Universitat de Girona
Facultat de Medicina

FINAL DEGREE PROJECT

CLASSICAL VERSUS WIRE-GUIDED BALLOON CATHETER PUNCTURE TECHNIQUE FOR VOICE PROSTHESIS INSERTION

A RANDOMIZED OPEN-LABEL CLINICAL

AUTHOR: Mireia Suñer Colomer

TUTOR: Dr. Ramos

Girona, January 2020
Oto-Rhino-Laryngological Department
Hospital Universitari Doctor Josep Trueta

ACKNOWLEDGMENTS

M'agradaria donar les gràcies a totes les persones que han fet possible aquest treball:

A en Marc Tobed, per les seves aportacions i la gran motivació que em va donar per, malgrat les adversitats, finalitzar aquest treball.

A en Marc Sàez, per la seva ajuda, dedicació i disposició en tot moment, i per la seva capacitat de convertir els problemes en senzilles solucions.

A en Rafel Ramos, per fer que, durant el meu Erasmus, els problemes es resolguessin més fàcilment.

I finalment, a la meva família, ja que sense el seu suport i la seva estima, no seria la persona que sóc ara.

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ABREVIATION LIST

ASIR	Age-standardized incidence rate
ASMR	Age-standardized mortality rate
CR	Complete response
CT	Computed tomography
ENT	Ear-nose-throat
FUHNT	Functional Unit of Head and Neck Tumors
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papilloma virus
HUDJT	Hospital Universitari doctor Josep Trueta
ICT	Induction chemotherapy
MI	Main investigator
MRI	Magnetic resonance imaging
NG	Nasogastric
PD	Progression Disease
PET	Positron emission tomography
PR	Partial response
RT	Radiotherapy
SCC	Squamous cell carcinoma
SD	Stable disease
TE	Tracheoesophageal
TEP	Tracheoesophageal puncture
TL	Total laryngectomy
TPF	Cisplatin, Docetaxel and 5-Fluororacil
VP	Voice prosthesis
WGBCP	Wire-guided balloon catheter puncture

ABSTRACT

Background: Tracheoesophageal puncture with voice prosthesis insertion is recognized as an effective and reliable method for voice restoration after total laryngectomy that may be performed as a primary, at the time of laryngectomy, or a secondary procedure. The same surgical procedure of voice prosthesis insertion in secondary time that was introduced by Singer and Blom decades ago, is still in use today. The use of this technique has a high success rate of vocal rehabilitation with some limitations and an acceptable complication rate. Tobed *et al.* In order to remove its complications and limitations, have developed a minimally invasive method for voice prosthesis insertion performed with a wire-guided balloon catheter puncture.

Objective: The aim of this study is to register and compare the post-intervention outcomes in patients rehabilitated with wire-guided balloon catheter puncture technique compared to those who received the classic procedure.

Design: This is a prospective, randomized, open-label and controlled clinical trial which will be carried out in Hospital Universitari Doctor Josep Trueta from February 2020 until October 2023.

Methods: The population of this study will be 18 years or older people diagnosed with locally advanced larynx carcinoma that have received a total laryngectomy for its treatment. A total of 54 patients, 27 per group, will be needed for the study. They will be recruited using a consecutive non-probabilistic method, and they will be randomly assigned with a ratio 1:1 to receive the classic technique (control group) or the wire-guided balloon catheter puncture technique (intervention group).

Keywords: Laryngeal carcinoma, Total laryngectomy, Tracheoesophageal puncture, Voice prosthesis, Voice recovery, Classic versus wire-guided balloon catheter puncture technique.

1 INTRODUCTION

1.1 ANATOMY AND FUNCTION OF LARYNX

The larynx is the complex organ of voice production composed of nine cartilages connected by membranes and ligaments and containing the vocal cords.

The larynx connects the oropharynx with the trachea and it is located in the anterior neck at the level of the bodies of C3–C6 vertebrae. Although most commonly known for its role as the phonating mechanism for voice production, its most vital function is to guard the air passages, especially during swallowing, when it serves as the sphincter valve of the lower respiratory, thus maintaining a patent airway.(1)

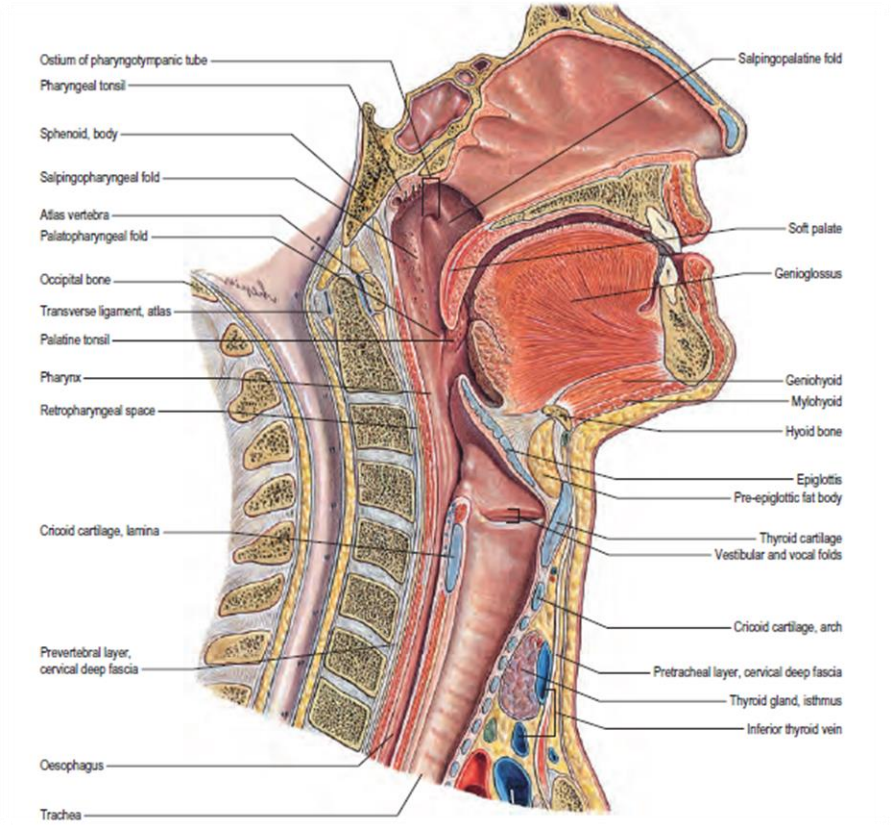


FIGURE 1: A sagittal section through the head and neck.
Source: Gray's Anatomy. The Anatomical Basis of Clinical Practice (41st Edition).

The laryngeal cavity extends from the laryngeal inlet, through which it communicates with the laryngopharynx, to the level of the inferior border of the cricoid cartilage, where is continuous with the cavity of the trachea.

The walls of the cavity are formed of the fibroelastic membranes and lined with mucous membrane that folds over the free edges of these membranes within the larynx. On either side, the continuity of the fibroelastic membrane is interrupted with the upper vestibular or false folds and lower true vocal folds or vocal cords.

The folds project into the lumen of the cavity and divide it into upper and lower parts, separated by a middle portion between the two sets of folds that leads into the laryngeal ventricle. The fissure between the folds is the glottis.

The true vocal folds are the primary source of phonation, whereas the vestibular folds normally do not contribute directly to sound production. (2)

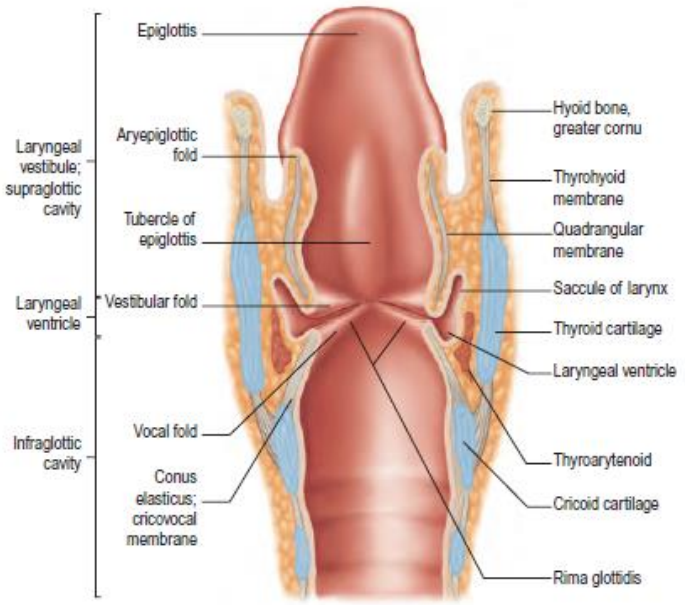


FIGURE 2: coronal section through the larynx and the cranial end of the trachea, posterior aspect.
Source: Gray's Anatomy. The Anatomical Basis of Clinical Practice (41st Edition).

The larynx can be divided into three parts: the supraglottis, the glottis, and the subglottis. The supraglottis extends from the tip of the epiglottis and vallecula superiorly to the ventricle and undersurface of the vestibular folds inferiorly; it includes the arytenoid cartilages, the aryepiglottic folds, the false vocal cords, and the epiglottis.

The glottis encompasses the vocal cords, extending from the ventricle between the true and false cords to 0.5 cm below the free edge of the true cords, including the anterior commissure and interarytenoid area.

The subglottic larynx extends from the inferior extent of the glottis to the inferior edge of the cricoid cartilage.(3)

1.2 EPIDEMIOLOGY

Head and neck cancer are the 7th most common type of cancer worldwide, accounting for approximately 6% of all cancer cases and responsible for an estimated 1–2% of all cancer deaths, with the larynx being the most common of all possible locations. Larynx cancer is most prevalent in the sixth and seventh decades of life and is more prevalent among lower socioeconomic groups, for whom it is often not diagnosed until more advanced stages.(3)

According to GLOBOCAN project, head and neck cancer account for more than 650.000 new cases and 330.000 deaths annually in 2018 worldwide. For larynx cancer, it is estimated to be 177.422 and 94.771 respectively.(4)

In Europe, the number of new estimated cases of larynx cancer in 2018 was 39.875, with 19.577 deaths.

The European estimated age-standardized incidence rate (ASIR) per 100,000 person-years in 2018, for all ages and both genders, is 2.9, the highest compared to the other continents. Evaluating sexes separately, the female ASIR decreases to 0.62, whilst the male increases to 5,5, making Europe the continent with the highest male ASIR.

The age-standardized mortality rate (ASMR) is 1,3 for 100.000 person-years, for all ages and both genders. It also increases at 2,6 when evaluating males, and decreases at 0,22 when females.

The current male-to-female ratio for larynx cancer is 4:1, but the relative percentage of women who suffer from it, as with other smoking-related illnesses, has been on rising. (5)

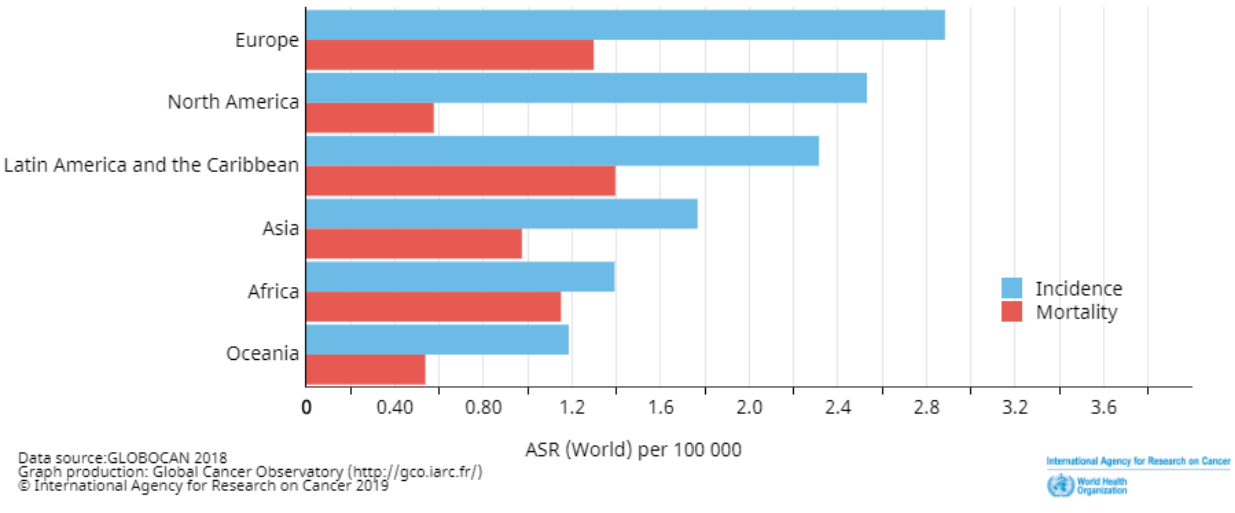


FIGURE 3: Estimated age-standardized incidence and mortality rates (World) in 2018, larynx cancer, both sexes, all ages. Source: GLOBOCAN 2018

If we focus on Europe, we can see that Central and Eastern Europe have higher rates than the rest of Europe, especially in mortality, with ASMR values of 1,8 for 100.000 person-years compared to a 0,9 in Southern Europe. It is believed that the differences are due to their socio-economic characteristics and the limited treatment facilities.(5)

In Spain, head and neck cancer is the 7th most prevalent malignant tumor (5th in males), with the larynx being the most common of all possible locations. The number of new estimated cases of larynx cancer during 2018 was 2.689, and the ASIR was 2,9 for 100.000 person-years. In 2018, 1.273 people died, which translates to an ASMR of 1,1.(5)(6)

Regarding the survival, according to results from EUROCARE-5 project, the relative survival rate after 5 years in both sexes is 61,7% in Southern Europe and 47,0% in Eastern Europe.(7)

Regarding the larynx cancer location, its distribution is not uniform, but varies in different countries: In Spain the supraglottic location is the most frequent, while in Italy or England is the glottic the predominant. These variations in incidence can be explained by the habits and lifestyle in each nation, as well as other environmental factors. Subglottic tumors are the least frequent in all countries. (8)

1.3 RISK FACTORS

The squamous cell carcinoma represents 95% of all the primary larynx tumors. More than 70% of head and neck squamous cell carcinoma (HNSCC) are estimated to be avoidable by lifestyle changes, particularly by effective reduction of exposure to well-known risk factors such as tobacco smoking and alcohol drinking. These risk factors have been long recognized as lifestyle-related risk factors correlated with increased risk of upper aerodigestive tract cancer with synergistic and multiplicative effect. (8)(9)(10)(11)

Tobacco possesses a much stronger impact on the larynx than on the other aerodigestive sites. It is estimated that cigarette-smoking increases the risk of laryngeal cancer 7 times, compared to non-smokers. The risk keeps elevated within the first 15 years of quitting smoking, but drops after 16 years or more of smoking cessation. (12)

There is a direct relationship between **alcohol** intake and risk of HNSCC, specifically it has an important impact on the oral cavity, oropharynx, hypopharynx and larynx, as head and neck sites susceptible to its toxicity. It is, however, difficult to isolate the role of alcohol from smoking because they are usually coexisting risk factors. However, it is estimated that the risk of developing a HNSCC in patients who drink and smoke is thirty times superior compared with patients that are not exposed to those toxics.(9)

Human papilloma virus (HPV) has also been found to be a major contributor to the development of oropharyngeal squamous cell carcinoma, especially for the tonsils and the base of the tongue, and less frequently larynx, oral cavity and hypopharynx. The prevalence of HPV in larynx ranges widely from 20% to 30% and it is increasing among the younger population. The overall incidence of HPV-positive HNSCC is increasing, whereas the incidence of HPV-negative (primarily caused by tobacco and alcohol) HNSCC is decreasing. The most common HPV type detected in laryngeal cancer is HPV16, followed by HPV18, HPV31 and HPV33. (9)(13)(14)

Other risk factors for larynx carcinoma include genetics, toxic exposures, environmental factors, nutritional deficiencies, previous neck irradiation and pharynx-laryngeal reflux. (3)(9)

1.4 CLINICOPATHOLOGIC PRESENTATION

Signs and symptoms of malignant laryngeal lesions include hoarseness, dysphagia, hemoptysis, a mass in the neck, throat pain, ear pain, airway compromise and aspiration. However, these vary depending upon location.

Because only the slightest change in contour, thickness, or vibratory characteristics of the vocal cord results in perceived changes in the voice, **glottic** larynx cancers is often diagnosed at an early stage of the disease. In more advanced stages, it often causes dyspnea and stridor.

Patients with **supraglottic** cancers are typically diagnosed at a more advanced stage, because tumors are bulkier before voice changes, dysphagia or airway compromise become apparent. In general, supraglottic tumors have more nonspecific symptoms such as foreign body feeling, odynophagia, pharyngeal paresthesia, otalgia, occasional choking and mild dysphagia. Furthermore, because the supraglottis has a richer lymphatic supply, supraglottic primary lesions tend to metastasize earlier and are more often diagnosed at the advanced N stage, for that reason, it is common for the patient to consult for the appearance of a cervical mass as the first symptom. Clinical cervical adenopathy at the time of diagnosis portends a poor prognosis and advances the overall stage.

Subglottic tumors, in spite of being the less frequent, are often diagnosed in advanced stages. The most frequent symptoms are dyspnea or a low cervical mass.

Significant weight loss often accompanies the diagnosis of an advanced larynx cancer, because of swallowing difficulties. Other symptoms include constitutional syndrome, halitosis, blood-tinged sputum and odynophagia. (3)(8)

1.5 IMAGING AND CLINICAL ASSESSMENT

When a larynx cancer is suspected, recording a good clinical history and a complete head and neck examination should be inherent in all good clinical practice.

The **medical history** should include not only a careful review of all the symptoms but also an assessment of associated medical problems, social history to conclude the amount and duration of tobacco and alcohol use and family history of all types of malignancies.

A **complete head and neck examination** requires that all regions above the clavicle have to be carefully palpated for evidence of enlarged lymph nodes or direct extralaryngeal extension.
The presence of metastatic cervical lymph nodes is the most important prognostic factor in the patient with head and neck cancer as it reduces survival by up to 50%. Extra diagnostic methods other than palpation are needed for the correct evaluation of the neck, especially because less than 80% is considered the positive predictive value.
To delimit the location of lymph nodes in the neck, the American Head and Neck Society (AHNS) in cooperation with the Committee for head and neck surgery and Oncology of the American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS), described a level system that divides the neck in 6 levels.
Anatomic division of the lymph nodes by levels can be found in Annex 1.

A **laryngoscopy** for the visualization of the larynx should be carried out next. It can be performed with a laryngeal mirror (indirect laryngoscopy) or with a rigid or flexible fiber-optic endoscope. The stroboscopic light may aid in detecting early glottic lesions by subtle changes in mucosal wave dynamics.

In the event of a possible lesion, imaging techniques will have to be carried out to confirm the diagnosis. A **Computed tomography** (CT) scan with contrast or a **magnetic resonance imaging** (MRI) with contrast, from the skull base to clavicles, will be performed to evaluate the main characteristics of the lesion and its local and distance extension. MRI is more sensitive for soft tissue abnormalities, whereas CT scan is better for bony and cartilaginous defects.

It has to be complemented with a histologic analysis, since it gives the definitive diagnostic.

The histological analysis consists of a **primary tumor biopsy**, and a **lymph node puncture** if necessary. The primary tumor biopsy is performed with a direct laryngoscopy in the operating room with the patient under general anesthesia. For patients who cannot tolerate a general anesthesia, it can also be performed as an office procedure with local anesthesia, using flexible fiber-optic laryngoscope with a working channel.
The lymph node puncture is performed with a fine-needle aspiration biopsy guided by ultrasound.

A **chest x-ray** is performed as part of a routine metastatic evaluation, to exclude the lungs spread, since these are the second most common site of spread after the regional cervical nodes. If there are any significant abnormalities noted on the chest x-ray, a CT scan of the chest should be performed to confirm the lesions.

Positron emission tomography (PET) combined with a CT scan could help on identifying occult nodal metastases. It has to be considered in stages III-IV since these are the patients with high risk of metastases. Performing a PET also helps on distinguish the recurrence of malignant growth on sequelae of prior treatment and identifying the location of an unknown primary cancer - when the patient is presented with a cervical lymph node metastasis without being able to find the primary tumor - . (3)(8)(15)(16)(17)

1.6 STAGING

The classification of cancer by anatomic disease extent is the major determinant of appropriate treatment and prognosis. The Union for International Cancer Control (UICC) published the 8th edition of the TNM classification of malignant tumors. The American Joint Committee on Cancer (AJCC) uses this TNM classification as well. The anatomically based system records the primary and regional nodal extent of the tumor and the absence or presence of metastases.

When TNM is described, tumors can be classified by stage, which helps to describe where a cancer is located, if or where it has metastasized and whether it is affecting other parts. The tumor's stage at diagnosis predicts survival rates and guide management.

TNM and staging tables can be found in Annex 2.

1.7 TERAPEUTIC APPROACH

The treatment of head and neck cancers is complex. The therapeutic approach for larynx squamous cell carcinoma is performed following the newest version (2017) of the Sociedad Española de Oncología Medica (SEOM) and Institut Català d'Oncologia (ICO) - Institut Català de la Salut (ICS) clinical practice guidelines.

Larynx tumors have to be classified in early stage disease, which includes clinical stages I and II, and locally advanced disease, which includes clinical stages III, IV-A, IV-B and IV-C.

1.7.1 EARLY STAGE DISEASE

Single modality treatment involving larynx-preserving surgery or radiotherapy (RT), provide similar locoregional control and survival outcomes of the early stage disease of larynx cancer. The choice of treatment modality depends on local institutional expertise, the availability of appropriate support and rehabilitative services, and patient and tumor factors, such as the functional outcome, the patient's wishes, the possibility of an adequate follow-up, the patient's general condition and the likelihood of developing a second primary tumor.
Single-modality treatment is sufficient and combining surgery with RT should be avoided as functional outcomes may be compromised by combined modality therapy. (17)(18)(19)

The American Society of Clinical Oncology recommends the initial larynx-preserving surgery, as the success may be higher compared with RT, based on retrospective studies. However, as it is explained before, it is subjected to diverse factors. (18)

Endoscopic resection or Transoral Laser Microsurgery (TLM) are preferred because of the equal or better outcomes compared with open partial laryngectomy, unless there are issues with tumor exposure or safety of the endoscopic approach. Surgical excision should be undertaken with the aim of achieving tumor-free margins.(18)

Most patients with T1 and T2 lesions of the glottis and clinically negative cervical nodes do not require routine elective treatment of the neck unless the risk of nodal metastasis exceeds 20–30%. It is for that reason that patients with advanced lesions of the glottis and all patients with supraglottic and subglottic lesions should have elective treatment of

the neck, even if clinically N0. The treatment of both, the ipsilateral and contralateral neck, should be considered, and it varies depending on the tumor location. Neck disease can be treated with a single modality, surgery or radiation.(3)(18)

1.7.2 LOCALLY ADVANCED DISEASE

Locally Advanced disease include larynx cancers classified as stage III or IV. These type of tumors are divided into resectable or unresectable. There is no universally accepted definition of unresectability, and for that reason, the final decision depends on some anatomical criteria, the institution and surgeon abilities, the possibility of achieving complete excision with adequate margins, the risk of the surgery due to age or comorbidities, the functional and aesthetic sequelae of surgery and the expectation of surgical cure, among others. Consequently, in the comprehensive approach of patients with HNSCC, individual evaluation and the definition of the therapeutic strategy in each case have to be defined within a multidisciplinary functional unit formed by a neck surgeon, an oncologist, a radiotherapist and a radiologist. (17)(19)

1.7.2.1 Resectable locally advanced disease

Advanced-stage larynx cancer was historically treated by dual-modality therapy with surgery and radiation. Nowadays, conventional treatments for locally advanced disease are multimodal, consisting of combinations of surgery, RT and chemotherapy.
Studies in the past showed promising results for organ preserving strategies, which led to a change from laryngectomy to chemo-radiation as a preferred first line treatment for advanced resectable laryngeal cancer. The first year's results from these trials concluded that organ preservation offered equivalent survival to primary total laryngectomy (TL), with the added benefit of an intact larynx. However, large-scale database studies have shown that not all advanced laryngeal cancers respond equally. Thus, personalized care with careful selection of patients who are likely to retain a functional larynx is important. (20)

Taking into account patient's preferences with a personalized care and selection, the following treatment possibilities are considered:

Surgical treatment: total or subtotal laryngectomy plus cervical lymphadenectomy neck dissection followed by RT or chemo-RT. Adjuvant concurrent chemo-RT with three-weekly cisplatin is recommended in patients with high risk of pathological features such as extracapsular lymph node extension and affected margins.(17)(19)

The type of the surgery chosen is guided by the extent of the neck disease. For T1, T2, and some T3 lesions, partial laryngectomy procedures with preservation of the voice can be considered.

TL entails the removal of the entire larynx, including the thyroid and cricoid cartilages, possibly some upper tracheal rings, and the hyoid bone. The proximal part of the trachea is anastomosed to an opening at the anterior wall of the neck in a permanent tracheostoma. This results in a complete anatomic separation of the respiratory and digestive tracts.

General Indications for TL are (3)(21):

- Neoplasic lesions of the larynx not amenable to partial laryngectomy procedures or organ preservation therapy with chemo-RT.
- Advanced laryngeal squamous cell carcinoma (T3 or T4) with extensive cartilage erosion or significant spread outside the endolarynx into the base of tongue beyond the circumvallate papillae, hypopharyx or surrounding soft tissues of the neck.
- Failure of organ preservation treatment.
- Extensive laryngeal cancer with irreversible laryngeal dysfunction.
- Chronic aspiration from glottic incompetence not amenable to conservative treatment.
- Hypopharyngeal tumors originating or extending into the postcricoid mucosa.
- Primary tumors of the cricoid or thyroid cartilages (chondrosarcomas).
- Chondroradionecrosis of the larynx failing medical therapy.

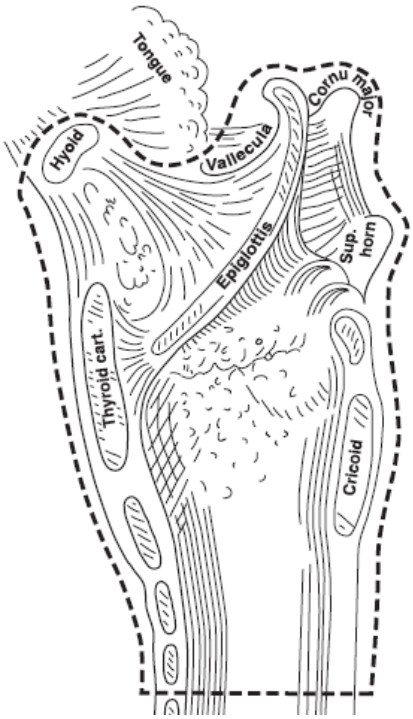


FIGURE4: Schematic of the anatomic resection for a total laryngectomy.

Source: Current diagnosis and treatment in otolaryngology - Head and neck surgery.

It is recommended that the surgical technique is adapted as much as possible to the recovery process, in accordance with the patient's demands. (22)

Non-surgical or **organ preservation treatment** is based on RT plus chemotherapy or biotherapy. In case of residual disease, salvage surgery may be used. The different options that are currently offered are (17):

- Concurrent Chemo-RT based on three-weekly cisplatin if patient refuses surgery.
- Bio-RT with cetuximab, especially for patients with some contraindication for cisplatin such as neuropathy, nephropathy, heart disease and hearing loss.
- Induction chemotherapy (ICT) with TPF schedule (Cisplatin, Docetaxel and 5-Fluororacil), except for subglottic tumors.

  After ICT, if there is:
  - Complete response (CR), defined as disappearance of all clinically tumor burden, the treatment can be continued with adjuvant RT.
  - Partial response (PR), defined as 50% reduction of primary tumor without lymph node progression:
    - TL should be considered as the best option to curative rescue followed by RT.
    - If the patient prefers organ preservation, concomitant RT with cisplatin or cetuximab is recommended.
  - If there is stable disease (SD), defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progression disease (PD), or PD defined as increase of tumor burden, salvage surgery such as TL including neck dissection has to be performed, followed by RT or chemo-RT.

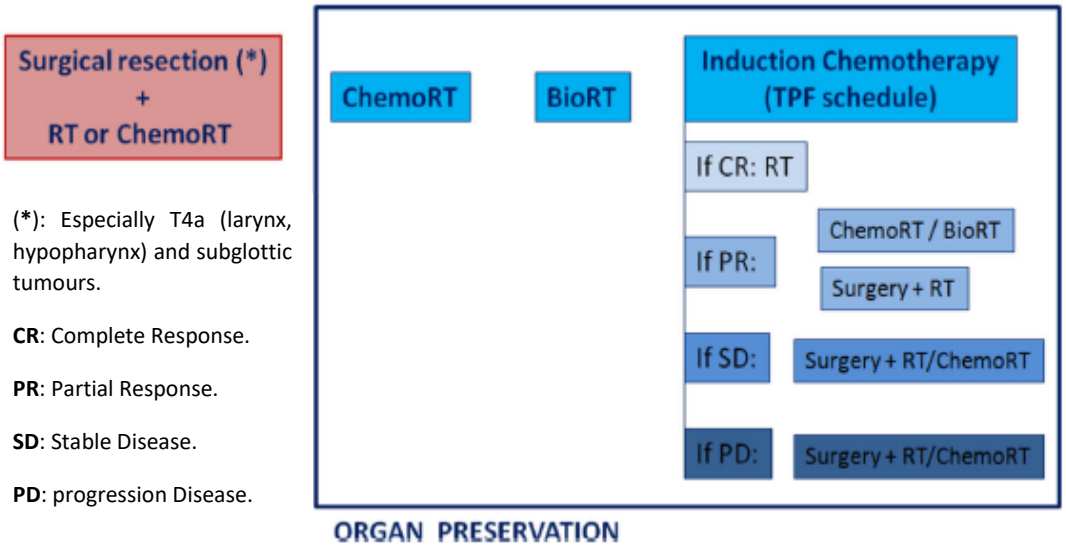


FIGURE 5: Larynx preservation algorithm (respectable locally advanced disease). Source: SEOM clinical guidelines for the treatment of head and neck cancer (2017)

1.7.2.2 Unresectable locally advanced disease

Different therapeutic strategies have been described in these cases:

- Concomitant chemo-RT based on three-weekly cisplatin. It is recommended in lower volume locally advanced disease (T4a, T3, N1-2a).
- Bio-RT with cetuximab should be considered if the use of cisplatin is contraindicated.
- ICT followed by locoregional treatment. This option has been reconsidered, especially in patients who require rapid response due to a greater volume (N3, N2c, important N2b, T4b), very symptomatic and fast-growing locally advanced disease, or are at increased risk of distant metastases. ICT is based on 3 cycles of TPF. After ICT:
    - If CR or PR: RT plus cisplatin or RT plus cetuximab.
    - If SD or PD: treatment should be individualized taking into account the supportive care that includes palliative radiotherapy.

In case of local complete response and persistent lymph node after locoregional treatment, lymph node salvage resection should be considered.(17)(19)

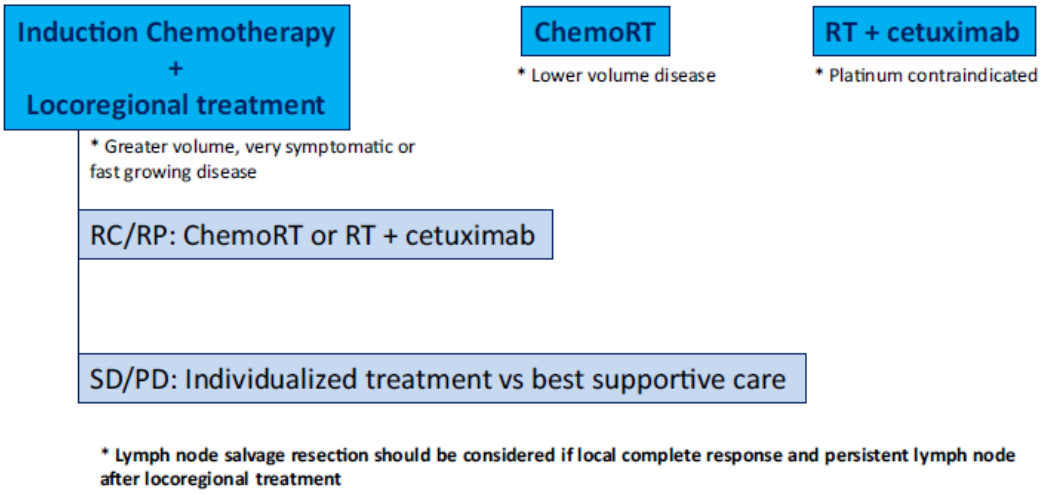


FIGURE 6: Treatment algorithm for unresectable locally advanced disease (IV-B)
Source: SEOM clinical guidelines for the treatment of head and neck cancer (2017)

1.7.2.3 Recurrent and metastatic disease treatment

The multidisciplinary team will assess the possibility of salvage surgery or re-irradiation with or without chemotherapy or cetuximab. In the presence of oligometastatic disease, treatment with curative intent should also be discussed. Once this option is discarded, the treatment of choice is palliative chemotherapy.(17)

1.8 COMPLICATIONS RESULTING FROM SURGICAL TREATMENT

Despite surgical and non surgical treatment advances in organ preservation, TL is still the most effective treatment for advanced laryngeal cancer.

Radical surgery complications involve major physical, but also social, psychological and emotional damage, which leads to a deterioration in the quality of life. It affects, among other factors, the ability to communicate because of phonation and speech difficulties or the loss of voice, swallowing and physical capacity.

After TL, anatomic changes result in a lack of airflow through the nose and mouth provoking breathing problems. The lack of airway protection may also result in increased risk of aspiration and drowning. It also changes the patient's sense of smell and, therefore, the sense of taste.

Swallowing disturbances leads to feeding and salivation disorders and also increase the risk of aspiration. Masticatory capacity and tongue's mobility are affected because of anatomic changes in the aero-digestive superior pathway. (3)(22)

After a TL, the permanent tracheostoma creates a disfigurement of a visible part of the body which may have an extremely negative impact on the patient's body image, provoking problems of self-esteem, self-imaging and difficulties in social and family relationships. These patients would be more likely to express anxiety, depressive symptoms and important levels of distress, more than other cancer patients would. It also causes a loss of emotions' expression; the effective meaning of what they want to convey can hardly be expressed since the acoustic features that transmit the emotions are deeply altered. Reduced sexual enjoyment and libido are also common problems after laryngeal cancer surgery. Psychological support is very important to act directly on emotional distress and psychosocial aspects, to get an emotional well-being and a better quality of life. Psychological needs should be addressed in all patients who have received laryngectomy and incorporated into their treatment plans.(23)

This new condition may also cause exacerbation of previous diseases such as respiratory diseases and related problems to Valsalva's maneuver.

Other complications are nervous and vascular injury, tissue fibrosis that manifests by stiffening, loss of range of motion and pain, hematoma, infection and fistula development due to the failure of the pharyngeal surgical closure. Acute and chronic pain are usual. (3)(22)

1.9 VOICE RESTORATION AFTER TOTAL LARYNGECTOMY

Losing voice after TL does not mean only to miss the ability to transmit a message through the verbal channel. In social interactions, the voice is an important indicator of identity, personality and mood. (23)

Since the first TL in 1873 by Billroth, voice restoration has been considered the leading post laryngectomy rehabilitation challenge. In fact, most of the patients who undergo laryngectomies rate communication as their most important concern regarding life quality (24). The three main methods for restoring oral communication after laryngectomy are esophageal speech, the use of an electrolarynx, and tracheoesophageal (TE) prosthetic speech. The choice of mechanism for speech rehabilitation should be influenced by multiple factors that relate to the underlying disease, treatment history, patient preferences and expertise and recommendations from a multidisciplinary team.(23) (25)

Although surgical voice restoration techniques dominate, it is important to consider the use of esophageal speech and the electrolarynx.

Esophageal speech is produced by insufflation of air from the oral cavity to the pharyngeal-esophageal segment, essentially by swallowing air. The air is released in a controlled manner back through the esophagus, allowing the mucosa of the upper esophagus or neopharynx to vibrate. Using the vibrations of the mucosa as a sound source, the vibratory air stream is channeled through the articulatory apparatus of the upper pharynx and oral cavity, where it can be modified and modulated to produce understandable voice, the erigmophonic voice.

The most important advantages compared with other voice rehabilitation methods include low cost and no need for additional surgeries, it is for that reason that this technique is the most commonly used in developing countries and is an option for patients who do not wish or tolerate further surgery or the possible complications. However, many patients find it difficult to learn initially. (25)

Electrolarynx uses an external vibratory source that is placed in the mouth or against the neck or cheek to produce sound.

The advantages of using the electrolarynx include the lack of need for further surgical procedures and ease of learning. Nevertheless, it is more expensive compared with Esophageal speech and it produces a mechanical voice sound which causes an important patient-perceived vocal handicap.(25)

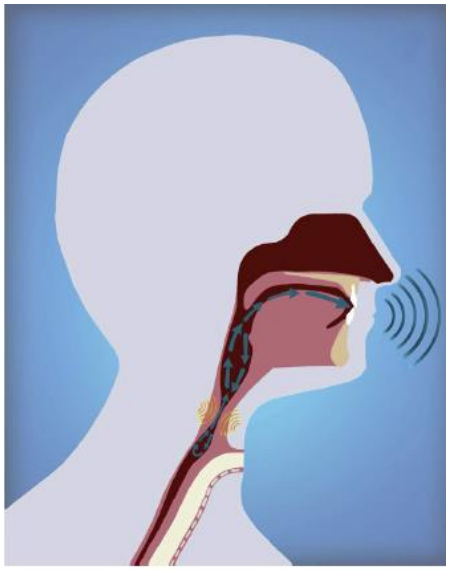


FIGURE 7: Oesophageal speech.

FIGURE 8: Electrolarynx.

Source: Voice Restoration After Total Laryngectomy. Otolaryngol Clin North Am

Among these options**, TE prosthetic speech** has been associated with the best speech quality and it is relatively safe and easy to learn; therefore, it is the gold standard for voice rehabilitation after TL. (23)(24)(26)(25)(27)

TE speech consists of the placement of a voice prosthesis (VP) inserted in a surgically created fistula between the trachea and esophagus, referred to as the tracheoesophageal puncture (TEP). PROVOX® is the most used brand of VP. It is a unidirectional valve that allows the air flow from the trachea to esophagus and avoids the aspiration of the intake from esophagus to trachea.

This technique allows air pressure generated from the lungs to go through the esophagus, where the pharingo-esophagic mucosa acts as a vibrating apparatus that generates a sound, which is the fundamental frequency of the new voice. This new voice is processed in the craniofacial tract, where it is modulated by articulatory mechanisms to get an intelligible speak. (25)

FIGURE 9: tracheoesophageal voice.
Source: Voice Restoration After Total Laryngectomy. Otolaryngol Clin North Am

After prosthesis placement, the patient, in a short span of time as it is technically easier to learn how to use it, may experience the production of a fluent alaryngral voice, which perceived quality and acoustic parameters are better than those acquired with electrolarynx and esophageal speech are. However, all these procedures entail an increased price of the TE voice, given the cost of the prostheses, which is a disadvantage. Other disadvantages include the dependence on the physician to change the VP.(23)(25)

This TEP can be created either at the time of the TL (primary TEP) or at a later timepoint after surgery (secondary TEP). Both methods are well documented in the published literature as safe and reliable procedures, with high rates of successful voice restoration and similar complication rates, as well as TE speech outcomes, even in geriatric patients and in postoperative RT (24)(25)(27)(28).

According to some studies, performing TEP as a primary procedure at the time of total laryngectomy is safe and provides a faster acquisition of speech, reducing the duration of postoperative aphonia and making a positive psychological impact on the patient's life quality, compared to secondary TEP. Additionally, it avoids a second procedure. (24)(27)(28)

However, the rehabilitation with a primary TEP is not as easy as it seems, as the patient is not focused on it until the adjuvant treatment is finished and the wound is healed. Furthermore, during the adjuvant treatment, the VP can be an irritant factor and cause

mucositis of the posterior wall of the traquea. Additionally, as the anatomy in the primary time is not the definitive, its changes can alter the TEP and the VP site.
Moreover, some studies have reported an increased risk for developing pharyngo-cutaneous fistula following TL in the post chemoradiation patients. In these cases, secondary TEP is a better option to achieve successful voice restoration and also to provide an opportunity for enhanced pre-TEP testing, education, and selection. (24)(25)(27)(28)(29)

1.9.1 SECONDARY TEP FOR VP INSERTION: CLASSIC PUNCTURE TECHNIQUE

The surgical procedure of VP insertion in secondary time was introduced by Singer and Blom in 1980, and still remains the optimal means of voice rehabilitation after TL.(30)
According to the Instructions for use of PROVOX® Vega™ Puncture Set described by Atos Medical, which is the trading firm, the classic technique follows the next steps (31):

The procedure is performed under general anesthesia with the patient positioned supine. A rigid esophagoscope is inserted trans-orally into the neopharynx and down the esophagus with the bevel facing anteriorly. The esophagoscope is advanced until it can be palpated through the laryngeal stoma.

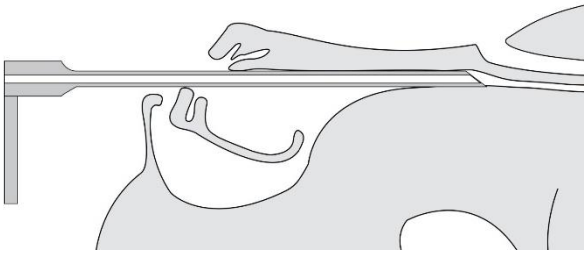


FIGURE 10: The rigid esophagoscope is introduced into the oesophagus.

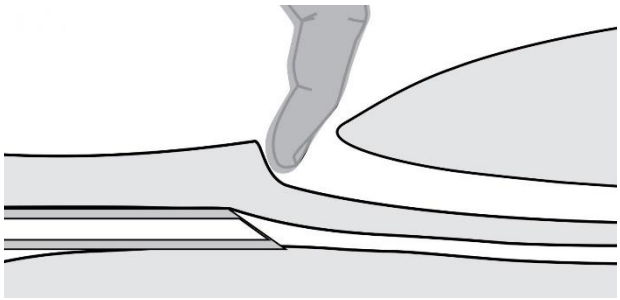


FIGURE 11: Verification of the correct location of the instrument by palpating the trachea.

Source: Instructions for Use. Illustrations PROVOX® Vega™ Puncture Set.

A puncture needle is inserted through the back wall of the tracheostoma and it reaches the lumen of the esophagoscope. Subsequently, a guidewire is inserted into the hub of the puncture needle and pushed through the distal end of the rigid esophagoscope.

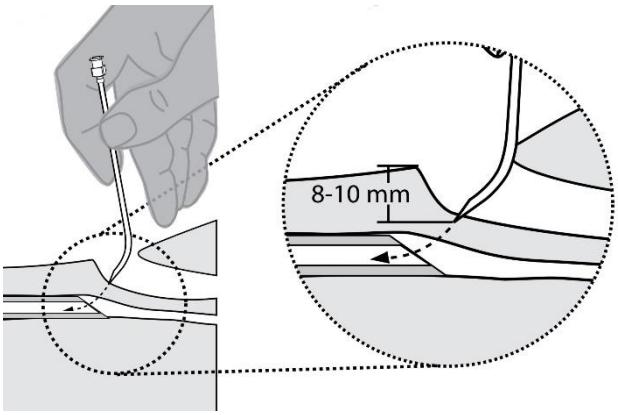


FIGURE 12: TEP realization.

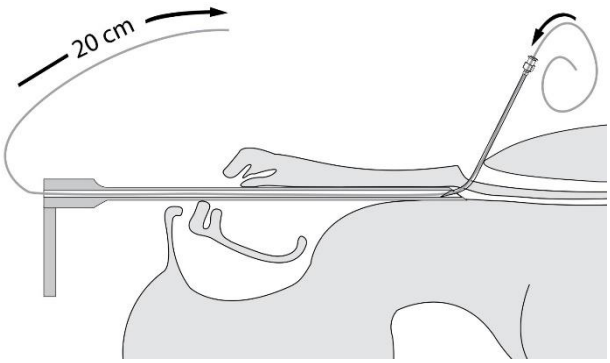


FIGURE 13: Guidewire insertion.

Source: Instructions for Use. Illustrations PROVOX® Vega™ Puncture Set.

Posteriorly, the puncture needle and the rigid esophagoscope are removed, maintaining the guidewire.

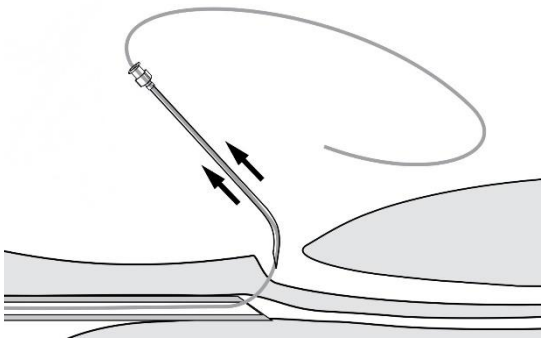


FIGURE 14: Puncture needle removal.

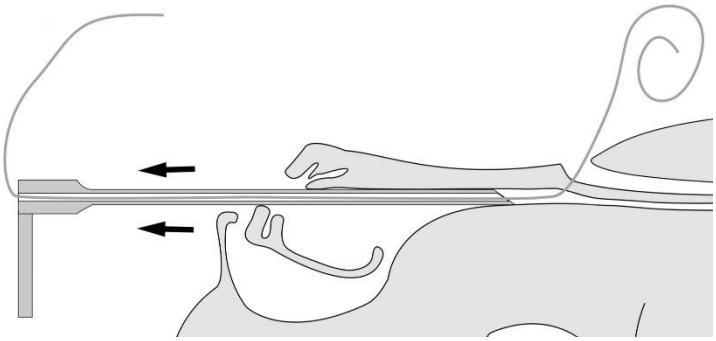


FIGURE 15: Rigid esophagoscope removal.

Source: Instructions for Use. Illustrations PROVOX® Vega™ Puncture Set.

Following all this procedure, the guidewire is fixed into the puncture dilator by its proximal end. Afterwards, the guidewire is pulled from its distal end while the patient is asked to swallow, to transport the puncture dilator, which travels from the mouth to the esophageal puncture site, where it is inserted.

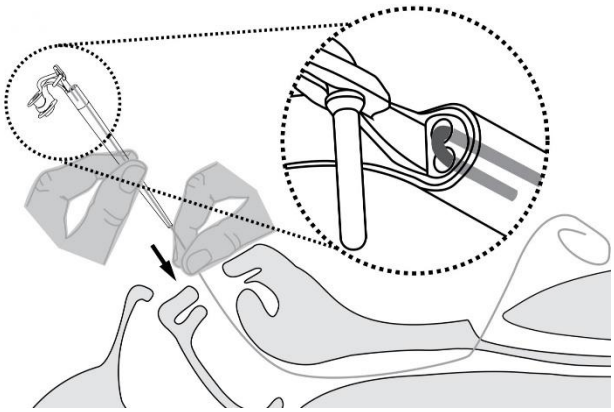


FIGURE 16: Insertion of the guidewire into the puncture.

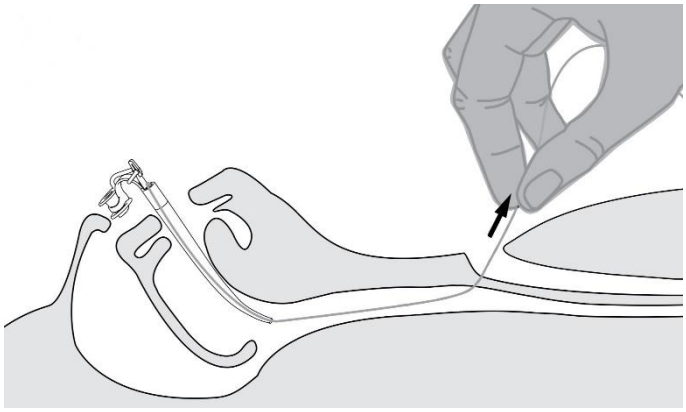


FIGURE 17: mobilization of the puncture dilator from the mouth to the puncture site.

Source: Instructions for Use. Illustrations PROVOX® Vega™ Puncture Set.

Doing a continuous smooth motion, the puncture site is dilated. Finally, the puncture dilator is removed through the puncture site and the VP is pushed and placed immediately inside the fistula.

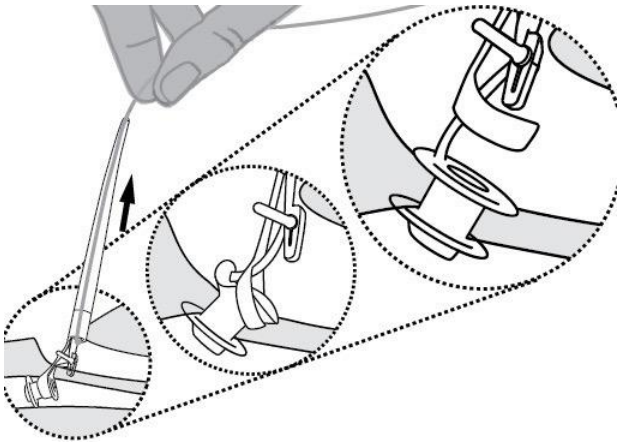


FIGURE 18: Removal of the puncture dilator and placement of the voice prosthesis inside the TEP.

Source: Instructions for Use. Illustrations PROVOX® Vega™ Puncture Set.

The use of this technique for VP insertion has a high success rate of vocal rehabilitation with an acceptable complication rate and limitations.
Some of these complications comprise breaking of the guidewire, bleeding, pain and esophageal wall laceration or perforation if the needle puncture cannot be placed inside the opening of the esophagoscope. (25) Unrecognized injuries of the esophageal wall may lead to the creation of a false passage, subsequent stenosis and infectious complications such as, although less frequent, mediastinitis or cervical cellulitis. (32)

Other described problems include long-term complications, such as valve displacement, stomal stenosis, obstruction from debris or secretions and hypertrophy or infection of the fistula. (25)(26)

Some limitations of the classical technique are the stapler suture of the esophagus in the primary time that can be damaged because of the rigidity of the esophagoscope and anatomic limitations, such as trismus and bad exposure, the need for total anesthesia, and a surgery room for the secondary time. (33)

To avoid some of these complications and remove the limitations described above, Hospital Universitari Doctor Josep Trueta (HUDJT) has developed a minimally invasive method for voice prosthesis insertion, performed with a wire-guided balloon catheter puncture (WGBCP). (33)

1.9.2 SECONDARY TEP FOR VP INSERTION: WIRE-GUIDED BALLOON CATHETER PUNCTURE TECHNIQUE (33)

For puncture, it is also used the PROVOX® Vega™ Puncture Set (Atos Medical) and an esophageal/colonic wire-guided balloon dilatation catheter, CRE ™ Wireguided (Boston Scientific, Natick, MA). This balloon catheter is capable of acquiring 3 distinct progressively larger size diameters, 18 mm, 19 mm, and 20 mm, achieved by inflation pressures of 3 atm, 4.5 atm, and 6 atm. The length of the balloon is 5.5 cm, which gives a margin of error to reach the right balloon position in the puncture time.

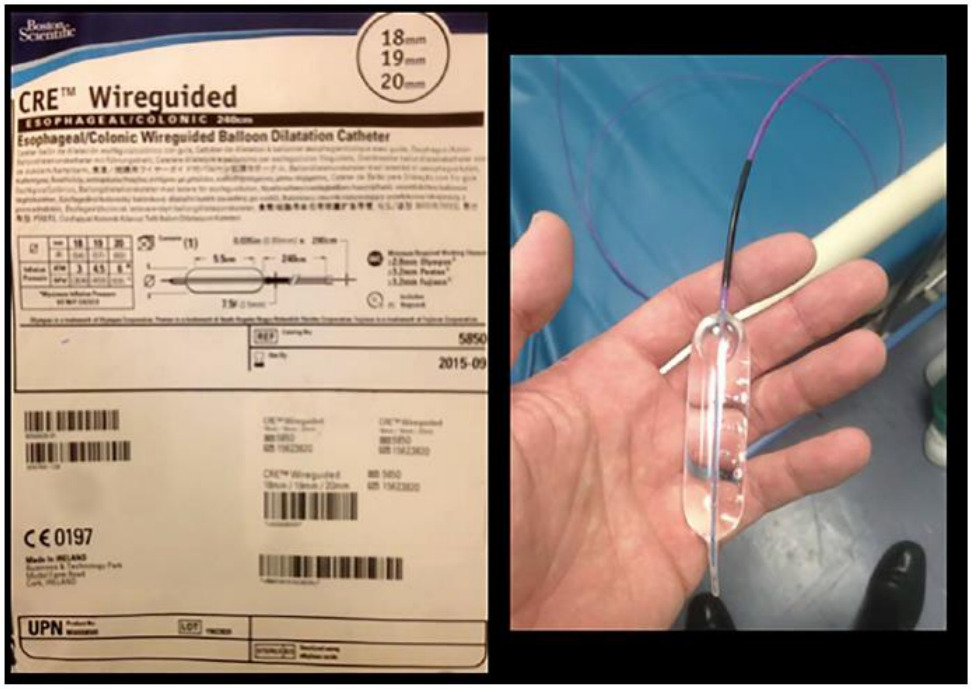


FIGURE 19: Esophageal/Colonic wire-guided balloon dilatation catheter.
Source: Minimally invasive wire-guided balloon catheter puncture for voice prosthesis insertion.

For the procedure, topical anesthesia in the nasal fossa (tetracaine hydrochloride 1%; 5 mL) is used, in addition to local anesthesia (mepivacaine 1%; 2 mL) in the posterior wall of the trachea, being careful to preserve the posterior wall anatomy avoiding overinfiltration, as this becomes particularly important in the following steps.

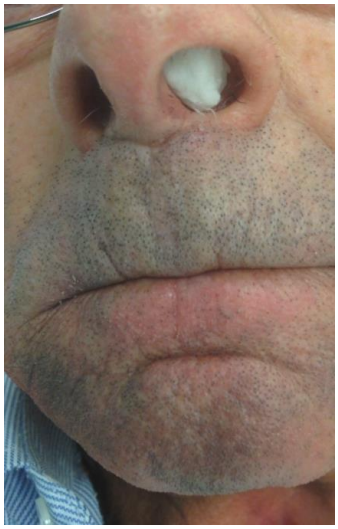


FIGURE 20: Instillation of topical anesthesia in the nasal fossa.

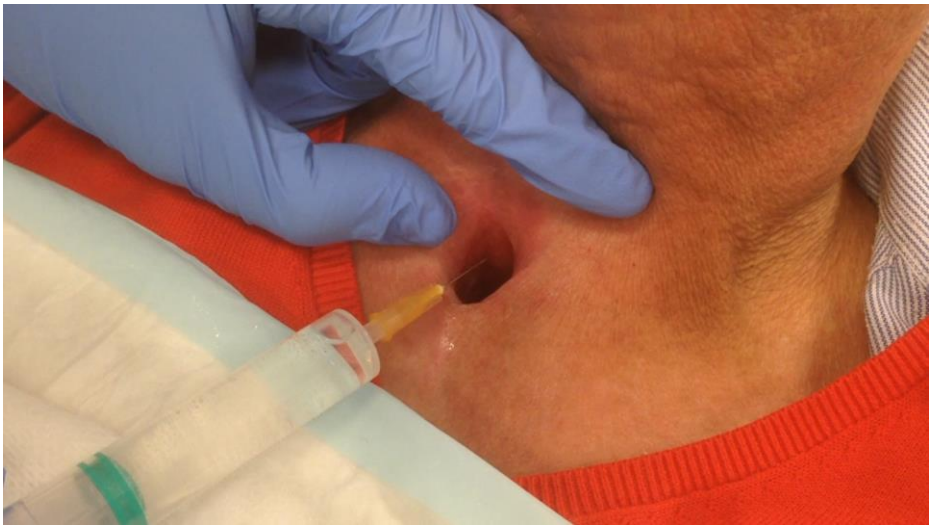


FIGURE 21: Infiltration of local anesthesia in the posterior wall of the trachea.

Source: Minimally invasive wire-guided balloon catheter puncture for voice prosthesis insertion.

Before starting, the distance between the nose and the tracheal stoma is measured and marked on the catheter. This mark helps to find out approximately the required depth to reach the balloon just behind the stomal posterior tracheal wall.

A nasoesophageal approach of the catheter is made as a common nasogastric tube insertion procedure.

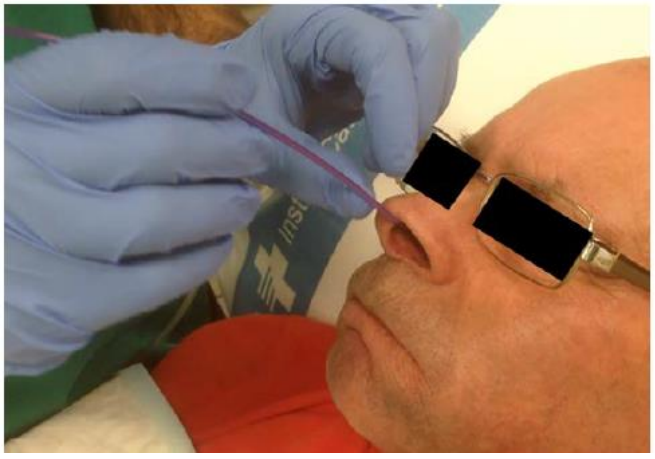


FIGURE 22: Nasoesophageal approach.
Source: Minimally invasive wire-guided balloon catheter puncture for voice prosthesis insertion.

When the esophagus is reached and the mark on the catheter is close to the nose, the balloon is inflated with air, showing its protrusion on the posterior tracheal wall. This can also be checked by touching the balloon in the right position just behind the stomal posterior tracheal wall.

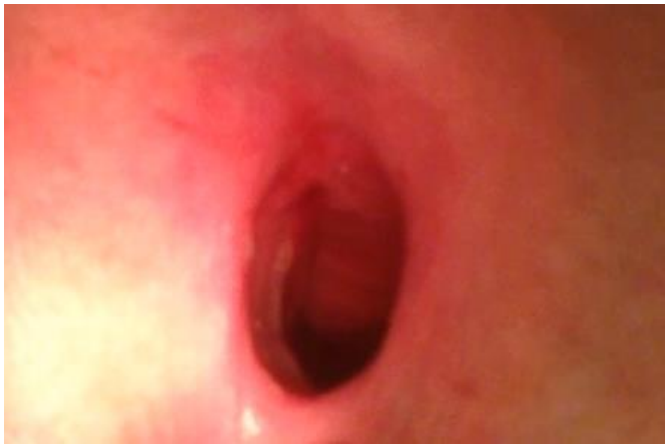


FIGURE 23: Posterior tracheal wall protrusion.
Source: Minimally invasive wire-guided balloon catheter puncture for voice prosthesis insertion.

Keeping the balloon inflated to protect the posterior esophageal wall, the puncture is performed using the PROVOX® Vega™ Puncture Set needle. Afterwards, a sound of the balloon deflating together with the loss of pressure in the syringe used to inflate the balloon indicates that the esophagus has been reached and that the puncture needle is in the correct position.

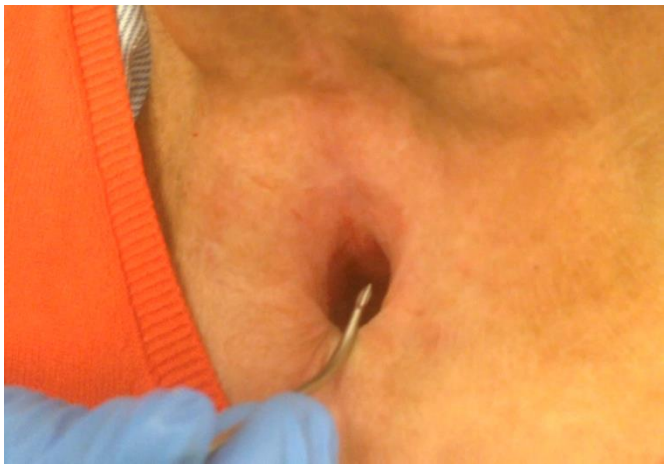


FIGURE 24: Realization of the TEP.
Source: Minimally invasive wire-guided balloon catheter puncture for voice prosthesis insertion.

At this time, as the protection of the balloon is lost, the punch must be supported carefully in the caudal margin of the tracheal stoma. Posteriorly, the balloon catheter can be removed.

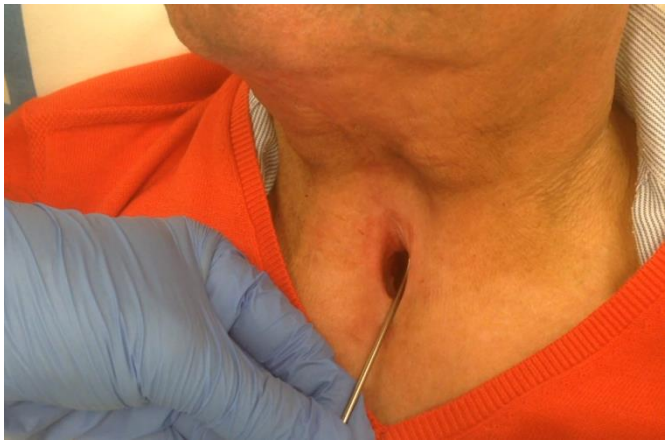


FIGURE 25: Punch position after the puncture.
Source: Minimally invasive wire-guided balloon catheter puncture for voice prosthesis insertion.

Using PROVOX® Vega™ Puncture Set guide-wire, retrograde catheterization of the guidewire, from the punch through the esophagus to the oropharynx is done. The patient is able to indicate when the guidewire has reached the oropharynx. Posteriorly, the Puncture needle is removed and the guidewire is taken out from the oropharynx.

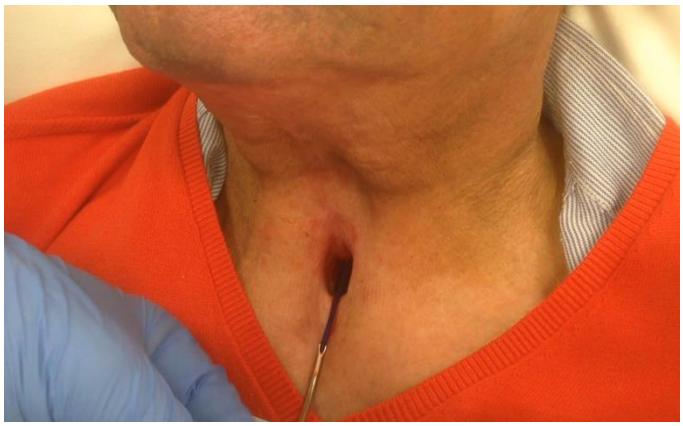


FIGURE 26: Puncture needle removal.

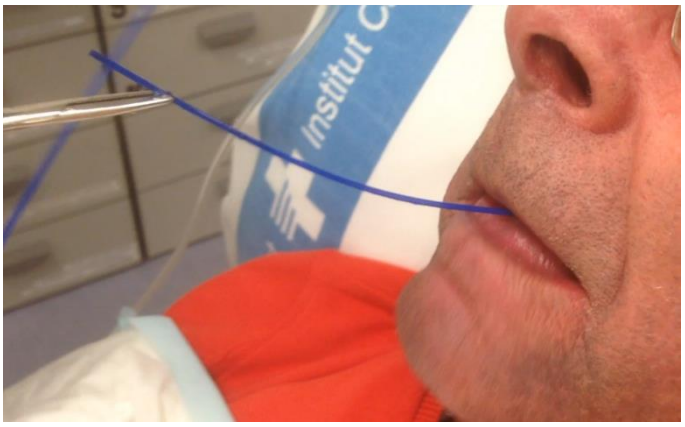


FIGURE 27: guidewire removal from the oropharynx.

Source: Minimally invasive wire-guided balloon catheter puncture for voice prosthesis insertion.

Afterwards, the next steps follow the common PROVOX® Vega™ Puncture Set procedure: The guidewire is inserted into the puncture dilator, fixing it on its proximal end.

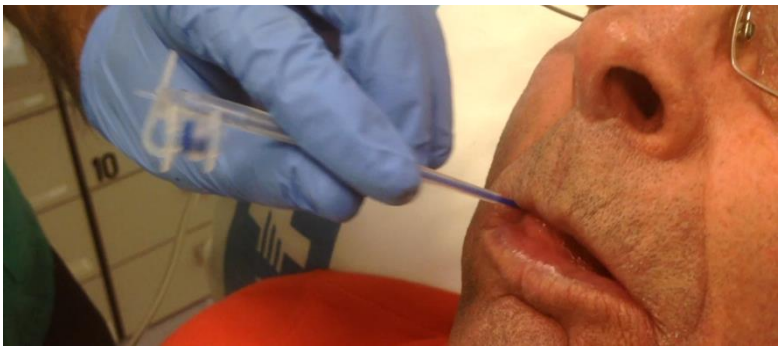


FIGURE 28: Puncture dilator attached on Guidewire proximal end.

Source: Minimally invasive wire-guided balloon catheter puncture for voice prosthesis insertion.

Posteriorly, the guidewire is pulled from its distal end while the patient is asked to swallow, thus transporting the puncture dilator, which travels from the mouth to the esophageal puncture site, where it is inserted. Doing a continuous smooth motion, the puncture site is dilated. Finally, the puncture dilator is taken out and the VP is pushed and placed immediately inside the fistula.

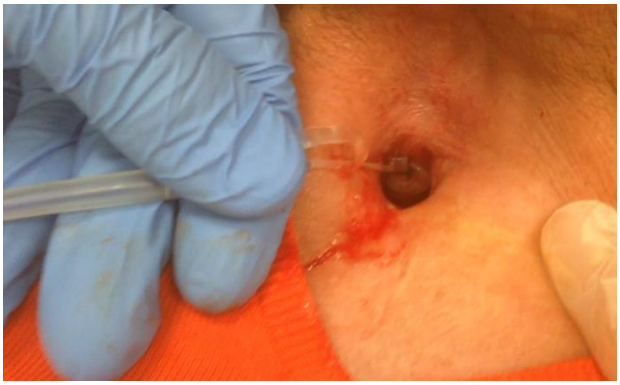


FIGURE 29: VP placed inside the TEP.

Source: Minimally invasive wire-guided balloon catheter puncture for voice prosthesis insertion.

In most cases, the patient is able to start speaking immediately, but if laryngeal surgery has been performed more than 1 year earlier, it is often necessary to give some instructions before speaking, concerning inhaling, closing the tracheal stoma, and exhaling the air through the prosthesis to the pharynx and oral cavity.

Although severe esophageal stenosis and a long TE distance are still limitations, this new technique has many advantages: it is a minimally invasive procedure, it represents a safe option to preserve the suture in primary time when a stapler suture is used, it reduces anatomic limitations, such as trismus or bad exposure secondary to previous surgical or RT treatments, it does not require total anesthesia and he procedure can be performed in outpatient settings.

2 JUSTIFICATION

Head and neck cancer is the seventh most common type of cancer worldwide, with the larynx being the most common of all possible locations.

Despite surgical and non surgical treatment advances in organ preservation, TL is still the most effective treatment for advanced cancer of the larynx. It involves major physical, but also social and emotional damage. Most of laryngectomized patients rate communication as their most important life quality concern. Losing voice after TL does not mean only to miss the ability to transmit a message through the verbal channel, as in social interactions, since the voice is also an important indicator of identity, personality and mood.

Within the methods that exist for voice recovery, TE prosthetic speech has been associated with the best speech quality and it is relatively safe and easy to learn. Therefore, it is the gold standard for voice rehabilitation after TL. TE voice depends on the placement of a one-way valved VP through a surgically created TEP. Puncture may be performed primarily at the time of the laryngectomy or as a secondary procedure. High rates of successful voice restoration and similar complication rates as well as TE speech outcomes have been found regardless of the TEP timing.

The surgical procedure of VP insertion in secondary time was introduced by Singer and Blom, and the same technique described by them decades ago is still in use today.

The use of this technique for VP insertion has a high success rate of vocal rehabilitation with an acceptable complication rate and limitations; some of these complications include bleeding, pain and esophageal wall laceration or perforation, which can lead to serious problems, such as the creation of a false passage, subsequent stenosis and severe infectious complications.

Limitations include the stapler suture of the esophagus in the primary time, that can be damaged because of the rigidity of the esophagoscope, anatomic limitations, such as trismus and bad exposure and the need for total anesthesia and a surgery room for the secondary time.

To avoid some of these complications and remove the limitations described above, in HUDJT, Ear-nose-throat (ENT) specialists, Tobed *et al*. have developed VP insertion method performed with a wire-guided balloon catheter puncture (WGBCP). This technique is a minimally invasive procedure that represents a safe option to preserve the suture in primary time when a stapler suture is used, it reduces anatomic limitations, such as trismus or bad exposure secondary to previous surgical or radiotherapeutic treatments, it does not require total anesthesia, and it can be performed in outpatient settings.

Nevertheless, there are no studies that compare the exact outcomes of the application of the WGBCP technique and the classical technique for VP insertion in patients who have received a TL due to a larynx cancer.

Therefore, the intention of this study is to undergo a prospective, randomized, open-label, clinical trial to compare and evaluate the time to phonation, the procedure duration, the need of nasogastric (NG) feeding tube, the amount of days of hospitalization and complications related to the intervention, such as bleeding and esophageal wall injury, in patients who, after a TL and as a secondary procedure, undergo the WGBCP technique for VP insertion, and in those who receive the classic procedure. This study pretends to know if our hypothesis is true and therefore, provide enough evidence to validate the new minimally invasive technique.

3 HYPOTHESIS AND OBJECTIVES

3.1 HYPOTHESIS

3.1.1 GENERAL HYPOTHESIS

In the secondary time voice rehabilitation approach of total laryngectomy patients due to larynx carcinoma, wire-guided balloon catheter puncture technique has better post-intervention outcomes compared to the classic procedure.

3.1.2 SPECIFIC HYPOTHESES:

- Wire-guided balloon catheter puncture technique reduces the time to phonation since the insertion of the VP.
- Wire-guided balloon catheter puncture technique is a faster procedure.
- Wire-guided balloon catheter puncture technique has fewer complications, such as bleeding and esophageal wall injury.
- Wire-guided balloon catheter puncture technique reduces the need of a NG feeding tube.
- Wire-guided balloon catheter puncture technique reduces the amount of days of hospitalization.

3.2 OBJECTIVES

3.2.1 GENERAL OBJECTIVE

The primary aim of this study is to register and compare the post-intervention outcomes in patients rehabilitated with wire-guided balloon catheter puncture technique compared to those who received the classic procedure.

3.2.2 SPECIFIC OBJECTIVES

- To register and compare the time to phonation since the insertion of the VP of both techniques.
- To register and compare the procedure duration since the anesthetic application until the patient is able to ventilate autonomously, of both techniques.
- To register and compare the complications (bleeding and esophageal wall injury) of both techniques.
- To register and compare the need of a NG feeding tube of both techniques.
- To register and compare the amount of days of hospitalization of both techniques

4 MATERIAL AND METHODS

4.1 STUDY DESIGN

A prospective randomized open-label clinical trial is proposed to compare and evaluate the time to phonation, the procedure duration, the need of NG feeding tube, the amount of days of hospitalization and complications related to the procedure, such as bleeding and esophageal wall injury, in patients who, after a TL due to a larynx carcinoma, and as a secondary procedure, undergo the WGBCP technique for VP insertion (intervention group) and in those who receive the classic procedure (control group).

Patients will be randomly assigned into 2 groups with a ratio 1:1. The first one, the intervention group, will be rehabilitated with wire-guided balloon catheter puncture technique, while the control group will receive the classic procedure.

The study will be performed entirely in HUDJT.

4.2 STUDY POPULATION

The population of this study will be 18 years or older people resident in the Girona Health Region (includes the Province of Girona except Cerdanya and has as reference the HUDJT), that are diagnosed of locally advanced larynx carcinoma and have received a TL for its treatment.

All patients must meet the inclusion and exclusion criteria.

4.2.1 INCLUSION CRITERIA:

- Patients over 18 years old.
- Either gender.
- Patients diagnosed of larynx carcinoma, in a resectable locally advanced stage (stages III and IV).
- Patients that have received a TL for its treatment.
- Patients who are willing to recover their voice through a VP.
- Patients who have read the information sheet for participants (Annex 3) and have signed the informed consent form (Annex 4).

4.2.2 EXCLUSION CRITERIA:

- Patients that, after a TL due to a larynx carcinoma, have required a reconstruction with a loco-regional or free pendant.
- Patients that have successfully received the VP insertion in primary time.
- Patients who only want to be rehabilitated with one of the VP insertion techniques, rejecting the other.
- Patients who have to be rehabilitated with one of the techniques due to the impossibility of performing the other.
- Patients in which one of the techniques for VP insertion, has previously failed.
- Previous head and neck oncological surgeries undergone due to expected articulatory compromise.
- Patients with previous psychiatric or non-psychiatric disorders that do not allow to express and asses the communicative ability.
- Patients who are not able to understand the surgical procedure that will be performed.

4.2.3 PARTICIPANT WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time upon request. When withdrawing from the study, the participant should let the research team know that he/she wishes to withdraw.

An investigator may terminate participation in the study if the patient meets an exclusion criterion (either newly developed or not previously recognized) that preclude further study participation.

Nevertheless, all patients who entry the study will be included in the statistical analysis so no substitutive patients will be added to the study in cases of withdrawal or termination.

4.3 SAMPLE

4.3.1 SAMPLE SIZE

In a two-sided test, with an alfa risk equal to 5% and a statistical power equal to 80%, assuming that the WGBCP technique is quite more effective than the classic procedure, and assuming a drop-out rate of 10%, a total of 54 will be needed, that is, 27 patients per group.

Computations were carried out with Prof. Dr. Marc Saez' software based on the library 'pwr' of the free statistical environment R (version 3.6.2).

4.3.2 PATIENT SELECTION AND ESTIMATED TIME OF RECRUITMENT

The sample will be obtained from the HUDJT with a non-probabilistic consecutive sampling method including all the patients meeting the inclusion and exclusion criteria. The recruitment will be carried out in the Functional Unit of Head and Neck Tumors (FUHNT) of HUDJT.

Total laryngectomy patients due to larynx carcinoma who fit in all inclusion and exclusion criteria will be informed about the study and invited to participate voluntarily if they are interested, after the TL and once they have finished the adjuvant treatment. They will receive a document with all the information explaining what entering this study involves (Annex 3), and the informed consent form (Annex 4) that has to be signed if they are willing to participate.

According to registered cases of last year, in the FUHNT of HUDJT, approximately 30 patients received TL due to larynx carcinoma. From these 30 patients, 27 fulfilled the inclusion and exclusion criteria to enter the study.
Therefore, we expect that approximately two years will be needed to recruit the 54 patients that are needed for this study.

4.3.3 RANDOMIZATION

After recruiting, in order to avoid the selection bias, a statistician expert will create a database containing ordered codes which will be assigned consecutively to participant patients. There will be as many codes as patients estimated on the sample size. These codes will be randomly distributed with a proportion of 1:1 into two groups.

Randomization will be generated by the Statistical Package for the Social Sciences (SPSS) software for Windows® by the statistician expert.

The main investigators will decide which intervention, the classical or the WGBCP technique, corresponds to each group. The patients will know in which group they fit.

4.3.4 MASKING TECHNIQUES

Studies applying surgical techniques have a detection bias because of the unfeasibility of blinding the surgeon. In this study, it is also not possible to blind the patients because they will know the treatment applied, as for instance, among other differences, the classic procedure implicates general anesthesia, but the WGBCP technique requires local anesthesia.
To minimize detection bias the examination will be done by a research assistant who will be unaware of which treatment group the patients have been assigned to. During the examination there will not be any sign that can reveal the intervention performed, and participants will be told not to reveal the type of treatment received, making this study an examiner-blind trial.

The statistical consultant will also not know what intervention is assigned to each patient. In this way, the detection bias will be reduced.

4.4 VARIABLES

4.4.1 DEPENDENT VARIABLES

- **Time to phonation** since the VP insertion is the main variable that is taken into consideration because it is the one that has the most impact on the quality of life, as most of laryngectomized patients rate communication as their most important concern.

  Patients will be considered to have an acceptable functional speech if they, autonomously, have the ability to count to 10 all in one go, with rare need to repeat oneself. Failure will be considered as the inability to achieve it or unexpected VP extrusion or TEP closure.

  All patients will be instructed to try every day to count to 10 and record whether or not they have been able to achieve it. They will register it on a specific record sheet (Annex 5).

  All patients will be evaluated for voice functional outcomes by an Otolaryngologist and a speech therapist. They will evaluate them within the first 3 hours after VP insertion (what is considered to be immediately), the third day, after 1 month, 3 months and 6 months.

  If the specialists consider and confirm an acceptable functional speech, the registration sheet will be assessed in order to know exactly at what day the patient was able to achieve the aim of autonomously counting to 10.

  Time to phonation is a discrete quantitative variable that will be expressed in days.

- The **procedure duration** is a discrete quantitative variable expressed in minutes, defined as the time interval between the infiltration of topical and local anesthesia in the WGBCP technique or the general anesthetic induction in the classical technique, until, after the VP insertion, the patient is able to ventilate autonomously.

  It is important to take into consideration that, with the WGBCP technique, the patient will be able to ventilate autonomously immediately after the VP insertion, since there will be no previous procedure that interrupts it, and therefore, the

procedure duration will be a short interval of time, while with the use of the classical technique, due to the general anesthesia and subsequent intubation, the time interval will be longer.
Hence, it is important to assess this variable and quantify the difference observed between both techniques.

- The **complications**. Bleeding and esophageal wall injury will be registered separately. These two complications have been chosen as they are the most important and the ones that affect the most the post-intervention outcomes.

    - **Bleeding** will be considered as a complication when surgical intervention is required to solve the episode. Bleeding may appear even more than 15 days after the surgery. It is for that reason that even if the patient has overcome the first days without any complication, it is important to stay aware.
      It is a dichotomous nominal qualitative variable (Yes/No).

    - **Esophageal wall injury.** It is really important to take this variable into account, because a minor esophageal lesion, that is when only the mucosa is affected, can already imply a lengthening of the time of diet application or even the need of a NG feeding tube, which implies hospital admission.
      If there is a major lesion, that is, the muscular layer is also affected, apart from needing a NG feeding tube, major complications will be derived from it and a longer hospital stay will be needed.

      Esophageal wall injury will be considered as a complication either if the surgeon is aware of producing it whilst performing the surgery or not, the latter being manifested through complications related to the injury, such as mediastinitis. It will be evaluated by the Otolaryngologist who performed the surgery.

      This is a dichotomous nominal qualitative variable with the following values:

      0: No injury.
      1: Minor (mucosa) or major (mucosa and muscular) injury.

      Initially, It was considered classifying esophageal lesions into three categories, but finally, so as not to complicate too much the aesthetic analysis, it was decided to classify it into two categories.

- **Need of a NG feeding tube**. The need of a nasogastric feeding tube represents a great limitation for the patient and increases the days and the costs of hospitalization.
  A NG feeding tube will be needed in those patients who, with preserved intestinal peristalsis, are not able to ingest orally. Some of the indications of enteral nutrition can be found in Annex section (Annex 6).
  This is a dichotomous nominal qualitative variable (Yes/No).

- **Days of hospitalization.**
  The hospitalization in a level 3 hospital (HUDJT) costs approximately 730€ / day.

  Apart from the cause for which the patient must be hospitalized, such as the need for a NG feeding tube, bleeding or esophageal lesion, long hospitalization is related to an increased risk of infections, among other complications.

  Therefore, it is important to determine the mean hospitalization length related to both groups.

  If hospitalization is necessary, it will conclude once the patient's feeding tube has been removed (if applicable), and the patient does not have acute complications, such as bleeding or infection that needs medical assistance.

  It will be expressed in number of days as a discrete quantitative variable.

4.4.2 INDEPENDENT VARIABLE

The independent variable of this study is the intervention performed for voice recovery after a total laryngectomy due to larynx carcinoma, that is, whether our patients receive the wire-guided balloon catheter puncture technique (intervention group) or the classic procedure (control group).

4.4.3 COVARIATES

There are participants' baseline characteristics which might potentially influence on the relation between the independent and the dependent variables, acting as a confounder variable, so covariates are going to be contemplated and it will be necessary to stratify participants according to these covariates to see if they influence the results. The covariates have been selected according to the literature review. Some of these variables will be obtained from the clinical history of the patients. These covariates are:

- **Age**: It is a discrete quantitative variable. It will be expressed in years.
- **Gender**: It is a dichotomous nominal qualitative variable. It will be assessed by male or female.
- **TNM:** It is an ordinal qualitative variable (I-IVC TNM stages). It will be assessed by clinic, radiologic and pathologic diagnostic registered on the clinical history.
- **Previous RT treatment**: It is a dichotomous nominal qualitative variable (Yes/no). It will be assessed by clinical history.
- **Time since laryngectomy to VP insertion**: It is a discrete quantitative variable (months), assessed by clinical history, where it figurates the exact date of the TL and of the VP insertion.
- **Trismus**: It is a nominal qualitative variable measured in cm and it will be defined as: normal opening (4-6cm), reduced opening (< 4cm) or increased opening (>6cm).
- **Comorbidities**: neurological disorders (cerebrovascular disease, Parkinson disease, multiple sclerosis, ELA…), infectious diseases (pharyngitis, tonsillitis oropharyngeal candidiasis…), esophageal – stomach disorders (gastroesophageal reflux and other esophagitis, Zenker's diverticulum, esophageal or stomach carcinoma, achalasia, esophageal stricture or spasm, hiatus hernia…). It is a dichotomous nominal qualitative variable (Yes/no).
- **Failure of the technique:** Inability to insert the voice prosthesis, either due to the patient's anatomical reasons or associated complications. It is a dichotomous nominal qualitative variable (Yes/no).

4.5 DATA COLLECTION

All professionals involved in the FUHNT of HUDJT, which includes, among other specialists, otolaryngologists and speech therapists, have to be informed about the trial in order to fulfill the objectives. All participating professionals will be informed about what they have to ask and how to collect the information. It is important to ensure that everyone who participates in this study knows their task and how to do it.

Patients will be also correctly informed (Annex 3) before entering the study and will sign the consent forms (Annex 4). It is important to explain to the participants the importance of not withdrawing from the study during the follow-up period, in order to correctly assess the outcomes. However, all patients entering the study will be included in the statistical analysis, so no substitute patients will be added to the study in cases of withdrawal or termination.

The study has a specific circuit that has to be followed:

- **Trial entry**

Total laryngectomy patients due to larynx carcinoma, which meet all the inclusion and exclusion criteria, will be informed about the study and invited to participate voluntarily if they are interested, once they have finished the adjuvant treatment.

Patients will be informed orally and will receive a document with all the information explaining what entering to this study involves (Annex 3) and a written informed consent (Annex 4). If the patient agrees to participate in the study, all the data needed will be collected, including his medical history. After consent is given, a code will be assigned to each patient to decide which treatment will be applied. It is important to emphasize that they can be assigned to any of the 2 techniques, and they must agree with the result.

If the classic procedure is assigned, the doctor will inform about it and the patient will be scheduled for the anesthesiologist and for the VP placement in the operating room, after having read the specific information sheet for the intervention and signed its respective informed consent (Annex 7).

If the wire-guided balloon catheter puncture technique is assigned, the physician will also inform about it and the patient will be scheduled for the VP placement directly at the outpatients setting, also after having read the specific information sheet for the intervention and signed its respective informed consent (Annex 8).

- **Anesthesiology visit** (only for patients assigned to the classic procedure).

Before the surgical procedure, the patients must have a visit with the anesthesiologist, who will decide if the patient can be operated and which is the operatory risk classified with the American Society of Anesthesiology Physical Status (ASA PS) classification system (Annex 9)

- **Intervention day:**
    - Classic technique, performed in the operating room.
      The patient has to arrive 1,5 hours in advance to get prepared.
      All members of the ENT surgical team know the procedure (*1.9.1 Secondary TEP for VP insertion: classic technique).*
      The procedure will be performed by two otolaryngologist surgeons, one instrumentalist nurse and one anesthesiologist.
      The time of surgery in minutes, from the general anesthesia induction until the patient is able to ventilate autonomously and any complication during the procedure (mainly bleeding and esophageal wall injury) must be registered.

      Post-intervention assessments:
      Patients will remain in the Post-Anesthesia Care Unit (PACU) until they recover from the anesthesia. This period is expected to last a minimum of 2 hours since the general anesthesia induction. The nursery team will register all the incidences during this period. After recovery the otolaryngologist and the speech therapist will assess whether the patient has an acceptable functional speech. Then, if there are no added complications, the ENT specialist will discharge the patient and schedule him for the follow-up visit. If there is any complication as well as the need for a NG feeding tube or hospitalization, it has to be registered, including the total amount of days of hospitalization.

    - Wire-guided balloon catheter puncture technique, performed in the outpatient setting.
      The otolaryngologist who is going to perform the VP insertion together with the help of a nurse knows the technique *(1.9.2 Secondary TEP for VP insertion: wire-guided balloon catheter puncture technique).*

      Time of the intervention, from the topical and local anesthesia application until, after the VP insertion, the patient is able to ventilate autonomously, has

to be registered. Since the patient that receives this technique does not require total anesthesia and subsequent intubation, it will be immediately after the insertion of the VP when the patient will be able to ventilate autonomously.

Any complications during the procedure (mainly bleeding and esophageal wall injury) must also be registered.

Post-intervention assessments:

Patients may remain a few minutes until they recover from the intervention. After recovery, the ENT specialist and the speech therapist will evaluate whether the patient has an acceptable functional speech. Then, if there are no added complications, the patient will be discharged, but before, the ENT will have scheduled him for the follow-up visit.

Although less usual, the occurrence of complications should also be recorded, as well as the need for a nasogastric tube or hospitalization, including the total amount of days of hospitalization.

- **Follow-up:**

Participants will be followed up for a total of 6 months after the intervention. The follow-up visits will be carried out in the outpatient clinic 3 days, 1 month, 3 months and 6 months after, by assistants who will be unaware of which intervention the patients received.

If any complication appears after the intervention the patient is informed to come back as soon as possible.

The main objective of this study is to analyze the time to phonation since the VP insertion, so patients will be followed up by a speech therapist and an otolaryngologist different from the one that performed the intervention. These specialists will assess if the patient has an acceptable functional speech. If the specialists decide an acceptable functional speech, the registration sheet that the patients have to fill, recording every day if they can or cannot autonomously count to 10, will be assessed in order to know exactly at what day the patient achieved the functional speech.

During the same follow-up visits, the complications that appear, mainly bleeding and posterior esophageal wall injury will be recorded.

A summary of all the process can be found in annex section (Annex 10).

4.6 INTERVENTION

The intervention is explained in the following sections:

- 1.9.1 Secondary TEP for voice prosthesis insertion: classic puncture technique.
- 1.9.2 Secondary TEP for voice prosthesis insertion: wire-guided balloon catheter puncture technique .

4.7 SAFETY

The classical technique has been previously applied and systematic reviews have already demonstrated the safety of the procedure.
The WGBCP technique has been previously applied and has already demonstrated the safety of the procedure.

Major postoperative complications, such as bleeding and esophageal wall damage, have already been considered in this research protocol.

4.8 STATISTICAL ANALYSIS

In all cases, a confidence interval of 95% will be assumed and $p<0.05$ will be considered statistically significant. All statistical analysis will be executed with Statistical Package for the Social Sciences (SPSS) version 25 (IBM, Armonk, NY, US) for Windows®.

4.8.1 DESCRIPTIVE ANALYSIS

The need of NG feeding tube and the complications (bleeding and esophageal wall injury) will be summarized through proportions, stratified by the intervention and the control group.

These analyses will be stratified by the covariates. When covariates are quantitative, they will be categorized into quartiles.

Time to phonation, procedure duration and days of hospitalization will be summarized by means of the median and the interquartile range, stratifying patients by the intervention received.
These analyses will be stratified by the covariates. When covariates are quantitative, they will be categorized into quartiles.

For the variables time to phonation, procedure duration and days of hospitalization, survival curves will be estimated and drawn, stratifying by intervention/control, using the Kaplan-Meier estimator.

4.8.2 BIVARIATE INFERENCE

The associations between the need of NG feeding tube and complications (bleeding and esophageal wall injury) and the independent variable, will be contrasted by the $\chi 2$ (Chi-Square) test. If the expected number in any of the cells is lower than 5, the exact Fisher's test will be used.

These analyses will be stratified by the covariates. When covariates are quantitative, they will be categorized into quartiles.

The associations between the time to phonation, procedure duration and days of hospitalization and our independent variable, will be evaluated by the Mann-Whitney's U test.

These analyses will be stratified by the covariates. When covariates are quantitative, they will be categorized into quartiles.

The difference between survival curves of intervention and control group will be tested by means of the log-rank test.

4.8.3 MULTIVARIATE ANALYSIS

A multivariate analysis will be carried out to adjust variables for covariates, thus potential confounders that could modify the results will be avoided. Covariates contemplated in this study are age, gender, TNM, previous RT treatment, time since laryngectomy to VP insertion, trismus, comorbidities and failure of the technique.

We will adjust the association between the need of NG feeding tube and the complications (bleeding and esophageal wall injury) and our independent variable, in logistic regressions controlling for all the covariates.

Regarding the time to phonation, procedure duration and days of hospitalization, the intervention effect will be adjusted by means of Cox regressions, controlling for all the covariates.

4.9 WORK PLAN AND CHRONOGRAM

The whole study will take approximately 3 years and 9 months. It will be divided in the following phases.

PHASE 0: Study design (3 months)

A protocol of the study will be designed by the main investigator (MI).
This protocol will contain a detailed explanation of the variables and objectives proposed for the study.

Protocol will be given to the Ethics Committee (CEIC) of HUDJT for its revision and approval. All suggested changes will be taken into account.

PHASE I: Preparation and coordination (2 months)

After CEIC approval, a chronogram will be prepared with all the detailed phases and procedures, and a general coordination meeting will be held. This meeting will include ENT specialists, nursing staff, speech therapists, administrative staff, statistics and every person that has a role in the study, to explain and discuss the design, aims and methods of the trial. All the participant professionals will be trained on what they have to enquire about and how to collect information. It is important to ensure that everyone who participates in this study knows their task and how to carry it out.

PHASE II: Field work and data collection (2 years and 6 months)

Sample recruitment will take 2 years. Total laryngectomy patients due to larynx carcinoma who meet the inclusion and exclusion criteria, recruited by a consecutive method, will be informed about the study and invited to participate voluntarily if they are interested, after the TL and once they have finished the adjuvant treatment. If they agree to engage in, along with the patient's medical history and the information he will give us, all data needed for the study will be collected.
Patients are going to be randomly placed in one of the two groups of the treatment.
In 2019 27 patients met the inclusion criteria. Hence, two years will be enough to recruit the 54 patients needed for this study.

Patients who are assigned to the control group will receive the classic technique and patients who are assigned to the intervention group will receive the WGBCP technique.

All patients will be followed up for six months after the treatment. In both cases, all the data necessary for the study will be recorded in the established periods. Data collection will start with the sample recruitment and it will last until the last day of the follow-up. It is important to emphasize that the ENT specialists who asses the post-intervention outcomes are unaware of what intervention the patient received (Annex 11 and 12).

PHASE III: Data analysis and interpretation (4 months)

Once data collection is completed a blinded statistician will analyse it and present the results to all the research team. A final meeting with all the team will be held for the analysis and interpretation of the data.

PHASE IV: Results publication (6 months)

The MI will elaborate the final article. It will be published in a ENT journal in order to properly disseminate the results of the study. Moreover, the results will be exhibited in national and international congress of specialists.

Years	2020						2021	2022		2023				
Months	FEB	MAR	APR	MAY	JUN	JUL-DEC	JAN-DEC	JAN-JUN	JUL-DEC	JAN-FEB	MAR-APR	MAY-JUN	JUL-AUG	SEP-OCT
ACTIVITY														
PHASE 0: STUDY DESIGN														
Protocol elaboration														
Protocol approbation (CEIC)														
PHASE I: PREPARATION AND COORDINATION														
Chronogram elaboration														
Coordination of research team														
PHASE II: FIELD WORK AND DATA COLLECTION														
Patient recruitment														
Intervention														
Data collection														
Follow-up														
PHASE III: DATA ANALYSIS AND INTERPRETATION														
Statistical analysis														
Interpretation														
PHASE IV: RESULT PUBLICATION														
Final Article elaboration														
Result publication														
Dissemination														

FIGURE 30: Chronogram.

5 LEGAL AND ETHICAL CONSIDERATIONS

The study will be performed following the human rights and the ethical considerations gathered in the World Medical Association Declaration of Helsinki of "*Ethical Principles for Medical Research Involving Human Subjects"* (1964, last revision October 2013). Both techniques used in our study have demonstrated safety on VP placement, thus, this study is in accordance with the Declaration of Helsinki about the Ethical principles.

The WGBCP technique has shown more advantages than the classical technique, and it could seem like an ethical problem. However, the classical, which has been used and assessed for years and all risks and benefits are known, is the one that would be used for all patients if no new technique would had been developed.

This study protocol will be evaluated by the Clinical Research Ethics Committee (CEIC) of HUDJT and will not be applied unless it has its approval. All the recommendations will be considered and relevant modifications will be made to get its approval.

An information sheet with all the important aspects of the study will be given to each participant (Annex 3), where all risks, benefits and alternatives to the procedures will be detailed using the best updated data available at that point, to ensure they perfectly understand the study before they sign the informed consent to entry the study (Annex 4). Thus, the principle of autonomy and the "*Ley Orgánica 41/2002, de 14 de Noviembre, de Autonomía del Paciente y de Derechos y Obligaciones en Materia de Información y Documentación Clínica*" will be respected.

The clinical trial will be performed following the "*Ley 14/2007, de 3 de Julio, de Investigación biomédica",* which regulates invasive procedures*,* particularly section II, where it specifies the basic principles, requirements, authorization and safety of studies in which a human being undergoes an invasive procedure. As this study includes invasive techniques, an Insurance policy will be contracted.

All data collected will be treated anonymously in order to guarantee and protect the confidentiality of the patient according to the *"Ley orgánica 3/2018, de 5 de Diciembre, de Protección de Datos Personales y garantía de los derechos digitales".*
To maintain the confidentiality of personal data, an identification number will be used instead of the patient's name.

To conclude, exclusion criteria have been established respecting the principles of justice and beneficence, since most patients can be part of the study, and doctors and other medical workers who take part in it are accredited and well trained for their assigned tasks, so the principle of non-maleficence will be respected.

The research team will assert that all the results will be published with transparency and clarity.

All investigators involved in the study will have to declare no conflict of interest.

6 STRENGTHS AND LIMITATIONS

Analyzing the study, some limitations that may interfere to the research have been detected and taken into consideration. They are the following ones:

- The consecutive recruitment proposed in this study is a non-probabilistic recruitment and may not obtain the best representative sample, so **selection bias** may occur. Moreover, due to the high prevalence among males, a low number of female participants are expected.

  Nevertheless, to minimize this bias, few exclusion criteria have been set and randomization has been performed, to help to distribute symmetrically the covariates on both groups to be able to extrapolate future results on the general population.

  Losses and withdrawals can also cause selection bias, which is why in the estimation of the sample size, a drop-out rate of 10% has already been taken into account.

- A limitation for the sample calculation is the possibility that not all patients will want or will be able to perform the 2 techniques.

  In case that the patient refuses one of the techniques once he has read the information sheet and signed the informed consent, in order to avoid a **sample bias**, it will be considered as a withdrawal.

- Not all patients will be able to receive general anesthesia, which is a limitation for the study. However, losses due to this fact are not expected, given that the patients enrolled in the study have previously undergone a TL that requires total anesthesia.

- An additional limitation of this study is related to the open-label design. Studies applying surgical techniques have a **detection bias** because of the unfeasibility of blinding the surgeon, and in this study, it is also not possible to blind the patients.

  To minimize detection bias, this study will be an examiner-blind trial. The follow-up visits will be done by an assistant who will be unaware of which treatment group the patients had been assigned to. During the examination, there will not be any sign that can reveal the intervention performed, and participants will be told not to reveal the type of treatment received.

The statistical consultant will also not know what intervention is assigned to each patient. In this way, the detection bias will be reduced.

– Establishing whether the patient has a functional speech or not without the help of a scale may seem subjective and therefore a limitation. However, since the evaluation is carried out by experts specialized in voice pathology, using the definition "Acceptable functional speech: ability of autonomously count until 10 with rare need to repeat oneself", and knowing that the transition of not speaking to speaking is very obvious, the problem that may result of this is diminished.
  The data collected from this variable are self-referenced, that is, it is the patient himself who, once the specialists have determined that he has an acceptable functional speech, must inform when it was exactly that he got it, through the recording sheet. If the patient reports erroneous data, it could cause information bias.

– The interpretation of the endpoints implies a certain degree of **inter-observer variability**. For this reason, all participating professionals will receive training on what they have to ask and how to gather information. It is important to ensure that everyone who participates in this study knows their task and how to carry it out, so data collection is similar.
– It would be interesting in the future to create a multi-center study in order to increase the sample size to enhance statistical power and reduce recruitment time.

The main strength of this study is that everything will be carried out in HUDJT and all interventions will be carried out by the same team of otolaryngologists.
Although the ENT team is made up by several specialists, they will have received sufficient training to standardize the procedure of the techniques, thus avoiding the variability between procedures.

Apart from that, due to the randomization process, both groups will be similar and comparable to each other.

Another strength of this study is that it compares two techniques for VP insertion that have never been compared before.

7 FEASIBILITY

This study will take place exclusively in HUDJT, Girona, where all the means necessaries for its development will be available and provided.
The whole FUHNT are all well trained and will work together to achieve the marked objectives.
The hospital will provide all the necessary means, such as personnel salaries, operation rooms and follow up. Computer devices and programs to elaborate the database and to carry out the statistical analysis will also be provided.

In case of presenting any complication that requires re-intervention, operating rooms will be available.

In HUDJT, around 30 patients undergo TL due to larynx carcinoma every year.
Therefore, within two years, the sample for this study will be completed.

8 BUDGET

All research team and personnel are employees of the Hospital, so it will not be necessary to hire any worker for clinical functions.

Apart from that, the VP insertion in the patients that are willing to recover their voice through a VP and are able to it, is part of the normal procedure used in the clinical practice, as well as the follow-up of our patients.

The evaluation of the need of a NG feeding tube and the complications, bleeding and esophageal wall injury, also form part of the routine activity related to these patients and will not suppose an extra cost.

Extra services

A statistician will be needed in order to create a data base, randomize the patients, and perform the statistical analysis. It is expected that 60 hours will be needed, and the salary of our statistician is 25 €/hour, so this will cost a total of 1.500 €.

In addition to the statistical analyses, a clinical researcher associated who will be responsible of data monitoring and control is also needed, to give assessment and coordinate the medical staff involved and the patients. 1 hour per week is necessary, adding up to a total of 104 hours. This will mean 2.600 € in a salary of 25 €/hour.

Material

To go on with our study we will need some extra material for our intervention group. An esophageal/colonic wire-guided balloon dilatation catheter (CRE ™ Wireguided) will be used for every patient. Each unit has an approximate cost of 350 €, so this will cost a total of 18.900 €.

No other extra material will be needed.

The information sheet, informed consent, notebook of data collection and all printed papers will be taken into account. It will be needed to invest 1 € for each patient, so a total of 54 € will be needed for printing and papers.

Insurance

As invasive procedures are performed, it is necessary to hire an insurance for the patients, with a total of 5.400 € (54 patients for 100 € each patient).

Publication and dissemination

The approximate cost for the publication of the results will be 2.300 € (500 € for the English correction and 1.800 € related to the publishing cost of an Open Access article).

The author will also attend to 2 National and 1 European ENT congress.
The costs of attending a National congress are:

- Registration: 500 €
- Flights, meals and accommodation: 300 €
- Total: 800 €

The costs of attending an International congress are:

- Registration: 800 €
- Flights, meals and accommodation: 1.800 €
- Total: 1.400 €

	CONCEPT	AMOUNT	COST	SUBTOTAL
STAFF COST	Expert statistician	60 hours	25€/h	1.500 €
	Clinical Research Associate	104 hours	25€/h	2.600 €
MATERIAL	CRE ™ Wireguided	54 units	350 €	18.900 €
	Printing and papers	54 units	1,00 €	54 €
INSURANCE	Insurance that covers damage	54 units	100 €	5.400 €
PUBLICATION AND DISSEMINATION	English correction	1	500 €	500 €
	Publishing cost (open access)	1	1.800 €	1.800 €
	National Congress	2	800 €	1.600 €
	European congress	1	1.400 €	1.400 €
			TOTAL COST	**33.754 €**

9 IMPACT OF THE STUDY

The use of the classical technique for VP insertion has a high success rate of vocal rehabilitation with an acceptable complication rate and some limitations. It is for that reason, in order to reduce and avoid its complications and limitations, in HUDJT a wire-guided balloon catheter puncture has been developed.

Given that there is no literature comparing both techniques and therefore there is no data that provides enough evidence to validate the new minimally invasive technique, this study was designed with such purposes.

If the presented hypothesis is confirmed, with a shorter procedure technique, after the VP placement, patients will need less time to achieve voice rehabilitation, will have fewer complications and an earlier recovery of oral diet reducing the need for a NG feeding tube, and therefore, a reduction of hospitalization days.

So, the WGBCP technique, that is a minimally invasive procedure, that does not require total anesthesia, that is possible to perform it in outpatients settings and reduces some limitations, has better post-intervention outcomes than the classical technique. Hence, if the presented hypothesis is confirmed and therefore the new technique is validated, it should be implemented in HUDJT and the results should be published to let other centers start using this new procedure.

As a whole, it will suppose an important change in the VP insertion management and a great improvement on the postoperative outcomes leading to an earlier recover, which, together with the advantages of the technique itself, would make the procedure cheaper, increasing the pool of patients who can be rehabilitated with a VP.
However, to demonstrate economic data, further studies would be needed.

10 BIBLIOGRAPHY:

1. Moore K, Dalley A, Agur A. Moore's clinically Oriented Anatomy. 7th ed. Barcelona: Lippincott Williams & Wilkins; 2014.

2. Standring S. Gray's Anatomy. The Anatomical Basis of Clinical Practice. 41st ed. Amsterdam: Elsevier; 2016.

3. Concus AP, Tran T-PN, Sanfilippo NJ, DeLacure M. Malignant laryngeal lesions. In: Lalwani AK, editor. Current diagnosis and treatment in otolaryngology - Head and neck surgery. 2nd ed. New York: McGraw Hill; 2008. p. 437–55.

4. IARC, GICR. Cancer Today [Internet]. Lyon: IARC; 2018 [cited 2019 Sep 20]. Available from: https://gco.iarc.fr/today/home

5. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin [Internet]. 2018 [cited 2019 Sep 15];68(6):394–424. Available from: https://onlinelibrary.wiley.com/doi/epdf/10.3322/caac.21492

6. SEOM. Las Cifras del Cáncer en España. Madrid: Sociedad Española de Oncología Médica; 2019.

7. Gatta G, Botta L, Sánchez MJ, Anderson LA, Pierannunzio D, Licitra L, et al. Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: The EUROCARE-5 population-based study. Eur J Cancer. 2015;51(15):2130–43.

8. Pérez Ortín, Polo López, Arnau Fragola. Tumores Malignos de la Laringe. In: Libro virtual de formación en ORL. Madrid: SEORL; 2015. p. 1–17.

9. Cohen N, Fedewa S, Chen AY. Epidemiology and Demographics of the Head and Neck Cancer Population. Oral Maxillofac Surg Clin North Am [Internet]. 2018 [cited 2019 Sep 20];30(4):381–95. Available from: https://doi.org/10.1016/j.coms.2018.06.001

10. Dhull AK, Atri R, Dhankhar R, Chauhan AK, Kaushal V. Major Risk Factors in Head and Neck Cancer: A Retrospective Analysis of 12-Year Experiences. World J Oncol. 2018;9(3):80–4.

11. Hashibe M, Brennan P, Chuang S, Boccia S, Castellsague X, Chen C, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the INHANCE consortium. Cancer Epidemiol Biomarkers Prev. 2009;18(2):541–50.

12. Zuo JJ, Tao ZZ, Chen C, Hu ZW, Xu YX, Zheng AY, et al. Characteristics of cigarette smoking without alcohol consumption and laryngeal cancer: overall and time-risk relation. A meta-analysis of observational studies. Eur Arch Oto-Rhino-Laryngology. 2017;274(3):1617–31.

13. Sánchez Barrueco A, González Galán F, Lora Pablos D, Villacampa Aubá JM,

Ballestín Carcavilla C, Cenjor Español C, et al. HPV in Larynx Squamous Cell Carcinoma: New Serotypes and Survival Study within 10-Year Follow-up. Otolaryngol - Head Neck Surg (United States). 2017;156(4):677–82.

14. Hughes RT, Beuerlein WJ, O'Neill SS, Porosnicu M, Lycan TW, Waltonen JD, et al. Human papillomavirus-associated squamous cell carcinoma of the larynx or hypopharynx: Clinical outcomes and implications for laryngeal preservation. Oral Oncol [Internet]. 2019 [cited 2019 Oct 10];98(August):20–7. Available from: https://doi.org/10.1016/j.oraloncology.2019.09.008

15. Haberal I, Çelik H, Göçmen H, Akmansu H, Yörük M, Özeri C. Which is important in the evaluation of metastatic lymph nodes in head and neck cancer: Palpation, ultrasonography, or computed tomography? Otolaryngol - Head Neck Surg. 2004;130(2):197–201.

16. Chu EA, Kim YJ. Laryngeal Cancer: Diagnosis and Preoperative Work-up. Otolaryngol Clin North Am. 2008;41(4):673–95.

17. Iglesias Docampo LC, Arrazubi Arrula V, Baste Rotllan N, Carral Maseda A, Cirauqui Cirauqui B, Escobar Y, et al. SEOM clinical guidelines for the treatment of head and neck cancer (2017). Clin Transl Oncol. 2018;20(1):75–83.

18. Forastiere AA, Ismaila N, Lewin JS, Nathan CA, Adelstein DJ, Eisbruch A, et al. Use of larynx-preservation strategies in the treatment of laryngeal cancer: American society of clinical oncology clinical practice guideline update. J Clin Oncol. 2018;36(11):1143–69.

19. Institut Català d'Oncologia, Institut Català de la Salut. Praxis para el tratamiento médico y con irradiación del cáncer de orofaringe, hipofaringe, laringe y nasofaringe. Barcelona: ICO, ICS; 2016.

20. Eskander A, Blakaj DM, Dziegielewski PT. Decision making in advanced larynx cancer: An evidenced based review. Oral Oncol [Internet]. 2018 [cited 2019 Oct 24];86(September):195–9. Available from: https://doi.org/10.1016/j.oraloncology.2018.09.019

21. Total laryngectomy. Head and Neck Protocols [Internet]. University of Iowa Health Care. Iowa: UI Health Care; 2019 [cited 2020 Jan 2]. Available from: https://medicine.uiowa.edu/iowaprotocols/total-laryngectomy

22. Díaz de Cerio Canduela P, Arán González I, Barberá Durban R, Sistiaga Suárez A, Tobed Secall M, Parente Arias PL. Rehabilitation of the laryngectomised patient. Recommendations of the Spanish Society of Otolaryngology and Head and Neck Surgery. Acta Otorrinolaringol Esp [Internet]. 2019 [cited 2019 Oct 31];70(3):169–74. Available from: https://doi.org/10.1016/j.otoeng.2018.01.003

23. Longobardi Y, Savoia V, Bussu F, Morra L, Mari G, Nesci DA, et al. Integrated rehabilitation after total laryngectomy: a pilot trial study. Support Care Cancer. 2019;3537–44.

24. Girotmer SA, Hutchenson KA, Christianson BL, Samuelson MB, Barringer DA, Roberts DB, et al. Influence of timing, radiation, and reconstruction on complications and speech outcomes with tracheoesophageal puncture. J Sci

Spec head neck. 2016;38(12):1765–71.

25. Tang CG, Sinclair CF. Voice Restoration After Total Laryngectomy. Otolaryngol Clin North Am. 2015;48(4):687–702.

26. Petersen JF, Lansaat L, Timmermans AJ, van der Noort V, Hilgers FJM, van den Brekel MWM. Postlaryngectomy prosthetic voice rehabilitation outcomes in a consecutive cohort of 232 patients over a 13-year period. Head Neck. 2019;41(3):623–31.

27. Chakravarty PD, McMurran AEL, Banigo A, Shakeel M, Ah-See KW. Primary versus secondary tracheoesophageal puncture: Systematic review and meta-analysis. J Laryngol Otol. 2018;132(1):14–21.

28. Luu K, Chang BA, Valenzuela D, Anderson D. Primary versus secondary tracheoesophageal puncture for voice rehabilitation in laryngectomy patients: A systematic review. Clin Otolaryngol. 2018;43(5):1250–9.

29. Emerick KS, Tomycz L, Bradford CR, Lyden TH, Chepeha DB, Wolf GT, et al. Primary versus secondary tracheoesophageal puncture in salvage total laryngectomy following chemoradiation. Otolaryngol - Head Neck Surg [Internet]. 2009 [cited 2019 Dec 13];140(3):386–90. Available from: http://dx.doi.org/10.1016/j.otohns.2008.10.018

30. Singer MI, Blom ED. An endoscopic technique for restoration of voice after laryngectomy. Ann Otol Rhinol Laryngol. 1980;89(6):529–33.

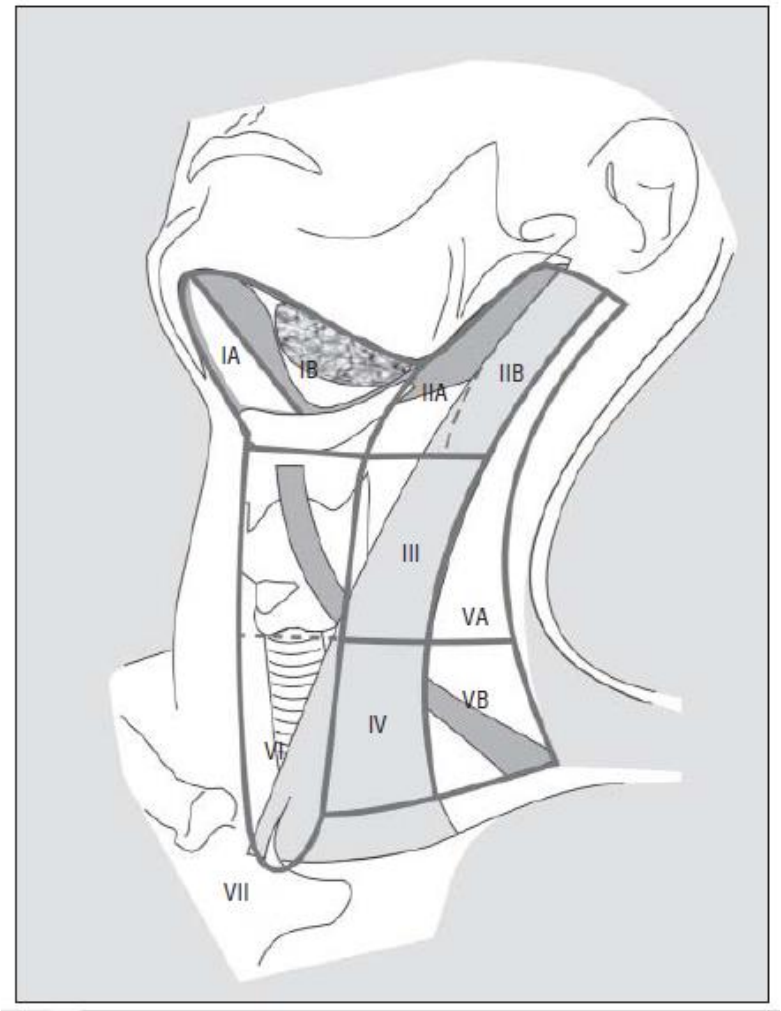
31. Instructions for Use PROVOX Vega ™ Puncture Set. Zürich: Atos Medical; 2018.

32. Bozec A, Poissonnet G, Chamorey E, Demard F, Santini J, Peyrade F, et al. Results of vocal rehabilitation using tracheoesophageal voice prosthesis after total laryngectomy and their predictive factors. Eur Arch Oto-Rhino-Laryngology. 2010;267(5):751–8.

33. Tobed Secall M, Bores T, Sambola I, Lop J, García Rica E, Lluansi J. Minimally invasive wire-guided balloon catheter puncture for voice prosthesis insertion. Head Neck. 2017;39(7):1459–61.

11 ANNEXES

ANNEX 1. Anatomic division of the lymph nodes by levels according to the Consensus Statement on the Classification and Terminology of Neck Dissection. Robbins et al.



ANNEX 2. Staging and TNM classification for larynx cancer according to the American Joint Committee on Cancer (AJCC), 8th Edition.

PRIMARY TUMOR (T)

Tx	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*

SUPRAGLOTTIS

T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility.
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx.
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage.
T4	Moderately advanced or very advanced disease.
T4a	Moderately advanced local disease. Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid or esophagus).
T4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

GLOTTIS

T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility.
T1a	Tumor limited to one vocal cord.
T1b	Tumor involves both vocal cords.
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility.
T3	Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space, and/or inner cortex of thyroid cartilage.
T4	Moderately advanced or very advanced.
T4a	Moderately advanced local disease. Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid or esophagus).
T4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

SUBGLOTTIS

T1	Tumor limited to the subglottis.
T2	Tumor extends to vocal cord(s) with normal or impaired mobility.
T3	Tumor limited to larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage.
T4	Moderately advanced or very advanced.
T4a	Moderately advanced local disease. Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid or esophagus).
T4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

REGIONAL LYMPH NODES (N)

Nx	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension and ENE (–).
N2	Metastasis in a single ipsilateral lymph node, > 3 cm but ≤6 cm in greatest dimension and ENE (–); **OR** in multiple ipsilateral lymph nodes, ≤ 6 cm in greatest dimension and ENE (–); **OR** in bilateral or contralateral lymph nodes, ≤ 6 cm in greatest dimension and ENE (–).
N2a	Metastasis in a single ipsilateral lymph node, > 3 cm but ≤6 cm in greatest dimension and ENE (–).
N2b	Metastasis in multiple ipsilateral lymph nodes, ≤ 6 cm in greatest dimension and ENE (–).
N2c	Metastasis in bilateral or contralateral lymph nodes, ≤ 6 cm in greatest dimension and ENE (–).
N3	Metastasis in a lymph node more than 6 cm in greatest dimension.
N3a	Metastasis in a lymph node > 6 cm in greatest dimension and ENE (–).
N3b	Metastasis in any lymph node(s) with clinically overt ENE (+).

ENE – extranodal extension

DISTANT METASTASIS (M)

M0	No distant metastasis
M1	Distant metastasis

ANATOMIC PROGNOSTIC STAGE GROUPS

	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1, T2, T3	N1	M0
IVA	T4a	N0, N1	M0
	T1, T2, T3, T4a	N2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

ANNEX 3: Information sheet for participants**.**

Hospital Universitari de Girona Doctor Josep Trueta Av. França s/n 17007 Girona	**HOJA DE INFORMACIÓN AL PACIENTE**	Classical versus wire-guided balloon catheter puncture technique for voce prosthesis insertion

HOJA DE INFORMACIÓN AL PACIENTE

PROJECT: Classical versus wire-guided balloon catheter puncture technique for voce prosthesis insertion.

INTRODUCCIÓN

Nos dirigimos a usted para informarle sobre un estudio de investigación que lleva a cabo el servicio de Otorrinolaringología del Hospital Dr. Josep Trueta de Girona, al que se le invita a participar. El estudio ha sido aprobado por el Comité Ético de Investigación Clínica del mismo Hospital.

Nuestra intención es que usted reciba la información correcta y suficiente para que pueda evaluar si quiere o no participar en este estudio. Antes de decidir si quiere participar o no, le rogamos que lea detenidamente este documento que incluye la información sobre este proyecto.
Puede formular todas las preguntas que le surjan y solicitar cualquier aclaración sobre cualquier aspecto. Puede consultar la decisión con las personas que considere oportunas.

PARTICIPACIÓN VOLUNTARIA

Debe saber que su participación en este estudio es voluntaria y que puede decidir no participar o cambiar su decisión y retirar el consentimiento en cualquier momento, sin que ello altere la relación con su médico ni se produzca ningún perjuicio en su atención sanitaria.

DESCRIPCIÓN DEL ESTUDIO:

La punción traqueo esofágica es el método común para la inserción de una prótesis de voz en pacientes laringuectomizados con el objetivo de rehabilitar el habla. Este método es el de elección para reestablecer la capacidad comunicativa.
La técnica utilizada para realizar esta punción, requiere el uso de una esofagoscopia rígida, anestesia general y la realización en quirófano.

En el HUDJT se ha desarrollado un método de inserción menos invasivo, en el que, mediante una sonda balonada que viaja vía nasal hasta el esófago, permite realizar esta punción con anestesia local sin la necesidad de anestesia general ni quirófano.

Este estudio quiere comparar ambas técnicas de inserción de la prótesis de voz en pacientes que han recibido una laringuectomia total debido a un carcinoma de laringe. Con este estudio se pretende conocer si la hipótesis es válida, es decir, si la técnica de punción con sonda balonada es un procedimiento más rápido, permite conseguir el habla con un menor tiempo, presenta menos complicaciones, reduce la necesidad de sonda nasogástrica y por lo tanto, reduce los días de hospitalización, con el fin de conseguir suficiente evidencia para validar la técnica.

PROCEDIMIENTOS DEL ESTUDIO

En nuestro estudio se dividirán los pacientes en dos grupos de forma aleatoria. Un grupo se tratará con la técnica de punción clásica y el otro grupo con la técnica de punción con sonda balonada.

Se realizará un estudio preoperatorio con anestesiología en los pacientes que vayan a recibir la técnica clásica.

Le solicitamos permiso para que, previamente a la intervención, se le puedan recoger los datos necesarios para el estudio, así como también, a lo largo de la intervención, inmediatamente después de esta, a los 3 días, al mes y a los 3 y 6 meses.

BENEFICIOS Y RIESGOS DERIVADOS DE SU PARTICIPACIÓN EN EL ESTUDIO

Los datos conseguidos en esta investigación pretenden confirmar nuestra hipótesis y así, proporcionar suficiente evidencia para validar la nueva técnica de punción traqueo-esofágica mínimamente invasiva, como el nuevo método estándar para la implantación de la prótesis de voz, para la rehabilitación de pacientes que han recibido una laringectomía total debido a cáncer de laringe. Si esto sucede, a parte de las ventajas que la técnica haya demostrado, los costes sanitarios del procedimiento resultaran significativamente menores a los del procedimiento clásico, dando la posibilidad de incrementar el número de pacientes rehabilitados.

Es posible que los conocimientos adquiridos con la investigación no lo beneficien a usted personalmente, sino a futuros pacientes con el mismo problema.

Si por algún motivo, usted quiere conocer los resultados de la investigación, adquiridos gracias a su colaboración, podrá ponerse en contacto con los responsables del proyecto.

CONFIDENCIALIDAD

Los datos recogidos serán estrictamente confidenciales. Sólo se autorizará para la recogida de datos de su historial médico a personas sometidas al secreto profesional siempre con el previo conocimiento del investigador principal.

El tratamiento, la comunicación y la cesión de los datos de carácter personal de todos los participantes se ajustará a la Ley de confidencialidad 03/2018, de protección de datos de carácter personal. De acuerdo a lo establecido en la legislación mencionada, usted puede ejercer los derechos de acceso, modificación, oposición y cancelación de datos, por eso se ha de dirigir a su médico del estudio. Los datos recogidos por el estudio estarán identificados mediante un código y sólo su médico del estudio / colaboradores podrán relacionar estos datos con usted y con su historia clínica.
En ningún caso su nombre aparecerá en la publicación de los resultados. Si usted decide retirar el consentimiento para participar en este estudio, ningún dato nuevo será añadido a la base de datos y se exigirá la destrucción de toda la información personal obtenida.

CONTACTO CON EL INVESTIGADOR

Para cualquier duda o información adicional que precise, o sobre sus derechos como participante en un ensayo clínico, debe contactar con el investigador.

ANNEX 4: Consent form to enter the trial.

Hospital Universitari de Girona Doctor Josep Trueta Av. França s/n 17007 Girona	**CONSENTIMIENTO INFORMADO**	Classical versus wire-guided balloon catheter puncture technique for voce prosthesis insertion

<u>CONSENTIMIENTO INFORMADO</u>:

Yo (nombre y apellidos) .....con DNI .....:

- He leído la hoja informativa que se me ha entregado sobre el estudio.
- He podido hacer preguntas sobre el estudio.
- He recibido suficiente información sobre el estudio.
- He hablado con: (nombre del investigador) .....
- Comprendo que mi participación es voluntaria.
- Comprendo que los resultados obtenidos serán guardados para mantener la confidencialidad de mis datos de acuerdo con la Ley de Biomedicina de 2018 (ley 03/2018 de Investigación Biomédica).
- Comprendo que puedo revocar mi consentimiento en cualquier momento, sin tener que dar explicaciones y sin que ello altere mi asistencia sanitaria.

Accede a que los investigadores principales del proyecto puedan contactar con usted en un futuro si lo consideran oportuno.

Doy libremente mi conformidad para participar en el estudio y doy mi consentimiento para el acceso y utilización de mis datos en las condiciones detalladas en la hoja de información.

☐ Si ☐ No

Firma del paciente:
Fecha: ____ / _____ / _____

Firma del investigador:
Fecha: _____/ _____/_____

Firma del representante legal,
familiar o persona vinculada de hecho:
Fecha: ____/_____/_____

Firma del investigador:
Fecha: ____/_____/_____

ANNEX 5: Example of Registration sheet.

ENERO						
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

FEBRERO						
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	

MARZO						
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

ABRIL						
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30			

MAYO						
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31

JUNIO						
1	2	3	4	5	6	7
8	9	10	11	12	13	14
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30				

JULIO						
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

AGOSTO						
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

SEPTIEMBRE						
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30				

• Marque con **X** el día de la intervención.

• Marque con **O** el día que consiga contar hasta 10 sin necesidad de repetirse.

• Marque con **X** los días que no consiga contar hasta 10.

ANNEX 6: General indications of enteral nutrition

1.1. Situaciones de riesgo de malnutrición:

- Pérdida del 10% de peso en un corto periodo de tiempo.
- Peso inferior al 85% de la población normal (de igual edad y sexo).
- Ingesta < 50% de los requerimientos durante 7-10 días: especialmente paciente con dificultades en deglución o masticación.
- Datos analíticos:
    - Albúmina sérica menor de 3g/dl.
    - Transferrina sérica inferior a 180 mg/dl.
    - Linfocitos plasmáticos inferior a 1500/ml.

1.2. Factores que modifican el estado nutricional del enfermo:

1.2.1. Disminución de la ingesta debido a:

- Persistencia tumoral en faringe, laringe, esófago (Disfagia / odinofagia).
- Dolor (relacionado con deglución, otalgia, mucositis).
- Efectos secundarios de los tratamientos (ayuno > 7 días).
    - Cirugía (resección, estenosis, trastornos funcionales de la masticación / deglución).
    - Quimioterapia (nauseas, vómitos, alteraciones metabólicas, mucositis),
    - Radioterapia (mucositis, xerostomía).

1.2.2. Alteraciones metabólicas asociadas al cáncer.

1.2.3. Estado nutricional previo alterado (ingesta de alcohol y otras sustancias).

1.2.4. Factores locales:

- Alteración de la capacidad para masticar (estado de la mandíbula y musculatura masticatoria; dolor con la masticación).
- Alteración de la capacidad para deglutir (estado de la lengua, paladar óseo, orofaringe, esófago cervical, pares craneales, áreas resecadas, estenosis, parálisis velo-faringo-laríngeas).
- Alteración de la capacidad para ingerir líquidos (falsas vías, fístulas).

1.3. Otros factores: Anorexia nerviosa, alteraciones inflamatorias, traumatismos.

ANNEX 7: Information sheet and Consent form to undergo the classic procedure.

DOCUMENTO DE INFORMACIÓN Y AUTORIZACIÓN PARA LA REALIZACIÓN
DE ESOFAGOSCOPIA MEDIANTE ESOFAGOSCOPIO RÍGIDO

Nombre y apellidos:.....

Edad: ..... D.N.I.: ..... Nº historia clínica: .....

Diagnóstico del proceso: ..... Fecha: .....

Médico informante: ..... Nº Colegiado: .....

Este documento informativo pretende explicar, de forma sencilla, la intervención quirúrgica denominada ESOFAGOSCOPIA, así como los aspectos más importantes del período postoperatorio y las complicaciones más frecuentes que, como consecuencia de esta intervención, puedan aparecer.

BREVE DESCRIPCIÓN DEL PROCEDIMIENTO QUIRÚRGICO

La esofagoscopia es una técnica de exploración del esófago –es decir, del tubo de la deglución– con fines o de diagnóstico o, generalmente, de tratamiento, ya que se emplea para extraer cuerpos extraños alojados en la mencionada estructura, entre otros fines.
Consiste en la introducción, por la boca, de un tubo rígido, que dispone de un sistema de iluminación, que nos permitirá explorar el trayecto esofágico y realizar diferentes tratamientos, tales como la extracción de cuerpos extraños.
Esta exploración se realiza bajo anestesia general, con el paciente ingresado y habiendo transcurrido varias horas tras la última ingesta de alimentos. Con ello se pretende evitar un posible vómito que pueda ocasionar el paso de los alimentos ingeridos previamente, a los pulmones.
Tras efectuar la esofagoscopia puede ser necesaria una hospitalización de varios días, en dependencia de las lesiones observadas, manteniendo el tratamiento oportuno y los controles radiológicos necesarios.

En caso de NO EFECTUAR esta intervención

al no extraerse el cuerpo extraño, la deglución se verá muy seriamente comprometida. Existe, por el cuerpo extraño alojado en el esófago, un gran riesgo de perforación del mismo y de una mediastinitis –infección grave en el interior del torax–. Si la intervención tiene fines diagnósticos, no podrá obtenerse la información necesaria.

BENEFICIOS ESPERABLES

La extracción del cuerpo extraño y los derivados de la exploración esofágica.

PROCEDIMIENTOS ALTERNATIVOS

La esofagoscopia flexible es muy eficaz en la exploración del esófago, si bien se encuentra limitada en la extracción de cuerpos extraños en algunos casos.

RIESGOS ESPECÍFICOS MÁS FRECUENTES DE ESTE PROCEDIMIENTO

En los casos de extracción de cuerpos extraños cortantes o punzantes, la complicación más importante es la perforación esofágica. A este respecto hay que considerar que el esófago puede estar perforado por el propio cuerpo extraño enclavado.

DOCUMENTO DE INFORMACIÓN Y AUTORIZACIÓN PARA LA REALIZACIÓN
DE ESOFAGOSCOPIA MEDIANTE ESOFAGOSCOPIO RÍGIDO

Nombre y apellidos: .....

Edad: ..... D.N.I.: ..... Nº historia clínica: .....

Diagnóstico del proceso: ..... Fecha: .....

Médico informante: ..... Nº Colegiado: .....

En las proximidades del esófago se encuentra un espacio, denominado mediastino, que aloja órganos vitales, tales como el corazón, los grandes vasos arteriales y venosos, etc. La perforación esofágica puede conllevar la entrada al mediastino de saliva, aire o sangre, y su posterior infección, dando lugar a una mediastinitis. Esta afección es sumamente grave y puede, incluso, suponer el riesgo de fallecimiento del paciente.

Esta eventualidad es rara en un esófago normal, si bien en esófagos con enfermedades previas como estenosis –estrecheces– postquirúrgicas, tumores, divertículos –eventraciones del esófago–, antecedente de ingestión de cáusticos –lejía, salfumán, etc.–, puede llegar a producirse con cierta frecuencia. En estos casos, el riesgo de la técnica aumenta considerablemente.

Cabe, también, la posibilidad de sufrir heridas a nivel de la boca o la garganta, lesiones a nivel dentario o mandibular y los derivados de la hiperextensión cervical, que es la postura en la que se coloca al paciente para la intervención.

Así, en pacientes con artrosis cervical, osteoporosis, u otras enfermedades de la columna cervical, la hiperextensión cervical puede ocasionar traumatismos en la columna vertebral en diferentes grados, si bien esta eventualidad es infrecuente.

Otras complicaciones que pueden aparecer son la disfagia –molestias al tragar que suelen ser pasajeras–, la disfonía –ronquera, que también suele ser pasajera–, hemoptisis o hematemesis –es decir la aparición de sangre procedente del aparato digestivo o respiratorio–, la fístula traqueoesofágica –es decir, una comunicación entre el conducto de tragar y el de respirar, que tiene un pronóstico grave–, y la estenosis esofágica –el estrechamiento del conducto del aparato digestivo–.

No hay que ignorar, además de todo ello, las complicaciones propias de toda intervención quirúrgica, y las relacionadas con la anestesia general: a pesar de que se le ha realizado un completo estudio preoperatorio, y de que todas las maniobras quirúrgicas y anestésicas se realizan con el máximo cuidado, se ha descrito un caso de muerte por cada 15.000 intervenciones quirúrgicas realizadas bajo anestesia general, como consecuencia de la misma. En general, este riesgo anestésico aumenta en relación con la edad, con la existencia de otras enfermedades, y con la gravedad de las mismas.

DOCUMENTO DE INFORMACIÓN Y AUTORIZACIÓN PARA LA REALIZACIÓN
DE ESOFAGOSCOPIA MEDIANTE ESOFAGOSCOPIO RÍGIDO

Nombre y apellidos: .....

Edad: ..... D.N.I.: ..... Nº historia clínica: .....

Diagnóstico del proceso: ..... Fecha: .....

Médico informante: ..... Nº Colegiado: .....

RIESGOS RELACIONADOS CON SUS CIRCUNSTANCIAS PERSONALES Y PROFESIONALES

OBSERVACIONES Y CONTRAINDICACIONES

DECLARACIONES Y FIRMAS

Declaro que he sido informado, por el médico, de los aspectos más importantes de la intervención quirúrgica que se me va a realizar, de su normal evolución, de las posibles complicaciones y riesgos de la misma, de sus contraindicaciones, de las consecuencias que se derivarían en el caso de que no me sometiera a la mencionada intervención y de las alternativas a esta técnica quirúrgica.
Estoy satisfecho de la información recibida. He podido formular todas las preguntas que he creído conveniente y me han sido aclaradas todas las dudas planteadas.
Declaro, además, no haber ocultado información esencial sobre mi caso, mis hábitos o régimen de vida, que pudieran ser relevantes a los médicos que me atienden.
Sé, por otra parte, que me intervendrá el facultativo que, dentro de las circunstancias del equipo médico en el día de la intervención, sea el más adecuado para mi caso.
Acepto que, durante la intervención, el cirujano pueda tomar las muestras biológicas que considere necesarias para el estudio de mi proceso, o las imágenes precisas para la adecuada documentación del caso.
Comprendo que, a pesar de las numerosas y esmeradas medidas de higiene del equipo asistencial que me atiende, el acto quirúrgico y la estancia en el hospital son un factor de las llamadas infecciones hospitalarias, que son excepcionales, pero posibles.
En el caso de que, durante la intervención quirúrgica, el cirujano descubra aspectos de mi enfermedad, o de otras enfermedades que pudiera padecer, que le exijan o le aconsejen modificar, de forma relevante, el procedimiento terapéutico inicialmente proyectado, consultará la decisión a tomar con la persona autorizada por mí a este respecto. Únicamente cuando las eventualidades acaecidas durante la intervención quirúrgica pongan en riesgo mi vida autorizo al cirujano para que adopte la decisión más conveniente para mi salud. Entiendo que es posible que el cirujano finalice la intervención sin haber completado los objetivos inicialmente planteados, al enfrentarse a circunstancias no previstas que pudieran requerir mi consentimiento expreso para ser resueltas.
Entiendo que, en este documento, se me informa de los riesgos y complicaciones más frecuentes y relevantes de la intervención quirúrgica. No obstante, si yo lo precisara, el médico podría facilitarme información complementaria sobre todos los riesgos y complicaciones

Nombre y apellidos:.....

Edad: ..... D.N.I.: ..... Nº historia clínica: .....

Diagnóstico del proceso: ..... Fecha: .....

Médico informante: ..... Nº Colegiado: .....

posibles de este procedimiento quirúrgico. En resumen, considero que la información ofrecida por el médico y la contenida en el presente documento resultan suficientes y adecuadas para comprender todos los aspectos de la intervención a la que voy a ser sometido y asumir sus riesgos y posibles complicaciones.
Tras todo ello, DOY MI CONSENTIMIENTO PARA SER SOMETIDO A ESTA INTERVENCIÓN, entendiendo, por otra parte, mi derecho a revocar esta autorización en cualquier momento.

En _____, a ___ de _____ de 20___

Fdo.: _____
El paciente

Fdo.: _____
El facultativo

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D./D.ª....., con D.N.I. .....
y en calidad de ....., es consciente de que el paciente cuyos datos figuran en el encabezamiento, no es competente para decidir en este momento, por lo que asume la responsabilidad de la decisión, en los mismos términos que haría el propio paciente.

En _____, a ___ de _____ de 20___

Fdo.: _____
El representante legal

REVOCACIÓN DEL CONSENTIMIENTO

Por la presente, ANULO cualquier autorización plasmada en el presente documento, que queda sin efecto a partir del momento de la firma.

Me han sido explicadas las repercusiones que, sobre la evolución de mi proceso, esta anulación pudiera derivar y, en consecuencia, las entiendo y asumo.

En _____, a ___ de _____ de 20___

DOCUMENTO DE INFORMACIÓN Y AUTORIZACIÓN PARA LA REALIZACIÓN
DE ESOFAGOSCOPIA MEDIANTE ESOFAGOSCOPIO RÍGIDO

Nombre y apellidos:.....

Edad: ..... D.N.I.: ..... Nº historia clínica: .....

Diagnóstico del proceso: ..... Fecha: .....

Médico informante: ..... Nº Colegiado: .....

Fdo.: _____
El paciente/representante legal

Consentimiento informado aprobado y consensuado por la
Sociedad Española de Otorrinolaringología y Patología Cérvico-Facial
SEORL PCF

ANNEX 8: Information sheet and consent form to undergo the wire-guided balloon catheter puncture technique.

Hospital Universitari de Girona Doctor Josep Trueta Av. França s/n 17007 Girona	**FULL D'INFORMACIÓ AL PACIENT I CONSENTIMENT INFORMAT**	Tècnica de punció amb sonda balonada per la inserció de la pròtesis de veu.

Nom i cognoms: .....

Edat: ..... DNI: ..... Nº Història Clínica .....

Diagnòstic del procés: ..... Data: .....

Metge responsable: ..... Nº de Col·legiat .....

BREU DESCRIPCIÓ DE LA TÈCNICA

La tècnica de punció amb sonda balonada és un procediment que s'utilitza en pacients que han rebut una laringectomia total, per tal de realitzar una punció traqueo-esofàgica per la posterior inserció de la pròtesis de veu.
És un mètode mínimament invasiu en el qual s'utilitza anestèsia local que s'aplicarà mitjançant la infiltració de la paret posterior traqueal i mitjançant l'ús d'anestèsia tòpica a les vies nasals. La sonda balonada entrarà per via nasal fins arribar just darrere el lloc de punció, i permetrà realitzar la punció traqueal evitant la lesió de les parets esofàgiques, i la inserció de la pròtesis fonatòria en el mateix temps.

PROCEDIMENTS ALTERNATIUS

Per la creació de la fístula traqueo-esofàgica per la posterior inserció de la pròtesis de veu, també es pot utilitzar la tècnica clàssica, en la qual, sota anestèsia total i en el quiròfan, s'utilitza una esofagoscòpia rígida. Pot ser especialment útil davant estenosis esofàgiques i quan el pacient presenta una gran distància des de la fosa nasal a la zona de punció.

BENEFICIS

Aquesta tècnica permet la realització d'una punció traqueo-esofàgica per a la inserció d'una pròtesi fonatòria, usant un mètode poc invasiu que no requereix l'ús d'anestèsia general ni la realització d'aquesta tècnica en quiròfan. Així mateix elimina alguns factors anatòmics de risc o que poden contraindicar el mètode estandarditzat actual (tècnica clàssica) com la rigidesa cervical o el trismus. El fet de no necessitar la canalització esofàgica mitjançant esofagoscòpia rígida minimitza riscos de danyar estructures de la

cavitat oral i l'esòfag, eliminant també els riscos inherents qualsevol procediment anestèsic general.

COST, RISCOS, INCONVENIENTS

La realització de la tècnica no suposarà cap cost econòmic per a vostè. El risc per a la salut de la punció guiada per sonda balonada no difereix als de la intervenció habitual, a curt termini poden aparèixer: molèsties a l'empassar, infecció o hemorràgia menor de la zona puncionada traqueal i /o esofàgica.
La via de canalització nasal pot ocasionar, en alguns casos, un sagnat nasal o epistaxi menor i auto limitada. Rarament el sagnat podria requerir mesures locals de tamponament. Aquestes complicacions podrien, en algun cas, suspendre el procediment de manera temporal o definitiva.
L'ús d'anestèsics locals en algunes ocasions pot generar reaccions al·lèrgiques locals o sistèmiques. Es molt important informar el personal sanitari sobre possibles al·lèrgies farmacològiques conegudes.
A llarg termini la punció traqueo-esofàgica pot resultar no viable per a l'ús de pròtesis fonatòries per mala adaptació dels teixits al material protèsic, apareixent granulomes (inflamació al voltant de la pròtesi) o fístules peri-protèsiques (sortida de contingut esofàgic per la zona de la punció). La majoria de casos es resolen mitjançant tractament farmacològic o mitjançant maniobres locals com la cauterització local de granulomes, la infiltració al voltant del trajecte fistulós de substàncies segellants o la realització d'un punt de sutura continu estenosant.
Rarament, si aquestes complicacions menors no es resolen, es pot optar per el segellat definitiu de la fístula mitjançant sutura simple i en algun cas mitjançant l'ús de penjolls locals que independitzarien de nou la via digestiva de la respiratòria.
Es prendran precaucions per evitar aquests inconvenients.

DECLARACIÓ I FIRMES

- Declaro que he estat informat, pel metge, dels aspectes més importants de la intervenció que em realitzarà, de la seva normal evolució, de les possibles complicacions i riscos de la mateixa, de les seves contraindicacions, de les conseqüències que es derivarien en el cas que no em sotmetés a l'esmentada intervenció i de les alternatives a aquesta tècnica quirúrgica.
- Estic satisfet de la informació rebuda. He pogut formular totes les preguntes que he cregut convenient i m'han estat aclarits tots els dubtes plantejats.
- Declaro, a més, no haver ocultat informació essencial sobre el meu cas, els meus hàbits o règim de vida, que poguessin ser rellevants als metges que m'atenen.
- Sé, per altra banda, que m'intervindrà el facultatiu que, dins de les circumstàncies de l'equip mèdic en el dia de la intervenció, sigui el més adequat per al meu cas.
- Estic d'acord amb que, durant la intervenció, es puguin prendre les mostres biològiques que consideri necessàries per a l'estudi del meu procés, o les imatges necessàries per a l'adequada documentació de el cas.
- Comprenc que, tot i les nombroses i acurades mesures d'higiene de l'equip assistencial que m'atén, la intervenció i l'estada a l'hospital són un factor de risc

per les anomenades infeccions hospitalàries, que són excepcionals, però possibles.

- En el cas que, durant la intervenció quirúrgica, el metge responsable descobreixi aspectes de la meva malaltia o d'altres malalties que pogués patir, que li exigeixin o li aconsellin modificar, de forma rellevant, el procediment terapèutic inicialment projectat, ha de consultar la decisió a prendre amb la persona autoritzada per mi a això.
- Únicament quan les eventualitats esdevingudes durant la intervenció posin en risc la meva vida, autoritzo el cirurgià perquè adopti la decisió més convenient per a la meva salut.
- Entenc que és possible que el cirurgià finalitzi la intervenció sense haver completat els objectius inicialment plantejats, a l'enfrontar-se a circumstàncies no previstes que puguin requerir el meu consentiment exprés per a ser resoltes.
- Entenc que, en aquest document, se m'informa dels riscos i complicacions més freqüents i rellevants de la intervenció quirúrgica. No obstant això, si jo ho precisés, el metge podria facilitar-me informació complementària sobre tots els riscos i complicacions possibles d'aquesta intervenció.
- En resum, considero que la informació oferta pel metge i la continguda en el present document són suficients i adequades per a comprendre tots els aspectes de la intervenció a la què seré sotmès i assumir els seus riscos i possibles complicacions.

Després tot això, DONO EL MEU CONSENTIMENT PER A SER sotmès a AQUESTA INTERVENCIÓ, entenent, d'altra banda, el meu dret a revocar aquesta autorització en qualsevol moment.

En ....., a ..... de ..... de 20 .....

Firma del Pacient Firma del Facultatiu

TUTOR LEGAL o FAMILIAR

Sr/Sra. ....., amb DNI ..... com a ....., és conscient de que el pacient, les dades del qual figuren a l'inici del document, no és competent per decidir en aquest moment, per la qual cosa, assumeix la responsabilitat de la decisió, en els mateixes termes que ho faria el propi pacient.

En ....., a ..... de ..... de 20 .....

Firma del representat legal

REVOCACIÓ DEL CONSENTIMENT

Per la present, ANUL·LO qualsevol autorització plasmada en el present document, que queda sense efecte a partir del moment de la signatura.

M'han estat explicades les repercussions que, sobre l'evolució del meu procés, aquesta anul·lació pot derivar i, en conseqüència, les entenc i assumeixo.

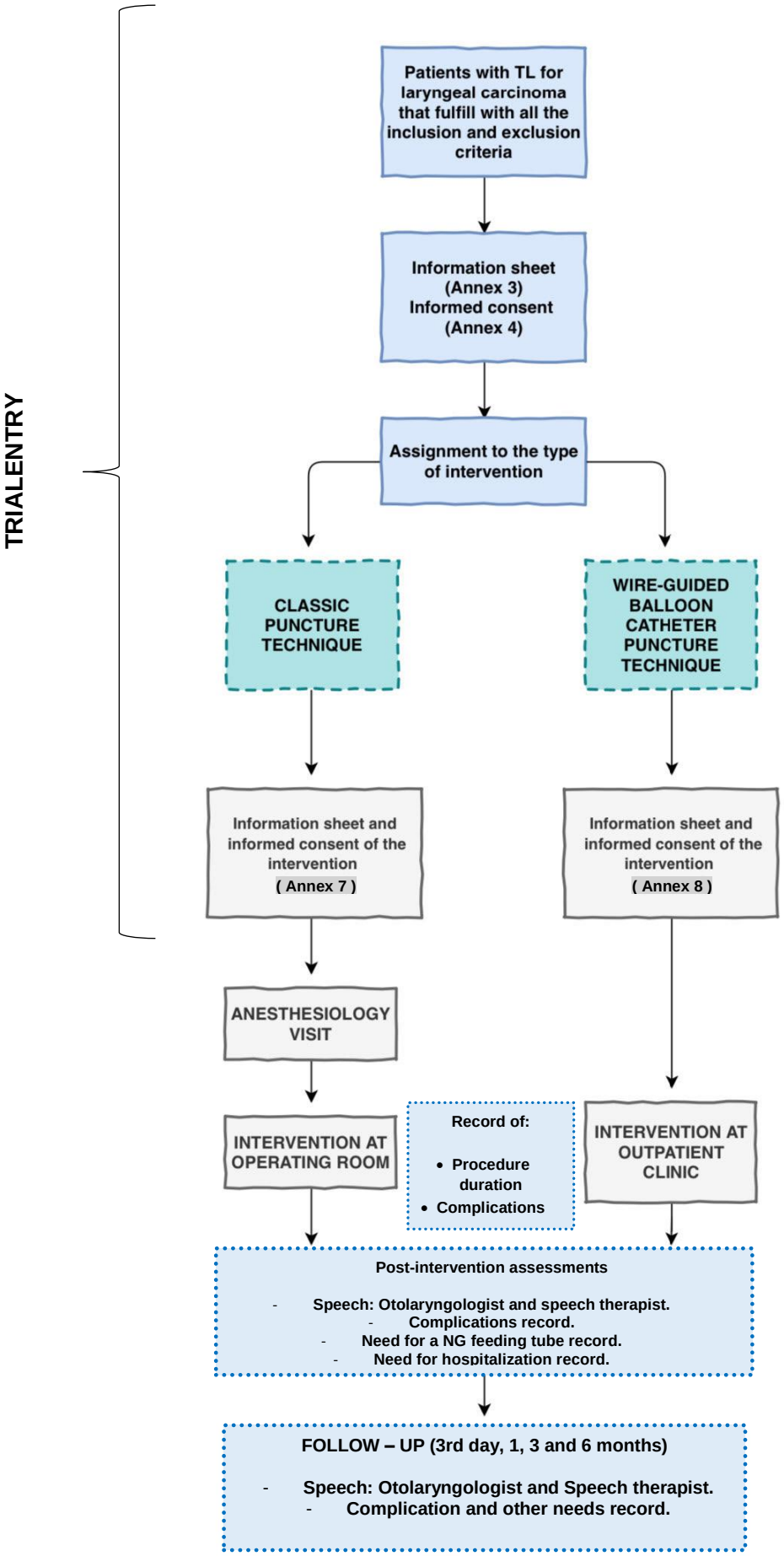
En ....., a ..... de ..... de 20 .....

Firma del pacient / representat legal

ANNEX 9: American Society of Anesthesiology Physical Status (ASA PS) classification system.

ASA PS Classification	Definition	Adult Examples, Including, but not Limited to:
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30<BMI<40), well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations; One or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA < 60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	A patient with severe systemic disease that is a constant threat to life	Examples include (but not limited to): recent (<3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Examples include (but not limited to): ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	
*The addition of "E" denotes Emergency surgery: (An emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part)		

ANNEX 10: Data collection summary diagram



ANNEX 11: Notebook 1 of data collection

FULL DE RECOLLIDA DE DADES

ESTUDI: Classic versus wire-guided balloon catheter puncture technique for Voice prosthesis insertion.

Etiqueta identificativa del pacient

Assistents responsables: _____

PREVI A L'INTERVENCIÓ

Grup d'intervenció	**A** ☐ **B** ☐
Edat	**_____ anys**
Sexe	**Dona** ☐ **Home** ☐
TNM	**_____**
Tractament amb Radioteràpia previ	**Si** ☐ **No** ☐
Trismus	☐ **Obertura reduïda (< 4cm)** ☐ **Obertura normal (4-6cm)** ☐ **Obertura augmentada (>6cm)**
Comorbiditats	**_____**
Data de la Laringuectomia total (LT)	**_____**

INTERVENCIÓ

Data de la inserció de la pròtesis de veu	**_____**
Temps entre la Laringectomia total i la inserció de la pròtesis de veu	**_____ mesos**
Duració de la intervenció	**_____ min**
Fracàs de la tècnica	**Si ☐ No ☐**
Complicacions observades	☐ **No** ☐ **Sagnat** ☐ **Lesió paret esofàgica** ☐ **Altres _____**

ANNEX 12: Notebook 2 of data collection

FULL DE RECOLLIDA DE DADES

ESTUDI: Classic versus wire-guided balloon catheter puncture technique for Voice prosthesis insertion.

Etiqueta identificativa del pacient

Assistents responsables: _____

POST-INTERVENCIÓ (primeres 3 hores)

Data de la inserció de la pròtesis de veu	**_____**
Capacitat de contar fins a 10 sense necessitat de repetir-se (capacitat de parla funcional acceptable) (Si la resposta anterior és si) **Data:**	**Si** ☐ **No** ☐ **_____**
Temps entre la inserció de la pròtesis de veu i la capacitat de parla funcional acceptable	**_____ dies**
Complicacions observades	☐ **No** ☐ **Sagnat** ☐ **Lesió paret esofàgica** ☐ **Altres _____**
Requeriment de sonda d'alimentació Naso-gàstrica	**Si** ☐ **No** ☐
Necessitat d'hospitalització	**Si** ☐ **No** ☐

SEGUIMENT (3r dia, 1r-3r-6è mes).

Capacitat de contar fins a 10 sense necessitat de repetir-se (capacitat de parla funcional acceptable) (Si la resposta anterior és si) **Data:**	**Si** ☐ **No** ☐ **_____**
Temps entre la inserció de la pròtesis de veu i la capacitat de parla funcional acceptable	**_____ dies**
Complicacions observades	☐ **No** ☐ **Sagnat** ☐ **Lesió paret esofàgica** ☐ **Altres _____**
Requeriment de sonda d'alimentació Naso-gàstrica	**Si** ☐ **No** ☐
Necessitat d'hospitalització	**Si** ☐ **No** ☐
(si la resposta a necessitat d'hospitalització en el post-intervenció o en el seguiment és Si) **Dies d'hospitalització**	**_____ dies**