

Peer Review File

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Reviewer A

You described a novel method of SP-TOETVA using the soft and flexible handmade single port system after performing five cases of surgery. In spite of some vivid benefits of your method, it seems necessary to consider some aspects to show the feasibility.

1. In figure 4, all trocar tips seem to be out of the patient body, that would make it difficult to insert the instruments to the surgical field. Because of fighting between surgical instruments, the surgery might be very demanding technically and it will make the operation longer.

Reply 1: Data lack the possibility of direct comparison yet.

Changes in the text: (Discussion) Using a single access may be demanding which could reflect the longer operation times compared to those reported in classic TOETVA in the literature. However, accurate comparison of procedural time to other approaches for thyroid resection might be possible after larger series.

(see Page 24+25, line 306-309)

2. Although your patients' thyroid volumes were not very large (hemigland and total thyroid volumes ranged from 5-35ml and 55ml, respectively), but in 40% (two of 5 patients), additional retroauricular incision was necessary for retrieval of the specimen. It is not a small deal in cosmesis-oriented surgery. I guess, the inner ring foil of the wound retractor they used, may disturb the extraction of the specimen.

Reply 2: This is an excellent suggestion, which we added in the discussion section.

Changes in the text: (Discussion) Removal of the inner ring of the handmade port might help for easier specimen harvest.

(see Page 25, line 329-330)

3. A few errors in spelling, grammar and use of comma or period need to be corrected.

Reply 3: Errors in spelling and grammar have been corrected.

4. In Figure 4, A and B pictures were exchanged.

Reply 4: The order of pictures A and B has been corrected.

Changes in the text: Picture A and B have been switched.

(see Page 8, line 128-135)

5. In figure 6, marking directions of right, left, head, and foot may help the readers to get the orientations.

Reply 5: This has been changed according to the comment.

Changes in the text: (Materials and Methods) F feet, H head, L left, R right

(see Page 11, line 176-182)

Reviewer B

1. Overall I think this paper presents a very innovative approach to transoral endoscopic vestibular approach surgery. Congratulations to the authors on this accomplishment.

2. I do see the value in the flexible port system in that it has the potential of minimizing stretch of the orbicularis muscle during surgery. We do find that patients have mild peri oral weakness post surgically due to this stretch and minimizing this would be beneficial. I would focus on that as a benefit as it gets us closer to making this approach minimally invasive.

Reply 2: An incision suitable for three five-millimeter instruments requires the length of 1.8 centimeter at least which is comparable with the incision of a 10 millimeter trocar (inner diameter). Therefore we are able to entirely prevent any trauma lateral to the incision. This is one of our key arguments to advocate this access. However, specimen retrieval might lacerate this incision.

Changes in the text: This was adapted in discussion.

(see Page 25, line 325-330)

3. It's important to note that the risk of the mental nerve with the established toetva approach is minimal. The approach has been adapted since its conception to place lateral ports in the region of the oral commissure which serves to avoid the mental nerves.

Reply 3: Modification of lateral port placement more lateral in the region of the oral commissure helped to minimize mental nerve injury but may increase the risk of vascular complications such as lacerating the inferior labial artery or facial artery.

Changes in the text: This has been edited in the discussion.

(see Page 24, line 296-299)

4. One of my concerns after reading through the paper is the possibility of burning the lips with either the scope or the liga sure as it comes in and out of the mouth. It seems that the flexible port system includes heat protection in some way but it would be beneficial to mention how this works specifically.

Reply 4: We never used cautery in the lips region in any of our patients in order to prevent burning. Specific heat protection other than air exchange via the AirSeal® System is not considered mandatory in this approach.

Changes in the text: see Page 7, line 114-116)

5. A major disadvantage is the inability to deliver the specimen through the single port incision and having to make a second incision for larger specimens. This is very relevant as it adds operative time and potential morbidity. I would mention that further dilation to allow for specimen retrieval may be better than doing the additional incision. This would be an interesting thing to investigate.

Reply 5: A limitation of this new technique might be the inability to deliver the specimen through the vestibular approach. This was the reason to add a retroauricular incision for specimen harvest.

Changes in the text: This was edited in the discussion section. Further, the possibility of

removing the inner Ring of the handmade port might help for easier specimen harvest. (see Page 25+26, line 328-330)

6. One of the challenges with toetva is angulating the instruments in the correct way to precisely dissect the region of the tracheoesophageal groove and berry's ligament. I would suggest endoscopic view photographs be included to demonstrate dissection at these points. A comment on your experience with this would also be helpful.

Reply 6: Angulation is achieved by inserting a 5 mm articulating grasping instrument. As suggested we added figures showing the inside view of the handmade port as well as endoscopic view photographs demonstrating key steps of the operation.

Changes in the text: We added figure 7 and 8
(see Page 12-14, line 191-213)

7. I agree with the statement on the limitations of the study and would like to see future studies comparing traditional toetva to this approach in particular looking at recovery times and patient satisfaction.

Reply 7: We agree to this statement.

Changes in the text: Further studies will show if there are statistically defined benefits to multiport TOETVA.

Reviewer C

Minimally invasive surgery has been used in the treatment of endocrine gland diseases for over 25 years. The dynamic development of new instrumentations, including robotic techniques and modern imaging methods, caused a significant advancement in this field of surgery. In the last few years, techniques using natural body orifices have become increasingly important. In thyroid surgery, procedures have emerged that use TOETVA, which leaves no scar on the skin. Of course, not every patient is a good candidate for this type of treatment, but the method is gaining popularity because it provides excellent cosmetic effects. Moreover, with the development of the new da Vinci single-port robotic system, additional incisions may not be necessary anymore. Currently, the large size of the central port limits its use to some extent.

The study Flexible Single Port Access in Transoral Endoscopic Thyroidectomy Vestibular Approach (SP-TOETVA)

With regard to the assessed work, the following should be taken into account:

- A properly structured survey
- Accuracy of the description and technique of the treatment
- Very carefully designed graphic page - figures, photos, tables
- Unfortunately: a small group (only 5 patients - no statistical evaluation possible) - also the authors' limits
- Inability to compare with the observations of other authors, but also insufficient reference to data from the world literature in relation to operations using one port.

- The technique cannot be standardized.
- No long-term ess the learning curve - the group is too small

In summary:

The use of modern techniques requires a very large experience of the surgical center, which is the authors have

BUT

..... Nevertheless, careful adoption is crucial for successful implementation as premature implementation can increase the rate of conversion and hence abandonment of the new technique — and all it has to offer...(R P. Tufano)

Reply: To the best of our knowledge the current English scientific literature on clinical use of single port/one port TOETVA has been added to our reference list.

The TOETVA technique has already been standardized. We only changed the approach from multi-trocar to single-trocar surgery. This paper did not aim to evaluate the learning curve. Therefore, we did not comment on this.

Changes in the text: We added a study of preclinical feasibility from Park et al to the reference list and to our discussion.

(see Page 25, line 312+313)

We want to emphasized that any implementation of premature SP-TOETVA might increase morbidity. We added this in the discussion section just before the limitations.

(see Page 26, line 347-348)

The dissection steps are well described and standardized in various publications. This was added to Materials and Methods.

(see Page 4, line 81+82)

Reviewer D

This case series with 5 patients describes a novel approach for an endoscopic thyroidectomy. The authors have submitted quite a fascinating manuscript. I hope that the authors would keep the study and submit your follow-up article with larger cases.

1. Introduction, page 3, Line, 45-48. Compared with the breast approach and ABBA, the axillary approach is more common in the field of remote-access thyroidectomy. The authors should reference this study that described the axillary approach: Ikeda Y et al. Journal of the American College of Surgeons. 2000;191(3):336-340.

Reply 1: This reference has been added to the introduction and the reference list.

Changes in the text: the endoscopic neck surgery by the axillary approach by Ikeda et al.

(see Page 3, line 47)

2. Materials and Methods, page 5, Line, 93. A long incision can result in mental nerve injury. The authors should describe the direction of the middle incision (horizontal or vertical incision). Is a 15mm incision appropriate for all races or does the length of the incision depend on the height of the patient or the shape of the chin? In addition, the authors need to

show the length limit of the incision to avoid mental nerve injury in the discussion section.

Reply 2: The 15 mm incision will be enlarged to 18 mm with respect to the tissue elasticity which is appropriate for either one 10 mm trocar (inner diameter) or the 5 mm camera and two 5 mm working instruments. Therefore the length of the incision does not directly depend to patients gender, race or anatomy.

Changes in the text: Changes have been made to the Materials and Methods section.

(see Page 5+6, line 99-102)

3. Materials and Methods, page 6, Line, 103-105. How many L/min is the CO2 flow when the authors use AirSeal?

Reply 3: We used 5l/min as minimal flow.

Changes in the text: (see Page 7, line 113)

4. Materials and Methods, page 12, Line, 193-195. I guess that the authors should have provided endoscopic retroauricular or axillary approaches for these two patients with tumors > 4cm? The authors should state the inclusion and exclusion criteria in the Method section and describe the adaptation and maladaptation of SP-TOETVA in the Discussion section.

Reply 4: We aimed to follow the inclusion and exclusion criteria predefined for classic TOETVA in the literature. However pretended maladaptation and harvest of the specimen through the retroauricular path was due to tissue rigidity that might have hampered a smooth enoral retrieval

Changes in the text: This has been added to the Materials and Method section.

(see Page 4, line 76-77)

5. Table 1-3. There are only 5 cases. So, it would be useful to demonstrate all data for each case instead of the mean (min-max) (i.e., use Case 1, 2, 3, 4, 5 as column items).

Reply: This has been edited.

Changes in the text: Table 1 has been modified to show all data for each case.

(see Page 19-21, line 272-275)

Reviewer E

The authors presented a modified transoral thyroidectomy, SP-TOETVA, using a soft single port device in five patients. The method is feasible in this series. The potential benefit of this method is to avoid complications from lateral trocar used in multiport TOETVA, and to remove the specimen easier.

My comments are as follows:

Congratulation to the authors for the success of SP-TOETVA in the case series.

1 There are various tries of single port TOETVA in the literature. The author compared the new method with the commercial single port multi-access platform, da Vinci SP, and TOVANS. They suggest the new technique avoided complications because of a soft device, small incision(1.5cm) and gas insufflation. However, the soft device may increase the learning curve. The true difference between various single port techniques need to be further investigated because all reported feasible and safe. The benefit of single port TOETVA over classic TOETVA also needs to be investigated because classic TOERTVA also proved safe in the previous large series. No obvious lateral trocar related complication in the literature.

Reply 1: Substantial complications related to the lateral trocars are given in the literature. We aim to prevent any unnecessary additional trocars in this project.

Changes in the text: Further information and literature is listed in the discussion section. (see Page 24, line 292-298)

2 We believe the author is proficient in single port surgery. However, whether the result can be generalized to other series is questionable because of the very steep learning curve.

Reply 2: We emphasized the awareness of sufficient surgical skills for this high end endocrine surgery. This is mentioned in the discussion section right before the limitations.

Changes in the text: (see Page 26, line 339-341, 347-348)

3 Because the author states that there is no need to widen the central incision in this technique to avoid complication, could the author show us the length of incision post operatively? In our experience, the central incision is likely to be teared by manipulation during thyroidectomy.

Reply 3: According to the reviewers suggestion the materials and methods as well as the discussion section have been adapted.

Changes in text: (see Page 25, line 324-329)In addition we added a scale to Figure 10. (see Page 16, line 232-233)

4 Because of the novelty of technique, could the author show us the picture or video of the various surgical steps during thyroidectomy?

Reply 4: We added several pictures with key steps of dissection and anatomy.

Changes in the text: Figure 7 and Figure 8A-C have been added. (see Page 12-14, line 191-213)

5 Could the author suggest the indication and contraindication of SP-TOETVA? Are there differences from classic TOETVA?

Reply 5: Indication and contraindication respond to the recommendations of multiport TOETVA.

Changes in the text: This was adapted in the Materials and Methods (see Page 4, line 76-78)

Reviewer F

The authors present their technique of 5 patients undergoing single port TOEVA

Lines 55-57-All of these these advantages are not certain for thyroid surgery

It's not clear how the glove is being used, better description and images are needed.

There are not enough patients in this series to ascertain the complication rates with the technique

Reply: The advantages are given in the reference section. The glove is being used to deliver one camera and up to four instruments. The glove mounted with standard trocars. To clarify how the port system is used in combination with trocars and instruments, images and descriptions have been added

Changes in the text: Figure 7 and Figure 8A-C have been added. (see Page 12-14, line 191-213)

Reviewer G

This is a preliminary report using handmade single port system for transoral thyroidectomy via vestibular approach.

The authors demonstrated the feasibility of using glove port for transoral endoscopic thyroidectomy in 5 patients without open conversion. However, there are some questions need to be answered and concerns that should be addressed.

- Major concerns

1. One rationale for single port is easier specimen retrieval, which is somehow difficult in traditional 3-port TOETVA. However, this was not the case in this study. 2 patients (2/5, 40%) required additional retroauricular incision for specimen removal. How do you justify this discrepancy?

Reply 1: An incision suitable for three five-millimeter instruments requires the length of 1.8 centimeter at least which is comparable with the incision of a 10 millimeter trocar (inner diameter). Therefore, the incision of single port TOETVA is comparable to the central incision of 3-port TOETVA with similar concerns and limitations when widening this incision. Moreover, the additional incision for specimen removal in these two cases was mainly due to tissue rigidity.

Changes in the text: (see Page 14, line 221-222 and Page 25, line 324-329)

2. In author's opinion, another reason for single port is to omit the two lateral wound, which might lead to injury in the lateral branch of mental nerve. Nevertheless, the single enlarged central wound might increase the risk of nerve injury by a) direct severance of the medial

branch of mental nerve, b) nerve traction/compression due to application of the double ring foil, and c) frequent instrument collision because of single incision. What is your strategy to prevent these possible complication?

Reply 2: a) As the incision ideally matches a 10mm trocar incision. Any enlargement is not due to the surgical technique but to the specimen retrieval

b) The elastic inner ring of the protection foil measuring 3.5cm in diameter can be squeezed during placement to softly pass the mucosal incision. Postoperative view of the vestibular wound showed only slight widening of the approach following specimen harvest but not due the port itself. Therefore we did not experience any laceration of the mental nerve branches in the study population.

c) Frequent instrument collision can be avoided by using articulating instruments and experience with handling these from single port surgery in other organ systems. To depict this, we added figures showing the inside view of the handmade port as well as endoscopic view photographs demonstrating key steps of the operation.

Changes in the text: (see Page 25, line 324-329) Figure 7 and Figure 8A-C have been added. (see Page 12-14, line 191-213)

3. Since mental nerve injury is a key outcome and major concern in this study. The definition and evaluation of mental nerve should be addressed clearly in the method section. Was the mental nerve injury defined by patient's objective response, or by finger touch on the lip and chin or by wisp of cotton swab? The numbness location is on the lip, chin or both?

Reply 3: It was documented by finger touch test, we added this to the Materials and Methods section.

Changes in the text: (see Page 16, line 243-244)

4. Because only 5 patients were enrolled, the author might present the data by listing all the patients one by one in a table rather than using the mean value and range. It would be more informative for the readers. In addition, many data were missing and some data are confusing.

a. How many patients received unilateral lobectomy, and how many patients received total thyroidectomy? The operative time of lobectomy and total thyroidectomy should be separate.

Reply a: 3 Patients received hemithyroidectomy and 2 patients thyroidectomy. We changed table 1 and listed every patient separately.

Changes in the text: Table 1 has been modified to show all data for each case. (see Page 19-21, line 272-275)

b. Table 1 showed that the mean nodule size was 3cm with a range of 1.8 to 3.6cm. However, in the result section (line 225), the author stated "... the largest nodule was 4.5cm in diameter."

Reply b: Typographical errors have been corrected in text and tables.

Changes in the text: Table 1 and in Materials and Methods and Discussion section.

Table 1 has been modified to show all data for each case. (see Page 19-21, line 272-275) (see Page 16, line 235-236 and Page 17, line 261-262)

c. In line 194-195, the author stated "...retroauricular removal was performed in two patients for specimen exceeding 4cm in diameter". However, in line 231, the nodule size that required retroauricular removal were 4.5cm and 3.6cm.

Reply c: Typographical errors are corrected in text and tables.

Changes in the text: Table 1 and in Materials and Methods and Discussion section.

d. Please check exactly how many patients require retroauricular specimen removal? The number is 2 in line 194-195, but 3 in line 229.

Reply d: Typographical errors have been corrected in text and tables.

Changes in the text: Table 1 has been modified to show all data for each case.

(see Page 19-21, line 272-275)(see Page 16, line 235-236 and Page 17, line 261-262)

e. In your surgical procedure, lymph node sampling was carried out in the central compartment (line 186). However, in Table 1, none of the patients had malignant histopathology result. Could you explain the criteria for lymph node sampling in your institute? Besides, the number of lymph node harvested was not reported.

Reply e: Lymph node sampling was due to suspicious intraoperatively lymph node enlargement and not to a preoperative malignant lymph node side which we would consider a contra indication for this new technique.

Change in text: Page Page 12, Line 189-190

- Minor issue

1. Could you provide picture that showed the inside view of the handmade single port after its insertion, especially the ring foil that anchored underneath the level of the chin. It would be better for the readers to understand the working space established by your design.

Reply 1: Please find the inside view and further endoscopic view pictures in Figure 7 and 8 A-C.

Changes in the text: Pictures Figure 7 and 8 A-C have been added.(see Page 12-14, line 191-213)

2. In patients whose specimens were extracted through the retroauricular access, how long was the length of retroauricular incision? Was there any complication associated with the retroauricular incision, such as regional paresthesia, bleedings, or hypertrophic scar?

Reply 2: We used incision, position and length according to the standardized procedure of EndoCATS and TOVARA. In this series no complication associated with the retroauricular incision occurred.

Changes in the text: Please see discussion section. (see Page 26, line 330-333)

3. Typographical error:

a. Table 1 maligne € malignant

b. The number should be present properly, Comma € Decimal point in Table 1 and Table 2, e.g. 1,8 € 1.8; 2,36 € 2.36

Reply 3: The typographical errors have been corrected.

Changes in text: (see Page 22, line 279). Table 1 has been modified to show all data for each case. (see Page 19-21, line 272-275)

Reviewer H

The authors demonstrated a method of SP-TOETVA with the soft and flexible handmade single port system and showed it feasible without the specific risk of lateral vestibular incisions.

The authors should only describe the differences from SP-TOETVA and TOETVA and show how this technique would lessen the possible complications. And the main differences is the lateral vestibular incisions, and they should focus on why these incision should be diminished.
Reply: To clarify this and to demonstrate the possible benefits of the method, the discussion section has been adapted .

Changes in the text: (see Page 24, line 292-300, Page)

Reviewer I

de Cilia at all show in a monocenter study their preliminary data of the SP-TOETVA. Three of the 5 presented patients also underwent a TOVARA; retrieval of the specimen via an alternative, retroauricular approach.

I have several questions:

1) what's the rationale to show these preliminary data in only 5 patients? Why don't they build a larger database?

Reply 1: This paper aims at precisely defining the novel approach. Further studies will be performed to develop adequate data for direct comparison of SP-TOETVA and multiport TOETVA.

2) Is the opinion of the authors that their technique is there to stay or is this an 'in between' solution? (waiting for better tools, provided by the industry)

Reply 2: The handmade port is technically easy and affordable to reconstruct and without a substantial draw back which could compromise the surgeons technique. In our opinion this handmade port can be an option in the armamentarium of endoscopic thyroid surgery. However, this development may entail the development of novel tools for preparation and tissue handling (such as articulation hooks or sealing devices)

3) which actual problem are they solving with this improvised technique? In literature, the chance of numbness due to neuropraxia of the mental nerves is 2% or less?

Reply 3: We try our best to reduce any complication by lateral trocars. This was emphasized in the discussion section.

Changes in the text: (see Page 24, line 292-300, Page)

4) Was the TOVARA addition in three patients a strategy that arised during surgery or already planned up-front?

Reply 4: The retroauricular specimen retrieval was not planned upfront but the decision was made during surgery to avoid laceration of the enoral incision due to rigid specimen.

Changes in the text: (see Page 18, line 258-262)

5) Shouldn't the TOVARA technique be mentioned in the title?

Reply 5: It was not our aim to improve the TOVARA Technique.

INTRO:

line 45 a visible scar

M&M:

line 71 consecutive

line 88 The surgeon

line 90 The scub nurse

Reply: Typographical errors were edited.

Changes in the text: (see Page 3, line 46, Page 4, line 74, Page 5, line 93+95)

Fig 3 can be left out, fig 4C shows the same

Reply: According to the suggestions of numerous other reviewers we increased the number of pictures instead of reducing them to clarify key steps of the procedure.

line 150-154 are these sutures always placed or only on indication?

Reply: we have always placed the stay sutures on used them on demand to enable better exposition if needed.

line 194: two patients underwent TOVARA, line 230: THREE patients underwent TOVARA...

Reply: Typographical errors are corrected in text and tables.

Changes in the text: Table 1 has been modified to show all data for each case.

(see Page 19-21, line 272-275)(see Page 16, line 235-236 and Page 17, line 261-262)

Table 2 and 3 can be left out, no addition.

Reply: According to other reviewers suggestion about listing information case by case we enlarged Table 1 instead of abbreviating these information.

line210: what's the rationale for a liquid diet on day 1 post-op?

Reply: The rational to administer was to prevent solid food exposure to a fresh wound in the mouth.

line 215: were PTH levels always checked in their institue after lobectomy?

Reply: Yes, we routinely check PTH levels after thyroid or parathyroid surgery.

line 227: is a scintigraphy still standard work-up for a thyroid nodule?

Reply: We consider this a standard in our institute.