of tumor and stained by appropriate antibodies using kits according to the manufacturers' instructions (anti-

PD-L1 DAKO22C3 PharmDx kit). The hNIS expression was studied also by immunohistochemistry using a rabbit polyclonal antibody against the C terminal end of hNIS (1 µg/ul at 1:4000 dilution) (Dohan et al.,2004) (a generous gift from Dr. Nancy Carrasco). Immunohistochemistry analysis was performed as described previously. (Dohan et al.,2004), Wapnir et al., 2003) All slides were counterstained with hematoxylin. Immunohistochemical stains were evaluated and scored by two expert pathologists with experience in PD-L1 and NIS staining both separately and with a multi-headed microscope.

Three groups were formed according to the proportion of the tumor cells showing PD-L1 staining (TPS). The first group showed no staining (score 0), the second group showed between 1 and 50% tumor-cell staining (score 1), and the third group showed more than 50% staining (score 2). Following the evaluation of the PD-L1 staining, NIS immunohistochemistry analysis was performed on 85 cases, the percentage of the tumor cells showing cytoplasmic and/or plasma membrane NIS expression was recorded.

4. Results

Lobectomy was performed in 11 cases, and one patient underwent isthmusectomy. In four cases, external hydrodissection was used to infiltrate the thyroid lobes' capsule under ultrasound guidance (Figure 1). With this unique technique, the preparation of the gland is easier, and in these cases, the operation times were shorter than in normal TOETVA cases. Of the 12 patients, ten were female, and two were male, with a mean age of 48 years (range 41–72). Ten procedures were performed on the right side, one on the left, and one involved an isthmusectomy. The histological report indicated papillary thyroid cancer (size 0.8cm-1.7cm) in four cases, follicular adenoma in five cases, colloid nodule in one patient, and cysts in two patients. TOETVA patients did not require drain placement and were discharged on the first postoperative day. The average operating time was 107 minutes (range 76–124 min) in normal cases and 89 minutes (range 63–95 min) with external hydrodissection. Injury to the recurrent laryngeal nerve was not detected, and no other complications were observed. Transient numbness of the lower lip disappeared in every case after 2–3 weeks.

The clinical records of patients undergoing total thyroidectomy with central lymphadenectomy and with/without lateral lymphadenectomy, between 2013 and 2018, presenting preoperative cytological evidence of differentiated thyroid cancer and with biopsy proven lymph node metastasis. In our retrospective study, 130 papillary thyroid cancer patients with proven lymph node metastasis were identified. These patients had undergone total thyroidectomy with central and with/ without lateral neck dissection in our department. In all cases, surgery was performed by the same two experienced neck endocrine surgeons. For each patient, a preoperative diagnosis of differentiated thyroid cancer had been obtained by ultrasound (US) - guided FNAB. The preoperative workup consisted of free thyroid hormone (FT3, FT4), thyrotropin (TSH), Tg and anti-Tg antibody (TgAb) measurements, and high- resolution US of the neck by a skilled sonographer. Neck ultrasound is the most effective tool for detecting thyroid disease, combined with the result of FNAB and serum Tg assays, neck US can reach an accuracy around 100%. Other imaging studies should be carried out if locoregional or/ and distant metastases are suspected. A pre- and postoperative laryngoscopy was

routinely performed in all patients. Patient demographics and postoperative complications were recorded,

recurrent laryngeal nerve was not detected. Any other complications were not detected. Transient numbness of the lower lip disapperared in every case after 2-3 weeks.

Table1. Surgical data of TOETVA patients

	age	sex	Nodule size/FNA	Operation	OP time	surgery	complication
1	49	f	29mm Follicul neoplasia	Lobectomia l.d.	142 min	TOETVA	0
2	70	f	34mm colloid nodule	Lobectomia l.d.	110 min	TOETVA	0
3	41	f	28mm follicular neoplasia	Lobectomia l.s.	120 min	TOETVA	0
4	42	f	15mm papillary cancer	Lobectomia l.d.	180 min	TOETVA	0
5	43	f	9mm papillary cancer	Isthmectomia	120 min	TOETVA	0
6	56	f	8mm papillary cancer	Lobectomia l.d.	210 min	TOETVA	0
7	48	m	15mm papill.cc	Lobectomia l.d.	140 min	TOETVA	0
8	52	f	27mm Hürthle-cell neoplasia	Lobectomia l.d.	123 min	TOETVA	Seroma punctio
9	35	f	42 mm cyst	Lobectomia l.d.	117 min	TOETVA	0

10	53	f	36 mm cyst	Lobectomia l.d.	60 min	TOETVA	0
11	40	f	30mm follicular neoplasia	Lobectomia l.d.	120 min	TOETVA	0
12	54	f	20mm follicular neoplasia	Lobectomia l.d.	87 min	TOETVA	0
13	44	f	36mm follicular neoplasia	Lobectomia l.d.	107 min	TOETVA	0

From January 2013 to December 2018, 130 patients with metastatic papillary thyroid cancer underwent total thyroidectomy with lymph node dissection. These patients included 85 women and 45 men, with an average age of 47.56 years (ranging between 19 and 90 years old). Forty-three patients had thyroidectomy with only central neck dissection, while 87 patients had both central and lateral neck dissections.

Transient hypocalcemia and temporary vocal cord palsy were observed in 30 (23%) and 12 (9%) patients, respectively, while 4 (3%) patients experienced definitive hypocalcemia and 3 (2%) had permanent recurrent nerve palsy.

On examination, unifocal cancer was identified on one side in 75.38% (98) of patients, and on both sides in 24.61% (32). Multifocal cancer was identified on one side in 83.07% (108) of patients, and on both sides in 16.92% (22). Capsular invasion was found in 57.7% (75) of patients, lymphatic invasion in 48.46% (63), and Hashimoto thyroiditis in 39.23% (51). Microcarcinoma was detected in 33.07% (43) of patients.

Fourteen patients (10.77%) received a completion thyroidectomy, with multifocality found in two cases and extrathyroidal extension (ETE) detected in 12 cases through the histological report before the second surgery.

Patients without capsule invasion have a significantly better cancer-free survival rate compared to those with capsular invasion ($p = 0.0368$). However, no significant correlation was reported with regard to vascular and lymphatic invasion.

The median follow-up period was 47 months (0 to 196 months). We compared tumor size, the number of metastatic lymph nodes, and age against capsular invasion, vascular invasion, lymphatic invasion, and Hashimoto thyroiditis.

With increasing age, rates of vascular and lymphatic invasion were higher. In patients with Hashimoto's, the tumor size was smaller, and the age of patients was younger. A significant correlation was found between the number of removed lymph nodes and the tumor size ($p = 0.0212$), but not with age ($p = 0.2406$, according to Spearman's rank correlation). There was no significant correlation between the survival rate and the number of removed lymph nodes ($p = 0.2405$, according to Cox regression).

Table 2.

Correlation among the tumor size, metastatic lymph nodes and age to the capsular, lymphatic, vascular invision and Hashimoto thyreoiditis

p-value (Mann-Whitney U-test)	Capsular invasion	Lymphatic invasion	Vascular Invasion	Hashimoto thyreoiditis
Tumor size	<0.001	<0.001	<0.001	0.0242
Number of metastatic lymph nodes	0.0151	0.0162	0.0133	0.5614
Age	0.0206	<0.001	<0.001	<0.001

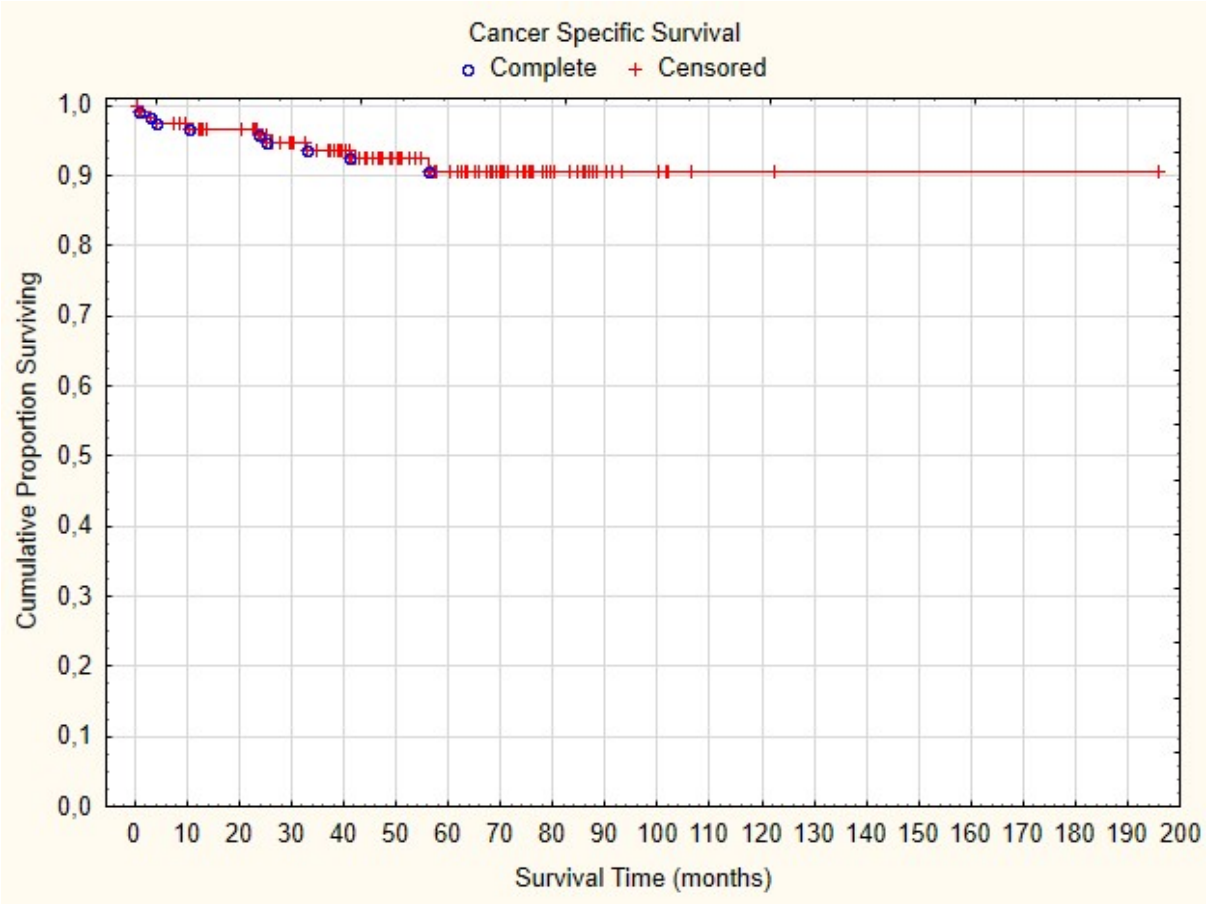

Figure 10.

Cancer specific survival is 91,5%

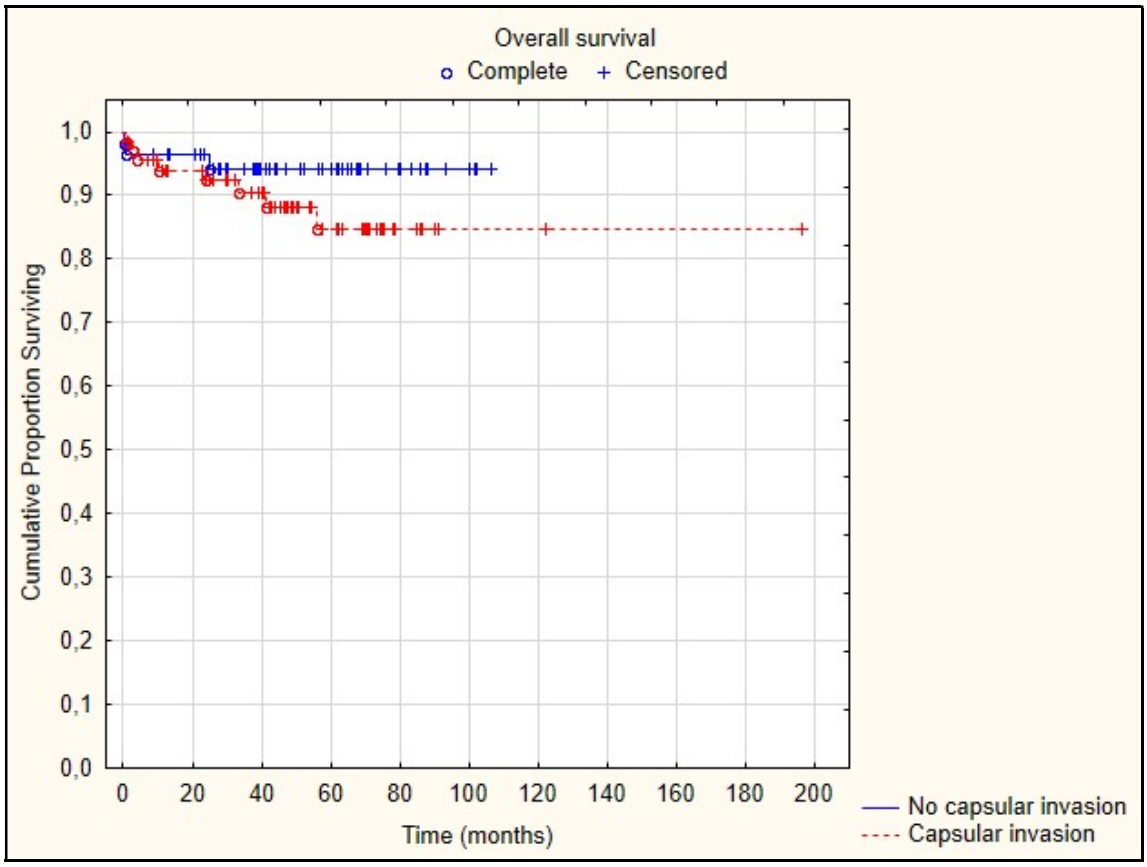

Figure 11.

Overall survival with and without capsular invasion. There was no difference in survival, p=0.2264 (Log-Rank test).

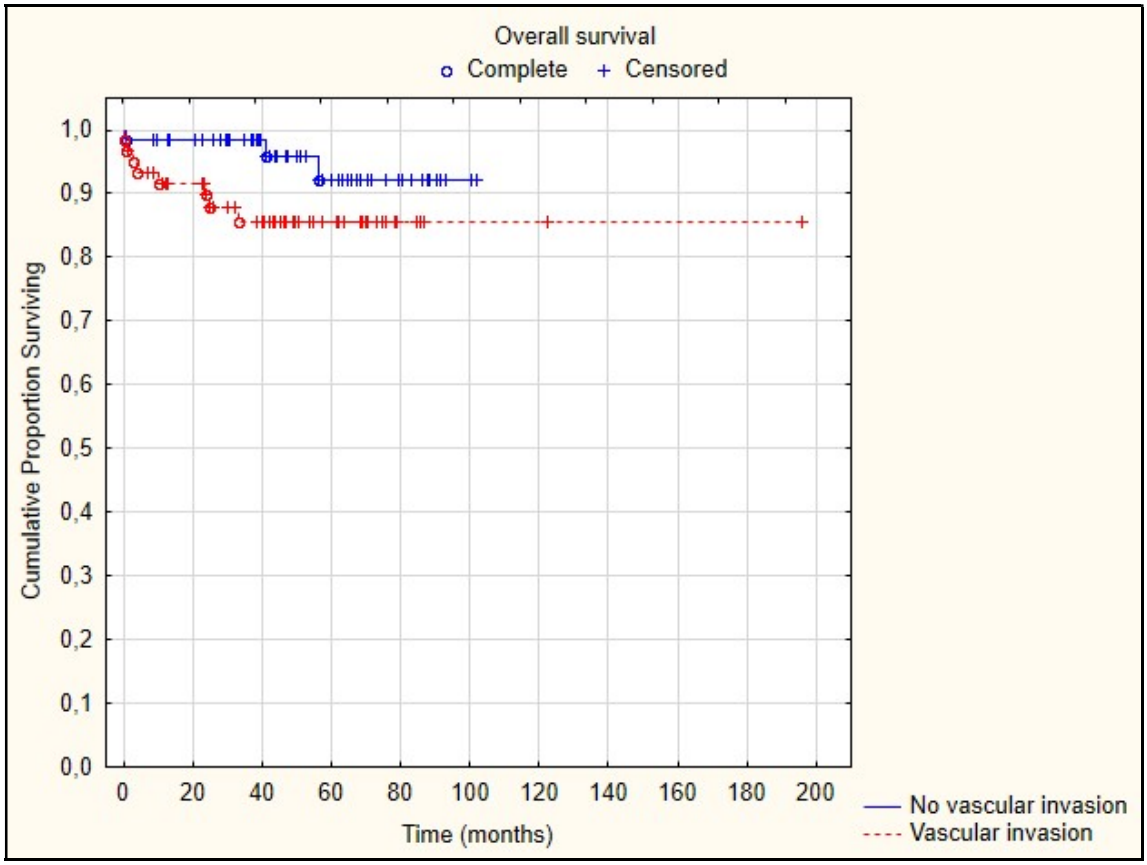

Figure 12.

Overall survival with and without vascular invasion. We found no difference between the groups, p=0.1088 (Log-Rank test).

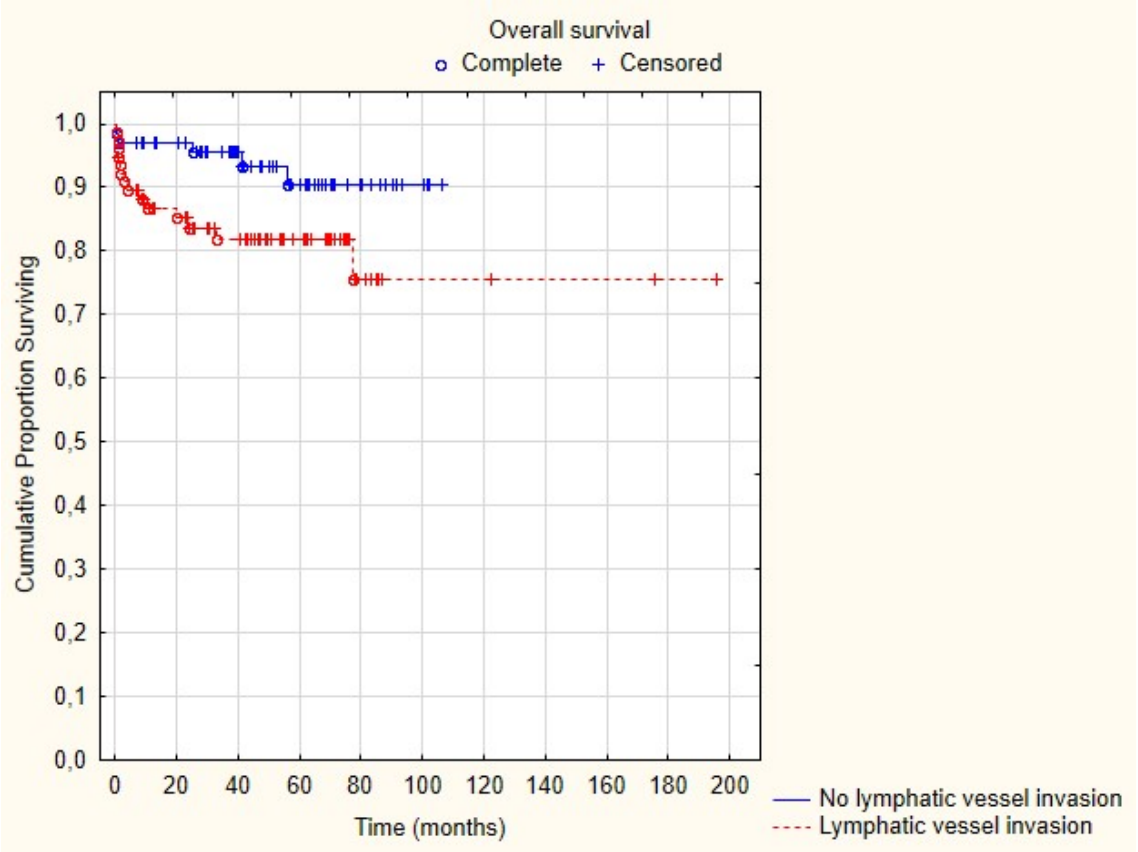

Figure 13.

Overall survival with and without lymphatic vessel invasion. No difference was shown, p=0.25 (Log-Rank test).

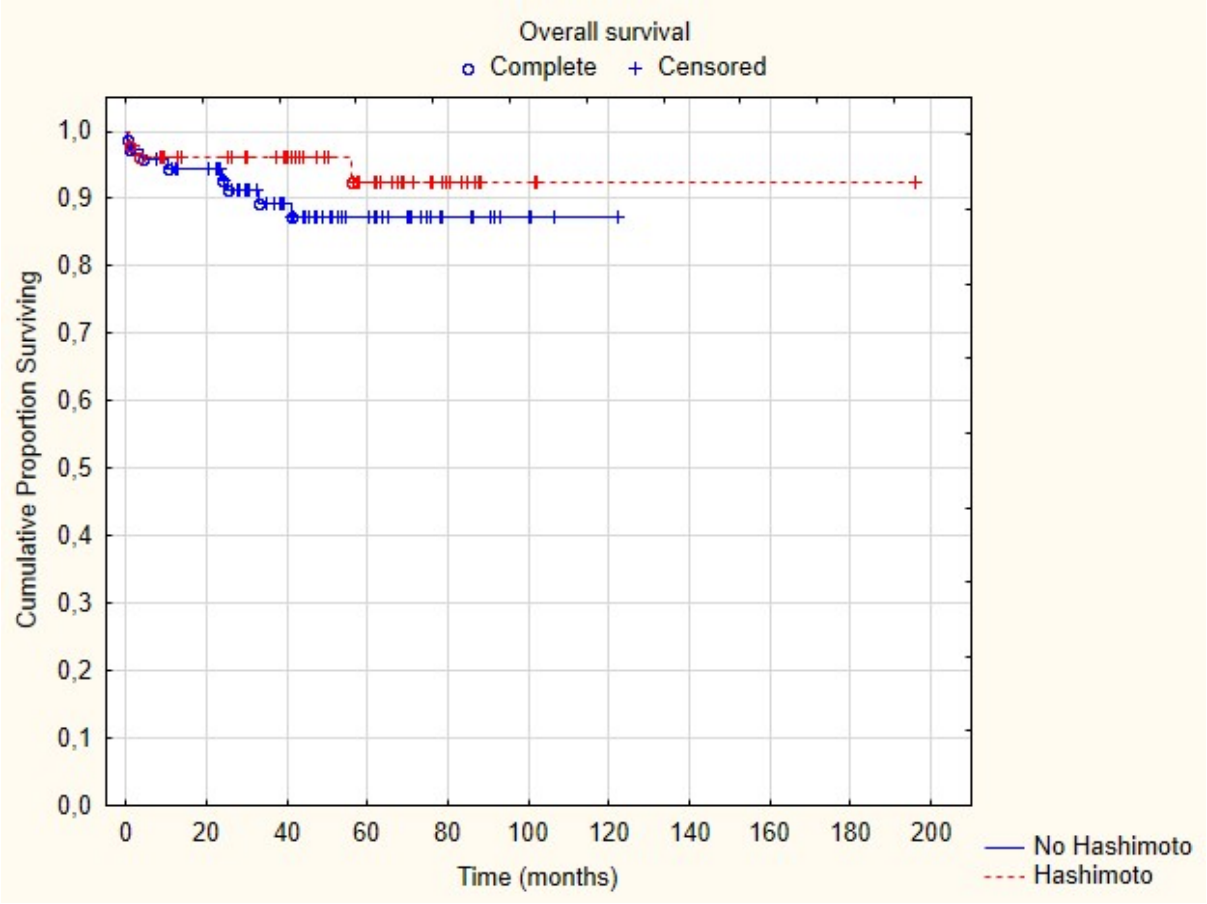

Figure 14.

Overall survival in Hashimoto and non-Hashimoto tumours. No difference was found in survival of Hashimoto versus non-Hashimoto tumours, p=0.2993 (Log-Rank test).

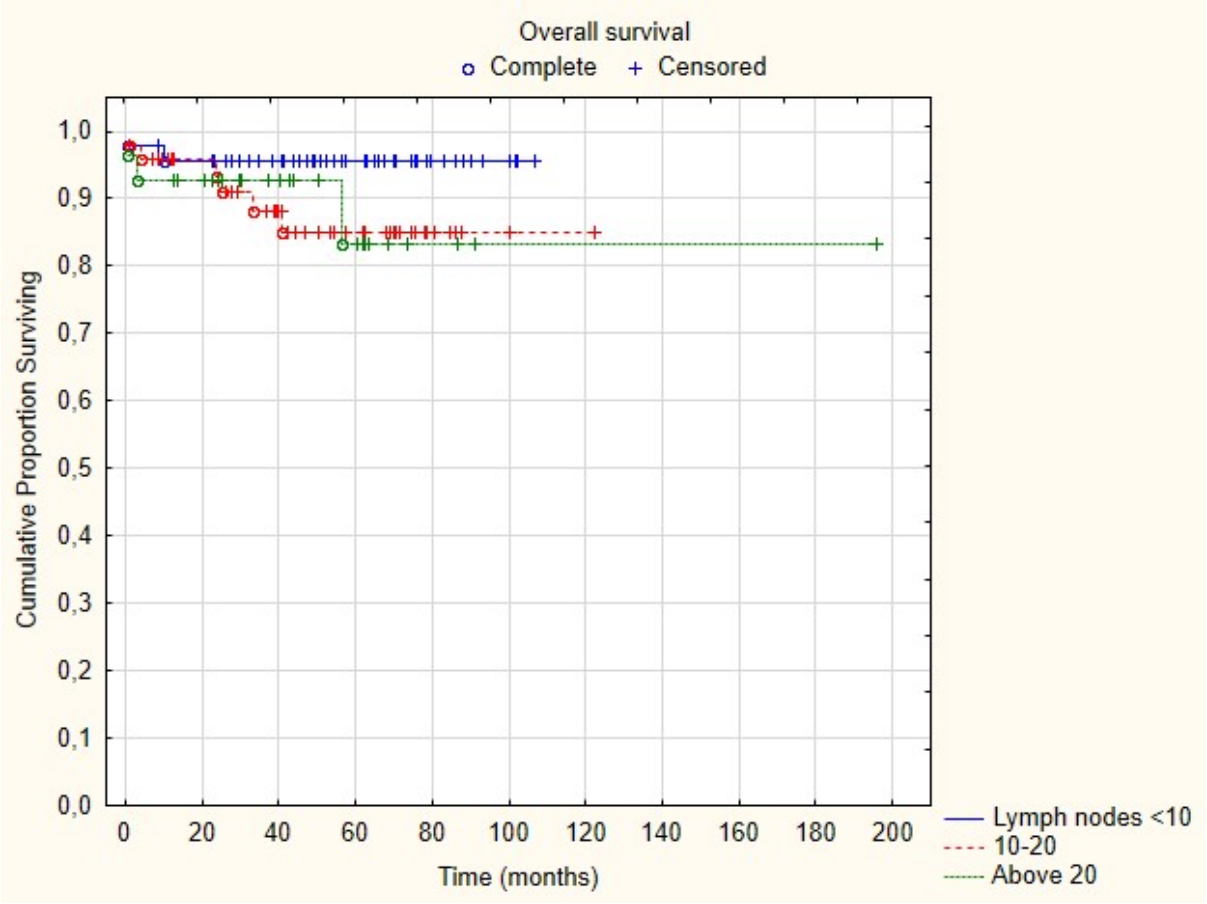

Figure 15.

Overall survival in tumours with less than 10, between 10 and 20, and above 20 positive lymph nodes. No difference was found in survival based of the number of positive lymph nodes, p=0.4044.

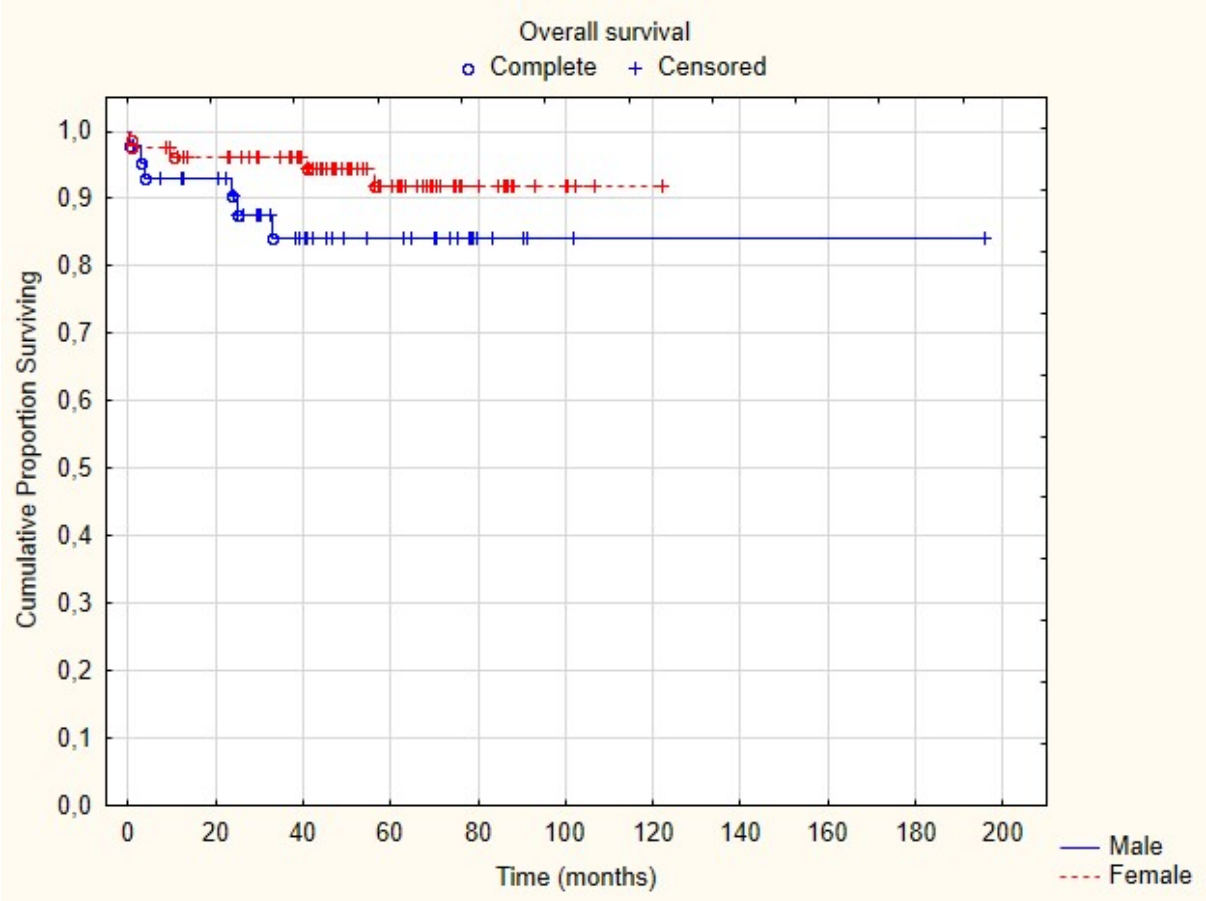

Figure 16.

Overall survival in female and male patients. There were no difference in survival between the genders, p=0.1391 (Log-Rank test).

Table 3. Comparison of OS, and complications of thyroid surgery in the institutional and international data

	OS	Transient hypocalcaemia	Permanent hypocalcaemia	Transient RLN palsy	Permanent RLN palsy
Institutional data	91%	23%	3%	9%	2%
International data	90%	14-60%	3-11%	3-7%	0-4%

Apically-expressed NIS in human tissue underlies I^- absorption from the intestine. The I^- is secreted into the lumen in the stomach and salivary glands by basolaterally-expressed NIS. The I^- is then again recirculated in the small intestine via apical NIS into the bloodstream.

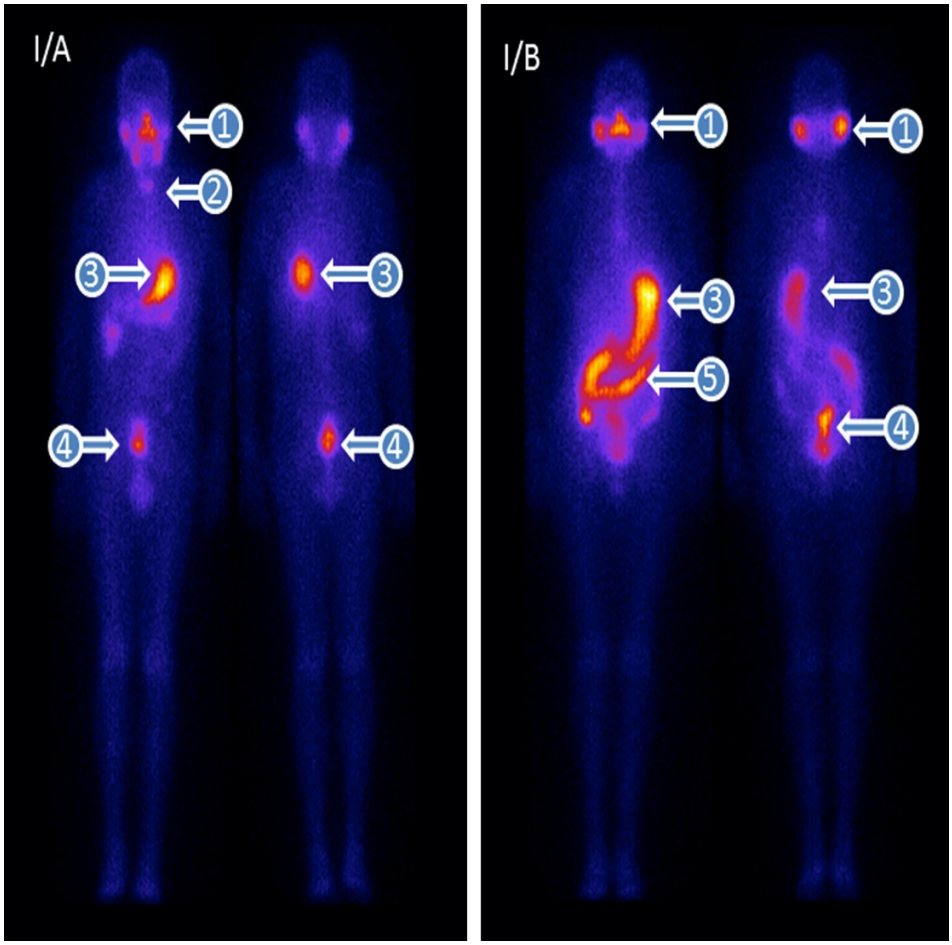

Figure 17.

Planar imaging of post-therapeutic I-131 distribution in a patient underwent thyroidectomy for thyroid cancer. The images were taken 72 hours following therapeutic administration of I-131.

(1): salivary gland, iodide is translocated into the saliva, (2) thyroid remnant: iodide is trapped in the thyroid gland, (3) stomach: iodide is translocated into the gastric juice, (4) iodide, as an anion simply filtered through the glomeruli and collected with the urine in the urinary bladder, (6) from the stomach the gastric juice gets into the small intestine, where iodide is an taken back from the intestinal lumen, and translocated into the blood stream.

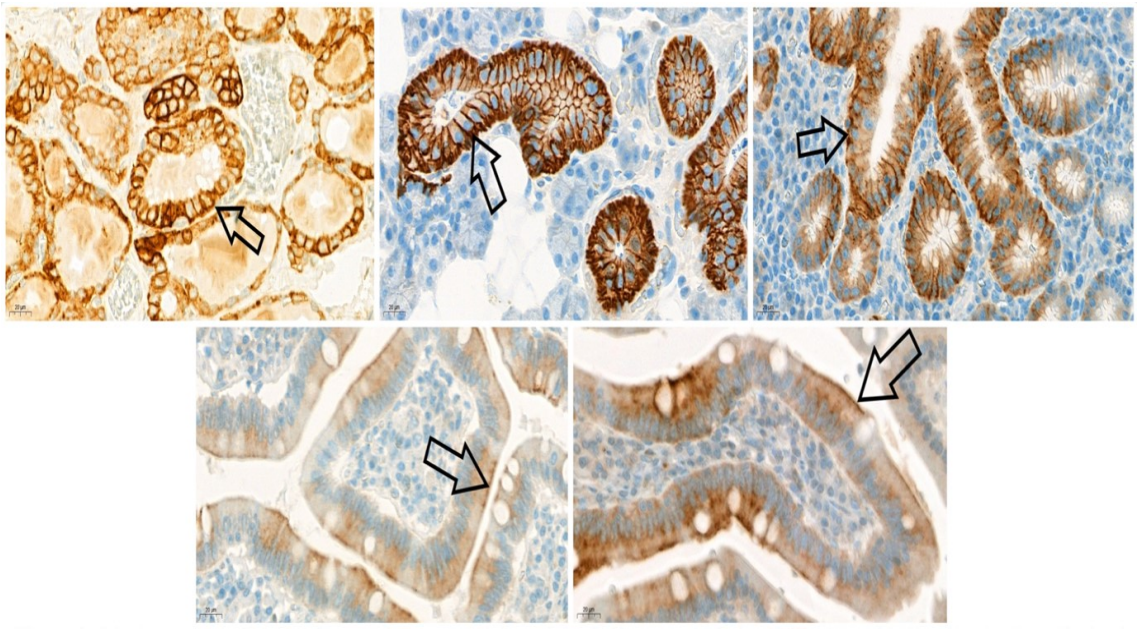

Figure 18.

Black arrows indicating the basolateral membranous staining of the iodide accumulating follicular epithelium in the thyroid gland (top left), the basolateral membrane staining of iodine excreting epithelial cells in the salivary gland acini (top middle) and in the gastric mucosa (top right).

Apical membrane staining of the epithelial lining on the surface of duodenal villi responsible for iodide absorption (bottom left: cross sectional, bottom right: longitudinal sectional plane) (NIS immunohistochemistry, 40x magnification)

In our present study we first reconfirmed previous observations that NIS expression is absent only in 33% of PTCs, and NIS expression is increased in the majority of thyroid cancer, but

retained in the cytoplasmatic membrane compartments, resulting absent or significantly decreased radioiodine accumulation in thyroid cancer cells. (Dohan et al., 2001,Wapnir et al., 2004)

Also in the line with results of others we also demonstrated that significant proportion , 72% of PTSs express PD-L1. (Wan et al., 2021)

Our aim was to evalute - first time ever - NIS and PD-L1 expression in the same tumoral tissue, and we could not find correlation between NIS and PD-L1 expression in the primary tumor of lymph node metastatic PTCs.

As our study is the first attempt to explore possible association between PDL1 and NIS expression, it has several limitations.

It has been described by Lubin at al., that PTC with a background of Hashimoto thyroiditis exhibit significant PD-L1 expression. (Lubin et al. 2018) Others reported that PTCs with a thyroiditis background demonstrated much higher PD-L1 expression compared to PTCs with a normal background. (Cunha et al., 2014, Bai et al., 2017) In our study we did not evalute the presence of thyroiditis, and it's association with PDL1 or NIS expression.

Several studies have demonstrated that during the dedifferentiation process in most thyroid cancer the expression of PDL1 increases (D'Andréa et al., 2021) and NIS functional expression decreases (Weitzman et al.,2019). The PD1/PDL-1 pathway in general is used by cancer cells to resist immune destruction, while lacking functional NIS expression leads to radioiodine resistance.

PDL1 expression was evaluated only in the cancer cells, and expressed as TPS, the PDL1 staining of tumor infiltrating immunocells was not recorded.

We also did not investigated PD-L1, or NIS expression in corresponding lymph node metastases, but others reported PD-L1 expression in metastatic PTC tissues were similar to their corresponding primary tumor in the thyroid. (Lubin et al., 2018)

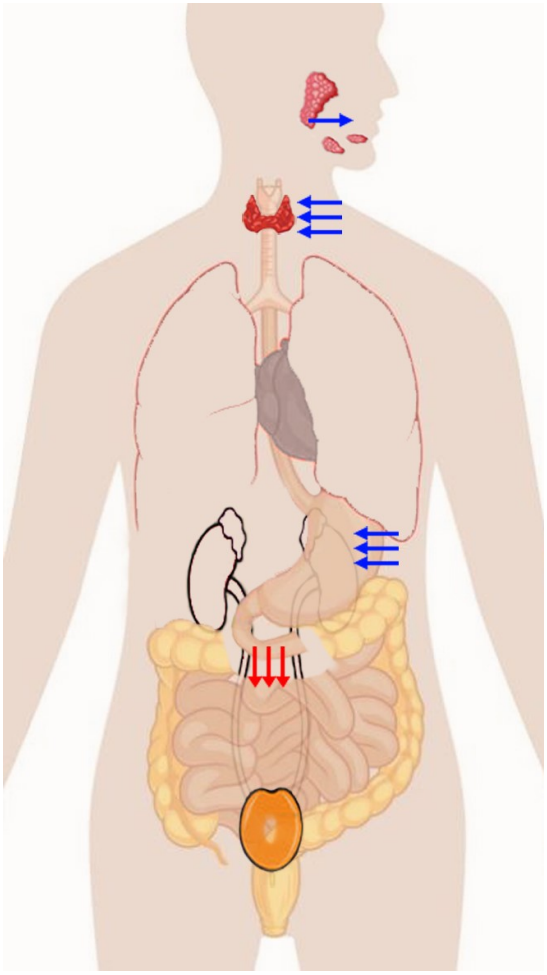

Figure 19.

Figure 3. Schematic representation of iodine metabolism

Schematic representation of iodine distribution in the human body regulated by tissue specific polarized (basolateral or apical) plasma membrane expression of hNIS in epithelial cells.

Blue arrows: basolaterally expressed NIS in epithelial cells translocates iodine in the saliva, in the gastric juice, and in the thyroid cells, where it is covalently bound to the tyrosyl residues of thyroglobulin. Red arrows: apically expressed NIS in the epithelial cells of the duodenal mucosa translocates iodine from the intestinal juice to the blood stream.

PD-L1 immunohistochemistry was performed on the primary tumor of regional lymph node metastatic 89 PTC cases. 25 (28%) of the tumors did not show PDL1 expression, while 58 (65%) and 6 (7%) of the tumor-tissues were in staining groups 1 and 2, respectively. (Table 1.)

NIS immunohistochemistry was performed on 86 primary papillary carcinomas. 51 (60%) out of 86 tumors showed NIS expression, only in 7 (8%) cases NIS was localized in the plasma

membrane, while in most tumors NIS was retained in the intracytoplasmic membrane compartments. (Figure 1.) (Table 1.) NIS and PD-L1 expression was evaluated on different tissue sections from the same tumor and we could not investigate NIS and PD-L1 colocalization in tumor cells.

The Sperman-Rank Order Correlation was run to determine the relationship between PD-L1 (TPS) and NIS expression in PTC tumors. There were no correlation between the PD-L1 and NIS expression (p=0.3199).

No correlations was found between PD-L1 expression (TPS) and metastatic lymph nodes, lymphogenic spread (data not shown).

We did not find any correlation between Hashimoto thyreoiditis and NIS-PD-L1 expression.

Table 4. Expression of PD-L1 and NIS

Case N	**PD-L1**	**Range**	**NIS**	**NIS citoplasmatic**	**NIS plasmamembrane**
1	0	1	30	30	0
2	10	2	0	0	0
3	0	1	20	20	0
4	20	2	0	0	0
5	1	2	0	0	0
6	10	2	1	1	0
7	0	1	0	0	0
8	20	2	0	0	0
9	0	1	0	0	0

10	30	2	0	0	0
11	0	1	10	10	0
12	0	1	0	0	0
13	1	2	0	0	0
14	10	2	0	0	0
15	0	1	0	0	0
16	0	1	1	1	0
17	0	1	1	0	1
18	0	1	0	0	0
19	30	2	1	1	0
20	1	2	1	1	0
21	0	1	0	0	0
22	30	2	0	0	0
23	5	2	0	0	0
24	0	1	20	20	0
25	0	1	60	50	10
26	0	1	0	0	0
27	5	2	0	0	0
28	30	2	5	5	0
29	10	2	0	0	0
30	20	2	0	0	0
31	30	2	0	0	0
32	40	2	0	0	0
33	20	2	0	0	0
34	20	2	10	0	10
35	40	2	30	0	30
36	90	3	0	0	0
37	20	2	70	70	0
38	50	2	0	0	0
39	20	2	80	80	0
40	0	1	5	5	0
41	1	2	1	1	0

42	0	1	10	10	0
43	40	2	0	0	0
44	10	2	1	1	0
45	60	3	20	20	0
46	50	2	1	1	0
47	5	2	100	100	0
48	10	2	1	1	0
49	50	2	90	90	0
50	5	2	90	70	20
51	90	3	0	0	0
52	0	1	10	10	0
53	80	3	70	40	30
54	30	2	0	0	0
55	30	2	30	30	0
56	5	2	60	60	0
57	0	1	90	90	0
58	30	2	20	20	0
59	0	1	40	40	0
60	50	2	0	0	0
61	10	2	10	10	0
62	40	2	70	70	0
63	40	2	0	0	0
64	10	2	0	0	0
65	30	2	10	10	0
66	50	2	0	0	0
67	10	2	0	0	0
68	10	2	40	20	20
69	20	2	60	60	0
70	1	2	0	0	0
71	5	2	70	70	0
72	5	2	100	100	0
73	60	3	0	0	0

74	70	3	0	0	0
75	0	1	5	5	0
76	0	1	10	0	10
77	20	2	0	0	0
78	5	2	0	0	0
79	0	1	0	0	0
80	0	1	10	10	0
81	1	2	0	0	0
82	0	1	0	0	0
83	1	2	5	5	0
84	5	2	5	5	0
85	20	2	20	20	0
86	30	2	30	30	0
87	0	1	60	60	0
88	10	2	70	70	0
89	10	2	40	40	0

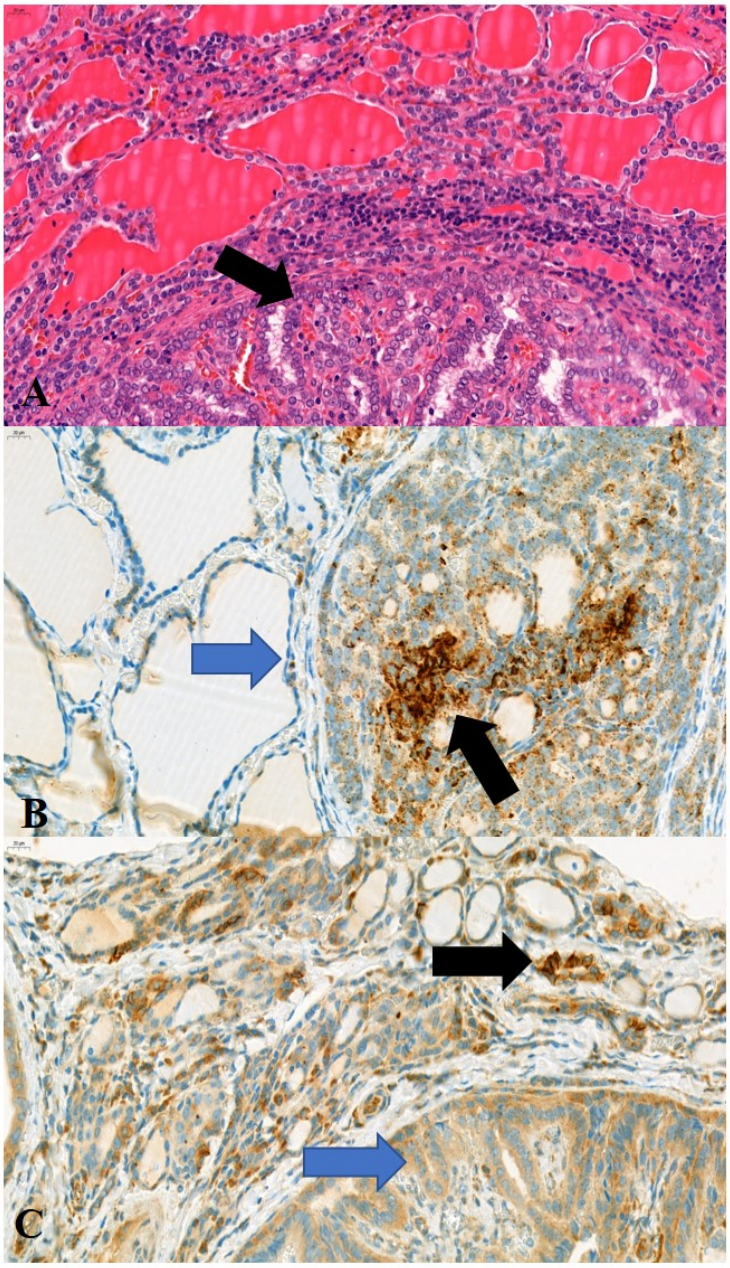

Figure 1. A: Papillary thyroid carcinoma shows typical architectural and cytomorphological features (black arrow). B: The carcinoma cells featuring membranous PD-L1 staining (black arrow) while the normal follicular cells show no staining (blue arrow). C: The normal follicular epithelial cells exhibiting heterogenous NIS staining on their membrane (black arrow) comparing the negative tumor cells (blue arrow). (A: HE staining; B: PD-L1 IHC; C: NIS IHC; 40x magnification, all pictures taken from the same tumor)

Figure 20. Papillary thyroid carcinoma with normal cytomorphological features, with membranous PD-L1 staining, with NIS staining

5.Discussion

The development of a new technique in thyroid surgery aimed to minimize scars and reduce surgical invasiveness. This was facilitated through endoscope-assisted procedures aimed at reducing scar size (Miccioli et al., 1999). Approaches such as ABBA (axilla-bilateral breast approach) and BABA (bilateral axilla-breast approach) offered vast operative fields but were accompanied by numerous complications (Shimazu et al., 2003; Ohgami et al., 2000). Robotic thyroid surgery, though innovative, is significantly costly due to its requirement for special equipment (Lee et al., 2011). The endoscopic thyroid surgery sublingual approach was discontinued due to the risk of lingual nerve injury. In 2016, Anuwong Angkhoon and Paul Jitpratoom initiated TOETVA operations on cadavers and subsequently applied the technique to humans (Jitpratoom et al., 2016). Since 2016, TOETVA has been accessible in several thyroid centers across North America, Europe, and Asia.

Nowadays, TOETVA is a recognized procedure for neck dissections at advanced thyroid centers in Asia. The most common complication of the vestibular approach is bacterial infection. Saliva contains Gram-positive aerobic and anaerobic species, whereas the subplatysmal plane is sterile. According to the relevant literature, no serious bacterial infections have been reported at centers performing TOETVA (Anuwong et al., 2016). Recurrent laryngeal nerve injury is a significant complication of both open and TOETVA surgeries. As such, intraoperative nerve monitoring can be a useful tool to record nerve function during open surgery. The rate of complications is similar with or without a monitor. Anuwong et al. reported comparable rates of hypoparathyroidism after both open and TOETVA procedures (Anuwong et al., 2017). This novel technique is recommended for surgeons who perform a high volume of thyroid surgeries and are capable of converting to open surgery during sudden serious situations (Luo et al., 2020).

Thyroid cancer is a prevalent malignant disease, with surgical intervention often representing the critical initial step. FNAB can distinguish between the types of cancer, and it is a useful tool for determining the extent of lymph node dissection in cases of metastasis. However, the impact of locoregional lymph node metastasis on survival

rates in DTC patients remains a subject of debate (Triantofillou et al., 2018). Various studies suggest that lymph node metastasis in the lateral compartment, particularly in older

patients, results in poorer clinical outcomes compared to metastases in the central compartment (Agrawal et al., 2017). Prior to surgery, all patients undergo an ultrasound or neck MR/CT. In our study, surgeons only carry out therapeutical dissections that are biopsy-proven without performing elective dissections.

Reports suggest that nodal dissection can potentially lower locoregional recurrence and enhance survival in differentiated thyroid cancer cases (Robbins et al., 2002). Randolph et al. highlighted the relationship between metastatic lymph nodes' size and number and the likelihood of recurrence. They found that cases with fewer than five sub-cm metastatic nodes had reduced recurrence risks. However, recurrence rates of over 20-30% were found in cases of larger lymph node metastases (>3 cm or >5–10 metastatic nodes) (Randolph et al., 2012). High-resolution cervical ultrasonography (US) is reportedly the most sensitive method for differentiating between metastatic and benign lymph nodes in patients with differentiated thyroid cancer and detecting locoregional metastases as small as 2-3 mm. Therefore, preoperative US can effectively identify metastatic lymph nodes that might go unnoticed with palpation alone in a significant number of patients with small macroscopic metastases (Russ et al., 2017).

Won et al. studied the optimal range of lateral neck dissection in patients with differentiated thyroid cancer (DTC) having clinically confirmed lateral neck lymph node metastases. They concluded that selective neck dissection could be recommended for well-differentiated DTC patients with lateral lymph node metastasis devoid of risk factors (Won et al., 2018). Wong et al. suggested that levels IIa, III, IV, and V should consistently be removed in well-differentiated TC patients to prevent recurrence, as per their study (Wong et al., 2011). They proposed prophylactic central neck dissection due to its lower morbidity rates compared to reoperation. Notably, reoperating central lymph node dissection poses a higher risk to the recurrent laryngeal nerve and parathyroid glands due to increased scarring. Scarring, edema, and tissue vulnerability, along with landmark distortion, make re-operative surgery dangerous. It is also linked with a higher postoperative hematoma and scarring risk (Shaha et al., 2012).

Many endocrine surgeons question the benefits of routine lymph node dissection, as it is often associated with increased morbidity, including injuries to the

lower parathyroid glands. Consequently, this procedure has been connected to rates of transient hypocalcemia of 14–60%, permanent hypocalcemia of 3–11%, temporary vocal cord
paralysis of 3–7%, and permanent recurrent laryngeal nerve injury of up to 4% (Gambardella et al., 2016, Won et al., 2018). Total thyroidectomy tends to have a lower morbidity rate, and with treatments such as radioiodine and TSH suppression therapy, locoregional lymph node recurrence rates are often low. However, Molteni et al. suggested that skilled, high-volume surgeons could achieve a low incidence of new recurrent laryngeal nerve palsy and permanent hypoparathyroidism when reoperating the central lymph node dissection for recurrent or persistent thyroid cancer (Molteni et al., 2019). Furthermore, Agrawal et al. developed practical guidelines for when a central neck dissection should be performed on patients with papillary thyroid cancer. Their consensus advised that proven lymph node metastases in the central neck should be addressed with comprehensive compartmental central neck dissection.

Only in certain cases is prophylactic central neck dissection deemed appropriate. As indicated in these statements, recurrent central neck dissection should ideally be conducted by highly experienced surgeons who frequently perform such procedures. This is to reduce the risk of complications compared to having the procedure carried out by a less experienced, low-volume surgeon (Agrawal et al., 2017).

In fact, the recent American Thyroid Association Guidelines suggest routine central lymph node dissection for all DTCs, particularly for high-risk patients (Haugen et al., 2016). They reached this recommendation after carefully weighing all the advantages and disadvantages.

Our study observed lower survival rates associated with tumor size, multifocality, and capsular invasion, aligning with other literary reports. Age and gender demonstrated no significant relevance, corroborating further reports in the literature.

We have correlated in vivo radioiodine distribution of human body and polarized NIS expression by immunohistochemistry in iodine accumulating organs. I^- is a tracer mineral in the environment, and humans ingest it via food. Because of its scarcity, I^- has to be adsorbed through a very specific and efficient mechanism. I^- anions are quickly filtered from the bloodstream by the kidney and excreted via the urine. I^- is also “trapped” by the thyroid gland; It is transported by NIS into the thyrocytes, where I^- is

covalently bound to the tyrosyl residues of thyroglobulin. NIS is highly specific and efficient in accumulating I^- into the thyroid cells, but I^- is also quickly cleared from the circulation by glomerular filtration. Thus, it is imperative that I^- has to remain in the circulation for a sufficiently long time. (Martin el al., 2019, Dohan et al., 2001)

Nicola et al. first demonstrated NIS over the entire length of small intestine in rodents. They studied the duodenum to the ileum and found that NIS is localized in the apical surface of small intestine enterocytes where it mediates intestinal I^- absorption. They also reported that -similar to thyroidal NIS- enteral NIS is autoregulated by I^-, and high I^- concentration decreases its own intestinal transport. In this report we used immunohistochemistry to show apical NIS expression of enterocytes for first time in human small intestine. This corroborates prior rodent work by Nicola. (Nicola et al., 2015)

Studies of human samples are limited by availability and tissue auto-digestion, and thus we could not evaluate NIS expression through small intestine. Our samples were from the duodenum and all showed apical NIS expression in the enterocytes. It is difficult to study the regulation of expression and polarized plasma membrane targeting enteric NIS expression in humans. Martín et al. reported the presence of a highly conserved monoleucine-based sorting signal on the NIS carboxy terminus that is responsible for basolateral plasma membrane targeting in polarized canine kidney epithelial (MDCK) cells. Disrupting this basolateral sorting signal results in apical targeting of NIS protein in epithelial cells. This sorting determinants have to be recognized by cell-specific sorting machinery.

This sorting machinery is cell-specific and characterized by specific adaptor proteins.

Currently, very little known in NIS-expressing tissues about the presence, function, and regulation of cell-specific factors that interact with and determine the polarized targeting of NIS in the plasma membrane. In the human body, polarized NIS expression can be basolateral (thyroid, salivary gland, stomach) or apical (small intestine). (Nicola et al., 2012)

This distribution ensures that I^- absorbed in the small intestine, accumulates in the thyroid gland and secreted into the gastric lumen. This is then reabsorbed in the

small intestine, finally removed from the circulation via glomerular filtration into the urine. (Figure 13.)

Our aim was to evalute - first time ever - NIS and PD-L1 expression in the same tumoral tissue, and we could not find correlation between NIS and PD-L1 expression in the primary tumor of lymph node metastatic PTCs.

As our study is the first attempt to explore possible association between PDL1 and NIS expression, it has several limitations.

It has been described by Lubin at al., that PTC with a background of Hashimoto thyroiditis exhibit significant PD-L1 expression. (Lubin et al. 2018) Others reported that PTCs with a thyroiditis background demonstrated much higher PD-L1 expression compared to PTCs with a normal background. (Cunha et al., 2014, Bai et al., 2017) In our study we did not evalute the presence of thyroiditis, and it's association with PDL1 or NIS expression.

Several studies have demonstrated that during the dedifferentiation process in most thyroid cancer the expression of PDL1 increases (D'Andréa et al., 2021) and NIS functional expression decreases (Weitzman et al.,2019). The PD1/PDL-1 pathway in general is used by cancer cells to resist immune destruction, while lacking functional NIS expression leads to radioiodine resistance.

PDL1 expression was evaluated only in the cancer cells, and expressed as TPS, the PDL1 staining of tumor infiltrating immunocells was not recorded.

We also did not investigated PD-L1, or NIS expression in corresponding lymph node metastases, but others reported PD-L1 expression in metastatic PTC tissues were similar to their corresponding primary tumor in the thyroid. (Lubin et al., 2018)

6.Conclusion

A TOETVA is the only scar-free, effective procedure for the thyroid gland that offers a satisfactory cosmetic outcome. The extensive operation time can decrease with experience, typically after 15 to 20 surgeries. The ideal practitioner for this procedure would be a surgeon highly experienced in thyroid surgeries. Operating field avascularity can be achieved via external hydrodissection, which facilitates safer, more feasible blunt preparation. The authors have successfully combined thyroid capsule sheath infiltration, a technique employed in regional thyroid surgeries, with the TOETVA procedure. Their innovative method is a safe and effective surgical option for selected patients. In the future, the authors plan to broaden their approach, removing not only thyroid lobes but also central and lateral lymph nodes.

Thyroid cancer is a prevalent disease with a favorable survival rate. Surgery can significantly contribute to the treatment plan. We do not conduct preventative dissections. The utility of prophylactic central lymph node dissection in treating differentiated thyroid cancer is quite unclear. To date, there is no decisive evidence suggesting that preventative central neck dissection decreases recurrence or mortality rates. This procedure, even when executed by well-versed surgeons, is linked to increased morbidity. It primarily results in temporary complications, primarily hypoparathyroidism. However, the rate of permanent complications is incredibly low and not significantly different from those of a total thyroidectomy conducted individually.

In our study, tumor size, the number of metastatic lymph nodes, and advanced age were all correlated with capsular, lymphatic, and vascular invasion, which is consistent with similar studies.

Patients with capsular, lymphatic, and vascular invasion, as well as those with larger tumors, had lower survival rates. Contrary to numerous studies supporting the effectiveness of metastatic lymph node dissection, our data showed no correlation between the number of dissected and metastatic lymph nodes and survival rate, eliminating the necessity for prophylactic dissection. Survival rates were higher in patients who underwent radioiodine therapy after surgery - a well-documented fact. Hashimoto thyroiditis is associated with larger tumor size.

Lymphatic and vascular invasions tend to be more frequent in older patients compared to younger ones.

In summary, we advocate for prophylactic central neck dissection only for high-risk patients. We have found that certain factors increase the recurrence risk, such as tumor size, certain histological varieties (namely Hürthle cell and, especially, tall cell variant), multifocality, and locoregional infiltration. Using a wider range of immunocytochemical and genetic markers may enhance preoperative diagnosis. Furthermore, the creation of methods to detect metastatic lymph nodes during surgery could greatly benefit patient selection for prophylactic or therapeutic central neck dissection in the near future.

Prophylactic central neck dissection is appropriate only in specific cases. According to these statements recurrent central neck dissection should be performed by high volume experienced surgeons to minimize the complication rate , than for a low volume surgeon to perform prophylactic dissection. (Agrawal et al., 2017)

As a matter of fact, the recent American Thyroid Association Guidelines, whilst taking into consideration all the pros and cons, recommend routine central lymph node dissection for all differentiated thyroid cancers, especially in high-risk patients.(Haugen et al.,2016)

In our study, tumor size, multifocality, capsular invasion also presented a lower survival rate, in line with other reports in the literature. We found no differences in relation to age or gender, in agreement with other reports in the literature.

In our present study we first reconfirmed previous observations that NIS expression is absent only in 33% of PTCs, and NIS expression is increased in the majority of thyroid cancer, but

retained in the cytoplasmatic membrane compartments, resulting absent or significantly decreased radioiodine accumulation in thyroid cancer cells. (Dohan et al., 2001,Wapnir et al., 2004)

Also in the line with results of others we also demonstrated that significant proportion , 72% of PTSs express PD-L1. (Wan et al., 2021) TSH and iodine are the two main factors that regulate thyroidal I^- transport: TSH stimulates it and iodine decreases transport. (Paroder et al., 2011, Tazebay et al., 2000) Hence, TSH stimulation and I depletion are the two most important modulators routinely used to optimize radioiodine treatment of metastatic thyroid carcinoma. Both tissue specific expression and polarized expression of NIS determines the distribution of I^- in the human body. As an anion, absorbed I^- quickly filtered from the circulation by the kidney into the urine. Gastrointestinal recirculation can led to a prolonged plasma retention time for I^- thust resulting in better I^- availability for thyroidal I^- accumulation. NIS is the first theranostic molecule ever used for both diagnostic and therapeutic purposes -it is used in thyroid imaging, as a reporter gene in gene therapy, and as a radioiodine treatment of metastatic thyroid cancer. Manipulating intestinal recirculation of I^- can optimize radioiodine availability in the bloodstream for NIS- mediated targeted radiotherapy, and reporter imaging. (Spitzweg et al., 2021)

In summary we found no correlation between the percentage of NIS and PD-L1expressing tumor cells in the primary tumors of lymph node metastatic PTCs. We could not perform co-localization studies of NIS and PDL1 expression at the cellular level, so we could not evaluate association between NIS and PD-L1 in the same cancer cell.

Several studies have demonstrated that during the dedifferentiation process in most thyroid malignancies the expression of PD-L1 increases. (D'Andréa et al., 2021)

and NIS functional expression decreases, but may also be independent consequences of dedifferentiation process. (Weitzman et al., 2019)

It is tempting to speculate whether manipulation of the PD-1/PD-L1 axis by anti-PD-L1 or anti-PD-1 antibodies, could restore NIS functional expression.

Based on the present study we can only conclude that the percentage of NIS expressing or PD-L1 expressing tumor cells does not correlate in the primary tumor of lymph node metastatic PTC.

7.Summary

A TOETVA is the only scar –free, and effective procedure of the thyroid gland, which provides good cosmetic outcome. The long operative procedure time will be shortened with experience after a learning curve of 15-20 operations. The surgeon must be a high volume surgeon on the field of thyroid surgery. With external hydrodissection the operative field becomes avascular, the blunt preparation is safer and more feasible. The thyroid capsule sheath infiltration is used in regional thyroid surgery what authors combined with TOETVA procedure. Authors' unique method is a safe and effective surgical procedure on selected patients. Thyroid cancer is a common disease with a good survival rate. In our data capsular invasion, lymphatic and vascular invasion were correlated with tumor size, also with the number of metastatic lymph nodes, and with the elderly age according to similar studies. Survival rate was lower in patients with capsular, lymphatic and vascular invasion, and also in patients with larger tumor size. In our data the number of dissected and metastatic lymph nodes do not correlate with the survival rate. This fact suggests absolutely no need for prophylactic dissection. Survival rate was higher in patients with radioiodine therapy after surgery than the patients without the radioiodine ablation as it has been well known. Hashimoto thyroiditis correlates with larger tumor size. In older patients, lymphatic- and vascular invasion occur more often than in younger age. To summarize, we believe that prophylactic central neck dissection should be performed in high-risk patients only. Unfortunately, no clinical or pathological factors are able to predict with any certainty the presence of nodal metastasis. In our experience, tumor size is related to an increased risk of recurrence, as are some histological types (Hürthle-cell and, particularly, tall cell variant), multifocality, and locoregional infiltration. We examined first apically-expressed NIS in human tissue underlies I^- absorption from the intestine. The I^- is secreted into the lumen in the stomach and salivary glands by basolaterally-expressed NIS. The I^- is then again recirculated in the small intestine via apical NIS into the bloodstream.

Since NIS and PD-L1 expression has never been investigated together in thyroid cancer , the aim of our study was to investigate and correlate PD-L1 and NIS expression in the same tumor samples of metastatic lymph nodes. We do not detect any correlation between PD-L1 and NIS expression.

Összefoglalás

Az ismertetett új technika az elmúlt évtizedekben egyre nagyobb népszerűségnek örvendő endoszkópos beavatkozások egyike, mely gyakorlott kézben hegmentes, a nyitott műtétekhez hasonlóan alacsony szövődmény rátájú megoldás a megfelelően szelektált beteganyagon. A TOETVA-t nagy számban végző centrumokban az átlagos műtéti idő rövidül: lobectomia esetén 76 perc, total thyreoidectomia esetében 124 perc.

Hazánkban, a módszert az Országos Onkológiai Intézetben végezzük a műtéteket, melyeket kiválasztott beteganyagon, megfelelő indikációval, az onkológiai elveket szem előtt tartva egyre nagyobb számban kívánjuk alkalmazni.

A jól differenciált pajzsmirigyrák gyakori, de jó prognózisú betegség, melynek felfedezésében az ultrahang diagnosztikának kiemelkedő fontossága van, illetve a sebészi beavatkozás döntő szerepet kap a terápiás algoritmusban. Beteganyagunkban a posztoperatív szövődményráta a nemzetközi adatokkal összevetve is alacsonynak mondható.

Relatív kis méretű daganat, vagyis a microcarcinoma 43 esetben (33%) adott nyaki áttétet. Az eltávolított nyirokcsomó blokkoknak 48%-a volt áttétes, mely csak a tumormérettel mutatott szignifikáns korrelációt. A pajzsmirigydaganatok kezelése a multidiszciplinaritás miatt elsősorban centrumokban végzendő.

A teljes test scan alkalmas a radiojód disztribúció kimutatására, mely jól ábrázolja a NIS szerepét jód gyomornedvben történő szekréciójában. Továbbjutva a duodenum lumenébe az apicalisan elhelyzekedő NIS segítségével ismét visszakerül a véráramba. Végül a vesével választódik ki glomerulus filtráció után. Munkacsoportunknak elsőként sikerült a NIS apikális expresszióját igazolnunk humán duodenum entrocytákban.

Elsőként vizsgáltuk a PD-L1 és NIS expressziót pajzsmirigyrák esetén. Nem találtunk korrelációt nyirokcsomó áttétes PTC daganatokban NIS és PD-L1 expresszió között.

Ebből arra következtethetünk hogy a PD-L1 intrinsic jelátvitele vélhetően nincs befolyással a NIS expresszióra, plazmamembrán targetálásra.

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Nyilvános idéző összesen: 1, Független: 1, Függő: 0, Nem jelölt: 0

Levay, B ; Boer, A ; Kocsis, A ; Agocs, L

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Nyilvános idéző összesen: 25, Független: 23, Függő: 2, Nem jelölt: 0

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Nyilvános idéző összesen: 5, Független: 5, Függő: 0, Nem jelölt: 0

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Nyilvános idéző összesen: 2, Független: 2, Függő: 0, Nem jelölt: 0

Agócs, László ; Lévay, Bernadett ; Kocsis, Ákos ; Szabó, Györgyi ; Gamal, Eldin Mohamed ; Rojkó, Lívia ; Sándor, József ; Wéber, György

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Szabó, Györgyi ✉ ; Gamal, Eldin Mohamed ; Sándor, József ; Ferencz, Andrea ; Lévay, Bernadett ; Csukás, Domokos ; Dankó, Titanilla ; Wéber, György

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Szakcikk (Folyóiratcikk) | Tudományos[2460478] [Egyeztetett]

Nyilvános idéző összesen: 2, Független: 0, Függő: 2, Nem jelölt: 0

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Szakcikk (Folyóiratcikk) | Tudományos[3110383] [Nyilvános]

Nyilvános idéző összesen: 1, Független: 1, Függő: 0, Nem jelölt: 0

Kocsis, A ; Markóczy, Z ; Agócs, L ; Molnár, M ; Fillinger, J ; Lévay, B ; Vadász, P

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Nyilvános idéző összesen: 2, Független: 2, Függő: 0, Nem jelölt: 0

Kocsis, A ; Agocs, L ; Kostic, S ; Torok, K ; Molnar, M ; Levay, B ; Toth, F ; Vadasz, P ; Renyi-Vamos, F
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Bilateralis endoscopos thoracalis sympathectomia (ETS) palmaris és axillaris hyperhydrosis esetén - 22 eset összefoglalása. Egynapos sebészeti lehetőség a mellkassebészetben?
MAGYAR SEBÉSZET 65 : 5 pp. 380-382. , 3 p. (2012)
Rövid közlemény (Folyóiratcikk) | Tudományos[2161398] [Nyilvános]
Nyilvános idéző összesen: 3, Független: 3, Függő: 0, Nem jelölt: 0

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Lévay, B ; Agócs, L ; Heiler, Z ; Kocsis, Á ; Csekeő, A

Primer suppuratív costochondritis sebészi kezeléséről 4 sikeresen kezelt esetünk kapcsán
MAGYAR SEBÉSZET 63 : 4 pp. 228-228. , 1 p. (2010)
Absztrakt / Kivonat (Folyóiratcikk) | Tudományos[32171008] [Nyilvános]

Agócs, László ; Kocsis, Ákos ; Tamás, Róbert ; Lévay, Bernadett ; Csekő, Attila
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Lóderer, Zoltán ; Kovács, István ; Bognár, Gábor ; Bulyovszky, István ; Győri, Sándor ; Kovács, Gyula ; Lévay, Bernadett ; Tamás, Róbert
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Absztrakt / Kivonat (Folyóiratcikk) | Tudományos[32185029] [Nyilvános]

Agócs, L ; Heiler, Z ; Kocsis, Á ; Lévay, B ; Csekeő, A
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Absztrakt / Kivonat (Folyóiratcikk) | Tudományos[32184999] [Nyilvános]

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Nyilvános idéző összesen: 2, Független: 2, Függő: 0, Nem jelölt: 0

Kocsis, A ; Agocs, L ; Kostic, S ; Levay, B ; Torok, K ; Renyi-Vamos, F
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Nyilvános idéző összesen: 3 | Független: 3 | Függő: 0 | Nem jelölt: 0 | Scopus jelölt: 2 | WoS/Scopus jelölt: 2 | DOI jelölt: 3

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Agócs, László ; Lévay, Bernadett ; Kocsis, Ákos ; Szabó, Györgyi ; Gamal, Eldin Mohamed ; Rojkó, Lívia ; Sándor, József ; Wéber, György

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Nyilvános idéző összesen: 1 | Független: 1 | Függő: 0 | Nem jelölt: 0 | WoS jelölt: 1 | Scopus jelölt: 1 | WoS/Scopus jelölt: 1 | DOI jelölt: 1

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Zárolt Közlemény:32607146 Admin láttamozott Forrás Folyóiratcikk (Jelentés) Tudományos

Agócs, László ; Lévay, Bernadett ; Boér, András ; Elek, Jenő
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Vajda, A ; Lévay, B ; Tamás, R ; Baló-Banga, JM
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Lévay, B ; Boér, A ; Kocsis, Á ; Agócs, L
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Közlemény:32171008 Nyilvános Forrás Folyóiratcikk (Absztrakt / Kivonat) Tudományos

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Lévay, B ; Furka, I ; Bráth, E ; Takács, EI ; Schneider, F ; Mikó, I. ; Gamal, E.M.
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Közlemény:32185029 Nyilvános Forrás Folyóiratcikk (Absztrakt / Kivonat) Tudományos

Kiss, A ; Zelenai, F ; Lévay, B ; Oberna, F
Regionális anesztéziával végzett pajzsmirigy műtétekkel szerzett kezdeti tapasztalataink intézetünkben
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Közlemény:32187976 Admin láttamozott Forrás Folyóiratcikk (Absztrakt / Kivonat) Tudományos

Lévay, B ; Révész, M ; Oberna, F
Heg nélküli pajzsmirigyműtét - TOETVA

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Közlemény:32187981 Admin láttamozott Forrás Folyóiratcikk (Absztrakt / Kivonat) Tudományos

Lévay, Bernadett ; Révész, Mónika ; Oberna, Ferenc
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Közlemény:32546621 Admin láttamozott Forrás Folyóiratcikk (Absztrakt / Kivonat) Tudományos

Levay, Bernadett ; Oberna, Ferenc
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Közlemény:33138985 Admin láttamozott Forrás Folyóiratcikk (Absztrakt / Kivonat) Tudományos

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Közlemény:34343416 Nyilvános Forrás Folyóiratcikk (Absztrakt / Kivonat) Tudományos

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Közlemény:32153412 Nyilvános Forrás Egyéb (Nem besorolt) Tudományos

Herczeg, Adrienn ; Fodor, István ; Zámbó, Orsolya ; Koltai, Pál ; Koltai, László ; Bártfai, Réka ; Doleviczényi, Zoltán ; Lévay, Bernadett ; Boér, András ; Remenár, Éva

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Közlemény:32156209 Nyilvános Forrás Egyéb (Nem besorolt) Tudományos

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11. Appendix

Heg nélküli pajzsmirigyműtét – a TOETVA mint új eljárás a hazai pajzsmirigysebészetben

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Országos Onkológiai Intézet, Fej-nyaki Daganatok Multidiszciplináris Központ, Budapest

Bevezetés és célkitűzés: A pajzsmirigyműtétek során a nyakon jól látható és nehezen takarható heg keletkezik, mely a páciensek életminőségét hosszú távon befolyásolhatja. Az elmúlt két évtizedben számtalan, minimálisan invazív műtéti behatolást dolgoztak ki, amelyek méretben csökkentették, vagy kevésbé látható régióba helyezték a pajzsmirigyműtétek hegeit. A módszerek sokszínűsége azt jelzi, hogy egyik eljárás sem tudta megfelelően biztosítani az elvárt klinikai és kozmetikai eredményt. A természetes testnyílásokon keresztül végzett műtétek látható heg nélküli gyógyulást eredményeznek. A szájüregi behatolásból kidolgozott műtétek közül a szájon (vestibulum oris) keresztüli thyreoidectomia (TOETVA – transoral endoscopic thyroidectomy vestibular approach) bizonyult a legbiztonságosabb és legjobb eredményt adó műtéti eljárásnak. Indikációs területét a kisebb méretű cisztás pajzsmirigylebenyek, göbös lebenyek, kisebb méretű papillaris carcinoma, valamint a mellékpajzsmirigy-adenoma adják.
Módszer: Az Országos Onkológiai Intézet Fej-nyaki Daganatok Multidiszciplináris Központjában 2018. 06. 12. és 2020. 02. 18. között 7 betegen végeztünk pajzsmirigyműtétet szájon keresztüli behatolásból, endoszkópos technikával. A szövettani vizsgálat 4 esetben papillaris carcinomát, 2 esetben follicularis adenomát, illetve 1 esetben benignus kolloid göböt véleményezett. Az 10–30 mm-es képletek eltávolítása 1 esetben isthmectomiával, 6 esetben lobectomiával történt.
Eredmények: Műtét során 2 esetben kényszerültünk vérzés miatti konverzióra. Az 5, endoszkópos műtét végén drént nem helyeztünk be, betegeinket az 1. posztoperatív napon hazabocsátottuk. A két, konvertált műtétes pácienst a 2. posztoperatív napon, a nyaki drén eltávolítását követően emittáltuk. A daganatok eltávolítása a hisztológia alapján megfelelt az onkológiai elveknek, a nervus recurrens sérülését vagy egyéb szövődményt nem észleltünk. Az átlagos műtéti idő 127 perc volt.
Következtetés: A TOETVA a pajzsmirigy-eltávolítás egyetlen olyan műtéti módszere, amely külső heggel nem jár, keloidképződést nem okoz. 15–20 műtétben adják meg a tanulási fázist, mely után a műtéti idő csökken. Biztonságos és eredményes kivitelezéséhez azonban nagyszámú nyitott pajzsmirigyműtétet végzett, endoszkópos sebészetben is gyakorlott specialista szükséges.
Orv Hetil. 2020; 161(41): 1764–1768.

Kulcsszavak: (TOETVA) transoral endoscopic thyroidectomy vestibular approach, pajzsmirigyműtét

Thyroid surgery without scars – TOETVA as a new surgical procedure of the thyroid

Introduction and objective: In thyroid surgery, it is a very important issue to maintain good cosmesis of the scar which can always be visible. Even smaller incisions have been utilized in order to improve satisfaction of the patient. In the last decades, new endoscopic techniques were applied using breast or axillary approach with unfavourable cosmetic outcome. In the last couple of years, a new endoscopic technique was developed known as transoral endoscopic thyroidectomy vestibular approach (TOETVA) which is suitable for patients with small thyroid carcinomas without extrathyroidal extension, for benign nodules up to 4–5 cm, and also for parathyroid adenomas. Metastatic thyroid diseases and large substernal goiters should be operated with conventional open surgery.
Method: From June 2018 to February 2020, a total of 7 patients with thyroid cancer or nodule (size of 1–3 cm) were reviewed in the National Institute of Oncology. Lobectomy was performed in 6 cases, and 1 patient had ithmusectomy.
Results: In 2 cases, conversion was needed due to bleeding from the superior pole. TOETVA patients had no drain placement, and were discharged on the 1st postoperative day. The average operating time was 127 minutes. Injury of the recurrent laryngeal nerve was not detected.

Conclusion: TOETVA is the only scar-free and effective procedure of the thyroid gland, which provides good cosmetic outcome. The long operative procedure time will be shortened with experience after a learning curve of 15–20 operations. The surgeon must be a high-volume surgeon in the field of thyroid surgery.

Keywords: (TOETVA) transoral endoscopic thyroidectomy vestibular approach, thyroid surgery

Lévay B, Oberna F. [Thyroid surgery without scars – TOETVA as a new surgical procedure of the thyroid]. Orv Hetil. 2020; 161(41): 1764–1768.

(Beérkezett: 2020. április 14; elfogadva: 2020. május 4.)

Rövidítések

ABBA = axillo-bilateral-breast approach; BABA = bilateral axillo-breast approach; INM = intraoperatív neuromonitorozás; MIT = (minimally invasive thyroid surgery) minimálisan invazív pajzsmirigysebészet; MIVAT = (minimally invasive video-assisted thyroid surgery) minimálisan invazív, videoasszisztált pajzsmirigysebészet; TOETVA = (transoral endoscopic thyroidectomy vestibular approach) szájüregi behatolásból, szájon keresztül végzett pajzsmirigy-eltávolítás

A pajzsmirigy sebészete különösen fontos részét képezi a fej-nyaki régióban végzett műtéti beavatkozásoknak, egyrészt a jóindulatú elváltozások nagy száma, másrészt a pajzsmirigydaganatok világszerte növekvő incidenciája miatt A korai stádiumú és lokoregionálisan előrehaladott, differenciált pajzsmirigyrák kezelése elsősorban műtéti. A pajzsmirigysebészetben az 5–10 cm-es nyaki metszés, amely kiváló feltárást és biztonságos műtéti feltételeket biztosított, az 1990-es évekig „arany standard"-nak számított. A metszésvezetés egyetlen hátránya, hogy az emberi test legnehezebben takarható régiójában helyezkedik el, ami sebgyógyulási zavar esetén kozmetikai szempontból rendkívül hátrányos. Már *Theodor Kocher*t is esztétikai szempontok vezették, amikor az eredeti vertikális metszés helyett horizontális nyaki metszést alkalmazott [1]. Fehér bőrszínű pácienseken végzett vizsgálat azt mutatta ugyan, hogy az operáltak nagy része általában elégedett a nyaki metszés utáni kozmetikai eredménnyel, de ez a vizsgálat nem terjedt ki az ázsiai és a fekete bőrszínnel rendelkező populációra [2]. A fiatal nőbetegek számára elsősorban a távol-keleti kultúrákban jelent hátrányt a nyaki heg, melyet a közhiedelem ezeken a földrajzi és történelmi területeken a halál jelének tekint [3]. A keloidképződés, mely nem ritka a nyaki régióban, a páciensek életminőségét rontja [4]. Ezen érvek vezettek először a minimálinvazív technikák alkalmazásához, amelyek a heg méretének redukciójával (minimally invasive thyroid surgery [MIT], minimally invasive video-assisted thyroid surgery [MIVAT]) vagy a heg más régióba helyezésével (emlő, mellkas, axilla, a nyak hátsó része) próbáltak kedvezőbb kozmetikai eredményt elérni. A látható heg nélküli technikát végül a természetes testnyíláson keresztül végzett műtétek eredményezték. A transoralis beavatkozások közül a szájtornácon (vestibulum oris) keresztül történő behatolás bizonyult a legoptimálisabb műtéti eljárásnak [5].

Módszer

Az Országos Onkológiai Intézet Fej-nyaki Daganatok Multidiszciplináris Központjában 2018. 06. 12. és 2020. 02. 18. között 7 betegen (5 nő/2 férfi) végeztünk pajzsmirigyműtétet szájon keresztüli behatolásból, endoszkópos technikával. A szövettani vizsgálat 4 esetben papillaris carcinomát, 2 esetben follicularis adenomát, 1 esetben kolloid göböt véleményezett. A 10–30 mm-es daganatok eltávolítása 1 esetben isthmectomiával, 6 esetben lobectomiával történt.

A TOETVA (transoral endoscopic thyroidectomy vestibular approach) indikációs területe a kisebb méretű ciszták vagy göbös lebenyek, melyeknél a göb nagysága nem haladja meg a 4–5 cm-t, illetve kisebb méretű papillaris carcinoma, follicularis adenoma, de a technika mellékpajzsmirigy-adenoma eltávolítására is alkalmas. Ellenjavallatot jelenthetnek az ultrahangvizsgálat során 5–10 cm-nél nagyobb lebenyek, a substernalis struma, az extrathyreoidalis terjedés jeleit mutató és nyaki áttétet adó vagy nyelőcsövet, légcsövet infiltráló pajzsmirigyrákok, valamint a nyaki terület korábbi besugárzása, mely kritériumok egy része a tapasztalat és a gyakorlat gyarapodásával relatívvá válik [6].

A műtétet antibiotikumprofilaxisban (amoxicillin-klavulánsav 1,2 g iv.) lokális dezinficiálás után (klórhexidin 0,2%), nasotrachealis intubálást követően narkózisban végezzük. A beteg a műtőasztalon a fejét extenzióban tartva fekszik, válla alatt felfújható kiemeléssel. A vestibulum orisban 2%-os lidokain-adrenalin infiltrációt követően a középvonalban a frenulum felett az ajak belső felszínén egy 10 mm-es, az első kisőrlő magasságában két 5 mm-es metszést ejtünk. A nervus (n.) mentalis épségét megőrizzük. A középső metszésen át Veres-tűvel a subplatysmalis rétegben hydrodissectiót végzünk kb. 30–50 ml folyadékkal (1 mg adrenalin 500 ml fiziológiás sóoldattal hígítva). A dissectio alsó határa a jugulum, kétoldalt a musculus sternocleidomastoideus. A teret speciálisan erre a célra kifejlesztett, 40 cm hosszú, 8 mm

Eredmények

Az ismertetett technikával 2018 júniusa és 2020 februárja között 7 beteget (5 nő/2 férfi) operáltunk. A műtét során 2 esetben kényszerültünk vérzés miatt konverzióra. Az endoszkópos műtét végén drént nem helyeztünk be, betegeinket az 1. posztoperatív napon, a konvertált műtéteseket a 2. posztoperatív napon, a nyaki drén eltávolítását követően emittáltuk. A preoperatív aspirációs citológiai vizsgálatot minden esetben megerősítette a végleges szövettani eredmény, amely onkológiai szempontból is igazolta a daganatok biztonságos eltávolítását. A posztoperatív szakban műtéti feltárást igénylő gyulladást, folyadékretenciót, n. recurrens sérülést nem észleltünk. Az átlagos műtéti idő 127 perc volt. A késői posztoperatív szakban a minimális nyaki fájdalom és az alsó ajak átmeneti zsibbadása minden esetben megszűnt. Hypocalcaemia nem fordult elő *(1. táblázat)*.

Megbeszélés

A nyakon végzett pajzsmirigyműtétek hegének komplikációja, valamint a sebészi invazivitás csökkentésére való törekvés vezetett egyre újabb műtéti technikák kifejlesztéséhez. Az endoszkóppal asszisztált pajzsmirigyműtétek lehetővé tették a metszés méretének csökkentését [7]. Az ABBA- (axillo-bilateral-breast approach), illetve BABA- (bilateral axillo-breast approach) eljárás nagy műtéti feltárást igényelt, és a komplikációk relatíve magas aránya miatt nem terjedt el [8, 9]. A műtéti robot alkalmazása – bár bizonyos előnyökkel jár a hagyományos endoszkópos, minimálisan invazív technikákkal szemben – az eszköz hozzáférhetősége miatt korlátozott [10]. A teljes endoszkópos transoralis műtétet korábban a nyelv alatti behatolásból végezték, de számos észlelt szövődmény – mint például a n. lingualis sérülése – miatt nem folytatták [1]. *Anuwong és mtsai* számos, állaton és kadáveren végzett TOETVA-műtét után betegeiken is alkalmazták a szájtornácon keresztüli technikát [5]. Számos pajzsmirigycentrumban végeznek nyaki endoszkópos műtéteket. A pajzsmirigy és mellékpajzsmirigy eltávolításán kívül paratrachealis nyaki blokkdissectio is elvégezhető TOETVA-feltárásból. A TOETVA mint szájüregből kezdett műtét lehetséges szövődménye a bakteriális fertőzés. A szájüregben számos Gram-pozitív aerob és anaerob patogén törzs fordul elő, míg a nyak subplatysmalis rétege sterilnek számít. A releváns szakirodalomban eddig reoperációt igénylő fertőzésről vagy tályogról nem számoltak be a TOETVA-t végző munkacsoportok [11]. A n. recurrens sérülés szintén egy lehetséges komplikáció, csakúgy, mint a kevés nyitott műtétet végző sebészek esetén. Az INM (intraoperatív neuromonitorozás) nem jelent kevesebb idegsérülést *Jitpratoom és mtsai* közleménye szerint sem [12]. *Anuwong* tanulmányából kiderül, hogy a hypoparathyreosis előfordulásának gyakorisága sem tér el a nyitott műtétet végző, a pajzsmirigysebészetben nagy gyakorlattal rendelkező sebészek eredményeitől [13]. Az új műtéti eljárás azon pajzsmirigysebészetben és endoszkópos technikai sajátosságokban jártas kollégáknak ajánlott, akik hisznek az endoszkópos szemléletben, és el tudják hárítani az akut intraoperatív szövődményeket [14].

Következtetés

Az ismertetett új technika az elmúlt évtizedekben egyre nagyobb népszerűségnek örvendő endoszkópos beavatkozások egyike, mely gyakorlott kézben hegmentes, a nyitott műtétekhez hasonlóan alacsony szövődményrátájú megoldás megfelelően szelektált beteganyagon. A TOETVA-t nagy számban végző centrumokban az átlagos műtéti idő rövidül: lobectomia esetén 76 perc, totális thyreoidectomia esetében 124 perc.

Hazánkban – a módszert a meghonosító külföldi csapat támogatásával elkezdve – az Országos Onkológiai Intézetben végezzük a műtéteket, melyeket kiválasztott beteganyagon, megfelelő indikációval, az onkológiai elveket szem előtt tartva egyre nagyobb számban kívánunk alkalmazni.

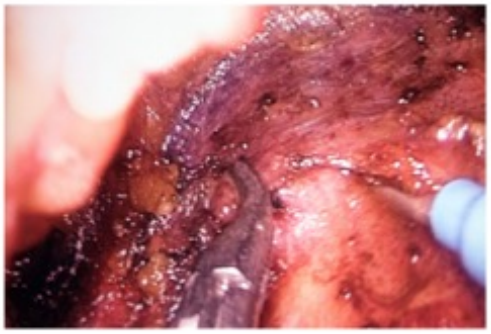
Anyagi támogatás: A szerzők a közlemény megírásával kapcsolatban anyagi támogatásban nem részesültek.

1. táblázat | TOETVA-műtéten átesett betegek adatai

	Kor	Nem	Göbméret (aspirációs citológia)	Opus	Műtéti idő	Műtét	Nervus recurrens sérülés/ hypocalcaemia
1.	49 év	Nő	29 mm adenoma folliculare	Lobectomia l.d.	142 min	Konverzió	0
2.	70 év	Nő	34 mm kolloid göb	Lobectomi l.d.	110 min	TOETVA	0
3.	41 év	Nő	28 mm adenoma folliculare	Lobectomia l.s.	120 min	TOETVA	0
4.	42 év	Férfi	15 mm papillaris carcinoma	Lobectomia l.d.	180 min	TOETVA	0
5.	43 év	Nő	9 mm papillaris carcinoma	Isthmectomia	120 min	TOETVA	0
6.	56 év	Nő	8 mm papillaris carcinoma	Lobectomia l.d.	210 min	TOETVA	0
7.	48 év	Férfi	15 mm papillaris carcinoma	Lobectomia l.d.	140 min	Konverzió	0

TOETVA = transoral endoscopic thyroidectomy vestibular approach

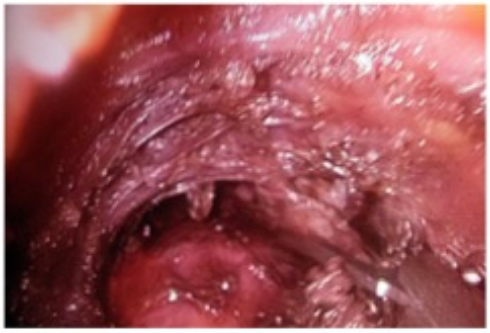
1. ábra | A behatolás-portok helyzete



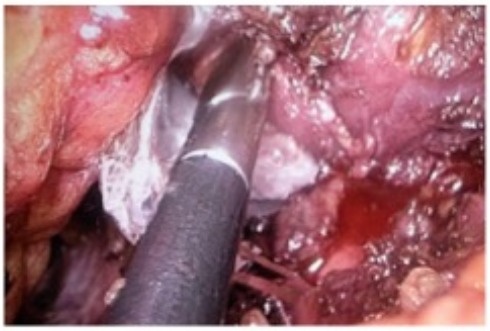
2. ábra | A linea alba behasítása

3. ábra | A felső pólus képleteinek ellátása

vastag kör átmérőjű, végén kb. babnyi megvastagított résszel rendelkező fémeszközzel disszekáljuk . A 10 mm-es trokár helyét peánnal tágítjuk, majd a mandibula felett a subplatysmalis rétegbe jutunk. Ezután behelyezzük a 10 mm-es műanyag trokárt, melyen át a 0 vagy 30 fokos optikát vezetjük be, amely az endoszkópos toronyhoz



4. ábra | A jobb oldali lebeny kifejtése



5. ábra | A jobb oldali lebeny eltávolítása

csatlakozik. A craniocaudalis irányú nézet segítségével a n. recurrens identifikálása könnyebb, mint a hagyományos műtét esetén. A trokárra csatlakoztatjuk a CO_2-insufflatort, a nyomást 6 Hgmm-re állítjuk. Szemellenőrzés mellett a 2 oldalsó műanyag segédtrokár kerül a subplatysmalis rétegbe *(1. ábra)*. A hasi endoszkópos sebészetben használatos eszközöket alkalmazzuk. 'Hook' segítségével a műtéti területen a szálagokat oldjuk. Azonosítjuk az egyenes nyakizmokat, majd a linea alba behasítása következik *(2. ábra)*. Ekkor optimális esetben a lebeny látótérbe kerül. A jobbkezes sebészeknek a tanulási fázisban a jobb oldali pajzsmirigylebeny eltávolítását javasoljuk. Az egyenes nyakizmokat tompán leválasztjuk a lebenyről, majd transcutan öltés segítségével eltartjuk. Az isthmust lepreparáljuk a tracheáról, majd megfogva a felső pólus érképleteit hozzuk látótérbe, nagy energiájú égető és vágó endoszkópos eszköz segítségével ezeket ellátjuk *(3. ábra)*. Identifikáljuk a mellékpajzsmirigyeket és a n. recurrenst is. A lebenyt tompa preparálással az ágyából kifejtjük, az arteria thyreoidea inferiort szintén ultrahangkészülékkel égetjük és vágjuk át *(4. ábra)*. A lebenyt 'endobag'-be helyezve a középső trokárral együtt vesszük ki *(5. ábra)*.

Szerzői munkamegosztás: A szerzők egyenlő mértékben járultak hozzá a közlemény elkészítéséhez. A cikk végleges változatát mindkét szerző elolvasta és jóváhagyta.

Érdekeltségek: A szerzőknek nincsenek érdekeltségeik.

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„Perseverentia vincit."
(Az állhatatottság győzedelmeskedik.)

Nyaki áttétet adó papillaris pajzsmirigyrák sebészi kezelésének eredményei – 5 éves anyagunk feldolgozása

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A papillaris pajzsmirigyrák prognózisát a gyakori nyaki nyirokcsomóáttét-képzés befolyásolja. Sebészi kezelésük minősége a betegek túlélését és a recidíva előfordulási gyakoriságát is meghatározza. Az Országos Onkológiai Intézet Fej-Nyaki Daganatok Multidiszciplináris Központjában a fej-nyak sebész szerzők által 2013 és 2018 között operált, nyaki áttétet adó papillaris carcinomás betegek adatait vizsgáltuk. 130, nyaki áttétet adó papillaris pajzsmirigy-carcinomás beteg esetében az ATA (American Thyroid Association) 2015 . évi irányelvei alapján teljes pajzsmirigy-eltávolítást és nyaki nyirokcsomó-dissectiót végeztünk. Az eltávolított anyagokat szövettani feldolgozásra küldtük, vizsgáltuk a nyirokcsomóáttét(ek) arányát az életkor, a nem, a tumor-multifokalitás, a kétoldaliság, a tokon kívüli terjedés, a nyirok-, érinvázió függvényében. Elemeztük a műtét után fellépő szövődményeket is. 43 betegnél thyreoidectomia, totális és centrális nyaki dissectio (VI. régió), 87 esetben centrális (VI. régió) és laterális (II–V. régió) nyaki dissectio történt. Átmeneti (6 hónapon belül normalizálódó) hypocalcaemia 30 betegnél (23%), permanens hypocalcaemia 4 betegnél (3%) fordult elő. Átmeneti nervus recurrens bénulás 12 esetben (9,2%), permanens bénulás 3 (2,3%) esetben történt. A szövettani értékeléskor érbetörés és tokinvázió 75 betegnél (57,7%), nyirokér-invázió 63 betegnél (48,5%), Hashimoto-thyreoiditis 51 betegnél (39,2%) igazolódott. Microcarcinoma (1 cm-nél kisebb daganat) 43 esetben fordult elő (33%). Az eltávolított nyirokcsomók átlagosan 48%-a volt áttétes. Ez csak a tumorérettel mutatott szignifikáns korrelációt, az életkorral nem találtunk összefüggést. Az oldaliság, a többgócúság, valamint a tok-, nyirokér- és érinvázió, a Hashimoto-status és a beteg neme nem mutatott összefüggést az áttétes nyirokcsomók számával. A túlélést befolyásolta a tok-, ér- és nyirokér-invázió, valamint a tumorméret is. A nyaki áttétet adó, differenciált pajzsmirigyrákos beteganyagunk kezelésében a kivizsgálási protokollt követően a teljes pajzsmirigy-eltávolítás és a megfelelő régiókat tartalmazó nyaki dissectio döntő fontosságú, a radiojód-terápiával kiegészítve az irányelveknek megfelelő kezelési modul. A pajzsmirigydaganat a leggyakoribb endokrin daganatos megbetegedés, melynek sebészi kezelése a multidiszciplináris terápia legfontosabb eleme. 5 év alatt operált, nyaki áttétet is adó, differenciált pajzsmirigyrákos beteganyagunkat feldolgozva ismertetjük eredményeinket az olvasóval.
Orv Hetil. 2024; 165(3): 83–88.

Kulcsszavak: differenciált pajzsmirigyrák, papillaris rák, nyirokcsomóáttét, nyirokcsomó-dissectio

Results of surgical treatment of papillary thyroid cancer with lymph node metastasis – review of our data in a 5-year period

Papillary thyroid cancer carries an excellent prognosis. Although long-term survival rates are high, regional lymph node metastases are common. Surgical management of thyroid cancer and cervical lymph nodes are ready to define the survival. This article focuses on observational data of metastatic papillary thyroid cancer patients operated in the Head and Neck Multidisciplinary Cancer Center of the National Institute of Oncology between 2013 and 2018. In the National Institute of Oncology, consecutive series of 130 metastatic papillary thyroid cancer patients were treated by the two authors between 2013 and 2018. Thyroidectomy and central neck dissection (level VI) were per-

Megbeszélés

A pajzsmirigyrák a leggyakoribb endokrin daganatos megbetegedés, a protokoll szerint elsődlegesen sebészileg kezelendő. Vékonytű-aspirációs biopszia vagy intraoperatív fagyasztásos vizsgálat igazolja a nyirokcsomó-érintettséget, mely befolyásolja a műtéti tervet [9]. *Wong és mtsai* egyetértenek abban, hogy a laterális nyaki nyirokcsomóáttét idősebb betegek esetében rosszabb túlélést jelent, mint a centrális nyirokcsomóáttétek [10]. *Randolph és mtsai* hangsúlyozták a metastaticus nyirokcsomók számának és méretének korrelációját a recidíva kialakulásával. Kisebb volt a kiújulás kockázata az 5 mm alatti érintett nyirokcsomók esetében, mely több mint 20–30%-ban fordult elő [11]. A nagy felbontású nyaki ultrahangvizsgálat az elsődleges a nyaki áttétet adó pajzsmirigyrák és a jóindulatú elváltozások differenciáldiagnosztikájában, csakúgy, mint a 2–3 mm-es nagyságú lokoregionális áttétek kimutatásában. A nem tapintható nyaki nyirokcsomóáttétek a legtöbb esetben ultrahangvizsgálattal kimutathatók [12]. *Won és mtsai* vizsgálták a nyaki nyirokcsomó-dissectiók optimális kiterjesztését, és megállapították, hogy a jól differenciált pajzsmirigyrákok esetében az aspirációval igazolt nyaki áttétek kezelésében a szelektív nyaki dissectio elfogadott eljárás, és beteganyaguk alapján arra a következtetésre jutottak, hogy a laterális kompartmentekbe áttétet adó, jól differenciált pajzsmirigyrákos betegek műtéte során a IIa, III., IV., V., VI. régiót mindig el kell távolítani, minimálisra csökkentve ezáltal a kiújulás kockázatát [13]. A másik sarkalatos kérdés a profilaktikus dissectiók létjogosultsága. A centrális régió reoperáció során történő eltávolításakor megnőhet a n. recurrens, illetve a mellékpajzsmirigyek sérülésének aránya. Valóban, a hegszövet, az ödéma megváltoztathatja az anatómiai viszonyokat, amelyek a kevésbé gyakorlott sebész számára komoly kihívást jelenthetnek nagyobb szövődményrátával. Sok munkacsoport számol be rutinszerűen végzett profilaktikus centrális nyaki nyirokcsomó-dissectio után jelentkező átmeneti hypocalcaemiáról (14–60%), tartós hypocalcaemiáról (3–11%), átmeneti hangszalagbénulásról (3–7%), tartós hangszalagbénulásról (0–4%) [14]. *Agrawal és mtsai* irányelveket fogalmaztak meg a papillaris rákok centrális nyaki dissectiójának indikációjában. Ez segítheti a sebészt a műtéti javallat, valamint a műtéti terv felállításában [15]. Profilaktikus nyirokcsomó-eltávolításnak kizárólag speciális esetekben van helye. Az ATA-irányelvek nagy kockázatú differenciált pajzsmirigyrákos betegek esetében javasolják a profilaktikus centrális nyirokcsomók kimetszését, így a T3-, T4-tumorméret, illetve a laterális nyirokcsomó-régiókban előforduló igazolt áttét esetében. Ezeket figyelembe véve centrális nyaki dissectiót kizárólag nagy tapasztalattal rendelkező sebész végezzen a szövődmények minimalizálása érdekében [6]. *Resende de Paiva és mtsai* 64 628 beteg esetében vizsgálták a Hashimoto-thyreoiditis és a pajzsmirigyrák közötti kapcsolatot. A Hashimoto-betegek 9%-ában fordult elő papillaris pajzsmirigyrák, míg a papillaris pajzsmirigyrákos betegek 19%-ában volt igazolható Hashimoto-thyreoiditis [16]. A *Shaha* vezette munkacsoport az extrathyreoidalis terjedést mutató, lokálisan invazív, agresszív típusú differenciált rákok esetében írták le a távoli áttét kialakulásának megnövekedett esélyét [17]. Hazai szempontból érdekes kérdést vetett fel a *Kovács és mtsai* által T1–2-es stádiumú, differenciált pajzsmirigyrák miatt totális thyreoidectomián átesett 81 beteg szövettani lelete, miszerint az ellenoldali lebenyben lévő, szövettani lelettel igazolt, de ultrahangvizsgálattal nem észlelt microcarcinomák léte megváltoztatja az utókezelés tervét [18].

Következtetés

A jól differenciált pajzsmirigyrák gyakori, de jó prognózisú betegség, melynek felfedezésében kiemelkedő fontossága van az ultrahang-diagnosztikának, illetve a sebészi beavatkozás döntő szerepet kap a terápiás algoritmusban [19]. Beteganyagunkban a posztoperatív szövődményráta a nemzetközi adatokkal összevetve is kicsinek mondható.

Relatíve kis méretű daganat, vagyis a microcarcinoma 43 esetben (33%) adott nyaki áttétet. Az eltávolított nyirokcsomóblokkoknak a 48%-a volt áttétes, mely csak a tumorérettel mutatott szignifikáns korrelációt. A pajzsmirigydaganatok kezelése a multidiszciplinaritás miatt elsősorban centrumokban végzendő. Nagy betegszámot tartalmazó anyagunk feldolgozását követően bemutatjuk a nyaki áttétet adó differenciált rákos betegek hazai ellátását.

Anyagi támogatás: A közlemény megírása anyagi támogatásban nem részesült.

Szerzői munkamegosztás: L. B.: Operáló orvos, a cikk megírása. B. A.: Operáló orvos. K. A.: Adatgyűjtés, műtéti asszisztencia. T. E., P. I.: Szövettani leletezés. O. F.: A kézirat javítása. F. G.: Statisztika készítése. D. O.: A betegek kivizsgálása, endokrinológiai-onkológiai gondozás. A cikk végleges változatát valamennyi szerző elolvasta és jóváhagyta.

Érdekeltségek: A szerzőknek nincsenek érdekeltségeik.

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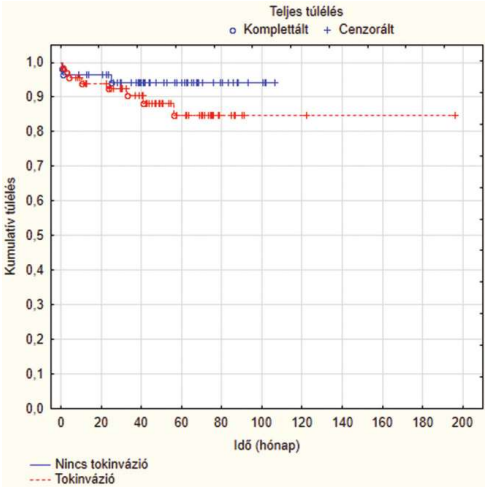
Microcarcinoma 43 esetben igazolódott (33%). Sebészi intervenciót igénylő nyirokfolyás 3, n. accessorius sérülés 1 esetben fordult elő. A követett beteganyagunkban 2 beteg hunyt el, az egyik esetben primer tüdőtumor, a másik esetben cardialis ok miatt. Összehasonlítottuk a tok-, nyirokér-, vascularis inváziót a tumorérettel, a metastaticus nyirokcsomók számával, illetve a betegek életkorával. Idősebb betegek esetében gyakoribb volt a nyirokér-, illetve a vascularis invázió. Az eltávolított nyirokcsomók átlagosan 48%-a volt áttétes (tartomány: 4–100%). Ez csak a tumorérettel mutatott szignifikáns korrelációt (p = 0,0212, R = 0,2018), az életkorral nem találtunk összefüggést (p = 0,2406, mindkettő Spearman-féle rangkorreláció). Az oldaliság (p = 0,4857), a multiplicitás (p = 0,1913), valamint a tokinvázió (p = 0,4579), az érinvázió (p = 0,7072) és a nyirokér-invázió (p = 0,6504), a Hashimoto-status (p = 0,9811) és a nem (p = 0,3413) sem jelezte előre az áttétes nyirokcsomók relatív számát (Mann–Whitney U-teszt) *(1. táblázat)*. A tok-, ér- és nyirokér-invázó összefüggést mutatott a tumor méretével, az áttétes nyirokcsomók számával, valamint az idősebb korral. A Hashimoto-thyreoiditis a nagyobb tumorérettel korrelál. Idősebb korban az ér- és nyirokér-invázió gyakrabban fordult elő, mint a fiatalabb korosztályban.

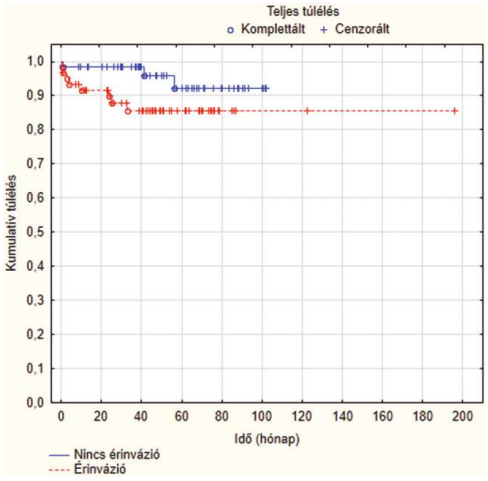
A túlélés rövidebb volt a tokinvázió (p = 0,0255) *(1. ábra)*, az érinvázió (p = 0,0078) *(2. ábra)* és a nyirokér-invázió (p = 0,0416) *(3. ábra)* esetén, illetve összefüggést mutatott a nagyobb tumorérettel (p<0,001) is.

1. táblázat | A tumorméretnek, az áttétes nyirokcsomók számának és az életkornak a hatása a tok-, nyirokér-, érinvázióra és a Hashimoto-thyreoditis-statusra

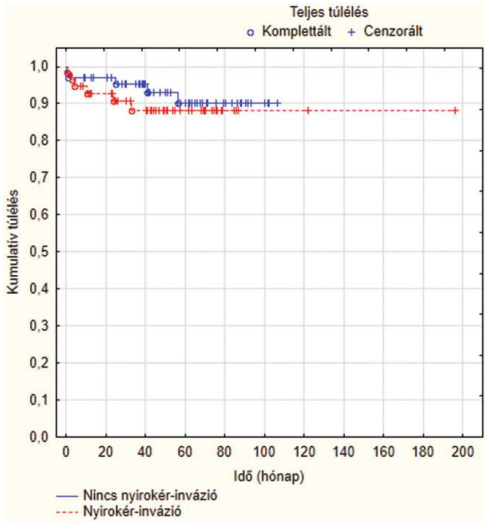
p-Érték (Mann–Whitney U-teszt)	Tokinvázió	Nyirokér-invázió	Érinvázió	Hashimoto-thyreoiditis
Tumorméret	<0,001	<0,001	<0,001	0,0242
A metastaticus nyirokcsomók száma	0,0151	0,0162	0,0133	0,5614
Életkor	0,0206	<0,001	<0,001	<0,001



1. ábra | Teljes túlélés tokinvázió nélküli és tokot áttörő tumorok esetén



2. ábra | Teljes túlélés érinvázió nélküli és az ereket áttörő tumorok esetén



3. ábra | Teljes túlélés nyirokér-invázió nélküli és a nyirokereket áttörő tumorok esetén

helye. Néhány megnagyobbodott vagy kórosnak vélt nyirokcsomó eltávolítása („berry picking") helytelen, nem megfelelő műtéti megoldás [7].

Anyagok és módszerek

Az Országos Onkológiai Intézet Fej-Nyaki Daganatok Multidiszciplináris Központjában 2013 és 2018 között 130, nyaki nyirokcsomóáttétet adó papillaris carcinomás beteget kezeltünk. A műtét feltétele a preoperatív ultrahangvizsgálat és a vékonytű-aspirációs biopszia által vagy intraoperatív fagyasztással igazolt nyaki áttét volt. A teljes pajzsmirigy eltávolítása mellett centrális nyaki dissectio vagy centrális és laterális nyaki dissectio történt. A műtét előtt laborvizsgálat (FT3, FT4, TSH), valamint nagy felbontású nyaki ultrahangvizsgálat zajlott. A nyaki ultrahangvizsgálat a pajzsmirigy-elváltozások felismerésének az alapja, kombinálva a vékonytű-aspirációs biopsziával. Kiegészítő képalkotó vizsgálatnak lokoregionális vagy távoli áttét gyanúja esetén van létjogosultsága, amikor az ultrahangvizsgálat nem tudja megítélni a primer daganat vagy áttét kiterjedését, az erekhez való pontos viszonyát. Pre- és posztoperatív gégészeti vizsgálattal minden beteg esetében ellenőriztük a hangszalagok mozgását. A műtéti szövődményeket – mint az átmeneti vagy végleges hangszalagbénulás, átmeneti vagy végleges hypoparathyreosis – is vizsgáltuk (hypocalcaemia: <2,1; normálérték 2,15–2,65 mmol/l; véglegesnek számít, ha 6 hónapon túl sem normalizálódik az érték). A kontroll laboratóriumi vizsgálatok FT3-, FT4-, Tg-, TgAb- és TSH-meghatározást tartalmaztak. A betegek hormonszubsztitúcióját levotiroxin (1,8 µg/kg) adásával végeztük a Magyar Endokrinológiai és Anyagcsere Társaság ajánlása alapján [8].

Műtétek

A műtétek során teljes pajzsmirigy-eltávolítást és centrális vagy centrális és laterális nyirokcsomó-dissectiót végeztünk. Minden műtét során a n. recurrensek azonosítására, valamint a műtéti területen lévő mellékpajzsmirigyek megkímélésére törekedtünk. Amennyiben a mellékpajzsmirigy(ek) eltávolításra kerültek, azokat a műtét végén apró (kb. 1 mm-es) szeletekre vágva, fiziológiás sóoldatba keverve, a m. sternocleidomastoideus izomba implantáltuk/injektáltuk. A centrális nyaki dissectio során a praelaryngealis, praetrachealis, valamint mindkét oldali paratrachealis nyirokcsomók eltávolítására törekedtünk. A laterális nyaki nyirokcsomók eltávolítása során a dissectio kiemelkedő fontosságú része a n. auricularis magnus, a n. accessorius, a n. hypoglossus, a n. vagus, az a. carotis communis azonosítása, megőrzése, csakúgy, mint a vena (v.) jugularis internáé, azonban előfordult az áttét nagysága és elhelyezkedése vagy infiltráló jellege miatt a véna lekötése. A supraclavicularis áttétek kipreparálásakor fontos megemlíteni a bal oldalon a ductus thoracicus sérülésének lehetőségét. A mély nyaki fasciát elérve a supraclavicularis részen a nyirokcsomókat lekötések után távolítottuk el a nyirokfolyás elkerülése céljából. A szérumkalciumszint ellenőrzése az 1. posztoperatív napon történt, hypocalcaemia esetén kalcium-, illetve D-vitamin-pótlást indítottunk.

Radiojód-kezelés

Minden beteg részesült radiojód-terápiában, melyet a műtét után 8–10 héten belül kezdtünk el. Célja, hogy eliminálják a maradék pajzsmirigyállományt, valamint a kisebb daganatos reziduális gócokat, csökkentve a recidíva kialakulását. A kezelés előtt 3–4 héttel felfüggesztettük a betegek hormonszubsztitúcióját, vagy TSH-stimulációra rekombináns humán tirotropin- (rhTSH, Thyrogen) injekciót kaptak. A poszterápiás teljestest-képalkotó vizsgálatot a kezelés után 4–7 nappal végeztük.

Követés

A betegek utánkövetése 6 havonta nyaki ultrahangvizsgálattal és a Tg, TgAb, TSH, FT4 szérumszintjének ellenőrzésével történt.

Statisztikai analízis

Mann–Whitney U-tesztet használtunk (Statistica 12.5, StatSoft, Tulsa, OK, USA) a tok-, nyirok- és érinvázió, a Hashimoto-status, a nyirokcsomó-dissectio, valamint az életkor, a tumornagyság és a metastaticus nyirokcsomók közötti összefüggések vizsgálatára. Log-rank teszttel vizsgáltuk a teljes túlélést a tok-, nyirok-, érinvázió, a Hashimoto-status, a nyirokcsomó-dissectio, az életkor, a szövettan és az oldaliság függvényében. Cox-regresszióval elemeztük a tumorméretnek, az áttétes és nem áttétes nyirokcsomók számának és az életkornak a hatását a teljes túlélésre.

Eredmények

2013. január és 2018. december között 130, nyirokcsomóáttétet adó papillaris pajzsmirigyrákos beteg került műtétre (85 nő és 45 férfi). Átlagéletkoruk 47,6 év (19–90) volt. 43 beteg esetében thyreoidectomia és centrális nyaki dissectio, míg 87 betegnél centrális és laterális nyaki kimetszés is történt. Az átlagosan eltávolított nyirokcsomók száma 13 volt (1–48); nem vettük külön a csak centrális és a centrális és laterális régiók együttes dissectiója során eltávolított nyirokcsomók számát. Átmeneti (6 hónapon belül normalizálódó) hypocalcaemia 30 betegnél, permanens hypocalcaemia 4 betegnél fordult elő. Átmeneti n. recurrens bénulás 12, permanens bénulás 3 esetben történt. Érbetörés és tokinvázió 75 betegnél (57,7%), nyirokér-invázió 63 betegnél (48,5%), Hashimoto-thyreoiditis 51 betegnél (39,2%) fordult elő.

formed in every case with/without lateral neck dissection (level II–V) according to the ATA (American Thyroid Association) 2015 guidelines. All excised specimens were examined by experienced pathologists. We evaluated the influence of age, gender, tumor multifocality, bilaterality, capsular, vascular, lymphatic invasion on lymph node metastasis. We also analyzed the postoperative complications. 43 patients out of 130 underwent total thyroidectomy with only central lymph node dissection, 87 had dissection on both lateral (level II–V) and central (level VI) lymph nodes. Transient hypocalcemia occurred in 30 patients (23%), permanent hypocalcemia occurred in 4 patients (3%). Transient recurrent laryngeal nerve palsy was diagnosed in 12 (9,2%), permanent in 3 (2,3%) cases. Pathologists revealed vascular and capsular invasion in 75 cases (57.7%). Lymphatic invasion occurred in 63 cases (48.5%), Hashimoto thyroiditis was found in 51 cases (39.2%). Microcarcinoma (tumor size smaller than 1 cm) occurred in 43 cases (33%). 48% of the dissected lymph nodes were metastatic. This was associated only with the size of the primary tumor, but did not correlate with the age. Associations between lymph node metastasis and multifocality, capsular, lymphatic, vascular invasion, Hashimoto thyroiditis or gender were not statistically significant. Survival rate was correlated with capsular, vascular and lymphatic invasion, and also with the tumor size. Total thyroidectomy and adequate lymph node dissection are the key points in the therapy. With completion radioiodine treatment, this is the optimal oncological procedure. Thyroid cancer is the most common endocrine tumor. Adequate surgical intervention is the most important factor of the multidisciplinary therapy. The authors review their 5-year experiences with metastatic papillary thyroid cancer patients.

Keywords: differentiated thyroid cancer, papillary thyroid cancer, lymph node metastasis, neck dissection

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Rövidítések

ATA = (American Thyroid Association) Amerikai Pajzsmirigy-szövetség; FT3 = (free T3) szabad trijód-tironin-frakció; FT4 = (free T4) szabad tetrajód-tironin-frakció; NCCN = (National Comprehensive Cancer Network) Nemzeti Átfogó Rák Hálózat (Egyesült Államok); rhTSH = (recombinant human thyroid-stimulating hormone) rekombináns humán pajzsmirigy-stimuláló hormon; Tg = tireoglobulin; TgAb = (thyroglobulin antibody) tireoglobulin elleni antitest; TSH = (thyroid-stimulating hormone) pajzsmirigy-stimuláló hormon

A rosszindulatú pajzsmirigy-elváltozások incidenciája a 2014–2018-as adatokat tekintve 22,8/100 000 a nők, míg 8/100 000 a férfiak esetében [1]. A papillaris pajzsmirigyrák a leggyakoribb pajzsmirigydaganat, mely a rosszindulatú pajzsmirigy-elváltozások 75%-át, a differenciált rákok 90%-át teszi ki. A kezelt esetek prognózisa kiváló, a 10 éves túlélés 90% feletti [2]. Annak ellenére, hogy lassú növekedési tendenciát mutat, a kihívást mégis a lokoregionális kiújulások kezelése jelenti. Ezért döntő fontosságú és a teljes kezelés meghatározója a műtét [3]. Klinikailag észlelhető nyirokcsomóáttét az esetek 15–30%-ában fordul elő. A nyirokcsomóáttét előfordulása klinikailag negatív esetekben 50%, 10 mm vagy annál kisebb papillaris rák (microcarcinoma) esetében 15–50%. A micrometastasisok előfordulása 80% körüli. A pajzsmirigydaganat tokon kívüli terjedése, a férfinem, az idősebb életkor hajlamosít agresszívabb daganat előfordulására. A nyaki áttét kialakulása szintén rontja a túlélést, elsősorban a centrális, azaz a VI. régióban megjelenő, mivel a pajzsmirigy nyirokelvezetése elsősorban a centrális nyirokcsomókba történik [4]. A pajzsmirigylebenyben lévő daganat elhelyezkedése utalhat a nyirokcsomóáttét valószínű helyére. Az isthmusban, a középső és alsó részen lévő daganatok a centrális, míg a felső pólusban elhelyezkedő daganatok az azonos oldali laterális nyirokcsomóláncba közvetlenül is adhatnak áttétet [5]. A nyaki nyirokcsomó-régiók sebészi anatómiája és kompartmentek szerinti beosztása az American Joint Committee on Cancer és az American Academy of Otolaryngology–Head and Neck Surgery ajánlása alapján történt. A centrális kompartment, melyet sokszor VI-os régiónak neveznek, felső határa a nyelvcsont, laterális határai a nyaki nagyerek, alsó határa az arteria (a.) brachiocephalica. Centrális nyaki dissectión az ezen a területen lévő nyirokcsomók eltávolítását értjük. A laterális nyaki nyirokcsomó-kompartmenteket a II–V. régiók alkotják. A II. régió határai a submandibularis nyálmirigy, a koponyaalap, a musculus (m.) sternocleidomastoideus és az a. carotis bifurcatio (sebészi határ), a nyelvcsont (klinikai határ); a II/a alrégió a nervus (n.) accessorius előtti, míg a II/b a n. accessorius feletti nyirokcsomókat foglalja magában. A III. régió határai a m. sternohyoideus, az a. carotis bifurcatio/nyelvcsont, a m. sternocleidomastoideus, a m. omohyoideus (sebészi határ), a gyűrűporc alsó széle (klinikai határ), míg a IV. régió határai a m. sternocleidomastoideus, a m. omohyoideus/gyűrűporc alsó széle, a m. sternocleidomastoideus és a clavicula [6].

A nyirokcsomó-dissectiónak az ATA 2015. és az NCCN 2019. évi irányelveinek megfelelően kizárólag terápiás, azaz pozitív citológia vagy biopszia után van

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original article

The master role of polarized NIS expression in regulating iodine metabolism in the human body

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ABSTRACT

Objective: The aim of this study was to investigate how polarized sodium iodide symporter (NIS) expression may regulate iodide metabolism *in vivo*. **Materials and methods:** Polarized NIS expression was analyzed in tissues that accumulate iodide by the use of immunohistochemistry and polyclonal antibody against the C-terminal end of human NIS (hNIS). **Results:** Iodide absorption in the human intestine occurs via NIS expressed in the apical membrane. Iodide is secreted into the lumen of the stomach and salivary glands via NIS expressed in the basolateral membrane and then circulates back from the small intestine to the bloodstream via NIS expressed in the apical membrane. **Conclusion:** Polarized NIS expression in the human body regulates intestinal-bloodstream recirculation of iodide, perhaps prolonging the availability of iodide in the bloodstream. This leads to more efficient iodide trapping by the thyroid gland. Understanding the regulation and manipulating gastrointestinal iodide recirculation could increase radioiodine availability during theranostic NIS applications.

Keywords
NIS; thyroid gland; iodine absorption; iodine metabolism

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INTRODUCTION

Iodine is an essential component of thyroid hormones which, in turn, are key factors for human physiology and development before and after birth. Active iodide transport into thyroid epithelial cells is mediated by the sodium iodide symporter (NIS), a plasma membrane glycoprotein. Diagnosis and therapy of thyroid diseases using radioiodine have been applied since 1940 (1,2), but NIS was only cloned in 1996, in the laboratory of Nancy Carrasco (3-5).

A secondary structure model for NIS, with 13 transmembrane segments, has been proposed based on experimental data (6-8). NIS couples the inward translocation of sodium and the simultaneous inward "uphill" translocation of iodide against their electrochemical gradients. The sodium gradient that provides the driving force for cellular iodide uptake is maintained by the sodium-potassium ATPase. Two sodium cations are transported for each iodide anion (9). In the thyroid, both NIS and sodium-potassium ATPase are located in the basolateral surface of thyroid follicular cells, close to the gland's blood supply (8,10,11).

Thyroid-stimulating hormone (TSH) and iodide are the two main factors regulating iodide transport in the thyroid, which is stimulated by TSH and decreased by iodide. Hence, TSH stimulation and iodide depletion are the two most important modulators routinely used to optimize radioiodine treatment in metastatic thyroid carcinoma (8,12,13).

NIS-mediated radioiodine therapy for thyroid cancer is the oldest routinely applied molecular targeted radiotherapy

available today. Currently, the *NIS* gene is one of the most promising candidates for gene therapy applications, both as a therapeutic and a reporter gene (8,14).

A major drawback of available traditional cytotoxic anticancer therapies is their lack of selectiveness for cancer cells and their substantial toxicity against normal cells. Therefore, the ultimate aim of any new anticancer therapy is to achieve selective destruction of cancer tissue with minimal harm to healthy cells. One of the most promising approaches to accomplishing this is targeted radiation therapy. Radioiodine therapy is a prime example of targeted radiation therapy via selectively expressed plasma membrane transporters (2,14,15). Radioiodine therapy has been employed with great success for over 60 years for the destruction of thyroid cancer remnants and metastases after thyroid surgery. The presence of NIS in thyroid cancer cells ensures that the administered radioiodine accumulates selectively in these cells, thus causing little damage to other cells and only minimal side effects. Thus far, radioiodine therapy has been viewed as applicable only to thyroid cancer. However, NIS can concentrate various radionuclides in target cells and facilitate exciting applications, including diagnostics and gene therapy (11,14). Indeed, recent observations have raised the possibility of the application of radioiodine therapy to breast cancer and other cancers by the introduction of *NIS* into tumors via viral vectors or upregulating the tumors' endogenous *NIS* expression, if present. As a transgene, *NIS* can be used for image-guided radiotherapy, monitoring of gene and vector biodistribution, and evaluation of trafficking of therapeutic cells. A potential limitation of ectopic (extrathyroidal) NIS expression is the fact that extrathyroidal tissues are unable to perform iodide organification. Therefore, the accumulation of iodide is the sum of cellular uptake and efflux, largely dependent on the plasma availability (absorption and clearance) of the tracer (8,11,14,16).

NIS is a master molecule of iodine metabolism. In rodents, NIS has been shown to be responsible for intestinal iodide absorption (8,17). Some of the absorbed iodide undergoes organification in the thyroid. Iodide is secreted via NIS in the salivary glands, stomach, and gastrointestinal lumen and is then again absorbed via NIS in the small intestine. Iodide is finally excreted by the kidneys via glomerular filtration (5,8).

Polarized NIS expression in epithelial cells results in vertical transepithelial transport of iodide. Polarization of NIS expression may occur across all cells, as NIS is located in the basolateral plasma membrane in all tissues where it is expressed, except for enterocytes in the small intestine, where NIS is confined to the apical membrane (17,18). NIS localized in the basolateral membrane transports iodide into the cell lumen, while NIS localized in the apical membrane transports iodide from the lumen into the cells. Interestingly, NIS is regulated differently in each of these tissues. Currently, apical expression of NIS in the small intestine epithelium has only been demonstrated in rodents (17).

Based on these considerations, the aim of our study was to follow the distribution of radioiodine in the human body by using whole-body single-photon emission computed tomography (SPECT) imaging and correlate the findings with NIS immunohistochemistry in human tissues that accumulate radioiodine. We were particularly interested in evaluating NIS expression in the human small intestinal epithelium and understanding the possible role of NIS in iodide absorption and recirculation.

MATERIALS AND METHODS

NIS can be considered a master molecule of iodine metabolism. We studied the polarized NIS expression in tissues that accumulate iodide by using immunohistochemistry and a polyclonal antibody against the C-terminal end of NIS. Notably, NIS is expressed in the basolateral membrane of epithelial cells from salivary glands, thyroid, and stomach, while in the intestinal epithelium, the expression of NIS occurs in the apical membrane. NIS is regulated differently in each of these tissues and is responsible for iodide absorption from the intestine. Some of the absorbed iodide undergoes organification in the thyroid. In the gastrointestinal lumen, iodine is secreted via NIS into the stomach and salivary glands and is again absorbed via NIS in the small intestine. The role of this recirculating mechanism of iodine in the gastrointestinal system remains unclear. Iodine is finally excreted by the kidney via glomerular filtration.

In the present study, we performed immunohistochemistry of NIS using paraffin-embedded samples.

This study was approved in 2020 by the local ethics committee of the National Institute of Oncology in Hungary.

Imaging

Radioiodine distribution in the human body was evaluated using planar whole-body imaging after

by iodide and that high iodide concentration decreases the intestinal transport of this ion (17,23).

In this study, we used immunohistochemistry to show apical NIS expression in enterocytes for the first time in the human small intestine. The findings of our study corroborate the previous work by Nicola and cols., which was performed in rodents (22).

Studies of human samples are limited by availability and tissue autodigestion, and thus we could not evaluate *NIS* expression in the small intestine. Our samples, obtained from the duodenum, showed apical NIS expression in the enterocytes. It is difficult to study the regulation of expression and polarized plasma membrane targeting enteric NIS expression in humans. Martín and cols. reported the presence of a highly conserved monoleucine-based sorting signal in the NIS carboxy-terminus, which is responsible for basolateral plasma membrane targeting in polarized canine kidney epithelial (MDCK) cells. Disrupting this basolateral sorting signal results in apical targeting of NIS protein in epithelial cells. This determinant must be recognized by sorting machinery that is cell-specific and characterized by distinct adaptor proteins.

Very little is known currently about NIS-expressing tissues regarding the presence, function, and regulation of cell-specific factors that interact with and determine the polarized targeting of NIS in the plasma membrane (18,24). In the human body, polarized NIS expression may occur in the basolateral membrane (thyroid, salivary gland, stomach) or apical membrane (small intestine). This distribution ensures that the iodide absorbed in the small intestine accumulates in the thyroid and is secreted into the gastric lumen. Iodide is then reabsorbed in the small intestine to be finally removed from circulation to the urine through glomerular filtration (Figure 3).

In conclusion, iodine and TSH are the two main factors regulating thyroidal iodide transport, in which the transport is stimulated by TSH and decreased by iodine (3-5). Hence, TSH stimulation and iodine depletion are the two most important modulators routinely used to optimize radioiodine treatment in metastatic thyroid carcinoma.

Both tissue-specific expression and polarized NIS expression determine the distribution of iodide in the human body. As an anion, absorbed iodide is quickly filtered from the circulation by the kidney into the urine. Gastrointestinal recirculation can lead to prolonged plasma retention of iodide, thus resulting in higher iodide availability and accumulation into the thyroid. NIS is the first theranostic molecule ever used, as it is used in thyroid imaging, as a reporter gene in gene therapy, and in radioiodine treatment of metastatic thyroid cancer. Manipulating intestinal recirculation of iodide can optimize radioiodine availability in the bloodstream for NIS-mediated targeted radiotherapy and reporter imaging.

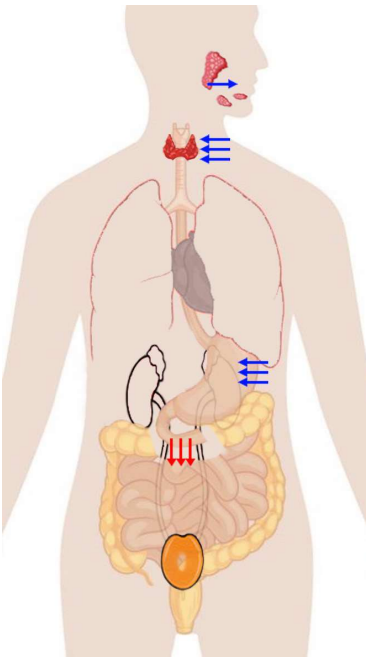

Figure 3. Schematic representation of iodine metabolism. Iodide distribution in the human body is regulated by tissue-specific polarized (basolateral or apical) plasma membrane expression of human sodium iodide transporter (NIS) in epithelial cells. Blue arrows: NIS expressed in the basolateral membrane in epithelial cells transporting iodide into the saliva, gastric juice, and thyroid cells, where it is covalently bound to the tyrosyl residues of thyroglobulin. Red arrows: NIS expressed in the apical membrane in the epithelial cells of the duodenal mucosa transporting iodide from the intestinal lumen to the bloodstream.

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Individual contributions: BL – manuscript preparation. AL and AS – histological examination, contributions to analysis of data.

RESULTS

Routine planar imaging during whole-body radioiodine distribution showed an accumulation of iodide (via NIS) in the stomach, salivary glands, and gastrointestinal lumen. Iodine dissolved in the gastric juice progresses to the duodenal lumen and is absorbed via NIS in the small intestine, in a similar process described in rodents. No significant radioiodine accumulation was observed in the distal part of the small intestine or in the colon. In the circulation, iodide is trapped by the thyroid (when this gland is present) or finally excreted by the kidney through glomerular filtration (Figure 2).

The results of NIS immunohistochemistry showed the localization of the NIS protein in the basolateral membrane in epithelial cells from salivary glands, thyroid, and stomach and in the apical membrane in epithelial cells from the small intestine (Figure 2).

The images showing the distribution of radioiodine correlated well with NIS polarized expression. The NIS expressed in the apical membrane was responsible for iodide absorption from the intestine. In the stomach and salivary glands, iodide was secreted into the lumen by NIS expressed in the basolateral membrane; then, in the small intestine, iodide circulated back to the bloodstream via apical NIS (Figure 2).

DISCUSSION

We have correlated the *in vivo* distribution of radioiodine in the human body and the polarized NIS expression using immunohistochemistry in iodide accumulating organs. Iodine is a trace mineral in the environment and is ingested by humans via food. Because of its scarcity, iodine must be absorbed through a very specific and efficient mechanism. Iodide anions are quickly filtered from the bloodstream by the kidney and excreted via urine. Iodide is also "trapped" by the thyroid; it is transported by NIS into thyrocytes, where it is covalently bound to the tyrosyl residues of thyroglobulin. NIS is highly specific and efficient in accumulating iodide into thyroid cells, but iodide is also quickly cleared from circulation by glomerular filtration. Thus, it is critical that iodide remains in circulation for a sufficiently long time (17,21).

Nicola and cols. were the first authors to demonstrate NIS expression across the entire length of the small intestine in rodents (22). The authors analyzed the segment from the duodenum to the ileum and found that NIS is located in the apical surface of small intestine enterocytes where it mediates intestinal iodide absorption. They also reported that – similar to NIS expressed in the thyroid – enteral NIS is autoregulated

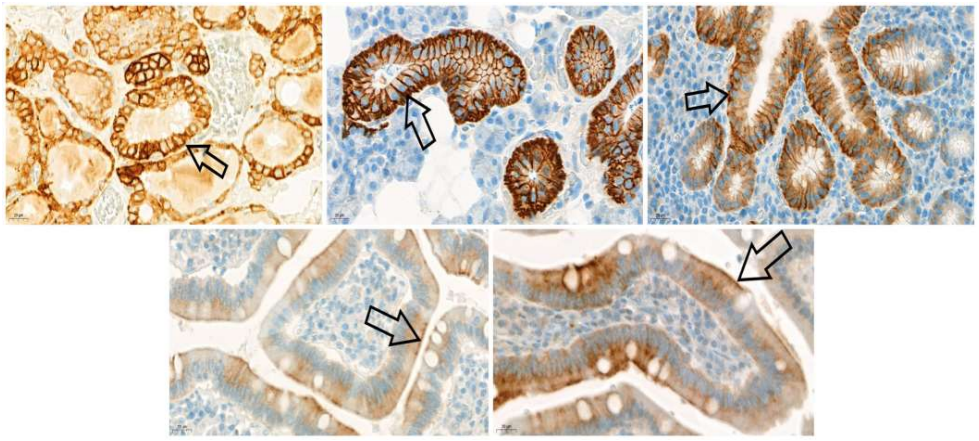

Figure 2. Sodium iodide transporter (NIS) immunohistochemistry. Black arrows show basolateral membrane staining indicating iodide accumulated in the follicular epithelium in the thyroid gland (top left); basolateral membrane staining indicating iodine excreted by epithelial cells in salivary gland acini (top middle) and in the gastric mucosa (top right). Apical membrane staining of the epithelial lining on the surface of duodenal villi responsible for iodide absorption (bottom left: cross-sectional, bottom right: longitudinal plane; NIS immunohistochemistry, 40x magnification).

therapeutic administration of radioiodine-131 in patients who had undergone thyroidectomy for cancer. Post-therapeutic whole-body scan is routinely performed in anterior and posterior images (Figure 1).

A whole-body scanner was used to image the distribution of radioiodine-131 across the entire body. In the case of radioiodine-131, a high-energy collimator (up to 450 keV) was used with a scanning speed of 12 cm/min and a window setting of 364 keV ± 15%. Counts were obtained from the regions of interest over the entire body and thyroid in anterior and posterior images. Geometric averages for anterior and posterior counts were used. The counts were calibrated to the counts at time t < 60 min before any voiding.

NIS immunohistochemistry

The local Institutional Review Board of the National Institute of Oncology reviewed and approved the immunohistochemistry examination of stored paraffin-embedded tissues. Human NIS (hNIS) polarized expression was studied in iodide accumulating tissues by immunohistochemistry using a polyclonal antibody against the C-terminal end of hNIS (6,11), as previously described (16,19,20). Briefly, 5-µm sections were sliced from stored surgical blocks of iodide accumulating tissues obtained from the thyroid, salivary gland, stomach, and small intestine. All slides were deparaffinated, rehydrated, and subjected to antigen retrieval. Endogenous peroxidase activity and biotin activity were blocked using a commercial blocking system (Ventana Medical Systems, Tucson, AZ, USA). Sections were stained using anti-hNIS rabbit polyclonal antibody (1 µg/mL in 1:4000 dilution) directed against the C-terminal end (a generous gift from Dr. Nancy Carrasco) using a commercial immunohistochemistry kit (Ventana Medical Systems). All slides were counterstained with hematoxylin.

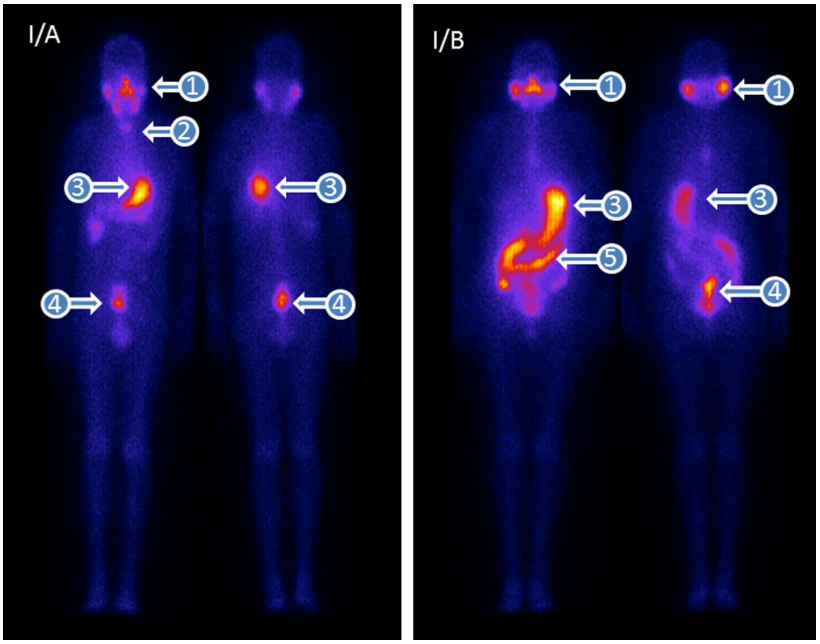

Figure 1. Planar images of post-therapeutic radioiodine-131 distribution in a patient who had undergone thyroidectomy due to thyroid cancer. The images were obtained 72 hours after the therapeutic administration of radioiodine-131. (1) Salivary gland, iodide is transported into the saliva; (2) thyroid remnant, iodide is trapped in the thyroid gland; (3) stomach, iodide is transported into the gastric juice; (4) iodide, as an anion, undergoes glomerular filtration into the urine in the bladder; (5) from the stomach, the gastric juice progress to the small intestine, where iodide is reabsorbed from the intestinal lumen and transported to the bloodstream.

IS – methodology, manuscript preparation. ET – manuscript revision, final approval of the version to be published. OD – contribution to the conception of the study design, methodology, manuscript preparation.

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