Development of a Scarless and Gasless Trans-Oral Video-Assisted Thyroidectomy

A thesis submitted in partial fulfilment

of the requirements for the award of

Doctorate in Philosophy

Christian Camenzuli

Faculty of Medicine and Surgery

Department of Anatomy

University of Malta

2021

To my patients, this work is for you.

Acknowledgments

I would like to thank Prof Jean Calleja Agius, my supervisor, for her relentless support and encouragement especially in the darkest hours. Many thanks also to Prof Pierre Schembri Wismayer, my co-supervisor, for his help and directions. I would like to recognise the invaluable help of Prof Jonathan C Borg, Ing John Paul Borg, Mr Josef Attard, Ing. Lucianne Gauci and Dr Ing Owen Falzon from the Faculty of Engineering at the University of Malta with whom I have worked very closely in the past 6 years and without whom it would have been impossible to develop the prototype for the device and to collect data in my analyses. Thanks also to Prof Neville Calleja for sharing his expertise in statistics. I would also like to extend thanks to the staff at the dissection laboratory of the Department of anatomy headed by Dr Sherif Suleiman for their relentless help.

I would like to offer my heartfelt thanks to Dr Andee Agius, my partner and research assistant, who has been relentless in her support and who has offered me the inspiration to embark on this project.

Finally, I would like to thank Endeavour Scholarship Scheme Malta for their financial assistance.

Abstract

Background: Endoscopic techniques have been developed over the years to mitigate the visible curvilinear scar resulting from open thyroid surgery. The trans-oral endoscopic thyroidectomy via a vestibular approach (TOETVA) is the latest technique which offers visibly scarless surgery.

Aim and Objectives: The aim was to develop a novel gasless modification to TOETVA. The objectives were: to reproduce the TOETVA with CO_2 insufflation using Thiel embalmed cadavers; to develop a retraction device with the aim of eliminating CO_2 insufflation; to compare the original TOETVA using CO_2 insufflation with the gasless technique in embalmed cadavers; and to explore relative contraindications for gas insufflation in the neck and assess whether a gasless adaptation would improve outcomes.

Methods: A new retraction device has been built in collaboration with the Faculty of Engineering and the Department of Anatomy. Nine Thiel embalmed cadavers were used: to replicate the standard TOETVA technique (n=3); to test the new device in a gasless technique (n=3) and to compare the intrajugular venous pressure using the standard TOETVA with the new technique (n=3). Using a blinded questionnaire, 4 thyroid surgeons compared the images retrieved from the standard TOETVA and the gasless modification.

Results: Thiel embalmed cadavers are an appropriate medium to reproduce TOETVA, for the purpose of training and further development of the technique. The retracting device was successfuly developed to eliminate the need of insufflation during TOETVA whilst still maintaining equivalent visualisation of anatomical landmarks. There was significantly higher intrajugular venous pressures with insufflation.

Conclusion: Gasless TOETVA with the developed device is a viable modification to the technique that offers an augmented safety profile to patients undergoing TOETVA.

Abbreviations

BAET: Bilateral Areolar Endoscopic Thyroidectomy

CO2: Carbon dioxide

eMIT: Endoscopic Minimally Invasive Thyroidectomy

ETAA: Endoscopic Thyroidectomy by Areola Approach

ETOVA: Endoscopic Thyroidectomy using the Oral Vestibular Approach

HD: High Definition

IONM: Intraoperative Neuromonitoring

LaVa: Lateral Vestibular approach

LED: Light Emitting Diode

NOTES: Natural Orifice Transluminal Endoscopic Surgery

PTC: Papillary Thyroid Cancer

TOET: Trans-oral Endoscopic Thyroidectomy

TOETVA: Trans-Oral Endoscopic Thyroidectomy via a Vestibular Approach

TOPP: Trans-oral Partial Parathyroidectomy

TOVANS: Trans-Oral Video-Assisted Neck Surgery

TOVAT: Totally Trans-oral Video-assisted Thyroidectomy

TSH: Thyroid Stimulating Hormone

VAS: Visual Analogue Score

Publications and Presentations

Publications

Camenzul, C., Schembri Wismayer, P. and Calleja Agius, J,. 2018. Trans-oral Endoscopic Thyroidectomy: A Systematic Review of the Practice So Far. *JSLS*, doi:10.4293/JSLS.2018.00026

Camenzuli, C., Schembri Wismayer, P. and Calleja Agius, J. ,2019. Using thiel embalmed cadavers for training in trans-oral endoscopic thyroidectomy vestibular approach (TOETVAVA): is it feasible? *Minerva Chir*., **4**(5), pp. 440-442. doi: 10.23736/S0026-4733.19.08066-0.

Camenzuli, C., Attard, J., Borg, J.P., Schembri Wismayer, P., Borg, J. and Calleja Agius, J., 2020. Cadaveric Evaluation of a Device Supporting Gasless Trans-oral Endoscopic Thyroidectomy. *Surg Innov*. **27**(4), pp. 410-411. doi: 10.1177/1553350620944513.

Camenzuli, C., Schembri Wismayer., P. and Calleja Agius, J, 2021.. Association between carbon dioxide insufflation in endoscopic thyroidectomy and intra-ocular pressure (IOP). Is insufflation contra-indicated in glaucoma patients? *Oral Oncol.* doi: 10.1016/j.oraloncology.2020.105022.

Camenzuli. C., Schembri Wismayer, P. and Calleja Agius, J., 2021. The effect of carbon dioxide insufflation during TOETVA on internal jugular vein pressure changes: Is there a safer alternative? *Surg Innov*. doi:10.1177/15533506211035252

Submitted paper–awaiting publication

Camenzuli. C., Schembri Wismayer, P. and Calleja Agius, J. Gasless approaches to trans-oral endoscopic thyroidectomy: A systematic review of the literature. Submitted to Oral Oncology

Awards

Winner of Scientific Initiative from the Malta Intellectual Property Awards 2020.

Medal for Scientific Initiative given by the World Intellectual Property Organisation (WIPO)

Device Registration

Design Registration by the European Union Intellectual Property Office (EUIPO) Number 007793666-0001

Patent Registration in progress. International application number PCT/EP2021/055173

Presentations

Trans-oral Endoscopic Thyroidectomy: A Systematic Review of the Practice So Far.
Poster presentation 10th Malta Medical School Conference November 2018

Using Thiel embalmed cadavers for training in trans-oral endoscopic thyroidectomy vestibular approach (TOETVA): Is it feasible?
Oral Presentation 10th Malta Medical School Conference November 2018

Thiel Embalmed Cadaver Use for Training in NOTES Neck Surgery:
Is this a Suitable Platform?
Poster Presented International Federation of Associations of Anatomists (IFAA) Congress August 2019

Thiel Embalmed Cadavers For training in trans-oral endoscopic thyroidectomy vestibular approach (TOETVA): Is it a suitable Platform?
Oral Presentation at the University of Malta Doctoral Symposium February 2020

Outreach

National news: https://www.tvm.com.mt/mt/news/tobba-u-inginiera-maltin-btaghmir-li-se-jevita-qasma-fl-ghonq-waqt-operazzjoni-tat-thyroid/?fbclid=IwAR39j2teJxmo_GofExFdY4EDrpjLjGzw4X3o8BylQjh1M-0gk4orgelmZ8Q#.YKf162KuOaM.twitter

Technology website: https://gadgetsmalta.com/general/maltese-research-team-develops-new-method-of-thyroid-surgery/?fbclid=IwAR3YBfpZkoaLtg2SBq9z0E0GAl2IoA6fqDzvseALJyveU3GToRUzq2t37OA

University of Malta NewsPortal: https://www.um.edu.mt/newspoint/news/2021/05/novel-medical-device?utm_source=update&utm_campaign=update&utm_medium=email&utm_content=other

Table of Contents

List of Tables

List of Figures

Chapter 1:

Literature review

1.1 Introduction

Thyroid surgery is one of the treatment options for several benign and malignant thyroid pathologies. Thyroid disease affects around 11% of the population in the United States of America (Canaris et al. 2000). In Malta, the incidence of thyroid cancer for 2013 was 13.42 (95%CI 12.95, 13.88) per 100,000 population for females and 4.05 (95%CI 3.82, 4.28) per 100,000 population for males. This incidence has been showing an upward trend over the past years with data from 2017 showing an incidence of 18.47 (95%CI 17.97, 18.98) per 100,000 population for females and 5.98 (95% CI 5.69, 6.27) per 100,000 population for males (Malta Department of Health Information and Research 2019). This trend has been observed in several countries including the UK and the USA (Leese et al. 2008, Davies, Welch 2014, Kitahara, Sosa 2016, Wang, Tracy, Sosa 2018), as well as low- and middle-income countries (Lortet-Tieulent et al. 2019). Consequently thyroid surgery is common, amounting to more than 80,000 (approximately 27 per 100,000 population) procedures yearly in the United States of America (Bhattacharyya, Fried 2002, Sanabriai et al. 2018, Davies, Hoang 2021). In Malta, 203 (approximately 40.4 per 100,000 population) thyroid surgeries were carried out in 2019 (Medical Administrator's Office 2019). The important economic impact of this surgery as well as the cosmesis affected by the traditional scar in the neck, has driven the development of many alterations to the traditional surgical technique in an attempt to improve patients' outcome and satisfaction.

1.2 History of Thyroid Surgery

The advances made in thyroid surgery offer a glimpse in the reality of anatomical studies and development of operative technique. The obvious large neck lumps that develop in areas of iodine deficiency were described more than 3500 years ago (Dorairajan, Pradeep 2013). Although the contemporaries could describe them, the cause remained elusive. They were thought to represent an extension of the bronchus or to be due to excessive phlegm and were therefore called 'bronchocoele'. This term, used by illustrious personalities like Hippocrates, remained in use for many centuries. It was only in the 16th century that the thyroid gland was identified as an independent structure in the neck. It was consequent to its Ancient Greek shield-like morphology just in front of the thyroid cartilage that this novel structure was given the name of *glandulae thyroideae*. This independent anatomical structure that could give rise to swellings called goitres (from gutter or throat), had an unknown function. Leonardo da Vinci, the first scientist who drew an anatomically correct picture of the thyroid gland, thought that this structure's sole purpose was to fill the space in the lower neck that was devoid of muscle and to keep the trachea separate from the sternal notch (Sarkar et al. 2016). It is with this basic anatomical and lack of physiological understanding that surgery on the thyroid gland started to develop.

The first attempt at thyroid surgery was performed by the historic surgeon of the Islamic world, Abu al-Qasim al-Zahrawi in 952 AD (Smith, Coughlin 2016). Charaf ed-Din's manuscript from 1465 illustrates thyroid surgery performed using a Turkish sabre (Martino et al. 2021). From the earliest days of thyroid surgery, there were major concerns about the viability of this technique. The main initial concern was peri-operative haemorrhage since this structure is highly vascularized. Having survived this, patients needed to survive post-operative infection and the consequences of severe hypothyroidism. The initial mortality after thyroid surgery was around 40%, and this remained so for many centuries (Rogers-Stevane, Kauffman 2008). It is therefore not surprising that Samuel D. Gross, an American academic surgeon in the 19th century commented:

"Can the thyroid gland, when in the state of enlargement be removed with a reasonable hope of saving the patient? Experience emphatically answers 'No'!!! . . . If a surgeon should be so foolheartedly as to undertake it . . .every step he takes will be environed with difficulty, every stroke of his knife will be followed by a torrent of blood, and lucky will it be for him if his victim lives long enough to enable him to finish his horrid butchery . . . no honest and sensible surgeon would ever engage in it" (Tapscott 2001)

Despite the negative attitude and the poor results achieved, several surgeons decided to work on making thyroid surgery safe and accessible. The most prominent of these is Emil Theodore Kocher, a Swiss surgeon and researcher, who presented the first positive results for surgery on the thyroid gland. Indeed his 5000 case series with a mortality of 0.5% led him to be honoured with a Nobel Prize in 1909. He was joined by Theodor Billroth, William Halsted, Charles Mayo, Thomas Dunhil, Frank Lahey and George Crile (Hannan 2006, Vellar

1999). Over the course of a century, these distinguished surgeons have revolutionised the surgical management of thyroid pathologies. They took advantage of the novel techniques of anaesthesia, antisepsis and haemostasis to promote new surgical techniques. The improved understanding of the thyroid physiology made it possible to take care of the post-operative patient and prevent the hormonal consequences related to thyroid surgery (DuBose et al. 2004, Dorairajan, Pradeep 2013). It has been this cumulative effort by some of the biggest names in the medical field of the 19th and 20th centuries, that has made thyroid surgery one of the safest surgical interventions in the 21st century (Sarkar et al. 2016).

1.3 Surgical Anatomy

The thyroid gland starts to develop between the first and second pharyngeal pouches through a thyroid diverticulum at the base of the tongue at around day 20-24. From the latter position, the thyroid tissue migrates caudally maintaining a central position. During this journey, which starts in the fifth week of development and is usually finished by the seventh week, the gland passes anterior to the larynx and hyoid bone and remains attached to the tongue through the thyroglossal duct. The gland continues to develop in its new position by solidifying through the development of thyroid follicles and subsequently dividing into two lobes. The thyroglossal duct typically disintegrates in the tenth week, leaving behind the foramen caecum in the tongue (Rosen, Sapra 2020). At its full development, the thyroid is a ductless butterfly-shaped gland located in the anterior aspect of the lower neck. It lies just inferior to the larynx and typically surrounds the anterior and lateral aspects of the cranial part of the trachea. Inferiorly, the normal thyroid gland typically reaches down to the fourth and fifth tracheal rings.

The gland, normally weighing around 20g in healthy adults, is composed of two lateral lobes joined together in the centre by a thin film of thyroid tissue known as isthmus. The lateral lobes form the majority of the gland and are approximately conical in shape. On the posterior aspects of the lateral lobes, there is usually a small horn of tissue known as the Zuckerkandl's tubercle. The isthmus typically lies superficial to the second and third tracheal rings. Occasionally an additional section is found extending superiorly from the middle portion of the isthmus to a variable distance. The latter is known as the pyramidal lobe and represents an embryological remnant. Sometimes the pyramidal lobe is attached to the hyoid bone with a fibrous band or with a thin film of muscle known as levator glandulae thyroideae (Ozgur et al. 2011).

The pretracheal fascia envelops the gland completely and may extend within the gland substance itself, dividing the thyroid mass in smaller distinct portions. This fascia condenses posteriorly adjacent to the cricoid cartilage to form the ligament of Berry (Fancy et al. 2010). Superficial to the gland lie the strap muscles consisting of the sternothyroid, thyrohyoid and sternohyoid muscles. The strap muscles, particularly the sternothyroid, will be thinned down and plastered to the thyroid gland when the latter enlarges. Separating the strap muscles from the skin is a thin layer of muscle known as the platysma (Watkinson, Gleeson 2021).

The thyroid gland is supplied by two arteries and is drained by three veins. The superior thyroid artery, the first branch of the external carotid artery, enters the lateral lobe at the upper pole. The superior thyroid vein, which drains into the internal jugular, typically lies in close proximity to the superior thyroid artery. Passing in close proximity to the superior lobe vessels is the external branch of the superior laryngeal nerve. The latter nerve supplies the cricothyroid muscle whose function is to increase the voice pitch. The inferior thyroid artery, a branch of the thyrocervical trunk, enters the thyroid gland through the inferior pole of the lateral lobe. Accompanying this vessel is the inferior thyroid vein which drains into the brachiocephalic veins. This vascular bundle lies in close proximity to the recurrent laryngeal nerve near Zuckerkandl's tubercle. The recurrent laryngeal nerve supplies all the muscles of the vocal cords, except the cricothyroid. The middle thyroid vein, sometimes found as a number of small veins rather than a single structure, drains into the internal jugular vein (Thiagarajan 2015).

Posterior to the lateral thyroid lobes, there are classically four parathyroid glands: two superior and two inferior. These glands usually derive their blood supply from the inferior thyroid artery, although variations have been observed (Ellis 2007). There is also a lot of variation in the anatomical location of the parathyroid glands themselves. In fact the thyroid gland and its surrounding structures constitute the most variable anatomical areas, leading to potentially challenging dissections (Ozgur et al. 2011, Joshi et al. 2010) and incidental parathyroidectomy (Zheng et al. 2017, Caglià et al. 2017). These variabilities make the knowledge of surgical anatomy imperative for the endocrine surgeon (Bliss et al. 2000, Jin, Sugitani 2021).

1.4 Open Thyroid Surgery

Thyroidectomy is a very effective treatment modality for a vast array of benign and malignant thyroid pathologies. This treatment is beneficial even in areas of the world where health care resources and patient follow up is a major problem (Jafari et al. 2017).

There are four types of thyroidectomy namely thyroid lobectomy, subtotal thyroidectomy, total thyroidectomy and substernal thyroidectomy. The open technique is the conventional one and remains the gold standard with which newer thyroidectomy techniques are compared. The open operative technique follows the following steps:

- After endotracheal intubation, the patient is positioned supine with an extended neck. The horizontal cervical incision is marked 1-2 fingerbreadths above the sternal notch within a skin crease and extending symmetrically on either side not more than 1-2cm lateral to the medial border of sternocleidomastoid.

- A curvilinear incision is performed through the skin, subcutaneous fat and platysma. The subplatysmal plane is then developed up to 1 cm above the thyroid notch cranially and down to the sternal notch caudally.
- The strap muscles are separated in the midline through the *linea alba cervicalis,* thus exposing the underlying thyroid gland
- The strap muscles are then bluntly pushed off the thyroid gland laterally to develop a plane for dissection of the thyroid tissue. When the thyroid mass is large, the strap muscles can be divided. This should always be done superiorly to preserve the ansa cervicalis nerve supply of the muscles.
- The thyroid gland is gradually delivered medially. When the middle thyroid vein is limiting this manoeuver, this should be ligated and divided at this point to allow proper delivery of the gland.
- The superior thyroid pole is dissected. The superior thyroid artery and vein are identified. The external branch of the superior laryngeal nerve should be identified at this point and protected. The superior thyroid vascular bundle is then dissected free, ligated and divided close to the thyroid gland to preserve the vasculature to the superior parathyroid glands.
- The trachea-oesophageal groove close to the Zuckerkandl's tubercle is then carefully dissected in order to identify the recurrent laryngeal nerve. Once identified, the nerve needs to be followed in the neck to its insertion in the trachea. Through this identification process, the nerve can be protected for the rest of the operation.

- The inferior thyroid artery and vein are identified in the inferior thyroid pole and dissected free from the surrounding structures. These vessels are divided and ligated close to the thyroid gland in order to preserve blood supply to the inferior (and sometimes even the superior) parathyroid glands.
- The thyroid gland is then mobilized off the underlying trachea by dissecting the ligament of Berry.
- For thyroid lobectomy, the isthmus is divided close to the opposite lobe to be removed and the raw surface is sutured/sealed for homeostasis. In the case of total thyroidectomy, the above steps are repeated on the other side and the thyroid gland is removed *en bloc*.
- The strap muscles are approximated lightly in the midline. Some surgeons use closed drainage under suction although this was never proven to be of benefit (Samraj, Gurusamy 2007). The platysma muscle is closed using interrupted suturing whilst the skin is closed using a continuous subcuticular suture.

The above operative technique describes the traditional method of performing thyroidectomy (Wiseman et al. 2004, Simental, Myers 2003, Adams, Doherty 2009, Roman et al. 2019). In recent years, modifications have been proposed to improve the outcome of thyroid surgery. For example, the use of suture ligation in the conventional technique has been criticised and linked to longer operative times and increased blood loss (Al-Dhahiry, Hameed 2016). The sutureless modification of the conventional technique, where the vessels are sealed using ultrasonic or bipolar-based devices instead of being ligated, has been studied extensively. There is sufficient evidence proving that this technique is superior to the previously practiced suture ligations (Mohamed, W., Ahmed,A. 2017, Cheng et al. 2015, Ruggiero et al. 2018).

1.5 The impact of the cervical scar

Conventional open thyroidectomy, considered as the gold standard procedure for thyroid pathologies requiring surgical treatment, offers excellent results and very low morbidity. Despite this, there is a subset of patients who suffer from morbidity secondary to having a scar in the neck. In the latter subgroup of patients, the scar resulting from open thyroidectomy in the visible neck leads to negative impact on their body imaging and consequently effects their quality of life in a bad way (Arora, et al. 2016, Sethukumar et al. 2018, Chaung et al. 2017).

Over the years, a number of mitigating factors have been developed to try to decrease the morbidity of bad cosmetic outcomes in patients undergoing open thyroidectomy (Henry 2008). These included proper placement of the curvilinear scar within a skin crease in the neck and using subcuticular suturing rather then interrupted skin suture. Having a longer scar especially if it involves jagged edges has been shown to give worse patient satisfaction and therefore should be diminished though appropriate planning of the scar (Liu et al. 2021). These technical modifications to the traditional technique have improved patient satisfaction of wounds following open thyroidectomy (Pradeep 2021). Despite this improvement in patient satisfaction, patients who have a cervical scar still report high levels of anxiety about having a visible scar which makes them self conscious (Felix et al. 2019).

The evaluation of cosmetic outcomes is not an easy exercise and requires a number of tools that assess the subjective and objective outcomes both in the short term and in the long term (Dordea, Aspinall 2016). This makes interpretation of outcomes for various groups difficult to interpret. Notwithstanding, it has been shown that there is an important group of patients in whom the motivation to avoid a scar in the neck is robust (Qiu et al. 2020). In these groups, who are found across various geographical locations, if patients are presented with the possibility of having scarless thyroid surgery, they would choose having a thyroidectomy without a scar in the neck as opposed to having the traditional cervical scar, as long as all other risks are equivalent (Chen et al. 2021).

1.6 Endoscopic Thyroidectomy

1.6.1 Development of Endoscopic Thyroidectomy

The increasing concerns with the cosmetic results of the neck incision in addition to the ever-increasing influence of minimally invasive surgery in other specialties, have led to several modifications to the conventional technique (Biello et al.. 2021). Minimally invasive thyroid surgery (MITS) is a modification to the conventional technique (Sabuncuoglu et al. 2014). This modified approach to the thyroid gland demanded new instrumentation to perform the dissection and adapt to the increasingly restrictive field of view. Such techniques include the use of intraoperative monitoring of the recurrent laryngeal nerve, even though there appears to be no added benefit over visual identification (Cirocchi et al. 2019). This equipment is used to identify the recurrent laryngeal nerve and the external branch of the superior laryngeal nerve during the dissection (Terris 2009, Alvarado et al. 2008, Liu, et al. 2020).

The increasingly restrictive space through which thyroid surgery has to be carried out led to the introduction of rigid endoscopes. Minimally invasive video-assisted thyroidectomy (MIVAT) exploits the laparoscopic high-definition projections and its amplification of anatomical structures to render thyroidectomy through small cervical incisions possible. This technique, in addition to offer better cosmetic results, is also linked to significantly less post-operative complications and less post-operative pain. It is however associated with longer operative times (Liu et al. 2012, Zhang et al. 2015, Sahm et al. 2019).

However, the promise that MITS and MIVAT techniques decrease morbidity in patients undergoing thyroid surgery by decreasing the cervical scar has been questioned. A number of studies found that, contrary to the belief of many surgeons, these new techniques did not improve the morbidity (Kim et al. 2015, Linos et al. 2013, Dordea, Aspinall 2016). It is the presence of a scar and not how extensive it is, that gives the morbidity. The psychological burden of having a visible scar in the neck for some individuals cannot be underestimated (Kim, Hyewon, Kim et al. 2021).

1.6.2 Extra-cervical Endoscopic Thyroidectomy

Since early minimally invasive techniques which drastically decreased the size of the incision in the neck with the help of endoscopic assistance did not offer improved outcomes when long term cosmetic assesments were performed (Alesina et al. 2021, Sahm et al 2019, Linos et al 2013), extra-cervical endoscopic techniques attempot to mitigate this by removing the scar from th neck. A number of endoscopic extra-cervical approaches have been described over the past few years. These procedures all share the property that they do not leave a visible scar in the neck and are therefore collectively known as scarless endoscopic thyroidectomy (SET) (Tan et al. 2008, Sephton 2019).

1.6.2.1 Trans-Axillary Approach

The trans-axillary endoscopic approach to the thyroid gland has been one of the original extra-cervical approaches described in literature (Ikeda et al. 2000). In this operation, the surgeon acquires access to the thyroid gland through skin incisions performed in the anterior axillary line. After insertion of the ports, dissection needs to be carried out to develop a plane superficial to the pectoralis major but deep to the platysma. The original ports described included one 10mm port for the endoscope and two 5 mm ports for the working instruments. This has however been a subject of debate with single incision access being proposed as another safe and feasible method of gaining access (Cho et al. 2017, Lee, Chung 2013). Once the plane is developed, the sternocleidomastoid has to be identified and access to the thyroid gland achieved by dissecting between the sternal and clavicular heads of the muscle. The thyroid gland is dissected from the inferior pole towards the superior pole using mainly blunt dissection. The vessels are then divided using ultrasonic or bipolar-based devices. Intra-operative nerve monitoring can be used to identify and protect the recurrent laryngeal and the external branch of superior laryngeal nerves as the dissection plane is developed. The parathyroid glands are also identified and protected. Berry's ligament is then divided and the isthmus transected using the previously mentioned devices. The thyroid gland is then removed within an endobag. Finally, the wound is closed after appropriate homeostasis (Tan et al. 2008).

The trans-axillary technique is deemed to be more favourable to the conventional technique not only because of a better cosmetic result but also because it offers better nerve and parathyroid gland visualization (Rao 2009, Jeong et al. 2009, Kim et al. 2021). However, this technique comes with a steep learning curve (Kwak et al. 2014).

1.6.2.2 Breast/Chest Approach

In this approach, the access to the thyroid gland is gained through the infraclavicular region and/or through incisions performed in the peri-areolar space of the breast. The dissection then progresses in a caudo-cranial fashion with the identification of the recurrent laryngeal nerve and parathyroid glands. This approach has the advantage of giving access to both lobes of the gland and have been deemed a feasible method (Hur et al. 2011, Bhargav, Amar 2013). Lateral neck dissection is also carried out successfully with this approach although this has been associated with significantly higher rates of internal jugular vein injury (Yan et al. 2020). Whilst this technique has been extensively used by some with good outcomes (Yan et al. 2019), the long operating times, steep learning curves and the need for specialized equipment for this procedure has largely limited its uptake (Sephton 2019).

1.6.2.3 Hybrid Approach

The axillo-bilateral-breast approach (ABBA) combines the two previously described approaches to exploit the access offered by the bilateral breast approach to both lobes of the thyroid gland whilst at the same time having the adequate triangulation needed by the operating surgeon to carry out the procedure (Jin et al. 2014, Bärlehner, Benhidjeb 2008).

Robotic modifications to the endoscopic techniques have also been examined (Tolley, Camenzuli 2020). These techniques offer the advantage of improved visualization of anatomy, a shorter learning curve when compared to the endoscopic techniques and easier dissections due to the ergonomic construction of the robotic arms (Bhatia et al. 2015). Other advantages include shorter operative times and decreased postoperative swallowing discomfort for the patient (Lee, Chung 2013).

The improved ergonomics of the robotic technique also offers the possibility of more remote access anatomical areas to the thyroid gland. The retroauricular approach is one such anatomical location (Alabbas et al. 2016, Kandil et al. 2020, Tae 2020b). Despite all these advantages, the costs of running a robotic service remain prohibitive. Consequently, whilst some of the techniques may be feasible technically, their economical viability remains a major stumbling block for their implementation (Bhatia, et al. 2015).

All the extra-cervical endoscopic approaches to the neck offer a better cosmetic result since they avoid a visible scar in the neck. However, because these procedures require dissection which is more extensive than that needed in the conventional approach, they cannot be considered to be minimally invasive (Henry, 2008).

1.7 Development of the Trans-oral Technique

The researcher carried out a systematic review in order to identify all the published literature available on the subject of trans-oral thyroidectomy. For this systematic review seven databases were searched. These were Pubmed, Google Scholar, Medline, BioMed Central, Cochrane Library, OVID and Web of Science. The search strategy consisted of a combination of keywords. These included: “human”, “trans-oral”, “floor of mouth”, ‘vestibule”, “endoscopic”, “scarless”, “video-assisted”, “natural orifice” and “thyroidectomy”. The comprehensive search strategy was modified to comply with the different search engines. In addition to the latter search strategy, a manual search of important journals in the field of thyroid surgery was performed. The study protocol for the initial searches was registered on PROSPERO (CRD42017075758).

1.7.1 Preclinical Stage

The novel technique in which the thyroid gland is approached through the mouth was proposed by Witzel and his team in 2008, who focused on delivering a proof of concept and on the analysis of the anatomical viability of the technique. For the purpose of the latter a mixture of fresh frozen human cadavers and live pigs were used in an experimental setup.

The initial efforts consisted of an exclusively floor of mouth approach to the neck. Whilst this approach was used successfully in the context of both human cadavers and pigs, increasingly there was interest to use the vestibule for additional access. Dionigi et al 2009 proposed that an exclusively floor of mouth approach did not offer sufficient triangulation for the surgeon to operate comfortably. The latter group added working ports through the vestibule. Whilst the floor of mouth approach was found to be anatomically viable (Wilhelm et al. 2010), a number of groups commented on the limitations of this access particularly in individuals who have full dentation (Guo et al. 2014, Ng 2013). Lee et al. 2014 first investigated the trivestibular approach, which moved the access from the floor of mouth to the lower vestibule. This group claimed that this improved on the floor of mouth approach by decreasing the risk of mentalis muscle damage and damage to Wharton's duct. Whilst some groups investigated alternative approaches such as the trans-tracheal approach (Liu et al. 2012), these were limited by the surrounding anatomy and therefore not explored further.

The possible risks particularly to the mental nerve were noted through these anatomical explorations. The floor of mouth approach offered additional risk to the lingual artery, hypoglossal nerve, Wharton's duct, mentalis muscles and sublingual salivary glands (Karakas et al. 2011). Notwithstanding, the trans-oral approach to the thyroid gland was found to be viable in the cadaveric and pig platforms. A summary of the available literature is shown in Table 1.

					Operation				
Authors	**Year**	**Location**	**Type**	**Number of subjects**	**Access**	**CO_2 (mmHg)**	**Type**	**Operating time (mins)**	**Complications**
Witzel *et al.*	2008	Austria	LP	10	SL	6	TT	50	None
Benhidjeb *et al.*	2009	Germany	FC	2	FOM + BV	4 to 6	STL	60	None
Wilhelm *et al.*	2010	Germany	FC	8 (5M,3F)	SL + BV	NA	NA	NA	NA
Guo *et al.*	2011	China	FC	20	FOM + BV	NA	NA	NA	None
Karakas *et al.*	2011	Germany	LP	10	FOM	NA	TL	96.5	None
			Cadaver not specified	10	FOM	NA	NA	61	Injury to the posterior pharyngeal wall, the laryngeal cartilages and oesophagus with posterior-to-hyoid approach
			Patients	2	FOM	NA	TOPP	NA	Temporary hypoglossal nerve injury, difficulty with swallowing
Liu *et al.*	2012	China	EC	15	tTr + SL	NA	NA	NA	None
Su *et al.*	2013	China	FC	6	TV vs SL vs FOM + BV	NA	NA	NA	NA
Ng	2013	China	FC	2	FOM + BV	NA	NA	NA	NA
Park *et al.*	2014	Korea	FC	6 (5M,1F)	TV	5 to 6	TL +CND	NA	1 flap perforation
Lee *et al.*	2014	Korea	LP	7	Mandibular periosteal +/- SL	4 to 6	TT	122.9	Seroma x3
Guo *et al.*	2014	China	FC	15 (8M,7F)	FOM + BV	6 to 8	TT + SND	NA	None
Cai *et al.*	2015	China	FC	5 (2M,3F)	FOM + BV	NA	TOPP	NA	None

Table 1: Pre-clinical literature on the feasibility of the transoral approach
Legend BV, Bivestibular; CND, Central neck dissection; EC, Formalin Embalmed Cadavers; F, Female; FC, Fresh Cadavers; FOM, Floor of Mouth; LP, Live pigs; M, Male; NA, Not available; SL, Sublingual; SND, Selective neck dissection; ST, Subtotal thyroid lobectomy; TL, Thyroid lobectomy; TOPP, Tansoral parathyroidectomy; TT, Total thyroidectomy; tTr, Trans-Tracheal; TV, Tri-vestibular.

1.7.2 Clinical Stage

As this minimally invasive trans-oral endoscopic approach gained popularity within the endocrine surgical community and as the available preclinical evidence presented the trans-oral approach as safe and feasible, the technique migrated from human cadavers and live pig to live patients.

The inclusion and exclusion criteria for patients to undergo transoral endoscopic thyroidecotomy varied considerably between the various groups. Whilst initial literature had focused mainly on benign nodules of up to 40mm (Yang et al. 2016), as more evidence in support of the safety of the transoral technique accumulated, the indications in which this procedure is considered viable have increased. The maximum size of benign or indeterminate thyroid nodules that are now considered for the transoral technique has increased to 60mm (Le, Ngo et al. 2020, Fernandez-Ranvier et al. 2020). TOETVA has also been used in patients suffering from differentiated thyroid cancer up to 30mm in diameter (Hong et al. 2020, Wang et al. 2021). Autoimmune thyroiditis (including Graves disease) were initially considered a contra-indication due to increased risk of bleeding in these conditions (Dionigi et al. 2017). These conditions are now also included by some surgeons in the spectrum of pathologies amenable for TOETVA (Fernandez-Ranvier et al. 2020). Patients who were unfit for surgery, had previous neck surgery or irradiation or had evidence of metastasis or local invasion were excluded in almost all the groups. The presence of a substernal goitre and oral infections were other common contraindications (Dionigi et al. 2017, Anuwong et al. 2018, Le et al. 2020). The positoning of the neck in hyperextension is identical to the one used in open thyroidectomy. Whilst patients with limited neck extension might not be the best candidates for this procedure, none of the groups specifically excluded them. Upper pole nodules and patients who are obese or have shorter necks are known to offer more challenging thyroid surgery and they were therefore excluded by some groups (Kadem et al 2019).

Groups lead or trained by Wilhelm persisted in the use of the floor of mouth for the camera port access (Wilhelm, Metzig 2010, Wilhelm et al. 2016, Fu et al. 2018). All the other groups used a completely vestibular approach (Figure 1). When the outcomes from these two approaches were compared, the complications associated with the technique which used the floor of mouth for access were more common when compared to the tri-vestibular approach (Camenzuli et al. 2018). The floor of mouth approach has therefore fallen out of favour.

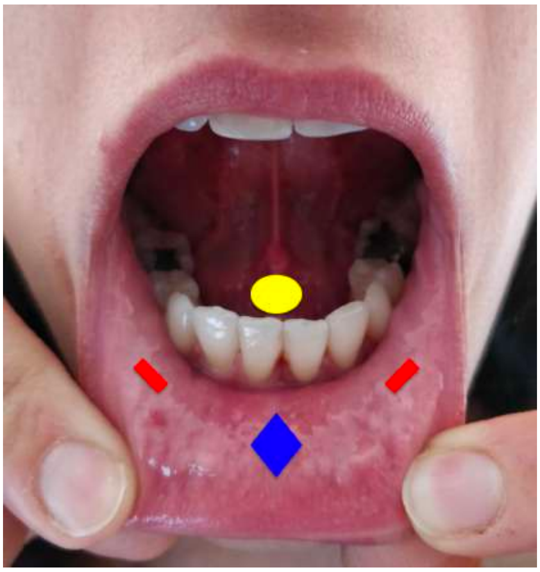


Figure 1 This figures shows the different approaches to the sublatysmal space. The floor of mouth approach is marked with a yellow circle whilst the vestibular approach is marked with a blue diamond. The incisions carried for the access ports in both techniques are marked with red lines.

1.7.2.1 Risks and Challenges of TOETVA

The main concerns in adopting the transoral endoscopic thyroidectomy via vesitublar approach (TOETVA) have been the risk of infection, the challenges in developing the subplatysmal plane while avoiding skin perforation, damage to the mental nerve, and last but not least, surgical emphysema and CO_2 embolism.

The risk of wound or deep neck infection after TOETVA was a concern initially since the mouth harbours a significant amount of bacteria while the neck is sterile. Different groups addressed this concern in different ways. Whilst most groups use chlorhexidine mouthwash to cleanse the oral cavity before the mucosa is incised, some groups recommend a week long post-operative use of chlohexidine (Yang et al. 2015, Rege et al. 2019). Antibiotics were used prophylactically by most groups with some groups extending their use for up to 7 days post-operatively (Anuwong 2016). Whilst this concern existed, the incidence of wound infections after TOETVA were very low whatever the prophylactic regimen adopted by the clinical team. From all the groups using a completely vestibular approach, only 10 (1%) cases were reported in the analysed literature (Yang et al. 2016, Wang et al. 2017, Xu et al. 2019, Li et al. 2019, Pérez-Soto et al. 2019, Fernandez Ranvier et al. 2020, Kim et al. 2020). These cases were successfully managed with antibiotics without clinical sequela. Consequently, postoperative infections did not seem to be a major problem.

The development of the subplatysmal plane is a particularly challenging part of the procedure particularly in males since the laryngeal prominence is more pronounced (Kadem et al. 2019). The combination of blunt and sharp dissection causes a risk of thermal injury or perforation to the overlying skin. Whilst this only happened in 17 (1%) of the cases analysed in the literature review, when it happened it resulted in poor patient satisfaction (Tesseroli et al. 2018). Since this goes against the principle of scarless surgery, more careful consideration has to be given to reduce their possibility as much as possible.

In order to retract the strap muscles during dissection, a number of groups used a suture which was introduced through the neck skin and hooked around the strap muscles (Park 2017, Pérez-Soto et al. 2019, Kim et al. 2020). None of these groups comment on the possible cosmetic impact of this suture but since the needle leave minimal injury to the skin this should be minimal. Kim et al. 2020 took this a step further by developing a device that was introduced through the skin in the neck and hooking the strap muscles (Patent KR Registration 30-0926522). Whilst the group reported good retraction with this device, the cosmetic price due to the small skin incision needed does not justify its use.

Another novel complication that was associated with TOETVA was the development of chin paraesthesia secondary to mental nerve injury. This happened in 109 (6%) of cases (Fernandez Ranvier et al. 2020, Kim et al. 2020, Nguyen et al. 2020). Although often temporary, given its frequent nature, it is important to consent the patient properly for this complication. The ports as used in TOETVA have been shown to offer the least possibility of mantle nerve injury (Yang et al. 2020). Therefore, keeping these ports positions is imperative for any modification of the technique to try to mitigate the risk of mental nerve injury.

Carbon dioxide (CO_2) insufflation at 5-9mmHg is typically used to keep the planes open during the operation and therefore enable the operating surgeon to visualize the anatomy. Whilst the majority of groups used an insufflation pressure of 6mmHg (Anuwong 2016, Bakkar et al. 2018, Li et al. 2019), some differences were observed in other groups. The spectrum of insufflation pressures used ranged form 4 mmHg to 12 mmHg (Fu et al. 2018, Rege et al. 2019). Whilst CO_2 insufflation was very effective in its retraction of tissues, it was associated with a number of novel complications. These include development of pneumothorax, extensive surgical emphysema, hypercarbia and increased intracranial pressure (Rubino et al. 2000, Lee et al. 2012). The most common of these complications is the development of surgical or mediastinal emphysema. The latter happened in 15 (1%) of cases and was always self-limiting and therefore clinically insignificant (Bakkar et al. 2018, Li et al. 2019, Ahn 2020). The researcher was however concerned with a number of documented cases of CO_2 embolism. Whilst this was rarely reported (6 [0.3%] cases), in the cases in which it happens suffers, the patient suffers a cardiovascular collapse and this can lead to asystole requiring cardiopulmonary resuscitation (Wilhelm et al. 2016, Fu et al. 2018, Hong et al. 2020). This potentially fatal complication has been reported in a number of cases and is usually attributed to injury to the anterior jugular veins (Tae 2020a). Whilst no mortality has been reported yet secondary to CO_2 embolism during TOETVA, there has been a number of close shaves (Wilhelm et al. 2016, Fu et al. 2018, Hong et al. 2020).

This is an unacceptable outcome for a procedure which aims to improve morbidity. Most of the cases happened in those patients in whom the floor of mouth was used for access. Therefore whilst avoiding the floor of mouth access is an important step to limit the incidence of this complication, eliminating the use of CO_2 completely is the pragmatic step forward to improve the safety of TOETVA.

Overall, when compared with other endoscopic approaches, patients were more satisfied with the transoral approach since it was completly scarless (Wang et al. 2014, Yang et al. 2015, Xu et al. 2019). When compared to the gold standard of open thyroidecotmy, the complication rates were comparable but patients who underwent TOETVA gave higher satisfaction scores (Anuwong et al. 2018, Pérez-Soto et al. 2019, Ahn 2020, Wang et al. 2020).

A summary of the available literature is presented in Table 2.

							Operation						
Authors	**Year**	**Location**	**Type**	**Number of patients**	**Inclusion**	**Exclusion**	**Access**	**CO_2 (mmHg)**	**Type**	**Operating time (min)**	**Average Bleeding (ml)**	**Complications**	**LOS (Days)**
Wilhelm, Metzig	2010	Germany	Case study	1	Benign nodule	NA	FOM+BV	6	TL	NA	NA	Minor swelling; small haematoma	2
Wang et al.	2014	China	PCrS: ETOVA vs ETAA	24 12 each (10F, 2M)	Benign nodule	Not scar conscious; Not surgical candidates; Malignant disease	TV	6	TL\TT	60.4	10.8	2 ECC	4.9
Yang et al.	2015	China	PCrS: ETOVA vs ETAA	82 41 each (33F,8M)	Suspicious cancer without metastasis; Hyperthyroidism not exceeding degree II; Max tumour diameter <5cm	Infected lesions; Substernal goitre; Previous surgery	TV	6	TL (19); STT (18); TT + CND (4)	72	11.1	2 ECC; 1 flap perforation; 1 skin burn; 1 t-RLN injury	5
Udelsman et al.	2016	USA	RCS	7 (F only)	pHPT; Benign thyroid nodules	NA	TV	6	PT (2), TL (3), TT (1), TT+CND (1)	222	<20	None	1
Yang et al.	2016	China	PCS	6	Benign nodules; Max diameter 4cm	Standard surgical contraindications	TV	6	TL (5); STT (1)	122	30	1 wound infection	8.2
Anuwong	2016	Thailand	PCS	60 (57F, 3M)	Thyroid gland smaller than 10cm; Benign nodules; Follicular neoplasm; Graves disease, Micropapillary	Unfit for surgery; Previous surgery/irradiation; Dental braces	TV	6	TL (34), TT (22)	90 TL; 135.5 TT	30	3 t-HP; 2 t-RLN injury; 1 haematoma	3.6

							Operation						
Authors	**Year**	**Location**	**Type**	**Number of patients**	**Inclusion**	**Exclusion**	**Access**	**CO_2 (mmHg)**	**Type**	**Operating time (min)**	**Average Bleeding (ml)**	**Complications**	**LOS (Days)**
Jitpratoom et al.	2016	Thailand	RCA: TOETVA vs OT	94 (45 TOETVA; 49 OT)	Graves disease with suspicious nodules; Failure of medical treatment of Graves disease; Compressive symptoms; Side-effect of drugs	Unfit for surgery; previous surgery or irradiation to neck, Thyroid gland diameter >10cm	TV	6	TT	134.11	62.8	4 t- RLN injury; 10 t- HP	NA
Wilhelm et al.	2016	Germany & China	Prospective bi-centre cohort	96 (92 F; 4M)	Benign nodules	NA	FOM+BV	NA	10 IS; 66 TL; 10 STT; 7 TT	78- 38 IS; 283- 49 TL; 258 - 88 STT; 305- 126 TT	15 IS; 20 TL; 30 STT; 65 TT	3 Conversion to OT; 1 p-RLN injury, 15 t-MN injury; 1 intra-oral wound infection; 5 neck site infections; 3 CO2 embolism; 1 mediastinal emphysema	NA
Dionigi et al.	2017	Italy	PCS	15 (12F, 3M)	Thyroid gland <10cm; Thyroid volume ≤45ml; Main nodule ≤50mm; Benign tumours; Follicular neoplasm; Papillary microcarcinoma without metastasis	Unfit for surgery; Previous irradiation to head, neck or upper chest; History of neck surgery; recurrent goitre; Thyroid volume >45ml; main nodule >50mm; Evidence of metastasis or local invasion; RLN palsy Hyperthyroidism; Oral infection;	TV	6 + ECNS	TL (10); TT (5)	96.26	36.8	1 Emphysema; 1 HP	1.6

Authors	Year	Location	Type	Number of patients	Inclusion	Exclusion	Operation: Access	CO_2 (mmHg)	Type	Operating time (min)	Average Bleeding (ml)	Complications	LOS (Days)
Park et al.	2017	Korea	RCA	17 (13F, 4M)	Thyroid cancer without metastasis or invasion; No previous neck surgery; Thyroid cancer <25mm or benign nodule of < 80mm	None	TV	5-6	TL (8); TL+CND(8); TT (1); TT+CND (1)	TL 165.75; TT 185	NA	2 seroma; 1 t- HP	6.7
Sivakumar, Amizhthu	2018	India	PCS	11 (F only)	Benign thyroid nodule; Nodule <40mm; Thyroid up to 30ml	History of neck surgery or neck irradiation	TV	6	TT	126.27	1.8	None	NA
Chai et al.	2017	Korea	RCA	10 (F only)	PTC (micro)	Evidence of metastasis or local invasion	TV	6	TL (7); IS (3)	121.1 TL; IS 90	NA	2t- RLN injury	3.6
Anuwong et al.	2018	Thailand	RCA: TOETVA vs OT	422 (389F, 33M)	NA	Previous neck surgery; Substernal goitre; Evidence of metastasis or local invasion;	TV	6	TL (245); TT (177)	76.8 TL; 124.1 TT	25.7 TL; 52.3 TT	3 Conversion; 25 t- RLN injury; 46 t-HP; 1 Haematoma; 20 seroma; 3 t-MN injury	NA
Bakkar et al.	2018	Jordan	PCS	5 (F only)	Highly motivated to avoid a scar; Single nodule up to 40mm	NA	TV	6	TL	122	NA	1 Conversion; 5 subcutanous emphysema; 5 pulling sensation along surgical tract; 1 flap perforation;	1.2
Fu et al.	2018	China	PCS	81 (79F, 2M)	Benign tumours <50mm; Thyroid cancer without metastasis or invasion; Patients with cosmetic concerns	Graves disease; History of surgery or irradiation; Severe bleeding disorders	FOM+BV	4 - 8	TL (65); IS (6); TT (5); TT+CND (5)	TL (90.1); IS (60.3); TT (100); TT + CND (115)	26.3 TL; 15.2 IS; 28.6 TT; 55 TT + CND	2 perioral numbness;; 2 mouth opening pain; 3 neck discomfort; 6 infection; 2 CO_2 embolism	4.77

							Operation						
Authors	**Year**	**Location**	**Type**	**Number of patients**	**Inclusion**	**Exclusion**	**Access**	**CO_2 (mmHg)**	**Type**	**Operating time (min)**	**Average Bleeding (ml)**	**Complications**	**LOS (Days)**
Russell et al.	2017	USA	PCS (Robotic & endoscopic)	14 (F only)	History of hypertrophic scarring; Cosmetic motivations; Thyroid nodule smaller the 60mm	History of thyroiditis or neck irradiation	TV	5-7	Endoscopic: TL (6); PT (2); Robotic: TL(6)	Endoscopic: 242.6; Robotic: 348	Minimal	1 t- lip numbness; 1 t- RLN injury	1
Wang et al.	2017	China	PCS	150 (138f, 12m)	Benign thyroid nodules up to 60mm; Thyroid cancer with stage up to T1 or T2 ≤3 cm, cN0 or cN1a, M0	NA	TV	NA	TL+CND; TT +CND	146 TL+CND; 187 TT +CND	NA	2 Conversion; 3 t-RLN injury; 2 p- RLN injury; 1 local infection; 1 t- MN injury; 22 t- HP;	3.5
Wang et al.	2018	China	PCS	18 (F only)	Benign tumours <60mm; T1 thyroid cancer less than 20mm with no signs of metastasis or invasion	Upper pole nodules; history of neck/mouth surgery; Autoimmune thyroiditis	TV	6	TL (3); TT +CND (2); IS (3) STT (2); TL+CND (8)	193 TL; 167.5 TT+CND; 93.3 IS; 67.5 STT; 172.25 TL+CND	35 TL; 40 TT +CND; 23.3 IS; 15 STT; 26.9 TL +CND	3 t- SLN injury; 1 t- MN injury	4.1
Rege et al.	2019	India	PCS	10	Bethesda II nodules <40mm; Bethesda III <40mm; Thyroid cyst recurring after 2 aspirations	History if neck surgery or neck irradiation; Unfit for anaesthesia	TV	12	TL (6); TT (4)	TL 69.5; TT 80	20.5	2 Haematoma	1
Kadem et al.	2019	Iraq	PCS	10 (F only)	Cosmetically concerned female patients; Benign solitary nodule <40mm; Multinodular goitre with each lobe <40mm; Right sided	M; Obese; thyroiditis; Short neck; history of neck surgery/irradiation; Oral infections/sores	TV	5-6	TL (9); STL (1)	109.4 TL; 150 STL	NA	1 cervical emphysema; 1 t-MN injury	1.7

							Operation						
Authors	**Year**	**Location**	**Type**	**Number of patients**	**Inclusion**	**Exclusion**	**Access**	**CO_2 (mmHg)**	**Type**	**Operating time (min)**	**Average Bleeding (ml)**	**Complications**	**LOS (Days)**
Tesseroli et al.	2018	Brazil	PCS	9 (F only)	18-65 years; ASA I/II; Thyroid volume up to 35cm^3; Thyroid nodule up to 40mm	History of neck surgery or irradiation; Hyperthyroidism	TV	6-9	TT (7); TL (1); TT + PT (1)	205 TT ; 150 TL , 180 TT + PT	NA	3 chin bruises; 1 Dehiscence of labial suture; 1 thermal skin injury; 1 nodule rupture	2.1
Xu et al.	2019	China	RCA: TOET vs Bilateral Areolar approach	48 (44F; 4M)	PTC	History of neck surgery/irradiation; enlarged fused lymph nodes; evidence of invasion or RLN involvement	TV	6	TL+CND	107.2	21.5	3 swollowing discomfort; 1 t- RLN injury; 1 postoperative haemorrhage; 1 postoperative infection	3.7
Li et al.	2019	China	RCA	140 (130F, 10M)	NA	NA	TV	6	TL (59); TL+CND (63); TT+CND (18)	100.8 TL ; 112.1 TL + CND; 185.3 TT+CND	NA	1 Converted to OT; 3 t- RLN injury; 2 p- RLN injury; 4 t-HP; 2 infection; 1 seroma; 3 subcutaneous emphysema	3.76
Hefetz Khafif et al.	2019	Israel	PCS	10	NA	NA	TV	6	TT (5); PT (5)	198	NA	1 t- RLN injury; 1 altered chin sensation; 1 seroma;	NA

							Operation						
Authors	**Year**	**Location**	**Type**	**Number of patients**	**Inclusion**	**Exclusion**	**Access**	**CO_2 (mmHg)**	**Type**	**Operating time (min)**	**Average Bleeding (ml)**	**Complications**	**LOS (Days)**
Pérez-Soto et al.	2019	Mexico	RCA: TOETVA vs OT	20 (18F, 2M)	Over 18 years, any gender; thyroid cancer <20mm; Indeterminate nodules <50mm	History of neck surgery/irradiation; evidence of invasion or metastasis	TV	6-8	TT (13); TL (3); STT (1); TT +CND (1)	216.7	38.25	3 Converted to OT; 1 cervical haematoma; 1 infection; 5 t-HP; 2 t- RLN injury; 3 t-MN injury;	2
Luna-Ortiz et al.	2020	Mexico	RCA	46 (37F, 9M)	T1 Thyroid cancer	Evidence of lymph node metastasis	TV	6	TT (44); TL (2)	207	105	6 Converted to OT; 2 p-HP; 1 t- RLN injury; 2 p- RLN injury	1.2
Fernandez Ranvier et al.	2020	USA, Spain, Switzerland, Taiwan	PCS	149 (137F, 12M)	Cosmetically concerned; Symptomatic benign nodules < 60mm; indeterminate nodules <60mm; estimated thyroid diameters of up to 100mm; estimated thyroid volume of up to 45ml; symptomatic Hashimoto's; Graves; differentiated thyroid cancer <30mm with no evidence of invasion of metastasis	Unfit; substernal goitre; history of neck surgery or irradiation	TV	6	TL (111); TT (38); CT (3)	161.8 TL; 213.4 TT; 136.7 CT	18.6	3 Converted to OT; 9 skin lesions (from ulcers to perforation); 3 postoperative bleeding; 2 tracheal perforation with Veress; 51 lower lip numbness- 1 permanent; 57 t- chin numbness; 7 t-HP; 5 t- RLN injury; 3 p-RLN injury; 1 infection	1.6

							Operation						
Authors	**Year**	**Location**	**Type**	**Number of patients**	**Inclusion**	**Exclusion**	**Access**	**CO_2 (mmHg)**	**Type**	**Operating time (min)**	**Average Bleeding (ml)**	**Complications**	**LOS (Days)**
Kim et al.	2020	Korea	RCA	132 (123F, 9M)	PTC	Capsular invasion; Lymph node metastasis	TV	6	TT+CND (8); TL+CND (110); IS+CND (14)	87.6	NA	6 t- RLN injury; 1 t-HP; 1 haematoma; 1 seroma; 2 t-MN injury; 1 p-MN injury; 1 infection	NA
Ahn, Yi	2020	Korea	PCrS: TOETVA vs OT	150 (145F, 5M)	PTC	NA	TV	5-7	TL (110); TT (40)	102.1 TL ; 132.6 TT	48.5 TL ; 48 TT	7 t-RLN injury; 1 p-RLN injury; 5 t-HP; 2 p-HP; 4 Subcutaneous emphysema; 1 haematoma; 1 Horner syndrome; 2 seroma; 1 oral wound problems	3.64
Hong, Ahn et al.	2020	Korea	RCA	82 (79F, 3M)	PTC less than 30mm; follicular neoplasm/benign nodule less than 60mm;	Extra-thyroidal extension; lateral lymph node metastasis; prior neck or oral surgery	TV	NA	TL (70); TT (12)	112.3 TL ; 155.9 TT	NA	2 Converted to OT; 3 t-RLN injury; 2 seroma; 1 t-HP; 2 wound infection; 1 tracheal injury; 1 CO_2 embolism; 3 chin bruise; 3 chin skin dimpling	3.8
Wang et al.	2020	China	PCS: TOETVA vs OT	80 (F only)	PTC; Female; 15-50 years old; tumour size <30mm	History of neck or mandible surgery; lateral lymph node metastasis, tumour at upper pole	TV	6	TT+CND	193	18.65	1 MN injury; 1 infection; 5 t- RLN injury; 1 p- RLN injury; 2 t-HP	4

							Operation						
Authors	**Year**	**Location**	**Type**	**Number of patients**	**Inclusion**	**Exclusion**	**Access**	**CO_2 (mmHg)**	**Type**	**Operating time (min)**	**Average Bleeding (ml)**	**Complications**	**LOS (Days)**
Le et al.	2020	Vietnam	PCS	28 (F only)	Cosmetically concerned; Thyroid lobe up to 100mm; Benign nodule up to 60mm; Suspicious nodule; T1 thyroid cancer	History of neck surgery or irradiation; hyperthyroidism; oral infection; not fit	TV	6	TL	91	NA	1 t-chin numbness;	4.1
Nguyen et al.	2020	Vietnam	PCS	29 (28F, 1M)	PTC (micro) with no evident lymph nodes metastasis preoperatively	NA	TV	8-10	TT+CND (7); TL +CND (21); TL+CND + contra lateral tumour resection (1)	17.9 TT+CND; 12.4 TL +CND; 20TL + CND + contra-lateral tumour resection	144.3 TT + CND ; 113.9 TL +CND ; 130 TL + CND + contra lateral tumour resection	1 haematoma; 4 t-RLN injury; 1 t-HP; 3 chin numbness	6.2

							Operation						
Authors	**Year**	**Location**	**Type**	**Number of patients**	**Inclusion**	**Exclusion**	**Access**	**CO_2 (mmHg)**	**Type**	**Operating time (min)**	**Average Bleeding (ml)**	**Complications**	**LOS (Days)**
Fernandez-Ranvier et al.	2020	USA	PCS	50 (44F,6M)	Cosmetically concerned; Symptomatic benign nodules < 60mm; indeterminate nodules <60mm; Estimated thyroid diameters of up to 100mm; Estimated thyroid volume of up to 45ml; symptomatic Hashimoto's; Graves; Differentiated thyroid cancer <30mm with no evidence of invasion of metastasis	Substernal goitre; history of neck/chin surgery or irradiation	TV	6	TT (12); STT (1); TL (37)	217.6 TT; 149 STT/TL	33	2 Full thickness flap tear; 2 skin burns; 16 t-MN injury; 1 p-MN injury; 13 t- chin numbness; 2 t- RLN injury; 1 p- RLN injury; 1 t-HP; 1 Tracheal perforation (through Veress)	0.2

Table 2: Clinical studies that evaluate the feasibility and safety of the transoral approach.
Legend: ASA, American society of anesthesiologists risk classification; BV, Bi-vestibular; CT, Completion thyroidectomy; ECC, Ecchymosis; ECNS, External central neck suture; ETAA, Endoscopic thyroidectomy by areola approach; ETOVA, Endoscopic thyroidectomy using the oral vestibular approach; FOM, Floor of mouth; ; HP, Hypoparathyrodism; IS, Isthmusectomy; LOS, Lenght of stay; Max, Maximum; MN, Mental nerve; NA, Not available; OT, Open/conventional thyroidectomy; p-, Permanent; PCrS, Prospective controlled study; PCS, Prospective case series; pHPT, Primary hyperparathyroidism; PT, Parathyroidectomy; PTC, Papillary thyroid cancer; RCA, Retrospective cohort analysis; RCS, Retrospective case series; RLN, Recurrent laryngeal nerve; SLN, Superior laryngeal nerve; STL, Subtotal thyroid lobectomy; STT, Subtotal thyroid lobectomy; t-, Temporary; TL, Thyroid lobectomy; TOETVA, Trans-oral endoscopic thyroidectomy via a vestibular approach; TT, Total thyroidectomy; TV, Tri-vestibular

1.7.3 Gasless TOETVA

CO_2 is a very soluble gas and it offers minimal physiological insult to most patients. It is therefore the gas of choice is most cases including in the context of neck endoscopic procedures (Menes, Spivak 2000, Yu et al. 2017, Kessler et al. 2009). Despite the overall safety profile of CO_2, in the context of TOETVA it has been associated with a number of complications including the potentially fatal CO_2 embolism (as discussed in Section 1.7.2,1).

Therefore, in order to improve the safety profile of TOETVA, there has been increasing interest in eliminating the use of gas and replace its function of retraction with other devices. A number of groups have worked on gasless techniques in which the role of the CO_2 insufflation is taken over by the use of retracting devices (Kim et al. 2017, Kang et al. 2009). This is currently already used in the transaxillary thyroidetomy particularly with the integration of robotic arms to assist the surgeon (Alzahrani et al. 2017). In this case, CO_2 is avoided using the Chung retractor (Marina Medical, Sunrise, USA), otherwise known as the modified thyroidectomy retractor. This is setup on the operating table opposite to the side of operation. The strap muscles and sternocleidomastoid and retracted with this device keeping the operating space open (Alzahrani et al. 2017).

The initial attempt to avoid CO_2 insufflation in TOETVA was undertaken by Nakajo et al. 2013. This group developed an alteration to the technique which they called Trans-Oral Video-Assisted Neck Surgery (TOVANS). In this technique the central vestibular incision is considerably larger at 25 mm. After blunt dissection to create the subplatysmal space a number of skin stab incisions are carried out and Krischner wires with a diameter of 1.2mm are inserted in a horizontal fashion. The wires are then elevated and kept in place through an L-shaped pole and fixed above the patient's neck. Whilst this retraction allowed the required space for good visualisation, the stab incisions in the skin of the neck were against the completely scarless principles of TOETVA. Consequently, this technique never gained traction.

Three out of the 5 groups who published a gasless modification of TOETVA utilised the commercially available U-shaped metal retractors (Park et al. 2019, Yang et al. 2020, Richmon 2020). These devices are inserted in the subplatysmal space after it has been developed with blunt dissection. Whilst these devices performed the required retraction in the published cases, the central vestibular wound which is needed for access is considerably larger then the 10-15mm used in TOETVA. Park et al. 2019 used a 3cm wound whilst Yang et al. 2020 used a 5cm wound. Whilst the argument in favour of a large incision is that the specimen can be retrieved without difficulty and that the large space provides aeration of extraction of diathermy fumes, the impact of the increased dissection of the mentalis muscle and the mental nerve is not known. Richmon 2020 developed a completely new approach to the subplatysmal space. A lateral vestibular approach (LaVa) to neck was proposed, which takes the incision to the lateral aspect of the vestibule extending from the canine to just medial to the retromolar trigone following the curve of the mandible. This approach exposes the marginal branch of the mandibular nerve and therefore potentially increases another morbidity.

Park, Wang et al. 2019 developed a modified laryngoscope which they called the 'thyroidoscope'. To insert this scope, the midline vestibular incision needed to be 20mm which is bigger than that used in standard TOETVA. This device was fixed in placed using a standard laryngoscope holder. The groups claims that the gasless TOETVA was carried out without any difficulty in the cadaveric setting. However, the device used is large and cumbersome, making it inappropriate in the very restrictive space of the vestibule.

The gasless modifications for the TOETVA presented so far all attempt to overcome the use of CO_2 and consequently eliminate the potential complications that may arise from this (Table 2). The current solutions do however present novel problems which are mainly due to more extensive dissection for the midline access and, in the case of Richmon 2020, a complete modification of the technique was used to create access to the subplatysmal plane. This gasless concept has to be further developed to allow the improved safety profile of gasless TOETVA, whilst attempting not to modify a technique which has given excellent results and in which the practicing surgeons had already overcome the learning curve of eleven to fifteen cases (Razavi et al. 2018, Lira et al. 2020).

A summary of all the published literature is presented in Table 3.

							Operation						
Authors	**Year**	**Location**	**Type**	**Number of patients**	**Inclusion**	**Exclusion**	**Access**	**Retractor**	**Type**	**Operating time (min)**	**Average Bleeding (ml)**	**Complications**	**LOS (days)**
Nakajo et al.	2013	Japan	PCS	8 (7F,1M)	Follicular neoplasm; Symptomatic large nodular goiter; Graves' disease; Papillary microcarcinoma without evident lymph node metastases	NA	TV	1.2mm Kirschner wires inserted through the neck skin and elevated with the help of a self-retaining retractor	5 TL; 3 STT+CND	208 TL; 361 STT +CND	97	8 chin paraesthesia; 1 RLN injury	4.25
Park, Wang et al.	2019	Korea	CS	1	NA	NA	TV	Thyroidoscope (self-retaining)	TT	NA	NA	None	NA
Park et al.	2019	Korea	RCA	15 (11F,4M)	Thyroid cancer without evidence of invasion/metastasis; Thyroid cancer if middle/lower pole of less than 20 mm and of the upper pole less than 10mm; Benign nodules less than 80mm	History of neck surgery	TV	U shaped self-retaining retracting blade	12 TL; 1 IS; 2 TT	129.25 TL; 70 IS; 180 TT	NA	1 t-HP	4.1
Yang et al.	2020	Korea	PCS	31 (21F,10M)	Benign thyroid nodule more than 40mm	Oral infection/ inflammation; History of head and neck cancer or surgery	SV	U shaped retracting blade	TL	90.2	72.82	1 t-RLN injury	NA
Richmon	2020	USA	CS	7	NA	NA	LVA	U shaped self - retaining retracting blade	NA	NA	NA	None	NA

Table 3: Literature discussing gasless approaches to transoral thyroidectomy
Legend: BV, Bivestibular; CND, Central neck dissection; CS, Cadaveric study; F, Female; HP, Hypoparathyrodism; IS, Isthmusectomy; LVA, Lateral vestibular approach; M,Male; NA, Not available; PCS, Prospective case series; RCA, Retrospective cohort analysis; RLN, Recurrent laryngeal nerve; SND, Selective neck dissection; STL, Subtotal thyroid lobectomy; STT, Subtotal thyroidectomy; SV, Single vestibular incision; t-, Temporary; TL, Thyroid lobectomy; TT, Total thyroidectomy; TV, Tri-vestibular.

1.8 Surgical models

1.8.1 Live pigs vs cadavers

Animal models, especially live pigs, have been used extensively in surgical translational research work and training throughout the years with good result (Alcalá Rueda et al. 2021, Higuchi et al. 2020, Milner et al. 2020). Infact, live pigs have been the animal model of choice in the previously published studies involving minimally invasive thyroid syrgery, including TOETVA (Witzel et al. 2008, Karakas et al. 2011, Lee et al. 2014).

Whilst the live pig model offers a relatively affordable and more available medium to study surgical anatomy (Kehinde 2013), there have been a number of issues. A robust program of animal care and experimental use requires regulatory compliance, while addressing public sensitivities and moral obligations to the animals themselves. (Brown et al. 2018, National Research Council (US) Committee for the Update of the Guide for the Care and Use of Laboratory Animals. 2011). The availability of a live pig laboratory to enable the experiments to be carried out in a scientific manner is a very limited commodity. This is a direct consequence of the difficulty in procuring large live animals such as pigs that have been bred with the purpose of being used in research, in addition to the myriad of supporting services that need to be in place for such a laboratory to be accredited. Such a specialised unit requires the employment of veterinarians who care for the animal during its life and specialized veterinarians who are able to monitor the animals during the experiments. Of these, the main specialty of veterinarians would be the anaesthetists who would be able to keep the pig intubated and anaesthetised during the experiments and help to sacrifice the animal using the 3 R's principles (Replacement, Reduction and Refinement) (Bradbury et al. 2016, Carbone, Austin 2016). There have been growing concerns regarding the ethics of this practice and animal welfare in general, that have further questioned the use of animal models (Robinson et al. 2019). The cost of having such a setup keeps increasing when the equipment and the disposal facilities needed are added to the equation.

Additionally, the translatability of skills and techniques developed in the animal model to the human body have been seriously questioned (Ruan et al. 2020, Shanks et al. 2009). This is mainly due to the limitations in the anatomical similarities between the animal model and the human model. Specifically for the thyroid gland, although the morphological features of the thyroid gland does not vary greatly between the pig and the human, the dimensions of the neck are completely different. This alters the technique for accessibility to the organ thereby limiting the transferability of most of the skills from the animal to the human. For these reasons the human cadaveric model would be preferred.

1.8.2 Thiel embalmed cadavers as surgical models

Embalming of cadavers has been a long-established method of preserving the human body after death, for a myriad of reasons (Brenner 2014). The process of embalming requires the body to undergo three processes namely fixation, disinfection and preservation. These processes allow the body to circumvent the natural process of decomposition.

Ever since the substance acetaldehyde was described in the 18th century, formalin has formed the main part of the chemical composition used to fix cadavers (Musiał et al. 2016). Whilst the use of formalin to preserve the cadaver leads to prolonged conservation of tissues and therefore served its purpose for many years, it does lead to problems. In addition to the alteration of soft tissue properties, there has long been awareness on the toxicity formalin has on the staff handling the embalmed body parts (Méhes, Beke 2014). Very commonly, individuals in contact with formalin-preserved cadavers develop acute symptoms which include watery eyes, headaches, lack of concentration and a general feeling of tiredness (Aung et al. 2021, Tiruneh 2021). This has led to the development of multiple alterations in the embalming techniques over the years (Balta et al. 2019).

Thiel described his method of cadaver preservation in 1992. Although still not widely utilized (Benkhadra et al. 2011), this technique has been shown to give an overall better experience in terms of natural tissue colour, plasticity and flexibility when compared to the traditional formalin embalming (Kennel et al. 2018, Venne et al. 2020, Eisma et al. 2011). Handling of Thiel embalmed cadavers also leads to less health hazards to the technical staff of the laboratory and to the researcher performing the investigations. In particular, Thiel embalmed cadavers were found to offer less irritation (particularly to the eyes, nose and throat) then formalin-embalmed cadavers (Balta et al. 2015). This is in addition to the long known hazardous effects to the lungs and the upper gastrointestinal tract that inhaled formalin can cause (Fischer 1900, Committee to Review the Formaldehyde Assessment in the National Toxicology Program 12th Report on Carcinogens et al. 2014).

Another longstanding available technique used for cadaveric preservation is the use of phenol. The latter chemical, mainly a disinfectant, was first used for the preservation of human tissue more than a century ago by Laskowski and multiple modifications of the protocol were published over the years (Brenner 2014). This method offers a preservation technique that provides soft embalming of the cadaver. In one study, phenol preserved cadavers were preferred over Thiel embalmed ones from participants taking part in surgical training workshops (Venne et al. 2020). There is however no published data that evaluated the phenol based cadaveric embalming protocols in thyroid tissue. Additionally, phenol shares similar characteristics to formalin in that it is also a potent irritant to the eyes, skin and upper airways. There is a lack of experience worldwide with thyroid preservation using these protocols and the toxicity related to phenols.

Most of the pre-clinical studies in the transoral approach to thyroid surgery presented in Section 1.7.1 utilised fresh frozen cadavers with good effect and this model has been shown to have good validity for minimally invasive surgery, including thyroidectomy (Sharma et al. 2012, Aoyama et al. 2019). This preservation offers perfect preservation of the cadaver if the storage conditions are well regulated with the cadaver being preserved, after cleansing, at a temperature of -20°C within one week of death (Lloyd et al. 2011). This model has also been shown to offer good construct validity for training in minimally invasive surgery particularly surgery on internal organs which tend to be well preserved when the cadaver is frozen (Sharma et al. 2012). However, the use of un-embalmed human cadavers carries with it an undetermined risk of infections (de Perio et al. 2014). Whilst individuals who are suffering from a highly contagious infection or a new and yet poorly defined infection (e.g., SARS- COV2) are routinely not accepted for donation in the local scenario, the risk of infection transmission due to bacterial growth from the un-embalmed cadaver to the handler is poorly studied. The process of Thiel embalming was shown to be only second best to formalin for disinfection abilities (Balta et al. 2019). These cadavers therefore offer a safer platform for both the researcher and the staff when the utilised cadavers are handled.

1.8.2.1 Local scenario

When all the aforementioned reasons were considered, the Thiel embalmed cadavers were found to be better models for anatomical and surgical teaching and surgical research (Villacorta, Hernando et al. 2019, Kennel, Martin et al. 2018). On this basis, several medical schools, including the Department of Anatomy at the Faculty of Medicine and Surgery, University of Malta have long converted to Thiel embalming of cadavers donated for medical studies. This process and was fine-tuned to adapt to the local environment (Appendix 2). Thiel embalmed cadavers have also been used with very good results in surgical research and training. The specialties in which the use of Thiel embalmed cadavers has been validated vary widely from gynaecology to gastrointestinal and urological surgery (Usami et al. 2018, Ruiz-Tovar et al. 2019, Bele, Kelc 2016). In all these interventions, Thiel embalmed cadavers were found to have tissues loyal to the *in vivo* ones in terms of colour and flexibility. The locally embalmed cadavers have been used extensively for various teaching and training programmes and have been shown to offer good quality tissue that enables good surgical training (Mantica et al. 2020).

Whilst there is an initial cost of performing the Thiel embalming, these cadavers have more life-like features with the ability to position limbs and joints within their anatomical limits (Kennel et al. 2018, Hayashi et al. 2016). This delivers the best conditions to offer surgical training on a realistic platform that is ideal for transferability of skills. Apart from the reduction in odours, this type of embalming lends itself to a more realistic experience for surgeons when operating on a Thiel embalmed body, which can be re-used multiple times and therefore offer a more sustainable model (Waerlop et al. 2020, Blaschko et al. 2007). Given that availability of cadavers is becoming increasingly problematic in the developed world (Ghosh 2017, Gürses et al. 2018, Chen et al. 2018), using a whole cadaver for a single exercise is ill-advised.

1.9 Rationale for the study

TOETVA has been deemed safe after being performed on an extensive number of patients (Anuwong et al. 2018, Camenzuli et al. 2018). The overall morbidity of TOETVA is similar to conventional thyroidectomy. However, looking deeper in the reported complications of this procedure, it is evident that the use of CO_2 insufflation leads to a significant portion of the morbidity. As discussed in Section 1.7.2.1 the complications associated with the use of insufflation are common, and include surgical emphysema CO_2 embolism (Ahn, Yi 2020, Li, Peng et al. 2019).

The researcher opted to explore the modification of the standard technique of TOETVA to a gasless one to make the procedure even safer. Despite offering the advantage of decreasing the morbidity directly related to the CO_2, the experience in the trans-axillary approach had shown that gasless approaches do not come without impediments of their own. The gasless technique for trans-axillary endoscopic thyroidectomy has been associated with longer operating times mainly due to lack of operating space (Aidan et al. 2013). The latter leads to decreased visibility of anatomy, in addition to poor manoeuvrability of instruments. Gasless trans-axillary thyroidectomy was also associated with longer hospital stay (Jantharapattana, Leelasawatsuk 2020).

Notwithstanding the disadvantages of the gasless technique as reported for the trans-axillary approach, eliminating the possibility of fatality as a consequence of CO_2 embolism is an important step to make TOETVA a reliable alternative to the conventional open thyroidectomy. CO_2 is normally required during TOETVA to keep the surgical space open and therefore allow the surgeon performing the procedure to visualize the anatomy clearly and to navigate the instruments in a safe and effective manner. In order to replace the function of CO_2 insufflation, while maintaining a scarless TOETVA technique, a series of experiments had to be carried out bythe researcher in order to address this challenge..

1.9.1 Aim and objectives

The aim of this PhD is to develop a novel gasless modification to the completely scarless trans-oral video-assisted thyroidectomy (TOETVA).

The objectives of this research are:

a. To reproduce the technique of scarless TOETVA with CO_2 insufflation using Thiel embalmed cadavers;

b. To develop a retraction device with the aim of eliminating CO_2 insufflation;

c. To compare the original TOETVA using CO_2 insufflation with the gasless technique in embalmed cadavers;

d. To explore relative contraindications for gas insufflation in the neck and assess whether a gasless adaptation would improve outcomes.

Chapter 2:

Materials and Methods

2.1 Cadavers

During this research, nine Thiel embalmed cadavers have been utilised (Figure 1). These had been donated to the Department of Anatomy, Faculty of Medicine and Surgery at the University of Malta, following signed informed consent. All the operative dissection work has been carried out at the Department of Anatomy. Approval from the Faculty Research Ethics Committee was sought and granted before the start of the experiments (Appendix 1)

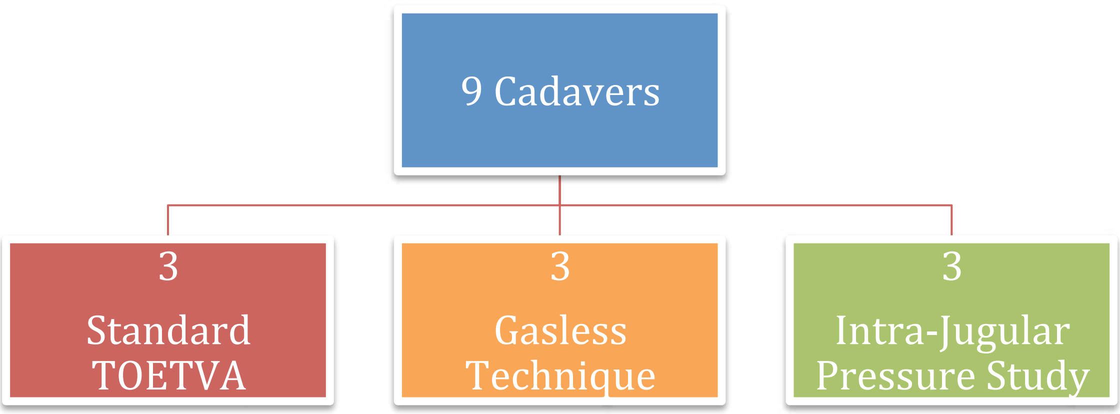


Figure 2: Flow chart showing the number of Thiel embalmed cadavers utilised in the different stages of the study

2.2 Gas insufflation for standard TOETVA

The first three cadavers were utilised by the researcher to reproduce the standard TOETVA technique using the Thiel embalmed human cadaver platform. The role of the researcher in this stage of the study included the study design, the selection of the cadavers, performing TOETVA on all the cadavers, collecting data and interpretation of outcomes. More detail on the method used for these experiments are given in Section 3.2.

2.3 Building the novel device

The process of building the instrument was central to modify TOETVA into a gasless procedure. From the data collected during the first cadaveric experiments and from information retrieved from the literature review, the researcher developed a new device that integrates the endoscope within it in order to eliminate the need for CO_2 insufflation. The role of the researcher in the development of the device consisted of the evaluation of other devices already in the market for adaptation and use in TOETVA, concept development, design development and prototype modification. The physical manufacturing of this device was done in collaboration with the Department of Industrial and Manufacturing Engineering, Faculty of Engineering at the University of Malta and the Faculty of Materials Science and Engineering, Warsaw University of Technology, Poland. More detail on the method used for these experiments are given in Section 4.2. The innovative steps of the invention of this novel device were registered as a patent in collaboration with the Knowledge Transfer Office at the University of Malta (Appendix 4 and 5).

2.4 Gasless Technique

The developed prototype was trialled in 3 Thiel embalmed cadavers in order to evaluate its viability. This process also allowed the researcher to modify the novel retractor according to feedback gained from the experiments. The role of the researcher in this part of the research included the study design, the selection of the cadavers, performing the modified TOETVA on all the cadavers, collecting data and comparing the outcomes from the modified procedure with those from the standard TOETVA. Apart from the latter subjective comparison, the researcher also designed and carried out a blinded questionnaire with 4 thyroid surgeons in order to get a more objective comparison. More detail on the method used for these experiments are given in Section 4.2.

2.5 Intra-jugular venous pressures

During the course of the experiments, the researcher identified a link between insufflation in the neck and increased intraocular pressure. The hypothesis was that the rise in intraocular pressure was secondary to an increased pressure on the internal jugular veins. The researcher therefore developed an experimental setup to evaluate whether with the use of the newly developed device, the rise in intrajugular pressures was less when compared to the use of CO_2 insufflation during TOETVA. The researcher first designed and developed a system to allow the upper body to have a neo-circulation as close as possible to the physiological state. Using the novel device, the intrajugular pressures were assessed in three Thiel embalmed cadavers in three standard stages of TOETVA using 15mmHg CO_2 insufflation, 6mmHg CO_2 insufflation and 0mmHg. The role of the researcher in this experiment included the study design, the selection of the cadavers, the design and development of the segmental neo-circulation, insertion of the internal jugular vein probe, setting up of the pressure recording system,performing TOETVA on all the cadavers, collecting data and interpretation of data. The role of the collaborators from the Centre of Biomedical Cybernetics, Faculty of Engineering at the University of Malta was to advise on the most appropriate low pressure reading system to be used and on the operations of the software of this system during data collection by the researcher. More detail on the method used for these experiments were given in Section 5.2.

A summary of all the equipment used during the course of all the research is presented in Table 4.

Equipment	**Model**	**Manufacturer**	**City**	**Country**
10mm 30 degree endoscope	PE909A	Aesculap®	Tuttlingen	Germany
5mm 30 degree endoscope	PE610A	Aesculap®	Tuttlingen	Germany
3 chip Full HD camera system	PV460	Aesculap®	Tuttlingen	Germany
LED light source	OP940	Aesculap®	Tuttlingen	Germany
CO_2 high flow insufflator	PG080	Aesculap®	Tuttlingen	Germany
Maryland dissector	NA	Grena®	London	United Kingdom
Laparoscopic scissors	NA	Grena®	London	United Kingdom
Laparoscopic graspers	NA	Grena®	London	United Kingdom
10mm port	VERSAONE™ bladed trocar	Covidien®	Dublin	Ireland
5mm ports (x2)	VERSAPORT™ V^2 trocars	Covidien®	Dublin	Ireland
Peristaltic pump	RS385-635	INTLLAB™	Kuala Lumpur	Malaysia
Low pressure reading system	TSD104A	BIOPAC® Systems Inc	Goleta	USA

Table 4: The insruments used during the course of the analysis.

2.6 Statistical analysis

During the course of this research, statistical analysis was used in two instances. Initially, the outcomes of the questionnaire were analysed. For this purpose, the outcomes of the visual analogue scale (VAS) scorings given by the panel of experts for the insufflation group were compared with those given for the images captured from the gasless group in which the retractor was used. This analysis was carried out using IBM SPSS Statistics for Windows Version 25.0. (IBM Corp. Released 2017, Armonk, NY: USA). The scores from the two groups were then statistically analysed using the Wilcoxon signed-rank test. This test was selected since it examines non-parametric data, given the limited number of experts (n=4). Since the stages of the operations being compared were standard as described in Section 4.2, it was decided to use a paired analysis.

Statistical analysis was also carried out to evaluate the outcomes of the investigations comparing the increase in pressure in the internal jugular vein when using different insufflation pressures as described in Section 5.2. To this end, a paired t-test was used to compare the relative change in pressures in the internal jugular vein at every stage of the procedure between the insufflation pressures of 6mmHg, 15mmHg and no insufflation pressure (using the retractor). This parametric paired t-test test, which was carried out using IBM SPSS Statistics for Windows Version 27.0. (IBM Corp. Released 2020, Armonk, NY: USA), was utilised since the data recorded over the 4 minutes was extensive. A multivariate regression analysis was also carried out with the help of the same software using data from all of the three cadavers used for analysis to investigate whether the anatomical constitution of the individual cadaver played a role in the relative changes in intra-jugular pressures exerted when using the different insufflation pressures.

Chapter 3:

The viability of TOETVA in the Thiel embalmed cadaver

3.1 Introduction

Globally there have been increasing pressures on the training of surgeons. These have been mainly due to safety concerns for the patients especially since every new procedure carries a learning curve (Hopper et al. 2007). To add to this burden, working time directives that limit the period of time during which surgical trainees are exposed to new techniques have been a concern in the past decade (Canter 2011, Gough 2011). Multiple solutions to have been considered in order to address this problem including the use of surgical simulators such as Forcesense (MediShield BV, Delft, The Netherlands) and cadaveric surgical workshops (Hardon et al. 2021). In fact, the use of human cadavers has become an important part of a trainee's surgical training.

The use of cadaveric based surgical training workshops has obtained positive feedback both from the trainees and from the trainers alike although there is a lack of high level of evidence which shows the transfer of the skills to live surgery (Gilbody et al. 2011, James et al. 2019, James et al. 2020). When the use of Thiel embalmed cadavers (see Section 1.7.2) was assessed by a group of surgeons from different specialties, they were deemed to be a suitable medium for simulation of surgical procedures (Yiasemidou et al. 2017). Thiel embalmed cadavers were also found to be suitable in NOTES (Porzionato et al. 2015). Thiel embalmed cadavers were found to offer a superior model when compared to the traditional formalin preserved cadavers specifically for thyroid surgery (Eisma et al. 2011).

Whilst several groups have used the cadaveric platform to develop the technique for TOETVA especially in the early phases of the procedure as discussed in Chapter 1, the setup used was usually that of fresh frozen cadavers. Thiel embalmed human cadavers were never utlised for the study or training of TOETVA. The initial phases of the investigations carried out by the researcher was to assess the Thiel embalmed human cadaveric platform in the context of its feasability for use in reproducing the standard TOETVA with CO_2 insufflation. The researcher also wanted to assess whether this platform could be utilised to train surgeons who are novices in TOETVA in order to flatten the learning curve.

3.2 Materials and Methods

The standard technique of TOETVA was reproduced by the researcher in three Thiel embalmed cadavers. From the cadavers available, the researcher chose those bodies who had virginal neck anatomy and that were intact from the chest upwards. Cadavers with central venous access or signs of radiotherapy to the neck were excluded. This was done in order to offer the best possible anatomical model whilst eliminating known risk factors for difficulties in TOETVA.

The researcher first positioned the cadavers supine with the neck hyperextended using a shoulder bolster (Figure 3). The laparoscopic equipment was positioned on the right lower side of the cadaver in order to allow the maximum operating space possible for the researcher and the assistant at the cranial end of the cadaver.

Figure 3: Cadaver 2 after positioning with the neck hyperextended. Position of bolster shown with arrow.

Figure 4: Cadaver 3 with the laparoscopic tower in place.

The procedural steps used in these cadavers by the researcher were those described by Dionigi et al. 2016. The latter steps were considered as the standard operating procedure by most groups as discussed in Chapter 1. The researcher first performed a 10-15mm incision in the centre of the lower vestibule. Through this incision, the researcher carried out blunt dissection in the subplatysmal layer until enough space for the central 10-12mm port (VERSAONE™ bladed trocar, Covidien®, Dublin, Ireland) was created and this port was inserted. The researcher at this point established CO_2 insufflation. The researcher used CO_2 insufflation at a maximum insufflation pressure of 12mm Hg for the first cadaver and 6mmHg for the following two. The maximum flow rate of 15 liters per minute was set using a CO_2 high flow insufflator (Aesculap® PG080, Tuttlingen, Germany).

A 10mm 30-degree full HD scope (Aesculap® PE909A, Tuttlingen, Germany) with a 3 chip full HD camera system (Aesculap® PV460, Tuttlingen, Germany) was inserted through the established port by the assistant under the researcher's guidance to allow visualisation. The light supply to the endoscope was delivered through LED light source (Aesculap® OP940, Tuttlingen, Germany). Subsequently, the researcher created two 5mm incisions opposite the lower canine teeth on both sides and 5mm ports (VERSAPORT™ V^2 trocars, Covidien®, Dublin, Ireland) were inserted under vision.

The subplatysmal space was then further developed down to the sternal notch caudally and sternocleidomastoid muscles laterally, using a combination of blunt and sharp dissection by the researcher. The linea alba cervicalis was then opened and the thyroid isthmus identified. The thyroid isthmus was then lifted and dissected off the underlying trachea in the centre. Once completely off the trachea, the isthmus was then divided centrally by the researcher. The latter allowed the thyroid lobe to be retracted medially and cranially and the overlying strap muscles were dissected off and retracted laterally. The researcher took a cranio-caudal approach for the dissection of the thyroid lobe with an attempt to identify the superior and inferior thyroid vessles, recurrent laryngeal nerve and parathyroid glands. For the purpose of the cadaveric dissection, a Maryland dissector (Grena®, London, United Kingdom), endoshears (Grena®, London, United Kingdom) and laparoscopic graspers (Grena®, London, United Kingdom) were used. The superior thyroid artery and vein were first identified, dissected clean by the researcher and transected. The researcher then gently mobilized the thyroid lobe medially using a subcapsular approach. The researcher performed the dissection subcapsularly in order to preserve the recurrent laryngeal nerve as well as the parathyroid glands. An attempt was made by the researcher to identify the parathyroid glands and the recurrent laryngeal nerve at this point. The inferior thyroid artery was identified, dissected free and transected. When all the vessels were cleared, Berry's ligament was dissected off the remaining part of the trachea and the lobe was freed. The researcher then performed identical dissection on the contralateral side. The right lobe was always dissected first since the researcher was right-handed (Fama, Zhang et al. 2019).

When the researcher freed both thyroid lobes, the specimen was removed through the midline 10mm port. During the procedure, the researcher recorded a number of parameters. These included the gender of the cadaver, the length from the chin to the sternal notch and from the chin to the thyroid cartridge, the length of the procedure, the clarity of anatomical structures at the time of operation and whether the space in which the procedure had to be carried out (including the ability to manoeuver the instrumentation) was appropriate. At the end of every procedure, the researcher performed a cervicotomy and carried out a postprocedural assessment with the aim of assessing any damage to the surrounding structures. The anatomical structures that the researcher evaluated for any damage included recurrent laryngeal nerve, trachea, carotids, jugular vein and oesophagus.

3.3 Results

Three Thiel embalmed cadavers, one female and two males, were utilised in this part of the study. The first step assessed was the ability to position the cadaver in the supine position with the neck hyperextended. This was mandatory in order to align the neck and make the operation possible. All three cadavers maintained enough tissue and joint flexibility to allow the researcher to achieve appropriate positioning as shown in Figure 3. The space the researcher and the assistant had at the cranial end of the patient was sufficient for the researcher to carry out the procedure unhindered. The anatomical measures taken at this stage are shown in Table 5.

Measurement parameters	Length (in cm)		
	Cadaver 1 (F)	Cadaver 2 (M)	Cadaver 3 (M)
Mandible to Sternum	13.7	19	14
Mandible to thyroid cartilage	5.3	8	5.5
Mandible to isthmus	7.5	11	8

Table 5 Anatomical measurements taken with the neck hyperextended during the TOETVA procedure carried out in the Thiel embalmed cadavers. M: Male; F: Female

The vestibular access was uneventful in all three cadavers. The vestibular tissue maintained elasticity. This permitted a 10-15mm central incision and blunt dissection in the subplatysmal plane, without major problems. For the researcher, the more difficult step of this procedure was the development of the subplatysmal plane over the chin and, in the case of the male cadavers, over the laryngeal prominence. Despite this, there were no flap perforations. This insufflation was carried out uneventfully in the cadavers, with the tissues in the Thiel embalmed cadavers maintaining enough elasticity so that only minimal leaks from around the ports were recorded by the researcher. The vestibular space in the cadavers utilised in this assessment was large enough for the ports to lie comfortably in their position (Figure 5).

Figure 5: Cadaver 1 after port insertion and with CO_2 insufflation.

The researcher could develop the subplatysmal space completely to the limits detailed in Section 3.2. The sternocleidomastoids, strap muscles, linea alba cervicalis and fat retained similar colour and texture to that which the reseracher usually expierences during open thyroidectomy in the living patient (Figure 6).

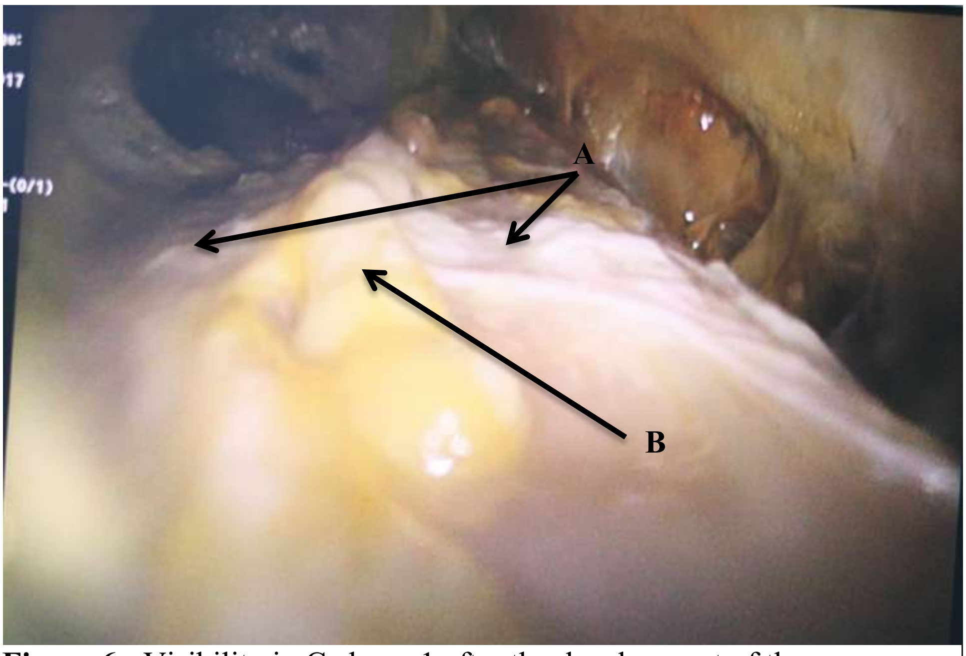


Figure 6 : Visibility in Cadaver 1 after the development of the subplatysmal space, indicating the strap muscles (A) with intact linea alba cervicalis (B).

The researcher could easily make out the anatomical differentiation between the thyroid isthmus and trachea in all of the three cadavers. In addition, the researcher could develop the surgical plane between the isthmus and trachea without difficulty.

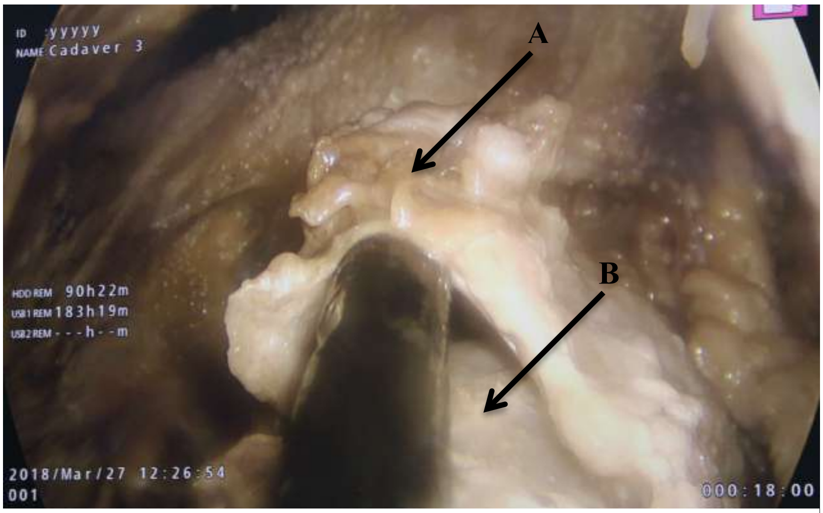


Figure 7: Thyroid isthmus(A) dissected off the trachea (B) centrally and elevated in Cadaver 3.

The texture of the thyroid tissue was preserved. This allowed the researcher to be able to appropriately retract the thyroid lobe being dissected in order to visualise the anatomical landmarks. The dissection was particularly challenging in Cadaver 2 since the researcher experienced difficulties in the manoeuvrability and triangulation at the caudal end of the neck. The recurrent laryngeal nerves and the parathyroid glands were identified by the researcher as shown in Table 6.

	Recurrent Laryngeal Nerves	Parathyroid Glands
Cadaver 1	None	1
Cadaver 2	Right yes; Left No	2
Cadaver 3	None	2

Table 6 Number of structures identified during dissection in the three Thiel embalmed cadavers used in the reproduction of TOETVA.

The specimen, after both lobes were dissected free by the researcher, was retrieved through the central incision without any difficulty and without the need to either extend the incision or to break down the specimen. In all three cases, the excised thyroid did not contain any pathological nodules on macroscopic assessment by the researcher (Figure 8).

Figure 8 The gland after delivery presented on the neck of Cadaver 3

After the completion of the procedure, all of the cadavers had extensive subcutaneous emphysema. On post-procedural open assessment by the researcher, none of the three Thiel embalmed cadavers had damage to the recurrent laryngeal nerve, trachea, oesophagus, carotid arteries or jugular veins. The parathyroid glands were not identifiable at open assessment of the neck. The visibly scarless principle of TOETVA was achieved with the only scars being found in the vestibule as shown in Figure 9.

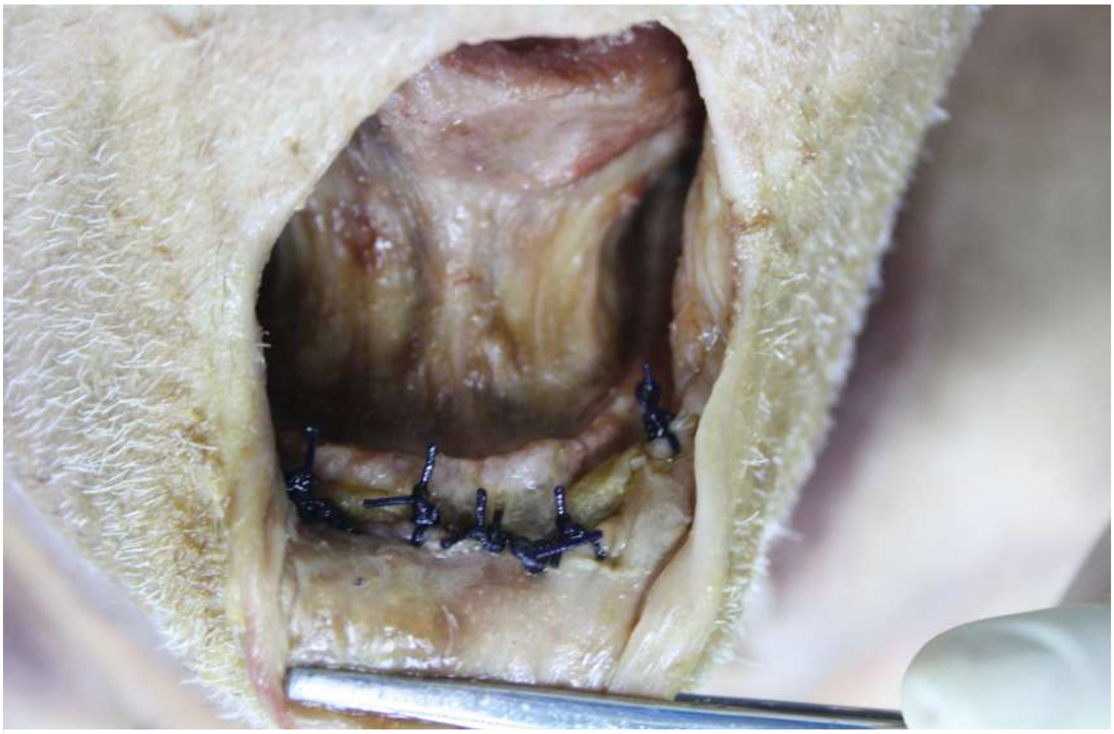


Figure 9: Residual closed wounds after TOETVA in the edentulous Cadaver 2

3.4 Discussion

.

The initial phases of the research carried out by the researcher were focused on reproducing the standard TOETVA technique in Thiel embalmed cadavers and assess the suitability of this model for training in this novel technique. As detailed in Section 1.2.1, the technique has been performed extensively in the fresh cadaver model. Whilst the open thyroidectomy had been satisfactorily reproduced in Thiel embalmed cadavers (Eisma et al. 2011), no published reports on TOETVA in the Thiel embalmed cadavers were available prior to the publication by the researcher (Camenzuli et al. 2019) (Appendix 8).

The three Thiel embalmed cadavers utilised for this analysis were very well suited for this procedure. The tissues of the vestibule and the subplatysmal planes allowed the researcher to carry out the dissection adequately with the tissue maintaining life-like elasticity and colour. The vestibular tissue was elastic enough to seal around the ports and prevent substantial air leaks. This translated in good retraction of tissues and good visualization. The main structures, including muscles (strap muscles and sternocleidomastoid), trachea and thyroid tissue were easily visible in all patients. The cadavers used allowed the researcher to develop good spatial recognition in addition to developing the required hand-to-eye coordination, which is imperative in the context of a small operative space. The central incision was also elastic enough to allow the retrieval of the specimen at the end of the procedure.

Cadaver number 2 (see Table 5) had a longer neck and this led to more challenging triangulation of the instruments and more difficult visualisation of the sternal end of the thyroid lobe. Whilst the procedure could still be carried out to completion, the increased level of difficulty was not deemed ideal for individuals who were in their initial stages of training in this procedure. A number of risk factors have been identified to be responsible for increasing the level of difficulty of thyroid surgery in all the available techniques. The length of the neck has been one of these risk factors in minimally invasive thyroidectomy, although in the conventional open surgery, it is a short neck rather than a long one that increases the level of difficulty (Del Rio et al. 2008). High BMI, inability to extend the neck, male sex, a large thyroid, hypervascularity and autoimmune disease all increase the difficulty level of thyroid surgery by decreasing the visualisation of the anatomy and manoeuvrability of the thyroid tissue itself (Del Rio et al. 2014). In the researchers' experience, there were no differences between the two male and one female cadavers during the dissection process.

Having normal thyroids in the cadavers used during this research offered a lower level of difficulty to the researcher. It would have been ideal to filter the available cadavers so that they are standardised and offer the lowest level of morphological difficulty for the researcher. Whilst as reported in Section 3.2 the researcher excluded cadavers without virginal anatomy, no further selection criteria were used. The lack of such filtering was done on purpose, because the patients in real practice present with varied and sometimes challenging anatomy. Whilst most studies presented in Section 1.2.2 have excluded patients with autoimmune disease, large thyroids and/or hypervascularity in order to try to limit the difficulty of the procedure, anatomical exclusion criteria in terms of neck length or BMI were seldom implemented. This research needed to be faithful to these selection criteria. In addition, there is evidence that, whilst the above-mentioned criteria increase the difficulty of the procedure, this does not always translate in increase morbidity (D'Orazi et al. 2019).

The major limitation that was encountered by the researcher during the procedures was the identification of the recurrent laryngeal nerves and the parathyroid glands. These structures are intimately related to the thyroid gland and need to be dissected free and preserved (Miller 2003). In the researchers expeirence with the three Thiel embalmed cadavers used, only 1 out of the 6 recurrent laryngeal nerves were identified during TOETVA (See Table 6). The researcher applied the principle that the use of a capsular dissection of the thyroid gland in case of difficultly in the identification of the recurrent laryngeal nerve, should protect the nerve (Delbridge et al. 1992, Das et al. 2016). The strategy adopted by the researcher was effective since all the recurrent laryngeal nerves were preserved at open assessment.

The preservation of the recurrent laryngeal nerve during any form of thyroidectomy is paramount. This nerve, which is a branch of the vagus nerve, gives the motor supply to all the laryngeal muscles except the cricothyroid and the sensory supply to the infraglottic region. Although the anatomical location of these nerves tends to follow a predictable pattern (e.g. the recurrent laryngeal nerve passes behind the tubercle of Zuckerkandl and crosses the inferior thyroid artery (Henry et al. 2017, Vural et al. 2021), the variety of routes that the nerve can take increases the complexity of the procedure, making it more difficult to identify during surgery (Sheikh et al. 2019, Thomas et al. 2020). Damage to the recurrent laryngeal nerve unilaterally leads to lowering of the pitch of the voice. If both recurrent laryngeal nerves are damaged, this can lead to difficulty with breathing which might necessitate a surgical airway to allow ventilation (Lo et al. 2000). The rate at which one of these nerves is damaged permanently in the conventional technique stands at around 1.8% (Van Slycke et al. 2021) whilst that of TOETVA lies at around 0.9% (Chai et al. 2021). The latter might be due to the magnification of tissues given by the endoscope during TOETVA which helps with better preservation of the nerve. Neuromonitoring devices are available to help the surgeon identify the nerve in the living patient (Erol et al. 2020, Zhang et al. 2018). This is usually implemented through an especially designed probe and the nerve is intermittently stimulated in order to identify it and make sure there is no injury. Intra-operative neuromonitoring (IONM) has been shown to offer decreased morbidity for patients undergoing thyroidectomy particularly for thyroid cancer and recurrent disease (Wu et al. 2018). The amalgamation of magnification through the endoscope, cranio-caudal approach, top-down view and the use of the IONM in TOETVA, help to reduce the risk of nerve injury (Zhang et al. 2020). Whilst the risk of recurrent laryngeal nerve injury is not increased with TOETVA, this is not the case with all approached to endoscopic thyroidectomy. ETAA offers an increased risk of injury (Zhang et al. 2019)

In the researcher's expierence, 8 out of 12 parathyroid glands were identified in the three cadavers during the procedure with the help of the magnification offered by the endoscope, but not in the open assessment. The evidence of parathyroid tissue preservation in Thiel embalmed cadavers is limited. In Eisma et al. 2011, parathyroid tissue was identified more easily in Thiel embalmed than in formalin-embalmed cadavers. Intra-operative identification of the parathyroid glands is always challenging (Chang, Lang 2017, Gschwandtner et al. 2018). This is mainly due to the high variability of position these glands occupy. Whilst most individuals (89.3%) have four or more glands in the neck, parathyroid glands can be absent or found outside the neck (Hojaij et al. 2011, Melo et al. 2013). In the living patient, as the parathyroid gland is manipulated and dissected free, there is a typical change in colour as it gets slightly bruised. The absence of such a change in colour in the Thiel embalmed cadavers dissected by the researcher, further limited the ability to identify these glands. Parathyroid injury, causing either temporary or permanent hypocalcaemia, is one of the commonest morbidities following thyroid surgery. Whilst temporary hypoparathyroidism is high, the risk of permanent hypoparathyroidism after open conventional thyroidectomy is around 5.4% (Astl et al. 2021). In TOETVA, the reported cases for permanent hypoparathyroidism are negligible (Camenzuli et al. 2018, Menderico et al. 2021). The more parathyroid glands identified and preserved intra-operatively, the less likely it is for the patient to develop a permanent hypoparathyroidism (Melo et al. 2015). It is therefore imperative to attempt as much localisation and preservation of parathyroid glands as possible during the procedure.

Despite the limitations described above, the Thiel embalmed cadavers offered an adequate platform for the reproduction of TOETVA. This type of embalming allows for a safe environment in which the training surgeon would be able to use a realistic model to develop the skills needed to shorten the appreciable learning curve for this technique, before operating on live patients (Lira et al. 2020, Chai et al. 2021).

Chapter 4:

Gasless Technique for Endoscopic Thyroidectomy

4.1 Introduction

The standard TOETVA technique has been shown to be safe and effective when compared to open thyroidectomy (Wang et al. 2021). Notwithstanding the safety profile of this endoscopic approach, when the researcher looked closely at the complications associated with TOETVA in the published literature, a number of adverse outcomes related to the use of CO_2 insufflation during the procedure were identified. These included surgical emphysema (occurring at a rate of 2-10%), mediastinal emphysema and pneumoperitoneum, which are usually self-limiting and occur as a consequence of prolonged surgery and higher CO_2 insufflation pressures. While the latter complications are not of major clinical significance, the possibility of another complication, that is CO_2 embolism, is very worrying. Gas embolism may develop in case of anterior jugular vein damage during flap development and carries a risk of mortality. To date, four cases of embolism were reported in the literature (Tae 2020a).

The scope of using CO_2 insufflation during TOETVA is to keep the surgical space open, hence allowing the operating surgeon to visualise the anatomy during the procedure and manoeuvre the working instruments under vision. Proper visualisation in endoscopic procedures is critical to be able and deliver safe surgery. In order to eliminate the risk for CO_2 embolism and make the already safe TOETVA procedure safer, the researcher needed to have a retracting device to replace the function of CO_2 insufflation whilst offering equivalent visualisation.

4.2 Materials and Methods

The researcher addressed the issue of eliminating CO_2 insufflation in TOETVA by first developing a novel retracting device, then trialling this device in three Thiel embalmed cadavers and subsequently comparing the outcomes of the gasless modification with the results presented in Chapter 3.

4.2.1 The retractor

4.2.1.1 Commercially available retractors

The researcher first considered the possibility of using commercially available retractors in TOETVA to reach the goal of eliminating CO_2 insufflation.

The first devices that were considered were the metal retractors that were used in other approaches for endoscopic thyroidectomy particularly for the transaxillary approach. These retractors are made of an elongated metal strip that is introduced through the incision. Traction on the handle of these retractors results in the desired retraction. Two particular retractors that the researcher identified and assessed for suitability where Chung's thyroidectomy retractor (Marina Medical, Sunrise, USA) and Modena retractor (MR, CEATEC Medizintechnik, German). Both these devices have the possibility of a self-retaining option and have been shown to be effective in the transaxillary approach (Prete et al. 2019, Shah et al. 2016). After evaluation by the researcher, these devices were not deemed fit for integration in TOETVA because, in order to introduce the retractor in the subplatysmal space through the vestibule, a bigger incision needed to be made. The concern with the latter manoeuvre was the damage to the mentalis muscle and potential damage to the mental nerve which could induce further morbidity (e.g., chin paraesthesia, difficulty with shaving, neuropathic pain). The researcher therefore excluded the use of these retractors.

The endoscopic fan retractor typically used in laparoscopic abdominal surgery to retract the liver was another commercially available retractor that has been considered by the researcher. Several models of this retractor are available on the market with some being disposable and others being reusable. Examples of the latter included Endo Retract™ II (AutoSuture®- Covidien®, Dublin, Ireland) and Sklartech 5000™ Fan Retractor (Sklar®, Pennsylvania, USA). These retractors are composed of a straight rod with an external diameter of 10mm or 5mm (which enables them to be delivered through standard laparoscopic ports). The tip of the retractor is made of five fins which can be collapsed into one during insertion and are then expanded into a fan-like structure on deployment via a rotatory movement at the handle. In addition, some of these retractors can also rotate the tip at various angles. This was done via an additional mechanism within the retractor and the assistant can operate it via a rotatory knob at the handle. This retractor is small enough to be inserted through the vestibule but requires an additional port or incision which is ill-afforded in the limited space offered by the vestibule. Adding an additional port in the limiting space of the vestibule was already shown to cause the instruments to collide making the procedure more difficult (Lee et al. 2014). The principle of a collapsible tip that could be deployed when the retractor was in position was of great interest to the researcher, but the tip of the commercially available models was deemed too thick and the number of fins too many, for the purpose of TOETVA. The straight rod that characterised this type of retractor and which worked well in the context of abdominal laparoscopic surgery was not a viable option in case of endoscopic neck surgery. The straight nature and length of this rod (approximately 33cm depending on the model and make) meant that the assistant needed to keep the device with one hand and the endoscope with the other hand on the face of the patient. This would be uncomfortable for the assistant and a hindrance for the operating surgeon. In addition, in individuals in whom the nasal protuberance is particularly pronounced, the straight nature of the device would offer an additional hurdle for the comfort of the assistant. Therefore, the researcher excluded this retractor for the use in gasless TOETVA on the basis of all these disadvantages and limitations.

Another endoscopic retractor which was assessed by the researcher was the Snowden-Pencer® Diamond-Flex® (Diamedical USA, Michigan, USA). This was another retractor which is typically used in laparoscopic abdominal surgery in order to retract the liver. It consists of a straight shaft (which was available in 5 and 10mm sizes) with several articulating parts at the tip. The internal mechanism allows the articulating tip to contort when an actuating knob at the handle is rotated. On deployment, the tip of this retractor takes the shape of a triangle, circle, pretzel, hook or a simple angle depending on the model being used. This device has the same disadvantages of the fan retractors since it needs to be inserted through a separate incision and it also has a straight shaft which limits comfort for usage. In addition, the mechanism of deployment in the neck is also limiting in the context of TOETVA. The smallest available retractor has a 6 cm tip which needs to rotate in the neck until it formed its final shape. This would be difficult to achieve within the context of the subplatysmal plane, which is collapsed, and it might be dangerous since visualisation would be difficult. For these reasons, the researcher excluded the use of this retractor in the gasless TOETVA procedure.

4.2.1.2 The Magnetic Option

Since none of the commercially available retracting devices were deemed to be suitable for use in TOETVA, the researcher embarked on an exploration for the development of a novel retracting device. Using the experience of the anatomical limitations of the surgical space and tissues that was gathered by the researcher in the Thiel embalmed cadavers dissected for the initial investigations (as outlined in Chapter 3), the researcher developed the idea of using a retracting device that utilises magnets in order to retract the skin and platysma away for the surgical field.

For this magnetic retractor to work, metallic implants would need to be implanted in the platysma internally after developing the subplatysmal space with blunt dissection. The implantation of these magnets was deemed problematic by the researcher since the potential subplatysmal space would be collapsed at this stage of the procedure. Strong magnets would then be used externally, held by a fixed self-retaining stand, to pull the metal implants and secondary to this, pull the platysma and underlying skin away from underlying structures. This would allow for the required space to remain open and would be faithful to the principle of scarless surgery. The researcher acknowledged the potential advantage of this system to eliminate the need of having an assistant and consequently give more space for the operating surgeon at the cranial end of the cadaver. Since titanium is only weakly magnetic, a ferromagnetic metal made of medical grade alloys would be the metal of choice for the development of the implant. Whilst similar metallic implants are used and left in the body in abdominal laparoscopic surgery (mainly in laparoscopic hernia repair) without any major long-term morbidity, this would be problematic since the tissues in the neck (skin, subcutaneous fat and platysma) are significantly thinner. The initial experience of the researcher in TOETVA in the Thiel embalmed cadavers led to the appreciation of the fragility of the tissues being retracted. This would mean that, if the metallic implants were left inside the neck after the procedure, these implants could be visible externally and could be easily palpated. Consequently, if any metal implant was used, this would need to be taken out at the end of the procedure. The researcher was concerned that the extraction of the implants could involve tissue damage which could in turn result in bleeding or poor cosmetic outcomes. The setup for the external magnets would involve a mechanism that would be fixed with the operating table or a fixed stand close to the operating table. In order to allow the best pull, these magnets would need to be applied close to the neck. This was a major concern for the researcher since it offered an important barrier to access the neck, should the need for urgent conversion to open surgery arise. Due to these concerns, this idea was not developed further.

4.2.1.3 Integrated retractor

The researcher developed the concept of inventing a novel hybrid retractor. This retractor had to replace the function of the central 10mm vestibular port as well as perform the required retraction to keep the operating space opened and allow sufficient visualisation of anatomy. The latter concept was to create a device that uses a commercially available standard high-definition endoscope through which visualisation and light can be provided and combine it with a novel retractor so that the assistant needed to use only one hand to manipulate the endoscope-retractor device. The researcher wanted to use a standard commercially available endoscope since this would impose less of an investment of the healthcare system that opts to adopt this adaptation. In order to directly replace the central vestibular port, the shaft of the device had to be limited to 10mm in its external diameter. Since the endoscope had to be standard and at the same time integrated within this limited space, the researcher decided to work with the understanding that the 10mm 30-degree high definition endoscope used for the standard technique (which uses the central 10mm port and gas insufflation) had to be replaced with a 5mm 30 degree high definition endoscope. This would allow enough space for the mechanism of the retracting part of the device to be installed and function properly. To allow for the 5mm endoscope to pass through with ease, an inbuilt channel was created by the researcher using a brass tubing with an internal diameter of 5 mm and external diameter of 5.5mm. This tube had a length of 12cm, an internal diameter of 5mm and a wall thickness of 0.355mm. This allowed for the 5 mm endoscope to go through the channel comfortably but tightly, thus limiting any independent movement once the endoscope was positioned. The channel ran along the whole length of the straight part of the shaft and was situated in the bottom part so that the endoscope emerged below the tip connecting the shaft with the collapsible part for the retractor. For the purpose of this prototype, the researcher used a channel made of brass. However should the use of this new device move from a cadaveric setting to a live patient setting, this channel should be made of stainless steel or thick plastic in order to be inert and non-toxic.

The idea of having a collapsible tip to the retractor which is used in the available fan retractors (See Section 1.3.1), was deemed by the researcher to be a good fit for this new device. The area which needed to be exposed and the weight of the tissues that needed to be pushed away to allow enough space for visualisation (i.e., skin, subcutaneous fat and platysma) were very limited, as experienced by the researcher in the setting of the Thiel embalmed cadavers. The latter formed the basis of the rationale used when constructing the collapsible tip of this device. The idea of developing a three-fin collapsible tip was developed with a minimum width of 10 mm when collapsed and a maximum width of 50mm when fully deployed. Each of the three fins had a total length of 70mm and were anchored within the tip. When in the collapsed position the fins protruded beyond the tip by 50mm. However, when deployed the tips were pushed forwards in addition to opening up in a fan-like manner. Consequently, in the deployed position the tips protruded beyond the tip by 55mm. The distal edge of these fins had a gentle cup-like upward curvature which helped the retractor to push away the overlying tissues whilst avoiding sharp trauma. The tip was developed according to the design of the researcher, in collaboration with the team from the Faculty of Engineering (See Section 2.3).

The part that the researcher found most challenging during the process of the development of this retractor was the development of the tip that joined the straight part of the shaft with the collapsible fins whilst allowing enough space to manoeuvre the 30 degree angle of the endoscope. This part of the retractor took the most pressure forces of the whole device and therefore its construction was paramount. The researcher developed a design in which the tip could allow for the anchoring of the fins of the fan retractor whilst at the same time be slim enough to allow the maximum visualisation. The initial attempts at producing this tip were made in collaboration with the engineering team at the Faculty of Engineering at the University of Malta using 3D printers (i.e. additive manufacturing). The material chosen by the researcher was thick plastic. This helped in the evaluation of the size and shape. It was also essential to produce a 3D model to help the researcher assess whether the space left for the endoscope in the bottom part of the tip was enough for manipulation of the scope, should the need arise. After the 3D printed prototype was built, the researcher made a number of modifications of the thickness and length of the tip. This was an exercise made in order to reach a compromise between the space allocated for the endoscope to protrude through and the strength of the tip itself. The end result was that the proximal part of the tip was anchored within the shaft. Beyond the shaft, the tip decreased to 5mm with a further inlaid curved groove of 2mm to allow for the endoscope groove. When the plastic tip was exposed to pressure by the researcher, the material bent. The researcher therefore decided that the plastic used for the production of the first prototype had to be changed with to a stronger material. The researcher opted to use the metal titanium due to its accessibility, strength and poor conductivity. After consultation with the engineers, it was noted that the choice of machinery available to produce such a metal part was between additive (3D printing) and subtractive manufacturing. The available equipment for 3D printing machines within the Faculty of Engineering at the University of Malta was not able to work with titanium and the subtractive manufacturing machine available lacked the wire erosion technology needed to finish the curvatures. This part was therefore manufactured under the researchers' design by the process of 3D printing at the Faculty of Materials Science and Engineering, Warsaw University of Technology, Poland.

The design of the shaft of the new device had to allow enough space for the camera head to fit below the handle and at the same time afford a safe distance between the device complex (i.e. device + anchored endoscope and camera head) and the patient's face. In order to mitigate this challenge, the researcher developed the concept of producing an angulated device. To this end, the shaft of the device had to have three parts: a straight part with the integrated channel for the endoscope and the tip at the end, a curved part and another straight section with an integrated handle. The most challenging part of the device was the curved section. The researcher wanted the bend in the device to take off just beyond the exit of the endoscope channel so that the device curves away from the patient as soon as it emerged from the vestibule. This presented the researcher with the need to compromise between the acuteness of the angle and the integrity of the internal mechanism that drove the opening of the tips. In collaboration with the engineering team and after four attempts, an angle of 20 degrees away from the face, which develops in a length of 45mm, was made.

This satisfied the requirements of the researcher to take the shaft away from the face whilst allowing the internal mechanism to properly open the fan retractor. The latter mechanism was similar to that used in Endo Retract™ II (AutoSuture®- Covidien®, Dublin, Ireland) and was adapted to the device.

The last part to be developed was the end part of the device, which was the section handled by the assistant. The main criteria the researcher put for the creation of this part were the following: a) that the handling had to be as comfortable as possible and, b) that the device and the endoscope (with the camera head attached) had to be integrated in a way that the whole device-endoscope complex was handled as one by the assistant. In order to make the manoeuvering of the device as comfortable as possible and reduce the stress on the assistant's hand, the handle was designed by the researcher as a rounded knob made out of rubber and with integrated gripping spikes. This knob, apart from giving a comfortable handle to grip to the assistant, had also the integrated mechanism that allows for opening and closing of the fan tip of the retractor. When the knob was twisted in a clockwise fashion the three fins at the tip opened up when in the collapsed position. Conversely, when the fins were in the expanded position, turning the knob in an anti-clockwise fashion resulted in the collapse of the fins. This mechanism was integrated within the knob by the engineering team.

When this device was trialled by the researcher on Thiel embalmed cadavers (refer to Section 4.2.1.4), it became evident that despite the design, the endoscope and the device could not be moved as one and the assistant needed to keep both in one hand to be able to manoeuvre the device-endoscope complex satisfactorily during the procedure. The researcher therefore developed an additional adaptation to the device prototype. A silicone adjunct was constructed that was fixed to the shaft of the retracting device on one end and had a channel of 5mm on the other end which could be opened. The endoscope was passed through this adjunct prior to its insertion in the integrated channel. When the best position was achieved, the silicone adjunct was tightened, and the endoscope fixed. The researcher opted for silicone to be used for this adjunct so that when the endoscope was gripped within the adjuncts' channel, the material was soft and did not damage the delicate structure of the 5mm endoscope. For the purpose of the prototype, the tightening mechanism was attained by the researcher by using a simple toggle bolt and nut mechanism in which there was a bolt fixed within the adjunct. When the toggle bolt was unscrewed, the adjunct opened up enough for the endoscope to pass through it comfortably and when the toggle bolt was screwed in, the silicone adjunct tightened with the endoscope. The whole process of prototype development lasted for 4 years.

4.2.2 Thiel embalmed Cadaveric Trial

The prototype retractor which was developed as described in Section 4.2.1.3, was then trialled in three Thiel embalmed cadavers since this platform was found to be a suitable one (See Chapter 3). For this assessment the researcher chose Thiel embalmed cadavers that had a virginal neck anatomy and that were intact from the chest upwards. Cadavers with central venous access through the neck or a history of radiotherapy to the area were also excluded by the researcher in order to be consistent with the cadavers used for the previous analysis detailed in Chapter 3. During the procedure a number of parameters were recorded by the researcher. These included the gender of the cadaver, the length from the chin to the sternal notch and from the chin to the thyroid cartridge, the length of the procedure, the clarity of the anatomical structures at the time of the operation and whether the space in which the procedure had to be carried out (including the ability to manoeuvre the instrumentation) was appropriate.

The researcher first positioned the cadavers supine on the dissection tables, with the neck hyperextended. The initial vestibular incision was performed by the researcher in the centre of the lower vestibule similar to the standard insufflation technique. The subplatysmal space was then developed by the researcher using blunt dissection with a large artery forceps until enough space was created to introduce the device and the working ports were under vision. The device was coupled with the working 5mm 30 degrees endoscope (Aesculap® PE610A, Tuttlingen, Germany). The researcher fixed the lens of the endoscope to face inferiorly to get the best visualisation. The researcher then introduced the device-endoscope complex with the fins of the fan-retractor in the collapsed position. A 5 mm incision was made in the lower lip vestibule just opposite the lower canines on either side and 5 mm working ports were inserted under vision. With the fins of the retractor still in the collapsed position, a mixture of blunt and sharp dissection was carried out by the researcher under vision in order to develop the subplatysmal space. The space was defined laterally by the sternocleidomastoid and caudally by the sternal notch.

When the plane was completely developed by the researcher, the assistant was asked to turn the knob of the retractor in a clockwise fashion which enabled the three fins at the tip of the retractor to expand in a fan-like manner. The assistant was then instructed by the researcher to push the device-endoscope complex slightly towards the face allowing the tip of the retractor to push upwards. The latter manoeuvre, although subtle, allowed the space to open up better and subsequently gave enough room for the instruments to be moved with ease and for the anatomy to be visualised better by the researcher. This was possible because of the angulation of the shaft as discussed in Section 4.2.1.3.

The subsequent steps of the procedure carried out by the researcher in these three Thiel embalmed cadavers were identical to those of the gas insufflation technique (refer to Section 3.2) until the thyroid gland had been dissected completely and excised. At this point, the researcher instructed the assistant to turn the handle of the retractor anti-clockwise, which enabled the fins at the tip to collapse on each other. The specimen was secured by the researcher using a laparoscopic grasper. The assistant was then instructed by the researcher to withdraw the device-endoscope complex from the cadaver and the specimen was delivered through the middle wound. The incisions were then closed by researcher with interrupted sutures.

All three cadavers were then explored by the researcher using the traditional collar incision after the procedure was completed in order to evaluate surrounding tissues for inadvertent damage. The tissues assessed included the recurrent laryngeal nerves, parathyroids, trachea, carotids, jugular veins and oesophagus.

4.2.3 Comparison

The information retrieved from the gasless experiments carried out on the three Thiel embalmed cadavers (see Section 4.2.2), was then compared by the researcher to that retrieved from the three Thiel embalmed cadavers in which the standard technique was carried out (See Chapter 3).

In addition to the subjective comparison of the researcher as described in the previous paragraph, an objective comparison was needed in order to re-inforce the findings. The researcher identified all the surgeons who perform thyroid surgery as their main practice. These surgeons hailed either from the specialty of Ear, Nose and Throat (ENT) surgery or from Endocrine Surgery (a subspecialty of General Surgery). Since minimally invasive thyroidectomy is no carried out in Malta, whilst these surgeons were experts in the open standard thyroidectomy, none of the eligible surgeons had substantial experience in endoscopic thyroidectomy. ENT and General surgeons who did not perform regular thyroid surgery were excluded. The five thyroid surgeons identified were invited to participate by the researcher through an email in which they were supplied with 6 photos. Three of the latter photos originated from the standard TOETVA group and three from the gasless group (Appendix 3).

The photos supplied by the researcher depicted three standard stages of TOETVA. The stages of the procedure supplied were as follows: when the subplatysmal plane had been developed; at the stage of the procedure when the linea alba cervicalis had been opened and the thyroid isthmus lifted off the trachea; and at the stage when the thyroid isthmus had been divided centrally and the strap muscles dissected off the left thyroid lobe. The researcher provided the specialists with a brief description of the stage of the procedure each picture was taken in. This was done to give the specialists some orientation to the anatomy being presented to them since although they did thyroid surgery regularly, TOETVA was still a novel approach to them. In order to blind the specialists, the technique used in the provided pictures (standard vs gasless) was not documented in the descriptions (Appendix 3).

No personal data was collected by the researcher. A scoring sheet was then given to all the members of the specialist panel (Appendix 3). Each specialist was asked to rate the ease with which they could identify anatomical structures. A visual analogue score (VAS) was utilised for this purpose. The VAS ran from 1 to 10 where a score of 1 represented completely unidentifiable anatomical structures and a score of 10 signified that all structures were identifiable with extreme ease. The specialists were also given the opportunity to write any comments they deemed fit within a free text box provided for every picture. The results retrieved from this panel were first anonymised and then statistically analysed using a Wilcoxin signed ranks test since the collected data was non-parametric and the pictures were paired.

4.3 Results

4.3.1 Results from Cadaveric Trials

The researcher trailed the novel retracting device in three Thiel embalmed cadavers (2 males and 1 female). (see Section 4.2.1.3). The prototype of the device is shown in Figures 10-11.

Figure 10: The developed integrated retractor with the 5mm 30-degree endoscope inserted and fixed in place. The tips of the retractor are collapsed. Top view. Additional images can be seen in Appendix 6

Figure 11: The developed integrated retractor with the 5mm 30-degree endoscope inserted and fixed in place. The tips of the retractor are collapsed. Side view. Additional images can be seen in Appendix 6

The anatomical details of the three cadavers used for this investigation are outlined in Table 7.

Measurement parameters	Length (in cm)		
	Cadaver 1 (M)	Cadaver 2 (M)	Cadaver 3 (F)
Mandible to sternum	13	12	16
Mandible to thyroid cartilage	7	4	5
Mandible to isthmus	9	7	9

Table 7: Anatomical measurements taken with the neck hyperextended from the cadavers used to assess gasless TOETVA. M: Male; F: Female

In all three cases, the dissection carried out by the researcher proceeded smoothly and the retracting device allowed adequate visualisation for the investigator to carry out the procedure. The operating space which was kept open with the use of the device allowed for good manoeuvrability of the working instruments under vision. This surgical space was equivalent to that offered by CO_2 insufflation in the cadavers in which the standard TOETVA was performed by the researcher. The assistant, who stood on the right of the cadavers' head, was comfortable holding the retractor-endoscope device, without encroaching on the physical space of the researcher who was performing the procedure. The modification which was performed on the device after operating on the first cadaver (See Section 4.2.1.3), allowed for easier one-hand handling of the retractor-endoscope device. The retraction of the flap was achieved effortlessly with minimal downward traction on the device (Figures 12-13)

Figure 12: Comparison between the device as used in Cadaver 1 (A) and after the modification as used in Cadaver 3 (B)

Figure 13: The device in the deployed position and retracting the superficial flap.

During the dissection, there was adequate visualisation of the structures including the strap muscles, linea alba cervicalis, thyroid and trachea (Figures 14-15). The recurrent laryngeal nerve and parathyroid tissues were identified, as detailed in Table 8.

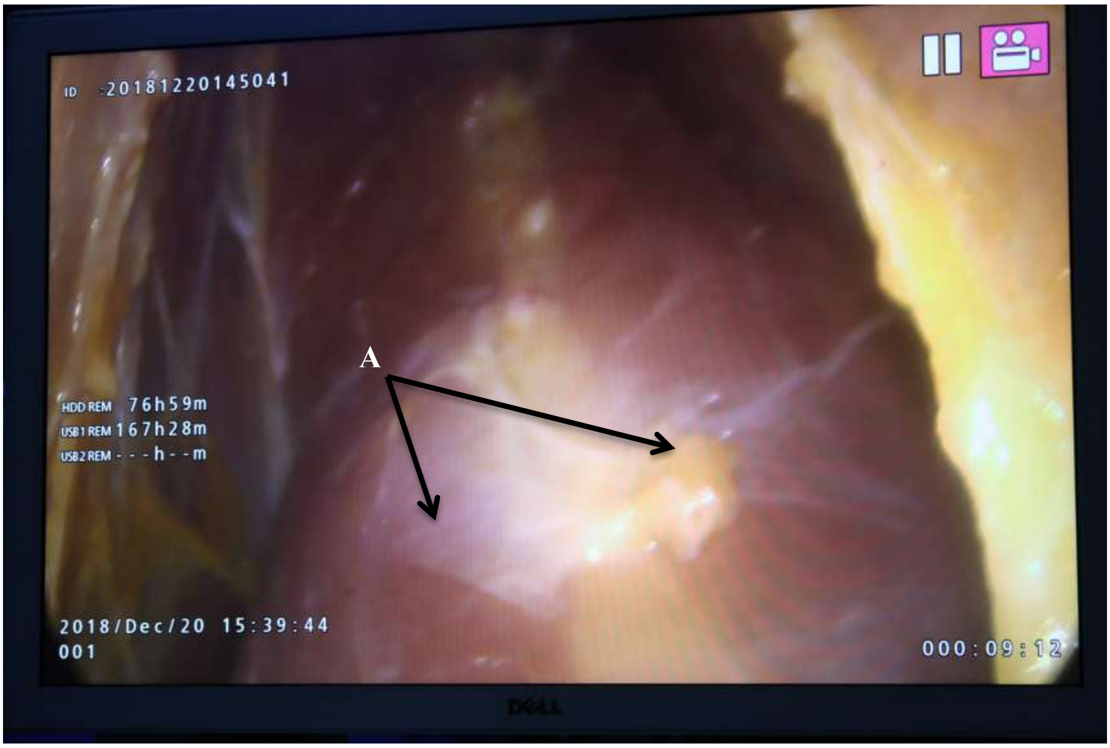


Figure 14: View in Cadaver 3 with the strap muscles (A) still closed with an intact linea alba cervicalis (B)

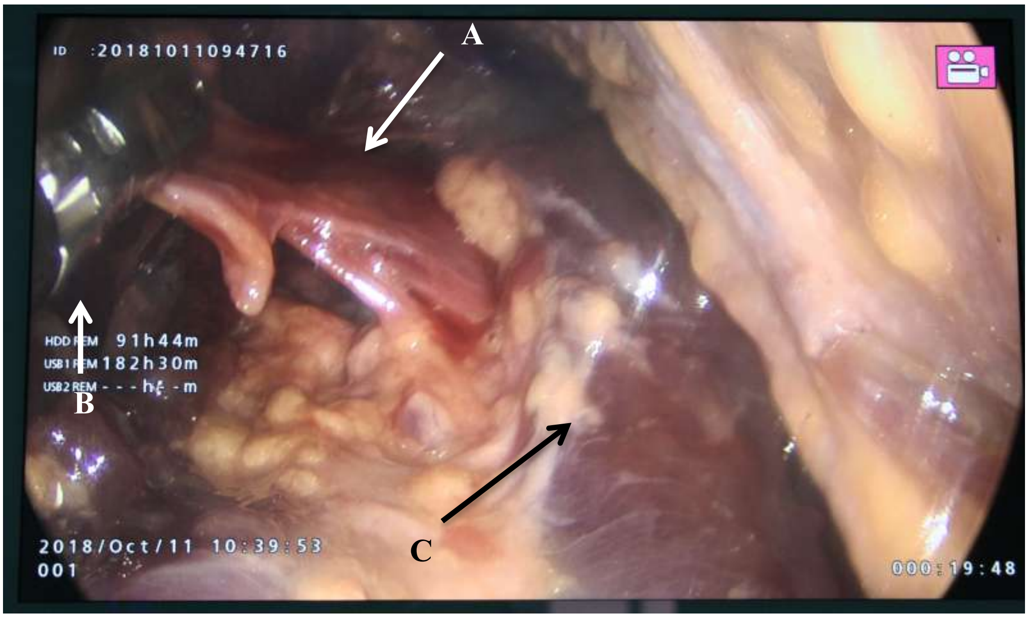


Figure 15: View in Cadaver 1 with the right thyroid lobe (A) retracted medially with a laparoscopic grasper (B). The strap muscles were opened and retracted laterally (C).

	Recurrent Laryngeal Nerves	Parathyroids
Cadaver 1	None	0
Cadaver 2	2	1
Cadaver 3	None	1

Table 8 Number of structures identified during dissection in the three Thiel embalmed cadavers used for the assessment of gasless TOETVA.

Similar to the experience in the standard technique presented in Chapter 3, the thyroid tissue was delivered by the researcher through the central wound without needing to extend the incision (Figures 16-17). All three glands were normal. When the neck was explored by the researcher through a curvilinear collar incision after the procedure, none of the cadavers had any damage to the recurrent laryngeal nerve, trachea, oesophagus, carotid arteries or jugular veins. Similar to the experience presented in Chapter 3, the researcher could not identify any parathyroid glands at open assessment of the neck.

Figure 16: Thyroid tissue in Cadaver 3 displayed on the neck of the cadaver after it was extracted from the centre of the vestibule

Figure 17: Wound after closure in Cadaver 2.

4.3.2 Objective Assessment

Among the five invited specialist, 4 thyroid surgeons accepted to be enrolled. When these thyroid specialist surgeons compared the standard technique with the gasless modification as described in Section 4.2.2, there was no significant difference between the visibility of all the structures in the two techniques. The p value achieved with the Wilcoxon signed ranks test was 1. The VAS scores from the individual specialists is shown in Table 9.

Picture	Expert 1	Expert 2	Expert 3	Expert 4
A	2	3	7	4
B	9	7	8	2
C	9	3	8	6
D	8	6	7	5
E	5	4	7	4
F	7	8	7	4

Table 9: Individual scores by the experts for the pictures supplied (see Appendix 2).

4.4 Discussion

The retractor developed and investigated by the researcher offered minimal modification to the standard technique whilst eliminating completely the need for CO_2 insufflation. The rationale used by the researcher to keep the modified technique as similar to the standard technique was two-fold. In the first instance, the researcher aimed to eliminate the complications associated with CO_2 insufflation whilst keeping the remaining outcomes identical to the standard technique. This was because there is ample published evidence to shows that the overall morbidity of the standard technique was acceptable (Camenzuli et al. 2018). Therefore, by modifying the technique as little as possible, outcomes such as mental nerve injury and flap perforation rates were not altered when compared to the standard technique. Additionally, by keeping the modified technique as close as possible to the standard technique, the learning curve needed for surgeons already practicing standard TOETVA to take up the new modification, was kept to a minimum.

Whilst the device did not offer a self-retaining option, it integrated the device with the endoscope and therefore did not change the work that was performed by the assistant in the standard technique. This was reinforced after the modification that further integrated the device and the endoscope by fixing them together and making them work as one unit. Additionally, given the angle of the shaft of the novel retractor, the hand of the assistant controlling the device-endoscope complex migrated further away from the patient's face. This gave more space for the operating surgeon to manoeuver the instruments.

The inventive steps of the device developed by the researcher offered were mainly centred around the integration of the endoscope with the retracting device whilst keeping an external diameter of 10mm. These included: the fixation of the endoscope with the device thereby integrating the two instruments into one, the angle of the shaft that offers the advantages discussed above and the rounded handle of the retractor that helps the assistant to be more comfortable when holding the device. The device developed by the researcher satisfied the inventive steps needed for patent registration (PCT/EP2021/055173) (see Appendix 3) and its development was therefore proven to be non-obvious.

The main limitation of the prototype of the device as developed by the researcher was the tip of the retractor. The tip used in the prototype was a compromise between strength and the ability to allow appropriate visualization through access from the endoscope. Whilst visibility in the three Thiel embalmed cadavers as experienced by the researcher and confirmed by the thyroid surgeons was adequate, the shape of the tip only allowed the 30-degree 5mm endoscope to be kept face down only. Any lateral visualisation had to be achieved by the researcher instructing the assistant to rotate the device-endoscope complex. These restrictions arose due to the limited technology available at a research level to build the designed tip despite the researcher collaborating with two institutions. Nevertheless, the researcher was able to use the prototype and successfully delivered a proof of concept that should be further developed as the retractor is taken forward.

The objective analysis delivered by the panel of thyroid surgeons had deemed the two procedures to offer identical visibility of anatomy in the presented steps of the operation (*p* value 1). This assessment had its limitations since it evaluated the procedures, which were dynamic processes, through stationary photographic material. Using videography was a viable alternative option to overcome this limitation. However, since the thyroid surgeons enrolled lacked experience in endoscopic thyroidectomy, the researcher opted to present standardised stages in order to orient the thyroid surgeons better. It also could not to assess the manoeuvrability of instruments in the available space afforded by the CO_2 insufflation and the retracting device respectively. Deeper analysis of the scores provided by the specialist showed that there was considerable inter-observer variability in the ability to identify structures. This could have been due to either the quality of the photos provided or due to the novelty of the cranio-caudal views to the thyroid specialists. Despite this, the four thyroid surgeons who were blinded to the technique used, were able to identify the relevant anatomy in an equivalent manner between the two groups. This objective assessment increases the rigor and validity of the findings described.

The main limitation of the Thiel embalmed cadaveric platform used by the researcher for this assessment was the lack of bleeding. It is well known that gas insufflation during laparoscopic surgery decreases bleeding by causing mainly venous tamponade (Hayden, Cowman 2011). Whilst this can sometimes mask significant bleeding, it is often used as one of the haemostatic techniques in endoscopic surgery. It has also been proposed as a haemostatic technique in abdominal bleeding after trauma (Velmahos et al. 2007, Sava et al. 2003). In the context of TOETVA, bleeding from small veins might be controlled by insufflation. The proposed gasless technique eliminated this haemostatic effect. The Thiel embalmed model used by the researcher precluded the investigation of this aspect. Alternative published techniques to gasless TOETVA that were investigated on live patients did not find bleeding to be a prohibitive issue (Nakajo et al. 2013, Yang et al. 2020, Park, Wang et al. 2019). Nevertheless, all of these studies used different approaches and were themselves limited in number. The issue of bleeding in gasless TOETVA needs to be further evaluated. Larger studies with different operating surgeons using cadavers are needed. Eventually, further clinical trials would be needed using the novel medical device, in order to be able to use this on live patients.

Chapter 5:

Investigation of Intra-Jugular Venous Pressure

5.1 Introduction

In the standard TOETVA technique, CO_2 is insufflated in the subplatysmal space to keep it open and allow good exposure of the anatomy as well as providing enough space to manoeuvre the instruments. Following a literature review done by the researcher, a link was identified between sudden increase of pressure on the neck and increase in intraocular pressures. The sudden compression of the neck in dogs, which is generated by the pulling against the collar, has been shown to increase the intra-ocular pressure (Rajaei et al. 2018, Pauli et al. 2006). In the dog model, when both the internal jugular veins are compressed through external pressure on the neck and the intraocular pressures are then measured, there is a significant increase (of 3mmHg) from baseline readings (Klein et al. 2011). In humans such a link has also been established in the context of tight neck ties (Teng et al. 2003, Bozić et al. 2012).

The clinical relevance of a significant increase in the intraocular pressure lies in its association with glaucoma since small changes may have a damaging effect on vision in this condition (McMonnies 2015). Glaucoma is a heterogenous group of serious medical conditions in which there is a high intraocular pressure that might result in optic nerve neuropathy (Jonas, Aung et al. 2017). This makes glaucoma the main cause of irreversible blindness worldwide (Mincione et al. 2021). This disease is common across populations, with the prevalence of 5.9 cases per 1,000 in the United States of America, whilst in Norway it is higher with 14.3 cases per 1,000 population (Clark et al. 2019, Slettedal et al. 2020). In Malta the current prevalence of glaucoma is not known. Although it is thought that around 60 million individuals suffer from glaucoma internationally and that the older population are more effected by this disease (1-2% >40 years and 10% >70 years), over half of these are undiagnosed in the developed world (Mohammadi et al. 2014). It is therefore pragmatic to consider every patient to be at risk of glaucoma.

To date, there is lack of understanding of the effect of CO_2 insufflation in the neck during TOETVA on the intraocular pressures. The researcher carried out a systematic review using a combination of the following keywords: carbon dioxide, insufflation, endoscopic thyroidectomy, intraocular pressure (Camenzuli et al. 2021). This systematic review was run through 5 databases including PubMed, Medline, BioMed Central, OVID, and Web of Science. This search was not limited by either language or date of publication. The latter search resulted in 195 papers and after back chaining a further manual search in Google Scholar a further 5 papers were inserted. After reviewing these papers, those which did not include the topic of the association between CO_2 insufflation in the neck and raised intraocular pressure were excluded. After these exclusions, only 2 papers remained (Appendix 10) (Kim et al. 2013, Gao et al. 2012). Both studies compared the intraocular pressure changes between a conventional open thyroidectomy group and an endoscopic thyroidectomy group. A slight decrease in the intraocular pressure has been recorded in the initial phase of both groups. Whilst this low intraocular pressure was maintained in the conventional thyroidectomy group, the endoscopic groups experienced a sustained significant increase in intraocular pressure (p values <0.001 and <0.05 respectively). These constantly elevated intraocular pressures only resolved when the neck was decompressed from the insufflation.

The association between sudden increase in pressure on the internal jugular veins and the rise of the intraocular pressure is not well understood. A possible hypothesis is that by increasing the pressure on the internal jugular vein rapidly, the blood flow through the vein is reduced leading to a build-up of pressure in the venous system of the head and neck. This in turn limits the venous drainage from the episcleral venous system of the eyes leading to an increase in pressure in this system as well. The latter is thought to be the underlying pathophysiological process responsible for the raised intra-ocular pressure (Teng et al. 2003).

At this stage, the researcher focused on investigating whether there was any pressure increase within the internal jugular veins during TOETVA. The aim of this set of experiments was to assess whether the pressure on the internal jugular veins could be reduced by applying the gasless modification to the standard technique, as outlined in Chapter 4.

5.2 Materials and Methods

To be able to investigate whether there was any pressure increase within the internal jugular veins during TOETVA, a novel experimental setup was designed by the researcher. Three Thiel embalmed cadavers were used for this experiment. Any cadavers with a history of intervention or radiotherapy to the upper body (included thorax, head, neck and upper limbs), a history of central lines in the neck and those who were not intact bodies, were excluded.

The first step that the researcher did was to device a system that attempted to reproduce the normal circulation to the upper body of the living patient in the Thiel embalmed cadavers. This was done in order to offer a closer resemblance to the normal physiological state in the Thiel embalmed cadavers during the ensuing experiments. To achieve this, the researcher first dissected the cadavers using a clamshell incision just below the nipple level. In order to gain access to the big vessels of the thorax. In cases when this did not give enough exposure, a mini-sternotomy was carried out by the researcher whilst making sure not to disturb the base of the neck. When exposure was achieved, the next step performed by the researcher was to open the pericardium and isolate the superior vena cava and the ascending aorta. Subsequently, the researcher rotated the left of the cadavers, identified the descending aorta and clamped it in order to isolate the upper body. The superior vena cava was first dissected clean by the researcher and then attached to a wide bore tubing with the use of a Silk 0 purse-string suture. The researcher initially flushed out the venous system with 3 litres of blue stained saline. In order to allow the venous system to remain patent at low pressure, the blue stained fluid was left dripping at a rate of 1 litre per hour under gravity.

The next step performed by the researcher was to dissect the ascending aorta and then this was attached to wide bore tubing in a similar fashion to the superior vena cava. Subsequently, the researcher flushed the arterial system with 3 litres of red stained fluid. In order to attempt to recreate the arterial physiology the researcher attached the tubing attached to the ascending aorta to a commercially available peristaltic pump system (INTLLAB™, Kuala Lumpar, Malaysia). This arrangement allowed the isolated upper body arterial system to be pumped with red-coloured fluid at a maximum flow rate of 100ml/min. This system reached a maximum pressure of 2.5 PSI (equivalent to 129mmHg) (See Figures 18 and 19).

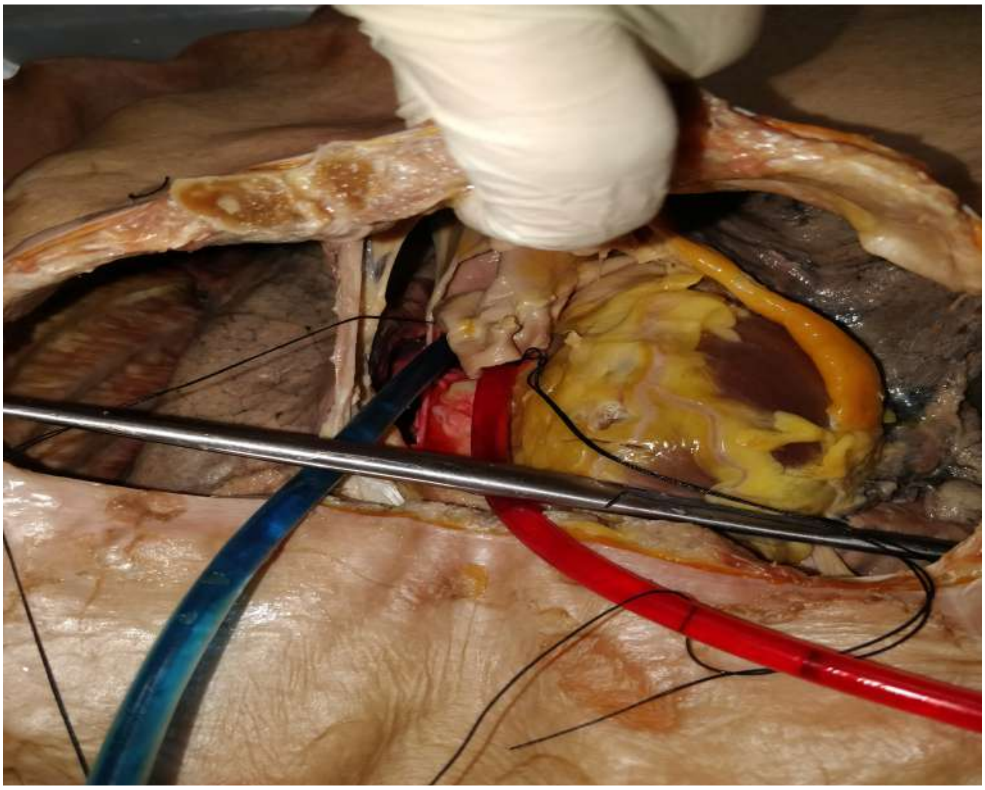


Figure 18: Photo showing the wide bore tubing inserted and fixed in the superior vena cava (blue) and ascending aorta (red) in Cadaver 2. A clamp was placed on the descending aorta.

Figure 19: The neo-circulation setup in Cadaver 3. The arterial system was kept pressurised and pulsatile with a peristaltic pump seen in more in detail in B, whilst the venous system was kept patent at low pressure with fluid draining under gravity (black arrow in A)

After the segmental neo-circulation was established by the researcher as discussed above, the next step was to insert a cannula in the internal jugular vein. The right side of the neck was always used. In order to introduce the cannula, the researcher first positioned the head of the cadaver by slightly turning it towards the left side. The probe (with the needle) was then inserted at the apex of the anterior triangle of the neck lateral to the pulsations of the carotid and at an angle of 30 to 40 degrees to the skin. The probe was then inserted until a backflow of the blue coloured fluid was visible. The backflow confirmed the position of the probe in the right internal jugular vein. When this backflow was not forthcoming, or red colour fluid was withdrawn, the cannula was removed and another attempt was undertaken by researcher until the right position was found. The cannula was then flushed to eliminate any air bubbles (Figure 20).

After discussion with colleagues from the Centre of Biomedical Cybernetics at the Faculty of Engineering department of the University of Malta, the researcher decided to utilise a system offered by BIOPAC® Systems Inc., Goleta, U.S.A. to allow the recording of minute changes in pressures. The margin of error for the system at room temperature was up to 1 mmHG. The researcher first connected the cannula to a transducer which was also flushed to make sure no air bubbles were trapped within its tubing. The function of the latter equipment was to translate the pressure in the fluid into an electrical impulse. The transducer was subsequently attached to the receiver end of the recording system (TSD104A, BIOPAC® Systems Inc., Goleta, U.S.A.). At this point the researcher zeroed the recording system since the aim of this investigation was to assess any change in pressure rather than the actual pressures inside the internal jugular vein (Figure 21 a-c).

Figure 20: Pressure probe in-situ (black arrow) and attached to the pressure transducer (red arrow) in Cadaver 1.

Figure 21a: The transducer for the pressure recording system used for these experiments.

Figure 21b: The receiving unit for the pressure recording system used for these experiments.

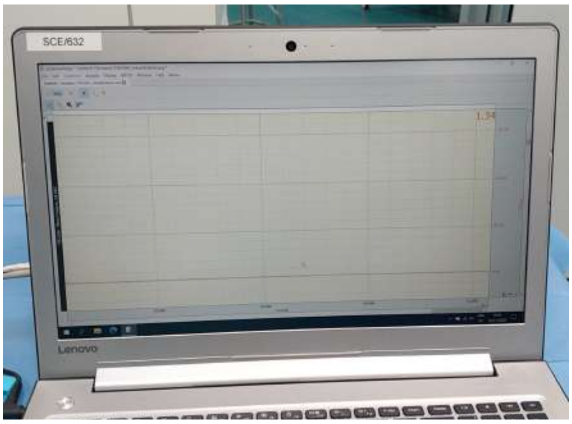


Figure 21c: BSL4 being used for the pressure recording system used for these experiments.

When the whole experimental setup was assembled, the researcher then started the TOETVA procedure using the technique as described in Chapter 3 and 4. To enable the researcher to compare changes in pressure, three standard stages of the operation were chosen during which the readings were taken in each cadaver. These stages are illustrated in Figure 22.

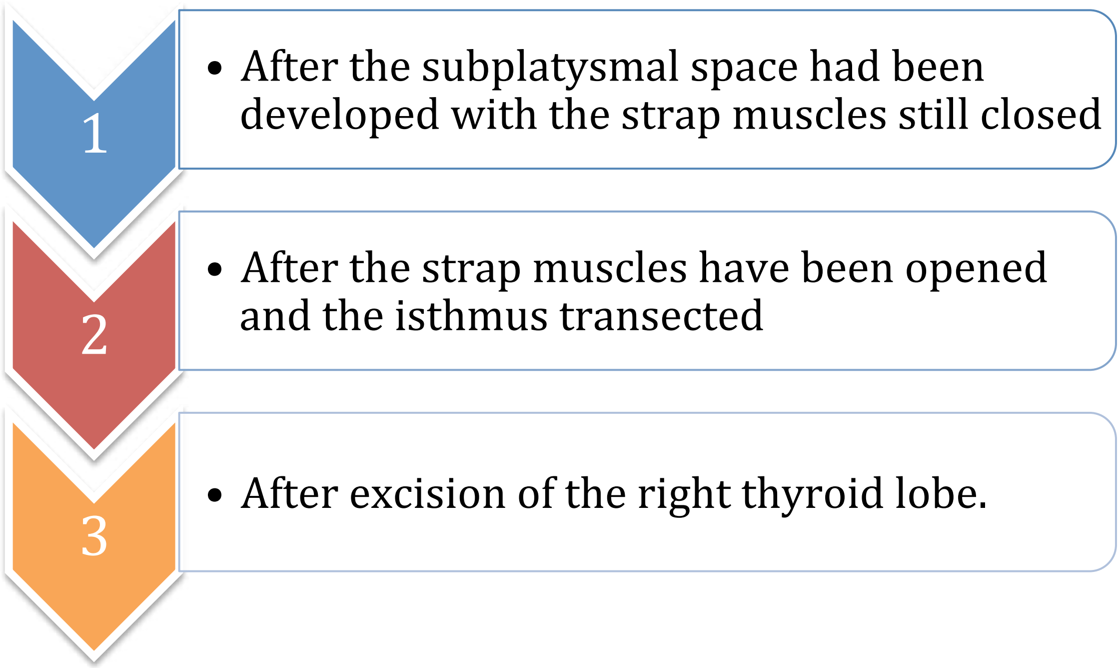


Figure 22: The three operative stages during which the pressure readings were taken.

When the researcher reached each stage of the operation, the procedure was paused, the probe was checked to confirm it was still in place and the system was zeroed. For each run of readings, readings were taken for 4 minutes with an insufflation pressure of 15mmHg, then with a pressure of 6mmHg and then without insufflation and with the retractor *in situ*. Whilst the researcher was making sure that the endoscopic system was delivering the required insufflation and that the retracting device was positioned correctly during the recording, an engineer from the Centre of Biomedical Cybernetics at the Faculty of Engineering, University of Malta was operating the Biopac Student Lab software (BSL 4) (BIOPAC® Systems Inc., California, USA) which was attached to the system. The software interpreted the electric impulse recieved by the recieving unit and translated it into a reading. The recording device was able to give a reading every 0.004 seconds and gave a pressure reading up to the 14th decimal number.

The collected data were then cleaned and analaysed by the reaseracher. A paired t-test was chosen by the researcher to evaluate whether the pressure changes within the internal jugular veins were significantly different when usiing CO_2 insufflation when compared to the gasless technique. In order to assess whether any observed changes were comparable between the three cadavers utilised during this investigation, the researcher chose to perform a multivariate analysis. The variables taken for this analysis where the three individual cadavers at the three stages being investigated and using the three different set of readings (i.e. using 15mmHg CO_2 insufflation, using 6mmHg CO_2 insufflation and using the gasless modification).

5.3 Results

The recorded data are presented in Tables 11-13 as the recorded mean pressure and the 95% Confidence intervals. This is followed by a graphical representation of the raw data in Figures 22-24.

	0mmHg		6mmHg		15mmHg	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Cadaver 1	0.386	0.395, 0.378	2.387	2.391,2.383	9.486	9.497,9.475
Cadaver 2	-0.043	0.011,-0.054	2.839	3.115,2.563	10.902	11.916,10609
Cadaver 3	-0.385	-0.348,-0.423	5.764	6.075,5.452	8.270	8.637,7.903

Table 10 Mean pressure difference from baseline in mmHg at different pressures, taken at the phase of the procedure when the subplatysmal plane had been already developed but the strap muscles were still closed.

	0mmHg		6mmHg		15mmHg	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Cadaver 1	2.013	2.015,2.010	4.887	4.895,4.879	9.493	9.503,9.489
Cadaver 2	5.891	5.934,5.848	8.920	9.037,8.802	10.689	10.831,10.546
Cadaver 3	0.731	0.765, 0.697	3.061	3.100, 3.022	6.841	6.954, 6.728

Table 11 Mean pressure difference from baseline in mmHg at different pressures, taken at the phase of the procedure when the strap muscles were opened and the thyroid isthmus transected.

	0mmHg		6mmHg		15mmHg	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Cadaver 1	1.316	1.318,1.314	5.778	5.795, 5.760	6.85	6.856,6.844
Cadaver 2	-0.06	-0.017, -0.099	4.065	4.167,3.962	9.909	10.185,9.633
Cadaver 3	**-**1.318	-1.261, -1.374	4.87	4.900, 4.841	11.673	11.954, 11.392

Table 12 Mean pressure difference from baseline in mmHg at different pressures, taken after the thyroid lobe was excised.

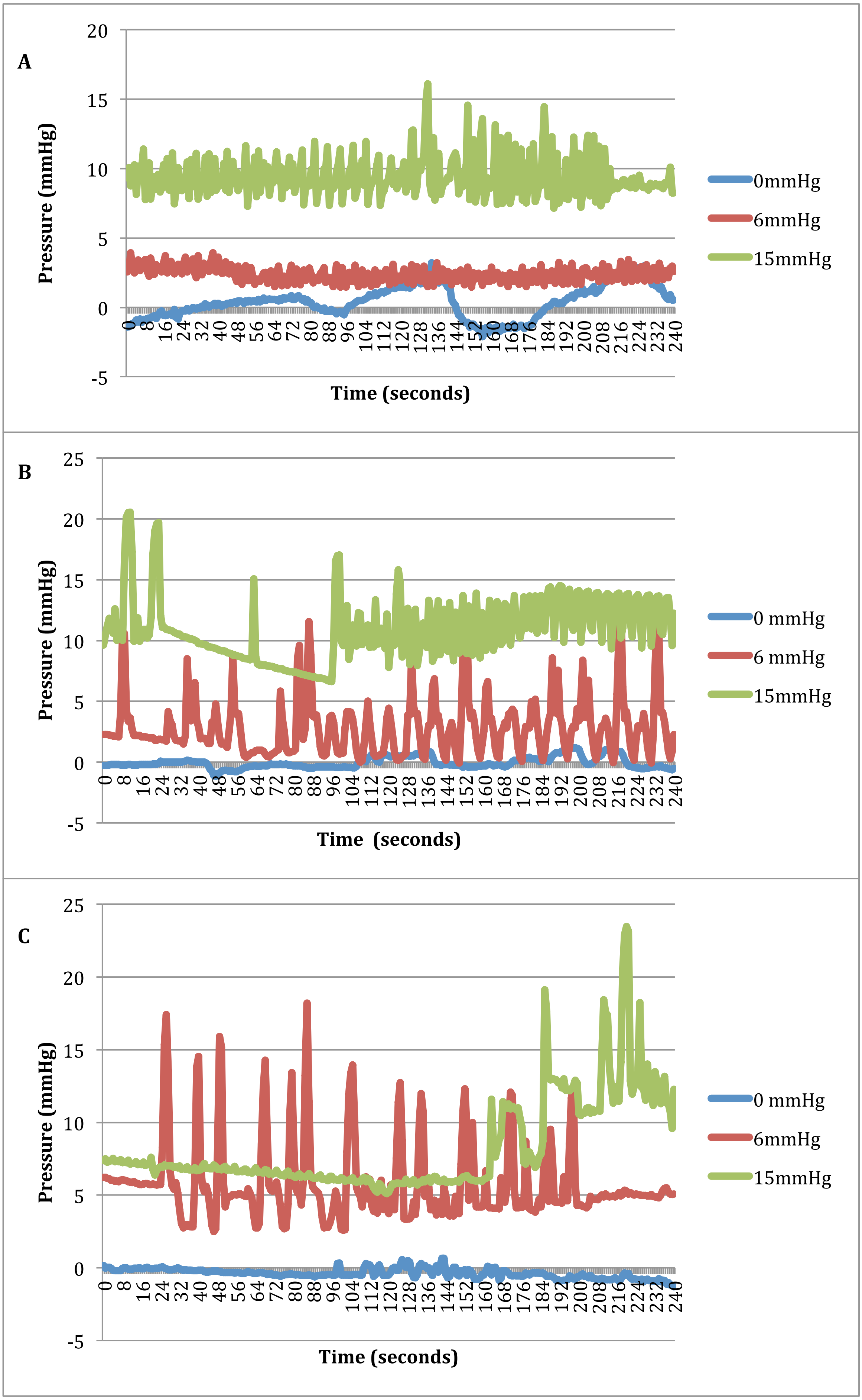


Figure 23: Graphical representation of the readings taken at the three different pressures when the subplatysmal space was developed but the strap muscles were still closed in Cadaver 1 (A), Cadaver 2 (B) and Cadaver 3 (C).

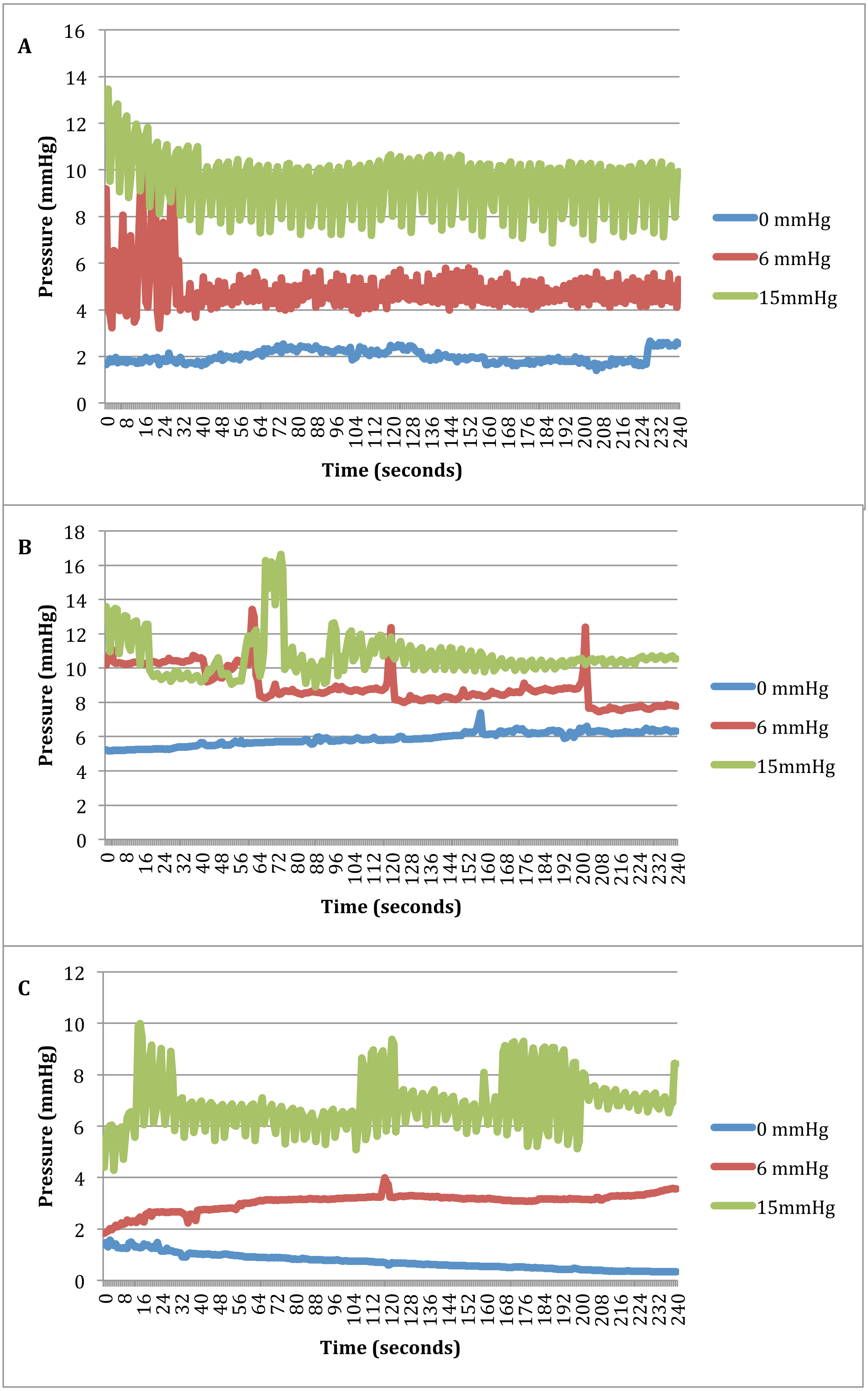


Figure 24: Graphical representation of the readings taken at the three different pressures after the lineal aba cervicalis was opened and the isthmus was dissected off the trachea centrally and transected in Cadaver 1 (A), Cadaver 2 (B) and Cadaver 3 (C).

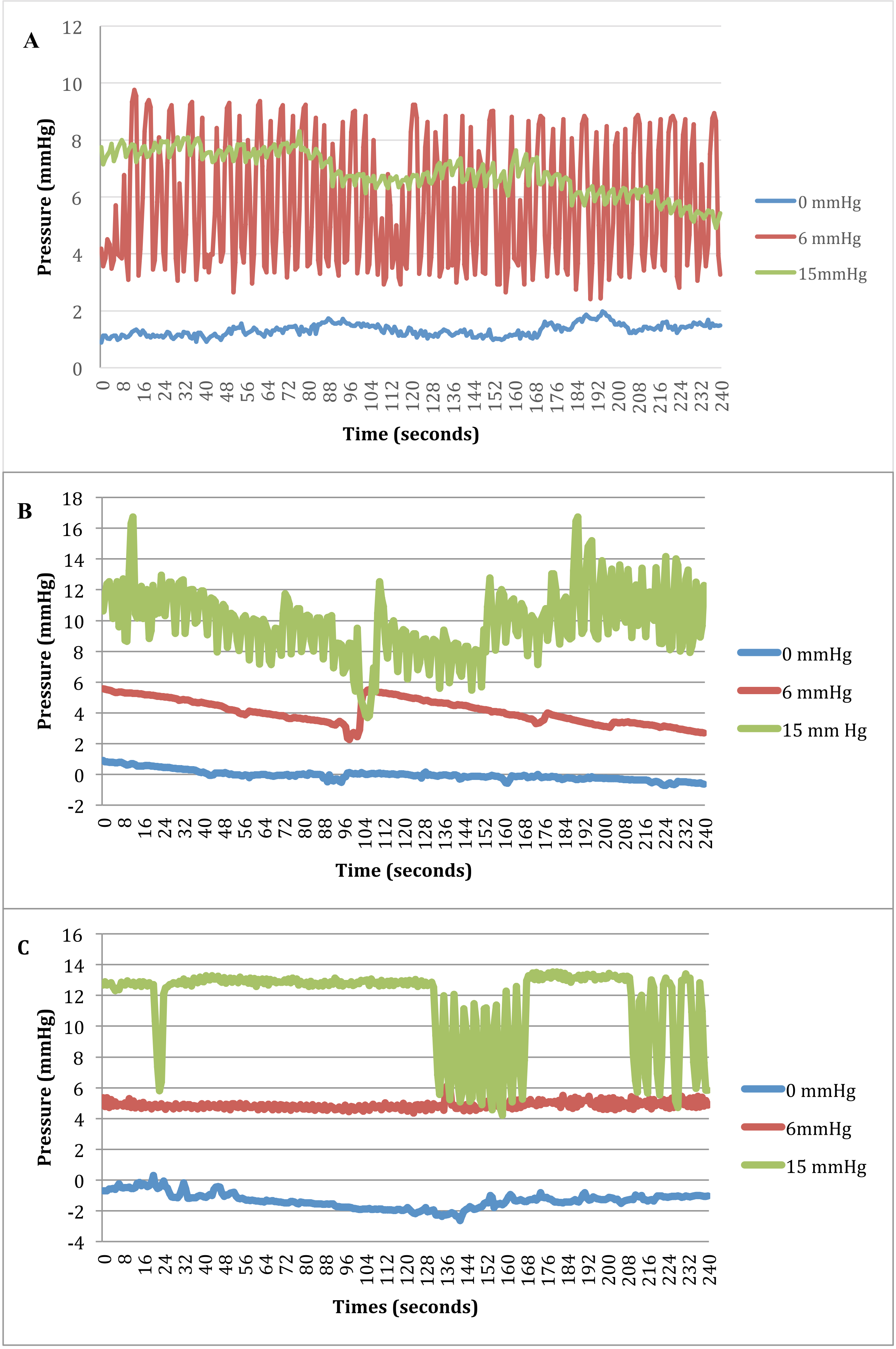


Figure 25: Graphical representation of the readings taken at the three different pressures after the thyroid lobe was excised in Cadaver 1 (A), Cadaver 2 (B) and Cadaver 3 (C)

Statistical analysis using paired t-test comparing the intra-jugular pressures recorded during the gasless intervals and the ones recorded during the CO_2 insufflation periods showed a significant difference (p value <0.0001). This significant difference was presents in every cadaver and in all the three recoded stages. Further analysis using paired t-test comparing intra-jugular pressures recorded during the period using 6mmHg CO_2 insufflation with the period using 15mmHg CO_2 insufflation also revealed significantly higher intra-jugular pressure when using 15mmHg CO_2 insufflation (p value <0.0001). Similar to the previous comparison, this significant difference was present in all cadavers and at all the recorded stages. The multivariate analysis that was carried out as described in Section 5.2 showed that the extent of change in pressures within the internal jugular veins was significantly different between the three investigated cadavers (p value <0.0001). Details of the latter analysis are presented in Table 13.

	Sample size	**Co-efficient**	**95% Confidence Intervals**	**Standard Error**	**R^2**
Device	903	0.000019	-0.0002758, 0.0003138	0.0001502	0.99340
6mmHg	903	-0.002507	-0.0036344, -0.0013809	0.0005741	0.92950
15mmHg	903	-0.004230	-0.0060666, -0.0023925	0.0009360	0.67820

Table 13 Details of the multivariate analysis carried out at the different insufflation pressures.

5.4 Discussion

This research was the first to show significant changes in the intra-jugular venous pressures in the context of CO_2 insufflation during a perfused cadaveric simulation of TOETVA. The complications associated with CO_2 insufflation in the neck as used during TOETVA have been described by a number of groups and are discussed in Chapter 1. However, the association between insufflation in the neck and changes in the intraocular pressures has not been adequately investigated. Whilst minimal changes in the intraocular pressures in the general population might be well tolerated and inconsequential, these changes in patients who are either suffering from or are susceptible to developing glaucoma, might have more serious consequences leading to loss of vision. In the latter group of patients, the optic disc is more susceptible to smaller changes in the intraocular pressure particularly when the changes happen over a short span of time (McMonnies 2015).

The pathophysiological process that underlies this link is hypothesised to be due to the direct pressure on the internal jugular veins that limit venous outflow from the head and neck. The latter leads to decreased venous outflow from the eyes as well. Another process that contributes to the raised intraocular pressure when CO_2 insufflation is used is the raise in the intravascular partial pressure of CO_2 (pCO_2). This is postulated to be due to choroidal vasodilatation. Despite having a contributing factor, this mechanism seems to be a secondary cause since it has been shown that when pCO_2 is kept constant during TOETVA, the intraocular pressure still increases (Kim et al. 2013)

Given that the main hypothesised mechanism causing the increase in the intraocular pressures in TOETVA is compression of the internal jugular veins which in turn causes an increase in pressure within these structures, a system that causes less compression should be perused. This is needed in order to decrease the possible damage inflicted to the optic nerve. The analysis carried out by the researcher in the experimental model using Thiel embalmed cadavers as described in Section 5.2 has shown that by eliminating CO_2 in TOETVA and replacing it with the gasless modification as discussed in Chapter 4, the pressure increases within the internal jugular veins in significantly decreased. The latter was evident even at the low insufflation pressure of 6mmHg. The inference from this finding is that by using the gasless adaptation developed by the researcher, patients who are at risk of optic nerve injury due to raised intraocular pressure are protected. Therefore, apart from the advantage of avoiding a visible scar and the risk of CO_2 embolism, this is an added advantage for the gasless technique as developed by the researcher.

Analysis of the raw data as presented graphically in Figures 22 to 24 shows that during the recorded period the variations in the recorded pressures are considerable. These are particularly marked in the periods during which CO_2 insufflation was being used. The researcher speculates that the main reason for these rapid fluctuations is the way the gas insufflator works in order to try to achieve the set insufflation pressure. This was achieved by pushing in CO_2 in a pulsatile manner. Consequently it often overshot and undershot its set maximum pressure. This means that although the maximum set pressure on the insufflator is set to 6mmHg by most groups performing TOETVA (Camenzuli, Schembri Wismayer et al. 2018), at any point the actual CO_2 pressure in the neck could have been higher. In the light of the researcher's finding that higher insufflation pressures cause significantly higher pressures within the internal jugular veins, the morbidity particularly for patient suffering from glaucoma (diagnosed or otherwise) offered by insufflation cannot be eliminated even if lower pressures are used. Additionally, as discussed above, small rapid changes in intraocular pressure are in themselves detrimental.

Whilst the changes in the internal jugular venous pressures were significant in all three cadavers and in all three stages recorded, the extent to which these changes occurred varied significantly between the three cadavers. Therefore, although the pattern linking CO_2 insufflation with significantly higher intra-jugular pressures was to be expected in every individual, the extent to which this happened was not predictable. The variation in the extent of change in pressure was postulated by the researcher to be due to differences in the anatomical makeup of the particular individual, which protects the internal jugular veins to a greater or lesser extent. The analysis did not monitor the anatomical dimension of the cadevers used in this analysis. The researcher proposes that, should this experimental evaluation be carried in a larger number of cadavers, neck circumference should be one of the recorded variables. This would enable future researcher to evaluate the extent to which the anatomical properties of the neck of the individual influence the extent of pressure change in the internal jugular vein during TOETVA.

Chapter 6:

Discussion

6.1 Introduction

The technique of scarless TOETVA with CO_2 insufflation using Thiel embalmed cadavers has been succesfully carried out by the researcher. A novel retraction device has been developed by the researcher, thus achieving the aim to eliminate CO_2 insufflation. The researcher compared the original TOETVA using CO_2 insufflation with the gasless technique in embalmed cadavers, with very promising results. The relative contraindications for gas insufflation in the neck were explored and the researcher showed that the gasless adaptation may improve the risk of raised intraocular pressure.

Therefore, gasless TOETVA using the novel retractor invented by the researcher has been successfully carried out on Thiel embalmed cadavers, with improved outcomes over the currently practised TOETVA procedure. TOETVA offers a visibly scarless surgical option whilst retaining the improved morbidity of minimally invasive surgery. This approach has been shown to be a safe and feasible option for thyroidectomy with similar (if not improved) morbidity when compared to the conventional open technique (Russell et al. 2019). TOETVA offers significantly improved cosmetic outcomes (Chen et al. 2020). The improved cosmetic outcome in TOETVA has been independently proven with the use of eye tracking devices from casual observers. After conventional thyroidectomy, the observers tend to focus on the neck rather than on the face of the individual. This visual distraction was totally eliminated in those patients who underwent TOETVA. In fact the observer gaze in the latter group was equivalent to the controls (Liao et al. 2020, Juarez et al. 2019). The combination of improved cosmetic outcome and comparable morbidity to the conventional open thyroidectomy were the main reasons why the researcher has focused on TOETVA.

The researcher directed all of the investigations in order to improve the safety profile of TOETVA itself whilst at the same time offering an alternative training platform for surgeons who are novices in the approach.

6.2 Thiel embalmed cadavers

The researcher's experience using Thiel embalmed cadavers was encouraging. There is a paucity of published data on whether Thiel embalmed cadavers are useful specifically in the setting of thyroid surgery. Indeed, the researcher was the first to publish a scientific paper on the use of Thiel embalmed cadavers as a platform for training in TOETVA (Camenzuli et al. 2019). Whilst the researcher could complete the trans-oral thyroidectomy in all of the dissected cadavers, the identification of the recurrent laryngeal nerves and the parathyroid glands were important limitations.

Whilst the researcher acknowledges that not all of the parathyroid glands were not identified during the endoscopic dissection (7 out of 24 glands identified), since these glands could also not be identified in the subsequent open assessment of the cadavers, it was difficult to ascertain whether these glands were actually injured during the procedure. Eisma et al. 2011, assessed the use of Thiel embalmed cadavers in open thyroid surgery. Whilst this group claim better identification of the parathyroid glands in Thiel embalmed cadavers than in formalin embalmed ones, they fail to report how many parathyroids could be identified in each neck. The lack of identification of the parathyroid glands in general when using Thiel embalmed cadavers could be due to a number of reasons. The loss of anatomical landmarks after excision of the thyroid lobe, lack of bruising, the limitations of the embalming process and the possibility of inadvertent excision are all possible causes.

The difficulty that the researcher reported in the identification of the recurrent laryngeal nerve could not be attributed to the limitations offered by Thiel embalming, since all of the nerves were identified at the open post-procedural assessment by the same researcher. No published data evaluating the recurrent laryngeal nerves in the Thiel embalmed platform is available for comparison. The published experience as described in Section 1.6.2 shows that in the hands of surgeons performing TOETVA in the living patient the recurrent laryngeal nerve is visualised without major problems.

The experience the researcher developed during the evaluation of the Thiel embalmed cadavers for use in TOETVA had an important role on how the next steps of the research carried out. Important issues were identified and addressed, which are all pivitol in understanding the real-world data, that could have not been appreciated from the literature and that were crucial in the development of the gasless technique. These included the spatial orientation, the understanding of the limitations of access allowed by the vestibular space, the limited space for the surgeon and the assistant and its dynamics at the head of the cadaver/patient and the appreciation of how thin the superficial layers of the neck.

6.3 Development of the gasless technique

The initial experiments (Chapter 3) had shown the platform using Thiel embalmed cadavers to be suitable for use in order to assess any potential changes in TOETVA. In order to eliminate to potential fatality associated with CO_2 embolisation, the researcher developed a retracting device to eliminate the use of CO_2 insufflation.

6.3.1 Developing the retractor

The researchers had set a list of criteria that the retracting system needed to have in order for it to offer an acceptable modification of TOETVA. The most critical of these was that apart from strictly adhering to the principle of scarless surgery, the retractor had to have a limit of 10mm in its outer diameter and that the maximum number of ports in the vestibule were to remain three. These were set by the researcher in order to keep to a minimum any changes that the new gasless technique offers when compared to the standard TOETVA. This meant that the safety profile of TOETVA is maintained and that the practicing surgeons do not have to undergo another learning curve to adapt to the new modification. Having a new learning curve is not desirable since it might lead to reluctance by the surgical community to take up the modification (Healey, Samanta 2008).

The initial exploration involved the evaluation of retractors which were already available on the market (See Section 4.2.1.1). The retractors evaluated by the researcher could not fit the required properties that were set up by the researcher, particularly with regards to the size of the central incision and the need for an additional access port on the vestibule. Avoiding any delay in converting to open surgery should this be required urgently, was another major limitation of some of the commercially available options evaluated by the researcher, since all the equipment needs to be dismantled before being able to access the front of the neck.

The researcher evaluated the use of titanium retractors, but this was excluded due to the substantially bigger vestibular incisions needed for this retractor to be positioned. This technique was later used by a number of groups (Park et al. 2019, Yang et al. 2020 and Richmon 2020). The vestibular incisions used by these groups ranged from of 30mm to 50mm, which are at least three times bigger than the acceptable target set by the researcher. Whilst these groups have reported overall positive results, Park et al. 2019 made the observation that to be able to introduce the relatively large retractor, the mentalis muscles had to be severed extensively. The authors do not comment on the long term repercussions resulting from the increased trauma to the mentalis and to the vestibular area, but the main concern is the loss of function of the mental nerve which anatomically is very closely related. The change of sensation and sometimes pain that mental nerve injury causes may also interfere with everyday activities (e.g., speaking, shaving, drinking) which can in turn, effect the quality of life of the patient (Andrabi et al. 2014). Whilst this option is therefore viable in terms of the operating space it affords, the increased morbidity it may incur on the patient was deemed still not acceptable by the researcher. Similarly, the gasless option offered by Nakajo et al 2013 which involves anchoring the skin of the neck with Kirschner wires and physically retracting them on a self-retaining stand was not deemed acceptable by the researcher since it went against the principle of scarless surgery.

The development of a novel surgical device involves a number of steps in order to build from a concept to a prototype and then eventually reach clinical practice. The researchers' initial concept of the new device was developed through theoretical work after extensive literature evaluation of the current practices and helped by the experience gained by the researcher whilst operating on the Thiel embalmed cadavers. The prototype was constantly modified and improved by the researcher throughout its development. This was particularly the case when considering the tip of the device which was particularly challenging to design. This was because it needed to be thick enough to withstand the pressures of retraction, while thin enough to allow as much space as possible for the endoscope to offer maximum visualisation.

Whilst Thiel embalmed cadavers have been used extensively for teaching and training purposes, these cadavers have also been also utilised to evaluate new devices in a platform that maintains tissue properties very similar to the *in vivo* situation. This platform has been utilised for testing novel surgical devices by a number of other groups and has been shown to give important feedback to the researchers that helped to modify the device in order to optimise such devices before reaching the patient (van den Haak et al. 2017, Saragas et al. 2021). The trial that the researcher made in the setting of the Thiel embalmed cadavers had also revealed that the device–endoscope complex could not be handled as one device by the assistant. This feedback that the researcher gathered led to further adaptation of the device by the addition of an adjunct that fixed the endoscope in place once the optimum position was found.

The device developed by the researcher has undergone the process of design registration with the European Union Intellectual Property Office (Registration Number: 007793666-0001) (See Appendix 3). It has also been submitted for patent registration in which it has progressed through the hurdle of proof required to confirm the inventive step. Both these processes are important for the next steps of development of the device, which would be at an industry level. When the device is produced at this level, it would be completely sterilisable and therefore able to be used on live patients. The researcher aims to do this in collaboration with experts in the field. This device was developed at the appropriate time in the history of development of TOETVA. The gasless approach to TOETVA has been an area of interest in recent years as evidenced by the increasing number of published alternatives to the device that the researcher developed (See Table 3). The latter proposed techniques all have major concerns that went against the criteria set by the researcher as discussed above. The very minor changes to the surgical approach this novel device offers when compared to the alternative techniques presented in the literature (Nakajo et al. 2013, Park et al. 2019, Park, Wang et al. 2019, Yang et al. 2020, Richmon 2020) should lead to a minimal learning curve. This therefore entices the surgeons who have already learnt the technique, to adopt this modification and improve the safety profile they offer to the patients.

6.3.2 Gasless TOETVA in Thiel embalmed cadavers

The researcher performed the gasless TOETVA in three Thiel embalmed cadavers as described in Chapter 4. The main difference in the new technique was the exclusion of CO_2 insufflation and the use of the novel device instead. The device allowed appropriate visualisation of the anatomy and the operative experience was similar to the standard technique for the researcher. Since the endoscope was fixed with the retracting device after the addition of the silicone adjunct as discussed in Section 4.2.1, when the researcher wanted to look more closely at a particular structure, the endoscope could not be moved without moving the whole device-endoscope complex. Whilst this meant that retraction varied during the procedure this was not felt to be a limitation since retraction was always delivered at the area of concern during that particular period of the procedure.

Whilst this was a positive outcome, the evidence presented was all subjective to the experience of the researcher and therefore a more objective assessment was also carried out amongst four thyroid surgeons. The limitation of assessing a dynamic process through a stationary image is recognised by the researcher.

However this was the only option available in order to completely blind the participants as to what group the images being seen were coming from. This is because during the procedure, the retractor would be visible in a number of instances and this would therefore be evident with the use of video. The latter analysis showed that the thyroid surgeons consulted could identify the anatomical landmarks equally well in those pictures taken during the gasless technique and in those derived from the standard TOETVA. This meant that the device successfully replaced the function of insufflation whilst not significantly altering the standard technique. This minimises the learning curve and therefore maximises the chances of clinical uptake by practicing surgeons (Hasan et al. 2000).

For the gasless modification as developed by the researcher to offer a viable alternative procedure, it has to be applicable in all of the aforementioned indications. The evaluation carried out in the Thiel embalmed cadavers was on normal thyroid glands. However, the space that had to be developed by the researcher for the gasless technique was identical to that developed in the standard TOETVA. This infers that if dissection of a thyroid nodule up to 60mm in benign cases and up to 30mm in malignant cases was possible with gas insufflation, it should be equally possible with the novel technique as well. The difficulty with extraction of the specimen through the vestibule remains there even when implementing the novel technique. The increase in size limit for the removal of thyroid nodules has been overcome by some groups by breaking up the specimen in the retrieval bag (Park, Sun 2017). This procedure, which is still controversial for indeterminate and malignant nodules (Benhidjeb et al. 2017), is possible in the gasless modification.

When the standard TOETVA is performed in patients with autoimmune thyroiditis, there is no reported increased morbidity when compared to the conventional open surgery (Jitpratoom et al. 2016). For the gasless modification, this has to be further evaluated since, as discussed in section 4.4. The loss of insufflation results in the loss of the tamponade. This merits to be further investigated, especially when there have been further advances using the neo-circulation that the researcher has developed (as described in section 5.2).

6.3.3 Robotic adaptation

The introduction of robotic equipment in various specialties has increased extensively in the last decade (Martin 2020). This has been the case in minimally invasive thyroidectomy approaches. The transaxillary approach has almost completely transitioned to the robotic technique (Yu et al. 2021) whilst other extra-cervical approaches have been assessed for robotic use (Chen, Chen 2021, Kandil et al. 2020).

The trans-oral approach has also been adapted for robotic use. This robotic approach was found to offer better outcomes than other robotic approaches to the thyroid gland (Yang et al. 2020). CO_2 insufflation is used in the robotic trans-oral approach similar to standard TOETVA and therefore carries the same risks of complications from it. The retractor developed by the researcher has been targeted for the endoscopic technique, but it could be modified to accommodate the robotic arms and eliminates the need for the assistant used in the endoscopic approach. This modification would entail an important investment and therefore its feasibility needs to be assessed further. The robotic trans-oral approach, although enticing and safe, is already disadvantaged by the high cost to run the system (Perrier, Angelos 2020). Having a dedicated camera arm with the integrated retractor to accommodate the trans-oral thyroidectomy only, is an extra cost for the healthcare system that might be difficult to justify.

6.3.4 Patient risk

TOETVA has been associated with a number of complications other than those associated with CO_2 insufflation. A number of reported complications were associated with the access that is developed in the subplatysmal space through the vestibule in the mouth. The latter include damage to the mental nerve with resultant chin and/or neck paraesthesia, bruising/ecchymosis of the neck skin, and even perforation and/or burns of the skin flap (Tae 2020a). Since this step of the operation has not been altered to accommodate the gasless modification developed by the researcher, these complications can still happen in the patient should the surgeon use gasless modification. By limiting the vestibular incision to 10mm in the centre of the vestibule, the risk of injury to the mental nerve has been mitigated as much as possible, but not eliminated. This is because, whilst the midline to mental foramen distance has been found to be an average of

29.2mm, which offers a safety zone in the midline, this is highly variable and so is the distribution of the branches of the mental nerve branches (King et al. 2020). In addition, damage to the mental nerve is also possible due to the 5mm working ports on each side of the vestibule which are essential both in the standard TOETVA and in the gasless modification developed by the researcher since they allow access to the working instruments.

An additional risk which has not been eliminated is the risk of surgical site infection. In the reported literature, this risk appears to be small. Whenever there was an infection, this was treated with antibiotics with good response in almost all cases (Menderico et al. 2021, Camenzuli et al. 2018). This risk is not eliminated with the gasless technique. Whilst the actual risk should be similar to the standard technique, it is difficult to predict this outcome before having a cohort analysis of patients.

6.4 Intra-jugular venous pressures

Endoscopic thyroidectomy, in particular TOETVA, is a relatively recent addition to the surgical armamentarium for the management of thyroid pathologies. Whilst the main complications associated with CO_2 insufflation have been reported (Camenzuli et al. 2018, Lira et al. 2020, Wang et al. 2021), the link between insufflation and increase in intra-ocular pressure has been only investigated sparingly in the context of TOETVA. Only two papers describe this phenomenon (Camenzuli et al. 2021).

The researcher studied the effect of CO_2 insufflation during TOETVA in Thiel embalmed cadavers and compared the intra-jugular pressure changes to those experienced within the same cadavers when the insufflation was stopped and the novel retracting device was used instead (see Chapter 5). The relative change in pressure within the internal jugular vein was significantly higher when CO_2 insufflation was used when compared to the device being used for gasless TOETVA in the same cadaver. Moreover, increasing levels of insufflation pressure in the neck during TOETVA was associated with increased intra-jugular pressure. Given the inference that increasing pressure in the internal jugular vein leads to increase in intra-ocular pressures (Kim et al. 2013), patients who are susceptible to damage from such an increase should not undergo CO_2 insufflation but be offered the gasless alternative of TOETVA.

The degree to which this finding can be extrapolated to the general population is undetermined. The analysis carried out by the researcher showed that whilst the relationship described above is significant in all three cadavers and at every stage of the procedure, the extent of the differences in intrajugular pressure changes when comparing gasless techniques and CO_2 insufflation was significantly different between cadavers. This implies that the anatomical make-up of the individual patient might have an important role to play in these changes. The sample investigated in this researchers' assessment was limited, and more studies need to be conducted in the future to further investigate this.

6.4.1 Neo-circulation

In order to investigate the effect of CO_2 insufflation on the intra-jugular pressures in Thiel embalmed cadavers whilst at the same time perform the measurements in conditions as close to the living ones as possible, a neo-circulation was developed by the researcher. The aim of the developed system, in the context of the researcher’s requirements, was to offer a low-pressure venous system and a pulsatile arterial system with peak pressures closer to the normal systolic pressure of 130mmHg. Since the investigations were carried out in the neck, the neo-circulatory system developed was segmentally limited to the upper body vasculature.

The perfused cadaveric model has been found to be beneficial in the context of surgical training. This has predominantly been the case for training in vascular procedures and trauma (Grabo, Polk et al. 2020, Grabo, Bardes et al. 2020, Nesbitt et al. 2019). This platform was found to have good face validity and to offer high fidelity to the clinical scenario (Faizer et al. 2020, Nesbitt et al. 2018). Whilst pulsatile cadavers have been used for video-assisted thoracoscopic surgery training, which is an endoscopic procedure, they have not been utilised for endoscopic neck surgery (Dell'Amore et al. 2020).

Other groups have described methods for neo-circulation of cadavers mainly using fresh cadavers and which are not commercially available (Aboud et al. 2015, Carey et al. 2014, Carey et al. 2015, Minetti, Baker, Sullivan 2017, Sarkar et al. 2018). Neo-circulation in Thiel embalmed human cadavers has been used by three groups. One group used it in the context of training in endovascular procedure and utilised an extra-corporeal circulation to pump fluid directly in the aorta. The venous system was not included in the neo-circulation developed (McLeod et al. 2017). A similar exercise was carried out by another group (Chevallier et al. 2014). This group used a heart-lung bypass machine to create the neo-circulation in the Thiel embalmed cadavers. The venous system is not circulated in this system. Additionally, this is expensive equipment which needs expertise to run it, and therefore might not offer the ideal solution for all cadaveric training centres. The third group utilised perfused Thiel embalmed cadavers in the context of flap dissection. Similar to the previous group, the venous system was not perfused (Wolff, et al. 2014). These systems were not suitable for the needs of the researcher since the investigations being carried out were on the venous system.

SimLife®, one of the most promising systems which combines a circulation system with a ventilation system for cadavers, was only validated in fresh cadavers (Danion et al. 2020, Delpech et al. 2017). This system was used for simulation of training in endocrine surgery including thyroid surgery (Donatini et al. 2021). The participants were very satisfied with the experience this system offers (Donatini et al. 2021). Regrettably, similar to the heart-lung bypass machine used by the previously mentioned group, this is a very expansive system to acquire and to run.

The neo-circulatory system developed by the researcher is simple and easily reproducible. It allowed the experiments discussed in chapter 5 to be carried out successfully. The limited number of cadavers on which this system was used by the researcher (3 Thiel embalmed cadavers) meant that this system was not completely validated. Further evaluation is therefore needed.

6.5 Limitations

The main limitation of the research presented was the number of cadavers utilised during the investigations. This was mainly due to the limited resources available to the researcher. The Department of Anatomy at University of Malta receives 12-15 cadavers a year through the process described in Section 1.4 (Zammit 2018). Despite having a good reserve of Thiel embalmed cadavers within the Department, most of these cadavers were not accessible to the researcher. The main reason is that most of these cadavers are used for teaching of undergraduate students within the same Department (Agius et al. 2018). Not all of the remaining cadavers could be used by the researcher. Some of these cadavers had not undergone the full process of embalming whilst others had either previous surgery to the neck or mouth or central venous lines inserted within the internal jugular vein. The latter were excluded to keep the explored necks as pristine as possible. In light of this, the researcher opted for a proof of concept and utilised the available resources to investigate the research questions using an odd number of cadavers.

Another limitation of this analysis was that, although the researcher was an experienced endocrine surgeon and therefore trained in both neck surgery and laparoscopic surgery, he was a novice in TOETVA. This limitation might have influenced the outcomes in terms of recurrent laryngeal nerve and parathyroid glands detection during the procedures.

Additionally, the machinery available to build the prototype of the retractor was also limited. Despite collaborating with external institutes to build the tip of the retractor, the thickness of this part of the retractor can be further addressed. The developed prototype is also limited by the fact that it is not sterilisable. This is because a number of components within it are made of plastic and/or rubber that cannot withstand high temperatures. This is a limitation that has to be overcome before the retractor can be submitted by approval by the major regulatory bodies (i.e., the United States Food and Drug Administration and the European Medicines Agency). These are important limiting factors in getting new medical devices introduced in the practice of surgeons who are already performing TOETVA and who would like to adopt the gasless modification as developed by the researcher.

The lack of bleeding during the procedures was another limiting factor offered by the Thiel embalmed cadavers' platform. This is an important feature during the operation and one of the main cause for conversion to open surgery during TOETVA (Jitpratoom et al. 2016). The inability of the Thiel platform to offer bleeding/oozing was particularly important when assessing the gasless modification as discussed in Section 6.5. Whilst the developed neo-circulation did allow some bleeding during the investigations carried out for intra-jugular venous pressures (see Chapter 5), this outcome was not the focus of the investigations carried out at that point of the research.

Plans to overcome these limitations are discussed below in discussed in Section 6.6.

6.6 Future considerations

Whilst this research work addressed a number of gaps in the current knowledge through a number of proof-of-concept analyses, there is room for further investigation in order to provide more robust data and to translate the evidence available from the cadaveric setting to live patients.

In the first instance, the technique must be performed on a larger number of Thiel embalmed cadavers ideally by surgeons already performing TOETVA in their practice. This would ensure that any structures not identified during the procedures were indeed not identified because they were not visible, and not because of lack of experience. Identification of the parathyroid glands remains a challenging part of the operation. In order to facilitate the identification of the latter structures, in the absence of the normal change in colour due to bruising that takes place in the living patient, it would be ideal to develop a system of tagging these structures before the procedure is attempted. A number of devices are already available in the endocrine surgical practice that help the surgeon to identify the parathyroid glands during operation. These include technologies that exploit the hypervascularity of the parathyroid gland in order to identify it via near-infra-red imaging or indocyanine green angiography (McWade et al. 2019, Spartalis et al. 2020). Other technologies use difference in tissue impedance in the neck to identify parathyroid tissue (Thomas et al. 2018). Whether these technologies work in the setting of Thiel embalmed cadavers, still needs to be investigated.

To make the platform as realistic as possible, and to investigate further the issue of bleeding during the procedure when performing the gasless technique, the development of an appropriate, simple and non-expensive neo-circulation would be another direction for development. The researcher had already created a segmental neo-circulation that was used to generate a realistic environment when measuring intra-jugular venous pressure (see Section 6.6.1). This system was a low-cost system that was, however, not validated in the experiments carried out. Validation of this system is important before further progress is made into integrating this system of segmental neo-circulation into the Thiel embalmed cadavers' platform for training in TOETVA.

Once the above system has been developed, the perfused Thiel embalmed cadaver platform can be used for official training programs for endocrine surgeons who are novices in the technique of gasless TOETVA. The benefits of surgical training in novel techniques using the cadaveric model has been proven many times over to be significant (see Section 1.7.2) (James et al. 2019, Gilbody et al. 2011, Mackenzie et al. 2018). The organisation of such training workshops would be beneficial also to promote the novel gasless adaptation of TOETVA with the experts in the field.

The next step for the developed retractor is to involve the industry to refine the instrument and create a platform for commercialisation. An additional development which needs to be explored is the possibility of developing a self-retaining option for the retractor which should eliminate the need for an assistant and offer more space for the surgeon to operate. In this process, after the instrument has been polished and rendered fully sterilisable, the instrument should be used by experienced surgeons on human patients. This would involve a rigorous ethics assessment and full consent from the enrolled patients taking part in the clinical trial. Additionally, approval by the United States Food and Drug Administration Agency as well as the European Medicines Agency will be sought after full development and after the patent from various jurisdictions is officially granted. Ideally, the assessment of the new technique in the live patient should be carried out as a randomised controlled trial that is appropriately powered for the main complication of CO_2 embolism and in which the gasless modification is compared to the standard TOETVA. As part of this extended analysis of the product, the intra-ocular pressures should be continuously monitored during the procedure in both arms of the study whilst keeping the partial pressure of CO_2 in the blood constant. In this way, the association between insufflation and intra-ocular pressure would be further explored and the relative contraindication consolidated.

In order to accommodate the possibility of a gasless robotic transoral thyroidectomy, a robotic arm with the integrated retractor could be developed. Most surgical robotic platforms, like the Da Vinci® platform (Intuitive Surgical Inc., Sunnyvale, CA, USA) and Flex® robotic system (Medrobotics Corp., Raynham, MA, USA), have four arms. Ideally the robotic arm should be developed on the same line of the endoscopic retractor in which the camera and retractor are integrated. This ensures that the access to the neck through the vestibule is not changed. However, as discussed in Section 6.3.3, for healthcare systems to have an arm which can only be used for a limited number of procedures, might not be an economically viable option. Consequently, the retracting arm might need to be developed using the fourth robotic arm and the standard robotic camera arm is used. All this development must ensure that the vestibular access is disturbed as little as possible. One way of ensuring this, is by increasing the angle of the shaft of the retractor so that both the retractor and the camera arms are introduced through the same midline vestibular scar whilst allowing enough space for the camera arm to move away from the face of the patient.

Another future consideration is to assess the use of the developed retractor in the setting of more extensive neck surgery including lateral neck dissection and laryngectomy. Lateral neck dissections take place when there is evidence of metastatic spread of cancers either within the thyroid gland or other organs within the head and neck. Laryngectomy is a surgical procedure which is performed in cases of laryngeal cancer. This assessment should ideally start from the cadaveric setting and proceed along the lines of the above investigations. The retractor can also be assessed in the setting of other endoscopic approaches to the thyroid gland including the transaxillary and the retroauricular approach. This is with the aim of expanding the gasless availability of endoscopic neck surgery.

6.7 Conclusion

The surgical treatment of thyroid pathology has undergone a major overhaul over the past century. Nowadays thyroid surgery is one of the safest surgical treatments in the surgical armamentarium. Whilst TOETVA offers to decrease the morbidity of a visible scar in the neck whilst offering the advantages of minimally invasive surgery. This reduces the risk of fatality from CO_2 embolism.

The researcher offered evidence, through the dissection of 6 cadavers, that the Thiel embalmed cadaver platform is suitable for the reproduction of TOETVA. Consequently, the Thiel embalmed platform can offer a safe environment for the surgeon novel to the technique to develop the skills need and flatten the learning curve.

The gasless modification developed by the researcher through a novel device eliminates the complications associated with the CO_2 insufflation used in the standard technique. The latter device has been granted design registration by the European Union Intellectual Property Office (Registration number 007793666-0001), was awarded the Malta Intellectual Property Award and is currently at an advanced stage in the process of patent registration in a number of jurisdictions. The device modifies the standard technique as little as possible and thereby attempting to preserve the otherwise excellent outcomes of the TOETVA. Further development of the device is needed for it to be used in routine clinical practice.

The researcher also provided evidence that CO_2 insufflation during TOETVA causes significant increase in the intra-jugular pressures when compared to the developed gasless TOETVA. When the latter is interpreted in the light of evidence showing that raised intra-jugular pressures are linked with increase in intra-ocular pressures, it is pragmatic to recommend the gasless technique for patients who either suffer from glaucoma or are at risk of this disease.

The promising results of this research show that gasless TOETVA, using the novel retractor which has been developed by the researcher, can be a safe and viable therapeutic option for scarless thyroidectomy.

References

ABOUD, E., ABOUD, G., AL-MEFTY, O., ABOUD, T., RAMMOS, S., ABOLFOTOH, M., HSU, S.P.C., KOGA, S., ARTHUR, A. and KRISHT, A., 2015. "Live cadavers" for training in the management of intraoperative aneurysmal rupture. *Journal of Neurosurgery,* **123**(5), pp. 1339-1346.

ADAMS, M. and DOHERTY, G., 2009. Conventional thyroidectomy. *Operative Techniques in Otolaryngology - Head and Neck Surgery,* **20**(1), pp. 2-6.

AGIUS, A., CALLEJA, N., CAMENZULI, C., SULTANA, R., PULLICINO, R., ZAMMIT, C., CALLEJA AGIUS, J. and POMARA, C., 2018. Perceptions of first-year medical students towards learning anatomy using cadaveric specimens through peer teaching. *Anatomical Sciences Education,* **11**(4), pp. 346-357.

AHN, J. and YI, J.W., 2020. Transoral endoscopic thyroidectomy for thyroid carcinoma: outcomes and surgical completeness in 150 single-surgeon cases. *Surgical Endoscopy,* **34**(2), pp. 861-867.

AIDAN, P., PICKBURN, H., MONPEYSSEN, H. and BOCCARA, G., 2013. Indications for the Gasless Transaxillary Robotic Approach to Thyroid Surgery: Experience of Forty-Seven Procedures at the American Hospital of Paris. *European thyroid journal,* **2**(2), pp. 102-109.

ALABBAS, H., BU ALI, D. and KANDIL, E., 2016. Robotic retroauricular thyroid surgery. *Gland Surgery,* **5**(6), pp. 603-606.

ALCALÁ RUEDA, I., VILLACAMPA AUBÁ, J.M., ENCINAS VICENTE, A., GABERNET, M.B., GUERRERO, C.C., REPARAZ, C.C.C., DE FREITAS, E.T., GONZÁLEZ, A.C. and ESPAÑOL, C.C., 2021. A live porcine model for surgical training in tracheostomy, neck dissection, and total laryngectomy. *European archives of oto-rhino-laryngology: official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS): affiliated with the*

German Society for Oto-Rhino-Laryngology - Head and Neck Surgery, **278**(8), pp. 3081-3090.

AL-DHAHIRY, J.K.S. and HAMEED, H.M., 2016. Total thyroidectomy: Conventional Suture Ligation technique versus sutureless techniques using Harmonic Scalpel or Maxium. *Annals of Medicine and Surgery,* **5**, pp. 29-34.

ALESINA, P.F., WAHABIE, W., MEIER, B., HINRICHS, J., MOHMAND, W., KAPAKOGLOU, A., KNIAZEVA, P. and WALZ, M.K., 2021. Long-term cosmetic results of video-assisted thyroidectomy: a comparison with conventional surgery. *Langenbeck's Archives of Surgery,* **406**(5), pp.1625-1633.

ALVARADO, R., MCMULLEN, T., SIDHU, S.B., DELBRIDGE, L.W. and SYWAK, M.S., 2008. Minimally invasive thyroid surgery for single nodules: an evidence-based review of the lateral mini-incision technique. *World Journal of Surgery,* **32**(7), pp. 1341-1348.

ALZAHRANI, H.A., MOHSIN, K., ALI, D.B., MURAD, F. and KANDIL, E., 2017. Gasless trans-axillary robotic thyroidectomy: the technique and evidence. *Gland Surgery,* **6**(3), pp. 236-242.

ANDRABI, S.M., ALAM, S., ZIA, A., KHAN, M.H. and KUMAR, A., 2014. Mental nerve paresthesia secondary to initiation of endodontic therapy: a case report. *Restorative Dentistry & Endodontics,* **39**(3), pp. 215-219.

ANUWONG, A., 2016. Transoral Endoscopic Thyroidectomy Vestibular Approach: A Series of the First 60 Human Cases. *World Journal of Surgery,* **40**(3), pp. 491-497.

ANUWONG, A., KETWONG, K., JITPRATOOM, P., SASANAKIETKUL, T. and DUH, Q., 2018. Safety and Outcomes of the Transoral Endoscopic Thyroidectomy Vestibular Approach. *JAMA surgery,* **153**(1), pp. 21-27.

AOYAMA, M., TAKIZAWA, H., TSUBOI, M., YAMASAKI, S., TSURUO, Y. and TANGOKU, A., 2019. Surgical training in video-assisted neck surgery-based thyroidectomy using fresh frozen human cadavers. *The journal of medical investigation: JMI,* **66**(3.4), pp. 293-296.

ARORA, A., SWORDS, C., GARAS, G., CHAIDAS, K., PRICHARD, A., BUDGE, J., DAVIES, D.C. and TOLLEY, N., 2016. The perception of scar cosmesis following thyroid and parathyroid surgery: A prospective cohort study. *International journal of surgery (London, England),* **25**, pp. 38-43.

ASTL, J., PLZÁK, J., LAŠTŮVKA, P. and BETKA, J., 2021. Morbidity and mortality associated with thyroid surgery - retrospective analysis 19912010. *Rozhledy V Chirurgii: Mesicnik Ceskoslovenske Chirurgicke Spolecnosti,* **100**(3), pp. 118-125.

AUNG, W., SAKAMOTO, H., SATO, A., YI, E., THEIN, Z., NWE, M., SHEIN, N., LINN, H., UCHIYAMA, S., KUNUGITA, N., WIN-SHWE, T. and MAR, O., 2021. Indoor Formaldehyde Concentration, Personal Formaldehyde Exposure and Clinical Symptoms during Anatomy Dissection Sessions, University of Medicine 1, Yangon. *International Journal of Environmental Research and Public Health,* **18**(2), pp. 712.

BAKKAR, S., AL HYARI, M., NAGHAWI, M., CORSINI, C. and MICCOLI, P., 2018. Transoral thyroidectomy: a viable surgical option with unprecedented complications-a case series. *Journal of Endocrinological Investigation,* **41**(7), pp. 809-813.

BALTA, J.Y., LAMB, C. and SOAMES, R.W., 2015. A pilot study comparing the use of Thiel- and formalin-embalmed cadavers in the teaching of human anatomy. *Anatomical Sciences Education,* **8**(1), pp. 86-91.

BALTA, J.Y., TWOMEY, M., MOLONEY, F., DUGGAN, O., MURPHY, K.P., O'CONNOR, O.J., CRONIN, M., CRYAN, J.F., MAHER, M.M. and O'MAHONY, S.M., 2019. A comparison of embalming fluids on the structures and properties of tissue in human cadavers. *Anatomia, Histologia, Embryologia,* **48**(1), pp. 64-73.

BÄRLEHNER, E. and BENHIDJEB, T., 2008. Cervical scarless endoscopic thyroidectomy: Axillo-bilateral-breast approach (ABBA). *Surgical Endoscopy,* **22**(1), pp. 154-157.

BELE, U. and KELC, R., 2016. Upper and Lower Urinary Tract Endoscopy Training on Thiel-embalmed Cadavers. *Urology,* **93**, pp. 27-32.

BENHIDJEB, T., WILHELM, T., HARLAAR, J., KLEINRENSINK, G.-., SCHNEIDER, T.A.J. and STARK, M., 2009. Natural orifice surgery on thyroid gland: totally transoral video-assisted thyroidectomy (TOVAT): report of first experimental results of a new surgical method. *Surgical Endoscopy,* **23**(5), pp. 1119-1120.

BENHIDJEB, T., STARK, M., GERNTKE, I., MYNBAEV, O. and WITZEL, K., 2017. Transoral thyroidectomy—from experiment to clinical implementation. *Translational cancer research,* **6**(S1), pp. S174-S178.

BENHIDJEB, T., WITZEL, K., STARK, M. and MANN, O., 2011. Transoral thyroid and parathyroid surgery: still experimental! *Surgical Endoscopy,* **25**(7), pp. 2411-2413.

BENKHADRA, M., GÉRARD, J., GENELOT, D., TROUILLOUD, P., GIRARD, C., ANDERHUBER, F. and FEIGL, G., 2011. Is Thiel's embalming method widely known? A world survey about its use. *Surgical and radiologic anatomy: SRA,* **33**(4), pp. 359-363.

BHARGAV, P.R.K. and AMAR, V., 2013. Operative technique of endoscopic thyroidectomy: a narration of general principles. *The Indian Journal of Surgery,* **75**(3), pp. 216-219.

BHATIA, P., MOHAMED, H.E., KADI, A., KANDIL, E. and WALVEKAR, R.R., 2015. Remote access thyroid surgery. *Gland Surgery,* **4**(5), pp. 376-387.

BHATTACHARYYA, N. and FRIED, M.P., 2002. Assessment of the morbidity and complications of total thyroidectomy. *Archives of Otolaryngology--Head & Neck Surgery,* **128**(4), pp. 389-392.

BIELLO, A., KINBERG, E.C. and WIRTZ, E.D., 2021. Thyroidectomy. *StatPearls.* Treasure Island (FL): StatPearls Publishing, https://www.ncbi.nlm.nih.gov/books/NBK563279/ (Accessed 23rd May 2021).

BLASCHKO, S.D., BROOKS, H.M., DHUY, S.M., CHAREST-SHELL, C., CLAYMAN, R.V. and MCDOUGALL, E.M., 2007. Coordinated multiple cadaver use for minimally invasive surgical training. *JSLS: Journal of the Society of Laparoendoscopic Surgeons,* **11**(4), pp. 403-407.

BLISS, R.D., GAUGER, P.G. and DELBRIDGE, L.W., 2000. Surgeon's approach to the thyroid gland: surgical anatomy and the importance of technique. *World Journal of Surgery,* **24**(8), pp. 891-897.

BOZIĆ, M., HENTOVA SENĆANIN, P., BRANKOVIĆ, A., MARJANOVIĆ, I., DORDEVIĆ JOCIĆ, J. and SENĆANIN, I., 2012. [Effect of a tight necktie on intraocular pressure]. *Medicinski Pregled,* **65**(1-2), pp. 13-17.

BRADBURY, A.G., EDDLESTON, M. and CLUTTON, R.E., 2016. Pain management in pigs undergoing experimental surgery; a literature review (2012-4). *British Journal of Anaesthesia,* **116**(1), pp. 37-45.

BRENNER, E., 2014. Human body preservation - old and new techniques. *Journal of Anatomy,* **224**(3), pp. 316-344.

BROWN, M.J., SYMONOWICZ, C., MEDINA, L.V., BRATCHER, N.A., BUCKMASTER, C.A., KLEIN, H. and ANDERSON, L.C., 2018. Culture of Care: Organizational Responsibilities.

In: R.H. WEICHBROD, G.A.H. THOMPSON and J.N. NORTON, eds, *Management of Animal Care and Use Programs in Research, Education, and Testing.* 2nd edn. Boca Raton (FL): CRC Press/Taylor & Francis, https://www.ncbi.nlm.nih.gov/books/NBK500402/. (Accessed 12thApril 2021).

CAGLIÀ, P., PUGLISI, S., BUFFONE, A., BIANCO, S.L., OKATYEVA, V., VEROUX, M. and CANNIZZARO, M.A., 2017. Post-thyroidectomy hypoparathyroidism, what should we keep in mind? *Annali Italiani Di Chirurgia,* **6**, pp. 371-381.

CAI, C., HUANG, Y., ZHANG, T., CHAI, L., WANG, G., SHI, L., WIEGAND, S., GÜLDNER, C., GÜNZEL, T. and WILHELM, T., 2015. Anatomical study of surgical approaches for minimally invasive transoral thyroidectomy: eMIT and TOPP. *Minimally invasive therapy & allied technologies: MITAT: official journal of the Society for Minimally Invasive Therapy,* **24**(6), pp. 340-344.

CAMENZULI, C., SCHEMBRI WISMAYER, P. and CALLEJA AGIUS, J., 2021. Association between carbon dioxide insufflation in endoscopic thyroidectomy and intra-ocular pressure (IOP). Is insufflation contra-indicated in glaucoma patients? *Oral Oncology,* **113**, pp. 105022.

CAMENZULI, C., SCHEMBRI WISMAYER, P. and CALLEJA AGIUS, J., 2019. Using thiel embalmed cadavers for training in transoral endoscopic thyroidectomy vestibular approach (TOETVAVA): is it feasible? *Minerva Chirurgica,* **74**(5), pp. 440-442.

CAMENZULI, C., SCHEMBRI WISMAYER, P. and CALLEJA AGIUS, J., 2018. Transoral Endoscopic Thyroidectomy: A Systematic Review of the Practice So Far. *JSLS: Journal of the Society of Laparoendoscopic Surgeons,* **22**(3), doi: 10.4293/JSLS.2018.00026.

CANARIS, G.J., MANOWITZ, N.R., MAYOR, G. and RIDGWAY, E.C., 2000. The Colorado thyroid disease prevalence study. *Archives of Internal Medicine,* **160**(4), pp. 526-534.

CANTER, R., 2011. Impact of reduced working time on surgical training in the United Kingdom and Ireland. *The Surgeon: Journal of the Royal Colleges of Surgeons of Edinburgh and Ireland,* **9**(1), pp. 6.

CARBONE, L. and AUSTIN, J., 2016. Pain and Laboratory Animals: Publication Practices for Better Data Reproducibility and Better Animal Welfare. *PloS One,* **11**(5), pp. e0155001.

CAREY, J.N., MINNETI, M., LELAND, H.A., DEMETRIADES, D. and TALVING, P., 2015. Perfused fresh cadavers: method for application to surgical simulation. *American Journal of Surgery,* **210**(1), pp. 179-187.

CAREY, J.N., ROMMER, E., SHECKTER, C., MINNETI, M., TALVING, P., WONG, A.K., GARNER, W. and URATA, M.M., 2014. Simulation of plastic surgery and microvascular procedures using perfused fresh human cadavers. *Journal of plastic, reconstructive & aesthetic surgery: JPRAS,* **67**(2), pp. 42.

CHAI, Y.J., CHAE, S., OH, M.Y., KWON, H. and PARK, W.S., 2021. Transoral Endoscopic Thyroidectomy Vestibular Approach (TOETVA): Surgical Outcomes and Learning Curve. *Journal of Clinical Medicine,* **10**(4), pp. 863.

CHAI, Y.J., CHUNG, J.K., ANUWONG, A., DIONIGI, G., KIM, H.Y., HWANG, K., HEO, S.C., YI, K.H. and LEE, K.E., 2017. Transoral endoscopic thyroidectomy for papillary thyroid microcarcinoma: initial experience of a single surgeon. *Annals of Surgical Treatment and Research,* **93**(2), pp. 70-75.

CHANG, Y.K. and LANG, B.H.H., 2017. To identify or not to identify parathyroid glands during total thyroidectomy. *Gland Surgery,* **6**(Suppl 1), pp. S20-S29.

CHAUNG, K., DUKE, W.S., OH, S.J., BEHR, A., WALLER, J.L., DANIEL, J. and TERRIS, D.J., 2017. Aesthetics in Thyroid Surgery: The Patient Perspective. *Otolaryngology--Head and Neck Surgery: Official Journal of American Academy of Otolaryngology-Head and Neck Surgery,* **157**(3), pp. 409-415.

CHEN, D., ZHANG, Q., DENG, J., CAI, Y., HUANG, J., LI, F. and XIONG, K., 2018. A shortage of cadavers: The predicament of regional anatomy education in mainland China. *Anatomical Sciences Education,* **11**(4), pp. 397-402.

CHEN, L.W., ASSADI, N., HEFETZ-KIRSHENBAUM, L., HONG, H., RAZAVI, C.R., GROGAN, R.H., TUFANO, R.P., KHAFIF, A. and RUSSELL, J.O., 2021. Preferences for thyroidectomy technique: Comparing traditional and transoral approaches. *Head & Neck,* **43**(6), pp. 1747-1758.

CHEN, L.W., RAZAVI, C.R., HONG, H., FONDONG, A., RANGANATH, R., KHATRI, S., MYDLARZ, W.K., MATHUR, A., ISHII, M., NELLIS, J., SHAEAR, M., TUFANO, R.P. and RUSSELL, J.O., 2020. Cosmetic outcomes following transoral versus transcervical thyroidectomy. *Head & Neck,* **42**(11), pp. 3336-3344.

CHEN, W. and CHEN, C., 2021. Postoperative quality of life and cosmetic outcome between minimally invasive video-assisted thyroidectomy and bilateral axillo-breast approach robotic thyroidectomy: a single center retrospective cohort study. *Updates in Surgery,* **73**(4), pp. 1459-1465.

CHENG, H., SOLEAS, I., FERKO, N.C., CLYMER, J.W. and AMARAL, J.F., 2015. A systematic review and meta-analysis of Harmonic Focus in thyroidectomy compared to conventional techniques. *Thyroid research,* **8**, pp. 15-1. eCollection 2015.

CHEVALLIER, C., WILLAERT, W., KAWA, E., CENTOLA, M., STEGER, B., DIRNHOFER, R., MANGIN, P. and GRABHERR, S., 2014. Postmortem circulation: A new model for testing endovascular devices and training clinicians in their use. *Clinical Anatomy,* **27**(4), pp. 556-562.

CHO, J., LEE, D., BAEK, J., LEE, J., PARK, Y. and SUNG, K., 2017. Single-incision endoscopic thyroidectomy by the axillary approach with gas inflation for the benign thyroid tumor: retrospective analysis for a single surgeon's experience. *Surgical endoscopy,* **31**(1), pp. 437-444.

CIROCCHI, R., AREZZO, A., D'ANDREA, V., ABRAHA, I., POPIVANOV, G.I., AVENIA, N., GERARDI, C., HENRY, B.M., RANDOLPH, J. and BARCZYÑSKI, M., 2019. Intraoperative neuromonitoring versus visual nerve identification for prevention of recurrent laryngeal nerve injury in adults undergoing thyroid surgery. *The Cochrane Database of Systematic Reviews,* **1**, pp. CD012483.

CLARK, L., TAUBMAN, S. and STAHLMAN, S., 2019. Update: Incidence of Glaucoma Diagnoses, Active Component, U.S. Armed Forces, 2013-2017. *MSMR,* **26**(2), pp. 15-19.

COMMITTEE TO REVIEW THE FORMALDEHYDE ASSESSMENT IN THE NATIONAL TOXICOLOGY PROGRAM 12TH REPORT ON CARCINOGENS, BOARD ON ENVIRONMENTAL STUDIES AND TOXICOLOGY, DIVISION ON EARTH AND LIFE SCIENCES and NATIONAL RESEARCH COUNCIL., 2014. *Review of the Formaldehyde Assessment in the National Toxicology Program 12th Report on Carcinogens.* Washington (DC): National Academies Press (US).

DANION, J., BREQUE, C., ORIOT, D., FAURE, J.P. and RICHER, J.P., 2020. SimLife® technology in surgical training - a dynamic simulation model. *Journal of Visceral Surgery,* **157**(3 Suppl 2), pp. S117-S122.

DAS, A.T., PRAKASH, S.B. and PRIYADARSHINI, V., 2016. Outcomes of Capsular Dissection Technique with Use of Bipolar Electrocautery in Total Thyroidectomy: A

Rural Tertiary Center Experience. *Journal of clinical and diagnostic research,* **10**(12), pp. MC01-MC03.

DAVIES, L. and HOANG, J.K., 2021. Thyroid cancer in the USA: current trends and outstanding questions. *The Lancet. Diabetes & Endocrinology,* **9**(1), pp. 11-12.

DAVIES, L. and WELCH, H.G., 2014. Current thyroid cancer trends in the United States. *JAMA otolaryngology-- head & neck surgery,* **140**(4), pp. 317-322.

DE PERIO, M.A., BERNARD, B.P., DELANEY, L.J., PESIK, N. and COHEN, N.J., 2014. Notes from the Field: Investigation of Infectious Disease Risks Associated With a Nontransplant Anatomical Donation Center. *Morbidity and Mortality Weekly Report (MMWR),* **63**(17), pp. 384-385.

DEL RIO, P., SOMMARUGA, L., CATALDO, S., ROBUSCHI, G., ARCURI, M.F. and SIANESI, M., 2008. Minimally Invasive Video-Assisted Thyroidectomy: The Learning Curve. *European Surgical Research,* **41**(1), pp. 33-36.

DEL RIO, P., ARCURI, M.F., CATALDO, S., DE SIMONE, B., PISANI, P. and SIANESI, M., 2014. Are we changing our inclusion criteria for the minimally invasive videoassisted thyroidectomy? *Annali Italiani Di Chirurgia,* **85**(1), pp. 28-32.

DELBRIDGE, L., REEVE, T.S., KHADRA, M. and POOLE, A.G., 1992. Total Thyroidectomy: The Technique of Capsular Dissection. *Australian and New Zealand Journal of Surgery,* **62**(2), pp. 96-99.

DELL'AMORE, A., SCHIAVON, M., BOSCOLO-BERTO, R., PANGONI, A., DE CARO, R. and REA, F., 2020. Video-assisted thoracic surgery lobectomy simulation and training with a new human cadaver model. *Multimedia manual of cardiothoracic surgery: MMCTS,* doi: 10.1510/mmcts.2020.029.

DELPECH, P.O., DANION, J., ORIOT, D., RICHER, J.P., BREQUE, C. and FAURE, J.P., 2017. SimLife a new model of simulation using a pulsated revascularized and reventilated cadaver for surgical education. *Journal of Visceral Surgery,* **154**(1), pp. 15-20.

DIONIGI, G., BACUZZI, A., LAVAZZA, M., INVERSINI, D., BONI, L., RAUSEI, S., KIM, H.Y. and ANUWONG, A., 2017. Transoral endoscopic thyroidectomy: preliminary experience in Italy. *Updates in Surgery,* **69**(2), pp. 225-234.

DIONIGI, G., BACUZZI, A., LAVAZZA, M., INVERSINI, D., PAPPALARDO, V., BONI, L., RAUSEI, S., BARCZYNSKI, M., TUFANO, R.P., KIM, H.Y. and ANUWONG, A., 2016. Transoral endoscopic thyroidectomy via vestibular approach: operative steps and video. *Gland Surgery,* **5**(6), pp. 625-627.

DIONIGI, G., ROVERA, F. and BONI, L., 2009. Commentary on transoral access for endoscopic thyroid resection: Witzel K, von Rahden BH, Kaminski C, Stein HJ (2008) Transoral access for endoscopic thyroid resection. Surg Endosc 22(8):1871-1875. *Surgical Endoscopy,* **23**(2), pp. 454-456

DONATINI, G., BAKKAR, S., LECLERE, F.M., DIB, W., SUAUD, S., ORIOT, D., BREQUE, C., RICHER, J.P., FAURE, J.P. and DANION, J., 2021. SimLife model: introducing a new teaching device in endocrine surgery simulation. *Updates in surgery,* **73**(1), pp. 289-295.

DORAIRAJAN, N. and PRADEEP, P., 2013. Vignette Thyroid Surgery: A Glimpse Into its History. *International surgery,* **98**(1), pp. 70-75.

D'ORAZI, V., SACCONI, A., TROMBETTA, S., KARPATHIOTAKIS, M., PICHELLI, D., DI LORENZO, E., ORTENSI, A., URCIUOLI, P., BIFFONI, M. and ORTENSI, A., 2019. May predictors of difficulty in thyroid surgery increase the incidence of complications? Prospective study with the proposal of a preoperative score. *BMC surgery,* **18**(Suppl 1), pp. 116.

DORDEA, M. and ASPINALL, S.R., 2016. Short and long-term cosmesis of cervical thyroidectomy scars. *Annals of the Royal College of Surgeons of England,* **98**(1), pp. 11-17.

DUBOSE, J., BARNETT, R. and RAGSDALE, T., 2004. Honest and sensible surgeons: the history of thyroid surgery. *Current surgery,* **61**(2), pp. 213-219.

DUNCAN, T.D., EJEH, I.A., SPEIGHTS, F., RASHID, Q.N. and IDEIS, M., 2006. Endoscopic Transaxillary Near Total Thyroidectomy. *JSLS : Journal of the Society of Laparoendoscopic Surgeons,* **10**(2), pp. 206-211.

EISMA, R., LAMB, C. and SOAMES, R.W., 2013. From formalin to Thiel embalming: What changes? One anatomy department's experiences. *Clinical Anatomy (New York, N.Y.),* **26**(5), pp. 564-571.

EISMA, R., MAHENDRAN, S., MAJUMDAR, S., SMITH, D. and SOAMES, R.W., 2011. A comparison of Thiel and formalin embalmed cadavers for thyroid surgery training. *The Surgeon: Journal of the Royal Colleges of Surgeons of Edinburgh and Ireland,* **9**(3), pp. 142-146.

EISMA, R. and WILKINSON, T., 2014. From "Silent Teachers" to Models. *PLOS Biology,* **12**(10), pp. e1001971.

ELLIS, H., 2007. Anatomy of the thyroid and parathyroid glands. *Surgery - Oxford International Edition,* **25**(11), pp. 467-468.

EROL, V., DIONIGI, G., BARCZYŃSKI, M., ZHANG, D. and MAKAY, Ö, 2020. Intraoperative neuromonitoring of the RLNs during TOETVA procedures. *Gland surgery,* **9**(Suppl 2), pp. S129-S135.

FAIZER, R., SINGAL, A., OJO, C. and REED, A.B., 2020. Development of a pulsatile cadaver-based simulation for training of open abdominal vascular surgery skills. *Journal of Vascular Surgery,* **72**(3), pp. 1076-1086.

FAMA, F., ZHANG, D., PONTIN, A., MAKAY, Ö, TUFANO, R.P., KIM, H.Y., SUN, H. and DIONIGI, G., 2019. Patient and Surgeon Candidacy for Transoral Endoscopic Thyroid Surgery. *Turkish Archives of Otorhinolaryngology,* **57**(2), pp. 105-108.

FANCY, T., GALLAGHER, D.,3rd and HORNIG, J.D., 2010. Surgical anatomy of the thyroid and parathyroid glands. *Otolaryngologic clinics of North America,* **43**(2), pp. 221-7, vii.

FELIX, C., RUSSELL, J.O., JUMAN, S. and MEDFORD, S., 2019. Cervical scar satisfaction post conventional thyroidectomy. *Gland surgery,* **8**(6), pp. 723-728.

FERNANDEZ RANVIER, G., MEKNAT, A., GUEVARA, D.E., LLORENTE, P.M., VIDAL FORTUNY, J., SNEIDER, M., CHEN, Y. and INABNET, W., 2020. International Multi-institutional Experience with the Transoral Endoscopic Thyroidectomy Vestibular Approach. *Journal of Laparoendoscopic & Advanced Surgical Techniques. Part A,* **30**(3), pp. 278-283.

FERNANDEZ-RANVIER, G., MEKNAT, A., GUEVARA, D., TAYE, A., SUH, H. and INABNET, W.B., 2020. Transoral Endoscopic Thyroidectomy Vestibular Approach: A Single-institution Experience of the First 50 Cases. *Surgical Innovation,* **27**(5), pp. 439-444

FISCHELL, T.A., FISCHELL, R.E., WHITE, R.I. and CHAPOLINI, R., 1990. Ex-vivo results using a new pullback atherectomy catheter (PAC). *Catheterization and Cardiovascular Diagnosis,* **21**(4), pp. 287-291.

FISCHER, M.H., 1900. THE TOXIC EFFECTS OF FORMALDEHYDE AND FORMALIN. *Journal of the Boston Society of Medical Sciences,* **5**(1), pp. 18-22.

FU, J., LUO, Y., CHEN, Q., LIN, F., HONG, X., KUANG, P., YAN, W., WU, G. and ZHANG, Y., 2018. Transoral Endoscopic Thyroidectomy: Review of 81 Cases in a Single Institute. *Journal of Laparoendoscopic & Advanced Surgical Techniques. Part A,* **28**(3), pp. 286-291.

GAO, Y, LIU, Y, ZHANG, Y, WANG, X and CAI, X, 2012. Effect of CO2 Insufflation on Intraocular Pressure during Endoscopic Thyroidectomy. *Chinese Journal of Modern Operative Surgery,* **4**, pp. 35-37.

GHOSH, S.K., 2017. Cadaveric dissection as an educational tool for anatomical sciences in the 21st century. *Anatomical Sciences Education,* **10**(3), pp. 286-299.

GILBODY, J., PRASTHOFER, A.W., HO, K. and COSTA, M.L., 2011. The use and effectiveness of cadaveric workshops in higher surgical training: a systematic review. *Annals of The Royal College of Surgeons of England,* **93**(5), pp. 347-352.

GIMM, O., BARCZYŃSKI, M., MIHAI, R. and RAFFAELLI, M., 2019. Training in endocrine surgery. *Langenbeck's Archives of Surgery,* **404**(8), pp. 929-944.

GOUGH, I.R., 2011. The impact of reduced working hours on surgical training in Australia and New Zealand. *The Surgeon: Journal of the Royal Colleges of Surgeons of Edinburgh and Ireland,* **9** (Suppl 1), pp. 8.

GRABO, D., BARDES, J., SHARON, M. and BORGSTROM, D., 2020. Initial report on the impact of a perfused fresh cadaver training program in general surgery resident trauma education. *American Journal of Surgery,* **220**(1), pp. 109-113.

GRABO, D., POLK, T., MINNETI, M., INABA, K. and DEMETRIADES, D., 2020. Brief report on combat trauma surgical training using a perfused cadaver model. *The Journal of Trauma and Acute Care Surgery,* **89**(Suppl 2), pp. S175-S179.

GSCHWANDTNER, E., SEEMANN, R., BURES, C., PRELDZIC, L., SZUCSIK, E. and HERMANN, M., 2018. How many parathyroid glands can be identified during thyroidectomy?: Evidence-based data for medical experts. *European surgery: ACA: Acta chirurgica Austriaca,* **50**(1), pp. 14-21.

GUNN, A., OYEKUNLE, T., STANG, M., KAZAURE, H. and SCHERI, R., 2020. Recurrent Laryngeal Nerve Injury After Thyroid Surgery: An Analysis of 11,370 Patients. *The Journal of Surgical Research,* **255**, pp. 42-49.

GUO, P., TANG, Z., DING, Z., CHU, G., YAO, H., PAN, T. and WANG, H., 2014. Transoral endoscopic thyroidectomy with central neck dissection: experimental studies on human cadavers. *Chinese Medical Journal,* **127**(6), pp. 1067-1070.

GUO, P., TANG, Z., DING, Z., CHU, G., YAO, H. and WANG, H., 2011. [Surgical anatomy of totally trans-oral video-assisted thyroidectomy]. *Zhonghua Wai Ke Za Zhi [Chinese Journal of Surgery],* **49**(10), pp. 934-937.

GÜRSES, İA., COŞKUN, O. and ÖZTÜRK, A., 2018. Current status of cadaver sources in Turkey and a wake-up call for Turkish anatomists. *Anatomical Sciences Education,* **11**(2), pp. 155-165.

HANNAN, S.A., 2006. The magnificent seven: a history of modern thyroid surgery. *International journal of surgery (London, England),* **4**(3), pp. 187-191.

HARDON, S.F., VAN GASTEL, L.A., HOREMAN, T. and DAAMS F., 2021. Assessment of technical skills based on learning curve analyses in laparoscopic surgery training. *Surgery*, **170**(3), pp. 831-840.

HASAN, A., POZZI, M. and HAMILTON, J.R.L., 2000. New surgical procedures: can we minimise the learning curve? *BMJ : British Medical Journal,* **320**(7228), pp. 171-173.

HAYASHI, S., NAITO, M., KAWATA, S., QU, N., HATAYAMA, N., HIRAI, S. and ITOH, M., 2016. History and future of human cadaver preservation for surgical training: from formalin to saturated salt solution method. *Anatomical Science International,* **91**(1), pp. 1-7.

HAYDEN, P. and COWMAN, S., 2011. Anaesthesia for laparoscopic surgery. *Continuing Education in Anaesthesia Critical Care & Pain,* **11**(5), pp. 177-180.

HEALEY, P. and SAMANTA, J., 2008. When Does the 'Learning Curve' of Innovative Interventions Become Questionable Practice? *European journal of vascular and endovascular surgery,* **36**(3), pp. 253-257.

HEFETZ KHAFIF, A., ALON, E. and ASSADI, N., 2019. [SCARLESS THYROIDECTOMY AND PARATHYROIDECTOMY BY TRANSORAL ENDOSCOPIC TRANSVESTIBULAR APPROACH (TOETVA): THE FIRST SERIES CASES IN ISRAEL]. *Harefuah,* **158**(11), pp. 716-720.

HENRY, B.M., SANNA, B., VIKSE, J., GRAVES, M.J., SPULBER, A., WITKOWSKI, C., TOMASZEWSKA, I.M., TUBBS, R.S. and TOMASZEWSKI, K.A., 2017. Zuckerkandl's tubercle and its relationship to the recurrent laryngeal nerve: A cadaveric dissection and meta-analysis. *Auris, Nasus, Larynx,* **44**(6), pp. 639-647.

HENRY, J.F., 2008. Minimally invasive thyroid and parathyroid surgery is not a question of length of the incision. *Langenbeck's archives of surgery,* **393**(5), pp. 621-626.

HIGUCHI, M., ABE, T., HOTTA, K., MORITA, K., MIYATA, H., FURUMIDO, J., IWAHARA, N., KON, M., OSAWA, T., MATSUMOTO, R., KIKUCHI, H., KURASHIMA, Y., MURAI, S., AYDIN, A., RAISON, N., AHMED, K., KHAN, M.S., DASGUPTA, P. and SHINOHARA, N., 2020. Development and validation of a porcine organ model for training in essential laparoscopic surgical skills. *International Journal of Urology: Official Journal of the Japanese Urological Association,* **27**(10), pp. 929-938.

HOJAIJ, F., VANDERLEI, F., PLOPPER, C., RODRIGUES, C.J., JÁCOMO, A., CERNEA, C., OLIVEIRA, L., MARCHI, L. and BRANDÃO, L., 2011. Parathyroid gland anatomical distribution and relation to anthropometric and demographic parameters: a cadaveric study. *Anatomical Science International,* **86**(4), pp. 204-212.

HONG, Y.T., AHN, J., KIM, J.H., YI, J.W. and HONG, K.H., 2020. Bi-institutional experience of transoral endoscopic thyroidectomy: Challenges and outcomes. *Head & Neck,* **42**(8), pp. 2115-2122.

HOPPER, A.N., JAMISON, M.H. and LEWIS, W.G., 2007. Learning curves in surgical practice. *Postgraduate Medical Journal,* **83**(986), pp. 777-779.

HUR, S.M., KIM, S.H., LEE, S.K., KIM, W.W., CHOE, J.H., LEE, J.E., KIM, J.H., NAM, S.J., YANG, J.H. and KIM, J.S., 2011. New endoscopic thyroidectomy with the bilateral areolar approach: a comparison with the bilateral axillo-breast approach. *Surgical laparoscopy, endoscopy & percutaneous techniques,* **21**(5), pp. 219.

IKEDA, Y., TAKAMI, H., SASAKI, Y., KAN, S. and NIIMI, M., 2000. Endoscopic neck surgery by the axillary approach. *Journal of the American College of Surgeons,* **191**(3), pp. 336-340.

JACOBS, J.P., ELLIOTT, M.J., HAW, M.P., BAILEY, C.M. and HERBERHOLD, C., 1996. Pediatric tracheal homograft reconstruction: a novel approach to complex tracheal stenoses in children. *The Journal of Thoracic and Cardiovascular Surgery,* **112**(6), pp. 1549-1560.

JAFARI, A., CAMPBELL, D., CAMPBELL, B.H., NGOITSI, H.N., SISENDA, T.M., DENGE, M., JAMES, B.C. and CORDES, S.R., 2017. Thyroid Surgery in a Resource-Limited Setting: Feasibility and Analysis of Short- and Long-term Outcomes. *Otolaryngol Head Neck Surg,* **156**(3), pp. 464-471.

JAMES, B.C., ANGELOS, P. and GROGAN, R.H., 2020. Transoral endocrine surgery: Considerations for adopting a new technique. *Journal of Surgical Oncology,* **122**(1), pp. 36-40.

JAMES, H.K., CHAPMAN, A.W., PATTISON, G.T.R., GRIFFIN, D.R. and FISHER, J.D., 2019. Systematic review of the current status of cadaveric simulation for surgical training. *The British Journal of Surgery,* **106**(13), pp. 1726-1734.

JAMES, H.K., PATTISON, G.T.R., FISHER, J.D. and GRIFFIN, D., 2020. Cadaveric simulation versus standard training for postgraduate trauma and orthopaedic surgical trainees: protocol for the CAD: TRAUMA study multicentre randomised controlled educational trial. *BMJ Open,* **10**(9), pp. e037319.

JANTHARAPATTANA, K. and LEELASAWATSUK, P., 2020. Transaxillary endoscopic thyroid lobectomy: gas insufflation versus gasless technique. *European archives of oto-rhino-laryngology: official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS): affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery,* **277**(7), pp. 2049-2054.

JEONG, J.J., KANG, S.W., YUN, J.S., SUNG, T.Y., LEE, S.C., LEE, Y.S., NAM, K.H., CHANG, H.S., CHUNG, W.Y. and PARK, C.S., 2009. Comparative study of endoscopic thyroidectomy versus conventional open thyroidectomy in papillary thyroid microcarcinoma (PTMC) patients. *Journal of surgical oncology,* **100**(6), pp. 477-480.

JIN, S. and SUGITANI, I., 2021. Narrative review of management of thyroid surgery complications. *Gland Surgery,* **10**(3), pp. 1135-1146.

JIN, X., LU, B., CAI, X., HUANG, Y., HUANG, L., LU, W., YAN, Y. and LI, J., 2014. Total endoscopic thyroidectomy via bilateral breast and ipsilateral axillary approach: a clinical feasibility study. *The Journal of craniofacial surgery,* **25**(3), pp. 738-741.

JITPRATOOM, P., KETWONG, K., SASANAKIETKUL, T. and ANUWONG, A., 2016. Transoral endoscopic thyroidectomy vestibular approach (TOETVA) for Graves' disease: a comparison of surgical results with open thyroidectomy. *Gland Surgery,* **5**(6), pp. 546-552.

JONAS, J.B., AUNG, T., BOURNE, R.R., BRON, A.M., RITCH, R. and PANDA-JONAS, S., 2017. Glaucoma. *Lancet (London, England),* **390**(10108), pp. 2183-2193.

JOSHI, S.D., JOSHI, S.S., DAIMI, S.R. and ATHAVALE, S.A., 2010. The thyroid gland and its variations: a cadaveric study. *Folia morphologica,* **69**(1), pp. 47-50.

JUAREZ, M.C., ISHII, L., NELLIS, J.C., BATER, K., HUYNH, P.P., FUNG, N., DARRACH, H., RUSSELL, J.O. and ISHII, M., 2019. Objectively measuring social attention of thyroid neck scars and transoral surgery using eye tracking. *The Laryngoscope,* **129**(12), pp. 2789-2794.

KADEM, S.G., HABASH, S.M. and JASIM, A.H., 2019. Transoral Endoscopic Thyroidectomy via Vestibular Approach: A series of the first ten cases in Iraq. *Sultan Qaboos University Medical Journal,* **19**(1), pp. e68-e72.

KANDIL, E., ATTIA, A.S., HADEDEYA, D., SHIHABI, A. and ELNAHLA, A., 2020. Robotic Thyroidectomy: Past, Future, and Current Perspectives. *Otolaryngologic Clinics of North America,* **53**(6), pp. 1031-1039.

KANG, S.W., JEONG, J.J., YUN, J.S., SUNG, T.Y., LEE, S.C., LEE, Y.S., NAM, K.H., CHANG, H.S., CHUNG, W.Y. and PARK, C.S., 2009. Gasless endoscopic thyroidectomy using trans-axillary approach; surgical outcome of 581 patients. *Endocrine journal,* **56**(3), pp. 361-369.

KARAKAS, E., STEINFELDT, T., GOCKEL, A., SCHLOSSHAUER, T., DIETZ, C., JÄGER, J., WESTERMANN, R., SOMMER, F., RICHARD, H.R., EXNER, C., SESTERHENN, A.M. and BARTSCH, D.K., 2011. Transoral thyroid and parathyroid surgery--development of a new transoral technique. *Surgery,* **150**(1), pp. 108-115.

KASEMSIRI, P., TRAKULKAJORNSAK, S., BAMROONG, P., MAHAWERAWAT, K., PIROMCHAI, P. and RATANAANEKCHAI, T., 2020. Comparison of quality of life between patients undergoing trans-oral endoscopic thyroid surgery and conventional open surgery. *BMC Surgery,* **20**, doi: 10.1186/s12893-020-0685-3

KEHINDE, E.O., 2013. They See a Rat, We Seek a Cure for Diseases: The Current Status of Animal Experimentation in Medical Practice. *Medical Principles and Practice,* **22**(Suppl. 1), pp. 52-61.

KENNEL, L., MARTIN, D.M.A., SHAW, H. and WILKINSON, T., 2018. Learning anatomy through Thiel- vs. formalin-embalmed cadavers: Student perceptions of embalming methods and effect on functional anatomy knowledge. *Anatomical Sciences Education,* **11**(2), pp. 166-174.

KESSLER, P.A., BUMILLER, L., KROCZEK, A., KESSLER, H.P. and BIRKHOLZ, T., 2009. Minimally invasive neck surgery. Surgical feasibility and physiological effects of carbon dioxide insufflation in a unilateral subplatysmal approach. *International Journal of Oral and Maxillofacial Surgery,* **38**(7), pp. 766-772.

KIM, E.Y., LEE, K.H., PARK, Y.L., PARK, C.H., LEE, C.R., JEONG, J.J., NAM, K.H., CHUNG, W.Y. and YUN, J.S., 2017. Single-Incision, Gasless, Endoscopic Trans-Axillary Total Thyroidectomy: A Feasible and Oncologic Safe Surgery in Patients with Papillary Thyroid Carcinoma. *Journal of laparoendoscopic & advanced surgical techniques.Part A,* **27**(11), pp. 1158-1164.

KIM, H., KIM, Y., SHIN, M., CHOI, K.W., CHUNG, M.K. and JEON, H.J., 2021. Risk of Suicide Attempt after Thyroidectomy: A Nationwide Population Study in South Korea. *Psychiatry Investigation,* **18**(1), pp. 39-47.

KIM, J., KIM, J., CHANG, M., YOO, Y. and KIM, D., 2013. Influence of carbon dioxide insufflation of the neck on intraocular pressure during robot-assisted endoscopic thyroidectomy: a comparison with open thyroidectomy. *Surgical Endoscopy,* **27**(5), pp. 1587-1593.

KIM, K., LEE, S., BAE, J. and KIM, J., 2021. Comparison of long-term surgical outcome between transaxillary endoscopic and conventional open thyroidectomy in patients with differentiated thyroid carcinoma: a propensity score matching study. *Surgical Endoscopy,* **35**(6), pp. 2855-2861.

KIM, S.M., CHUN, K.W., CHANG, H.J., KIM, B.W., LEE, Y.S., CHANG, H.S. and PARK, C.S., 2015. Reducing neck incision length during thyroid surgery does not improve satisfaction in patients. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery,* **272**(9), pp. 2433-2438.

KIM, S.Y., KIM, S., MAKAY, Ö, CHANG, H., KIM, B., LEE, Y.S., PARK, C.S. and CHANG, H., 2020. Transoral endoscopic thyroidectomy using the vestibular approach with an endoscopic retractor in thyroid cancer: experience with the first 132 patients. *Surgical Endoscopy,* **34**(12):5414-5420.

KING, S.D., ARELLANO, R., GORDON, V., OLINGER, A., SEIB, C.D., DUH, Q. and SUH, I., 2020. Anatomic Variations From 120 Mental Nerve Dissections: Lessons for Transoral Thyroidectomy. *The Journal of Surgical Research,* **256**, pp. 543-548.

KITAHARA, C.M. and SOSA, J.A., 2016. The changing incidence of thyroid cancer. *Nature Reviews. Endocrinology,* **12**(11), pp. 646-653.

KLEIN, H.E., KROHNE, S.G., MOORE, G.E., MOHAMED, A.S. and STILES, J., 2011. Effect of eyelid manipulation and manual jugular compression on intraocular pressure measurement in dogs. *Journal of the American Veterinary Medical Association,* **238**(10), pp. 1292-1295.

KWAK, H.Y., KIM, S.H., CHAE, B.J., SONG, B.J., JUNG, S.S. and BAE, J.S., 2014. Learning curve for gasless endoscopic thyroidectomy using the trans-axillary approach: CUSUM analysis of a single surgeon's experience. *International journal of surgery (London, England),* **12**(12), pp. 1273-1277.

LE, Q.V., NGO, D.Q., TRAN, T.D. and NGO, Q.X., 2020. Transoral Endoscopic Thyroidectomy Vestibular Approach: An Initial Experience in Vietnam. *Surgical Laparoscopy, Endoscopy & Percutaneous Techniques,* **30**(3), pp. 209-213.

LEE, D.Y., LEE, K.J., HAN, W.G., OH, K.H., CHO, J., BAEK, S., KWON, S., WOO, J. and JUNG, K., 2016. Comparison of transaxillary approach, retroauricular approach, and conventional open hemithyroidectomy: A prospective study at single institution. *Surgery,* **159**(2), pp. 524-531.

LEE, H.Y., HWANG, S.B., AHN, K., LEE, J.B., BAE, J.W. and KIM, H.Y., 2014. The safety of transoral periosteal thyroidectomy: results of Swine models. *Journal of Laparoendoscopic & Advanced Surgical Techniques. Part A,* **24**(5), pp. 312-317.

LEE, J. and CHUNG, W.Y., 2013. Robotic thyroidectomy and neck dissection: past, present, and future. *Cancer journal (Sudbury, Mass.),* **19**(2), pp. 151-161.

LEE, S.N., LEE, J.H., LEE, E.J., LEE, J.Y., KIM, J.I. and SON, Y.B., 2012. Anesthetic course and complications that were encountered during endoscopic thyroidectomy -A case report-. *Korean journal of anesthesiology,* **63**(4), pp. 363-367.

LEESE, G.P., FLYNN, R.V., JUNG, R.T., MACDONALD, T.M., MURPHY, M.J. and MORRIS, A.D., 2008. Increasing prevalence and incidence of thyroid disease in Tayside, Scotland: the Thyroid Epidemiology Audit and Research Study (TEARS). *Clinical endocrinology,* **68**(2), pp. 311-316.

LI, H., PENG, X.W., LI, Z., PENG, W., ZHOU, X., SONG, D.J., ZHOU, B., LYU, C.L., WU, P., OU, Y., MAO, H.X. and LIU, Z.Y., 2019. [The clinical applied analysis of the modified transoral endoscopic thyroidectomy vestibular approach]. *Zhonghua Wai Ke Za Zhi [Chinese Journal of Surgery],* **57**(9), pp. 686-690.

LIAO, D., ISHII, L.E., CHEN, L.W., CHEN, J., JUAREZ, M., DARRACH, H.M., KUMAR, A.R., RUSSELL, J.O., TUFANO, R.P. and ISHII, M., 2020. Transoral neck surgery prevents attentional bias towards the neck compared to open neck surgery. *The Laryngoscope,* **130**(6), pp. 1603-1608.

LINOS, D., ECONOMOPOULOS, K.P., KIRIAKOPOULOS, A., LINOS, E. and PETRALIAS, A., 2013. Scar perceptions after thyroid and parathyroid surgery: comparison of minimal and conventional approaches. *Surgery,* **153**(3), pp. 400-407.

LIRA, R.B., RAMOS, A.T., NOGUEIRA, R.M.R., DE CARVALHO, G.B., RUSSELL, J.O., TUFANO, R.P. and KOWALSKI, L.P., 2020. Transoral thyroidectomy (TOETVA): Complications, surgical time and learning curve. *Oral Oncology,* **110**, pp. 104871.

LIU, H., XIE, Y., XU, Y., LI, C. and LIU, X., 2012. Applied anatomy of a new approach of endoscopic technique in thyroid gland surgery. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao. Acta Academiae Medicinae Sinicae,* **34**(5), pp. 515-522.

LIU, J., SONG, T. and XU, M., 2012. Minimally invasive video-assisted versus conventional open thyroidectomy: a systematic review of available data. *Surgery today,* **42**(9), pp. 848-856.

LIU, M.Y., CHANG, C.P., HUNG, C.I., HUNG, C.J. and HUANG, S.M., 2020. Traction Injury of Recurrent Laryngeal Nerve During Thyroidectomy. *World Journal of Surgery,* **44**(2), pp. 402-407.

LIU, Y.H., XUE, L.B., ZHANG, S., YANG, Y.F. and LI, J., 2021. Appearance characteristics of incision, satisfaction with the aesthetic effect, and quality of life in of thyroid cancer patients after thyroidectomy. *The International Journal of Health Planning and Management,* **36**(3), pp. 784-792.

LLOYD, G.M., MAXWELL-ARMSTRONG, C. and ACHESON, A.G., 2011. Fresh frozen cadavers: an under-utilized resource in laparoscopic colorectal training in the United Kingdom. *Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland,* **13**(9), pp. 303.

LO, C.Y., KWOK, K.F. and YUEN, P.W., 2000. A prospective evaluation of recurrent laryngeal nerve paralysis during thyroidectomy. *Archives of Surgery (Chicago, Ill.: 1960),* **135**(2), pp. 204-207.

LORTET-TIEULENT, J., FRANCESCHI, S., DAL MASO, L. and VACCARELLA, S., 2019. Thyroid cancer "epidemic" also occurs in low- and middle-income countries. *International Journal of Cancer,* **144**(9), pp. 2082-2087.

LUNA-ORTIZ, K., GÓMEZ-PEDRAZA, A. and ANUWONG, A., 2020. Lessons Learned from the Transoral Endoscopic Thyroidectomy with Vestibular Approach (TOETVA) for the Treatment of Thyroid Carcinoma. *Annals of Surgical Oncology,* **27**(5), pp. 1356-1360.

L-UNIVERSITÀ TA' MALTA, 2020-last update, Donate your body for science - Department of Anatomy. https://www.um.edu.mt/ms/anatomy/bequest (Accessed 9th February 2021].

LUO, J., XIANG, C., WANG, P. and WANG, Y., 2020. The Learning Curve for Transoral Endoscopic Thyroid Surgery: A Single Surgeon's 204 Case Experience. *Journal of Laparoendoscopic & Advanced Surgical Techniques. Part A,* **30**(2), pp. 163-169.

MACKENZIE, C.F., BOWYER, M.W., HENRY, S., TISHERMAN, S.A., PUCHE, A., CHEN, H., SHALIN, V., PUGH, K., GAROFALO, E. and SHACKELFORD, S.A., 2018. Cadaver-Based Trauma Procedural Skills Training: Skills Retention 30 Months after Training among Practicing Surgeons in Comparison to Experts or More Recently Trained Residents. *Journal of the American College of Surgeons,* **227**(2), pp. 270-279.

MAHADEVAN, V., 2009. Using unembalmed cadavers in surgical training. *Annals of the Royal College of Surgeons of England,* **91**(3), pp. 80-81.

MALTA DEPARTMENT OF HEALTH INFORMATION AND RESEARCH, 2019. *Thyroid Cancers.* https://deputyprimeminister.gov.mt/en/dhir/Documents/Cancer/2020/cancers%20pdfs/Thyroid_2017.pdf (Accessed 19th February 2021).

MANTICA, G., PINI, G., MARCHI, D.D., PARABOSCHI, I., ESPERTO, F., MERWE, A.V.D., DEVENTER, H.V., GARRIBOLI, M., SUARDI, N., TERRONE, C. and LEONARDI, R., 2020. Intensive simulation training on urological mini-invasive procedures using Thiel-embalmed cadavers: The IAMSurgery experience. *Archivio Italiano di Urologia e Andrologia,* **92**(2), doi: 10.4081/aiua.2020.2.93.

MARTIN, R.F., 2020. Robotic Surgery. *The Surgical Clinics of North America,* **100**(2), pp. xiii-xiv.

MARTINO, E., MACRÌ, L. and MARIOTTI, S., 2021. A case of thyroidectomy in the Charaf ed-Din's manuscript (1465). *Journal of Endocrinological Investigation,* **44**(4), pp. 881.

MCLEOD, H., COX, B., ROBERTSON, J., DUNCAN, R., MATTHEW, S., BHAT, R., BARCLAY, A., ANWAR, J., WILKINSON, T., MELZER, A. and HOUSTON, J., 2017. Human Thiel-Embalmed Cadaveric Aortic Model with Perfusion for Endovascular Intervention Training and Medical Device Evaluation. *Cardiovascular and interventional radiology,* **40**(9), pp. 1454-1460.

MCMONNIES, C., 2015. An examination of the hypothesis that intraocular pressure elevation episodes can have prognostic significance in glaucoma suspects. *Journal of Optometry,* **8**(4), pp. 223-231.

MCWADE, M.A., THOMAS, G., NGUYEN, J.Q., SANDERS, M.E., SOLÓRZANO, C.C. and MAHADEVAN-JANSEN, A., 2019. Enhancing Parathyroid Gland Visualization Using a Near Infrared Fluorescence-Based Overlay Imaging System. *Journal of the American College of Surgeons,* **228**(5), pp. 730-743.

MEDICAL ADMINISTRATOR'S OFFICE, 2019. *SURGICAL OPERATIONS @ MDH THEATRES .* Msida: Mater Dei Hospital. pp. 17

MÉHES, G. and BEKE, L., 2014. [Tissue fixation in clinical practice: the 120-year-old formalin]. *Orvosi Hetilap,* **155**(14), pp. 550-553.

MELO, C., BERNARDES, A. and CARVALHO, L., 2013. [Identification and preservation of parathyroid glands in cadaver parts]. *Acta Medica Portuguesa,* **26**(3), pp. 195-199.

MELO, C., PINHEIRO, S., CARVALHO, L. and BERNARDES, A., 2015. Identification of parathyroid glands: anatomical study and surgical implications. *Surgical and radiologic anatomy: SRA,* **37**(2), pp. 161-165.

MENDERICO, G.M., WEISSENBERG, A.L., BORBA, C.M., SALLANI, G.M. and POY, J.D.O., 2021. Complications of transoral endoscopic thyroidectomy vestibular approach (TOETVA). *Revista Do Colegio Brasileiro De Cirurgioes,* **48**, pp. e20202557.

MENES, T. and SPIVAK, H., 2000. Laparoscopy: searching for the proper insufflation gas. *Surgical Endoscopy,* **14**(11), pp. 1050-1056.

MILLER, F.R., 2003. Surgical anatomy of the thyroid and parathyroid glands. *Otolaryngologic Clinics of North America,* **36**(1), pp. 1-7, vii.

MILNER, T.D., OKHOVAT, S., MCGUIGAN, M., CLEMENT, W.A. and KUNANANDAM, T., 2020. Feasibility of ovine and porcine models for simulation training in parotid surgery and facial nerve dissection. *European archives of oto-rhino-laryngology: official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS): affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery,* **277**(4), pp. 1167-1175.

Minetti, M., Baker, C. and Sullivan, M., 2017. The Development of a Novel Perfused Cadaver Model With Dynamic Vital Sign Regulation and Real-World Scenarios to Teach Surgical Skills and Error Management. *Journal of Surgical Education,* **75**(3), pp. 820-827.

MINCIONE, F., NOCENTINI, A. and SUPURAN, C.T., 2021. Advances in the discovery of novel agents for the treatment of glaucoma. *Expert Opinion on Drug Discovery,* doi: 10.1080/17460441.2021.1922384.

MOHAMED, W., AHMED,A., 2017. Sutureless versus conventional thyroidectomy. *International Surgery Journal,* **44**(4), pp. 1385-1388.

MOHAMMADI, S., SAEEDI-ANARI, G., ALINIA, C., ASHRAFI, E., DANESHVAR, R. and SOMMER, A., 2014. Is Screening for Glaucoma Necessary? A Policy Guide and Analysis. *Journal of Ophthalmic & Vision Research,* **9**(1), pp. 3-6.

MORENO LLORENTE, P., A GONZALES LAGUADO, E., ALBERICH PRATS, M., FRANCOS MARTÍNEZ, J.M. and GARCÍA BARRASA, A., 2021. Surgical approaches to thyroid. *Cirugia Espanola,* **99**(4), pp. 267-275.

MÜLLER, V., MOGL, M., SEIKA, P., JÖNS, T., SAUER, I., PRATSCHKE, J., ANUWONG, A. and ZORRON, R., 2018. How I Do It: New Dissector Device Allows for Effective Operative Field in Transoral Endoscopic Thyroid Surgery Using Vestibular Approach. *Surgical Innovation,* **25**(5), pp. 444-449.

MUSIAŁ, A., GRYGLEWSKI, R.W., KIELCZEWSKI, S., LOUKAS, M. and WAJDA, J., 2016. Formalin use in anatomical and histological science in the 19th and 20th centuries. *Folia Medica Cracoviensia,* **56**(3), pp. 31-40.

NAKAJO, A., ARIMA, H., HIRATA, M., MIZOGUCHI, T., KIJIMA, Y., MORI, S., ISHIGAMI, S., UENO, S., YOSHINAKA, H. and NATSUGOE, S., 2013. Trans-Oral Video-Assisted Neck Surgery (TOVANS). A new transoral technique of endoscopic thyroidectomy with gasless premandible approach. *Surgical Endoscopy,* **27**(4), pp. 1105-1110.

NATIONAL RESEARCH COUNCIL (US) COMMITTEE FOR THE UPDATE OF THE GUIDE FOR THE CARE AND USE OF LABORATORY ANIMALS., 2011. *Guide for the Care and Use of Laboratory Animals.* 8th edn. Washington (DC): National Academies Press (US).

NESBITT, C.I., TINGLE, S.J., WILLIAMS, R., MCCASLIN, J.E., SEARLE, R., MAFELD, S. and STANSBY, G.P., 2019. Educational Impact of a Pulsatile Human Cadaver Circulation Model for Endovascular Training. *European Journal of Vascular and Endovascular*

Surgery: The Official Journal of the European Society for Vascular Surgery, **58**(4), pp. 602-608.

NESBITT, C., TINGLE, S.J., WILLIAMS, R., MCCASLIN, J., SEARLE, R., MAFELD, S. and STANSBY, G., 2018. A Pulsatile Fresh Frozen Human Cadaver Circulation Model for Endovascular Training: A Trial of Face Validity. *Annals of Vascular Surgery,* **46**, pp. 345-350.

NG, W., 2013. Transoral endoscopic thyroidectomy. *Surgical Practice,* **17**(2), pp. 77-78.

NGUYEN, H.X., NGUYEN, H.X., NGUYEN, H.V., NGUYEN, L.T., NGUYEN, T.T.P. and LE, Q.V., 2020. Transoral Endoscopic Thyroidectomy by Vestibular Approach with Central Lymph Node Dissection for Thyroid Microcarcinoma. *Journal of Laparoendoscopic & Advanced Surgical Techniques. Part A,* **31**(4), pp. 410-415.

OTTONE, N.E., VARGAS, C.A., FUENTES, R. and DEL SOL, M., 2016. Walter Thiel's Embalming Method: Review of Solutions and Applications in Different Fields of Biomedical Research. *International Journal of Morphology,* **34**(4), pp. 1442-1454.

OZGUR, Z., CELIK, S., GOVSA, F. and OZGUR, T., 2011. Anatomical and surgical aspects of the lobes of the thyroid glands. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery,* **268**(9), pp. 1357-1363.

PARK, J., KIM, C.S., SONG, J., KIM, J., NAM, I., LEE, S., CHUN, B., CHO, J., JOO, Y., CHO, K., PARK, Y.H., KIM, M. and SUN, D., 2014. Transoral endoscopic thyroidectomy via the tri-vestibular routes: results of a preclinical cadaver feasibility study. *European archives of oto-rhino-laryngology: official journal of the European Federation of Oto-Rhino-*

Laryngological Societies (EUFOS): affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery, **271**(12), pp. 3269-3275.

PARK, J., PARK, Y.J., KIM, M.R., SUN, D., KIM, M. and KOH, Y.W., 2019. Gasless transoral endoscopic thyroidectomy vestibular approach (gasless TOETVA). *Surgical Endoscopy,* **33**(9), pp. 3034-3039.

PARK, J. and SUN, D., 2017. Transoral endoscopic thyroidectomy: our initial experience using a new endoscopic technique. *Surgical Endoscopy,* **31**(12), pp. 5436-5443.

PARK, J., WANG, S., PARK, D., BAE, I., LEE, J., LEE, B. and SHIN, S., 2019. The Feasibility of a Prototype Thyroidoscope for Gasless Transoral Endoscopic Thyroidectomy: A Preclinical Cadaver Study. *Journal of Laparoendoscopic & Advanced Surgical Techniques. Part A,* **29**(7), pp. 953-957.

PAULI, A.M., BENTLEY, E., DIEHL, K.A. and MILLER, P.E., 2006. Effects of the application of neck pressure by a collar or harness on intraocular pressure in dogs. *Journal of the American Animal Hospital Association,* **42**(3), pp. 207-211.

PÉREZ-SOTO, R.H., PONCE DE LEÓN-BALLESTEROS, G., MONTALVO-HERNÁNDEZ, J., SIERRA-SALAZAR, M., PANTOJA MILLÁN, J.P., HERRERA-HERNÁNDEZ, M.F. and VELÁZQUEZ-FERNÁNDEZ, D., 2019. Transoral Endoscopic Thyroidectomy by Vestibular Approach-Initial Experience and Comparative Analysis in the First Reported Mexican Cohort. *Journal of Laparoendoscopic & Advanced Surgical Techniques. Part A,* **29**(12), pp. 1526-1531.

PERRIER, N.D. and ANGELOS, P., 2020. Distant-Access Robotic Thyroidectomy—Is It Worth the Cost? *JAMA Surgery,* **155**(11), pp. 1010-1012.

PHITAYAKORN, R., KELZ, R.R., PETRUSA, E., SIPPEL, R.S., STURGEON, C., PATEL, K.N. and PERRIER, N.D., 2017. Expert consensus of general surgery residents' proficiency with common endocrine operations. *Surgery,* **161**(1), pp. 280-288.

PORZIONATO, A., POLESE, L., LEZOCHE, E., MACCHI, V., LEZOCHE, G., DA DALT, G., STECCO, C., NORBERTO, L., MERIGLIANO, S. and DE CARO, R., 2015. On the suitability of Thiel cadavers for natural orifice transluminal endoscopic surgery (NOTES): surgical training, feasibility studies, and anatomical education. *Surgical Endoscopy,* **29**(3), pp. 737-746.

PRADEEP, P.V., 2021. Scar satisfaction assessment after conventional thyroidectomy: follow-up results. *Acta Otorhinolaryngologica Italica: Organo Ufficiale Della Societa Italiana Di Otorinolaringologia E Chirurgia Cervico-Facciale,* **41**(1), pp. 39-42.

PRETE, F.P., MARZAIOLI, R., LATTARULO, S., PARADIES, D., BARILE, G., D'ADDETTA, M.V., TOMASICCHIO, G., GURRADO, A. and PEZZOLLA, A., 2019. Transaxillary robotic-assisted thyroid surgery: technique and results of a preliminary experience on the Da Vinci Xi platform. *BMC surgery,* **18**(Suppl 1), pp. 19.

QIU, T.Y., LAU, J., WONG, O., OH, H.B., BOON, T.W., PARAMESWARAN, R. and NGIAM, K.Y., 2020. Preoperative scar perception study comparing 'scarless' in the neck endoscopic thyroidectomy with open thyroidectomy: a cross-sectional study. *Annals of the Royal College of Surgeons of England,* **102**(9), pp. 737-743.

RAJAEI, S.M., ASADI, F., RAJABIAN, M.R., OSTADHASSAN, H. and CRASTA, M., 2018. Effect of body position, eyelid manipulation, and manual jugular compression on intraocular pressure in clinically normal cats. *Veterinary Ophthalmology,* **21**(2), pp. 140-143.

RAO, R.S. and DUNCAN, T.D., 2009. Endoscopic total thyroidectomy. *JSLS : Journal of the Society of Laparoendoscopic Surgeons,* **13**(4), pp. 522-527.

RAZAVI, C.R., TUFANO, R.P. and RUSSELL, J.O., 2019. Starting a Transoral Thyroid and Parathyroid Surgery Program. *Current Otorhinolaryngology Reports,* **7**(3), pp. 204-208.

RAZAVI, C.R., VASILIOU, E., TUFANO, R.P. and RUSSELL, J.O., 2018. Learning Curve for Transoral Endoscopic Thyroid Lobectomy. *Otolaryngology--Head and Neck Surgery: Official Journal of American Academy of Otolaryngology-Head and Neck Surgery,* **159**(4), pp. 625-629.

REGE, S.A., JANESH, M., SURPAM, S., SHIVANE, V., ARORA, A. and SINGH, A., 2019. Transoral endoscopic thyroidectomy using vestibular approach: A single center experience. *Journal of Postgraduate Medicine,* **65**(2), pp. 81-86.

RICHMON, J.D., 2020. Lateral Vestibular Approach to the Central Neck for Thyroid and Parathyroid Surgery: A Cadaveric Study. *Journal of Laparoendoscopic & Advanced Surgical Techniques. Part A,* **31**(5), pp. 579-583.

ROBINSON, N.B., KRIEGER, K., KHAN, F.M., HUFFMAN, W., CHANG, M., NAIK, A., YONGLE, R., HAMEED, I., KRIEGER, K., GIRARDI, L.N. and GAUDINO, M., 2019. The current state of animal models in research: A review. *International Journal of Surgery (London, England),* **72**, pp. 9-13.

ROGERS-STEVANE, J. and KAUFFMAN, G.L.,Jr, 2008. A historical perspective on surgery of the thyroid and parathyroid glands. *Otolaryngologic clinics of North America,* **41**(6), pp. 1059-67, vii.

ROMAN, B.R., RANDOLPH, G.W. and KAMANI, D., 2019. Conventional Thyroidectomy in the Treatment of Primary Thyroid Cancer. *Endocrinology and Metabolism Clinics of North America,* **48**(1), pp. 125-141.

ROSEN, R.D. and SAPRA, A., 2020. Embryology, Thyroid. *StatPearls.* Treasure Island (FL): StatPearls Publishing, https://www.ncbi.nlm.nih.gov/books/NBK551611/ (Accessed 21st May 2020).

RUAN, Y., ROBINSON, N.B., KHAN, F.M., HAMEED, I., RAHOUMA, M., NAIK, A., OAKLEY, C.T., RONG, L., GIRARDI, L.N. and GAUDINO, M., 2020. The translation of surgical animal models to human clinical research: A cross-sectional study. *International Journal of Surgery (London, England),* **77**, pp. 25-29.

RUBINO, F., PAMOUKIAN, V.N., ZHU, J.F., DEUTSCH, H., INABNET, W.B. and GAGNER, M., 2000. Endoscopic endocrine neck surgery with carbon dioxide insufflation: the effect on intracranial pressure in a large animal model. *Surgery,* **128**(6), pp. 1035-1042.

RUGGIERO, R., DOCIMO, G., BOSCO, A., LANZA VOLPE, M., TERRACCIANO, G., GUBITOSI, A. and DOCIMO, L., 2018. Update on sutureless thyroidectomy. *Il Giornale Di Chirurgia,* **39**(1), pp. 45-50.

RUIZ-TOVAR, J., PRIETO-NIETO, I., GARCÍA-OLMO, D., CLASCÁ, F., ENRIQUEZ, P., VILLALONGA, R. and ZUBIAGA, L., 2019. Training Courses in Laparoscopic Bariatric Surgery on Cadaver Thiel: Results of a Satisfaction Survey on Students and Professors. *Obesity Surgery,* **29**(11), pp. 3465-3470.

RUSSELL, J.O., CLARK, J., NOURELDINE, S.I., ANUWONG, A., AL KHADEM, M.G., YUB KIM, H., DHILLON, V.K., DIONIGI, G., TUFANO, R.P. and RICHMON, J.D., 2017. Transoral thyroidectomy and parathyroidectomy - A North American series of robotic and endoscopic transoral approaches to the central neck. *Oral Oncology,* **71**, pp. 75-80.

RUSSELL, J.O., RAZAVI, C.R., SHAEAR, M., CHEN, L.W., LEE, A.H., RANGANATH, R. and TUFANO, R.P., 2019. Transoral Vestibular Thyroidectomy: Current State of Affairs and Considerations for the Future. *The Journal of Clinical Endocrinology and Metabolism,* .

SABUNCUOGLU, M.Z., SABUNCUOGLU, A., SOZEN, I., BENZIN, M.F., CAKIR, T. and CETIN, R., 2014. Minimally invasive surgery using mini anterior incision for thyroid diseases: a prospective cohort study. *International Journal of Clinical and Experimental Medicine,* **7**(10), pp. 3404-3409.

SAHM, M., OTTO, R., PROSS, M. and MANTKE, R., 2019. Minimally invasive video-assisted thyroidectomy: a critical analysis of long-term cosmetic results using a validated tool. *Annals of the Royal College of Surgeons of England,* **101**(3), pp. 180-185.

SAMRAJ, K. and GURUSAMY, K.S., 2007. Wound drains following thyroid surgery. *The Cochrane database of systematic reviews,* doi: 10.1002/14651858.CD006099.pub2.

SANABRIA, A., KOWALSKI, L.P., SHAH, J.P., NIXON, I.J., ANGELOS, P., WILLIAMS, M.D., RINALDO, A. and FERLITO, A., 2018. Growing incidence of thyroid carcinoma in recent years: Factors underlying overdiagnosis. *Head & Neck,* **40**(4), pp. 855-866.

SARAGAS, N.P., FERRAO, P.N.F. and STRYDOM, A., 2021. A new lesser metatarsophalangeal joint replacement arthroplasty design - in vitro and cadaver studies. *BMC musculoskeletal disorders,* **22**(1), pp. 424.

SARKAR, A., KALSI, R., AYERS, J.D., DRUCKER, C.B., KAUSHAL, V., SUTTON, W. and CRAWFORD, R.S., 2018. Continuous Flow Perfused Cadaver Model for Endovascular Training, Research, and Development. *Annals of Vascular Surgery,* **48**, pp. 174-181.

SARKAR, S., BANERJEE, S., SARKAR, R. and SIKDER, B., 2016. A Review on the History of 'Thyroid Surgery'. *The Indian journal of surgery,* **78**(1), pp. 32-36.

SAVA, J., VELMAHOS, G.C., KARAISKAKIS, M., KIRKMAN, P., TOUTOUZAS, K., SARKISYAN, G., CHAN, L. and DEMETRIADES, D., 2003. Abdominal insufflation for prevention of exsanguination. *The Journal of Trauma,* **54**(3), pp. 590-594.

SEPHTON, B.M., 2019. Extracervical Approaches to Thyroid Surgery: Evolution and Review. *Minimally Invasive Surgery,* doi: 10.1155/2019/5961690.

SETHUKUMAR, P., LY, D., AWAD, Z. and TOLLEY, N.S., 2018. Scar satisfaction and body image in thyroidectomy patients: prospective study in a tertiary referral centre. *The Journal of Laryngology and Otology,* **132**(1), pp. 60-67.

SHAH, S.B., HARIHARAN, U., KULKARNI, A. and DABAS, N.C., 2016. Anaesthesia for robotic thyroidectomy for thyroid cancer and review of literature. *Indian Journal of Anaesthesia,* **60**(1), pp. 55-57.

SHANKS, N., GREEK, R. and GREEK, J., 2009. Are animal models predictive for humans? *Philosophy, ethics, and humanities in medicine: PEHM,* **4**, pp. 2.

SHARMA, M., MACAFEE, D., PRANESH, N. and HORGAN, A.F., 2012. Construct validity of fresh frozen human cadaver as a training model in minimal access surgery. *Journal of the Society of Laparoendoscopic Surgeons,* **16**(3), pp. 345-352.

SHEIKH, N.A., KHATTAK, S.F., ALEEM, A. and NADEEM, K., 2019. Diverse Anatomical Configuration Of Recurrent Laryngeal Nerve In Relation To Inferior Thyroid Artery, An Experience With 51 Thyroidectomies. *Journal of Ayub Medical College, Abbottabad: JAMC,* **31**(2), pp. 168-171.

SIMENTAL, A.A. and MYERS, E.N., 2003. Thyroidectomy: Technique and applications. *Operative Techniques in Otolaryngology-Head and Neck Surgery; Thyroid/Parathyroid Surgery,* **14**(2), pp. 63-73.

SIVAKUMAR, T. and AMIZHTHU, R.A., 2018. Transoral endoscopic total thyroidectomy vestibular approach: A case series and literature review. *Journal of Minimal Access Surgery,* **14**(2), pp. 118-123.

SLETTEDAL, J.K., TRAUSTADÓTTIR, V.D., SANDVIK, L. and RINGVOLD, A., 2020. The prevalence and incidence of glaucoma in Norway 2004-2018: A nationwide population-based study. *PloS One,* **15**(12), pp. e0242786.

SMITH, R.B. and COUGHLIN, A., 2016. Thyroidectomy Hemostasis. *Otolaryngologic clinics of North America,* **49**(3), pp. 727-748.

SPARTALIS, E., NTOKOS, G., GEORGIOU, K., ZOGRAFOS, G., TSOUROUFLIS, G., DIMITROULIS, D. and NIKITEAS, N.I., 2020. Intraoperative Indocyanine Green (ICG) Angiography for the Identification of the Parathyroid Glands: Current Evidence and Future Perspectives. *In Vivo,* **34**(1), pp. 23-32.

SU, Y., TANG, Z., DING, Z., WANG, H., WU, T., LIANG, J., CEN, H., ZHAO, X., DING, J., HUA, W. and TANG, C., 2013. [Total trans-oral endoscopic thyroidectomy and cervical lymphadenectomy: a human cadavers surgery study]. *Zhonghua Wai Ke Za Zhi [Chinese Journal of Surgery],* **51**(6), pp. 552-555.

TAE, K., 2020a. Complications of Transoral Thyroidectomy: Overview and Update. *Clinical and Experimental Otorhinolaryngology,* **4**(2): pp169–178.

TAE, K., 2020b. Transoral Robotic Thyroid Surgery: Technical Considerations. *Journal of Head & Neck Physicians and Surgeons,* **8**(2), pp. 53-60.

TAN, C.T., CHEAH, W.K. and DELBRIDGE, L., 2008. "Scarless" (in the neck) endoscopic thyroidectomy (SET): an evidence-based review of published techniques. *World journal of surgery,* **32**(7), pp. 1349-1357.

TAPSCOTT, W.J., 2001. A brief history of thyroid surgery. *Current surgery,* **58**(5), pp. 464-466.

TENG, C., GURSES-OZDEN, R., LIEBMANN, J.M., TELLO, C. and RITCH, R., 2003. Effect of a tight necktie on intraocular pressure. *The British Journal of Ophthalmology,* **87**(8), pp. 946-948.

TERRIS, D.J., 2009. Novel surgical maneuvers in modern thyroid surgery. *Operative Techniques in Otolaryngology-Head and Neck Surgery,* **20**(1), pp. 23-28.

TESSEROLI, M.A.S., SPAGNOL, M. and SANABRIA, Á, 2018. Transoral endoscopic thyroidectomy by vestibular approach (TOETVA): initial experience in Brazil. *Revista Do Colegio Brasileiro De Cirurgioes,* **45**(5), pp. e1951.

THIAGARAJAN, B., 2015. Anatomy of thyroid gland Surgeon's perspective. *Otolaryngology online journal,* **5**(3), ISSN :2250-0359.

THOMAS, A.M., FAHIM, D.K. and GEMECHU, J.M., 2020. Anatomical Variations of the Recurrent Laryngeal Nerve and Implications for Injury Prevention during Surgical Procedures of the Neck. *Diagnostics (Basel, Switzerland),* **10**(9), pp. 670

THOMAS, G., MCWADE, M.A., PARAS, C., MANNOH, E.A., SANDERS, M.E., WHITE, L.M., BROOME, J.T., PHAY, J.E., BAREGAMIAN, N., SOLÓRZANO, C.C. and MAHADEVAN-JANSEN, A., 2018. Developing a Clinical Prototype to Guide Surgeons for Intraoperative Label-Free Identification of Parathyroid Glands in Real Time. *Thyroid,* **28**(11), pp. 1517-1531.

TIRUNEH, C., 2021. Acute Adverse Effects of Formaldehyde Treated Cadaver on New Innovative Medical Students and Anatomy Staff Members in the Dissection Hall at Wollo University, Northeast Ethiopia. *Advances in Medical Education and Practice,* **12**, pp. 41-47.

TOLLEY, N.S. and CAMENZULI, C., 2020. Robotic Thyroidectomy. In: M.L.K. KAPRE, ed, *Thyroid Surgery.* Boca Raton: CRC Press, pp. 91-95.

UDELSMAN, R., ANUWONG, A., OPREA, A.D., RHODES, A., PRASAD, M., SANSONE, M., BROOKS, C., DONOVAN, P.I., JANNITTO, C. and CARLING, T., 2016. Trans-oral Vestibular Endocrine Surgery: A New Technique in the United States. *Annals of Surgery,* **264**(6), pp. e13-e16.

USAMI, T., FUJIOKA, T., YOSHIDA, A., MIYAUE, H., YASUOKA, T., UCHIKURA, Y., TAKAGI, K., MATSUBARA, Y., MATSUMOTO, T., MATSUBARA, K. and SUGIYAMA, T., 2018. Assessment of laparoscopic training for gynecological malignancies using Thiel-embalmed human cadavers. *Molecular and Clinical Oncology,* **9**(5), pp. 511-514.

VAN DEN HAAK, L., ALLEBLAS, C., RHEMREV, J.P., SCHELTES, J., NIEBOER, T.E. and JANSEN, F.W., 2017. Human cadavers to evaluate prototypes of minimally invasive surgical instruments: A feasibility study. *Technology and Health Care: Official Journal of the European Society for Engineering and Medicine,* **25**(6), pp. 1139-1146.

VAN SLYCKE, S., VAN DEN HEEDE, K., BRUGGEMAN, N., VERMEERSCH, H. and BRUSSELAERS, N., 2021. Risk factors for postoperative morbidity after thyroid surgery in a PROSPECTIVE cohort of 1500 patients. *International Journal of Surgery (London, England),* **88**, pp. 105922.

VELLAR, I.D., 1999. Thomas Peel Dunhill: pioneer thyroid surgeon. *The Australian and New Zealand Journal of Surgery,* **69**(5), pp. 375-387.

VELMAHOS, G.C., SPANIOLAS, K., DUGGAN, M., ALAM, H.B., TABBARA, M., DE MOYA, M. and VOSBURGH, K., 2007. Abdominal insufflation for control of bleeding after severe splenic injury. *The Journal of Trauma,* **63**(2), pp. 285-290.

VENNE, G., ZEC, M.L., WELTE, L. and NOEL, GEOFFROY P. J. C., 2020. Qualitative and quantitative comparison of Thiel and phenol-based soft-embalmed cadavers for surgery training. *Anatomia, Histologia, Embryologia,* **49**(3), pp. 372-381.

VILLACORTA, P.R., HERNANDO, H.C., ABDULLA, A.J. and BARROA, J.K., 2019. A Comparative Study of Thiel Soft-embalmed and Formalin Preserved Cadavers for Anatomy Dissection. *ACTA MEDICA PHILIPPINA,* **53**(1), pp. 12-20.

VURAL, V., COMCALI, B., SAYLAM, B. and COSKUN, F., 2021. Identification of the recurrent laryngeal nerve during thyroidectomy can affect the complication rate. *Annali Italiani Di Chirurgia,* **92**, pp. 217-226.

WAERLOP, F., RASHIDIAN, N., MARRANNES, S., D'HERDE, K. and WILLAERT, W., 2020. Thiel embalmed human cadavers in surgical education: Optimizing realism and long-term application. *American Journal of Surgery,* **221**(6), pp. 1300-1302.

WANG, C., ZHAI, H., LIU, W., LI, J., YANG, J., HU, Y., HUANG, J., YANG, W., PAN, Y. and DING, H., 2014. Thyroidectomy: a novel endoscopic oral vestibular approach. *Surgery,* **155**(1), pp. 33-38.

WANG, T., WU, Y., XIE, Q., YAN, H., ZHOU, X., YU, X., CHEN, Y., XIANG, C., YAN, H., ZHAO, Q., ZHANG, M., QI, M., WANG, P. and WANG, Y., 2020. Safety of central compartment neck dissection for transoral endoscopic thyroid surgery in papillary thyroid carcinoma. *Japanese Journal of Clinical Oncology,* **50**(4), pp. 387-391.

WANG, T.S. and SOSA, J.A., 2018. Thyroid surgery for differentiated thyroid cancer - recent advances and future directions. *Nature Reviews. Endocrinology,* **14**(11), pp. 670-683.

WANG, Y., XIE, Q.P., YU, X., XIANG, C., ZHANG, M.L., ZHAO, Q.Z., YAN, H.C., WANG, P. and XU, S.M., 2017. [Preliminary experience with transoral endoscopic thyroidectomy via vestibular approach: a report of 150 cases in a single center]. *Zhonghua Wai Ke Za Zhi [Chinese Journal of Surgery],* **55**(8), pp. 587-591.

WANG, Y., ZHOU, S., LIU, X., RUI, S., LI, Z., ZHU, J. and WEI, T., 2021. Transoral endoscopic thyroidectomy vestibular approach vs conventional open thyroidectomy: Meta-analysis. *Head & Neck,* **43**(1), pp. 345-353.

WANG, Y., ZHANG, Z., ZHAO, Q., XIE, Q., YAN, H., YU, X., XIANG, C., ZHANG, M. and WANG, P., 2018. Transoral endoscopic thyroid surgery via the tri-vestibular approach with a hybrid space-maintaining method: A preliminary report. *Head & Neck,* **40**(8), pp. 1774-1779.

WILHELM, T., HARLAAR, J., KERVER, A., KLEINRENSINK, G.J. and BENHIDJEB, T., 2010. Transoral endoscopic thyroidectomy. Part 1: rationale and anatomical studies. *Der Chirurg; Zeitschrift fur alle Gebiete der operativen Medizen,* **81**(1), pp. 50-55.

WILHELM, T., HARLAAR, J.J., KERVER, A., KLEINRENSINK, G. and BENHIDJEB, T., 2010. Surgical anatomy of the floor of the oral cavity and the cervical spaces as a rationale for trans-oral, minimal-invasive endoscopic surgical procedures: results of anatomical studies. *European archives of oto-rhino-laryngology: official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS): affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery,* **267**(8), pp. 1285-1290.

WILHELM, T. and METZIG, A., 2010. Endoscopic minimally invasive thyroidectomy: first clinical experience. *Surgical endoscopy,* **24**(7), pp. 1757-1758.

WILHELM, T., WU, G., TEYMOORTASH, A., GÜLDNER, C., GÜNZEL, T. and HOCH, S., 2016. Transoral endoscopic thyroidectomy: current state of the art—a systematic literature review and results of a bi-center study. *Translational Cancer Research,* **5**(7), pp. S1521-S1530.

WISEMAN, S.M., TOMLJANOVICH, P.I. and RIGUAL, N.R., 2004. Thyroid lobectomy: Operative anatomy, technique, and morbidity. *Operative Techniques in Otolaryngology-Head and Neck Surgery; Surgery for Neck Masses,* **15**(3), pp. 210-219.

WITZEL, K., VON RAHDEN, B. H. A., KAMINSKI, C. and STEIN, H.J., 2008. Transoral access for endoscopic thyroid resection. *Surgical Endoscopy,* **22**(8), pp. 1871-1875.

WOLFF, K., FICHTER, A., BRAUN, C., BAUER, F. and HUMBS, M., 2014. Flap raising on pulsatile perfused cadaveric tissue: a novel method for surgical teaching and exercise. *Journal of Cranio-Maxillo-Facial Surgery: Official Publication of the European Association for Cranio-Maxillo-Facial Surgery,* **42**(7), pp. 1423-1427.

WU, C., DIONIGI, G., BARCZYNSKI, M., CHIANG, F., DRALLE, H., SCHNEIDER, R., AL-QUARYSHI, Z., ANGELOS, P., BRAUCKHOFF, K., BROOKS, J.A., CERNEA, C.R., CHAPLIN, J., CHEN, A.Y., DAVIES, L., DIERCKS, G.R., DUH, Q.Y., FUNDAKOWSKI, C., GORETZKI, P.E., HALES, N.W., HARTL, D., KAMANI, D., KANDIL, E., KYRIAZIDIS, N., LIDDY, W., MIYAUCHI, A., ORLOFF, L., RASTATTER, J.C., SCHARPF, J., SERPELL, J., SHIN, J.J., SINCLAIR, C.F., STACK, B.C., TOLLEY, N.S., SLYCKE, S.V., SNYDER, S.K., URKEN, M.L., VOLPI, E., WITTERICK, I., WONG, R.J., WOODSON, G., ZAFEREO, M. and RANDOLPH, G.W., 2018. International neuromonitoring study group guidelines 2018: Part II: Optimal recurrent laryngeal nerve management for invasive thyroid cancer-incorporation of surgical, laryngeal, and neural electrophysiologic data. *The Laryngoscope,* **128 Suppl 3**, pp. S18-S27.

XU, Z., SONG, J., WANG, Y., TAN, L., SUN, S. and MENG, Y., 2019. A comparison of transoral vestibular and bilateral areolar endoscopic thyroidectomy approaches for unilateral papillary thyroid microcarcinomas. *Wideochirurgia I Inne Techniki Maloinwazyjne = Videosurgery and Other Miniinvasive Techniques,* **14**(4), pp. 501-508.

YAN, H., WANG, Y., HUANG, P., HONG, Y., YE, Q., XIE, Q., ZHAO, Q. and WANG, P., 2019. Scarless neck endoscopic thyroidectomy via the breast approach: A preliminary report of 45 cases with total or near-total thyroidectomy plus central compartment dissection. *Nigerian Journal of Clinical Practice,* **22**(12), pp. 1772-1777.

YAN, H., XIANG, C., WANG, Y. and WANG, P., 2020. Scarless endoscopic thyroidectomy (SET) lateral neck dissection for papillary thyroid carcinoma through breast approach: 10 years of experience. *Surgical Endoscopy,* **35**(7), pp. 3540-3546.

YANG, H., SHIN, K., MIN, J. and WOO, S.H., 2020. Anatomical study of gasless transoral thyroidectomy and clinical application. *Surgical Endoscopy,* **34**(8), pp. 3414-3423.

YANG, J., WANG, C., LI, J., YANG, W., CAO, G., WONG, H., ZHAI, H. and LIU, W., 2015. Complete Endoscopic Thyroidectomy via Oral Vestibular Approach Versus Areola Approach for Treatment of Thyroid Diseases. *Journal of Laparoendoscopic & Advanced Surgical Techniques. Part A,* **25**(6), pp. 470-476.

YANG, K., DING, B., LIN, C., LI, W. and LI, X., 2016. The Novel Transvestibule Approach for Endoscopic Thyroidectomy: A Case Series. *Surgical Laparoscopy, Endoscopy & Percutaneous Techniques,* **26**(1), pp. e25-e28.

YANG, S.M., PARK, W.S., YOU, J.Y., PARK, D.W., KANGLEON-TAN, H.L., KIM, H.K., DIONIGI, G., KIM, H.Y. and TUFANO, R.P., 2020. Comparison of postoperative outcomes between bilateral axillo-breast approach-robotic thyroidectomy and transoral robotic thyroidectomy. *Gland Surgery,* **9**(6), pp. 1998-2004.

YI, J.W., YOON, S.G., KIM, H.S., YU, H.W., KIM, S., CHAI, Y.J., CHOI, J.Y. and LEE, K.E., 2018. Transoral endoscopic surgery for papillary thyroid carcinoma: initial experiences of a single surgeon in South Korea. *Annals of Surgical Treatment and Research,* **95**(2), pp. 73-79.

YIASEMIDOU, M., ROBERTS, D., GLASSMAN, D., TOMLINSON, J., BIYANI, S. and MISKOVIC, D., 2017. A Multispecialty Evaluation of Thiel Cadavers for Surgical Training. *World Journal of Surgery,* **41**(5), pp. 1201-1207.

YU, D.Y., CHANG, Y.W., LEE, H.Y., KIM, W.Y., KIM, H.Y., LEE, J.B. and SON, G.S., 2021. Detailed comparison of the da Vinci Xi and S surgical systems for transaxillary thyroidectomy. *Medicine,* **100**(3), pp. e24370.

YU, T., CHENG, Y., WANG, X., TU, B., CHENG, N., GONG, J. and BAI, L., 2017. Gases for establishing pneumoperitoneum during laparoscopic abdominal surgery. *The Cochrane Database of Systematic Reviews,* **6**, pp. CD009569.

ZAMMIT, M., 2018-last update, More Maltese donate their corpse for University research - TVM News. Available: https://www.tvm.com.mt/en/news/more-maltese-donate-their-corpse-for-university-research/ (Accesed 29th May 2019).

ZHANG, D., PARK, D., SUN, H., ANUWONG, A., TUFANO, R., KIM, H.Y. and DIONIGI, G., 2019. Indications, benefits and risks of transoral thyroidectomy. *Best Practice & Research. Clinical Endocrinology & Metabolism,* **33**(4), pp. 101280.

ZHANG, D., SUN, H., TUFANO, R., CARUSO, E., DIONIGI, G. and KIM, H.Y., 2020. Recurrent laryngeal nerve management in transoral endoscopic thyroidectomy. *Oral Oncology,* **108**, pp. 104755.

ZHANG, D., WU, C., INVERSINI, D., KIM, H.Y., ANUWONG, A., BACUZZI, A. and DIONIGI, G., 2018. Lessons Learned From a Faulty Transoral Endoscopic Thyroidectomy Vestibular Approach. *Surgical Laparoscopy, Endoscopy & Percutaneous Techniques,* **28**(5), pp. e94-e99.

ZHANG, D., ZHANG, J., DIONIGI, G., LI, F., WANG, T., LI, H., LIANG, N. and SUN, H., 2019. Recurrent Laryngeal Nerve Morbidity: Lessons from Endoscopic via Bilateral Areola and Open Thyroidectomy Technique. *World Journal of Surgery,* **43**(11), pp. 2829-2841.

ZHANG, P., ZHANG, H.-., HAN, X.-., DI, J.-. and ZHENG, Q., 2015. Meta-analysis of comparison between minimally invasive video-assisted thyroidectomy and conventional thyroidectomy. *European Review for Medical and Pharmacological Sciences,* **19**(8), pp. 1381-1387.

ZHENG, J., SONG, H., CAI, S., WANG, Y., HAN, X., WU, H., GAO, Z. and QIU, F., 2017. Evaluation of clinical significance and risk factors of incidental parathyroidectomy due to thyroidectomy: A single-center retrospective clinical study. *Medicine,* **96**(39), pp. e8175.

Appendix 1: Approval by the Research Ethics Committee

L-UNIVERSITÀ TA' MALTA
Msida - Malta
SKOLA MEDIKA
Sptar Mater Dei

UNIVERSITY OF MALTA
Msida - Malta
MEDICAL SCHOOL
Mater Dei Hospital

Ref No: **38/2015**

Tuesday 6th October 2015

Mr Christian Camenzuli
192, Ignazio Saverio Mifsud Street
Birkirkara

Dear Mr Christian Camenzuli,

Please refer to your application submitted to the Research Ethics Committee in connection with your research entitled:

Development of a Scarless and Gasless Trans-Oral Video-Assisted Thyroidectomy

The University Research Ethics Committee granted ethical approval for the above mentioned protocol.

Yours sincerely,

Dr. Mario Vassallo
Chairman
Research Ethics Committee

E-MAIL: umms@um.edu.mt WEB: www.um.edu.mt/ms

Appendix 2: The process of procuring and Thiel embalming cadavers for research.

The University of Malta has a programme through which, individuals who, during their life, express a wish to leave their body for medical studies and research, can do so in a transparent way. These individuals will have to declare their intention when they are still alive where they give informed consent through a bequeathal form. In this form, which has to be signed in the presence of a next-of-kin as a witness, the individual declares his medical and surgical co-morbidities. The prospective donors had to insert a codicil in their will that clearly states their wish. The latter requirement was revoked as of February 2020 (L-Università ta' Malta 2020). The individual can choose to limit the period of time during which his body is available for research. They can also choose whether this applies to all the body or limited to certain body parts. In the process, the individuals are also asked to consent for use of images (in the form of photography or scans) or videos for the use of teaching or research. Individuals are encouraged to make their caring doctors and close family members and next of kin aware of their wishes. When the individual passes away, the lab manager at the Department of Anatomy, University of Malta has to be notified within 12 hours and arrangements are made to transfer the body once the death certificate is signed. There are exceptional circumstances when a body (of an individual who consented through the bequeathal form to donate their body) would not be accepted. These circumstances include presence of communicable disease with substantial risk at time of demise, body weight of more then 120kg and the need for a forensic autopsy (L-Università ta' Malta 2020).

The process of Thiel embalming used to preserve the cadavers which were utilised for this research entails the dual process of initial intravenous infusion and subsequent whole body immersion. Several chemicals are used to perform this process (Table 4). For the intravenous infusion phase of the embalming process, a total of 15.8 litres of embalming solution is pumped through the venous access (typically attained through the femoral artery and vein) using a peristaltic pump achieving a flow rate of 0.17 to 19ml/min. The embalming solution is made up of 14.3 litres of solution A, 0.5 litres of solution B, 300 millilitres of formalin, 700 grams of sodium sulphite and then topped up with water to achieve the 15.8 litres. After the intravenous infusion phase the whole body is submerged for a minimum of 4 to 6 weeks in the same embalming solution with the use of specialised tanks. Modifications to this recipe for Thiel embalming of cadavers have been developed over the years to accommodate local requirements and improve efficiency (Ottone, Vargas et al. 2016)

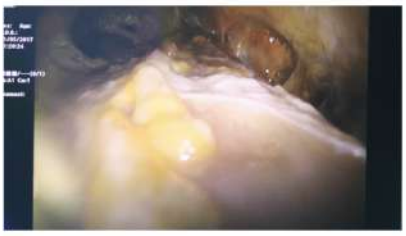
Reagent		Manufacturer	City	Country
Solution A	Boric acid 3%	ETiMADEN	Ankara	Turkey
	Mono-ethylene glycol 30%	Chemic Ltd	Sliema	Malta
	Ammonium nitrate 20%	YaraTera™	Oslo	Norway
	Potassium nitrate 5%	Azoty Chorzów	Chorzów	Poland
	Water	NA	NA	NA
Solution B	Monoethylene glycol 10%	Chemic Ltd	Sliema	Malta
	4-chloro-3-methylphenol 1%	Scharlau	Barcelona	Spain
Formalin 300mls		Brenntag	Essen	Germany
Sodium Sulphite 700g		Esseco	San Martino	Italy

Reagents used for the Thiel embalming of cadavers

The Thiel embalming method offers fixation of tissues mainly by 4-chloro-3-methylphenol but also with the help of a relatively small amount of formalin. Disinfection, mainly bactericidal activity, is delivered to the tissue through the use of boric acid. Finally, the use of ethylene glycol contributes to the process that helps maintain tissue plasticity. The salts that are used to develop the embalming solution have the dual function of extracting water from tissues (a function mainly attributed to sodium sulphite) and giving a more pronounced colour to the tissues (mainly due to the nitrates used).

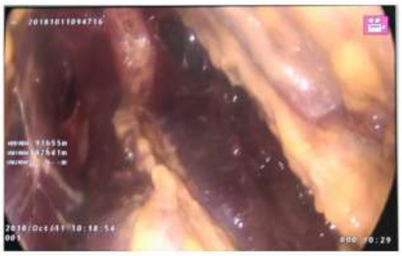
Appendix 3: Stages as presented to the expert panel

A



At this stage of the procedure the subplatysmal plane has been developed. In the field of vision one should be able to see the strap muscles divided by the linea alba cervicalis.

B



At this stage of the procedure the subplatysmal plane has been developed. In the field of vision one should be able to see the strap muscles divided by the linea alba cervicalis.

C

At this stage of the procedure the linea alba cervicalis has been opened. The thyroid isthmus has been dissected centrally off the trachea and is being lifted on the working instrument.

D

At this stage of the procedure the linea alba cervicalis has been opened. The thyroid isthmus has been dissected centrally off the trachea and is being lifted on the working instrument.

E

At this stage of the procedure the thyroid isthmus has been divided centrally and and the strap muscle dissected of the left thyroid lobe. The lobe is retracted supero-medially using a grasper.

F

At this stage of the procedure the thyroid isthmus has been divided centrally and and the strap muscle dissected of the right thyroid lobe. The lobe is retracted supero-medially using a grasper.

A	/10	
B	/10	
C	/10	
D	/10	
E	/10	
F	/10	

Kindly score each picture from 1 to 10 were a score of 1 means completely unidentifiable structures and score of 10 means all structures identifiable with extreme ease. A box for remarks is also provided.

Appendix 4: Initial phase approval for patent grant

Intellectual Property Office

University of Malta
c/o J A Kemp LLP
14 South Square
Gray's Inn, Holborn
LONDON
WC1R 5JJ

Patents Directorate

Concept House
Cardiff Road, Newport
South Wales, NP10 8QQ

Direct Line: 01633 814098
[1]**E-Mail:** Elinor.Styles-Davis@ipo.gov.uk
Switchboard: 0300 300 2000
Fax: 01633 817777
Minicom: 0300 0200 015

Your Reference: N418442GB
Application No: GB2003311.4

21 August 2020

Dear Sirs

Patents Act 1977: Search Report under Section 17(5)

I enclose a copy of my search report. Please note that published patent documents mentioned in my report may be obtained for free on the internet and are usually freely available from http://worldwide.espacenet.com.

Other search results

If you have applied to another patent office for a patent for this invention you will be receiving from them the results of their search. If you decide to proceed with the present application you are asked to provide a copy of any such official search report or details of any documents cited and category assigned in the report. You may file such information electronically using the online patent filing services detailed in https://www.gov.uk/government/publications/how-to-file-documents-with-the-intellectual-property-office.

Cut-off date This request applies to search reports that you have received before the date when you send a response to our first examination report under section 18(3) or section 18(4); if you make no response to an initial section 18(4) report the cut-off date is two months after the date of that report. Tell us about a search report sooner rather than later if that would allow it to be considered during our first examination.

Exceptions You do not have to supply details of a search report that (1) shows a nil response, or (2) has been published by WIPO or EPO, or (3) you have already supplied to us on a previous GB application.

[1]**Use of E-mail:** Please note that e-mail should be used for correspondence only.
Disclaimer: Please note the documents we send you may be subject to copyright.

Intellectual Property Office is an operating name of the Patent Office www.gov.uk/ipo

Intellectual Property Office

Publication

I estimate that preparations for publication of your application will be completed soon after **27 July 2021**. At this time you will receive a letter confirming the exact date of the completion of the preparations for publication. This letter will also tell you the publication number and date of publication of your application. However, it should **NOT** be relied upon as a reminder if you are intending to withdraw your application before publication, as it may not be issued in time for you to do so.

On the date of publication details of your application, including your name and address, will be entered in the Register of Patents and will become publicly available, including on our website. Some documents and correspondence from your application file will also be made publicly available on our website at http://www.ipo.gov.uk/p-ipsum.

Withdrawal

If you wish to withdraw your application to prevent publication you must withdraw it before the preparations for publication are complete. One way that you can withdraw your application is by emailing withdraw@ipo.gov.uk. Further details on withdrawal are available from https://www.gov.uk/patent-your-invention. **WARNING** – once preparations for publication are complete it will NOT be possible to prevent publication.

Amendment

If you wish to file amended claims for inclusion with the published application you must do so before the preparations for publication are completed.

Correspondence

If you write to the Office less than 3 weeks before 27 July 2021 please mark your letter prominently: **"URGENT - PUBLICATION IMMINENT"**.

Yours faithfully

Dr Elinor Styles-Davis

Dr Elinor Styles-Davis
Examiner

Intellectual Property Office

Application No:	GB2003311.4	**Examiner:**	Dr Elinor Styles-Davis
Claims searched:	1-15	**Date of search:**	20 August 2020

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
A	--	US 2018/0303314 A1 (NOYES) See especially Figures 43 and 44, noting endoscope 1447 and balloon dilator 1466
A	--	US 2016/0106300 A1 (NOYES) See especially Figure 6, noting endoscope 102 and manually actuatable tool portion 132

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^{X} :

Worldwide search of patent documents classified in the following areas of the IPC

A61B; A61M

The following online and other databases have been used in the preparation of this search report

WPI, EPODOC

International Classification:

Subclass	Subgroup	Valid From
A61B	0001/273	01/01/2006
A61B	0001/00	01/01/2006
A61B	0001/24	01/01/2006
A61B	0001/32	01/01/2006
A61B	0017/02	01/01/2006
A61M	0016/04	01/01/2006

RETRACTOR DEVICE FOR TRANSORAL INSERTION TO A SURGICAL SITE, AND METHOD OF VIEWING A SURGICAL SITE

This invention relates to a retractor device for supporting transoral surgery, particularly transoral thyroid surgery.

The principals of the transoral approach to thyroid surgery see their origin in 2010 with anatomical studies that assessed the anatomical feasibility of this approach. The technique has since gained ground with systematic reviews showing that the technique is safe and feasible. See, for example, *Camenzuli C, Schembri Wismayer P, Calleja Agius J (2018) Transoral Endoscopic Thyroidectomy: A Systematic Review of the Practice So Far. JSLS; and Camenzuli C, Schembri Wismayer P, Calleja Agius J (2018) Transoral Endoscopic Thyroidectomy: A Systematic Review of the Practice So Far. JSLS.* Transoral thyroidectomy has been deemed superior to previous minimally invasive techniques since it offers effectively scarless surgery whilst keeping the anatomical dead-space between access and gland to a minimum.

An established technique for the transoral approach to thyroid surgery is known as transoral endoscopic thyroidectomy through a vestibular approach (TOETVA). This technique involves the use of carbon dioxide insufflation to keep the surgical space open and therefore allow good visualization during the procedure. Cases of carbon dioxide embolization with potentially lethal consequences secondary to this insufflation have been published. In addition, insufflation might lead to other, usually self-limiting complications. These include surgical emphysema and mediastinal emphysema. It is thought that the risk of such complications can be lessened by reducing the pressure and flow rate of carbon dioxide, but they are not eliminated.

A gasless modification to the transoral technique is known in which a working space is kept open by engaging the skin in the neck with Kirschner 1.2 mm wires and retracting on these (*Nakajo A, Arima H, Hirata M, Mizoguchi T, Kijima Y, Mori S, et al (2013); Trans-Oral Video-Assisted Neck Surgery (TOVANS). A new transoral technique of endoscopic thyroidectomy with gasless premandible approach. Surg Endosc. 27(4):1105-10*). This technique is not completely scarless, however, since the wires need stab incisions in the skin to be engaged.

It is an object of the invention to provide an improved way of allowing the operating space to be kept open during thyroid surgery while avoiding use of gas.

According to an aspect, there is provided a retractor device for transoral insertion to a surgical site, the device comprising: an integral endoscope or an endoscope receiving member configured to receive an endoscope; and a retractor arrangement, the retractor arrangement comprising: an elongate body having a distal end for insertion to a surgical site in a patient and a proximal end that remains outside of the patient during use; an expander member at or adjacent to the distal end of the elongate body, the expander member being switchable between a radially contracted state and a radially expanded state; and a manually actuatable member at or adjacent to the proximal end of the elongate body, the manually actuatable member being coupled to the expander member by an actuation mechanism that switching of the expander member between the radially contracted state and radially expanded state by manipulation of the manually actuatable member, wherein the device is configured such that the endoscope and the elongate body: extend along parallel or coincident longitudinal axes in a proximal direction from the expander member to a longitudinally intermediate position along the elongate body; and diverge from each other in the proximal direction from the longitudinally intermediate position.

The inventors have found that the device as thus configured allows an operator to insert the device with a high degree of control to a surgical site and reliably hold the surgical site open to allow viewing of the surgical site via an endoscope integral with the device or inserted through an integrated port (endoscope receiving member). The device does not require any gas-based mechanism to hold tissue open, nor external incisions of any kind (such as stab incisions). The divergence of axes of the endoscope and elongate body in the proximal direction enhances ease of use by provided greater leverage for a user holding the device, including in respect of small rotations or twists about the longitudinal axis of the device, as well as providing room for a sensor device to be attached to the endoscope at a similar distance from the surgical site to the manually actuatable member. Furthermore, the radial width of the device can be kept small for the portion of the device that will be within the body when the device is inserted to the surgical site, thereby minimizing the risk of injury caused by the device.

In an embodiment, the endoscope extends linearly from the expander member to at least a position that is as far from the expander member as the manually actuatable member. The linear path facilitates guiding of a 5mm 30 degree standard endoscope to allow visualisation.

In an embodiment, a mechanical support member is provided that mechanically couples the endoscope to the elongate body at a position on a proximal side of the longitudinally intermediate position and spaced apart from the longitudinally intermediate position. The mechanical support member ensures that the rigidity of the device can be kept high while making the elongate body sufficiently thin to allow transoral access. It also allows the device and the endoscope to become one unit in embodiments where the endoscope is non-integral (i.e. received in an endoscope receiving member), which means the whole device can be manipulated safely with one hand if necessary (e.g. by an assistant of a primary surgeon). This may be important to allow the primary surgeon enough space to work without having the assistant in the way.

In an embodiment, the expander member comprises a plurality of fingers pivotably coupled to each other and the switching between the radially contracted state and the radially expanded state comprises rotation of the fingers about the pivotable couplings. This arrangement can be implemented reliably without requiring excessive bulk either at the expander member itself or in the actuation mechanism connecting the manually actuatable member to the expander member.

In an embodiment, the pivotable coupling is such that a plurality of the fingers rotate about a common axis of rotation. Arranging for the fingers to rotate about a common axis of rotation means that the fingers spread out within a common plane, which facilitates effective retraction of tissue and optical access to the surgical site. Preferably, the fingers have elongate cross-sections with axes of elongation perpendicular to the common axis of rotation. Thus, the fingers may be relatively flat in the plane in which they spread out, which further supports optimal tissue retraction and optical access.

In an embodiment, the expander member comprises a first finger, a second finger and a third finger; the first finger is fixed to be aligned with the longitudinal axis of the distal portion of the elongate body in the radially contracted state and in the radially expanded state; and the second and third fingers are pivotably coupled to each other so as to rotate in opposite directions about a common axis of rotation during switching of the expander member between the radially contracted state and the radially expanded state. This arrangement provides a highly robust and symmetrical expansion which can be implemented with minimal complexity and high reliability. In one implementation, the number of fingers is three, for example with the above arrangement being provided with the first, second and third fingers described and no other fingers. The inventors have found that this approach provides an optimal balance of retraction points and mechanically solidity and compactness. The arrangement can be implemented with high rigidity without exceeding an outer diameter of 10mm, providing high performance without any increase in the size of incisions in the mouth being needed in comparison with standard alternative approaches.

The invention will now be further described, merely by way of example, with reference to the accompanying drawings, in which:

Figure 1 is a schematic perspective view of a retractor device with an expander member in a radially expanded state;

Figure 2 is a schematic perspective view of the device of Figure 1 with the expander member in a radially contracted state;

Figure 3 is a schematic perspective view of a distal portion of the device of Figures 1 and 2, rotated by 180 degrees to show a distal end of an endoscope; and

Figure 4 is a schematic perspective view of a proximal portion of the device of Figures 1-3.

Figures 1-4 depict a retractor device 1. The device 1 is configured to be suitable for transoral insertion to a surgical site. Dimensions of the device 1 (length and width) are thus suitable for insertion via the mouth. In the description that follows, the term distal is used to refer to features that are furthest from a user during use of the device 1 (i.e. within the body). The term proximal is used to refer to features that are nearest to the user during use of the device 1 (i.e. outside of the body).

The device 1 may comprise an integral endoscope (e.g. fixedly attached to other elements of the device, such as to the elongate body 8 described below) or an endoscope receiving member 2 configured to receive an endoscope 4. In the particular example shown, the device 1 comprises an endoscope receiving member 2. The endoscope receiving member 2 may, for example, comprise a guiding member such as a cylindrical tube having an inner diameter slightly larger than an outer diameter of an endoscope 4 suitable for the intended surgery, such as a standard 5mm 30 degrees endoscope. When the device 1 is to be used, an endoscope 4 is inserted into the guiding member (e.g. along the cylindrical tube). Regardless of whether the endoscope is integral or inserted into an endoscope receiving member 2, the endoscope 4 is configured to receive light reflected from the surgical site. The endoscope 4 may also illuminate the surgical site. The endoscope 4 may comprise an optically transparent surface that faces the surgical site. One or more optical elements such as lenses may be provided. The endoscope 4 may further comprise one or more optical waveguides or optical fibres for guiding reflected light and/or illuminating light from/to the surgical site to a region outside of the body. The endoscope 4 may be connected to a sensor device 6 such as a CCD. The sensor device 6 may detect reflected light received by the endoscope 4 to provide a signal for generating a viewable image of the surgical site.

The device 1 further comprises a retractor arrangement. The retractor arrangement comprises an elongate body 8. The elongate body 8 has a distal end 8A for insertion to a surgical site in a patient and a proximal end 8B that remains outside of the patient during use.

The retractor arrangement further comprises an expander member 10. The expander member 10 is positioned at or adjacent to the distal end 8A of the elongate body 8. The expander member 10 is switchable between a radially contracted state and a radially expanded state. Switching into the radially contracted state makes the expander member 10 more compact in the radial direction (thinner), thereby facilitating insertion of the expander member 10 to the surgical site and minimising the size of any required incision within the mouth. Indeed, in embodiments of the present disclosure the expander member 10 is dimensioned to not exceed an outer diameter of 10mm in the radially contracted state, such that no increase in the size of an incision in the mouth will be needed in comparison with known alternative approaches for transoral thyroid surgery. The radially expanded state is suitable for pushing away tissue at the surgical site to improve a view of the surgical site by the endoscope 4. When viewed along a longitudinal axis of at least a portion of the elongate body 8 adjacent to the expander member 10, a radially maximal portion of the expander member 10 is nearer to the longitudinal axis when the expander member 10 is in the radially contracted state than when the expander member 10 is in the radially expanded state. A maximum outer diameter of the expander member 10 in the radially expanded state may, for example, be significantly larger than 10mm. Examples of the radially expanded and radially contracted states of the expander member 10 are shown in Figures 1 and 2 respectively.

The retractor arrangement further comprises a manually actuatable member 12 at or adjacent to the proximal end 8B of the elongate body 8. The manually actuatable member 12 is coupled to the expander member 10 by an actuation mechanism. The actuation mechanism allows a user to switch the expander member 10 between the radially contracted state and radially expanded state by manipulation of the manually actuatable member 12. The actuation mechanism is configured such that forces and/or torques imparted by manipulation of the manually actuatable member 12 are transmitted to the expander member 10. The transmitted forces and/or torques cause the expander member 10 to switch from the radially expanded state to the radially contracted state or from the radially contracted state to the radially expanded state. In an embodiment, the manually actuatable member 12 comprises a rotatable handle. The rotatable handle is rotatable under manipulation by a user of the device 1 about a longitudinal axis of a portion of the elongate body 8 adjacent to the manually actuatable member 12. The rotatable handle may be provided with gripping portions (as shown) to facilitate reliable gripping of the rotatable handle by the user. Any of various suitable known mechanisms for transmitting forces and/or torques (including mechanisms for transforming rotary motion into linear motion and vice versa) may be used to achieve the desired actuation. In an embodiment, the actuation mechanism comprises one or more tensioning members extending from the manually actuatable member 12 to the expander member 10 and the manually actuatable member 12 is configured such that rotation of the rotatable handle transmits forces to the expander member 10 via the one or more tensioning members. The tensioning members may comprise one or more strings or wires for example.

The device 1 is configured such that the endoscope 4 (regardless of whether it is integral or provided in an endoscope receiving member 2 as shown in the figures) and the elongate body 8 extend along parallel or coincident longitudinal axes 14, 16 in a proximal direction from the expander member 10 (i.e. away from the surgical site) to a longitudinally intermediate position 18 along the elongate body 8. In the example shown in the figures, the longitudinal axis of the elongate body 8 is labelled 14 and the longitudinal axis of the endoscope 4 is labelled 16. In the example shown, the endoscope 4 and the elongate body 8 thus extend along substantially coincident (or nearly coincident) longitudinal axes 14, 16 up to the longitudinally intermediate position 18.

plurality of the fingers 31-33 rotate about a common axis of rotation 24. This causes the fingers 31-33 to spread out in a common plane. In such an embodiment, the fingers 31-33 preferably have elongate cross-sections (i.e. are relatively flat). Axes of elongation (i.e. long axes) of the fingers 31-33 are preferably perpendicular to the common axis of rotation 24 (i.e. such that the fingers are flat within the common plane). This arrangement minimizes a size of the expander member 10 in a direction of overlap of the fingers 31-33 (e.g. parallel to the axis 24 in the example shown)

In the example shown, the expander member 10 comprises three fingers 31-33, but fewer or more fingers may be provided if desired. The fingers 31-33 are configured such that the fingers 31-33 are more aligned in the radially contracted state (as depicted in Figure 2) than in the radially expanded state (depicted in Figures 1 and 3). In some embodiments, the fingers 31-33 are all substantially aligned with each other (e.g. lying on top of one another, as in the example shown) in the radially contracted state. In an embodiment, the fingers 31-33 are pivotably coupled to each other at or near proximal ends of the fingers 31-33. In the example shown, the fingers 31-33 are pivotably coupled to each other so as to be rotatable about a common axis 24. The expander member 10 is configured to cause the fingers 31-33 to fan out to switch the expander member 10 from the radially contracted state to the radially expanded state. In the example shown, the switching comprises fingers 31 and 33 rotating in opposite directions about the axis 24.

In an embodiment, the expander member 10 comprises a first finger 31, a second finger 32 and a third finger 33. The first finger 31 is fixed to be aligned with the longitudinal axis 14 of the elongate body 8 adjacent to the distal end 8A in the radially contracted state and in the radially expanded state. The second and third fingers 32, 33 are pivotably coupled to each other so as to rotate in opposite directions about a common axis of rotation 24 during switching of the expander member 10 between the radially contracted state and the radially expanded state.

The device according to any of the embodiments described above may be used in methods for viewing a surgical site, in particular where the surgical site is for thyroid or other transoral endoscopic surgical procedures. Such methods may comprise inserting the device 1 orally to bring the expander member 10 of the device 1 to the surgical site. The device 1 may be inserted while the expander member 10 is in the radially contracted state. The expander member

10 is switched from the radially contracted state to the radially expanded state after the expander member 10 has reached the surgical site. The expander member 10 is used in the radially expanded state to displace tissue to improve a view of the surgical site. The endoscope of the device 1 or an endoscope in the endoscope receiving member 2 of the device 1 is used to detect reflected light from the surgical site to provide an image of the surgical site.

Demonstration of Efficacy

The following study was performed to demonstrate efficacy of the retractor device.

A team consisting of anatomists, engineers and a surgeon was established and the project was approved by the University of Malta ethics board committee. A retractor device according to the above description was provided. The device was made from non-toxic and non-conductive material to be safely used in humans. To remain as faithful to the scarless principle of TOETVA as possible, the device was configured to be introduced to its position through the vestibule of the mouth without the need for it to be inserted or otherwise stabilized in place through the use of skin incisions.

Three Thiel embalmed cadavers were used to reproduce the standard operative technique of TOETVA. This technique utilizes carbon dioxide at a pressure of 6mmHg to keep the operative space open. When the device was developed, the technique without gas insufflation was trialed in three Thiel embalmed cadavers using the otherwise standard technique for TOETVA except the insufflation. In all of the six cadavers, pictures were taken at the following three standard operative stages:

I. When the subplatysmal plane has been developed and the view showed the strap muscles divided by the intact linea alba cervicalis.

II. When the linea alba cervicalis has been opened, the thyroid isthmus has been dissected centrally off the trachea and being lifted on the working instrument.

III. When the thyroid isthmus has been divided centrally and the strap muscle dissected off the left thyroid lobe. The lobe is retracted supero-medially using a grasper.

The best available picture of each stage from the three cadavers with insufflation and the three cadavers with the gasless technique was chosen. The pictures were then sent to a panel of four specialists in thyroid surgery. Each specialist was asked to rank the visibility of structures on a visual analogue score of 1 to 10 were a score of 1 meant completely unidentifiable structures and score of 10 meant all structures identifiable with extreme ease. The specialists did not know to what group the picture being scored belonged two. The scores from the two groups were then statistically analysed using the Wilkoxin Rank test using IBM SPSS Statistics for Windows, Version 25 (Released 2017. Armonk, NY: IBM Corp.)

The cadavers utilized for this study were similar in both groups in terms of gender and neck dimensions. The most important difference between the two groups was the dissection times taken for the development of the subplatysmal space. Despite not being significantly longer in the gasless technique, using carbon dioxide insufflation helped in the dissection and made this step more efficient. Once this space was open, the working space offered by both techniques was sufficient for the operation to take place. The performing surgeon could identify the essential anatomical structures and the space offered in both techniques allowed enough space for the dissection to take place safely. After the procedure, all cadavers in whom carbon dioxide insufflation was used had surgical emphysema that extended up to middle part of the chest wall. The latter was absent in the gasless technique. Post procedural open assessment of the necks of the cadavers in this study revealed no unintended damage to surrounding structures in both techniques.

When the scores given by the panel at each stage for the two techniques were compared, the p value achieved was 1. The standard deviation for the mean scores given for the insufflation technique and gasless technique were similar at 1.7 and 2.2 respectively. Therefore for the panel of experts assessing the various stages, the two techniques were equivalent in their operative space and ability to identify anatomical structures.

The advancement of minimally invasive techniques is intrinsically linked with these practices offering a safety profile which is identical or superior to the gold standard. TOETVA has already deemed to be a safe procedure when compared to the conventional open thyroidectomy. Carbon dioxide insufflation was however found to offer a number of complications most of which self-limiting but occasionally life-threatening. Our group developed a technique that eliminates the need for gas insufflation altogether whilst remaining faithful to the scarless principals of TOETVA. The experimental implementation of the new device on cadavers has shown that when compared with the standard technique for TOETVA, the gasless alternative has equivalent safety profile. The device developed is aimed for the endoscopic variant of TOETVA but can be easily adapted to the robotic technique should the need for this arise.

CLAIMS

1. A retractor device for transoral insertion to a surgical site, the device comprising:

an integral endoscope or an endoscope receiving member configured to receive an endoscope; and

a retractor arrangement, the retractor arrangement comprising:

an elongate body having a distal end for insertion to a surgical site in a patient and a proximal end that remains outside of the patient during use;

an expander member at or adjacent to the distal end of the elongate body, the expander member being switchable between a radially contracted state and a radially expanded state; and

a manually actuatable member at or adjacent to the proximal end of the elongate body, the manually actuatable member being coupled to the expander member by an actuation mechanism that allows switching of the expander member between the radially contracted state and radially expanded state by manipulation of the manually actuatable member,

wherein the device is configured such that the endoscope and the elongate body:

extend along parallel or coincident longitudinal axes in a proximal direction from the expander member to a longitudinally intermediate position along the elongate body; and

diverge from each other in the proximal direction from the longitudinally intermediate position.

2. The device of claim 1, wherein the endoscope extends linearly from the expander member to at least a position that is as far from the expander member as the manually actuatable member.

3. The device of claim 1 or 2, wherein the elongate body comprises an elbow at the longitudinally intermediate position where a longitudinal axis of the elongate body changes direction.

4. The device of any preceding claim, wherein the longitudinally intermediate position is such that the expander member can be brought to a surgical site suitable for thyroid surgery

while the longitudinally intermediate position is inside the oral cavity of a patient or outside of the body of the patient.

5. The device of any preceding claim, further comprising a mechanical support member configured to mechanically couple the endoscope to the elongate body at a position on a proximal side of the longitudinally intermediate position and spaced apart from the longitudinally intermediate position.

6. The device of any preceding claim, wherein the manually actuatable member comprises a rotatable handle configured to be rotatable under manipulation by a user of the device about a longitudinal axis of a portion of the elongate body adjacent to the manually actuatable member.

7. The device of claim 6, wherein the actuation mechanism comprises one or more tensioning members extending from the manually actuatable member to the expander member and the manually actuatable member is configured such that rotation of the rotatable handle transmits forces to the expander member via the one or more tensioning members.

8. The device of any preceding claim, wherein the expander member comprises a plurality of fingers pivotably coupled to each other and the switching between the radially contracted state and the radially expanded state comprises rotation of the fingers about the pivotable couplings.

9. The device of claim 8, wherein the pivotable coupling is such that a plurality of the fingers rotate about a common axis of rotation.

10. The device of claim 9, wherein the fingers have elongate cross-sections with axes of elongation perpendicular to the common axis of rotation.

11. The device of any of claims 8-10, wherein:

the expander member comprises a first finger, a second finger and a third finger;

the first finger is fixed to be aligned with the longitudinal axis of the elongate body adjacent to the distal end in the radially contracted state and in the radially expanded state; and

the second and third fingers are pivotably coupled to each other so as to rotate in opposite directions about a common axis of rotation during switching of the expander member between the radially contracted state and the radially expanded state.

12. The device of any of claims 8-11, wherein the fingers are pivotably coupled to each other at or near proximal ends of the fingers.

13. The device of any of claims 8-12, wherein the number of fingers is three.

14. The device of any preceding claim, dimensioned to be suitable for insertion to a surgical site via the mouth, preferably wherein the surgical site is suitable for performing thyroid surgery.

15. A method of viewing a surgical site, preferably a surgical site for thyroid surgery, the method comprising:

inserting the device of any preceding claim orally to bring the expander member of the device to the surgical site, while the expander member is in the radially contracted state;

switching the expander member from the radially contracted state to the radially expanded state after the expander member has reached the surgical site;

using the expander member in the radially expanded state to displace tissue to improve a view of the surgical site; and

using the endoscope to detect reflected light from the surgical site to provide an image of the surgical site.

ABSTRACT

Retractor devices for transoral surgery are disclosed. In one arrangement, a device is provided having an integral endoscope or an endoscope receiving member for receiving an endoscope. A retractor arrangement is further provided. The retractor arrangement has an elongate body with a distal end and a proximal end. An expander member is provided at or adjacent to the distal end. A manually actuatable member is provided at or adjacent to the proximal end. A user can switch the expander member between a radially contracted state and a radially expanded state by manipulation of the manually actuatable member. The endoscope and the elongate body: extend along parallel or coincident longitudinal axes to a longitudinally intermediate position along the elongate body; and diverge from each other in the proximal direction from the longitudinally intermediate position.

Appendix 5: Design Registration approval

EUROPEAN UNION INTELLECTUAL PROPERTY OFFICE

OPERATIONS DEPARTMENT

SLI_A

Alicante, 16/04/2020

J A KEMP SNC
75 Boulevard Haussmann,
F-75008 PARIS
FRANCIA

Your reference:	**D400540EM**
Community design(s) registration number(s):	**007793666-0001**
Number of designs:	**1**
Name of the applicant:	**UNIVERSITY OF MALTA**

Notification of the registration of the Community design(s)

The Office is pleased to inform you that your application has been accepted. It has been allocated the above registration number(s).

Publication will take place online in the Community Designs Bulletin within three working days on the website https://euipo.europa.eu .

The details of the applicant and the identification of the registration as encoded by the Office are attached. Where the registration concerns a multiple application, the attachment shows the data for the first design only.

All future contact or correspondence with the Office in relation to the Community design registration should include the above registration number(s).

Certificate of registration

The certificate of registration will only be stored as an online document. It will be available for you to download and print from the day after publication. A paper copy of the certificate of registration will not be issued. However, certified or uncertified copies of the registration certificate may be requested.

To download the PDF registration certificate, go to eSearch plus: https://euipo.europa.eu/eSearch/ . From there, search for the RCD number mentioned above. Once you have the eSearch plus design information page in the Publication section click on the Registration Certificate icon.

Avenida de Europa, 4 • E - 03008 • Alicante, Spain
Tel. +34 965139100 • www.euipo.europa.eu

The certificate contains information from the Community Designs Register at the date of registration (see code 15 on the certificate). If you have filed a request for modification of data on or after that date, no new certificate will be issued. You will be notified separately of the change after which an extract from our database may be requested to reflect the administrative status of the design.

For an explanation of the codes on the certificate please consult the Vademecum on EUIPO's website: https://euipo.europa.eu/eSearch/#advanced/s .

If for any reason you do not agree with the content of this certificate please send the Office a letter indicating your objections.

Maria TRIER-MØRK

Enc.: attachment

ATTACHMENT: Community design No 007793666-0001

Filing date

06/04/2020

Languages of application

First language EN
Second language FR

Applicant

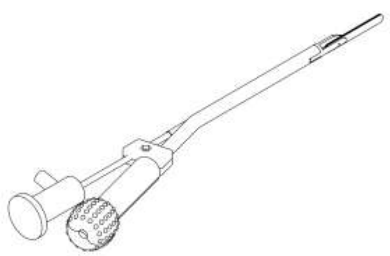
ID: 655377
UNIVERSITY OF MALTA
-
Msida MSD 2080
MALTA

Representative

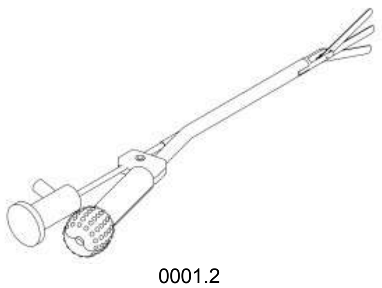
ID: 89710
J A KEMP SNC
75 Boulevard Haussmann,
F-75008 PARIS
FRANCIA

Identification of the design

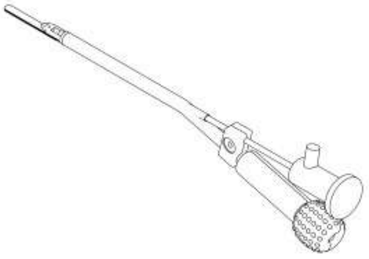
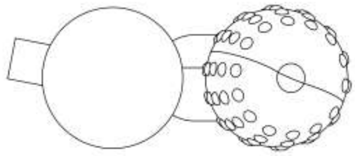
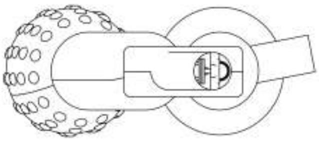
Representation



0001.1



0001.2

 0001.3	 0001.4
 0001.5	 0001.6
 0001.7	

Indication of the product(s)	Surgical instruments
Classification	24-02
Description	☐
Request for deferment	☐
Citation of the designer	☑

IMPORTANT WARNING

Misleading requests for payment for trade mark and design services such as publication, registration or entry in business directories.

Users in Europe are receiving an increasing amount of unsolicited mail from companies requesting payment for trade mark and design services such as publication, registration or entry in business directories.

Please note that these services are not connected with any official trade mark or design registration services provided by public bodies within the European Union such as the EUIPO.

If you receive a letter or invoice please check carefully what is being offered to you, and its source. Please note that the **EUIPO never sends invoices to users or letters requesting direct payment for services.**

If you have any doubts or detect any new cases, please check with your legal advisers or contact us at +34 965139100 or by email at information@euipo.europa.eu .

For some sample letters from firms or registers that have nothing to do with EUIPO's registers or official publications, click on:

https://euipo.europa.eu/ohimportal/en/rcd-misleading-invoices

Appendix 6: Additional images of the developed retractor

Appendix 7: Camenzuli C, Schembri Wismayer P, Calleja Agius J. 2018. Transoral Endoscopic Thyroidectomy: A Systematic Review of the Practice So Far. JSLS. doi: 10.4293/JSLS.2018.00026.

REVIEW JSLS

Transoral Endoscopic Thyroidectomy: A Systematic Review of the Practice So Far

Christian Camenzuli, MD, Pierre Schembri Wismayer, MD, PhD, Jean Calleja Agius, MD, PhD

ABSTRACT

Background and Objectives: Thyroid disease largely affects young females, but the incidence is also increasing among males. In an effort to avoid the scarring of the neck that is synonymous with conventional thyroidectomy, endoscopic techniques have been developed over the years. The transoral endoscopic approach is the latest of these innovations that promises a scarless surgical outcome. This review evaluates whether this technique is safe and feasible in live patients and outlines the outcomes in published literature so far.

Database: PubMed, Medline, BioMed Central, Cochrane Library, OVID and Web of Science were systematically searched by using a Medical Subject Heading (MeSH)–optimized search strategy. The selection of papers followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines after setting strict inclusion and exclusion criteria. Sixteen studies were included in the final analysis.

Discussion: This systematic review presents cases of 785 patients. Surgeons in 15 of the studies used a completely vestibular approach, whereas those in the remaining 2 used the floor of the mouth for primary access. Conversion to open surgery took place in 1.3%. In total, 4.3% of patients experienced transient laryngeal nerve palsy, whereas 0.1% had permanent recurrent incidences of the condition. Transient hypocalcemia occurred in 7.4% of cases, with no recorded permanent cases. Carbon dioxide embolism occurred in 0.6% of cases, and another 0.6% had a deep-seated neck infection. The complication rates within the review were deemed acceptable and the overall technique feasible. A prospective randomized controlled trial was proposed to compare this technique with conventional thyroidectomy.

Key Words: Natural orifice endoscopic surgery, Oral endoscopy, Scarless, Thyroidectomy, Transoral.

INTRODUCTION

Over the past centuries, procedures to surgically remove all or part of the thyroid gland from the neck have gone from infamy to fame. What Samuel D. Gross in the 19th century considered to be "horrid butchery," through the brave work of surgeons like Emil Theodor Kocher, has become one of the most common and safest of surgeries.[1–3] The gold-standard approach for thyroidectomy has been open or conventional surgery. Recently, there has been increased interest in applying the principles of minimally invasive surgery to thyroid surgery. This development was initially promoted by Miccoli and his colleagues[4] in 1999 and has continued to expand and improve throughout recent years. The aims of minimally invasive surgery include better cosmesis and earlier recovery without compromising the excellent results achieved with open surgery.[5] The approaches taken in thyroid surgery include mainly a transaxillary approach with later additions of areolar, anterior chest wall, and mixed approaches.[6–10] The extent of dissection and difficulty of these procedures despite robotic help has limited the uptake of these techniques.[11,12]

The transoral endoscopic technique, an adaptation of the concept of natural orifice transluminal endoscopic surgery (NOTES) to the neck, is a technique that promises to improve the aesthetic aspect by offering a scarless operation while retaining the advantages of minimally invasive surgery.[13,14] The pioneers of this technique were the group led by Witzel and his colleagues,[15] who presented their first paper on the subject in 2008. In their study on cadavers and live pigs, they managed to present a proof of concept that formed the basis for the extensive work that is being carried out by multiple groups around the world.

Department of Anatomy, Faculty of Medicine and Surgery, Biomedical Sciences, University of Malta, Msida, Malta (all authors).

Disclosures: none reported.

Informed consent: Dr. Camenzuli declares that written informed consent was obtained from the patient/s for publication of this study/report and any accompanying images.

The authors thank Ms. Andee Agius and Ms. Roberta Sultana for proofreading the text and Endeavour Scholarship Malta for funding.

Address correspondence to: Christian Camenzuli, MD, Anatomy, Faculty of Medicine and Surgery, Biomedical Sciences Building, University of Malta, Msida Malta. Tel: +35679257480; E-mail: christian.camenzuli.04@um.edu.mt

DOI: 10.4293/JSLS.2018.00026

Transoral endoscopic thyroidectomy is performed with the patient under general anesthesia. The patient is placed supine with the neck extended. The mouth is cleansed with 0.05% chlorhexidine in water, and the patient is usually given a broad-spectrum antibiotic (eg, amoxicillin/clavulanic acid). The primary surgeon stands at the patient's head facing the monitor and the first assistant stands to the patient's left. Access through the mouth is gained with the use of a 10-mm port and two 5-mm ports, the position of which varies according to different techniques. The subplatysmal space is developed with the use of hydrodissection. Carbon dioxide insufflation is usually used to keep the working space open. The working space is developed keeping the larynx as the superior border, the suprasternal notch as the inferior border, and the anteromedial borders of the sternocleidomastoid muscles bilaterally as lateral borders. Strap muscles are divided at the linea alba cervicalis. The dissection continues in a craniocaudal fashion with the use of energy sealing devices. The thyroid isthmus is first identified, elevated, and divided. The veins and arteries supplying the thyroid gland are sealed as close as possible to the thyroid gland. The superior laryngeal nerve, recurrent laryngeal nerve, and parathyroid glands should be identified and protected. Berry's ligament is then dissected. The thyroid specimen is retrieved in an Endobag (Medtronic, Minneapolis, Minnesota, USA). The space is irrigated with saline, and drains are inserted if needed. The mucosal wounds are closed with an absorbable 5-0 suture.[16]

The procedure was shown to be feasible and safe in several cadaveric[17,18] and animal model studies[19,20] and subsequently was translated to implementation in human patients. In view of these developments, this systematic review was conducted to identify the current experience of transoral endoscopic thyroidectomy and to assess the safety and feasibility of this technique according to the outcomes set.

MATERIALS AND METHODS

For this systematic review, 6 databases were searched up to January 31, 2018: PubMed, Medline, BioMed Central, Cochrane Library, OVID, and Web of Science. Keywords used for the search strategy included "human," "transoral," "floor of mouth," "vestibule," "endoscopic," "scarless," "video-assisted," "natural orifice," and "thyroidectomy." The comprehensive search strategy was adapted to the different search engines. In addition to the aforementioned searches, back-chaining of references and manual searches of key journals were conducted. Key experts in the field were also contacted. The study protocol was registered on PROSPERO (CRD42017075758).

The primary outcome was to elucidate whether, from the available literature, the technique of transoral video-assisted endoscopic thyroidectomy is safe and feasible. Several secondary outcomes were identified for this systematic review. These included the following: population demographics, type of access used, use of carbon dioxide insufflation, blood loss, length of surgery, use of intraoperative neuromonitoring (IONM), use of drains, rate of conversion to open, rate of complications associated with the procedure (including recurrent laryngeal nerve damage, parathyroid damage, and mental nerve damage), time to oral intake, and time to discharge. The Population, Intervention, Comparison, and Outcomes (PICO) framework was used to develop the research question. Inclusion criteria encompassed studies involving patients with thyroid disease who underwent transoral endoscopic thyroidectomy, with or without the use of gas insufflation and in whom the primary and secondary outcomes were investigated. Observational studies, randomized controlled studies, case–control studies, and case series were included. Only literature published in English was considered for this systematic review. No restrictions on date of publication or country of origin were applied. Studies investigating neck pathology other than thyroid or in which robotic or open procedures or endoscopic surgery that did not use the transoral approach were performed were excluded. Qualitative studies, case reports, abstracts, editorials, conference proceedings, and systematic reviews were also excluded.

After excluding all duplicates, 2 separate researchers independently reviewed the titles and abstracts of all downloaded citations to decide whether to include or exclude the studies. When it was not possible to determine whether a citation was relevant, it was included at this stage. In cases of disagreement between the reviewers about a citation, the citation was also included. Full copies of the potentially included papers were obtained and reviewed by the independent reviewers. In cases of disagreement a third researcher was involved to discuss and settle any divergences. The number of studies included and excluded at each stage of the review was recorded with a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart diagram that illustrated the number of studies screened, the number of studies assessed for eligibility, and the number of studies included in the review (**Figure 1**). Data was extracted from all the studies that fulfilled the inclusion criteria. A data extraction form was developed for the purpose of

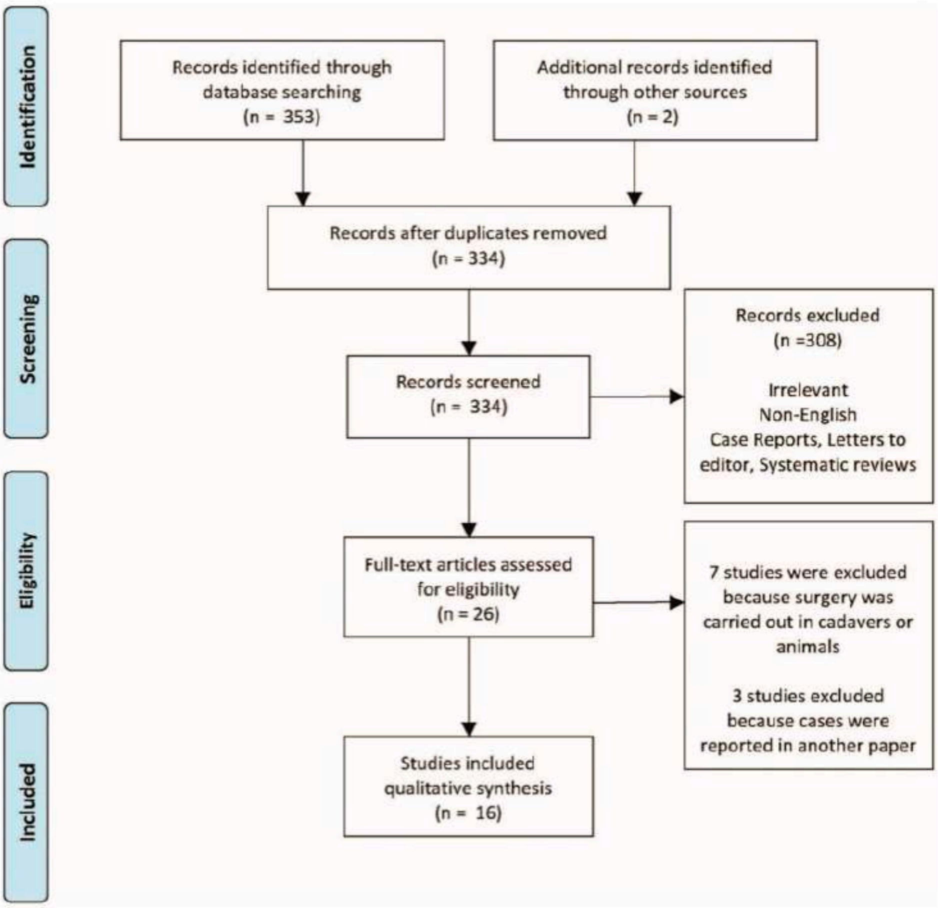


Figure 1. The PRISMA flow diagram for the selection of articles for review. The articles present at each stage of the review are represented and reasons for exclusion are given.

standardization. Data quality assessment was carried out by 2 independent reviewers using the Quality Appraisal Tool for Case Series studies developed by the National Institutes of Health.[21]

RESULTS

Sixteen studies are included in this review. The earliest published series was in 2011 by Wilhelm et al[22] from Germany. Patients in that study were integrated into a later paper by the same team, and therefore this original paper was excluded. Since then, several other case series have been published, mostly from Thailand, Republic of Korea, and China. The studies reviewed sum to a total of 785 patients of which 713 (91%) were female and 68 (8%) were male. Zeng et al[23] did not specify the gender of the 4 participants in their study. The weighted mean age of the patients in the included studies was 35 years. Fourteen of the studies included were considered to be of good quality.[24–37] The other 2 lacked detail and focus and were therefore considered to be of fair quality.[23,38]

The inclusion and exclusion criteria used in the different studies were heterogeneous; however, general themes were present. Fourteen studies declared their inclusion criteria. Patients with benign disease (proven on imaging and cytology) or papillary microcarcinoma, in whom the nodules' maximum diameter was <5 cm, the total thyroid volume was ≤45 mL, and in whom there was no lymph node metastasis, were included. Fourteen studies declared the exclusion criteria. Patients in whom there was history of neck surgery or radiotherapy, recurrent disease, presence of intraoral infection or characteristics that did not fit the inclusion criteria, were excluded. Altogether there were 396 hemithyroidectomies, 249 total thyroidectomies, 10 isthmusectomies, and 31 subtotal thyroidectomies. Zeng and his colleagues[23] did not indicate what type of thyroidectomy their 4 participants underwent (**Table 1**).

The access to the neck through the mouth was mostly through a completely vestibular approach (14 out of 16 studies). This approach involves a central 10-mm port that

Table 1.
Demographic Characteristics

Study	Number (Gender)	Inclusion Criteria	Exclusion Criteria	Mean Age (years)
Nakajo et al.[24]	8 (7 F, 1 M)	Follicular neoplasm, symptomatic large nodular goiter, Graves' disease and papillary microcarcinoma.	Evidence of lymph node metastasis.	54.9
Wang et al.[25]	12 (10 F, 2 M)	Benign tumor on B-scan US and CT confirmed on cytology, patient consent, mass ≤6 cm, healthy patient.	Mass >6 cm, advanced cardiac or pulmonary disease, patient not a candidate for minimally invasive techniques, patient indifferent regarding unscarred skin.	24
Yang et al.[26]	41 (33 F, 8 M)	18–50 years old, maximum tumor diameter <5 cm, hyperthyroidism not exceeding degree II, suspicious cancer without metastasis in cervical lymph nodes, endoscopic surgery required.	Infected lesions (e.g. oral ulcer), history of neck surgery, substernal goiter.	31.9
Udelsman et al.[27]	5 F	Toxic thyroid adenoma, multinodular goiter, indeterminate thyroid nodule and papillary thyroid microcarcinoma.	NA	42.8
Zeng et al.[23]	4 (gender not reported)	NA	Malignancy, hyperthyroidism, previous neck surgery/radiotherapy, ≥5 cm nodule.	NA
Yang et al.[28]	6 (5 F, 1 M)	Tumor with maximum diameter <5 cm, good mobility under palpation, clear boundary, I- or II-degree thyroid enlargement.	Hyperthyroidism or parathyroid disease, history of neck surgery, adhesions to surrounding benign tissue.	34.3
Jitpratoom et al.[29]	45 (40 F, 5 M)	Controlled Graves' disease with suspicious nodule or toxic multinodular goiter, failure of medical treatment, or local compressive symptoms.	Unfit for surgery, previous neck surgery/radiotherapy, could not tolerate general anesthesia, thyroid diameter ≥10 cm.	F, 32.47 ± 4.74; M, 35.80 ± 11.70
Wilhelm et al.[30]	96 (92 F, 4 M)	12 adenomas, 1 cystic lesion, 66 uninodular and 14 multinodular changes, 11 Hashimoto thyroiditis and 2 micropapillary carcinoma.	NA	F, 36 ± 10; M, 48 ± 4

Continued

Table 1.
Continued

Study	Number (Gender)	Inclusion Criteria	Exclusion Criteria	Mean Age (years)
Dionigi et al.[31]	15 (12 F, 3 M)	US showing estimated thyroid gland diameter ≤10 cm, thyroid volume ≤45 mL and max nodule size ≤5 cm; benign nodules, follicular neoplasms, papillary microcarcinoma without metastasis.	Patients unfit for surgery or cannot tolerate general anesthesia, previous radiation or surgery in neck, recurrent goiter, thyroid volume >45 mL, dominant nodule size >5 cm, evidence of LN metastasis or tracheal/ esophageal invasion, RLN palsy, hyperthyroidism, oral abscess.	29.4
Russell et al.[38]	6 F	Hypertrophic scarring, motivated to avoid cervical scar.	Thyroiditis, external beam radiotherapy, nodule >6 cm.	37.2
Sivakumar et al.[32]	11 F	Nodular thyroid disease, nodule size <4 cm, thyroid volume ≤30 mL.	History of neck surgery, neck radiotherapy, nodules or thyroid volumes large than inclusion criteria.	24.8
Park et al.[33]	18 (13 F, 4 M)	Consent for the new approach, thyroid cancer <2.5 cm or a benign tumor <8 cm.	Extrathyroid extension or lymph node metastasis on preoperative US, surgical treatment of head and neck.	F, 39.6; M, 48.3
Chai et al.[35]	10 F	Papillary microcarcinoma.	Suspected capsular invasion and lymph node metastasis.	43.3 ± 11.5
Bakker et al.[36]	5 F	Solitary thyroid nodule, Bethesda II, III, or IV, US thyroid volume of ≤45 mL, thyroid diameter ≤10 cm, noncancerous nodules up to 5 cm.	Previous neck irradiation.	36
Anuwong et al.[34]	422 (389 F, 33 M)	NA	Previous neck/chin surgery, substernal goiter, clinical evident lateral neck lymph node, distant/ local metastasis.	35.3
Fu J. et al.[37]	81 (79 F, 2 M)	Benign tumor diameter <5 cm evaluated by US, malignant tumor, patients with cosmetic requirements.	Maximum tumor diameter >5 cm, cancer with metastasis to cervical LN, Graves' disease, history of surgery or radiation to neck, severe coagulation disorders.	34.2 ± 9.4

US, ultrasonography; LN, lymph node; RLN, recurrent laryngeal nerve; GA, general anesthesia.

is used to accommodate the endoscope and two 5-mm ports inserted at the junction between the incisors and canine bilaterally; these ports are used as routes of access for the working instruments.[24–29,31–36,38] Zeng et al[23] modified this technique by using a central 12-mm port. The only exceptions to this approach are presented by Wilhelm et al and Fu et al.[30,37] Both of these groups used the floor of mouth as the access point for the 10-mm port that received the endoscope. The working 5-mm ports were inserted at the previously described position in the vestibule (**Figure 2**).

In most studies, the working space was kept open with the use of carbon dioxide insufflation. Fourteen studies reported the use of carbon dioxide. The maximum insufflation pressures used in most instances was 6 mm Hg.[25–29,31,32,34,36] Some researchers allowed a range of pressures ranging from as low as 4 mm Hg[37] and up to 8 mm Hg.[23,37,38] Wilhelm et al[30] reported the use of carbon dioxide insufflation but did not report the pressures accepted. Nakajo et al[24] attempted to eliminate carbon dioxide insufflation in the neck by using Kirschner wires of 1.2-mm thickness. These were inserted through the skin of the neck and used to elevate the skin and platysma, therefore maintaining the working space needed.

IONM was used in only 4 of the studies.[30,31,35,38] The weighted average length of operation reported in the 16 studies included for isthmusectomy was 53.3 minutes, for hemithyroidectomy was 85.5 minutes, for subtotal thyroidectomy was 115.4 minutes, and for total thyroidectomy was 136.6 minutes, giving an overall weighted average operating time of 94.9 minutes. In total, 10 (1.3%) conversions to open surgery were reported: 3 by Wilhelm et al,[30] 3 by Anuwong et al,[34] 1 by Jitpratoom et al,[29] 1 by Bakker et al,[36] and 2 by Fu et al.[37] The weighted average loss of blood reported in 12 studies was 34.3 mL. Three groups used drains routinely after both total and hemithyroidectomy,[24,29,32] whereas another 3 groups used drains almost exclusively for total thyroidectomy only.[31,33,34] Fu et al[37] never used drains in the first 49 cases and subsequently used them in all the remaining 32 cases. The rest of the study groups used no drains in their procedures.[23,25–28,30,35,36,38] (**Table 2**).

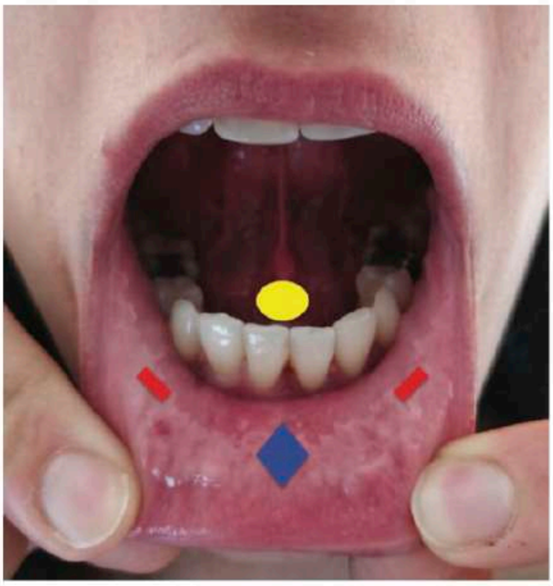


Figure 2. Position of ports. Red lines: position of 5-mm ports in both techniques. Blue line: position of the 10-mm port in the totally vestibular approach. Yellow circle: 10-mm port position of the floor-of-the-mouth approach.

Several complications were reported in the studies. Overall, 34 (4.3%) cases of temporary recurrent laryngeal nerve palsy were described.[26,29,34,35,38] One (0.1%) case was reported by Wilhelm et al,[30] and 1 case by Nakajo et al[24]; however, they did not clarify whether the condition was temporary or permanent.[24] Fifty-eight (7.4%) cases of transient postoperative hypocalcemia were reported.[29,31,33,34] In all cases, there was full recovery of the function of the parathyroid glands with no resultant permanent hypocalcemia. Fu et al[37] did not report any cases of postoperative hypocalcemia but stated that 2 patients had perioral numbness. Eighteen (2.29%) cases of temporary mental nerve palsy occurred overall.[24,30,34] Nakajo et al[24] did not report any specific cases of mental nerve damage; however, they mentioned that all their participants had altered sensation in the chin area that persisted for a period exceeding 6 months. Twenty-two (2.8%) occurrences of seroma are reported throughout the studies.[33,34] There were 6 (0.8%) cases of subcutaneous emphysema that were all self-limiting[31,36] and an additional case (0.1%) of mediastinal emphysema that did not carry long-term consequences.[30] Yang et al[26] reported 1 case of anterior flap perforation and another of neck skin burn, and Bakker et al[36] also reported 1 case of flap perforation (0.3%). Five cases (0.6%) of carbon dioxide–induced gas embolism were reported; 3 by Wilhelm et al[30] and 2 by Fu et al.[37] In 4 cases (0.5%), the patients developed extensive ecchymosis after surgery.[26,39] One case (0.1%) of operative site hematoma required emergency decompression through an open neck incision.[34] Five cases (0.6%) of deep-seated neck infections were reported by Wilhelm et al.[30] In addition, 6 cases (0.8%) of wound infections were reported.[28,30,37] Fu et al[37] had 4 cases of inflammatory masses in the neck, and they reported 2 patients with pain on opening the mouth, 2 with excessive salivation, and 2 with neck discomfort.[37] The occurrence of lower lip swell-

Table 2.
Operative Characteristics

Study	Type of Surgery (n)	Access	Average Length of Surgery (min)	Conversion to Open (n)	IONM	CO_2 Insufflation and Pressure (mm Hg)	Blood Loss (mL)	Drain
Nakajo et al.[24]	Hemithyroidectomy, 5; subtotal thyroidectomy, 3.	Completely vestibular (midline 10 mm and two 5 mm ports).	Hemithyroidectomy, 208; subtotal thyroidectomy, 361.	None	No	No, skin retraction with Kirschner 1.2 mm wires.	Hemithyroidectomy, 108; subtotal thyroidectomy, 80.	Yes
Wang et al.[25]	Hemithyroidectomy, 8 total thyroidectomy, 4.	Completely vestibular (midline 10 mm and two 5 mm ports).	60.4 ± 7.4	None	No	Yes, 6	10.8 ± 7.3	No
Yang et al.[26]	Hemithyroidectomy, 19; subtotal/near total, 18; total thyroidectomy, 4.	Completely vestibular (midline 10 mm and two 5 mm ports).	72.1 ± 19.5	None	No	Yes, 6	11.1 ± 7.1	No
Udelsman et al.[27]	Hemithyroidectomy, 3; total thyroidectomy, 2.	Completely vestibular (midline 10 mm and two 5 mm ports).	Hemithyroidectomy, 214.3; total thyroidectomy, 290.5.	None	No	Yes, 6	<20	No
Zeng et al.[23]	NA	Completely vestibular (midline 12 mm and two 5 mm ports).	189 ± 39.14	None	No	Yes, 8	7.50 ± 2.89	No
Yang et al.[28]	Hemithyroidectomy, 6	Completely vestibular (midline 10 mm and two 5 mm ports).	122	None	No	Yes, 6	30	No
Jitpratoom et al.[29]	Total thyroidectomy, 45	Completely vestibular (midline 10 mm and two 5 mm ports).	134.11 ± 31.48	1	NO	Yes, 6	62.81 ± 37.37	Yes
Wilhelm et al.[30]	Isthmusectomy, 10; hemithyroidectomy, 66; subtotal thyroidectomy, 10; and total thyroidectomy, 7.	Bivestibular and sublingual.	Isthmusectomy, 38; hemithyroidectomy, 49; subtotal thyroidectomy, 88; and total thyroidectomy, 126.	3	No	Yes but no pressure noted.	Isthmusectomy 15, hemi-thyroidectomy 20, subtotal thyroidectomy 30 and total thyroidectomy 67.	No
Dionigi et al.[31]	Hemithyroidectomy, 10; total thyroidectomy, 5.	Completely vestibular (midline 10 mm and two 5 mm ports).	Hemithyroidectomy, 86.8; total thyroidectomy, 115.2.	None	Yes	Yes, 6	Hemithyroidectomy, 36.5; total thyroidectomy, 62.	Yes, for total thyroidectomy only
Russell et al.[38]	Hemithyroidectomy, 6.	Completely vestibular (midline 10 mm and two 5 mm ports).	245.5	None	Yes	Yes, 5–7	NA	No
Sivakumar et al.[32]	Total thyroidectomy, 11.	Completely vestibular (midline 10 mm and two 5 mm ports).	126.3	None	No	Yes, 6	1.8	Yes
Park et al.[33]	Hemithyroidectomy, 16; total thyroidectomy, 2	Completely vestibular (midline 10 mm and two 5 mm ports).	Hemithyroidectomy, 168.8; total thyroidectomy, 185.	None	No	Yes, 5–6	NA	Yes, for total thyroidectomy and 1 case of hemithyroidectomy.
Chai et al.[35]	Hemithyroidectomy, 7; isthmusectomy, 3.	Completely vestibular (midline 10 mm and two 5 mm ports).	Isthmusectomy, 90.0 ± 9.2; hemithyroidectomy, 121.1 ± 30.7.	None	Yes	Yes, 6	NA	No

Continued

Table 2.
Continued

Study	Type of Surgery (n)	Access	Average Length of Surgery (min)	Conversion to Open (n)	IONM	CO_2 Insufflation and Pressure (mm Hg)	Blood Loss (mL)	Drain
Bakker et al.[56]	Hemithyroidectomy, 5.	Completely vestibular (midline 10 mm and two 5 mm ports).	122	1	No	Yes, 6	NA	No
Anuwong et al.[34]	Hemithyroidectomy, 245; total thyroidectomy, 177.	Completely vestibular (midline 10 mm and two 5 mm ports).	Hemithyroidectomy, 78.6; total thyroidectomy, 135.1.	3	No	NA	Hemithyroidectomy, 26.8; total thyroidectomy, 52.6.	Yes, for total thyroidectomy only.
Fu J. et al.[37]	Hemithyroidectomy (subtotal), 65; isthmusectomy, 6; subtotal thyroidectomy, 5; total thyroidectomy, 5.	10 mm port in floor of mouth anterior to frenulum, 5 mm vestibular port.	Hemithyroidectomy (subtotal), 90.1± 39.8; isthmusectomy, 60.3 ± 8.2; subtotal thyroidectomy, 100.0 ± 35.4; and total thyroidectomy, 115.0 ± 14.1.	2	No	Yes, 4–8	Hemi-thyroidectomy (subtotal), 26.3 ± 20.6; isthmusectomy, 15.2 ± 7.8; subtotal thyroidectomy, 28.6 ± 16.4; total thyroidectomy, 55.0 ± 31.6.	Yes (last 32 cases).

IONM, intraoperative neuromonitoring.

ing is common after transoral endoscopic thyroidectomy; however, this condition is usually self-limiting.[24,51]

From the 9 studies that recorded time to oral intake, most patients were allowed oral intake either on the day of surgery[26,31,33–35,37] or on day 1 after surgery.[24,29,32] Time for discharge, in the 12 studies that reported it, had a weighted mean of 4.3 d but this varied widely between the different studies, ranging from 1 day[38] to more than 8 days[28] (**Table 3**).

DISCUSSION

This systematic review extensively explores the published experience of transoral endoscopic thyroidectomy. The technique has been gaining ground, with this systematic review presenting the experience of various groups in 785 patients. As is usual with thyroid disease, most the patients were young females. The indications for surgery varied widely among the studies, and therefore there is no standard set of indications that can be proposed based on this systematic review. However, the contraindications of previous neck surgery or neck irradiation, intraoral infection, and recurrent disease seemed to be common throughout the studies. Other contraindications for this procedure, not encountered in this systematic review, include smoking and morbid obesity.[40]

Two slightly different access techniques were reported in the studies. Wilhelm et al[30] and Fu et al[37] (a group that reportedly was trained by Wilhelm) used a floor-of-the-mouth access in which the first camera port was inserted just anterior to the frenulum, whereas the working ports were inserted through the vestibule. The rest of the groups used a technique in which both the camera port and working ports were inserted through the vestibule. When comparing the complications reported from the 2 techniques, it was evident that using the floor-of-the-mouth access led to more carbon dioxide embolism, mediastinal emphysema, and both neck and surgical site infection. Otherwise, there was no major difference between the 2 reported techniques. Combining the transoral technique with other minimally invasive techniques has also been proposed.[41] Although the latter procedures may be easier, they have not been included in this systematic review, because they go against the scarless principle of the transoral technique.

Most groups used carbon dioxide insufflation to keep the working space open during the procedures. The pressure used varied, with the most commonly used pressure at a maximum of 6 mm Hg, but Zeng et al,[23] Russell et al,[38] and

Table 3.
Postoperative Outcomes

Study	RLN Injury	Hypocalcaemia	Mental Nerve Injury	Other Complications (n)	Time to Oral Intake (days)	Average Time to Discharge (days)
Nakajo et al.[24]	1 (not specified)	NA	No	Lower lip swelling and lower lip altered sensation lasting 6 months in all patients.	1	4.25
Wang et al.[25]	No	No	No	Ecchymosis, 2.	NA	4.9
Yang et al.[26]	1 transient	No	No	Ecchymosis, 2; skin pierced, 1; anterior skin burn. 1.	0	5 ± 1.4
Udelsman et al.[27]	No	No	No	No	NA	1.1
Zeng et al.[23]	No	No	No	No	NA	5
Yang et al.[28]	No	No	No	Wound infection, 1.	NA	8.2
Jitpratoom et al.[29]	4 transient	10 transient	No	No	1	NA
Wilhelm et al.[30]	1 permanent	NA	15 transient (resolved in three weeks).	Intraoral infection, 1; neck site infection, 5; CO_2 embolism, 3; mediastinal emphysema, 1.	NA	NA
Dionigi et al.[31]	No	1 transient	No	Mild emphysema.	0	2.1
Russell et al.[38]	1 temporary	NA	No	No	NA	1
Sivakumar et al.[32]	No	No	No	No	1	NA
Park et al.[33]	No	1 transient	No	2 seroma	0	4.1
Chai et al.[35]	2 transient	NA	No	No	4 hours	3
Bakker et al.[36]	No	NA	No	5 subcutaneous emphysema, 1 flap perforation.	NA	1.2
Anuwong et al.[34]	25 transient	46 transient	3 transients	20 seroma, 1 hematoma needed cervical incision for decompression.	0	NA
Fu J. et al.[37]	No	No	No	2 CO_2 embolism, 2 perioral numbness, 2 pains on opening mouth, 2 patients excessive salivation, 2 patients had neck discomfort, 4 wound infection, 4 inflammatory mass.	6 hours	4.77 ± 2.61

NA, not available.

Fu et al[37] allowed higher pressures. Nakajo et al[24] did not use carbon dioxide and opted to keep the working space open by pulling the skin of the neck with Kirschner wires. Although the results of this group were comparable to those of the rest of the groups that used insufflation, the technique has been criticized as going against the scarless concept of the transoral technique, because several small stab incisions were needed to anchor the wires in the skin. Wang et al[42] described a hybrid method in which the surgical working space is kept open by combining a cosmetically acceptable suspensory mechanism with carbon dioxide insufflation. Data regarding the outcomes of this technique are limited; further research is needed to assess its feasibility.

It is recognized that the transoral endoscopic thyroidectomy technique is challenging and the dissection can prove to be difficult. The rate of conversion to conventional dissection in this review was 1.3%, which is acceptable, given the length of experience with the technique and the arduous task involved. In terms of outcomes, the rates of recurrent laryngeal nerve palsy, postoperative hypocalcemia, infection, and bleeding after transoral thyroidectomy are comparable to those after conventional thyroidectomy.[29,43–45] Recurrent laryngeal nerve monitoring through a long probe has been used[31,38] and found to be safe and feasible,[46] thus enhancing the safety of the procedure. However, the technique presents several new complications that, although not common, have to be given due consideration. Mental nerve injury was reported in 2.29% of cases; however, a level of chin paresthesia was common in many patients. This condition is usually self-limiting, but patients should be cautioned regarding the possibility. Carbon dioxide embolism, flap perforation, and surgical emphysema are other examples of uncommon but potential complications that this technique presents. These findings are comparable to those published by Shan and Liu.[47]

Patients who underwent the procedure recovered early and were given fluids, either on the same day or the day after surgery, without any appreciable complications, despite having surgical wounds in the mouth. Notwithstanding the fast recovery, the technique was not performed as day surgery. Patients spent an average of 4.3 d in the hospital, although some groups discharged their patients on postoperative day 1. There is no clear explanation, given the studies, of the reason for this prolonged length of stay. Studies including patients who had longer hospital stays do not consistently report more complications than other groups. It could be that given that the technique is novel, some groups opted for longer postoperative observation to exclude complications including bleeding, airway impairment, and neck space infections. As experience and confidence in the procedure increase, the length of stay should decrease.

Excluding literature that was not in English meant excluding several studies in which extensive patient populations were studied. One such example is the case series published in Chinese by Wang et al[39] which included 150 cases. The reporting only of studies in English is one of the limitations of this study. The robotic experience was purposefully excluded from this review to keep the study topic clear. Notwithstanding the exclusion, robotic assistance in the transoral technique is an interesting concept that is being evaluated and developed. Another limitation of this review is the level of evidence carried by the included papers. The technique has now gained enough ground to be compared to conventional thyroidectomy in a prospective randomized trial that would carry a high level of evidence. Jitpratoom et al[29] and Anuwong et al[34] have performed this exercise; however, both studies were retrospective. In both the latter studies, the transoral approach was found to be as safe as the conventional cervical approach.

CONCLUSION

Transoral endoscopic thyroidectomy is a safe and feasible technique with acceptable complication rates and good outcomes. The completely vestibular approach seems to offer a safer alternative to floor-of-the-mouth access. More research, particularly using newly developed tools to further improve this technique, are needed, thus making it more available to patients worldwide.

References:

1. Tapscott WJ. A brief history of thyroid surgery. *Curr Surg.* 2001;58:464–466.

2. Hannan SA. The magnificent seven: a history of modern thyroid surgery. *Int J Surg.* 2006;4:187–191.

3. Fortuny JV, Guigard S, Karenovics W, Triponez F. Surgery of the thyroid: recent developments and perspective. *Swiss Med Wkly.* 2015;145:w14144.

4. Miccoli P, Berti P, Conte M, Bendinelli C, Marcocci C. Minimally invasive surgery for thyroid small nodules: preliminary report. *J Endocrinol Invest.* 1999;22:849–851.

5. Mohamed SE, Noureldine SI, Kandil E. Alternate incision-site thyroidectomy. *Curr Opin Oncol.* 2014;26:22–30.

6. Hakim Darail NA, Lee SH, Kang S, Jeong JJ, Nam K, Chung WY. Gasless transaxillary endoscopic thyroidectomy: a decade on. *Surg Laparosc Endosc Percutan Tech*. 2014;24:211.

7. Gao W, Liu L, Ye G, Lu W, Teng L. Bilateral areolar approach endoscopic thyroidectomy for low-risk papillary thyroid carcinoma: a review of 137 cases [published correction in *Surg Laparosc Endosc Percutan Tech*. 2015;25:373]. *Surg Laparosc Endosc Percutan Tech*. 2015;25:19–22.

8. Woo J, Kim SK, Park I, Choe JH, Kim J, Kim JS. A novel robotic surgical technique for thyroid surgery: bilateral axillary approach (BAA). *Surg Endosc*. 2017;31:667–672.

9. Chowbey PK, Soni V, Khullar R, Sharma A, Baijal M. Endoscopic neck surgery. *J Minim Access Surg*. 2007;3:3–7.

10. Chang EHE, Kim HY, Koh YW, Chung WY. Overview of robotic thyroidectomy. *Gland Surg*. 2017;6:218–228.

11. Berber E, Bernet V, Fahey TJ, et al. American Thyroid Association Statement on Remote-Access Thyroid Surgery. *Thyroid*. 2016;26:331–337.

12. Inabnet WB, Fernandez-Ranvier G, Suh H. Transoral endoscopic thyroidectomy-an emerging remote access technique for thyroid excision. *JAMA Surg*. 2018;153:376–377.

13. Witzel K, Hellinger A, Kaminski C, Benhidjeb T. Endoscopic thyroidectomy: the transoral approach. *Gland Surg*. 2016;5:336–341.

14. Pai VM, Muthukumar P, Prathap A, Leo J, Rekha A. Transoral endoscopic thyroidectomy: a case report. *Int J Surg Case Rep*. 2015;12:99–101.

15. Witzel K, von Rahden BHA, Kaminski C, Stein HJ. Transoral access for endoscopic thyroid resection. *Surg Endosc*. 2008;22:1871–1875.

16. Anuwong A, Kim HY, Dionigi G. Transoral endoscopic thyroidectomy using vestibular approach: updates and evidences. *Gland Surg*. 2017;6:277–284.

17. Park JO, Kim CS, Song JN, et al. Transoral endoscopic thyroidectomy via the tri-vestibular routes: results of a preclinical cadaver feasibility study. *Eur Arch Otorhinolaryngol*. 2014;271:3269–3275.

18. Cai C, Huang Y, Zhang T, et al. Anatomical study of surgical approaches for minimally invasive transoral thyroidectomy: eMIT and TOPP. *Minim Invasive Ther Allied Technol*. 2015;24:340–344.

19. Lee HY, Hwang SB, Ahn K, Lee JB, Bae JW, Kim HY. The safety of transoral periosteal thyroidectomy: results of swine models. *J Laparoendosc Adv Surg Tech A*. 2014;24:312–317.

20. Lee HY, You JY, Woo SU, et al. Transoral periosteal thyroidectomy: cadaver to human. *Surg Endosc*. 2015;29:898–904.

21. Study Quality Assessment Tools. Washington DC: U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute; Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed February 24, 2018.

22. Wilhelm T, Metzig A. Endoscopic minimally invasive thyroidectomy (eMIT): a prospective proof-of-concept study in humans. *World J Surg*. 2011;35:543–551.

23. Zeng Y, Li Z, Xuan W, He J. Trans-oral glasses-free three-dimensional endoscopic thyroidectomy-preliminary single center experiences. *Gland Surg*. 2016;5:628–632.

24. Nakajo A, Arima H, Hirata M, et al. Trans-oral video-assisted neck surgery (TOVANS): a new transoral technique of endoscopic thyroidectomy with gasless premandible approach. *Surg Endosc*. 2013;27:1105–1110.

25. Wang C, Zhai H, Liu W, et al. Thyroidectomy: a novel endoscopic oral vestibular approach. *Surgery*. 2014;155:33–38.

26. Yang J, Wang C, Li J, et al. Complete endoscopic thyroidectomy via oral vestibular approach versus areola approach for treatment of thyroid diseases. *J Laparoendosc Adv Surg Tech A*. 2015;25:470–476.

27. Udelsman R, Anuwong A, Oprea AD, et al. Trans-oral vestibular endocrine surgery: a new technique in the United States. *Ann Surg*. 2016;264:e16.

28. Yang K, Ding B, Lin C, Li W, Li X. The novel transvestibule approach for endoscopic thyroidectomy: a case series. *Surg Laparosc Endosc Percutan Tech*. 2016;26:25.

29. Jitpratoom P, Ketwong K, Sasanakietkul T, Anuwong A. Transoral endoscopic thyroidectomy vestibular approach (TOETVA) for Graves' disease: a comparison of surgical results with open thyroidectomy. *Gland Surg*. 2016;5:546–552.

30. Wilhelm T, Wu G, Teymoortash A, Güldner C, Günzel T, Hoch S. Transoral endoscopic thyroidectomy: current state of the art: a systematic literature review and results of a bi-center study. *Trans Cancer Res*. 2016;5(suppl 7):S1521–S1530.

31. Dionigi G, Bacuzzi A, Lavazza M, et al. Transoral endoscopic thyroidectomy: preliminary experience in Italy. *Updates Surg*. 2017;69:225–234.

32. Sivakumar T, Amizhthu RA. Transoral endoscopic total thyroidectomy vestibular approach: a case series and literature review. *J Minim Access Surg*. 2018;14:118–123.

33. Park J, Sun D. Transoral endoscopic thyroidectomy: our initial experience using a new endoscopic technique. *Surg Endosc*. 2017;31:5436–5441.

34. Anuwong A, Ketwong K, Jitpratoom P, Sasanakietkul T, Duh Q. Safety and outcomes of the transoral endoscopic thyroidectomy vestibular approach. *JAMA Surg*. 2018;153:21–27.

35. Chai YJ, Chung JK, Anuwong A, et al. Transoral endoscopic thyroidectomy for papillary thyroid microcarcinoma: initial experience of a single surgeon. *Ann Surg Treat Res.* 2017;93:70–75.

36. Bakkar S, Al Hyari M, Naghawi M, Corsini C, Miccoli P. Transoral thyroidectomy: a viable surgical option with unprecedented complications-a case series. *J Endocrinol Invest.* 2018; 41:809–813.

37. Fu J, Luo Y, Chen Q, et al. Transoral endoscopic thyroidectomy: review of 81 cases in a single institute. *J Laparoendosc Adv Surg Tech A.* 2018;28:286–291.

38. Russell JO, Clark J, Noureldine SI, et al. Transoral thyroidectomy and parathyroidectomy: a North American series of robotic and endoscopic transoral approaches to the central neck. *Oral Oncol.* 2017;71:75–80.

39. Wang Y, Xie QP, Yu X, et al. [Preliminary experience with transoral endoscopic thyroidectomy via vestibular approach: a report of 150 cases in a single center] (in Chinese). *Zhonghua Wai Ke Za Zhi.* 2017;55:587–591.

40. Razavi CR, Russell JO. Indications and contraindications to transoral thyroidectomy. *Ann Thyroid.* DOI:10.21037/aot.2017.

41. Witzel K, Benhidjeb T, Kaminski C, Messenbaeck FG, Weitzendorfer M. Hybrid techniques and patients' safety in implementing transoral sublingual thyroidectomy. *Endocrine.* 2018;60:50–55.

42. Wang Y, Zhang Z, Zhao Q, et al. Transoral endoscopic thyroid surgery via the tri-vestibular approach with a hybrid space-maintaining method: a preliminary report. *Head Neck.* DOI.org/10.1002/hed.25157.

43. Cannizzaro MA, Borzì L, Lo Bianco S, Okatyeva V, Cavallaro A, Buffone A. Comparison between Focus Harmonic scalpel and other hemostatic techniques in open thyroidectomy: a systematic review and meta-analysis. *Head Neck.* 2016;38:1571–1578.

44. Chadwick DR. Hypocalcaemia and permanent hypoparathyroidism after total/bilateral thyroidectomy in the BAETS Registry. *Gland Surg.* 2017;6(Suppl 1):S69–S74.

45. Aytac B, Karamercan A. Recurrent laryngeal nerve injury and preservation in thyroidectomy. *Saudi Med J.* 2005;26:1746–1749.

46. Dionigi G, Wu C, Tufano RP, et al. Monitored transoral endoscopic thyroidectomy via long monopolar stimulation probe. *J Vis Surg.* 2018;4:24.

47. Shan L, Liu J. A systemic review of transoral thyroidectomy. *Surg Laparosc Endosc Percutan Tech.* 2018;28:135–138.

Appendix 8: Camenzuli C, Schembri Wismayer P, Calleja Agius J. 2019. Using thiel embalmed cadavers for training in transoral endoscopic thyroidectomy vestibular approach (TOETVA): is it feasible? Minerva Chir. doi: 10.23736/S0026-4733.19.08066-0. Epub 2019 Jul 5. PMID: 31280547.

Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol 2017;3:524–48.

2. Kehlet H, Büchler MW, Beart RW Jr, Billingham RP, Williamson R. Care after colonic operation—is it evidence-based? Results from a multinational survey in Europe and the United States. J Am Coll Surg 2006;202:45–54.

3. Abrisqueta J, Ibañez N, Luján J, Hernández Q, Parrilla P. Intracorporeal ileocolic anastomosis in patients with laparoscopic right hemicolectomy. Surg Endosc 2016;30:65–72.

4. Sajid MS, Siddiqui MR, Baig MK. Single layer versus double layer suture anastomosis of the gastrointestinal tract. Cochrane Database Syst Rev 2012;1:CD005477.

5. Bracale U, Merola G, Cabras F, Andreuccetti J, Corcione F, Pignata G. The Use of Barbed Suture for Intracorporeal Mechanical Anastomosis During a Totally Laparoscopic Right Colectomy: Is It Safe? A Retrospective Nonrandomized Comparative Multicenter Study. Surg Innov 2018;25:267–73.

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Article first published online: May 2, 2019. - Manuscript accepted: April 10, 2019. - Manuscript revised: April 3, 2019. - Manuscript received: November 12, 2018.

(*Cite this article as:* Coppola S, Barbieri C, Faillace G, Longoni M. Enterotomy single layer closure with Filbloc in laparoscopic right colectomy with intracorporeal anastomosis: a single-center experience. Minerva Chir 2019;74:438-40. DOI: 10.23736/S0026-4733.19.07960-4)

Online version at http://www.minervamedica.it
Minerva Chirurgica 2019 October;74(5):440-2
DOI: 10.23736/S0026-4733.19.08066-0

Using thiel embalmed cadavers for training in transoral endoscopic thyroidectomy vestibular approach (TOETVA): is it feasible?

Transoral endoscopic thyroidectomy through a vestibular approach (TOETVA) is a relatively new technique that has been increasing in its importance when compared with other endoscopic platforms for thyroidectomy. The advantages that this technique offers over other endoscopic procedures for thyroidectomy include the absence of a scar and the short length that needs to be dissected so that the target organ is reached.

Throughout the world there are increasing limitations in the amount of time trainees are allowed to stay in hospitals during their formative years. This has resulted in an appreciable strain on the training quality of surgeons. Thiel embalming has been shown to offer a good alternative for surgical training experience in conventional thyroid surgery.[1] This study aimed to reproduce the published technique of TOETVA in Thiel embalmed cadavers to assess the feasibility of this setup for training surgeons.

This study was carried out at the cadaveric dissection lab of the Department of Anatomy, Faculty of Medicine and Surgery of the University of Malta after being approved by the University of Malta Ethics committee. The cadavers were all embalmed using a previously published method.[2] Three Thiel embalmed cadavers were dissected by a general surgeon with endocrine surgery interest who had never performed TOETVA before using the published standard technique.[3] This includes the following:

1. Positioning: supine position with the neck extended. The laparoscopic tower was placed at the feet.
2. Access: A 10-mm horizontal incision is made in the center of the vestibule and a curved artery forceps used to bluntly develop the subplatymsal space. After port insertion, 6 mmHg CO_2 insufflation was started. Two small incisions were made opposite the lower canine bilaterally and 5mm ports were inserted pointing towards the sternal notch under direct vision (Figure 1).
3. A 30° high definition endoscope was used with the first assistant on the right side and the surgeon at the head. The subplatysmal plane was developed using the sternal notch as the inferior border, the medial ends of sternocleidomastoid as the lateral borders and the superior border of the larynx as the superior border.
4. The strap muscles were opened through the *linea alba cervicalis* and dissected off the thyroid lobe.
5. The thyroid isthmus was identified, dissected off the trachea and divided (Figure 2).
6. Dissection proceeded using a cranio-caudal approach whilst keeping the lobe under supero-medial traction (Figure 3).
7. The superior thyroid artery and vein were identified and divided.
8. The recurrent laryngeal nerve was then identified and dissected off the thyroid lobe. An attempt was carried out to identify the parathyroid glands and dissect them off.
9. The inferior thyroid vessels were identified and divided.
10. Berry's ligament was divided.
11. The procedure was then repeated on the opposite side.
12. The specimen was removed through the vestibule.
13. Incisions were closed with Vicryl® 2/0 (Ethicon™, Somerville, New Jersey, USA) interrupted sutures.

Surface anatomy measurements from the midline of the chin to the sternal notch and operative time were recorded. After the procedure, all of the cadavers underwent open dissection with assessment of the anatomy in order to evaluate whether there was any damage to the recurrent laryngeal nerve, trachea, esophagus, internal jugular nerve and carotid artery.

One female and two male cadavers were utilized.

Figure 1.—Positioning of ports. 10-mm central port and two 5-mm ports inserted in Cadaver 2.

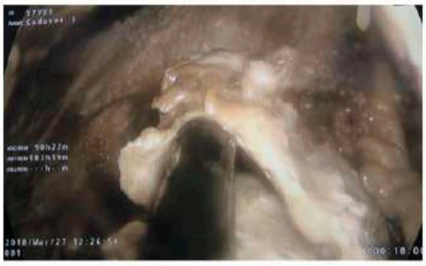


Figure 2.—Thyroid isthmus. Isthmus in cadaver 3 after it was dissected off the trachea centrally and elevated.

The procedures took 140 minutes, 215 minutes and 130 minutes. The cadavers could be positioned with ease using a wooden bolster. The mandible to sternal notch distance was 13.7 cm, 19 cm and 14 cm respectively. Vestibular tissues retained their elasticity and consistency. The blunt dissection used to develop the subplatsmal plane could be performed efficiently. The 6 mmHg pressure used for insufflation was enough to keep the plane open and allow for good visualization.

The *linea alba cervicalis* was easily identifiable. The thyroid tissue was identified in all cases although in one of the cadavers the gland was paler and less firm which could indicate a decomposition. The superior and inferior vascular pedicles were clearly identified. The recurrent laryngeal nerve was not well identified in two of the cadavers. Dissection was kept as close to the gland as possible to avoid damage. In two of the cadavers at least one parathyroid was identified. Difficulty was registered in the second cadaver due to poor triangulation of working instruments at the inferior thyroid poles. The specimen was easily retrieved through the central vestibular incision.

On post procedural assessment, there was no damage to the trachea, recurrent laryngeal nerves, carotid arteries (common, internal and external) and internal jugular veins. The parathyroid glands could not be identified at open assessment.

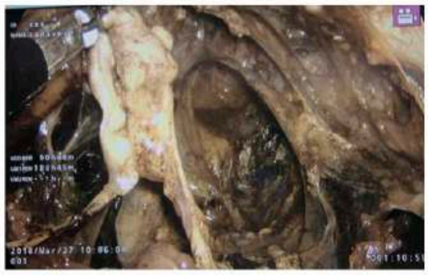


Figure 3.—Right thyroid lobe. The lobe in cadaver 2 is seen retracted supero-medially.

Having these life-like tissue characteristics is fundamental to allow proper positioning. The elasticity of the vestibular tissues is also important to allow a good seal around the ports and therefore avoid gas leak and loss of operating space. The operative experience when using Theil embalmed cadavers was satisfactory. The second cadaver was more difficult due to a longer neck making triangulation more difficult.

This safe setup offered the investigator the opportunity to develop confidence with the anatomy of the neck as visualized in this procedure as well as a good introduction to tissue handling in TOETVA. The main limitation was the lack of identification of the recurrent laryngeal nerves in two of the cases. This might be due to TOETVA being new to the surgeon since the nerves were identified at open assessment. Dissection close to the thyroid gland was able to preserve all of these structures. The other limitation is the lack of bleeding.

Training on Thiel embalmed cadavers was found to be a feasible option for surgeons who are starting to familiarize themselves with TOETVA. It offers a safe setup to develop the spatial acclimatization needed with realistic tissue handling and overall operative experience. Cadavers with a shorter neck are advisable in the initial phase.

Christian CAMENZULI *,
Pierre SCHEMBRI WISMAYER,
Jean CALLEJA AGIUS

Department of Anatomy, Faculty of Medicine and Surgery, University of Malta, Msida, Malta

*Corresponding author: Christian Camenzuli, Department of Anatomy, Center for Biobanking and Molecular Medicine, Faculty of Medicine and Surgery, University of Malta, Msida MSD2080, Malta. E-mail: christian.camenzuli.04@um.edu.mt

References

1. Eisma R, Mahendran S, Majumdar S, Smith D, Soames RW. A comparison of Thiel and formalin embalmed cadavers for thyroid surgery training. Surgeon 2011;9:142–6.

2. Kerckaert I, Van Hoof T, Pattyn P, D'Herde K. Endogent: Centre for Anatomy and Invasive Techniques. Anatomy. 2015;2:28–33.

3. Anuwong A, Sasanakietkul T, Jitpratoom P, Ketwong K, Kim HY, Dionigi G, *et al.* Transoral endoscopic thyroidectomy vestibular approach (TOETVA): indications, techniques and results. Surg Endosc 2018;32:456–65.

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Funding.—This research was partly funded by the ENDEAVOUR Scholarships Scheme Malta.

Authors' contributions.—Christian Camenzuli was part of the team that planned the study. He was the surgeon preforming the procedures and was involved with the write up. Pierre Schembri Wismayer was part of the team that planned the study. He supervised the work and reviewed the manuscript. Jean Calleja Agius was part of the team that planned the study. He supervised the work and reviewed the manuscript.

Acknowledgements.—We would like to acknowledge the contribution of Dr Andee Agius BSc (Hons), MSc, MClin Res, MD for proofreading of the text, and Mr Sherif Suleiman BSc (Medical Lab. Sciences), MSc (Biomedical Sciences), Lab Manager, for coordinating the use of the dissection hall at the Department of Anatomy.

Article first published online: July 5, 2019. - Manuscript accepted: June 28, 2019. - Manuscript revised: May 22, 2019. - Manuscript received: April 16, 2019.

(*Cite this article as:* Camenzuli C, Schembri Wismayer P, Calleja Agius J. Using thiel embalmed cadavers for training in transoral endoscopic thyroidectomy vestibular approach (TOETVA): is it feasible? Minerva Chir 2019;74:440-2. DOI: 10.23736/S0026-4733.19.08066-0)

Online version at http://www.minervamedica.it
Minerva Chirurgica 2019 October;74(5):442-4
DOI: 10.23736/S0026-4733.19.08057-X

Hypoxia inducible factor 1 inhibitors for cancer therapy

HIF-1 is a dimer transcription factor composed by the oxygen dependent HIF-1α subunit and continuous expressed HIF-1β subunit, which is important to maintain intracellular and systemic oxygen steady state. Expression and activity of the HIF-1α subunit determines the biological activities of HIF-1. Decrease of oxygen concentration in cells can be turned into increase of the activity of HIF-1 by the way of oxygen dependent modification process after translation. The expression of HIF-1α is regulated by oxygen concentration. ARD1 acetylase acetylates 532 lysine residues of HIF-1α, promotes combination of PVHL and HIF-1α, increases the ubiquitin and degradation of HIF-1α (Figure 1).

HIF-1 inhibitors are a kind of new and important therapeutic drugs specifically targeted to tumor-stromal cells respond. HIF-1 inhibitors inhibit angiogenesis, selection of tumor cell clone and the adaptation of tumor cells of hypoxia environment. Large amounts of data show that the oxygen of tumor cell invasion and metastasis rate increased, the patient mortality rate increased, HIF-1α mediated tumor cells to radiotherapy and chemotherapy tolerance. Therefore, inhibition of the HIF-1α activity is one important part of for united antiangiogenesis therapy. Increasing number of drugs have been reported to inhibit the activity or expression of HIF-1. According to their putative mechanism of action, HIF inhibitors could be tentatively divided in agents that module: HIF-1 mRNA expression, protein translation, protein degradation, DNA binding and transcriptional activity.

The accumulation and regulation of HIF-1 mainly exist at the level of protein translation or protein degradation, through which most of the existing HIF-1 inhibitors produce inhibitory effects. EZN-2968 is highly specific and can efficiently bind to HIF-1 mRNA, thereby reducing the expression level of HIF-1 protein. EZN-2968 treatment can inhibit the growth of tumor cells, down-regulate HIF-1 target gene, and further damage HUVEC cells. Current phase I clinical trial results indicate that ENZ-2968 can be safely used in patients with advanced cancer and that ENZ-2968 has potential activity in patients with metastatic renal cell carcinoma.

Another HIF-1α, aminoflavone (AF), is a ligand of the aryl-hydrocarbon receptor (AhR). Some researchers used AF drugs to activate the AhR pathway, and studies have shown that AF can inhibit the accumulation of HIF-1. It is currently supposed that AF may inhibit HIF-1 *via* regulating the expression of HIF-1 mRNA.

Topotecan is one of the earliest drugs observed that may affect the expression of HIF-1 protein and is currently used as a second-line treatment for small-cell lung cancer or ovarian cancer. Studies have shown that daily use of topotecan combined with anti-VEGF antibody bevacizumab has a synergistic anti-tumor effect in the xenograft tumor model, providing a theoretical basis for the clinical application of combined drug therapy.

EZN-2208 may have an effect on CPT-11 recurrent tumors by inhibiting the accumulation of HIF-1, thus acting on the tumor microenvironment rather than only on the cancer cells themselves.

Another drug reported to affect HIF-1 expression is cardiac glycosides. Among them, digoxin, as an inhibitor that can effectively inhibit HIF-1 activity at the cell level, has become an FDA-approved drug. The mechanism by which digoxin inhibits HIF-1 expression has nothing to do with mtor, and digoxin shows antitumor activity in xenograft models. Digoxin inhibited the growth of xenograft tumors of PC3 and p493-Myc, but had no effect on the growth of xenograft tumors capable of continuously expressing active HIF-1, indicating that HIF-1 was involved in the anti-tumor effect of digoxin.

It has been shown that another HIF-1 inhibitor, PX-478, has significant anti-tumor effects in a variety of

Appendix 9: Camenzuli C, Attard J, Borg JP, Schembri Wismayer P, Borg J, Calleja Agius J. 2020. Cadaveric Evaluation of a Device Supporting Gasless Transoral Endoscopic Thyroidectomy. *Surg Innov*. doi: 10.1177/1553350620944513. Epub 2020 Jul 15. PMID: 32664791.

Letter to the Editor

Cadaveric Evaluation of a Device Supporting Gasless Transoral Endoscopic Thyroidectomy

Surgical Innovation
2020, Vol. 0(0) 1–2
© The Author(s) 2020
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1553350620944513
journals.sagepub.com/home/sri
SAGE

Christian Camenzuli[1], Josef Attard[2], John P. Borg, MSc (CREST Lough)[2], Pierre Schembri Wismayer, PhD[1], Jonathan Borg, PhD[2], and Jean Calleja Agius, PhD[1]

To the Editor:

Transoral thyroidectomy has gained considerable ground over the past years, with systematic reviews showing that the technique is safe and feasible.[1] The main technique used is known as transoral endoscopic thyroidectomy via a vestibular approach (TOETVA). This involves the use of carbon dioxide insufflation to keep the surgical space open and allow good visualization.[2] Cases of carbon dioxide embolization with lethal consequences have been published.[3] Gas insufflation might lead to other self-limiting complications, including surgical emphysema and mediastinal emphysema. Experts in the field claim that by using an insufflation pressure of 6 mmHg, the risk of such complications is minimized but not eliminated.

Gasless TOETVA has been only sparsely investigated. The gasless techniques published involve engaging and retracting the skin of the neck with Kirschner wires[4] or using bulky devices[5] that offer an additional challenge to the operating surgeon in the limited space available.

With the aim of developing a viable gasless alternative that respects the scarless principle and offers good visualization of the operative field, a team consisting of anatomists, engineers, and a surgeon was built. To eliminate gas insufflation, a new retracting device was developed. The latter is introduced through the standard 10-mm incision of the midline of vestibule without a port. It has an integrated port that allows the introduction of a 30° 5-mm endoscope and collapsible fins at the tips which are deployed when in position for retraction. The retractor and endoscope are fixed together for ease of use through a securing adjunct. The shaft is angulated upward and therefore away from the operative field (Figure 1).

This device was trialed in 3 Thiel-embalmed cadavers, and the outcomes were compared to those of another 3 Thiel-embalmed cadavers using the standard technique (using 6 mmHg of carbon dioxide insufflation) at 3 different stages of the procedure. Four thyroid specialists ranked the visibility of structures on a visual analogue score from 1 to 10, where a score of 1 meant completely unidentifiable structures and a score of 10 meant all structures identifiable with extreme ease. The specialists did not know which group the cadavers being scored belonged to. The scores from the 2 groups were then statistically analyzed using the Wilcoxon rank test using IBM SPSS Statistics for Windows, version 25 (Released 2017. Armonk, New York: IBM Corp,). When the scores were compared, the P value was 1 with a standard deviation of 1.7 and 2.2. Therefore, for the panel of experts assessing the various stages, the 2 techniques were equivalent in their operative space and ability to identify anatomical structures.

The most important difference between the 2 groups was the dissection times taken for the development of the subplatysmal space. Despite not being significantly longer in the gasless technique (mean of 57 and 71 minutes), using carbon dioxide insufflation helped in the dissection and made this step more efficient. Once this space was open, the working space offered by both techniques was sufficient for the operation to take place. All cadavers in which carbon dioxide insufflation was used had surgical emphysema. The latter was absent in the gasless technique. This is a known consequence of gas insufflation in the neck that resolves quickly in the living patient.

We recognize some limitations in our assessment, including the limited amount of cadavers used and the limitations offered by the panel assessing from a photo. Despite all this, we think this is a promising and reproducible step forward in making this emerging technique safer. Although aimed for the endoscopic variant of TOETVA, the device can be easily adapted to the robotic technique.

Author Contributions

Christian Camenzuli is the originator of concept and contributed substantially to the concept of the work, and

[1]Department of Anatomy, Faculty of Medicine and Surgery, University of Malta, Malta
[2]Department of Industrial and Manufacturing Engineering, Faculty of Engineering, University of Malta, Malta

Corresponding Author:
Christian Camenzuli, Department of Anatomy, Faculty of Medicine and Surgery, University of Malta, Msida MSD2080, Malta.
Email: christian.camenzuli.04@um.edu.mt

Figure 1. Assembly image showing the integrated retracting device with the fins in the deployed state.

acquisition, analysis, or interpretation of data; drafted the manuscript; and approved the version to be published. Josef Attard contributed substantially to the design of the work and approved the version to be published. John Borg contributed substantially to the design of the work and approved the version to be published. Pierre Schembri Wismayer contributed substantially to the concept of the work, revised the manuscript critically for important intellectual content, and approved the version to be published. Jonathan Borg contributed substantially to the concept and design of the work and approved the version to be published. Jean Calleja Agius contributed substantially to the concept of the work, revised the manuscript critically for important intellectual content, and approved the version to be published.
Study concept and design: Christian Camenzuli, Josef Attard, John Borg, Pierre Schembri Wismayer, Jonathan Borg, and Jean Calleja Agius
Acquisition of data: Christian Camenzuli, Josef Attard, and John Borg
Analysis and interpretation: Christian Camenzuli
Study supervision: Pierre Schembri Wismayer, Jonathan Borg, and Jean Calleja Agius

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Endeavour Scholarship Scheme Malta.

ORCID iD

Christian Camenzuli https://orcid.org/0000-0002-8491-6061

References

1. Camenzuli C, Schembri Wismayer P, Calleja Agius J. Transoral endoscopic thyroidectomy: A systematic review of the practice so far. *J Soc Laparoendosc Surg*. 2018;22(3): e201800026 doi:10.4293/JSLS.2018.00026
2. Anuwong A, Sasanakietkul T, Jitpratoom P, et al. Transoral endoscopic thyroidectomy vestibular approach (TOETVA): Indications, techniques and results. *Surg Endosc*. 2019; 32(1):456-465.
3. Kim KN, Lee DW, Kim JY, Han K-H, Tae K. Carbon dioxide embolism during transoral robotic thyroidectomy: A case report. *Head Neck*. 2018;40(3):E25-E28.
4. Nakajo A, Arima H, Hirata M, et al. Trans-oral video-assisted neck surgery (TOVANS). A new transoral technique of endoscopic thyroidectomy with gasless premandible approach. *Surg Endosc*. 2013;27(4):1105-1110.
5. Park J-O, Wang S-G, Park D, et al. The feasibility of a prototype thyroidoscope for gasless transoral endoscopic thyroidectomy: A preclinical cadaver study. *J Laparoendosc Adv Surg Tech*. 2019;29(7):953-957.

Appendix 10: Camenzuli C, Schembri Wismayer P, Calleja Agius J. 2021. Association between carbon dioxide insufflation in endoscopic thyroidectomy and intra-ocular pressure (IOP). Is insufflation contra-indicated in glaucoma patients? *Oral Oncol.* . doi: 10.1016/j.oraloncology.2020.105022. Epub 2020 Sep 25.

Oral Oncology 113 (2021) 105022

ELSEVIER

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Letter to the editor

Association between carbon dioxide insufflation in endoscopic thyroidectomy and intra-ocular pressure (IOP). Is insufflation contra-indicated in glaucoma patients?

Dear Editor,

We have read with interest the paper by Lira RB et al. entitled 'Transoral thyroidectomy (TOETVA): Complications, surgical time and learning curve' [1]. We agree with the authors' conclusions in that TOETVA has been shown to be safe and feasible in many publications. However following our own work on novel techniques in endoscopic thyroid surgery, we would like to share with you our concern regarding rises in intraocular pressure (IOP), which is a rare but serious side-effect of insufflation, especially associated with endoscopic neck surgery.

Since open thyroidectomy leaves a very visible scar that is cosmetically undesirable in an important subset of the operated population, endoscopic techniques that take the incision outside the cervical region were developed. These are usually performed using laparoscopic tools but they have also been modified for robotic use. Carbon dioxide insufflation is commonly used to keep the working space open and therefore ensure the anatomy is visible. Whilst some (particularly the *trans*-axillary approach) have developed to eliminate gas insufflation, the majority of techniques still use this as a standard part of the procedure.

The association with any increase in IOP has been largely overlooked and poorly investigated. Despite an extensive literature search, only two papers discussing this topic were identified. These papers were published by Gao, Y et al. in 2012 [2] (translated from Chinese to English using an online translator) and Kim, J et al. 2013 [3]. The combined population of patients studied was of 67 patients. Both studies were prospective in nature and compared IOP taken at several standardized intervals during thyroidectomy in the conventional open approach and the robotic or endoscopic approach during which carbon dioxide insufflation was utilized. The pressure of the insufflation was kept to the international recognized limits of 6–8 mmHg. In addition to IOP, in both studies the mean arterial pressure (MAP) and heart rate (HR) were also monitored. In both studies, patients with pre-existing ophthalmic pathology or previous eye surgery were excluded. The conventional and endoscopic groups had similar demographics. The details of these studies can be found in Table 1.

Induction of anaesthesia has been shown to provide a temporary fall in IOP in both studies. Whilst this decrease was maintained throughout the operation in the conventional open thyroidectomy groups, this was not the case in the insufflation groups. The latter groups showed a significant increase in IOP during the procedure (p values: <0.001 and <0.05 respectively) which then resolved when the insufflating gas was released from the neck. The intra-operative IOP was also found to be significantly higher in the insufflation group when compared with the conventional group at the same stages of the procedure (p values: 0.014 and <0.05 respectively).

In terms of the secondary outcomes recorded, the changes in MAP and HR were similar between the two groups. Whilst in Kim et al. (2013) the partial pressure of carbon dioxide (pCO_2) was kept constant at all times of the peri-operative period in both groups, in Gao et al. (2012) pCO_2 was monitored and compared. In the latter study, pCO_2 was consistently higher during insufflation when compared to the conventional surgery ($p < 0.05$).

The mechanism leading to this increase is hypothesized to be due to a combination of hypercarbia and direct pressure on the internal jugular veins. Hypercarbia is associated with choroidal vasodilatation and is a common consequence of general anaesthesia [4]. Although this is a contributing factor to the increase in IOP during insufflation, when pCO_2 was controlled the changes in IOP still occurred [3]. Direct pressure on the jugular veins (which decreases blood flow through them) is postulated to increase the IOP by decreasing episcleral venous outflow. This phenomenon has also been recorded when external pressure is applied on the neck in humans.

Patients suffering from glaucoma are particularly susceptible to potential damage induced by having intermittent rises in IOP [5]. With evidence showing a significant rise in IOP with neck insufflation, it is prudent to consider glaucoma as a relative contraindication for techniques that require carbon dioxide insufflation in the neck until further evaluation. In patients who are suffering from glaucoma and in whom

Table 1
Summary of included studies.

Study	Intervention	Insufflation	IOP measurements	Patients	Outcomes
Kim, J et al (2013)	Prospective non-randomised Conventional Open Thyroidectomy vs Robotic-assisted BABA	6 mmHg	T0: supine before anaesthesia T1: 5 min after intubation T2: 5 min after extension T3: 5 min after docking or platymsa incision T4: closure of linea alba cervicalis T5: 30 min after end of anaesthesia	18 in OT 19 in RAT	Significant increase of IOP with CO2 ($p < 0.001$) Significant increase when compared with OT ($p = 0.014/0.015$)
Gao, Y et al (2012)	Prospective randomised Conventional Open vs Laparoscopic thyroidectomy	6–8 mmHg	T0: 1 min before anaesthesia T1: 5 min after anaesthesia T2: 10 min into the operation T3: 20 min into the operation T4: 40 min into the operation T5: 10 min after venting/end of procedure	15 OT 15 LT	Significant increase of IOP with CO2 ($p < 0.05$) Significant increase when compared with OT (p= <0.05)

OT: Open thyroidectomy; RAT: Robotic assisted thyroidectomy; LT: Laparoscopic thyroidectomy.

https://doi.org/10.1016/j.oraloncology.2020.105022
Received 18 September 2020; Accepted 19 September 2020
Available online 25 September 2020

endoscopic procedures are favoured, it is imperative to control the pCO_2 very closely and to try to use gasless alternatives. A large randomized controlled study would offer the best setup to investigate this issue more closely.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Lira RB, Ramos AT, Nogueira RM, et al. Transoral thyroidectomy (TOETVA): Complications, surgical time and learning curve. 104871 Oral Oncol 2020;30(110). https://doi.org/10.1016/j.oraloncology.2020.104871.
[2] Gao Y, Liu Y, Zhang Y, et al. Effect of CO2 insufflation on intraocular pressure during endoscopic thyroidectomy. Chin J Modern Operative Surg 2012;4:35–7.
[3] Kim J, Kim J, Chang M, et al. Influence of carbon dioxide insufflation of the neck on intraocular pressure during robot-assisted endoscopic thyroidectomy: a comparison with open thyroidectomy. Surg Endosc 2013;27(5):1587–93.
[4] Murphy DF. Anesthesia and intraocular pressure. Anesth Analg 1985;64(5):520–30.
[5] McMonnies C. An examination of the hypothesis that intraocular pressure elevation episodes can have prognostic significance in glaucoma suspects. J Optom 2015;8(4):223–31.

Christian Camenzuli*, Pierre Schembri Wismayer, Jean Calleja Agius
Department of Anatomy, Faculty of Medicine and Surgery, University of Malta, Msida MSD2080, Malta

* Corresponding author.
E-mail address: christian.camenzuli.04@um.edu.mt (C. Camenzuli).