

## Peer Review File

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### **Point-by-point response letter (Reviewer A)**

#### **Comment 1:**

The literature should be better analyzed, considering also the complications. Therefore, the following paper should be considered: "Docimo G, et al. Role of Absorbable Polysaccharide Hemostatic Powder in the Prevention of Bleeding and Wound Events after Thyroid Surgery. *J Clin Med.* 2023 Aug 31;12(17):5684. doi: 10.3390/jcm12175684. PMID: 37685750; PMCID: PMC10488928."

#### **Reply 1:**

We sincerely appreciate the valuable comments. We have checked the literature carefully. The aim of the current study (*Docimo G., et al. Role of Absorbable Polysaccharide Hemostatic Powder in the Prevention of Bleeding and Wound Events after Thyroid Surgery*) was the evaluation of drain output, the presence of significant postoperative blood loss and complications in patients treated with or without resorbable polysaccharide powder during thyroid surgery. From January to December 2022, postoperative bleeding, drainage output, and the postoperative wound events of patients undergoing thyroid surgery in a tertiary center, with hemostasis completion with resorbable polysaccharide powder (Group A) OR NOT (Group B), were retrospectively analyzed. The results show that 81 patients in Group A presented lower drainage output and lower neck hematoma and seroma incidence, also confirmed by multivariate analysis.

Our study did not use topical hemostatic agents intraoperatively ([see page 6, line 94](#)). During the ETAA procedure, our surgeon minimizes bleeding and achieves hemostasis. This typically involves the careful dissection and identification of blood vessels, the ligation or cauterization of vessels to seal them off, and hemostatic techniques and agents as needed.

#### **Changes in the text 1:**

As per the reviewer's suggestion, we have made supplementary modifications to our text: " Topical hemostatic agents were not used during the procedure because they might influence drainage output (15)." (see page 6 , line 94) "The most reliable approach involves the precise identification and dissection of blood vessels, followed by ligation or cauterization for vessel occlusion (16). During ETAA, our surgeon used meticulous techniques to minimize bleeding and achieve adequate hemostasis (14). " (see page 6 , line 96-98 )

#### References

(14) Wang C, Feng Z, Li J, et al. Endoscopic thyroidectomy via areola approach: summary of 1,250 cases in a single institution. *Surg Endosc* 2015; 29(1):192-201.

(15) Docimo G, Filograna Pignatelli M, Ferrandes S, et al. Role of Absorbable Polysaccharide Hemostatic Powder in the Prevention of Bleeding and Wound Events after Thyroid Surgery. *J Clin Med* 2023;12(17):5684.

(16) Khadra H, Bakeer M, Hauch A, et al. Hemostatic agent use in thyroid surgery: a meta-analysis. *Gland Surg* 2018;7(Suppl 1):S34-S41.

#### **Comment 2:**

The literature should be better analyzed, considering also the complications. Therefore, the following paper should be considered: "Gambardella C. et al. Transcutaneous laryngeal ultrasonography: a reliable, non-invasive and inexpensive preoperative method in the evaluation of vocal cords motility-a prospective multicentric analysis on a large series and a literature review. *Updates Surg.* 2020 Sep;72(3):885-892. doi: 10.1007/s13304-020-00728-3. Epub 2020 Mar 2. PMID: 32124271."

#### **Reply 2:**

We sincerely appreciate the valuable comments. We have checked the literature carefully. The aim of this study (*Gambardella C. et al. Transcutaneous laryngeal ultrasonography: a reliable, non-invasive and inexpensive preoperative method in the evaluation of vocal cords motility-a prospective multicentric analysis on a large series and a literature review*) is to assess transcutaneous laryngeal ultrasonography

reliability as an alternative painless and inexpensive method in the evaluation vocal folds function in patients amenable of thyroid surgery. The researchers conducted a prospective multicentric study on patients affected by thyroid disease referred to the thyroid surgery divisions of two tertiary hospitals. All patients preoperatively underwent transcutaneous laryngeal ultrasonography and subsequently were evaluated via laryngoscopy by a blinded otolaryngologist. The ultrasonographical and laryngoscopical findings were then compared by an external blinded investigator.

Due to space limitations, the details of ETAA have been omitted; however, we refer readers to our previous study for citation purposes. (see page 5, line 91-92). We have made a supplementary appendix to our manuscript and hope it can be easily understood. In our study, laryngoscopy was performed to assess vocal cord movement before and after surgery, which is widely employed as an efficacious diagnostic modality for patients with recurrent nerve injuries.

### **Changes in the text 2:**

As per the reviewer's suggestion, we have made a supplementary appendix to our manuscript and made supplementary modifications to our text: " The laryngoscopy was performed before and after surgery to assess vocal cord mobility (17). Blood tests were performed to evaluate thyroid function, intact parathyroid hormone (IPTH) levels, serum Ca<sup>2+</sup> levels, and coagulation function. Patients diagnosed with hyperthyroidism received antithyroid drugs for symptom control, followed by a three-week course of compound solution of iodine orally (14)." (see page 6, line 99-102 )

### **References**

(17) Fu J, Zhao Y, Sun H, et al. The feasibility of laryngeal nerve protection during thyroidectomy using sternocleidomastoid intermuscular approach with intraoperative neuromonitoring: a case series and step-by-step description of surgical procedure. *Gland Surg* 2022;11(10):1665-1672.

### **Comment 3:**

The literature should be better analyzed, considering also the complications. Therefore, the following paper should be considered: "Marotta V, et al. Germline Polymorphisms of the VEGF Pathway Predict Recurrence in Nonadvanced

Differentiated Thyroid Cancer. *J Clin Endocrinol Metab.* 2017 Feb 1;102(2):661-671. doi: 10.1210/jc.2016-2555. PMID: 27849428."

**Reply 3:**

We sincerely appreciate the valuable comments. We have checked the literature carefully. The main objectives of this study (*Marotta V et al. Germline Polymorphisms of the VEGF Pathway Predict Recurrence in Nonadvanced Differentiated Thyroid Cancer*) is to test the prognostic value of germline SNPs of VEGF-pathway in nonadvanced DTC. Analysis of germline VEGF-A SNPs could empower a prognostic approach to DTC.

In many countries, ET has been applied via various approaches to treat thyroid diseases. The incidence of postoperative bleeding, RLN injury, parathyroid gland injury, and other complications was low in these studies (*PMID: 18172709, PMID: 18305997, PMID: 18335750, PMID: 16323164, PMID: 12732493, PMID: 11213035*). Our primary endpoint was drainage output; secondary endpoints included the complications and safety after ETAA in 72h, and there is no analysis of the influencing factors of cancer recurrence and long-term recurrence. There are no complications have been documented. None of our patients had a massive hemorrhage or required conversion to open surgery. (see page 7, line 133-134). However, it is essential to acknowledge that the limited sample size could contribute to the absence of complications observed; nevertheless, these findings still hold significance and may impact clinical decision-making.

**Changes in the text 3:**

As per the reviewer's suggestion, we have made supplementary modifications to our text:

A. " No postoperative complications have been documented." (see page 7 and line 133).

B. "Third, the study did not include patients with other diseases or complications; no massive hemorrhage and conversion to open surgery. Thus, the effects of comorbidities on the surgical outcome warrant further investigation, and the comprehensive assessment of the safety and efficacy of different drainage outputs

after surgery necessitates a more extended follow-up period." (see page 11 , line 216-220)

### **Point-by-point response letter (Reviewer B)**

#### **Comment 1:**

How many surgeons performed the surgeries? If there were multiple surgeons, were there any differences among them? Were there any differences based on tumor size or the size of the thyroid gland itself?

#### **Reply 1:**

The surgeries are consistently performed by the same surgical team under the supervision of an experienced surgeon. The surgical procedure adheres to the standardized surgical protocol established by our institution. We have observed that tumor size may impact both the complexity and duration of surgery. However, due to limitations in our retrospective analysis, specific data regarding precise tumor size and weight were absent from the records. Consequently, we have excluded this variable from our current study but intend to incorporate it into future research endeavors.

#### **Changes in the text 1:**

As per the reviewer's questions, we have made supplementary modifications to our text: "under the supervision of an experienced surgeon" (see page 5 , line 82-83).

Furthermore, we have made supplementary modifications to our text in part of

Limitations: "Second, the effects of tumor size and weight were not assessed. Therefore, we intend to incorporate it into future research endeavors, and more extensive multicenter prospective trials are needed to validate our results." (see page 11 , line 214-216 )

#### **Comment 2:**

There are already numerous studies published on predicting drainage volume after thyroid surgery. Are there any analysis results highlighting the unique aspects of ETAA, such as differences based on the surgical method?

#### **Reply 2:**

Thanks to the reviewer for all the good questions. Several studies have conducted predictive analyses on drainage volume, particularly on open thyroidectomy. Surgical drains increase postoperative pain and hospital length of stay and do not decrease reoperation rates, hematomas, and seroma formation in patients undergoing OT (18). ETAA is a new surgical technique that is constantly being improved. The need for using drains in OT is controversial, and more evidence to support its effectiveness in ETAA is needed (19-22). Drains are recommended for thyroid surgery patients with extensive dead space (23).

Further, drains should be used cautiously after ETAA because this technique requires broader flap separation and may increase bleeding compared to OT. Notwithstanding, using an indwelling tube allows for detecting bleeding and estimating blood loss during surgery. A survey conducted among 35 surgeons across ten units revealed significant heterogeneity in indications for drain insertion and decisions on removal (24), underscoring the need to develop objective methods to improve decision-making. In early practice, we used drains in most cases of ETAA, and patients without drains were selected based on experience. Nonetheless, clinical risk factors for DV after ETAA had not been determined in previous studies. Based on the abovementioned reason defines the background and scholarly significance underpinning our study.

#### References

- (18)Portinari M, Carcoforo P. The application of drains in thyroid surgery. *Gland Surg* 2017; 6(5):563-573.
- (19)Tabaqchali MA, Hanson JM, Proud G. Drains for thyroidectomy/parathyroidectomy: fact or fiction? *Ann R Coll Surg Engl* 1999; 81(5):302-305.
- (20)Hurtado-López LM, López-Romero S, Rizzo-Fuentes C, et al. Selective use of drains in thyroid surgery. *Head Neck* 2001; 23(3):189-193.
- (21)Chen GX, Li C, Zhang H. Drainage During Endoscopic Thyroidectomy. *Jsls* 2019; 23(1).
- (22)Chen Y, Wang C, Bai B, et al. Drainage Tube Placement May Not Be Necessary

During Endoscopic Thyroidectomy Bilateral Areola Approach: A Preliminary Report. Front Surg 2022; 9:860130.

(23)Deveci U, Altintoprak F, Sertan Kapakli M, et al. Is the use of a drain for thyroid surgery realistic? A prospective randomized interventional study. J Thyroid Res 2013; 2013:285768.

(24)Keane E, Fitzgerald CW, Smyth DA, et al. Drain Usage in Head and Neck Surgery: A National Survey of Thirty-five Surgeons across Ten Units. Ir Med J 2018; 111(10):839.

### **Changes in the text 2:**

Following the reviewer's inquiries, we have retained the original text as it effectively introduces and addresses the topic in both the Introduction and Discussion sections. The remaining modifications are explained in a point-by-point response and marked in yellow in the manuscript.

### **Point-by-point response letter (Reviewer C)**

#### **Comment 1:**

I would suggest providing more details on the surgical procedure in paragraph 2.2.

#### **Reply 1:**

We greatly appreciate the valuable suggestion provided by the reviewer. Due to space limitations, the details of ETAA have been omitted; however, we refer readers to our previous study for citation purposes (see page 5, line 91-92). We have made a supplementary appendix to our manuscript and hope it can be easily understood.

#### **Changes in the text 1:**

Supplementary Appendix

##### 1. Preoperative management

B-ultrasound and computed tomography of the neck were performed before the surgery, and fine needle aspiration was performed in some cases. The laryngoscopy was performed before and after surgery to assess vocal cord mobility. Blood tests to evaluate thyroid function, intact parathyroid hormone (IPTH) levels, serum Ca<sup>2+</sup>

levels, and coagulation function. Patients diagnosed with hyperthyroidism received antithyroid drugs for symptom control, followed by a 3-week course of compound solution of iodine orally.

## 2. Surgical procedure (ETAA)

### 2.1 Working space

After endotracheal intubation under general anesthesia, the patient was positioned supine with all limbs abducted. Cushions were utilized to elevate the shoulders and slightly extend the neck. The patient underwent standard sterile prepping and draping. The surgeon assumed a position between the patient's legs while assistants stood on either side of the neck. Subcutaneous injection of an "inflation liquid" consisting of one mg adrenaline mixed with 500 ml saline was administered at the medial edge of the right areola. A curved incision measuring 12 mm in length was made based on two to four points along the areolar edge, followed by subcutaneous injection of approximately 50-100 ml "inflation liquid" into the deep fascia below the suprasternal notch using a water injector. A subcutaneous separation stick created a dissection plane from deep fascial layers toward the suprasternal notch through this incision site. Excess fluid was subsequently suctioned out after the formation of a subcutaneous tunnel. A trocar with an inner diameter measuring 10 mm was inserted, accompanied by a 10 mm, 30° laparoscope for visualization purposes. CO<sub>2</sub> pressure remained constant at six mmHg throughout the surgery.

At positions corresponding to 11 o'clock on both the left and right edges of the areola, a five mm trocar served as the primary and auxiliary operation ports. An ultrasonic scalpel and toothless graspers were introduced via these ports, respectively; specifically, the ultrasonic scalpel facilitated separation superiorly up to the upper border of cricoid cartilage within loose connective tissues beneath sternohyoid muscles' superficial layer extending laterally towards midline sternocleidomastoid muscle's deep layer.

### 2.2 Thyroidectomy

The midline of the infrahyoid muscles was opened using an ultrasonic scalpel. Following the separation of the infrahyoid muscles and thyroid capsule, a suture was

placed within the working space with its tail left outside the operative field. Subsequently, we sutured the muscle layers beneath the hyoid bone while keeping the head of the suture outside the working space. This allowed the suspension of the muscles to facilitate exposure of the thyroid gland by pulling on these sutures externally. Initially, using an ultrasonic scalpel, we separated and excised the isthmus from the trachea. Blunt dissection with endoscopic forceps enabled exposure of lower pole structures in the thyroid through which inferior thyroid arteries and veins were resected. Retraction superiorly and medially facilitated cutting Berry's ligament and middle thyroid vein using an ultrasonic scalpel while partially exposing (or not) recurrent laryngeal nerve (RLN) to identify its position and course via blunt dissection.

Further inferior retraction exposed superior thyroid arteries that were resected using an ultrasonic scalpel. Finally, lobes were excised following a similar procedure on the contralateral side. All excised tissues were collected in a specimen bag, removed through an observation port, and sent for intraoperative frozen pathology.

See our previous study for more details about ETAA, (Wang C, Feng Z, Li J, et al. Endoscopic thyroidectomy via areola approach: summary of 1,250 cases in a single institution. *Surg Endosc.* 2015;29(1):192-201. doi:10.1007/s00464-014-3658-8).

**Comment 2:**

The characteristics of the resected thyroid's specimens, such as thyroid volume, nodule diameter, etc., and how these features affect the drainage volume, were not analyzed in the results. This aspect could further strengthen the study by also clarifying certain points addressed only superficially in the discussion, such as the fact that thyroid volume can influence operative time.

**Reply 2:**

Thanks to the reviewer for all the good questions. We have observed that tumor size may impact both the complexity and duration of surgery. However, due to limitations in our retrospective analysis, specific data regarding precise tumor size and weight were absent from the records. Consequently, we have excluded this variable from our current study but intend to incorporate it into future research endeavors.

**Changes in the text 2:**

As per the reviewer's questions, we have made supplementary modifications to our text in part of Limitations: "Second, the effects of tumor size and weight were not assessed. Therefore, we intend to incorporate it into future research endeavors, and more extensive multicenter prospective trials are needed to validate our results." (see page 11 , line 214-216)

**Comment 3:**

I would also suggest including surgical complications in the results. Were there any postoperative hematomas or seromas? Does ETAA involve any unconventional complications compared to other types of remote-access thyroidectomy? Novel complications is a primary issue when introducing remote-access surgery. On this point, the authors could compare these techniques with other remote-access thyroidectomy approaches, such as robot-assisted transaxillary thyroidectomy.

**Reply 3:**

Thanks to the reviewer for all the good questions. ET has been applied to treat various thyroid diseases in many countries. The incidence of postoperative bleeding, RLN injury, parathyroid gland injury, and other complications was low in these studies (*PMID: 18172709, PMID: 18305997, PMID: 18335750, PMID: 16323164, PMID: 12732493, PMID: 11213035*). Our primary endpoint was drainage output; secondary endpoints included the complications and safety after ETAA in 72h, and there is no analysis of the influencing factors of cancer recurrence and long-term recurrence. There are no complications have been documented. None of our patients had a massive hemorrhage or required conversion to open surgery (see page 7 , line 133-134). However, it is essential to acknowledge that the limited sample size could contribute to the absence of complications observed; nevertheless, these findings still hold significance and may impact clinical decision-making.

**Changes in the text 3:**

As per the reviewer's suggestion, we have made supplementary modifications to our text:

A. " No postoperative complications have been documented." (see page 7 and line 133).

B. "Third, the study did not include patients with other diseases or complications; no massive hemorrhage and conversion to open surgery. Thus, the effects of comorbidities on the surgical outcome warrant further investigation, and the comprehensive assessment of the safety and efficacy of different drainage outputs after surgery necessitates a more extended follow-up period." (see page 11 , line 216-220)

**Comment 4:**

The tables are unclear and confusing; I would recommend reviewing the layout to make them easier to consult.

**Reply 4:**

We greatly appreciate the reviewer's valuable suggestion and have made revisions to the tables accordingly.

**Changes in the text 4:**

We express our sincere gratitude for the valuable suggestion provided by the reviewer. We have made revisions to our tables and hope it can be easily understood.

**Comment 5:**

Moreover, I would like to know the authors' opinion on the fact that the recurrent laryngeal nerve is not always exposed; are there reasons why it is not considered necessary to isolate it to ensure it has been preserved throughout its course?

**Reply 5:**

Transient or permanent damage to the recurrent laryngeal nerve (RLN) during thyroidectomy is paramount for patient quality of life. However, the debate on RLN is exposed or not caused during thyroid surgery still remains controversial. Kocher and his pupils, regarded by many as the fathers of modern-day thyroidectomy, believed that the best way to avoid injury was to avoid the nerve entirely. Thus, it became

dogmatic among thyroid surgeons that any RLN seen during thyroidectomy was very likely to have been injured. Lahey officially called this practice into question in the 1920s and 1930s. Lahey reported his experience with deliberate exposure and identification of the RLN during over 10,000 thyroidectomies. The less than 1% RLN injury rate was significantly lower than any previously published series and led him to advocate the routine identification and dissection of the nerve during thyroid surgery. In essence, it can be said that Lahey was the first surgeon to actively monitor the RLN during thyroidectomy with routine visualization of the structure. In an attempt to increase the margin of safety, numerous monitoring devices have been developed that are now readily available, of high specificity, and provide high negative predictive value in confirming the integrity of the RLN. At the same time, data regarding their efficacy in limiting or preventing injury to the nerve are inconclusive.

ETAA allows endocrine surgeons to remove the thyroid gland from a remote site while providing a scarless cosmetic appearance on the neck. However, the debate on RLN morbidity caused by surgical endoscopic approaches during thyroid surgery remains controversial. In cases where monitors are used, they should be used judiciously and interpreted cautiously. Such devices cannot and should not supplant clinical judgment, anatomic knowledge, and meticulous technique.

The RLN was fully exposed in our center when total thyroidectomy or lymph node clearance was carried out in the central zone, including the pre-laryngeal, pre-tracheal, and paratracheal areas.

#### References

1. Miller MC, Spiegel JR. Identification and monitoring of the recurrent laryngeal nerve during thyroidectomy. *Surg Oncol Clin N Am*. 2008;17(1):121-ix.
2. Davey MG, Cleere EF, Lowery AJ, Kerin MJ. Intraoperative recurrent laryngeal nerve monitoring versus visualisation alone - A systematic review and meta-analysis of randomized controlled trials. *Am J Surg*. 2022;224(3):836-841.
3. Wang C, Feng Z, Li J, et al. Endoscopic thyroidectomy via areola approach: summary of 1,250 cases in a single institution. *Surg Endosc*. 2015;29(1):192-201.

#### **Changes in the text:**

Following the reviewer's inquiries, we have retained the original text. The remaining modifications are explained in a point-by-point response and marked in yellow in the manuscript.

### **Point-by-point response letter (Reviewer D)**

#### **Comment 1:**

This is an important paper regarding an evolving technique, although the study design isn't the best one. Despite the small sample; these findings may influence clinical decisions. The authors can improve these findings by conducting a prospective study regarding the same topics further.

#### **Reply 1:**

Thanks very much for the reviewer's comment, which is highly appreciated. There are limitations in this study. First, the study had a retrospective single-center design and a small sample size. Second, the effects of tumor size and weight were not assessed. Therefore, we intend to incorporate it into future research endeavors, and more extensive multicenter prospective trials are needed to validate our results. Third, the study did not include patients with other diseases or complications; no massive hemorrhage and conversion to open surgery. Thus, the effects of comorbidities on the surgical outcome warrant further investigation, and the comprehensive assessment of the safety and efficacy of different drainage outputs after surgery necessitates a more extended follow-up period.

#### **Changes in the text 1:**

Following the reviewer's inquiries, we have retained the original text. The remaining modifications are explained in a point-by-point response and marked in yellow in the manuscript.