

# Transoral endoscopic thyroidectomy: current state of the art—a systematic literature review and results of a bi-center study

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**Abstract:** Transoral endoscopic approaches for thyroidectomy (TOET) have been developing since 2008. To date, single centers have gained great experience and patients treated worldwide (477 by February 2016) have resulted in complication rates [transient recurrent laryngeal nerve palsy (RLNP) 2.5%, permanent RLNP 0.4%, transient mental paraesthesia 5.9%, local or neck site infections 1.2%] comparable to conventional open and other endoscopic or robotic approaches. The conversion rate from TOET to open surgery is very low (0.6%). This data is based on a systematic literature review (PubMed search) and the results of a bi-centric study in Xiamen, P.R. China and Borna, Germany. TOET was performed on thyroid nodules or cervical masses in 93 patients. Isthmus resections, hemi, subtotal and total thyroidectomies were performed. A learning curve could be shown and cut-suture-times approached those of conventional thyroid surgery. One permanent RLNP was observed and a transient mental paraesthesia, which resolved within 3–4 weeks, was noted in 15 cases. In conclusion, TOET has left the stage of infancy and has proven to be a good alternative to conventional open or endoscopic/robotic-assisted thyroidectomy with the advantage of decreased postoperative pain and diminished swallowing disorders following thyroid surgery. Lastly, it secures an optimal cosmetic result since TOET leaves no visible scars even at the access points in the mouth.

**Keywords:** Transoral endoscopic thyroidectomy (TOET); endoscopic minimally invasive thyroidectomy (eMIT); systematic literature review; cohort study

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### Introduction

For the past 90 years, since its introduction in 1906, the thyroidectomy has remained a standardized surgical procedure in line with the experiences and developments of Emil Theodor Kocher (1). Intraoperative neuromonitoring and the use of optical aids have assisted in developing the procedure into a safe and successful operation (2-4). The rates of transient and permanent recurrent laryngeal never (RLN) palsy have dropped down to 2.7% and 0.8% respectively (5).

Nevertheless, complication rates in thyroid surgery remain high: in an Italian multicenter study of 14,934 patients, Rosato and colleagues found transient complications in 17.4% of patients and permanent complications in 7.1% (6). Patients are most affected by swallowing disorders, dysphonia and dyspnea, wrinkling, and the visible scars. Therefore, in the mid-nineties of the last century, first attempts were made to apply the very effective laparoendoscopic technique, then used in general surgery, to the surgery of thyroid and parathyroid glands. S1522

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Figure 1 Concept of the TOET. TOET, transoral endoscopic thyroidectomy.

Gagner from Cleveland, US, Hüscher from Esine, Italy, and Yeung from Hong Kong, China were the protagonists of this new approach, using small cervical incisions and laparoendoscopic instruments as well as endoscopes for this purpose (7-9).

At that time, endoscopic thyroid surgery developed in different directions in Europe, the United States and Asia. In Italy, Miccoli adopted the idea of the laparoendoscopic technique and developed his minimally invasive videoassisted thyroidectomy (MIVAT: minimized incision length in the classical position) which has since become wide spread in Europe and America (10,11); Terris stated in 2008 "that MIVAT now represents state-of-the-art management of carefully selected patients when performed in the hands of appropriately trained surgeons" (12). Moreover, MIVAT demonstrated superiority to the conventional thyroidectomy in regard to postoperative pain, patient satisfaction, voice function, and swallowing outcomes (13).

Extra cervical approaches (axillary, breast, chest, and combined approaches) were developed in Asia due to cultural and religious differences in the perception of scars on the visible neck region (14-16). However, the extensive dissection necessary to reach the target region means these approaches do not comply with the term minimally invasive, even though they have reached the goal of invisibility in the neck approach for thyroidectomy. Astonishingly, the postoperative pain in these extra-cervical approaches does not differ significantly to standard or minimized incision length (MIVAT) thyroidectomies (17-21). Ultimately, all extra-cervical approaches leave visible scars, even when not located in the anterior neck region.

Consequently, minimally invasive approaches located closer to the thyroid were sought. In 2008, Witzel reported a transoral, single port approach for thyroid surgery which had proved feasible in an animal study (22). This approach was further elaborated on by Karakas *et al.* and applied clinically to two patients (23,24) with serious complications in one patient. The group finally terminated the ongoing study due to the rate of serious complications and declared the single-port approach to be "nonsense" at that time (25).

At the same time, our group developed a 3-port transoral approach for endoscopic minimally invasive thyroidectomy (eMIT), which overcame the limitations of the principal communication of Witzel and Karakas (*Figure 1*); eMIT was proved feasible and safe in anatomical, ultrasound, and animal studies (26-28). On the 18th of March 2009, prior to the Karakas group, this approach was successfully applied clinically for the first time ever in a 53-year-old male (29) and was followed up by a proof-of-concept study (30).

In November 2011 the principal author was invited to Xiamen, China to attend a conference on thyroid surgery and to present the method. During this stay, the first Asian patient underwent a thyroidectomy via the transoral route (31). Subsequent to this successful start, we conducted a prospective cohort study in Xiamen, China and Borna, Germany, which will be reported on later.

Following the scope of the conference in China, a rapid upcoming interest in this challenging new approach was seen in the Asia-Pacific region (32-38). Most recently, Anuwong from Bangkok, Thailand published his experiences in the first 60 patients treated by transoral thyroidectomy (39): a hemi thyroidectomy (single nodules) was performed in 42 patients and a total thyroidectomy or Hartley-Dunhill procedure in 22 patients (multinodular goiters, Graves' disease). Two cases displayed a papillary carcinoma, and a total thyroidectomy with central neck dissection (level VII) was performed. Median cut-suture-time was 115.5 min and the median blood loss was 30 mL. Two patients complained of a 2-month long transient hoarseness. No mental nerve injury or infections were found. Anuwong



Figure 2 Results of the systematic literature search in PubMed with the following search strategy: "((((trans[All Fields] AND ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields])) OR transoral[All Fields]) OR trans-oral[All Fields]) AND ("endoscopy"[MeSH Terms] OR "endoscopy"[All Fields])) AND ("thyroidectomy"[MeSH Terms] OR "thyroidectomy"[All Fields])).

concluded the transoral endoscopic thyroidectomy (TOET) to be safe and feasible, and resulting in no visible scarring leading to ideal cosmetic results.

Based on the published data and the results of a prospective cohort study performed in China and Germany, we want to outline the current state of the art of TOET.

## Methods

A systematic literature search was performed in PubMed and the results of anatomical, animal, and other published studies regarding the transoral approach (single- or 3-port) were analyzed (*Figure 2*). Additionally, the results of studies on TOET from different centers, which were presented at the 1<sup>st</sup> International Thyroid NOTES Conference on the 3<sup>rd</sup> and 4<sup>th</sup> of February 2016 at the Police General Hospital in Bangkok, Thailand, were analyzed together with the published data.

After the first successful TOET procedure in Asia (11/12/2011), G. Wu from Xiamen, China also started a prospective cohort study according to the principles of the ongoing study by the principal author. The data was therefore pooled and analyzed together. The surgical method of the eMIT procedure (3-port sublingual) had

already been presented elsewhere (30). Indications for surgery, cut-suture-times, intraoperative blood loss, resected specimen volumes, histopathologic findings, and complications were recorded.

#### Results

#### Systematic literature review

The systematic search for related publications in PubMed (11/01/2016) revealed 25 eligible studies describing results of cadaver, animal and ultrasound studies as well as human applications; an additional 11 publications dealing with TOET were identified in different databases (Embase, grey literature).

There were only six suitable publications regarding the single-port approach proposed by Witzel *et al.* (22), three of which dealt with human applications (*Table 1*). Seven patients were treated by the approach and the group most familiar with it terminated an ongoing study due to serious complications (25).

The 3-port-approach (26,42), as developed and proposed by our group, gained more interest worldwide. The method proved feasible in 12 studies on 85 cadavers from Germany,

Authors	Country	Online	Study type	Ν
Witzel et al. (22)	Austria	12/28/2007	Pigs	10
Karakas et al. (23)	Germany	12/24/2009	Porcine/human cadaver + cadaver	10, 5
			Pigs	10
Karakas et al. (24)	Germany	03/31/2011	Pigs	10
			Cadaver	10
Woo (40)	Korea	05/09/2014	Human	1
Karakas et al. (25)	Germany	04/13/2014	Human	5
Witzel et al. (41)	Germany	06/14/2016	Human	1

Table 1 Published studies on transoral thyroidectomy—single-port approach

Table 2 Published anatomical studies—3-port approach

Authors	Country	Epub	Ν
Benhidjeb et al. (42)	Germany	03/05/2009	5
Wilhelm et al. (43)	Germany	11/27/2009	8
Richmon et al. (44)	USA	06/15/2011	2
Richmon et al. (45)	USA	07/21/2011	2
Guo <i>et al</i> . (32)	China	02/11/2012	25
Ng (37)	China	05/20/2013	2
Su <i>et al</i> . (46)	China	06/01/2013	6
Guo <i>et al</i> . (47)	China	03/14/2014	15
Park <i>et al</i> . (34)	Korea	02/05/2014	6
Lee et al. (35)	Korea	08/15/2014	7
Lee et al. (48)	Korea/USA	01/28/2015	2
Cai <i>et al</i> . (49)	China/Germany	08/04/2015	5

China, Korea, and the USA (*Table 2*). Additional animal studies in Germany and Korea were able to demonstrate the safety of the TOET in pigs (28,35,50).

On the 3<sup>rd</sup> and 4<sup>th</sup> of February 2016, the 1<sup>st</sup> International Thyroid NOTES Conference took place at the Police General Hospital in Bangkok, Thailand and all centers performing TOET worldwide (Germany, China, Japan, Korea, Thailand, and India) presented their experiences. Together with the published studies (*Table 3*) at this time, 477 patients had undergone transoral thyroidectomies worldwide. The complication rates were comparable or even better than the rates reported in conventional, MIVAT, endoscopic or robotic approaches and the postoperative course regarding pain and swallowing function seemed favorable for the TOET-procedures.

# The German-Sino bi-center study

A prospective cohort study was performed between March 2009 and January 2016 in Xiamen, China and Borna, Germany (authors T Wilhelm and G Wu). A total of 96 patients [92 females with a mean age of 36±10 years (standard deviation) and 4 males aged 48±4 years] were treated by TOET using the 3-port bi-vestibular and sublingual approach. Ten (11%) thyroid isthmus resections, 66 (71%) hemi thyroidectomy and isthmus resections, 10 (11%) subtotal thyroidectomies, and 7 (8%) total thyroidectomies were performed due to existing thyroid nodules or cervical masses. Three cases had to be converted to open surgery due to specimen volume. Therefore 93 cases were eligible for analysis. Cut-suture-times differed depending on the procedure performed (Figure 3) but a decrease in cutsuture-times was noted in all surgical procedures: 78 to 38 minutes in isthmus resection, 283 to 49 minutes in hemi thyroidectomy +/- isthmus resection, 258 to 88 minutes in subtotal thyroidectomy, and 305 to 126 minutes in total thyroidectomy. This was comparable to the study of Yang et al. (51).

As expected, the average blood loss also depended on the type of surgical procedure but it was considerably low (*Figure 4*). The same was true of the resected volumes (*Figure 5*).

In the histopathologic examination: 12 adenomas, 1 cystic lesion, 66 uninodulars, and 14 multinodular changes were described. Additionally a Hashimoto thyroiditis was diagnosed in 11 specimens and a micro papillary carcinoma

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Authors	Country	Published	z	RLNP trans	RLNP perm	Mental paraesthesia trans	Local infection @ incision site	Infection neck site	Conversion to open surgery
Wilhelm and Vetzig (30)	Germany	11/23/2010	ω	-	-	ω	÷	I	ო
<sup>–</sup> u <i>et al</i> . (31)	China	01/04/2012	5	I	I	I	I	I	I
Nakajo <i>et al.</i> (33)	Japan	11/21/2012	œ	I	-	8	I	I	I
_ee <i>et al.</i> (35)	Korea	08/15/2014	4	I	I	ო	I	I	I
<sup>o</sup> ai <i>et al</i> . (38)	India	04/08/2015	-	I	I	I	I	I	I
ɗang <i>et al.</i> (51)	China	11/06/2015	41+41	-	I	I	I	I	I
Anuwong (39)	Thailand	11/06/2015	60	2	I	I	I	I	I
Nilhelm <i>et al</i> .¹	Germany/China	2016	96	-	÷	15	۲	5	c
Anuwong*	Thailand	03/02/2016	171	80	I	N	I	I	I
Kim <i>et al.</i> *	Korea	03/02/2016	5	I	I	I	I	I	I
Nang <i>et al</i> .*	China	03/02/2016	50	I	I	I	I	I	I
<sup>-</sup> an <i>et al.</i> *	China	03/02/2016	20	I	I	I	I	I	I
Nang <i>et al</i> .*	China	03/02/2016	15	I	I	I	I	I	I
Fotal			477	12 (2.5%)	2 (0.4%)	28 (5.9%)	1 (0.2%)	5 (1.0%)	3 (0.6%)

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Figure 3 Boxplot of the cut-suture-times. Boxes represent mean +/- standard deviation; whiskers display minimum and maximum; grey bars, median.



Figure 4 Blood loss according to different TOET-procedures. TOET, transoral endoscopic.

in two cases.

In the analyzed 93 patients, one permanent recurrent laryngeal nerve palsy (RLNP) (1.1%) as well as 15 cases of transient mental paraesthesia (16.1%) were noted. The mental paraesthesia resolved in all patients within three to four weeks. One local intra oral (1.1%) and 5 neck site infections (5.4%) were noted which could easily be cured by antibiotic treatment and puncture. Three CO<sub>2</sub>-embolism



Figure 5 Resected volumes according to different TOET-procedures. TOET, transoral endoscopic thyroidectomy.

and in 1 case (1.1%) mediastinal emphysema following raised  $CO_2$ -pressure above 10 mmHg intraoperative was noted. These side effects also resolved spontaneously within a few days.

#### Discussion

Thyroidectomy is one of the most common procedures performed in developed countries. It is a safe procedure due to the advancements in surgical techniques, the development of intraoperative neuromonitoring, and the aid of optical magnifying devices (2,4,5). Despite the fact that serious side effects (recurrent laryngeal nerve palsies, hypoparathyroidism) have been able to be minimized over the decades, the procedure leaves a high percentage of patients with unpleasant consequences such as the visible scar and swallowing disorders (6).

During the last two decades therefore, endoscopic procedures have been developed to overcome these after effects. The establishment of the minimal invasive videoassisted thyroidectomy was a first step to minimize the visible consequences of the procedure (10) and this approach became widespread in Europe and the USA. At that time in Asia, more and more centers were attracted to the endoscopic approach from extracervical access points, which led to a rapid development of this approach. Different access points (breast, chest, and axilla) have been established and growing numbers of procedures have been performed in the Asia-Pacific region.

Ultimately however, these endoscopic approaches have not complied with the idea of a minimally invasive approach since the extensive dissection areas have led them to be maximally invasive. A novel concept in modern surgery emerged through the development of natural orifice surgery, first to be performed in a flexible endoscopic manner by Kalloo and colleagues (52). The idea of reaching preformed anatomical layers with a minimal risk of injuries to adjacent nerves and blood vessels seemed very promising. The rapid development of endoscopic instruments and the corresponding video technology have opened a window to apply this approach outside the indications described by Kalloo.

In 2008, Witzel *et al.* published a single-port approach for transoral thyroidectomy utilizing an axilloscope measuring 20 mm in diameter and their first results in an animal study (22). However, this approach was not purely endoscopic but rather a hybrid one, since they needed an additional skin incision above the larynx. Karakas and colleagues followed this initial idea and also performed cadaver and animal studies prior to their first clinical

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Figure 6 Classification of transoral approaches for thyroidectomy.

applications (23,24). The group finally aborted the singleport approach due to serious complications (permanent hypoglossal palsy) in their first patients (25).

In January 2008, inspired by the initial communication of Witzel, a new 3-port approach for TOET was developed (43) and further studied in cadavers and pigs (26,28). An ultrasound study on the distances to reach the target area via the transoral route showed that, when compared to conventional open thyroidectomy approaches, there was no significant difference (27).

Following the presentation of the technique at a conference of thyroid surgeons in Xiamen, China in November 2011, a widespread interest emerged in the Asia-Pacific region and many centers published their experiences of the new approach. Subsequently, a variety of colleagues claimed having developed the transoral approach by publishing new acronyms for the method. It was named TOVANS 2013 (transoral video assisted neck surgery), TOET 2013, ETOVA 2014 (endoscopic thyroidectomy vestibular approach), premandibular approach 2014, TOPOT 2014 (transoral periosteal thyroidectomy), TET 2015 (transoral endoscopic thyroidectomy), and finally TOETVA 2016 (TOET vestibular approach) by different authors (33,36-39,47,50). This has led to a Babylonian linguistic confusion since all approaches are based on the originally described approach. In principal, transoral approaches for thyroidectomy should be classified as singleor 3-port approaches where the latter can be divided into the bi-vestibular/sublingual and the bi-vestibular/ premandibular approach (Figure 6).

Nevertheless, the published and most recently (Bangkok, February 2016) communicated results of clinical studies have shown very promising results regarding the TOET. Complication rates are the same or superior to open or endoscopic/robotic assisted procedures and the patients have significant advantages: the procedure results in no visible scar even at the access points in the mouth, swallowing disorders are not communicated by the patients, and postoperative pain levels are significantly lower than in open and extracervical access procedures (51,53).

Therefore TOET has left its state of infancy and is a considerable alternative approach for thyroidectomy. Even in cases of thyroid malignancies, the procedure has proven suitable with or without central neck dissection (33,35,39,40,51) and the implementation of robotic assistance has already been demonstrated (19,44,48).

To further evaluate the transoral approach—including prospective randomized trials—we recommend an internetbased registry to obtain comparable data and establish a consented protocol for pre- and post-operative evaluation of serious complications, swallowing complaints, postoperative pain levels, and cosmetic outcomes. This could possibly be inaugurated by the new Transoral Thyroidectomy Association (TOTA), which was founded on the 4<sup>th</sup> of February 2016 during the 1<sup>st</sup> International Thyroid NOTES Conference in Bangkok, Thailand.

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