ΜΕΤΑΠΤΥΧΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΣΠΟΥΔΩΝ:

‘‘ΕΛΑΧΙΣΤΑ ΕΠΕΜΒΑΤΙΚΗ ΧΕΙΡΟΥΡΓΙΚΗ,

ΡΟΜΠΟΤΙΚΗ ΧΕΙΡΟΥΡΓΙΚΗ ΚΑΙ ΤΗΛΕΧΕΙΡΟΥΡΓΙΚΗ’’

ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ

ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

ΘΕΜΑ

ΔΙΑΣΤΟΜΑΤΙΚΗ ΕΝΔΟΣΚΟΠΙΚΗ ΘΥΡΕΟΕΙΔΕΚΤΟΜΗ-ΕΠΙΠΛΟΚΕΣ

ΣΥΣΤΗΜΑΤΙΚΗ ΑΝΑΣΚΟΠΗΣΗ

ΜΕΤΑΠΤΥΧΙΑΚΗ ΦΟΙΤΗΤΡΙΑ:

ΑΚΡΙΤΙΔΟΥ ΕΛΛΑΔΑ

Α.Μ.:20181022

ΕΠΙΒΛΕΠΩΝ:ΚΑΘΗΓΗΤΗΣ ΔΗΜΗΤΡΟΥΛΗΣ ΔΗΜΗΤΡΙΟΣ

ΑΘΗΝΑΝΟΕΜΒΡΙΟΣ 2021

POSTGRADUATE PROGRAM:

«MINIMALLY INVASIVE SURGERY

ROBOTIC SURGERY & TELESURGERY»

NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS

MEDICAL SCHOOL

MASTER THESIS

COMPLICATIONS OF TRANS-ORAL ENDOSCOPIC THYROIDECTOMY VESTIBULAR APPROACH:

A SYSTEMATIC REVIEW

POSTGRADUATE STUDENT:

AKRITIDOU ELLADA

A.M.: 20181022

SUPERVISOR:

DR DIMITROULIS DIMITRIOS

ATHENS NOVEMBER 2021

Περίληψη

Εισαγωγή/Σκοπός:Αυτή η βιβλιογραφικήανασκόπησηεστιάζει στις επιπλοκές που σχετίζονταιμε την διαστοματική ενδοσκοπική θυρεοειδεκτομή (Transoralendoscopicthyroidectomyvestibularapproach -TOETVA) και αποσκοπεί στο να διευκρινίσει την ασφάλεια της τεχνικής αυτής.

Υλικό και Μέθοδος:Με βάση τα προτεινόμενα στοιχειάναφοράς για συστηματικήανασκόπηση και μετά-αναλύσεις (PRISMA). Έως τον Μάιο του 2021 διενεργήθηκε μια συστηματική ανασκόπηση της βιβλιογραφίας (Βάσεις δεδομένων Pubmed, Embase και Cohrane).

Αποτελέσματα:Είκοσιοκτώάρθρα ,εννέαμελέτες παρατήρησης (cohort) και δεκαεννέασειρές περιστατικών (caseseries) επιλέχθηκαν.Οι σχετιζόμενες με την τεχνική επιπλοκές αναλύθηκαν και οι πιο σημαντικές ήτανο παροδικός υποπαραθυρειοειδισμός (διακύμανση :0,94%-22,2%), μόνιμος (διακύμανση:1,33%-2,22%). Κάκωση παλίνδρομου λαρυγγικού νεύρου: παροδική (διακύμανση:1,9%-8,8%), μόνιμη(διακύμανση:0,59%-1,42%). Αιμάτωμα ,εμφύσημα, διαπύηση και οι λοιπές επιπλοκές σχετιζόμενες με το χειρουργικό τραύμα αφορούσαν το 2,91%. Καμία θνητότητα δεν αναφέρθηκε.

Συμπέρασμα: Αν και η τρέχουσα εμπειρία δείχνει ότι η διαστοματική ενδοσκοπική θυρεοειδεκτομή φαίνεται να είναι ασφαλής και συνδέεται με αποδεκτά ποσοστά επιπλοκών η μέθοδος πρέπει να έρθει αντιμέτωπη με την goldstandard παραδοσιακή ανοικτή θυρεοειδεκτομή στο πλαίσιο επαρκών αριθμητικά τυχαιοποιημένων ελεγχόμενων δοκίμων .

Λέξεις Κλειδιά: Διαστοματική ενδοσκοπική θυρεοειδεκτομή, χειρουργική θυρεοειδούς επιπλοκές ,ελάχιστα επεμβατική θυρεοειδεκτομή , TOETVA, TORTVA.

REVIEW

Complications of Trans-Oral Endoscopic Thyroidectomy Vestibular Approach: a systematic review

Ellada Akritidou[1,2], Gerasimos Douridas[1], Eleftherios Spartalis[2,3], Gerasimos Tsourouflis[2,3], Dimitrios Dimitroulis[2,3], Nikolaos I. Nikiteas[2,3]

[1]Department of Surgery, Thriassio General Hospital, Athens, Greece, [2] Hellenic Minimally Invasive and Robotic Surgery (MIRS) Study Group, Athens, Greece, [3]2nd Department of Propaedeutic Surgery, National and Kapodistrian University of Athens, Medical School, Athens, Greece.

Authors

Dr. E. Akritidou **(corresponding author)**

Dr. G. Douridas 23 Ikarias Str., 14578 Ekali Athens Greece

Dr. EleftheriosSpartalis

Dr. GerasimosTsourouflis

Dr. DimitriosDimitroulis

Dr. N. Nikiteas

Key words:trans-oral, vestibule, thyroid surgery, complications, minimal invasive thyroid surgery, TOETVA, TORTVA

Running Title: Transoral endoscopic thyroidectomy: review of safety profile

Date of submission: August 13th, 2021.

Date of accept: October 6th ,2021

ABSTRACT

Objectives: This review focuses on complications linked to Trans-Oral EndoscopicThyroidectomy via Vestibular Approach (TOETVA)and aims to elucidate procedure's initial safety profile.

Materials and Methods: According to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Pubmed, Embase and the Cochrane databases were screened till May 2021.

Results: Twenty-eightarticles,nine cohorts and nineteen case series,met the inclusion criteria.Procedure-related complications were analyzed the most important being hypoparathyroidism:transient (range: 0,94%-22,2%), permanent(range: 1,33%-2,22%) and recurrent laryngeal nerve (RLN) injury:transient(range: 1,9%-8,8%), permanent (range:0,59%-1,42%). Surgical trauma related complications the most prevalent being seroma, emphysema, and hematoma accounted for 2,91%. Null mortality was reported.

Conclusions: Althoughcurrent evolving experience indicates that TOETVA seem to be safe and linked to acceptable complication rates the method need to be confronted with the gold standard of traditional thyroidectomy in the context of sufficiently numbered cohorts and ultimately randomized controlled trials.

Ευχαριστίες

Ευχαριστώ θερμά όλους τους καθηγητές, διδάσκοντες και προσωπικό του Π.Μ.Σ. ‘‘Ελάχιστα επεμβατική χειρουργική, ρομποτική χειρουργική και τηλεχειρουργική’’ για την ευκαιρία που μου δόθηκε. Ευχαριστώ τον Καθηγητή Χειρουργικής κ. Νικόλαο Νικητέα, τον Αναπληρωτή Καθηγητή κ. Δημήτριο Δημητρούλη, τον Επίκουρο Καθηγητή κ. Γεράσιμο Τσουρούφλη, τον Διδάκτορα και επιβλέποντα κ. Ελευθέριο Σπάρταλη. Φυσικά ευχαριστώ ιδιαιτέρως τον διευθυντή μου κ. Γεράσιμο Δουρίδα για την ουσιαστική συμβολή στη συγγραφή καιολοκλήρωσητης διπλωματικής εργασίας. Τέλος, πολύ ευγνώμων στην οικογένεια μου για τη διαχρονική βοήθεια, υπομονή και στήριξη τους.

INTRODUCTION

Surgical procedures addressing thyroid/parathyroid pathology are common in general surgery. Until today, to gain access to the thyroid gland a transverse-ellipsoid incision to the neck, named by Swiss doctor Emil Theodor Kocher (1841-1917) is utilized. Albeit meticulous suturing, a scar remains and marks the most visible area of the neck region, a measurable drawback especially for young women (1). Aiming at elimination of this "iatrogenic tattoo", surgeons conceived various minimal invasive endoscopic approaches to operate thyroid. In parallel, vision technology and surgical instruments developed, thus enabling surgeons to perform thyroid surgery from a remote site. Endoscopic and robotic thyroidectomy have evolved during this last decade in the context of minimal invasion pursuing scar-less surgery on the neck. Various proposed remote procedural innovations have been tried such as the axillary approach, the areola approach, the breast-chest approach, and the retro-auricular (2,3,4). Of special interest, being the topic of this short review, is a recently developed technique known as the transoral endoscopic thyroidectomy via the inferior vestibule (TOETVA).

TOETVA, is a natural orifice transluminal endoscopic surgical procedure which nowadays has drawn the attention of both "minimal invasivists" and young aged patients thirsty for ultimate cosmesis. TOETVA is realized via three internal incisions in the inferior vestibule, (one 10-mm port for endoscope and two additional 5-mm ports for instruments), thereby avoiding external visible incisions and scars. Carbon dioxide is insufflated under the anterior cervical platysma to create working space extending from the oral vestibule down to the sternal notch. Then, thyroid excisional procedures are executed endoscopically (or robotically assisted, TOVARA) using conventional laparoscopic instruments and energy-based devices (EBD) (4,5).

Compared to other remote approaches, TOETVA claims to be advantageous in term of cosmesis due to proximity of entry sites of the working ports to organ task (thyroid), the median symmetry of created surgical field and the invisible placed scars. On the other hand, the learning curve seems to be more than steep because the learner must train his perception to a new "up to down" endoscopic vision in an unexplored till now anatomic area, undoubtfully a great challenge. New laparoscopic skills, tips and tricks had to develop by field pioneers to avoid disastrous surgical complications (5-10). The primary aim of this review is to assess feasibility and safety profile of this modern minimal invasive thyroid surgical procedure and secondarily to address provisional complications. Whether such an ambitious modern procedure will survive head-to-head comparison with the gold standard of traditional thyroid operation remains to be proven.

MATERIALS AND METHODS

Search strategy: Three Databases namely PubMed, EMBASE and Cochrane were meticulously searched for relevantstudies. Publication year restrictions were not setandthe last search date was Maythe10th, 2021. The search process and elimination stepsare both described in (Fig. 1). Key words used in electronic research process were: TOETVA, trans-oral vestibular thyroidectomyandcomplications.Titles and abstracts were inspected and the article discarded if not relevant with complications. Duplicates were identified and discarded. Then, any articlewithin inclusion criteria set, was thoroughly read, and analyzed to extract data pertinent with TOETVA complications. Trials published from the same center or author, including different set/number of patients in different time periods were separately recorded and not excluded.

Inclusion and exclusion criteria: Original articles published in English language that assessed or/and describedcomplications following transoral vestibular approach for thyroidectomywere included. Detailed information of patient's characteristics, surgical procedure and peri-operative complications constituted eligibility criteria as well. Articles in other than English language, reviews, single case reports, letters, abstracts from conferences, videos, animal or cadaver studies were excluded.

Data recorded: Variables that were extracted from each included study consisted of: author, study type, patient characteristics such as sex and age, diagnosis, type of surgery, operation time, extracted specimen's dimensions and length of hospital stay. Regarding complications the following list was tabulated: recurrent laryngeal nerve, superior laryngeal nerve, mental nerve injuries, transient or permanent, hypo-parathyroidism, transient or permanent, surgical site infection, seroma, emphysema, postoperative bleeding, skin flap perforation.Other scarcely reported uncommon complications thus considered miscellaneous were not grouped and thoroughly analyzed.

RESULTS

Twenty-eight eligible studies, the majority of which were of Eastern hemisphere origin, were analyzed. Regarding type of publication there were 19 case series and 9 cohorts including 1887 patients with a mean age of 33,8 ± 6,6. One thousand seven hundred seventy-six (1776) were women (94,22%) and one hundred and eleven (111) were men (5,88%). Apart from one mixed series of TOETVA and TOVARA the remaining patients underwent TOETVA. Surgical indications comprised both of benign (n=1088) and malignant (n=799) either thyroid or parathyroid diseases namely: graves(n=78),primary hyperparathyroidism (n=2),goiters (n=583) (single or multiple), neoplasms (n=836) (papillary or follicular and atypical), thyroid adenomas

and other various benign pathologies (n=253) (cystic nodule, thyroglossal cystetc). Type of resections included cyst or nodule resections (n=3), hemithyroidectomy/lobectomies(n=1174), total/almost total thyroidectomy (n=712), parathyroidectomy (n=2). Thyroid resection of neoplasms was occasionally combined with central and/or lateral neck dissection (n=277). Median operation time in minutes was130 ± 36,19 and median length of hospital stay in days was 3,15± 1,47.Dimension of extracted specimen was expressed either in maximum axis length/diameter (2.85±1.98 cm) or in volume (30.11 ± 18.74 ml).A wide range of procedure-related complications were analyzed: (a) Nerve injuries such as recurrent (RLN) (n=85, transient 79, permanent 6), superior (SLN)(n=31,transient 13, permanent 18), mental nerve (MN) (n=102, transient 82, permanent 20), (b) hypo-parathyroidism (n=118 transient, 2 permanent), (c) surgical trauma related complications such as site infection (n=12), seroma (n=36), emphysema (n=11), skin flap perforation (n=8), postoperative bleeding/hematoma (n=10), (d) miscellaneous: tracheal injury (n=2), skin bruise/injury/dimpling (n=16), swallowing discomfort (n=5), long standing pulling sensation (n=5), horner's syndrome (n=1), C02 embolism (n=2), dehiscence (n=1), transient lip drop (n=1), chin numbness (n=26).

DISCUSSION

Endoscopic and robotic thyroidectomy have evolved during this last decade in the context of minimal invasion pursuing scar-less surgery on the neck. Of special interest, being the topic of this short review, is a recently developed technique known as the transoral endoscopic thyroidectomy via the inferior vestibule (TOETVA). TOETVA, is a natural orifice transluminal endoscopic surgical procedure which nowadays has drawn the attention of both "minimal invasivists" and young aged patients thirsty for ultimate cosmesis. A recent study aiming at quantification of social

perception of neck scars, utilized eye tracking technology and recorded measurable differences in visual attention attracted by a “marked neck” (2,3,4,7). A long neck, covered by white-colored skin, free of any scar/markconsistsa key feature of perceived attractiveness and facial beauty especially in eastern cultures. This fact might partly explain the fast-growing interest of eastern female patients in minimal invasive techniques of thyroid surgery. Most studies in the literature are of eastern origin and refer to young women. In this review the results of TOETVA refer to a populationof1887 patients with a mean age of 33,8 ± 6,6,1776of which were women (94,22%) and only 111 were men (5,88%).

Various remote access endoscopic thyroidectomy methods have been proposed, however the rather long distance of entry sites from thyroid bed demanded extensive tissue dissection paths leading to complications and prolonged operative time (8,11).

TOETVA is realized via three internal incisions in the inferior vestibule, (one 10-mm port for endoscope and two additional 5-mm ports for instruments), thereby avoiding external visible incisions and scars. Carbon dioxide is insufflated under the anterior cervical platysma to create working space extending from the oral vestibule down to the sternal notch. Then, thyroid excisional procedures are executed endoscopically (or robotically assisted) using conventional laparoscopic instruments and energy-based devices (EBD) (4,5). Cosmesis remains the major driving force of procedure’s innovation. Conventional thyroidectomy inevitably marks patient’s neck. Transoral approach produces no visible incision, neither scar or its physiological variants such as keloid or hypertrophic formation, contracture formation or dehiscence (12,13,14,15).

A sufficient number of papers have already been published but long-term follow-up results of TOETVA regarding its surgical and oncologic safety are lacking (16,17,18).

Although preliminary case series report favorable outcomes (19) and shorter learning curves compared to other MIS procedures (20), clear and robust data supporting safety issues and a non-inferiority identity compared to conventional thyroidectomy are still pending (4,21,22).A number of potential challenges should be considered preceding safe introduction of TOETVA to clinical practice. Expert pioneers, consent on the critical nature of the need for adequate training and prevention of novel complications. Safety validationof a surgical procedure should both consider conventional and unconventional complications (23). Unconventionaleventsare further classified into experience-related and procedure-related.Vestibular approach thyroidectomy related complications comprise new risksinherent to two-dimensional visualization, instrument's rigidity, restricted surgeon's maneuverability, and confined neck workspace (4).

TOETVA approach access thyroid gland through the oral vestibule of the lower lip transversing the premandibular space. Compared to other "remote access paths", dissection isminimized and the hypoglossal nerve is not in the operative field (24). This review focuses in TOETVA related technical and safety issues in an attempt to draw procedure's identity.

Nerve injuries

Although of transient clinical course in their majority they do consist one of the main inherent complications experienced postoperatively by the patient.

Mental nerve (MN) injury: Mental is a sensory nerve providing sensation to the front of the chin and lower lip, buccal gingivae of the mandibular anterior teeth and premolars. It is a common complication with a prevalence ranging 1-5% (22), thankful more oftentransient,lateral or bilateral, related with site of working trocar

placement, resulting in postoperative decreased lower lip/chin sensation (numbness and /or paresthesia and /or inability to sense hot liquids).

MN palsy was early reported with an overall incidence of 4,3% (28,35). In this review in a total of 1887 patients MN injury was recorded in 102 patients, (5,8%) 82 transient (80,4%) the rest 20 permanent (19,6%).

Repositioning 5mm port incisions to the vestibular mucosa just in the inner aspect of the inferior lip lateral to the level of the canines might spare tract of MN and avoid this complication (4,25).Clinical condition of altered sensation in the innerved area might persist for more than 6 months and usually occurs with other sensations such as prickling pain tingling or burning (23,26,27).

Recurrent Laryngeal nerve (RLN) injury: Of paramount importance, in any thyroid surgical procedure, is localization and preservation of recurrent laryngeal nerve. Prevalence of transient and permanent RLN injury in conventional open thyroidectomy in the literature ranges from 2.11% to 11,8% and from 0.2% to 5.9% respectively (2,22). In this review in a total of 1887 patients RLN injury was recorded in 85 patients, (4,5%) 79 transient (92,9%) the rest 6 permanent (7,1%).

Attributed to a high definition augmented (X6-X10) “up to down” vision in endoscopic methods, the RLN is rather easily and clearly identified at its most constant location (its insertion) making TOETVA at least theoretically a safe procedure on critical neck structures (23).

However, temporary and overall RLN injury rate in TOETVA seems to be comparable or slightly higher to open procedures (22,25). In the majority or reported RLN injuries via TOETVA, full recovery of vocal cord function was observed (2,24,28). Others proposed intraoperative neuromonitoring in TOETVA procedures with good results (29). At present, limited experience and number of patients preclude

firm conclusions regarding a provisional prophylactic effect of neuromonitoring in RLN injury. Intraoperative nerve monitoring (IONM) requires training, equipment, troubleshooting algorithms and training of both surgeons and anesthesiologists. Until then, further trials are needed to elucidate IONM's role in nerve protection (29,30).

Superior Laryngeal nerve injury (external branch) (EBSLN): "Voice symptoms" attributed to injury of the external branch of the superior laryngeal nerve can occur during dissection in upper thyroid pole area. The external laryngeal nerve is the sole motor nerve supply of the cricothyroid muscle, which is the tensor of vocal folds and raises the pitch of voice. Post-thyroidectomy EBSLN injury symptoms include voice fatigue, breathy voice, and a decrease in voice range. EBSLN injury is sometimes difficult to recognize clinically and its electromyographic incidence ranges from 0% to 58% (31). While the distal 1.5-2.0 cm of the superior thyroid vessels are meticulously dissected, exposed and ligated the external branch of SLN must preserved (32). EBSLN can be either visually identified and preserved or functionally localized with the assistance of IONM (cricothyroid muscle twitch)(33,34). In this review in a total of 1887 patients EBSLN injury was recorded in 31 patients, (1,9%) 13 transient (41,9%) the rest permanent (58,1%). Despite high quality vision during TOETVA trivial over-dissection of the upper pole might explain the above-mentioned percentages of this nerve injury.

Hypoparathyroidism Hypocalcemia

Hypoparathyroidism, almost solely transient, is one of the commonest complications in thyroid surgery. For obvious reasons, hypocalcemia an indirect index of parathyroid dysfunction, is more common in total thyroidectomy. Theoretically, since partial "ectomies" (lobectomy, nodule ectomy) comprise the majority of TOETVA operations, low percentages of hypoparathyroidism are anticipated (16,20).In our

review hypoparathyroidism occurred as Hypoparathyroidism, almost solely transient, is one of the commonest complications in thyroid surgery These figures are comparable to those of standard open thyroidectomy (transient range:0-11%, permanent range: 0-5,7%)(2,35,36,37). Fewins et al. (38) report an incidence of hypoparathyroidism in thyroid surgery between 6,9% and 46%. Reports of permanent hypoparathyroidism are scarce (39). When a lobectomy is attempted via TOETVA, cutting the gland at midline and proceeding dissection of the lobe to be removed from medial to lateral increase the risk for parathyroid damage. This man oeuvre might explain considerable rates of calcium metabolism disturbance even in lobectomies. Overzealous application of energy base devises could play a role in transient hypopathyroid dysfunction through a mechanism of thermic shock.

Skin complications

Minor injuries to the skin are not a surprise after TOETVA. Ecchymosis of the chin and anterior neck are common in the immediate postoperative period and resolve within 1-2 weeks (21,23,40,41). Other varieties of skin damage include tears at the lip commissures from traction and piercing of the skin caused by the Veress needle, electrocautery, or even with the use of clamps during dissection of the superior neck flap (42). Flap perforation consists an unconventional experience-related complication occurring while dissecting centrally through the mentalis muscle down to the tip of the chin (23). Dimpling on the chin, sometimes permanent, at the site of trocar insertion has also been reported, especially if the trocar is inserted near the level of the skin. In our review population of 1887 subjects skin complications wereskin flap perforation (n=8), skin bruise/injury/dimpling (n=16). Although rare, these complications directly and obviously visible to the patient undermine cosmetic expectations and ruins sensation of well-being.

Seroma formation, hematoma, Subcutaneous emphysema

Seroma is a minor complication, occurring 3.5% to 5% of published cases (n=36 in our review or 36/1887:1,91%), its risk increasing by the size of flap created to provide adequate working space, aspiration being the indicated treatment option without further sequela (2,43). Hematomas are even rarer, although this might be an underestimate due to limited pertinent literature (42). In our review among 1887 patients 10 (0,53%) suffered postoperative bleeding or hematoma.

Subcutaneous emphysema should be expected intraoperatively or postoperatively in most patients because of insufflation. Almost always is self-limited and resolves within 3-5 days (39,59). Presentation may be mild, with crepitus confined in the neck area, and usually diminishes in 6-12 hours (44). It may occur despite proper surgical technique, gas flow rate and pressure settings being the most important causal factors (44-49). In our review 11 (0,58%) patients were reported to suffer subcutaneous emphysema.

Infection

TOETVA is classified as a clean-contaminated operation given the diverse bacterial flora of the oral cavity (gram positive aerobic and anaerobic bacteria) (56). As such, perioperative antibiotic coverage against polymicrobial flora of the mouth is recommended (2,24,50). Amoxicillin-sulbactam or cefazolin combined with clindamycin or metronidazole consist logical choices (50). Careful oral preparation, meticulous technique minimizing tissue trauma and dead space eliminate risk of infection (19,51). A concomitant infectious process (ie periodontitis, tooth abscess etc) consists a contraindication for TOETVA until cured. Fortunately, infection rates reported at TOETVA series are negligible (2). This agrees with12 cases out of 1887 patients in our review (0.64%).

CO_2 related complications

Carbon dioxide embolism is a potential serious complication scarcely reported (46,52,53). In our review two cases of this ominous event was recorded among 1887 patients. Either vessel, (esp. vein), micro or macro lacerations while dissecting tissues to create essential "working space", or prolonged high insufflation pressure consist the two main mechanisms promoting entrance of CO_2 into circulation (23). Insufflation-related adverse events also include pneumomediastinum, pneumothorax or excessive hypercarbia. Continuous end tidal CO_2 (et CO_2) monitoring by the anesthetist (goal <35), CO_2 flow rates <15L/min, CO_2 pressure 6mmHg, intermitted release of gas, precise dissection under subplatysmal plane, meticulous hemostasis are key proposals to minimize CO_2 related complications (41,46,47,48,54,55,56). Gasless TOETVA utilized by a special retractor has also been invented as an alternative to avoid CO_2 related complications (4). Following extubation close monitoring and observation in the recovery room is strongly recommended to ensure safe return to homeostasis(39,49).

Pain pulling sensation and neck swallowing disorders

It seems that there is a short- and long-term difference in interpretation of pain comparing Open Thyroidectomy Approach (OTA) with TOETVA. In terms of intensity, as assessed by relevant questionnaires/survey tools such as VAS, TOETVA and OTA- related-postoperativepain was marginally different in terms of statistical significance but of minimum clinical importance (52). TOETVA is also linked with different nature of pains such as "brushing teeth", lower lip or chin pain. Interestingly, TOETVA is reported to produce reduced cervical back pain as less head hyperextensionis essential compared to OTA. Neck pain is also claimed to be less if the right subplatysmal plane is entered as smaller number of pain receptors are located

in the area compared to skin and subcutaneous level (56). Swallowing pain is reported to be equivalent or even better in TOETVA patients compared with OTA (22,25,56).

A pulling sensation along the surgical track, esp. below lower jaw, is constantly experienced by patients undergoing TOETVA. It has been defined as a feeling, a complaint, not linked with a specific clinical sign such as skin retraction or dimpling. It is postulated that extensive dissection and consequent fibrosis might explain this sensation which gradually disappears within 6 months following surgery. Although benign, this bothersome inherent-to-TOETVA symptom affects patient's quality of life and is referred as a serious reason of regretting their choice to select this approach (4,23).In this current review of 1887 subjects 5 patients experienced intractable long standing pulling sensation the rest becoming progressively asymptomatic or acquainted. Another n=5 reported excessive swallowing discomfort and n=36 chin numbness the majority of which faded in time.

Specimen extraction, size restrictions.

Thyroid specimen size is a determinant factor in choosing endoscopic vestibular approach (25,57). Oncologic reasons, (ie violation of tumor capsule), and mechanical-technical issues, (ie. size of midline intraoral incision, tightness of tissue in chin area) as well, constitute limiting factors and dictate definition of exclusion criteria. Intending to preserve a malignant specimen intact to avoid spillage (58), ensure "pathology readability" and minimize surgical trauma, an optimum specimen size of ≤20mm and a volume ≤30ml is generally suggested as a reasonable limit (58,36)eventhough larger dimensions have been attempted and proved feasible (19,23,40,41,54,55,59,60). In our review mean dimension of extracted specimens was expressed either in maximum axis length/diameter (2.85±1.98 cm) or in volume (30.11 ± 18.74 ml).To become extractable, larger in size or hard in consistency

specimens warrant fragmentation at the provisional expense of oncologic safety and specimen quality thus violating size limits set should be avoided (58).

Operative time and hospital stay

At present operative time of TOETVA, although variable among reports, is longer compared to OT (19) but shorter than other endoscopic techniques (retro auricular, axilla) (22,25,62,61).In various reports, mean operative time varies considerably from less than 100min (19,40,41,55) to more than 200min (28,54,64). Surgeon's experience and shape of mandible have been suggested as main determinants of operative time in TOETVA. When reaching twenty cases in learning curve operative time should decrease (55,63). When the mandible has a long and narrow basal arch more operation time is prolonged compared to that in cases with a short and wide arch (65).Port placement and flap dissection to create working space are time consuming especially if the surgeon is not familiar with endoscopic instruments and techniques. In our review median operative time in minutes was 130 ± 36,19.

Length of hospital stay does not seem to differ among TOETVA and OT but several factors may produce wide variability (22,25). Different treatment guidelines, health insurance policies, economic constraints, patient's culture or personal expectations determine length of hospital time. Series from USA or Europe report discharge after an overnight stay while those of eastern origin usually after 48-72 hours (40,66). In our review median length of hospital stay in days was 3,15 ± 1,47. As more experience buildsand perioperative management improves hospital stay will decrease (61).

CONCLUSION

At present,availabledata relevant to TOETV(R)A are extracted from case series and/or cohort studies. Twenty-eight studies, the majority of which were of Eastern

hemisphere origin, were analyzed in this review, nineteen being case series and nine cohorts summing up 1887patients.Recurrent and superior laryngeal nerve injury, hypoparathyroidism, trauma related complications, operative time, length of hospital stay, pain and postoperative discomfort seem to be acceptable and comparable with open approach. Acceptable safety profile of TOETVA seems to be also valid regarding inherent complications such as $C0_2$ related (emphysema, embolism).

Open thyroid operations remain the gold standard to compare with any novel procedure. At real life such a comparison is not realized and evolution for time being steps in few centers' initiatives (4). Anatomic considerations (jaw shape), obesity, patient's culture, health policies and economics formulate different evolution pathways between East and West.

Keeping in mind the low level of evidence of data available, it could be stated that TOETVA is at least not inferior, by means of safety and outcome, compared to OT. It is also realized that it is a highly technically demanding operation with a steep learning curve, requiring previous endoscopic experience and structured training. The number of cases required to achieve minimum mastery is fifteen to twenty in endoscopic experienced operators (20,67). Cadaveric or virtual reality stimulation training are currently under validation (4). The procedure should not be undertaken by unfamiliar teams in the absence of mentoring and training protocols (2,26)

In conclusion, this review suggests that TOETVA (or TORTVA) may be a safe treatment choice-approach for selected thyroid operative procedures in selected patients. Low level of evidence upon which this review was built is constrictive regarding reliability. Precise common terminology and clear indications remain to be defined. At present, structured training programs, evolution of instrumentation and equipment and analysis of data accumulated under the umbrella of official endocrine

surgery associations is the logical way to move on (61,67). Finally, apart from cosmesis other substantial reasons remain to be clarified before investing and adopting this skill demanding new operation.

Fig. 1

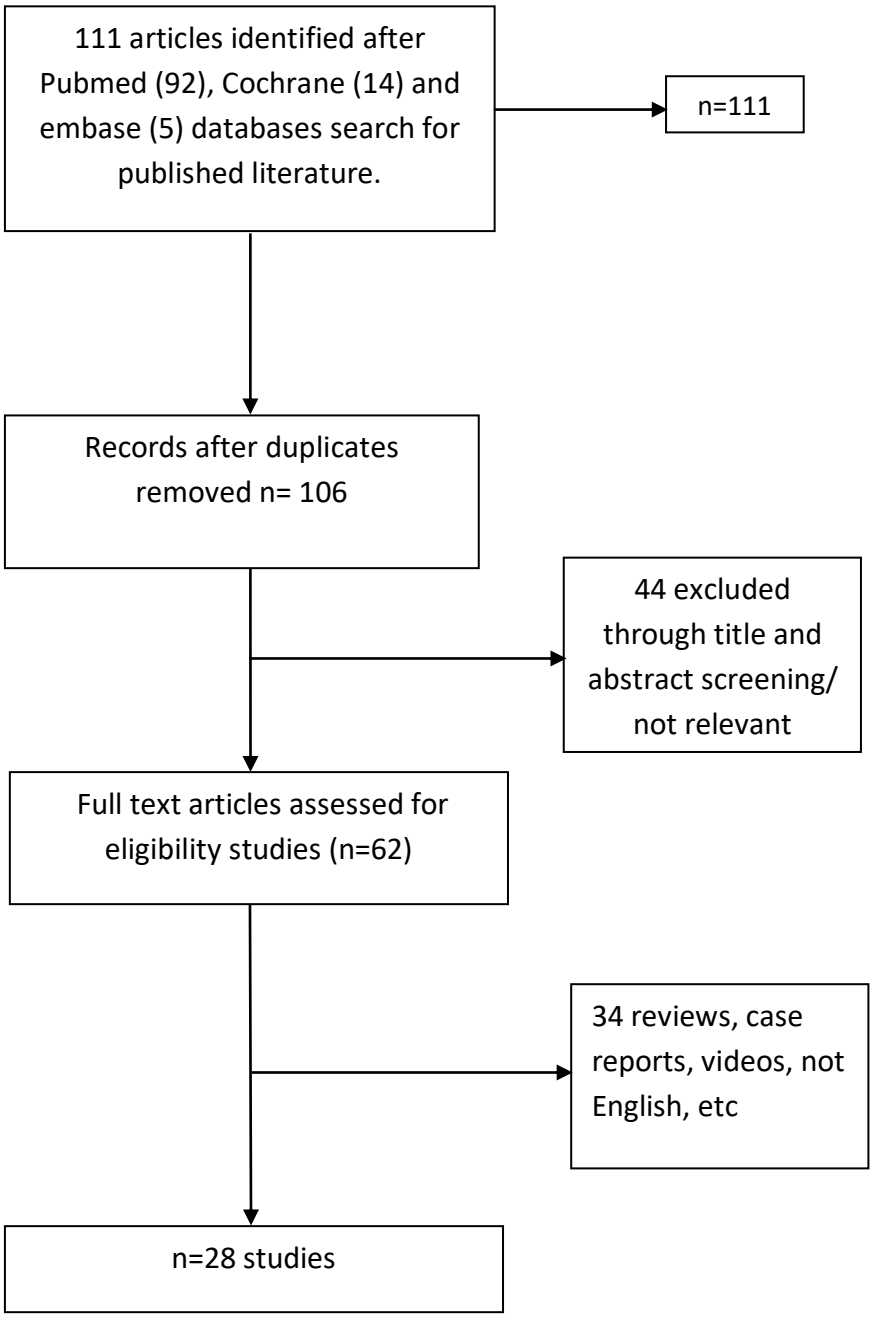
111 articles identified after Pubmed (92), Cochrane (14) and embase (5) databases search for published literature.
n=111
Records after duplicates removed n= 106
44 excluded through title and abstract screening/ not relevant
Full text articles assessed for eligibility studies (n=62)
34 reviews, case reports, videos, not English, etc
n=28 studies

Table 1. Clinicalinformation of patients

ID		Type of article	N	Sex (M/F)	Approach	Age (years) (median or ±SD)	Diagnosis
Karakas et al.(68)		Case series	70	5/65	Toetva/tovara	50 (23-74)	2 GD, 4 PTC, 2 PH, 1 TC
Xu Z. et al.(69)		Cohort study	48	4/44	Toetva	30.46 ± 6,93	PTC
Tan Y et al.(34)		Case series	20	1/19	Toetva	29.2 ± 5	PTC
Wang T et al.(70)		Cohort study	80	0/80	Toetva	31,48 ± 6,6	PTC
Guo F et al.(71)		Cohort study	40	0/40	Toetva	29,8 ± 0,96	PTC
Kadem SG et al.(72)		Case series	10	0/10	Toetva	30,3	1MG 9 NG
Ahn JH et al.(21)		Case series	150	5/145	Toetva	43 ± 10.9	133 PTC,11 FTC, 2A, 4B
Park JO et al.(73)		Case series	15	4/11	Toetva (gasless)	42 ± 10.91	14 PTC 1 FTC
Peng X et al.(74)		Cohort study	105	9/96	Toetva(MND vs NMND)	35.5 ± 10.8	41 NG, 5 TA, 58 PTC, 1 FTC
Russell JO et al.(67)		Cohort study	92	-	Toetva	-	-
Tesseroli M et al.(75)		Case series	9	0/9	Toetva	33-64	2 PTC 7 B

Bian C et al.(76)		Case series	30	1/29	Toetva	24 (17-41)	30 PTC
Razavi CR et al.(20)		Case series	30	3/27	Toetva	41 ± 12	2 PTC
Wang Y et al.(77)		Case series	18	0/18	Toetva	33 (23-45)	10 PTC 5 NG,1 FTC
Bakkar S et al.(23)		Case series	5	0/5	Toetva	36	5NG
Anuwong A et al.(19)		Cohort study	422	33/389	Toetva	35,3 (16-81)	NG 245, PTC 26, GD 33 MG118
Chen HK et al.(78)		Case series	20	4/16	Toetva	42.05 ± 10.8	7 PTC, 5 MG, 7 NG
Jipratoom P et al.(79)		Cohort studies	45	5/40	Toetva	32.84 ± 9.0.1	15 GD
Wang Y et al.(6)		Case series	10	1/10	Toetva	32.5	10 PTC
Sivakumar T et al.(80)		Case series	11	0/11	Toetva	26.5	10 MG,1 PTC
Zhang D et al.(56)		Case series	41	3/38	Toetva	33.7 ± 10.2	7 NG, 1 PTC, 8 NG
Lira et al.(81)		Cohort study	56	7/49	Toetva	40,8 (16-65)	14 GN, 42 PTC
Le.QV et al. (82)		Case series	28	0/28	Toetva	33.8 (18-46)	33.8 (18-46)
Dinc B.et al (83).		Case series	50	2/50	Toetva	44 (21-76)	38 B,14 PTC

Russel JO et al. (84)		Cohort study	200	23/177	Toetva	39 (16-71)	30 GD, 105 B, 4 FTC, 61 M
DeroideGeta l.(85)		Case series	90	3/87	Toetva	46 ± 12.4	11 PTC,13GD, 46 NG
Chai YJ.et al.(86)		Case series	110	0/110	Toetva	39.7 ± 9.7	92PTC, 8FTC, 9NG

GD: Grave's disease,PH:Primary hyperparathyroidism, PTC: Papillary thyroid cancer, TC:Thyroglossal cyst,A:Atypia,FTC:Follicular thyroid cancer,NG:Nodular goiter,MG:Multinodular goiter, B: Benign,M:Malignancy.

Table 2. Outcome measures of included studies

	Operation Time (min) (mean, or ± SD, or range)	Hospital stay (days)	Operation type	Specimen "size" Thyroid volume (ml ± SD) or size in cm, or diameter in cm, or weight in grams
Karakas et al. (68)	205 (96-370)	3	39 hemithyroidectomy, 29 total thyroidectomy,2 parathyroidectomy,1 thyroglossal cyst	<40 ml 60 patients >40 ml 10 patients
Xu Z et al.(69)	107 ± 11.8	3,9 ± 0,4	48 hemithyroidectomy + CND	-
Tan Y et al.(34)	146 ± 18.7	6,8 ± 1.3	20 hemithyroidectomy + CND	-
Wang T et al.(70)	193 ± 47	4 (3-5)	80 total thyroidectomy + CND	Tumor size 0,87±0,56
Guo F et al.(71)	171 ± 5.34	4,33 ± 0,88	40 total thyroidectomy + CND	Tumor diameter 0,608 ± 0.034
Kadem SG et al.(72)	113.5	1,7	9 lobectomies, 1total	Largest dimension of thyroid lobe 2.87 cm
Ahn JH et al. (21)	110.26 ± 35.74	3.64 ± 1,71	110 lobectomy, 40 total thyroidectomy	Tumor diameter 0.91 ± 1.00
Park JO et al (73)	135 ± 45	4,06	13 lobectomy, 2 total thyroidectomy	Tumor size 0,84 cm
Peng X et al.(74)	109,48 ± 29,8 120 ± 28.6	3,59 ± 0.94 3,64 ± 0,68	31 hemithyroidectomy 32 hemithyroidectomy + CND, 6 Bilateral thyroidectomy + CND 15 hemithyroidectomy, 17 hemithyroidectomy + CND, 4 Bilateral thyroidectomy + CND	Tumor size 2,6 ± 1.6 Tumor size 2,6 ± 1,5
Russell JO et al.(67)	126 (lobectomy) 172,5 (total thyroidectomy)	-	74 lobectomy,18 total thyroidectomy	-
Tesseroli M et al.(75)	196.11	1.77	9 total thyroidectomy 1partial thyroidectomy	Glandular volume 35ml
Bian C et al.(76)	145 (115-240)	3 (2-5)	30 unilateral lobectomy + CND	Tumor diameter 1.5cm (0.3-4.0)
Razavi CR et al.(20)	136 (76-343)	-	30 unilateral lobectomy	3.3cm
Wang Y et al.(77)	124	4,05	2 total thyroidectomy, 8 lobectomy, 8 hemithyroidectomy	-
Bakkar S et al.(23)	122	-	5 hemithyroidectomy	Average nodule size 3.5cm

Anuwong A et al.(19)	96.6	-	245 hemithyroidectomy, 177 total thyroidectomy	Thyroid lobe size 6.5 cm (median)
Chen HK et al. (78)	145 ± 50.34	-	12 hemithyroidectomy, 8 bilateral thyroidectomy	Mean weight thyroid lobe 17,76 ± 16.23 grams
Jipratoom P et al.(79)	134,11 ± 31,48	-	45 total thyroidectomy	Mean size 5,41±1,38
Wang Y et al. (6)	191.5	4,1	1 bilateral thyroidectomy, 9 unilateral thyroidectomy	Nodule size 0,5 - 1.3 cm
Sivakumar T et al.(80)	130	4	11 total thyroidectomy	-

Table 3. Adverse events of included studies

Study ID	approach	RLN injury (T/P)	SLN injury (T/P)	Mental nerve injury (T/P)	Hypo-para thyroidism (T/P)	Infection	Seroma	Emphysema	Perforation	Postoperative bleeding	Various
E.Karakas et al (68)	Tovara	0/1	-	4/0	2/0	-	-	-	-	-	-
	Toetva/tovra	5/1	-	21/2	5/0	-	-	-	-	-	1 skin lesion
Xu Z. et al (69)	Toetva	1/0	-	22/0	5/0	1	-	-	-	1	3 swallowing discomfort
Tan Y et al (34)	Toetva	1/0	0	0/0	0	0	-	-	-	0	2 effusion in the operative field
Wang T et al.(70)	Toetva	5/1	-	1/0	2/0	1	-	-	-	-	2 swallowing discomfort
Guo F. et al (71)	Toetva	-	-	-	-	1	-	-	-	-	1 pleural injury, 1 skin injury
Kadem SG et al.(72)	Toetva	0/0	-	1/0	0/0	0	0	1	0	0	0
Ahn JH et al (21)	Toetva	7/1	-	0/0	5/2	0	2	4	-	1 hematoma	1 horner's syndrome 2 "oral" wounds
Park JO et al. (73)	Toetva	0/0	-	0/0	1/0	0	-	0	0	0	0
Peng X et al.(74)	Toetva(MND) Toetva(NMN)	2/1 1/1	-	0/0 3/0	1/0 1/0	1 0	2 1	1 0	-	-	-
Rusell JO et al.(67)	Toetva	4/0	-	-/0	-/0	-	1	-	-	1	1conversion bleeding
Tesseroli M et al.(75)	Toetva	0/0	-	0/0	0/0	0	0	0	-	0	3 chin skin bruise 1 dehiscence
O.Russel et al. (67)	Toetva	-/0	-	-/0	-	-	0	-	1	0	1 conversion
Bian C et al.(76)	Toetva	-/0	-	17/0	-	0	-	-	1	0	1tracheal injury
Razavi CR et al.(20)	Toetva	-/0	-	-/0	-	-	-	-	-	-	1 conversion
Wang Y et al.(77)	Toetva	0/0	13/18	1/18	-	-	-	-	-	-	-

Bakkar S et al.(23)	Toetva	0/0	-	0/0	-	0	-	5	1	0	5 long standing pulling sensation 1chin burn (diathermy) 1conversion
Anuwong A et al. (19)	Toetva	25/0	-	3/0	46/0	0	20	0	-	3	3 conversion 1 hematoma
Chen HK et al.(78)	Toetva	0/0	-	1/0	3/0	0	-	-	-	-	-
Jipratoom P et al.(79)	Toetva	4/0	-	0/0	10/0	0	-	-	-	1	
Wang Y et al.(6)	Toetva	0/0	0	-	1/0	0	0	0	0	0	-
Sivakumar T et al.(80)	Toetva	0/0	-	0/0	0/0	0	0	0	0	0	0
Hong YT et al. (52)	Toetva	3/0	-	-/0	1/0	2	2	0	-	-	1 tracheal injury 1 C02 embolism 3 bruising on the chin 1 dimpling on the chin
Zhang D et al.(56)	Toetva	1/0	-	3/0	1/0	0	0	0	0	0	-
Lira et al.(81)	Toetva	2/0	-	0/0	4/0	1	1	-	0	-	disturbance in the chin, minor bruising
Le.QV et al.(82)	Toetva	0/0	-	0/0	0/0	0	0	0	0	1	CO2 embolism
Dinc B.et al (83)	Toetva	2/0	-	0/0	10/0	3	3	0	2	2	Temp.hyperpigmentation,2converrion.
Russell JO et al.(84)	Toetva	9/0	-	5/0	14/0	2	4	0	0	0	5 conversion,1 skin burn,26chin numbness
Deroide G. et al (85)	Toetva	7/0	-	-	6/2	0	0	0	3	0	-
Chai YJ et al. (86)	Toetva	5/1	-	0/0	1/0	0	1	0	-	1	-

SLN: Superior laryngeal nerve, RLN: Recurrent laryngeal nerve, MN: Mental nerve, T: transient, P: permanet

REFERENCES

1. Park JH, Bilegsaikhan SE and Suh YJ. A Novel Technique for Performing Transoral Endoscopic Thyroidectomy Vestibular Approach (TOETVA): A Single-port Platform. Surg LaparoscEndoscPercutan Tech. 2020 Feb;30(1):e4-e7.PMID: 31790081.doi: 10.1097/SLE.0000000000000739.
2. Anuwong A, Sasanakietkul T and Jitpratoom P. Transoral endoscopic thyroidectomy vestibular approach (TOETVA): indications, techniques and results. SurgEndosc. 2018 Jan;32(1):456-465.PMID: 28717869. doi: 10.1007/s00464-017-5705-8.
3. Juarez MC, Ishii L and Nellis JC. Objectively measuring social attention of thyroid neck scars and transoral surgery using eye tracking. Laryngoscope. 2019 Dec;129(12):2789-2794.PMID: 30900247. doi: 10.1002/lary.27933.
4. Zhang D, Park D and Sun H. Indications, benefits and risks of transoral thyroidectomy. Best Pract Res Clin Endocrinol Metab. 2019 Aug;33(4):101280. PMID: 31204296.doi: 10.1016/j.beem.2019.05.004.
5. Tan CT, Cheah WK and Delbridge L. "Scarless" (in the neck) endoscopic thyroidectomy (SET): an evidence-based review of published techniques. World J Surg. 2008 Jul;32(7):1349-57.PMID: 18360737. doi: 10.1007/s00268-008-9555-3.
6. Wang Y, Yu X and Wang P. Implementation of Intraoperative Neuromonitoring for Transoral Endoscopic Thyroid Surgery: A Preliminary Report. J Laparoendosc Adv Surg Tech A. 2016 Dec;26(12):965-971. PMID:27585396.doi: 10.1089/lap.2016.0291.
7. Lee HY, Lee JY and Dionigi G. The Efficacy of Intraoperative Neuromonitoring During Robotic Thyroidectomy: A Prospective, Randomized Case-Control Evaluation. J Laparoendosc Adv Surg Tech A. 2015 Nov;25(11):908-14.PMID: 26575249.doi: 10.1089/lap.2014.0544.
8. Miccoli P, Berti P and Raffaelli M. Comparison between minimally invasive video-assisted thyroidectomy and conventional thyroidectomy: a prospective randomized study. Surgery. 2001 Dec;130(6):1039-43. PMID: 11742335. doi: 10.1067/msy.2001.118264.

9. Miccoli P, Rago R, and Massi M. Standard versus video-assisted thyroidectomy: objective postoperative pain evaluation. Surg Endosc. 2010 Oct;24(10):2415-7. PMID: 20195641.doi: 10.1007/s00464-010-0964-7.
10. Dionigi G, Boni L and Rovera F. Wound morbidity in mini-invasive thyroidectomy. Surg Endosc. 2011 Jan;25(1):62-7. PMID: 20526624.doi: 10.1007/s00464-010-1130-y.
11. Tae K, Ji YB and Song CM. Robotic and Endoscopic Thyroid Surgery: Evolution and Advances. Clin Exp Otorhinolaryngol. 2019 Feb;12(1):1-11. PMID: 30196688.doi: 10.21053/ceo.2018.00766.
12. Kurumety SK, Helenowski IB and Goswami. Post-thyroidectomy neck appearance and impact on quality of life in thyroid cancer survivors. Surgery. 2019 Jun;165(6):1217-1221. PMID: 31030973. doi: 10.1016/j.surg.2019.03.006..
13. Choi Y, Lee JH and Kim YH. Impact of postthyroidectomy scar on the quality of life of thyroid cancer patients. Ann Dermatol. 2014 Dec;26(6):693-9. PMID: 25473220.doi: 10.5021/ad.2014.26.6.693.
14. Juarez MC, Ishii L, and Nellis JC. Objectively measuring social attention of thyroid neck scars and transoral surgery using eye tracking. Laryngoscope. 2019 Dec;129(12):2789-2794. PMID: 30900247.doi: 10.1002/lary.27933.
15. Felix C, Russell JO and Juman S. Cervical scar satisfaction post conventional thyroidectomy. Gland Surg. 2019 Dec;8(6):723-728. PMID: 32042680.doi: 10.21037/gs.2019.11.17.
16. Wilhelm T and Metzig A. Endoscopic minimally invasive thyroidectomy (eMIT): a prospective proof-of-concept study in humans. World J Surg.2011 Mar;35(3):543-51.PMID: 21088839. doi: 10.1007/s00268-010-0846-0.
17. Yi JW, Yoon SG and Kim HS. Transoral endoscopic surgery for papillary thyroid carcinoma: initial experiences of a single surgeon in South Korea. Ann Surg Treat Res. 2018 Aug;95(2):73-79.PMID: 30079323.doi: 10.4174/astr.2018.95.2.73.
18. Russell JO, Sahli ZT and Shaear M. Transoral thyroid and parathyroid surgery via the vestibular approach-a 2020 update. Gland Surg. 2020 Apr;9(2):409-416.PMID: 32420266.doi: 10.21037/gs.2020.03.05.

19. Anuwong A, Ketwong K and Jitpratoom P. Safety and Outcomes of the Transoral Endoscopic Thyroidectomy Vestibular Approach. JAMA Surg. 2018 Jan 1;153(1):21-27.PMID: 28877292.doi: 10.1001/jamasurg.2017.3366.
20. Razavi CR, Vasiliou E and Tufano RP. Learning Curve for Transoral Endoscopic Thyroid Lobectomy. Otolaryngol Head Neck Surg. 2018 Oct;159(4):625-629.PMID: 30126330.doi: 10.1177/0194599818795881.
21. AhnJHandYi JW. Transoral endoscopic thyroidectomy for thyroid carcinoma: outcomes and surgical completeness in 150 single-surgeon cases. Surg Endosc. 2020 Feb;34(2):861-867. PMID: 31139987.doi: 10.1007/s00464-019-06841-8.
22. Witzel K, von RahdenBHand Kaminski C. Transoral access for endoscopic thyroid resection. Surg Endosc. 2008 Aug;22(8):1871-5.PMID: 18163167.doi: 10.1007/s00464-007-9734-6.
23. Bakkar S, Al Hyari M and Naghawi M. Transoral thyroidectomy: a viable surgical option with unprecedented complications-a case series. J Endocrinol Invest. 2018 Jul;41(7):809-813. PMID: 29243180 doi: 10.1007/s40618-017-0808-6.
24. Anuwong A. Transoral endoscopic thyroidectomy vestibular approach: a series of the first 60 human cases. World J Surg 2016;40(3):491–7.PMID: 26546193.doi: 10.1007/s00268-015-3320-1
25. Kim HK, Chai YJ and Dionigi G. Transoral Robotic Thyroidectomy for Papillary Thyroid Carcinoma: Perioperative Outcomes of 100 Consecutive Patients. World J Surg. 2019 Apr;43(4):1038-1046.PMID: 30539261. doi: 10.1007/s00268-018-04877-w.
26. Colella G, Giudice A and Siniscalchi G. Chin numbness: a symptom that should not be underestimated: a review of 12 cases. Am J Med Sci. 2009 Jun;337(6):407-10. PMID: 19359984.doi: 10.1097/MAJ.0b013e31819299fa.
27. Ewbank RL. Mental nerve neuropathy. Oral Surg Oral Med Oral Pathol. 1980 Oct;50(4):325-6. PMID: 6935583. doi: 10.1016/0030-4220(80)90415-6.
28. Udelsman R, Anuwong A and Oprea AD. Trans-oral Vestibular Endocrine Surgery: A New Technique in the United States. Ann Surg. 2016 Dec;264(6):e13-e16.PMID: 27649533. doi: 10.1097/SLA.0000000000002001.

29. Dionigi G, Wu CW and Tufano RP. Monitored transoral endoscopic thyroidectomy via long monopolar stimulation probe. J Vis Surg. 2018 Jan 26;4:24.PMID: 29445610. doi: 10.21037/jovs.2017.12.25.
30. Dionigi G, Boni L and Rovera F. Neuromonitoring and video-assisted thyroidectomy: a prospective, randomized case-control evaluation. Surg Endosc. 2009 May;23(5):996-1003. PMID: 18806939. doi: 10.1007/s00464-008-0098-3.
31. Gavid M, Dubois MD and Larive E. Superior laryngeal nerve in thyroid surgery: anatomical identifcation and monitoring. EurArchOtorhinolaryngol. 2017 Sep;274(9):3519-3526. PMID: 28687919.doi: 10.1007/s00405-017-4666-9.
32. Lore JM Jr, Kokocharov SI and Kaufman S.Thirty-eight-year evaluation of a surgical technique to protect the external branch of the superior laryngeal nerve during thyroidectomy.AnnOtolRhinolLaryngol. 1998 Dec;107(12):1015-22. PMID: 9865631.doi: 10.1177/000348949810701204.
33. Gurleyik E and Gurleyik G. Intraoperative Monitoring of External Branch of the Superior Laryngeal Nerve: Functional Identification, Motor Integrity, and its Role on Vocal Cord Function. J Invest Surg. 2018 Dec;31(6):509-514.Epub 2017 Sep 27. PMID: 28952819. doi:10.1080/08941939.2017.1362489.
34. Tan Y, Guo B and Deng X. Transoral endoscopic selective lateral neck dissection for papillary thyroid carcinoma: a pilot study. Surg Endosc. 2020 Dec;34(12):5274-5282. PMID: 31834511 doi: 10.1007/s00464-019-07314-8.
35. Song CM, Jung JH and Ji YB.Relationship between hypoparathyroidism and the number of parathyroid glands preserved during thyroidectomy. World J Surg Oncol. 2014 Jul 7;12:200. PMID: 25000948.doi: 10.1186/1477-7819-12-200.
36. Ywata de Carvalho A and Chulam TC, Kowalski LP. Long-term Results of Observation vs Prophylactic Selective Level VI Neck Dissection for Papillary Thyroid Carcinoma at a Cancer Center. JAMA Otolaryngol Head Neck Surg. 2015 Jul;141(7):599-606.PMID: 25997016. doi: 10.1001/jamaoto.2015.0786.
37. Selberherr A, Scheuba C and Riss P. Postoperative hypoparathyroidism after thyroidectomy: efficient and cost-effective diagnosis and treatment. Surgery. 2015 Feb;157(2):349-53.PMID: 25532435. doi: 10.1016/j.surg.2014.09.007.

38. Fewins J, Simpson CB and Miller FR. Complications of thyroid and parathyroid surgery. Otolaryngol Clin North Am. 2003 Feb;36(1):189-206, x. PMID: 12803016.doi: 10.1016/s0030-6665(02)00129-9.
39. Shan L and Liu J. A Systemic Review of Transoral Thyroidectomy. Surg LaparoscEndoscPercutan Tech. 2018 Jun;28(3):135-138.PMID: 29389814 doi: 10.1097/SLE.0000000000000512.
40. Dionigi G, Bacuzzi A and Lavazza M. Transoral endoscopic thyroidectomy: preliminary experience in Italy. Updat Surg 69(2):225–234. PMID: 28405949.doi: 10.1007/s13304-017-0436-x.
41. Yang J, Wang C and Li J. Complete Endoscopic Thyroidectomy via Oral Vestibular Approach Versus Areola Approach for Treatment of Thyroid Diseases. J Laparoendosc Adv Surg Tech A. 2015 Jun;25(6):470-6.PMID: 26061132. doi: 10.1089/lap.2015.0026.
42. Fernandez-Ranvier G, Meknat A and Guevara DE. Transoral Endoscopic Thyroidectomy Vestibular Approach. JSLS. 2019 Oct-Dec;23(4):e2019.00036.PMID: 31719772 doi: 10.4293/JSLS.2019.00036.
43. Shan CX, Zhang W and Jiang DZ. Prevalence, risk factors, and management of seroma formation after breast approach endoscopic thyroidectomy. World J Surg. 2010 Aug;34(8):1817-22. PMID: 20414774.doi: 10.1007/s00268-010-0597-y.
44. Zhang D, Wu CW and InversiniD.Lessons Learned From a Faulty Transoral Endoscopic Thyroidectomy Vestibular Approach. Surg LaparoscEndoscPercutan Tech. 2018 Oct;28(5):e94-e99.PMID: 29975356.doi: 10.1097/SLE.0000000000000555.
45. Bellantone R, Lombardi CP and Rubino F. Arterial PCO2 and cardiovascular function during endoscopic neck surgery with carbon dioxide insufflation. Arch Surg. 2001 Jul;136(7):822-7.PMID: 11448398. doi: 10.1001/archsurg.136.7.822.
46. Kim SH, Park KS and Shin HY. Paradoxical carbon dioxide embolism during endoscopic thyroidectomy confirmed by transesophageal echocardiography. J Anesth. 2010 Oct;24(5):774-7. PMID: 20683735.doi: 10.1007/s00540-010-0992-4.
47. Ochiai R, Takeda J and Noguchi J, Ohgami M, Ishii S. Subcutaneous carbon dioxide insufflation does not cause hypercarbia during endoscopic thyroidectomy.

AnesthAnalg. 2000 Mar;90(3):760-2. PMID: 10702471.doi: 10.1097/00000539-200003000-00046.

48. Gottlieb A, Sprung J and Zheng XM. Massive subcutaneous emphysema and severe hypercarbia in a patient during endoscopic transcervical parathyroidectomy using carbon dioxide insufflation. AnesthAnalg. 1997 May;84(5):1154-6.PMID: 9141952 doi: 10.1097/00000539-199705000-00040.
49. Anuwong A. Strategy to Prevent Subcutaneous Emphysema and Gas Insufflation-Related Complications in Transoral Endoscopic Thyroidectomy Vestibular Approach: Reply. World J Surg. 2017 Oct;41(10):2649-2650.PMID: 28474274. doi: 10.1007/s00268-017-4042-3.
50. Salmerón-Escobar JI and del Amo-Fernández de Velasco A. Antibiotic prophylaxis in Oral and Maxillofacial Surgery. Med Oral Patol Oral Cir Bucal. 2006 May 1;11(3):E292-6. PMID: 16648771.
51. Liu N, Chen B and Li L. Subplatysmal or subfascial approach in totally endoscopic thyroidectomy has better postoperative efficacy for voice, sensory, swallowing symptoms and cosmetic result. Cohort study. Int J Surg. 2018 Dec;60:22-27. PMID: 30389533.doi: 10.1016/j.ijsu.2018.10.034.
52. Hong YT, Ahn JH and Kim JH. Bi-institutional experience of transoral endoscopic thyroidectomy: Challenges and outcomes. Head Neck. 2020 Aug;42(8):2115-2122. PMID: 32212365.doi: 10.1002/hed.26153.
53. Fu J, Luo Y and Chen Q. Transoral Endoscopic Thyroidectomy: Review of 81 Cases in a Single Institute. J Laparoendosc Adv Surg Tech A. 2018 Mar;28(3):286-291. PMID: 29297741 doi: 10.1089/lap.2017.0435.
54. Nakajo A, Arima H and Hirata M. Trans-Oral Video-Assisted Neck Surgery (TOVANS). A new transoral technique of endoscopic thyroidectomy with gasless premandibleapproach. Surg Endosc. 2013 Apr;27(4):1105-10. PMID: 23179070.doi: 10.1007/s00464-012-2588-6.
55. Wang C, Zhai H and Liu W. Thyroidectomy: a novel endoscopic oral vestibular approach. Surgery. 2014 Jan;155(1):33-8.PMID: 23890962. doi: 10.1016/j.surg.2013.06.010.

56. Zhang D, Caruso E and Sun H. Classifying pain in transoral endoscopic thyroidectomy. J Endocrinol Invest. 2019 Nov;42(11):1345-1351.PMID: 31187465. doi: 10.1007/s40618-019-01071-0.
57. You JY, Kim HY and Chai YJ, Kim HK. Transoral Robotic Thyroidectomy Versus Conventional Open Thyroidectomy: Comparative Analysis of Surgical Outcomes in Thyroid Malignancies. J Laparoendosc Adv Surg Tech A. 2019 Jun;29(6):796-800. PMID: 30785841. doi: 10.1089/lap.2018.0587.
58. Wu YJ, Chi SY and Elsarawy A. What is the Appropriate Nodular Diameter in Thyroid Cancer for Extraction by Transoral Endoscopic Thyroidectomy Vestibular Approach Without Breaking the Specimens? A Surgicopathologic Study. Surg LaparoscEndoscPercutan Tech. 2018 Dec;28(6):390-393.PMID: 30074529. PMID: 30074529.doi: 10.1097/SLE.0000000000000563.
59. Park JO and Sun DI. Transoral endoscopic thyroidectomy: our initial experience using a new endoscopic technique. Surg Endosc. 2017 Dec;31(12):5436-5443. PMID: 28523362. doi: 10.1007/s00464-017-5594-x.
60. Chen S, Zhao M and Qiu J. Transoral vestibule approach for thyroid disease: a systematic review. Eur Arch Otorhinolaryngol. 2019 Feb;276(2):297-304. PMID: 30460401. doi: 10.1007/s00405-018-5206-y.
61. Johri G, Chand G and Mishra A. Endoscopic versus Conventional Thyroid Surgery: A Comparison of Quality of Life, Cosmetic Outcomes and Overall Patient Satisfaction with Treatment. World J Surg. 2020 Dec;44(12):4118-4126. PMID: 32789681doi: 10.1007/s00268-020-05732-7.
62. Jeong JJ, Kang SW and Yun JS. Comparative study of endoscopic thyroidectomy versus conventional open thyroidectomy in papillary thyroid microcarcinoma (PTMC) patients. J Surg Oncol. 2009 Nov 1;100(6):477-80. PMID: 19653245. doi: 10.1002/jso.21367.
63. Liu S, Qiu M and Jiang DZ. The learning curve for endoscopic thyroidectomy: a single surgeon's experience. SurgEndosc. 2009 Aug;23(8):1802-6. PMID: 19247710.doi: 10.1007/s00464-009-0332-7.
64. Kim HY, Chai YJ and Dionigi G. Transoral robotic thyroidectomy: lessons learned from an initial consecutive series of 24 patients. Surg Endosc. 2018 Feb;32(2):688-694. PMID: 28726141. doi: 10.1007/s00464-017-5724-5.

65. Shulutko AM, Semikov VI and Osmanov EG. Evaluation Criteria and Surgical Technique for Transoral Access to the Thyroid Gland: Experimental Study. J Invest Surg. 2019 Aug;32(5):421-427.PMID: 29370544. doi: 10.1080/08941939.2018.1424271.
66. Witzel K, Messenbaeck F and WeitzendorferM.Transoral thyroidectomy: limitations, patients' safety, and own experiences. Updates Surg. 2017;69(2):193-198.PMID: 28573543.doi: 10.1007/s13304-017-0457-5.
67. Russell JO, Razavi CR and Garstka ME. Remote-access thyroidectomy: a multi-institutional north American experience with transaxillary, robotic facelift, and transoral endoscopic vestibular approaches. J Am Coll Surg. 2019 Apr;228(4):516-522. PMID: 30586640. doi: 10.1016/j.jamcollsurg.2018.12.005.
68. Karakas E,G.Klein and Schopf S.Transoral thyroid surgery vestibular approach: does size matter anymore?; Italian Society of Endocrinology (SIE) 2020 May;43(5):615-622. PMID: 31989449.doi: 10.1007/s40618-019-01149-9.
69. Xu Z, Song J and Wang Y, Tan L, Sun S, Meng Y. A comparison of transoral vestibular and bilateral areolar endoscopic thyroidectomy approaches for unilateral papillary thyroid microcarcinomas. WideochirInne Tech Maloinwazyjne. 2019 Dec;14(4):501-508.PMID: 31908695doi: 10.5114/wiitm.2019.84759.
70. Wang T, Wu Y and Xie Q. Safety of central compartment neck dissection for transoral endoscopic thyroid surgery in papillary thyroid carcinoma. Jpn J Clin Oncol. 2020 Apr 7;50(4):387-391.PMID: 31829423.doi: 10.1093/jjco/hyz195.
71. Guo F, Wang W and Zhu X. Comparative Study Between Endoscopic Thyroid Surgery via the Oral Vestibular Approach and the Areola Approach. J Laparoendosc Adv Surg Tech A. 2020 Feb;30(2):170-174. PMID: 31621490.doi: 10.1089/lap.2019.0562.
72. Kadem SG, Habash SM and Jasim AH. Transoral Endoscopic Thyroidectomy via Vestibular Approach: A series of the first ten cases in Iraq. Sultan Qaboos Univ Med J. 2019 Feb;19(1):e68-e72.PMID: 31198599.doi: 10.18295/squmj.2019.19.01.013.
73. Park JO, Park YJ and Kim MR. Gasless transoral endoscopic thyroidectomy vestibular approach (gasless TOETVA). Surg Endosc. 2019 Sep;33(9):3034-3039. PMID: 31087173.doi: 10.1007/s00464-019-06826-7.

74. Peng X, Li Z and Li H. The clinical application of mental nerve dissection in transoral endoscopic thyroidectomy via an oral vestibular approach. Surg Endosc. 2020 Jan;34(1):153-158. PMID: 30877568.doi: 10.1007/s00464-019-06743-9.
75. Tesseroli MAS, Spagnol M and Sanabria Á. Transoral endoscopic thyroidectomy by vestibular approach (TOETVA): initial experience in Brazil.Rev Col Bras Cir. 2018 Nov 14;45(5):e1951. Portuguese, English. PMID: 30462826.doi: 10.1590/0100-6991e-20181951.
76. Bian C, Liu H and Yao XY. Complete endoscopic radical resection of thyroid cancer via an oral vestibule approach. Oncol Lett. 2018 Nov;16(5):5599-5606.PMID: 30344714. doi: 10.3892/ol.2018.9369.
77. Wang Y, Zhang Z and Zhao Q. Transoral endoscopic thyroid surgery via the tri-vestibular approach with a hybrid space-maintaining method: A preliminary report. Head Neck. 2018 Aug;40(8):1774-1779.PMID: 29603475.doi: 10.1002/hed.25157.
78. Chen HK, Chen CL and Wen KS. Application of transoral continuous intraoperative neuromonitoring in natural orifice transluminal endoscopic surgery for thyroid disease: a preliminary study. Surg Endosc. 2018 Jan;32(1):517-525.PMID: 28643050. doi: 10.1007/s00464-017-5656-0.
79. Jitpratoom P, Ketwong K and Sasanakietkul T. Transoral endoscopic thyroidectomy vestibular approach (TOETVA) for Graves' disease: a comparison of surgical results with open thyroidectomy. Gland Surg. 2016 Dec;5(6):546-552.PMID: 28149798.doi: 10.21037/gs.2016.11.04.
80. Sivakumar T andAmizhthu RA. Transoral endoscopic total thyroidectomy vestibular approach: A case series and literature review. J Minim Access Surg. 2018 Apr-Jun;14(2):118-123. PMID: 29067943. doi: 10.4103/jmas.JMAS_3_17.
81. Lira RB, Ramos AT and Nogueira RMR. Transoral thyroidectomy (TOETVA): Complications, surgical time and learning curve. Oral Oncol. 2020 Nov;110:104871.PMID: 32619928 doi: 10.1016/j.oraloncology.2020.104871.
82. Le QV, Ngo DQ and Tran TD. Transoral Endoscopic Thyroidectomy Vestibular Approach: An Initial Experience in Vietnam. Surg LaparoscEndoscPercutan Tech. 2020 Jun;30(3):209-213. PMID: 32032330. doi: 10.1097/SLE.0000000000000764.

83. Dinç B, İlkerTuran M and RızaGündüz U. Transoral endoscopic thyroidectomy vestibular approach (TOETVA): Our outcomes from Turkey. Turk J Surg. 2020 Dec 29;36(4):340-346.. PMID: 33778392.doi: 10.47717/turkjsurg.2020.4765
84. Russell JO, Razavi CR and Shaear M. Transoral Thyroidectomy: Safety and Outcomes of 200 Consecutive North American Cases. World J Surg. 2021 Mar;45(3):774-781.PMID: 33205227.doi: 10.1007/s00268-020-05874-8.
85. Deroide G, Honigman I and Berthe A, Branger F, Cussac-Pillegand C, Richa H, AnuwongATrans oral endoscopic thyroidectomy (TOETVA): First French experience in 90 patients. J Visc Surg. 2021 Apr;158(2):103-110.PMID: 33676861.doi: 10.1016/j.jviscsurg.2021.02.001.
86. Chai YJ, Chae S and Oh MY. Transoral Endoscopic Thyroidectomy Vestibular Approach (TOETVA): Surgical Outcomes and Learning Curve. J Clin Med. 2021 Feb 19;10(4):863. PMID: 33669741. doi: 10.3390/jcm10040863.

CONFLICT OF INTEREST: The authors declare that they have no conflict of interest.

AKNOWLEDGEMENTS: GD for his tenacious mentoring and support, E.S. for his kind supervision and N.N. for his enthusiastic and fair approval

AUTHORS CONTRIBUTION

E.A contributed by research in electronic databases, reading and sorting articles and tabularizing results.

G.D. contributed by reading, writing and editing this manuscript

E.S. contributed by conceiving the idea and approving this manuscript

G.T., D.D, N.N. contributed by reading and approving the manuscript

FINANCIAL SUPPORT