Review Article

Up-to-date evidences of transoral thyroidectomy on how to overcome the obstacles?—A review

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Abstract: The progress in the field of minimally invasive surgery over the last twenty years has led to the application of natural orifice transluminal endoscopic surgery for thyroidectomy and parathyroidectomy via oral incisions. The true scarless nature of this approach had fascinated the early pioneers to prove the feasibility in the field of endocrine surgery. Through many trials and errors, the transoral thyroidectomy has now passed its experimental stage and is continually gaining momentum in obtaining worldwide popularity. However, the approach is yet to acquire status of the primary method of choice and therefore surgeons need to gain more evidence to standardize and popularize the approach. In this article we review the history, indications and contraindications, technical aspects of preserving the recurrent laryngeal nerve (RLN) and parathyroid glands, pros and cons regarding endoscopic or robotic approach, limitations and recent advancements in the field of transoral thyroidectomy

Keywords: Thyroidectomy; transoral; TOETVA; TORT

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Why did transoral thyroidectomy become popular?

Ever since Emil Theodor Kocher standardized the procedure in 1906, thyroidectomy has become a standard and a relatively efficient surgery (1). The conventional open thyroidectomy, however, leaves a visible scar, which may be disturbing, especially among young women of certain cultural background. The presence of neck scars, regardless of severity, may lead to an overall decrease in patient's self-perceived quality of life or in attractiveness perceived by others (2). A recent study even quantitatively demonstrated that neck scars diverted the attention of the observers from the face to the neck, which could be unfavorable in social situations (3). Although various methods, such as transaxillary, bilateral axillo-breast, subclavian, and retro-auricular approaches, have been devised in thyroid surgery to circumvent such scars, none of them are "scarless" by definition (4-7). True "scarless" surgery became possible with the introduction of Natural orifice transluminal endoscopic surgery in 2000 by Seifert (8), which was soon adapted in the field of thyroid surgery.

In 2008, Witzel performed the first proof-of-concept hybrid transoral thyroidectomy with 2 fresh human cadavers and subsequently 10 living pigs through a sublingual incision and an accessory anterior neck port (9). The authors mentioned the ease with which the procedure

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was performed despite the anatomic complexity of the region. The pioneering endeavors that followed (10,11) faced some unsolved questions such as feasibility of creating an ideal working space, risk of infections, obstacle to oral intake and difficulties in identifying crucial structures (12,13). The first clinical application was reported on 8 patients using 1 sublingual port and 2 vestibular ports (14). However, the resulting 6 mental nerve injury and 2 unilateral recurrent laryngeal nerve (RLN) palsies indicated the unfeasibility of this approach. The vestibular approach was first demonstrated by in 2011 through a preclinical feasibility study in 2 cadavers with the da Vinci® robotic surgical system (Intuitive Surgical Co., Sunnyvale, CA, USA), in which the nerves were identified without injury (15). A similar transoral approach in human cases was demonstrated through a 2.5 cm vestibular approach in 2012 (16). Transoral video-assisted neck surgery, as it was named, reduced the incidence of nerve injuries but the large flap area resulted in persistent sensory disorder around the chin in all patients. In the following years vestibular approaches using 3 trocars were developed in swine and cadaveric models to reduce the extent of flap dissection around the chin (17-19) and in 2016 the first large series report of the transoral endoscopic thyroidectomy vestibular approach (TOETVA) including 60 human cases was published (20). This was a landmark study because the postoperative complication rates of TOETVA, including the transoral specific mental nerve injury, were comparable to other minimally invasive and conventional open approaches and it catalyzed the spread of the TOETVA to many institutions around the world. The same group reported a comparison study between 432 propensity score matched TOETVA and conventional open thyroidectomy cases in which the results were comparable (21).

Whereas the concept of transoral approach was first conceived in Europe and was quickly adopted into clinical practice in Asia, there had been a paucity of North American clinical reports regarding this method up to the late 2010s. In 2019, a bi-institutional report of a collective experience in the United States and the first reported Mexican cohorts were published and others followed suit (22,23). This was indicative not only of the approach becoming global, but also of the fact that transoral thyroidectomy could be safe and feasible in patients with larger habitus compared to European or Asian population, a further testament to its generalizability (22). In sync with the global spread of the technique, more than 7 review articles have been further published, demonstrating the feasibility and generalizability of the transoral thyroidectomy (24-30).

In addition to the "scarless" nature of the operation, the median symmetric view which allows bilateral gland exploration to be done without additional incisions, minimal transoral specific complications such as mental nerve injury or oral infection, and easy access to the central lymph nodes have all propelled the widespread of the method to more than 80 centers from over 30 countries (29).

Indication and contraindication of transoral thyroidectomy

Although the procedure has passed its infantile stage in development, it is still relatively reserved to a select group of experts in comparison to conventional open or other minimally invasive thyroidectomy procedures. Therefore the published inclusion and exclusion criteria differ according to the amount of experience the surgeons have obtained on transoral thyroidectomy, although the criteria do not diverge too far from other minimally invasive thyroidectomies (27,28,31). In general, we propose the inclusion criteria for transoral thyroidectomy to include: (I) benign tumors or follicular neoplasms ≤3 cm in largest diameter and (II) papillary thyroid carcinomas or follicular neoplasm ≤2 cm in largest diameter. For those experienced in transoral thyroidectomy, however, the indication may be extended to controlled Graves' disease and papillary thyroid carcinomas >2 cm in largest diameter or with suspicious central lymph node metastasis. Unlike many pervious recommendations, we do not propose operating on nodules with the largest diameter up to 5–6 cm because of potential injury that may be caused during specimen retrieval. For the exclusion criteria we propose patients (I) with history of radiation in the head, neck, or upper mediastinum, (II) with history of previous neck surgery, (III) with documentation of lateral lymph node, distant metastases or tracheal/esophageal/posterior infiltration, and (IV) with poorly/undifferentiated histology.

RLN and external branch of superior laryngeal nerve

Preserving the function of RLN and external branch of superior laryngeal nerve (EBSLN) is of paramount importance in thyroid surgery, both conventional open and minimally invasive. The cephalo-caudal view of transoral thyroidectomy may cause spatial orientation issues to surgeons that are mostly accustomed to the caudo-

cephalic view of conventional open or previous minimally invasive thyroid surgeries (29). In addition, the RLN must be identified and preserved near the laryngeal entry point and Berry's ligament because of the cephalo-caudal orientation. Moreover, the difficulty in applying continuous nerve monitoring may cause a problem to surgeons who are accustomed to it. Finally, the lack of an additional arm (especially for endoscopic approach) and the resulting lack of counter-traction presents a challenge to inexperienced surgeons. Because of these challenges, surgeons should be recommended to have already overcome the learning curve of other approaches in thyroidectomy and have a complete understanding of the spatial orientation of all the structures in the neck before attempting transoral thyroidectomy for the first time.

Although the preservation of the EBSLN function in maintaining post-operative voice quality is critical, there are few comprehensive researches done on EBSLN identification regarding the transoral approach. Despite of concerns that the cephalo-caudal orientation will make it more difficult to properly expose the structure in transoral surgery, the following precautions will aid surgeons in finding the EBSLN. The first step is to expose the trachea after isthmectomy and to ligate the ipsilateral upper pole, which will provide mobility to the thyroid gland for nerve identification. By laterally retracting the upper portion of the gland with the contralateral instrument, an avascular plane between the upper pole and cricothyroid muscles attached to the thyroid cartilage named the Joll's space, is revealed. The superior thyroid vessels and EBSLN can be identified in this space. Secondly, a minor transection of the sternothyroid muscle will offer a greater vision of the operating field in case the nerve is hard to identify. Finally use of the intermittent intraoperative neuromonitor to identify the laryngeal twitch will help boost the surgeons' confidence that they have properly identified and preserved the structure (32).

The most important aspect of identifying the RLN in transoral thyroidectomy is safely exposing the structure at the laryngeal entrypoint. Because the location of the entrypoint is constant with no anatomic variation, spatially orienting its location will help surgeons to safely identify and preserve the RLN. Meticulous use of the ipsilateral dissecting forceps will expose the RLN without rupturing the vessels near it. Even more judicious usage of energy-based surgical device is advisable during this stage as they may cause inadvertent thermal damage to the nerve (33,34). After the RLN is identified at the entry point and along its caudal course, it should be laterally retracted to allow safe dissection of the Berry's ligament.

Although the small number of transoral post-operative outcome reports compared to that of traditional counterparts could lead to potential publication bias, the reported number of permanent RLN injury is very low (28). We expect future studies on transoral thyroidectomy to further reveal the generalizability of this approach (28).

Parathyroid glands

A systemic review reports the overall incidence of temporary hypoparathyroidism for transoral thyroidectomy 7.1% among a total of 211 cases (28). This result, however, should be interpreted with caution because 98 patients (46.4%) underwent thyroid lobectomy, to whom hypoparathyroidism is rarely an issue (35). With lobectomies excluded, the article would report 13.3% rate of temporary hypoparathyroidism among total thyroidectomy patients. The technical difficulty in identifying and preserving the parathyroid glands is much an issue for transoral thyroidectomy as it is for other minimally invasive thyroidectomies. The high resolution endoscopes allow surgeons to identify the parathyroid glands more easily than with the bare eyes. The lack of traction, however makes it difficult to preserve the microvasculatures near the parathyroid. This applies more for the lower parathyroids because of their redundant periglandular tissue, which makes it hard to properly countertract and preserve the microvasculature.

There are some attempts to assist surgeons in this endeavor. The indocyanine green (ICG) has been explored in other minimally invasive thyroidectomies for its ability to detect the parathyroid during thyroidectomy (36). Similar studies are known to be undertaken for transoral thyroidectomy, although the results have not been published to date (29). Likewise, a technique dubbed subcapsular saline injection (SCASI), has been reported to be useful in saving parathyroid for other minimally invasive thyroidectomies (37)—a point which could be noted for transoral thyroidectomy.

Endoscopic *vs.* robotic

Regardless of the approach, endoscopic thyroidectomy has its inherent limitations due to narrow working space, 2D image and non-articular instruments. Such limitations present a great challenge for surgeons and assistants in

maintaining a clear visualization of the operating field and conducting fine movements for delicate procedure, such as identifying and exposing the RLN. Such factors are amplified by the proximity of the port to the upper poles and the lack of an additional instrument for muscle retraction. Transoral robotic thyroidectomy (TORT) integrates the robot surgical system to TOETVA. With articulating forceps combined with three-dimensional visualization, the robotic system enables surgeons to perform more precise dissections around the structures such as the RLN. This is especially useful for operating male patients where the protruding thyroid notch can be circumvented in a manner difficult with endoscopic surgery. The major modifications required in TORT over TOETVA is the additional fourth robotic arm through the axilla. Theoretically, the axillary port is not an innate feature of the robotic system and both TOETVA and TORT can be performed using either 3 or 4 arms. The substantial value of the additional arm through the axillary port, however, lies in the traction of the muscle, perithyroidal tissues and perineural structures. Such value can be best exploited by applying the articulating movement of the robotic, rather than endoscopic arm. Moreover, additional axillary incision can be used for thyroid tissue removal.

Despite the such advantages, surgeons should be aware of the following drawbacks of TORT; lack of haptic feedback, additional time requirement for robot preparation and docking, dependent on availability of the robotic surgical systems, and higher cost. Unlike the other three issues, the absence of tactile feedback is an inherent characteristics of the robotic system that should be taken with extra caution with TORT as it may lead to injury in the oral mucosa or even the lateral commissure of the lips (38).

Limitations of transoral thyroidectomy

The advantages of transoral thyroidectomy have demonstrated in prospective studies and review articles, but these are still limited to a select group of patients and expert surgeons (28,39,40). Injury of the EBSLN or RLN is the most obvious complication for all thyroid surgeries, and this also applies to transoral thyroidectomy. The same applies for post-operative hypoparathyroidism, the other most important complication in thyroid surgery. Therefore, the transition to transoral thyroidectomy at an early stage of a surgeon's career without proper training may lead to nerve related complications. Around 10 to 11 is reported as the minimum number of cases required to overcome the technical learning curve of transoral thyroidectomy, although more experience will certainly help surgeons in gaining confidence (41).

Another aspect of transoral thyroidectomy that should be considered is the removal of specimen through the oral incision, especially when specimens are larger than 3 cm (42). Large or hard texture specimen retrieval is difficult, and may require tissue fragmentation before it can be removed. Such manipulation will prevent accurate pathologic diagnosis of the tumor and may increase cause tumor spillage in the neck (42). This issue can be solved by widening the midline incision with a large caliber Hegar dilator. In authors' experience, up to 3 cm tumor could be safely removed after widening the incision using an 18 mm Hegar dilator. If the tumor cannot be removed through an oral incision even after using the Hegar dilator, adding an axillary incision is an alternative to remove the specimen without fragmentation at the expense of minimal cosmetic value.

Other complications that are inherent to transoral thyroidectomy include mental nerve injury, CO_2 embolism caused by vessel injury during flap formation, and surgical site infection caused by oral incision (16,43). The incidence of mental nerve injury was initially reported to be between 1–5%, whereas recent incidence has decreased dramatically by anteriorly placing vestibular incision sites and placing the medial incision in between both mental nerves (29). Although very scarce, cases of CO_2 embolism caused by the tearing of the anterior jugular vein during flap formation have been reported (44). Such adverse events can be reduced by minimalizing the area of blind flap dissection, reducing the CO_2 pressure during operation, and maintaining a reversed Trendelenburg position during operation. If gas embolism is suspected, CO_2 infusion should immediately be stopped, 100% O_2 should be given, and cardiac pulmonary resuscitation should be considered (44). Moreover, the rate of surgical site infection in previous meta-analyses were reported to be between 0.1–1% (28,45). A randomized control trial also indicated that patients did not require post-operative antibiotics while maintaining their regular oral hygiene (39).

Recent advancements in transoral technique

There are some additional efforts by the leading group to facilitate and expand the indication of this approach. The first obstacle may beginners face is the flap formation especially in the initial stage. The thin but dense skin over

the mandible may force surgeons to cause inadvertent skin penetration, while the small initial space may further require surgeons to exert force that may injure the patients' skin, oral mucosa or lips. A recent study reported that using the foley catheter could facilitate creating the initial working space from which the surgeons could progress their flap formation (46). The pressure from the balloon can also assist in providing a solid hemostasis.

Another hump that surgeons face, especially in endoscopic surgery, is the missing arm which would help with counter-traction. In order to overcome this shortcoming a retractor that could be introduced transcutaneously to retract the strap muscles were patented and introduced (47). A study of 132 cases done with this retractor proved harmless regarding cosmetic results and also efficient in reducing the learning curve.

Lateral neck lymph node metastasis had been and still is a contraindication for transoral thyroidectomy. There is, however, a recent prospective pilot study that has been published in patients who underwent additional selective level III and/or IV dissections for T1 or less PTCs (48). Although the long-term oncologic results are pending, one transient RNL palsy and 2 operative field effusion reflects the potential technical feasibility of this operation.

Finally, a case of single port TOETVA was recently reported (49). The author suggests that by eliminating the need for lateral ports the possibility of potential mental nerve injury could also be reduced. Experience with flexible endoscopic instruments, however, is essential. Moreover, such technologic innovations should be confirmed with something more substantial than a case-report.

Conclusions

Transoral thyroidectomy may be the next step in minimally invasive surgery, and early clinical experiences have demonstrated its feasibility among selected patients. Transoral thyroidectomy is more technically demanding than open surgery, which why the widespread of this technique had been prevented till now. Today, however, the approach is practiced in over 30 countries and the phase of demonstrating its safety and feasibility has passed. Furthermore, with the introduction of new instruments and techniques to facilitate the procedure, the transoral approach possesses the potential to establish itself as a favorable approach compared to other remote access thyroidectomies that have yet to become mainstream. Further efforts to accumulate collective experience and evidence and to pioneer new frontiers with this approach is necessary for the potential to blossom.

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