Universitat de Girona
Facultat de Medicina

COMPARISON OF VOICE QUALITY AND FUNCTIONALITY BETWEEN MUSCLE AND FASCIOCUTANEOUS FLAPS USED FOR PHARYNGEAL RECONSTRUCTION AFTER A TOTAL LARYNGECTOMY

A MULTICENTRE, RANDOMIZED, CLINICAL TRIAL

FINAL DEGREE PROJECT

AUTHOR: Arnau Masó i Romero
CLINICAL TUTOR: Dr. Marc Tobed Secall
METHODOLOGICAL TUTOR: Dr. Abel López Bermejo

Girona, January 2021

I would like to show my gratitude to Marc Tobed for all his support and help during this project, and for all the enthusiasm shown since the very first moment.

I also really appreciate all the help and advices from Abel López for the methodological development of this project.

I would also like to thank to the entire otorhinolaryngology department of the Hospital Universitari Doctor Josep Trueta, especially to Marc Tobed and Toni Borés, to whom I am very grateful for the great treatment received, for taking me in as a member of the team and for their willingness to teach in such a good atmosphere.

Finally, thanks to my family, friends and my partner Claudia for all your support during these years, for having you always by my side. Without you it would not have been the same.

INDEX OF CONTENT

INDEX OF FIGURES

INDEX OF TABLES

1. ABREVIATIONS

ALT: Anterolateral thigh.

ASA: American Society of Anaesthesiology.

ENT: Ears, nose and throat.

ES: Oesophageal speech.

FNL: Flexible nasal laryngoscope.

HME: Heat and moisture exchanger.

ICO: Institut Català d'Oncologia.

ICT: Induction chemotherapy.

LA: Locally advanced.

PE: Pharyngoesophageal.

PM: Pectoralis Major.

PMMF: Pectoralis Major myocutaneous flap.

RFFF: Radial forearm fasciocutaneous Flap.

SCC: Squamous cell carcinoma.

SG: Supraglottic.

TE: Tracheoesophageal.

TEP: tracheoesophageal puncture.

TES: Tracheoesophageal speech.

TL: Total laryngectomy.

VC: Vocal cords.

VP: Voice prosthesis.

VHI: Voice Handicap Index.

2. ABSTRACT

BACKGROUND: Larynx cancer is the most frequent one in head and neck cancer and a huge part of these, especially the supraglottic ones, are diagnosed at locally advanced stages. In these cases, surgery by means of total laryngectomy followed by adjuvant treatment has shown to have better results in local disease control and survival than the organ preservation chemoradiotherapy protocols promoted from the 1980s onwards. In addition, in many times, total laryngectomy needs to be followed by a partial pharyngectomy in order to ensure disease-free surgical margins. In these cases, the reconstruction of the pharynx using a flap, either muscular or fasciocutaneous, takes on great importance because of the relevance of the pharynx in the rehabilitation of the patient. Even though, no experimental study has ever been designed to compare the quality and functionality of the voice produced by the patient according to the type of flap that has been used to reconstruct the pharynx.
Since we consider it is of vital importance to be able to offer the best quality of life to all patients operated on by oncological surgery, we believe that it should be studied which reconstruction techniques are capable of achieving a better voice in the laryngectomised patients, as the voice is a crucial element in our lives and its loss has a great psychological impact and a huge influence on the quality of life.

OBJECTIVE: The aim of this study is to prove that pharynx reconstruction with a muscular flap after a total laryngectomy produces a better quality and functionality voice than reconstruction with fasciocutaneuous flaps.

DESIGN AND SETTING: This is a multicentre, randomized, open-labelled clinical trial performed among five tertiary hospitals of Catalonia.

PARTICIPANTS: Subjects of this study will be those newly diagnosed locally advanced larynx or hypopharynx squamous cell carcinoma who are treated with a total laryngectomy and require a pharynx reconstruction.

METHODS: 60 patients will be recruited with a consecutive method. Recruitment of patients will last 24 months. They will be assigned randomly to one of the three treatment groups: group A: pharynx wall reconstruction with PMMF (n=30), group B: pharynx wall reconstruction with RFFF (n=15) and group C: pharynx reconstruction with ALT fasciocutaneous flap (n=15). After the intervention there will be a subsequent follow-up for 16 months. The voice quality and functionality will be evaluated with VHI-30 questionnaire during one year after the voice prosthesis placement. ANOVA test and a General Linear Model for repeated measures will be used for statistical analyses of the voice quality and functionality between the two groups of flaps.

KEYWORDS: Locally advanced larynx cancer, total laryngectomy, Pectoralis Major myocutaneous flap, radial forearm fasciocutaneous flap, anterolateral thigh fasciocutaneous flap, VHI-30, voice functionality, voice quality.

3. INTRODUCTION

3.1- HYPOPHARYNX AND LARYNX ANATOMY

The larynx is a hollow tubular structure composed of a 9 cartilages skeleton linked by muscles and ligaments located in the most anterior part of the neck at the heigh of C4 to C6 (1). The laryngeal lumen communicates with the oropharynx at the top and with the trachea at the bottom. Its posterior wall maintains an intimate relationship with the hypopharynx, so infiltrative processes from this location will have a great impact on the larynx (2).

The hypopharynx extends from the vallecula to the inferior cricoid cartilage and consists of three regions (3,4):

- **Pyriform sinus**: the invagination of the aryepiglottic folds and the thyroid cartilage on either side of the larynx.
- **Postcricoid area** (or pharyngoesophageal junction): the anterior wall of the hypopharynx at the level of the cricoid. It extends from the cricoarytenoid joints to the cricoid cartilage.
- **Posterior hypopharyngeal wall**: consisting of mucosa and the constrictor muscle.

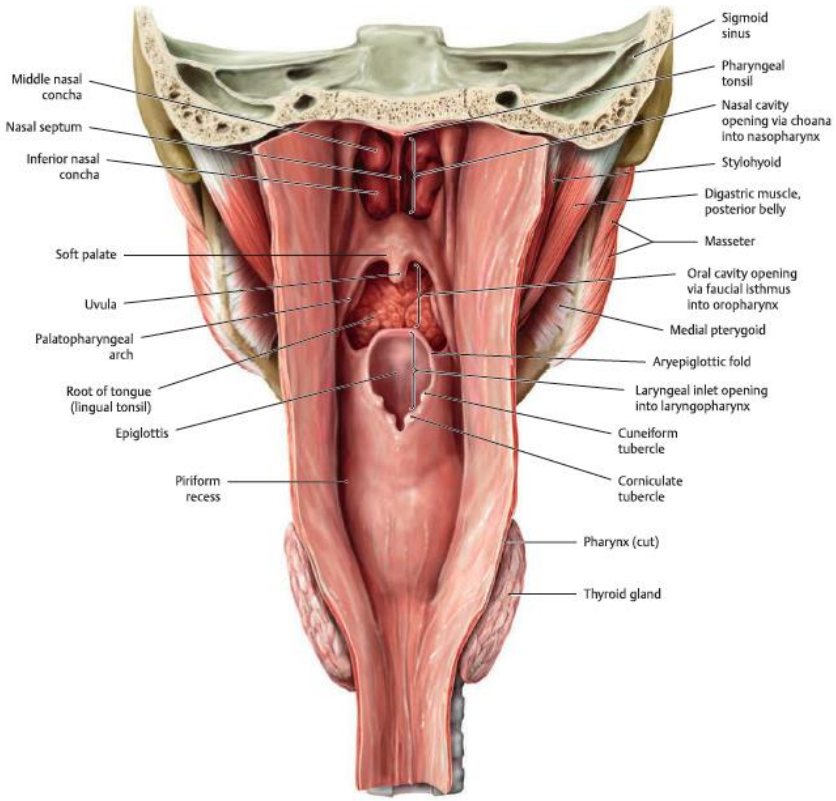

Figure 1. Posterior view of the opened pharynx. See the anatomical divisions of the hypopharynx (4).

The laryngeal cavity is not uniform. On each of its sides there are two superimposed reliefs: the vestibular fold (superior) and the vocal fold (inferior). The inferior one is also known as vocal cords (Figure 2). The space between the two folds is the laryngeal ventricle. These structures are used to divide the larynx into three sections (5,6):

- Supraglottis: From the epiglottis to the laryngeal ventricles.
- Glottis: The region including the vocal cords and the commissures.
- Subglottis: From the vocal cords' under-surface to the cricoid cartilage.

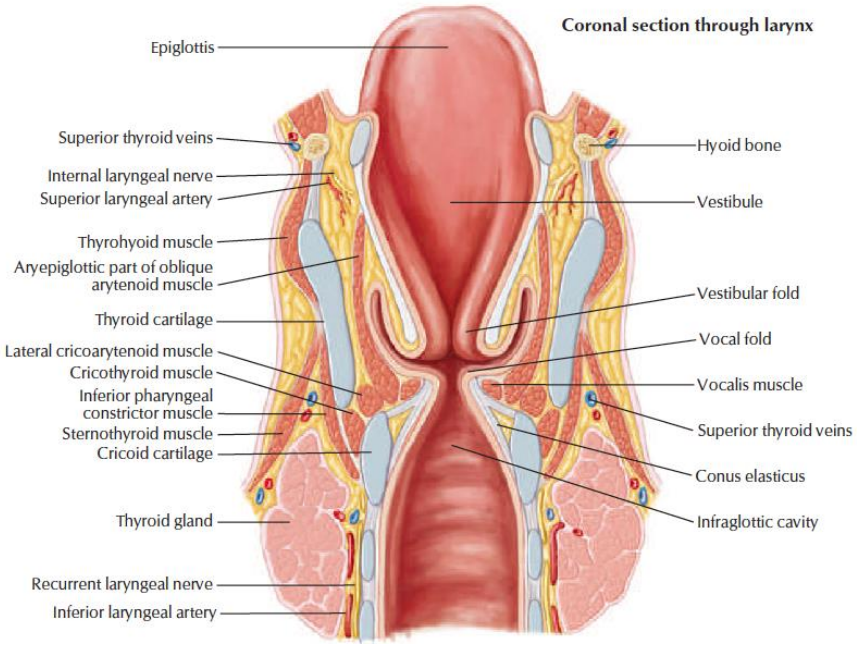

Figure 2. Coronal section through larynx (5).

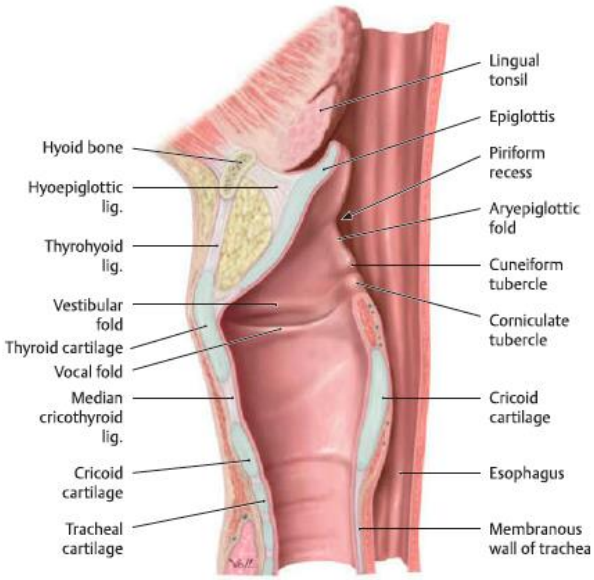

Figure 3. Midsagittal section through larynx where its 3 sections can be seen. Notice the tight relationship between the posterior wall of the larynx and the hypopharynx (6).

SITE	SUBSITES
Supraglottis	- Epiglottis. - Aryepiglottic folds (laryngeal surfaces). - Both arytenoids. - Both ventricular bands.
Glottis	- True vocal cords.
Subglottis	- No subsites.

Table 1. Anatomic sites and substites of the larynx.

Because of its location, the larynx is a key organ in the **breathing** mechanism. When breathing at rest, the glottis is open, allowing air to pass through. Moreover, the laryngeal musculature has the capacity to increase the diameter of the glottic lumen during forced inspirations (7,8).

If the musculature does just the opposite mechanism and narrows the glottic space while forcing out the air, a vibration is produced that generates the sound that will be converted into the articulated voice after going through the pharynx, the nasal cavities and the mouth. This process is called **phonation** (1,7).

Another very important function of the larynx is to protect the airway from the food bolus during **swallowing**. The upward and forward movement of the laryngeal block when swallowing allows to narrow the laryngeal space and its upper opening closure through the epiglottic cartilage bending (7).

Finally, the larynx is key in **Valsalva's manoeuvre**, as it is through its forced closure that intrathoracic air can be retained (7).

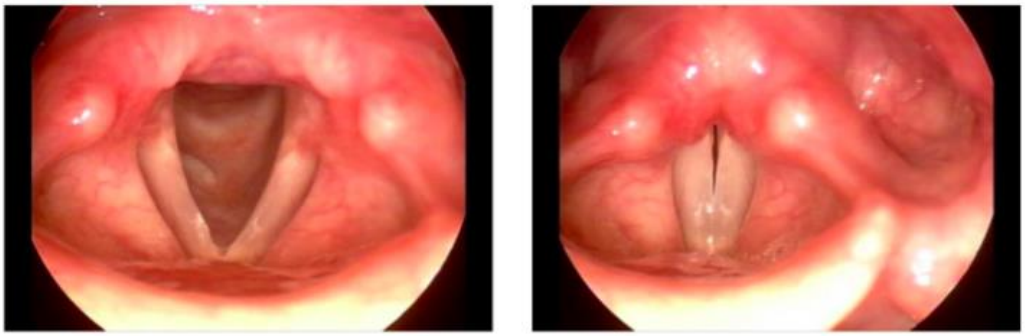

Figure 4. Vocal cords during breathing (left) and phonation (right).

3.2- LARYNX CANCER

3.2.1- EPIDEMIOLOGY

Head and neck cancer is a group of cancers that originate in one of the structures from the nose to the larynx. They are the 7th most common type of cancer worldwide, constituting around 6% of all cancer cases, with a total of 650.000 new cases and 333.000 deaths annually worldwide during 2018 according to GLOBOCAN (9).

Larynx cancer is by far the most common location of cancer in the head and neck group, and the second most common malignancy of the aerodigestive tract, only surpassed by the lung (10). It resulted in a total of 177.422 new cases and 94.771 deaths in 2018 all around the world (9).

Larynx cancer is typical to appear in the 6th and 7th decade of life and has been found to be more prevalent in lower socioeconomic groups, among which it is also often diagnosed later and in a more advanced stage (11).

The most common type of laryngeal cancer is squamous cell carcinoma, which accounts for 85% to 95% of all laryngeal malignancies (10). SCC is related to tobacco and alcohol, so for many years it has clearly been more common in men than in women, but as the number of smoking women has increased over the last decades, this gap has narrowed from a 15:1 ratio in 1960 to a 4:1 ratio in the last decade (10).

As regards for regions of the larynx affected by cancer, their distribution is not uniform across the world. In Spain, supraglottic cancer predominates, while in Italy and England the glottic cancer is the most frequent one. These variations in incidence could be explained by different lifestyles between countries and as well as by other environmental factors exposure. Subglottic tumours are the least common in all countries (12).

If we focus in Spain, the incidence of larynx cancer is the highest in the world, followed by other Mediterranean countries like Italy and France (12). Based on the latest epidemiological data, it was estimated that in 2020 around 3.221 people would be diagnosed with laryngeal cancer in Spain, of which an 88% would be men (13).

3.2.2- RISK FACTORS

The main risk factors for larynx SCC do not differ much to the ones from other head and neck's cancers (14). The most important for the larynx SCC are:

- Smoking **tobacco** is the most common aetiological factor for larynx SCC (15), causing mainly glottic cancer (16). Even if one quits smoking, laryngeal cancer risks remains elevated during the next 15 years (17).
- **Alcohol** is the second most important risk factor and is more associated with the risk of supraglottic cancer (16). It has been demonstrated that tobacco and alcohol have a **synergist effect**, and its combined use has a multiplicative effect on SCC risk (18). Over 90% of the incidence of larynx cancer could be prevented by avoiding tobacco and alcohol consume (16).
- **HPV infection** (6 and 11 serotypes) is strongly linked with other head and neck cancers like the oropharynx SCC. In relation to the larynx, it has been recently demonstrated the presence of HPV and/or p16 marker in a minority of laryngeal tumours (19).
- **Occupational toxic agents** like asbestos, polycyclic aromatic hydrocarbons, wood dust, coal dust and cement dust have been also linked to larynx SCC (15), but some of these relationships, like the asbestosis, are controversial (16).
- Some **genetic syndromes** such as congenital dyskeratosis (20) or Fanconi's anaemia (21) have a higher risk of developing laryngeal tumours (apart from other tumours in other parts of the organism).

3.2.3- NATURAL HISTORY AND CLINICAL PRESENTATION

As with most of the cancers, the laryngeal SCC may present local or systemic symptoms. Occasionally patients do present systemic signs, but in these cases, they also refer local symptoms. Paraneoplastic syndromes are very rare (15,22).

In most cases, the patients require medical attention due to local symptoms, which typically differ depending on the site where the primary tumour originates, allowing us to have a suspicion of the location of the tumour according to the symptoms referred by the patient.

It is not uncommon for a patient with a laryngeal cancer to present synchronously another tumour of the upper aerodigestive tract, typically of the same histological lineage (12).

GLOTTIC CANCER

The main symptom of glottic SCC is **dysphonia**.

Voice production is a very delicate process which depends on the integrity of the vocal cord's epithelium and the layers immediately below (see figure 5), so a very small lesion, even in situ carcinomas, can produce a significant voice change due to the alteration of the normal cord's vibration (15).

Glottic tumours remain localized in the glottis for a long time thanks to two main reasons: First, the natural anatomical barriers that offer protection against the spread of the tumour like ligaments, membranes and cartilages. Secondly, the glottis' lack of lymphatic drainage.
All of these conditions allow us to diagnose the glottic cancer in an early stage in most cases, but if the early symptoms are ignored, the lesion may grow and lead to the invasion of the other areas of the larynx, presenting symptoms like dyspnoea or stridor (10).

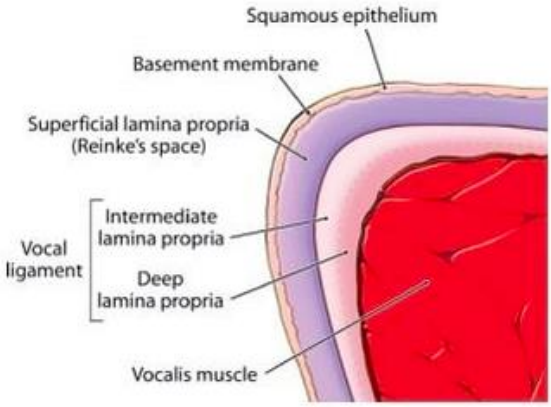

Figure 5. Normal vocal cord with all its layers (8).

SUPRAGLOTTIC CANCER

Supraglottic cancer can be asymptomatic until a quite large size is achieved, so by the time it is diagnosed, it is already in an advanced state (10,15). It is the location that has been most associated with paraneoplastic syndromes (22).
The small supraglottic cancers which don't reach the glottis do not alter the voice quality, and only cause laryngeal paraesthesia with **foreign body feeling** associated. Other symptoms will appear as the tumour size increases, which are determined by the direction of the tumour's extension: if the lesion extends to the glottis there will be dysphonia and/or hoarseness; while a laterally extension may cause referred otalgia, dysphagia, odynophagia or "hot potato" voice (10,15).

Supraglottic area is rich of lymphatic drainage, so cervical metastases are common. As the tumour can be asymptomatic, it is not rare for the first presentation of supraglottic SCC to be a neck lymphadenopathy.

SUBGLOTTIC CANCER

As with the supraglottic cancer, the early subglottic cancer symptoms are usually vague, so by the time it is diagnosed it is already at an advanced stage. The most common symptoms of subglottic SCC are **dyspnoea** and stridor (10,15).

DISTANT METASTASES

Laryngeal SCC metastases include both hematogenous metastases to distant organs (lung) and lymphatic metastases to nodal groups outside the neck (mediastinum).

Distant metastases are rare at initial presentation, being typically diagnosed in patients who had already diagnosed regional metastasis disease. In the same way as with lymphatic metastases, hematogenous ones are more common in the supraglottic cancer (10).

3.2.4- DIAGNOSIS

HISTORY AND PHYSICAL EXAMINATION

A patient with any of the symptoms mentioned in the previous section should be suspected of having larynx cancer, especially those with hoarseness for more than 4 weeks (23). In addition to the manifestations referred by the patient, a history of exposure to risk factors like alcohol and tobacco should be asked.

After this interview, a complete head and neck examination has to be performed, which includes the **palpation of the neck**, in which the laryngeal skeleton and the possible presence of lymph nodes must be evaluated, and the direct visualization of the upper airway by **flexible nasal laryngoscopy.** If there are any findings suggestive of malignancy, a biopsy should be performed.

BIOPSY

The biopsy may be taken during the FNL exploration through its working channel with topic anaesthesia, but it's usually performed in the OR under general anaesthesia (10).

IMAGING

When feasible, imaging by neck-CT with contrast is performed before the biopsy and its information is integrated with the endoscopic findings.

As soon as the pathological diagnosis of larynx cancer is obtained, an extension study should be carried out, including a neck and a thoracic CT.

3.2.5- STAGIN

A correct staging the tumour will determine the appropriate treatment. It is used the TNM classification staging system described by the American Joint Committee on Cancer (AJCC), from which the clinical stages have been described (See table 2). Complete TNM classification for larynx cancer can be seen in *Annex 1.*

STAGE 0	Tis	N0	M0
STAGE I	T1	N0	M0
STAGE II	T2	N0	M0
STAGE III	T1, T2	N1	M0
	T3	N0, N1	M0
STAGE IV-A	T1, T2, T3	N2	M0
	T4a	N0, N1, N2	M0
STAGE IV-B	Any T	N3	M0
	T4b	Any N	M0
STAGE IV-C	Any T	Any N	M1

Table 2. Stage group according to the TNM classification.

3.2.6- TREATMENT

Larynx cancer treatment approach is not easy. Many aspects must be taken into account in addition to the staging of the tumour when choosing a treatment, such as the tumour location or the patient's preferences. For this reason, all diagnoses of laryngeal cancer are presented to a Head and Neck **multidisciplinary committee** made up of otolaryngologists, radiotherapists, oncologists, plastic surgeons, pathologists and nurses in which all cases are discussed in order to choose the most appropriate treatment for each patient.

In general lines, it can be considered that the laryngeal cancer can be cured by surgery or RT, either separately or as an addition, and that in some cases adjuvant chemotherapy can also be indicated. The following therapeutic indications to be given are based on the latest publications of local reference guidelines: *Institut Català d'Oncologia* (ICO) and *Sociedad Española de Oncología Médica* (SEOM):

EARLY-STAGE SCC

Early SCC includes Stages I and II (T1-2 N0 M0). In these cases, the treatment of the tumour is carried out by a single modal preserving management, which has proved to be successful in controlling the disease without the need for a combination treatment.

Surgery or **radiotherapy** can be used without distinction as they both are similar in terms of locoregional control and survival outcome (10,24). Therefore, a treatment should be chosen according to the patient's functional outcome, the patient's wishes, the possibility of adequate follow-up and the general patient's condition (25).

Beside treating the tumour, a **cervical therapy** should be performed on all cases, even those that are clinically N0. Neck disease can be treated with single modality, either surgery or radiotherapy. There is an exception to the treatment of the neck: glottic T1 N0 M0, where it can be avoided due to its low risk of lymph node metastasis (10,15).

In summary, the first-line treatment recommended according to the location is (26):

Supraglottic	Transoral laser resection + functional neck dissection
Glottic	- T1a: Transoral laser resection - T1b: RT or cordectomy surgery - T2: Laser microsurgery + functional neck dissection
Subglottic	Radiotherapy over tumour and neck

Table 3. Recommended first-line therapeutic approach in early-stage larynx SCC. Adapted from (26).

RESECTABLE LOCALLY ADVANCED SCC

Advanced primary SCC includes Stages III and IVa (T3 and T4) without distance metastasis.

In this situation the treatment must be very well individualised according to the size of the tumour and its local extension, as the treatment differs according to whether it is a T3 or a T4, so the multidisciplinary assessment takes a major role in deciding a treatment for these patients (24).

Patients who do not meet the criteria of unresectable tumour may be offered various types of treatment:

a. SURGICAL TREATMENT

The surgical management of the locally advanced larynx SCC is based on a total or subtotal laryngectomy + cervical lymphadenectomy followed by radiotherapy or chemo-radiotherapy (24,26).

Surgery

While in T4a the surgical option is very clear and total laryngectomy is performed without hesitation, in T3 there is more doubt about which surgery to perform since recent systematic reviews showed that partial laryngectomies (opened or transoral) seemed to be efficient organ preserving methods in some cases (15). Therefore, in the case of choosing to operate on a patient with a T3, the choice of partial or radical surgery is individualised according to the characteristics of the tumour, the experience of the surgical team and the patient's preferences. More details about total laryngectomy will be discussed later.

Adjuvant treatment

After the laryngectomy and lymphadenectomy, all patients will receive adjuvant radiotherapy. Chemotherapy (three weekly administration of cisplatin) should be added to the adjuvant treatment in those cases with extracapsular lymph node extension and/or affected margins (24).

b. ORGAN PRESERVATION TREATMENT

Due to the aggressiveness and physical impact of the surgical treatment, multiple treatment options based on chemoradiotherapy have been attempted with the objective of treating the disease while preserving the larynx (10,15,24).

The most worldwide popular protocol is based on induction chemotherapy (ICT) with TPF schedule (Cisplatin, Docetaxel and 5-Fluoracil) for three weeks. After ICT, the treatment will be completed according to the results (24):

- CR: Complete response (disappearance of all clinically tumour): complete the treatment with adjuvant RT.
- PR: Partial response (reduction ≥50% of primary tumour without lymph node progression): the best curative option is a rescue TL followed by adjuvant RT, but if the patient still prefers organ preservation there is the possibility of treating with concomitant RT + cisplatin or cetuximab.
- SD: Stable disease (neither enough shrinkage to qualify for partial response nor enough increase to qualify for progression disease): TL + neck dissection + adjuvant RT/Chemo-RT
- PD: Progression disease: increase of tumour burden. TL + neck dissection + adjuvant RT/Chemo-RT

The outbreak of this organ preservation treatment during the 1980s seemed to be a change in the paradigm of the management of locally advanced laryngeal cancer, but the last few years have shown that this is not the case, since a **very accurate selection of patients** is required for the organ-preservation treatment to have good results because not all tumours are susceptible to this treatment (27,28). Furthermore, TL followed by adjuvant treatment has shown a better control of the **local disease** and a **better survival** than the non-surgical therapies (10,15).

In conclusion**,** the treatment of locally advanced laryngeal cancer should be individualized for each patient by a multidisciplinary team. There are, however, some situations in which the guidelines strongly recommend surgical treatment over radiotherapy. Those are larynx T4a and locally advanced subglottic tumours (24,26,29).

UNRESECTABLE LOCALLY ADVANCED SCC

Are considered unresectable those tumours staged as IVb or those that infiltrate the carotid artery, prevertebral space, mastoid apophysis, skull base or tongue base. In addition, even there is no universally accepted definition, those tumours that the surgical team does not see the possibility of achieving a complete excision with adequate margins without serious sequels will also be considered unresectable (24,30).

In these cases, there are different therapeutic options depending on the characteristics of the tumour and the state of the patient, either with a TPF chemotherapy induction or a concomitant chemotherapy with cisplatin/cetuximab (24,26).

In cases of local complete response with a persistent lymph node after the locoregional treatment, a savage resection of the lymph node should be considered.

RECURRENT AND METASTASIC SCC

Individualized treatment should be considered according to which treatment they have previously been treated with (24,26).

3.3- HYPOPHARYNX CANCER

Hypopharyngeal cancers, unlike laryngeal ones, are rare, as they only account for 3-5% of head and neck cancers (31). Out of the three anatomical portions of the hypopharynx, the most common site of origin is the **pyriform sinus** followed by the posterior pharyngeal wall and the postcricoid area, being the most common histology the SCC in all of them.

Its worldwide distribution is very diversified, being extremely rare in Africa, Eastern Asia and Northern Europe (with an incidence under 0,5/100.000) and very common in countries like India or France, in where the incidence can be over 15/100.000 men (31).

The typical patient is similar to other head and neck cancers because their risk factors are practically the same, with a special emphasis on the effect of **alcohol** and tobacco usage on hypopharyngeal cancer (32). Therefore, these cancers are more typical to occur in males on their 60s, but with one exception: post-cricoid tumours, which are commonly seen in women due to its association with **Plummer-Vinson syndrome** (33).
By the time of the initial diagnosis, a 60% of all patients are in a **stage IV disease**, a 5% present distant metastases and less than a 20% are diagnosed with a localised early stage of disease (34). When patients come for medical consultation, they usually refer dysphagia, hoarseness or reflex otalgia, and usually a **neck mass** is found during the exploration, as this area has a rich lymphatic drainage (31,32). Patients are **asymptomatic** during the early stages, especially those tumours involving the pyriform sinus. This is explained by the anatomical situation of the hypopharynx, which allows the tumour to grow much more than the tumours located in other regions of the neck as the hypopharynx boundaries with neighbouring structures are not so limiting (32).

Once hypopharyngeal cancer is suspected, a study equal to the one for larynx cancer is performed to confirm the diagnosis. Early lesions of the hypopharynx can be treated with equal effectiveness with either surgery or radiation. Due to its high capacity to **metastasize by lymphatic way,** all tumours treatment should include the elective treatment of cervical nodes, as occult nodal disease is present in 30-40% of patients with a cN0 (24).

For the locally advanced SCC, two options can be considered for its treatment (24,26):

a. Surgical resection: **total pharyngolaryngectomy + neck dissection** followed by radiotherapy or chemoradiotherapy.
b. Induction chemotherapy with TPF schedule:
    - If complete response: complete with radiotherapy ± chemotherapy
    - If partial response: complete with total laryngectomy to attempt the curative rescue followed by radiotherapy or chemoradiotherapy.
    - Is stable disease or progression: total pharyngolaryngectomy + neck dissection followed by radiotherapy or chemoradiotherapy.

Among these options, surgery is the one that will ensure a better loco-regional control rate, but this does not always translate into an improved survival, and therefore radiotherapy combined with chemotherapy seems to be the standard of care for most patients with an advanced disease as, replacing surgery with chemo-radiation has not caused a survival decrease (35). Even though, there is no strong evidence about the best treatment, so its election should always be individualized.

3.4- TOTAL LARYNGECTOMY

3.4.1- INDICATIONS OF TOTAL LARYNGECTOMY

Total laryngectomy is a radical surgery consisting in the removal of the entire larynx, including the thyroid and cricoid cartilages, the hyoid bone and part of the thyroid gland.

Main indications for TL are (11,30,36,37):

- Advanced laryngeal tumours with cartilage destruction and anterior extra-laryngeal spread with a damaged larynx which will not likely function again even if it is preserved anatomically (laryngeal dysfunction, airway obstruction or severe aspiration), making them **not amenable to preservation therapies**.
- **Circumferential submucosal disease** with or without bilateral vocal fold paralysis.
- Posterior commissure or bilateral **cricoarytenoid joint** tumour involvement.
- Extensive involvement of **thyroid cartilage**.
- Subglottic extension with extensive invasion of the **cricoid cartilage**.
- **Hypopharyngeal tumour** originated at or spreading to the postcricoid mucosa.
- Extensive pharyngeal or tongue base resections in patients at **high risk for aspiration problems.**
- **Failure** of organ **preservation** treatment.
- **Primary** tumours of the cricoid or thyroid **cartilages**.
- **Radiation necrosis** of the larynx failing to medical management.
- **Chronic aspiration** from glottic incompetence which makes the patient not a suitable candidate to conservative treatment.
- Advanced **thyroid cancer** with larynx invasion.

3.4.2- ROLE OF RECONSTRUCTIVE SURGERY AFTER TOTAL LARYNGECTOMY

Once the tumour has been removed along with the entire larynx, the pharynx must be closed. For its primary closure, the pharyngeal mucosa must measure at least **2.5 cm** on its longitudinal diameter (37), but achieving this volume of mucosa is not possible in the resection of LA hypopharynx tumours. In the case of LA larynx tumours, most of them require a partial pharyngectomy in order to achieve free-disease margins, especially in those tumours that have extended near the cricopharynx or into de retrochricoid area. In all these situations, additional tissue is needed to close the pharynx correctly (38).

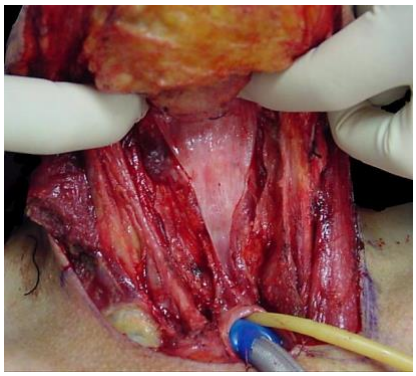

Figure 6. Insufficient pharyngeal mucosa for primary pharynx closure (37).

The main reconstructive options to provide additional tissue to the deficient mucosa include **regional muscular flaps** such as the Pectoralis Major one, or **micro-vascularised free fasciocutaneous flaps** such as the RFFF or ALT flap. The great advantage of reconstructing by means of flaps is that they can be used both to **increase** the pharyngeal surface by placing the flap as a patch and to **replace** completely the pharynx when it has had to be completely resected, since some of the flaps can be tabularized (38).

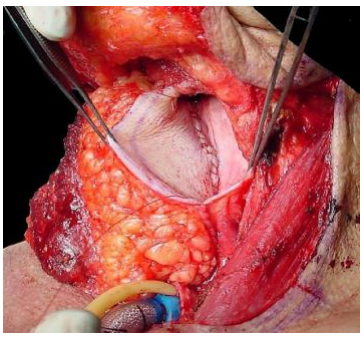

Figure 7. PMMF used for pharynx augmentation (37).

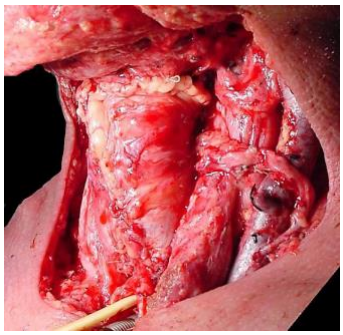

Figure 8. Tubularized ALT flap (37).

In addition, flaps can be also used as a solution to post-surgical defects such as tracheoesophageal fistula, a complication in which the PMMF has had a great impact on its resolution (39,40). Its use is so good in these situations that there are cases in patients with a high risk of fistula in which is considered the use of the PMMF in a prophylactic way (41).

There is no evidence that any flap is better than another in terms of voice quality, as studies have only been conducted comparing the different flaps according to patients' sequelae and complications. It has been found that free flaps, even involving a more complex surgical technique and a longer surgical time, do not lead to major complications in the patient, so it is safe to use them if there are no contraindications (42,43). Because of this situation, the reconstruction technique that is currently chosen depends above all on the comfort, skill and preference of the surgical team with each one of them (38).

3.4.3- MAIN COMPLICATIONS

EARLY COMPLICATIONS

Early complications are those that usually occur during the patient's postoperative hospitalization.

- Drain Failure

If it occurs, it is usually due to a leak in the pharynx or the skin and the stoma closure that needs to be closed.

- Hematoma

A rare but serious complication because of the possibility that the hematoma has to separate the repaired pharynx and to compress the upper trachea. It must be resolved in the operating room, evacuating the hematoma and controlling the bleeding if it exists. New drains must be inserted (30).

- Pharyngocutaneous fistula

Pharyngocutaneous fistula, defined as the leaking of saliva outside the pharynx, is an important complication that can occur between the first and the sixth week postoperatively. It is considered **the most frequent complication after a TL**, since it has been found to occur in almost 29% of all patients who undergo a salvage TL (44). Patients with poor preoperative nutritional status, positive surgical margins and those with diabetes are at higher risk for fistula development (30).

Initial management is made by regular, antiseptic gauze fistula-track packing, pressure dressings and antibiotic therapy while the patient's oral diet is completely suspended. This conservative therapy allows the fistula to close from the inside toward the skin.

If these measures are not enough to close the fistula, an excellent option for its closure is a pedicled muscle flap, such as pectorals major flap (40,41).

- Wound dehiscence

It can be caused by a tensioned skin closure, postradiation state, wound infection, fistula or ischemic flaps. For its treatment, it should be enough with local wound care for healing by secondary intention. In some cases, especially if the carotid becomes exposed, a vascularized muscle flap coverage can be indicated (30).

LATE COMPLICATIONS

- Stomal stenosis

A very annoying complication for the rehabilitation of the patient which fortunately is not very frequent since it can be avoided with a good surgical technique. If it occurs, it can be resolved in most cases with a small surgical procedure such as the removal of the concentric scar tissue or Z-plasties (30,45).

- Pharyngoesophageal stenosis

A recurrence of the tumour should be suspected in the first place, so it must be excluded by endoscopy. If the lumen is very narrow, it can lead to swallowing and speech production difficulties. In those cases, a dilatation is indicated and, if it is unsuccessful, a flap reconstruction should be practised (30).

- Pharyngoesophageal segment hypotonicity

This is a rare but very serious complication due to its great impact on the patient's quality of life and the impossibility of remedying it. The PE segment loses its tone, causing serious difficulties for the patient's swallowing and phonation abilities.

- Hypothyroidism

Postoperative RT combined with the hemithyroidectomy usually produces a low thyroid status. If it is suspected, a thyroid function test once the treatment is completed should be practised to assess the possible need for medication.

3.5- REHABILITATION AFTER TOTAL LARYNGECTOMY

3.5.1- CONSEQUENCES OF TOTAL LARINGECTOMY

As seen before, total laryngectomy consists of removing the entire larynx and the hyoid bone, resulting in a separate airway from the nose, mouth and oesophagus. In order to keep breathing, a **stoma** is created by suturing the trachea just above the sternal notch (Figure 9).

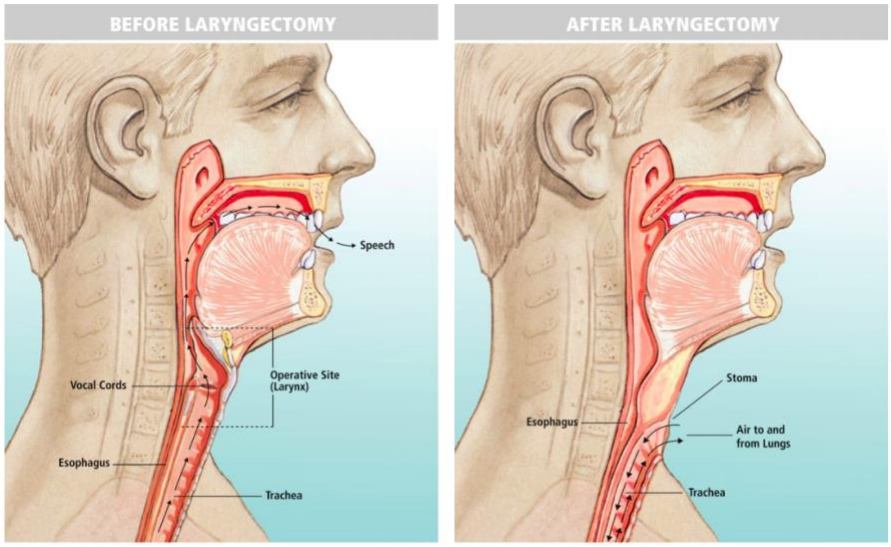

Figure 9. Anatomy before and after total laryngectomy (55).

Respiration through the stroma may lead to a decrease in the breathing resistance, causing a shift of the equal pressure point towards the periphery in the pulmonary tract, which has a negative effect on pulmonary physiology. This translates clinically into **excessive sputum, coughing and forced expectoration**, requiring further cleaning and care of the stroma (46).

As the air no longer circulates through the mouth and nose, the heat moisture exchange mechanism provided is removed, losing all the **warming**, **humidifying**, or **filtering** of the air (46,47). This aerial bypass situation also causes the loss of olfaction, also known as **anosmia** (48).

Swallowing is also altered in patients undergoing total laryngectomy, as the removal of the hyoid bone and the separation of the trachea and oesophagus into independent systems change the normal swallowing sequence (47). One of the main alterations in the physiology of swallowing in these patients is the tongue base interaction with pharyngeal wall, which must overcome the pressure at rest of the pharyngoesophageal segment in order to get the food bolus into the oesophagus (49). Due to this change in physiology, **dysphagia** is expected to be a common manifestation in patients who undergo a TL.

And last but not least, the removal of the larynx causes an obvious **loss of voice**, with a great immediate impact on the quality of life of patients (50). Moreover, losing your voice not only causes you to lose the ability to communicate, but you also lose your personality (51) as it involves the inexpressiveness of emotions such as laugh or weeping (52), causing a huge psychological and emotional impact on the laryngectomized patient.

As a conclusion, there are many affectations in the laryngectomised patient, so rehabilitation for each of these aspects should be started as soon as clinically possible, including phonatory, respiratory, olfactory and deglutition rehabilitation. Adjuvant treatment should not be a limitation to start the rehabilitation, although it may make it difficult (53).

3.5.2- VOICE RESTORATION AND REHABILITATION

For a good understanding of the voice rehabilitation after TL, it is needed to keep in mind the basics of the normal laryngeal voice production and speech. The speech process requires airflow from lungs, a sound source (VC vibration) and a cavity where the sound can be transformed into intelligible speech (mouth, nose, and throat cavities) (48). After a TL there is an obvious change in the natural sound source, as the entire larynx is replaced by a pharyngoesophageal segment. Added to this situation, the previously mentioned disconnection of the airway and the PE segment makes the lungs unable to provide a source of air if an intervention is not made.

In view of this situation, different options have been invented over the years to recover the patient's phonatory capacity. The following ones are the most used worldwide:

OESOPHAGEAL SPEECH

Oesophageal speech is based on the intake of air by swallowing it from the oral and pharyngeal space into the upper oesophagus, which serves as a reservoir. Then, the air is released in a controlled way allowing the pharyngoesophageal segment to vibrate and producing the speech (51).

The main advantages of ES compared to other techniques are its low cost and that no further surgery is required. On the other hand, this phonation technique has several important limitations: First, the intake of air into the oesophagus leads to frequent interruptions in the speech flow and, because of the small air reservoir of the upper oesophagus, the number of syllables that the patient is able to pronounce at the time is very short.

Second, this technique is difficult to master, so, in the course of various studies, it has been found that only a third of laryngectomized patients are able to use ES with a satisfactory communication and only 10% are able to speak clearly (49,51).

ELECTRONIC LARYNX

This method consists in generating the vibration with an external, hand held, battery-operated vibrator called electrolarynx, which is placed under the chin (54) (Figure 10). In this way, the vibration generated by the device reaches the throat and mouth. The user can modify the sound with his or her mouth to generate the speech (49) and, as the lungs are not used to produce a sound source, there is no need to exhale during the voice production (55).

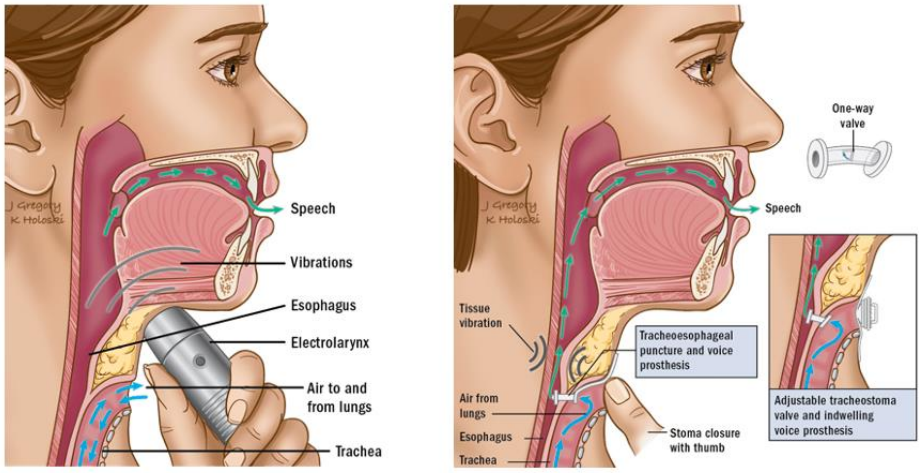

Figure 10. Electrolarynx (left) and voice prosthesis (right) (54).

The result of this method is a voice with an artificial sound that relies always on an expensive external device, so its use has been restricted to the patients who have been recently laryngectomized and are still hospitalized or those who are unable to learn oesophageal speech and cannot use a voice prosthesis (51).

VOICE PROSTHESIS

The speech through a voice prosthesis is considered the gold standard for voice restoration after TL as it an easy-to-learn speech method that has been associated with the best speech quality compared to other speech rehabilitation methods (49,56,57).

Tracheoesophageal speech consists of exhaling pulmonary air that can circulate from the trachea to the oesophagus through a small silicone voice prosthesis inserted which connects these two. The VP inserted has a one-way valve at the end on the oesophagus side, allowing the air to go into the oesophagus and avoiding swallowed liquids to reach the trachea and lungs (48,49,58).

In order to place the voice prosthesis, it is necessary for the surgeon to make a puncture in the back of the stoma that goes from the back of the trachea to the anterior wall of the oesophagus. This TEP can be performed during the same time of the TL (primary puncture) or after healing from the surgery has occurred (secondary puncture). Both methods have proven to be safe and reliable, with a significant rate of successful voice restoration and similar complication rates, although in some studies have found higher rates of pharyngocutaneous fistula in primary TE punctions (49,59).

Speaking is possible by occluding the stoma with a finger and exhaling, which allows the lung air exhaled to move through the prosthesis into the oesophagus, causing the pharyngeal walls to vibrate (See figure 10). These vibrations are used by the mouth to create the sounds of speech (47).

One of the greatest advantages provided by the VP is the facility with which people can speak again, even in patients with a complex pharyngeal reconstruction (49), since in most cases patients can begin to speak a few words on the same day that the prosthesis is fitted and they recover oral communication in less than two weeks (48), achieving the bests results in speech intelligibility in six months to a year.

3.5.3- SWALLOWING REHABILITATION

Dysphagia occurs as a physical process to the changes in normal swallowing mechanism produced due to the change of the anatomical structures after the total laryngectomy. To prevent it for occurring, a good surgical technique must be performed and possible complications such as oesophageal stenosis must be treated early (49).

The diet of the laryngectomised patient is adapted over time, so that the patient becomes used to swallowing little by little. The patients feeding during the first days is exclusive through a nasogastric tube and food is gradually incorporated into the oral diet while de wound is healing (60). Swallowing liquids is often the most complicated part of the early rehabilitation.

3.5.4- PULMONARY AND OLFACTION REHABILITATION

As explained before, the loss of the nasal functions of air humidification, filtration and warming causes, among other things, a mucus overproduction. To avoid this situation, a **heat and moisture exchanger** is used. It consists of a small filter contained in a cassette which is attached in front of the stroma and works as an artificial nose (47).

The use of HME has shown a clear benefit in reducing pulmonary symptoms and improving lung function, and should be used as soon as possible following TL, since it improves both short and long-term compliance (47,48).

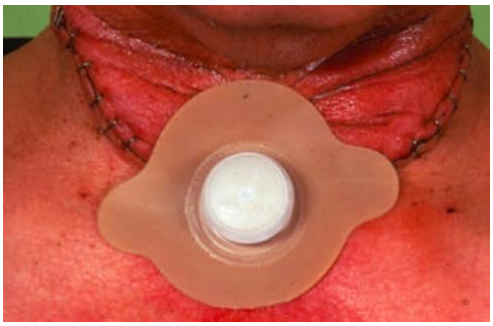

Figure 11. Early postoperative application of HME using an adhesive (48).

The loss of airflow through the nose also causes anosmia, as odour molecules no longer passively reach the olfactory epithelium. There are some techniques to try to improve nasal airflow like the NAIM (**nasal airflow inducing manoeuvre**), which consists of inducing a rapid increase in volume in the oral cavity while the lips are closed, resulting into an airflow through the nasal cavity. By repeating this manoeuvre quickly, a pumping effect is created and an enough airflow through the nose is restored to be able to smell again (48).

4. JUSTIFICATION

Larynx cancer is the second most frequent cancer of the aerial tract and the most common cancer between all the head and neck ones. Some of these are diagnosed in early stages, as it usually happens with glottic tumours, but there is a huge part of larynx cancers that are not diagnosed until they are already in a locally advanced stage, as it is often seen with supraglottic ones, which also turns out to be the most frequent location of larynx cancer in some Mediterranean countries like Spain.

Although several attempts have been made in recent years to find some alternative therapeutical options, total laryngectomy remains a crucial pilar in the management of larynx and hypopharynx LA carcinoma in spite of being a radical procedure with a great psychosocial and emotional impact on the patient. By losing the voice, the patient not only misses the ability to communicate through words, but also a very important source of the person's identity and personality is lost; and this, as expected, has a huge impact on the patient's quality of life.

A large number of TLs indicated for locally advanced laryngeal carcinoma and almost all TLs indicated for LA hypopharyngeal tumours need to be completed with a partial pharyngectomy in order to ensure disease-free surgical margins. Therefore, a subsequent flap is necessary to reconstruct the pharynx, as a primary closure of the pharynx is not possible when such a large part of the pharyngeal wall has been removed. This is a very important step, as the pharynx plays a crucial role in the patient's rehabilitation, both in swallowing and voice restoration.

For this reason, it is of utmost importance to perfect reconstructive surgical techniques in order to achieve optimum results in oncology with the least possible impact on patient's quality of life, a fundamental objective that should always be pursued in the medicine of our times.

The most commonly used reconstructive surgeries for the pharynx are the pediculated flap of the Pectoralis Major muscle, the radial forearm fasciocutaneous free flap and the anterolateral thigh fasciocutaneous free flap. These are all capable of producing a functional voice in patients who use a voice prosthesis and it has been shown in several studies that they are all equally safe as they have similar complication rates; but so far, to our knowledge, no clinical trial has ever been designed to compare and evaluate the quality and functionality of the laryngectomised patient's voice according to the surgical flap technique with which his or her pharynx has been reconstructed, so the flap to be used is currently chosen in accordance with the preferences and comforts of the surgical team.

Therefore, the aim of this study is to find evidence that muscle flaps produce a better quality and functionality voice than the fasciocutaneous ones, in order to have the PMMF as a reference flap which could be used in all reconstructions where it is possible, leaving the free fasciocutaneous flaps relieved to a second line use when the PMMF is contraindicated or when it has failed, as they would have the same complications rate but would be worse in terms of voice quality and functionality. In this way, we would face the reconstruction of the oncological surgery towards the objective of giving to the patient the best subsequent quality of life possible.

5. HYPOTHESIS

The muscular flaps used for the pharyngeal wall reconstruction after a total laryngectomy produce a better quality and functionality voice with a similar rate of complications than fasciocutaneous flaps.

6. OBJECTIVES

6.1- PRIMARY OBJECTIVE

To evaluate the voice functionality and quality in patients who undergo a total laryngectomy and require a pharynx reconstruction due to a locally advanced squamous cell carcinoma of the larynx or hypopharynx, comparing three different surgical techniques of pharynx reconstruction: Pectoralis Major myocutaneous flap, anterolateral thigh fasciocutaneous free flap and radial forearm fasciocutaneous free flap.

6.2- SECONDARY OBJECTIVES

1. To analyse the acute complications rate: pharyngocutaneous fistula and wound dehiscence.
2. To analyse the late complications rate: stomal and pharyngoesophageal stenosis.
3. To determine the time to reintroduce oral feeding.
4. To assess the presence of dysphagia rate once oral feeding has been restarted.

7. METHODOLOGY

7.1- STUDY DESIGN

This study will be carried out through a prospective, randomized, open-labelled clinical trial. Each patient will be randomly assigned to one of the following three groups:

- Group A: The patient will be treated with a TL and then the pharyngeal wall will be reconstructed with a Pectoralis major myocutaneous flap (PMMF).
- Group B: The patient will be treated with a TL and then the pharyngeal wall will be reconstructed with a radial forearm fasciocutaneous free flap (RFFF).
- Group C: The patient will be treated with a TL and then the pharyngeal wall will be reconstructed with an anterolateral thigh fasciocutaneous free flap (ALT).

Is spite of the fact that three independent intervention techniques will be performed, these will be classified into two groups according to the type of flap tissue used in order to carry out the statistical analysis:

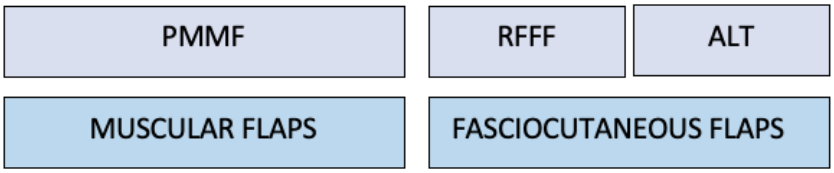

Figure 12. Study design, differentiating the three intervention groups with the two groups to be analysed.

All patients will be followed up during 16 months since the intervention.

7.2- STUDY SETTING

This will be a multicentre study in which a total of 5 Catalan tertiary hospitals will participate, which are all part of the national public health system:

- *Hospital Universitari Doctor Josep Trueta*, Girona.
- *Hospital Joan XXIII*, Tarragona
- *Hospital Universitari de Bellvitge*, L'Hospitalet de Llobregat.
- *Hospital de la Santa Creu i Sant Pau*, Barcelona.
- *Hospital de Germans Trias i Pujol*, Badalona.

The reference centre in this trial will be *Hospital Universitari Doctor Josep Trueta de Girona*. One researcher will be assigned as the representant and coordinator from each of the five hospitals in order to obtain a good communication and coordination between all of them.

7.3- POPULATION OF STUDY

The population of this study will include all the people who have as reference centre any of the hospitals participating in the study, which is estimated to be approximately 3.404.000 people.

- *Hospital Universitari Doctor Josep Trueta*, Girona: 800.000 inhabitants of reference.
- *Hospital Joan XXIII*, Tarragona: 1.200.000 inhabitants of reference.
- *Hospital Universitari de Bellvitge*, L'Hospitalet de Llobregat: 201.192 inhabitants of reference.
- *Hospital de la Santa Creu i Sant Pau*, Barcelona: 403.047 inhabitants of reference.
- *Hospital de Germans Trias i Pujol*, Badalona: 800.000 inhabitants of reference.

7.4- STUDY SUBJECTS

The study subjects will include patients diagnosed with larynx or hypopharynx locally advanced SCC treated with a total laryngectomy who require a reconstruction of the pharyngeal wall by using a flap.

The target of population will only include new diagnoses who have not been treated yet since the beginning of the study, so there will not be previous data collection.

7.4.1- INCLUSION CRITERIA

- Patients diagnosed with one of the following cancers:
  - Larynx SCC staged as T4a N0-1-2 M0.
  - Larynx SCC staged as a T3 N0-1-2 M0 in which significant pharyngeal removal is required to ensure free margins due to the size and localization of the tumour.
  - Hypopharynx SCC staged as T3-T4a N0-1-2 M0.
- Patients who are able to understand and answer the questionnaires by themselves.
- Patients who have signed the informed consent form.

7.4.2- EXCLUSION CRITERIA

- Patients not able to undergo surgery due to anaesthetic risk.
- Patients with an ASA score IV or higher (*Annex 2*)
- Patients classified as fragile according to psychological and functional status questionnaires (*Annex 3*).
- Patients with an unresectable tumour (Stage IVB).
- Disseminated disease (M1).
- Patients with prior neck irradiation.

- Patients in whom the adjuvant treatment cannot be completed within 3 months following the surgery.
- Patients with poor family and psychosocial support.
- Patients not able to understand and answer the questionnaires.
- Patients with any psychiatric or cognitive disorder that would limit the compromise compliance with the requirements of this protocol.
- Patients with possible great difficulty in attending the clinical controls.
- Congenital absence of pectoralis muscle (Poland's syndrome).
- Patients with prior chest wall trauma and/or prior chest wall surgery (mastectomy, breast implants, subclavian lines, cardiac pacemaker…) who have absented, scarred or poorly vascularized Pectoralis Major muscle.
- History of irreversible coagulopathy resulting into a hypercoagulable state.
- Severe peripheral vascular disease.
- Inadequate collateral blood flow to the hand via the ulnar artery.
- Prior surgical or traumatic injury to both radial arteries.
- Morbid obesity, due to unacceptable flap bulk.

7.4.3- WITHDRAWAL CRITERIA

Every effort should be made within the bounds of safety and patient choice to have all the participants to complete the study.

Patients who agree to participate in the study should be followed up according to the study's protocol unless there is a compelling reason for the patient to withdraw from the study. Reasons for patient removal from the study follow-up include:

- Request of the patient.
- Patients in whom the adjuvant treatment cannot be completed before 3 months following the surgery due to major comorbidity after surgery.
- Severe complications resulting from surgery that does not allow the patient to continue in the trial (*See 7.8-Safety*).
- Patients lost to follow-up. A patient should be considered lost to follow up only after the failure of the patient to attend scheduled visits and multiple efforts have been made to contact the patient without success.

All patients lost from the study should be noted with their documents along with the reason of withdrawal.

As the study includes patients through a consecutive sampling, it is possible to replace them during the recruitment period in order to recruit enough sample for the study.

7.5- SAMPLING

7.5.1- SAMPLE SELECTION

A non-probabilistic consecutive method will be carried out, involving all patients meeting the inclusion criteria who are treated in the hospitals participating in this study.

7.5.2- SAMPLE SIZE

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, **a total of 60 subjects** is necessary to detect as statistically significant a minimum difference of 18 units in the VHI-30 score *(See annex 4*) between the group of patients reconstructed with a muscle flap and the group of patients reconstructed with a fasciocutaneous flap. The 60 subjects will be distributed into these two groups in a 1:1 ratio.

The common deviation is assumed to be 20 based on the results of various studies, adapting these findings to our trial according to the criteria of experts in the subject (56,58,61,62). A 20% drop-out rate has been anticipated.

7.5.3- ESTIMATED TIME OF RECRUTIMENT

Based on the reference population of this study (*see 7.3- Population of study*) and the incidence of the diseases to be treated, we estimate that it will take 2 years to recruit the necessary 60 patients to complete the trial.

7.5.4- RANDOMIZATION METHODS

Once the patient recruited has undergone all the necessary examinations to rule out the exclusion criteria, he or she will be assigned to one of the 3 groups of intervention randomly. This randomization will be generated by nQuery Advisor 7.0 (Statistical Solutions Ltd., Cork, Ireland). All patient's data will be confidentially maintained by assigning every patient an identification number which will be generated automatically by the software.

7.5.5- MASKING TECHNIQUES

Usually, patients involved in clinical trials don't know which procedure is made to them and neither the professional who treats the patient knows what treatment the patient is undergoing. Unfortunately, as this is a surgical clinical trial, this blinding is not possible.

In order to reduce the possible bias, the statistical expert in charge of evaluating the procedure results will be blinded, not knowing which reconstruction technique has every patient undergone.

7.6- STUDY VARIABLES

7.6.1- INDEPENDENT VARIABLE

There is one independent variable in this study: the **surgical pharynx reconstruction**. This variable is divided into three categories according to the surgical technique performed:

1. Pediculated Pectoralis Major myocutaneous flap.
2. Radial forearm fasciocutaneous free flap.
3. Anterolateral thigh fasciocutaneous free flap.

At the same time, the three surgical techniques are grouped according to whether the flap is made of muscle (PMMF) or fascia (RFFF and ALT) for the sake of statistical analyses.

7.6.2- OUTCOME VARIABLES

MAIN OUTCOME

According to the main objective of measuring the quality and functionality of the voice, a self-assessment scale questionnaire named **Voice Handicap Index-30** will be used *(Annex 4).*

VHI-30 is one of the most used voice questionnaires world-wide (58,61,63–65), as it is validated by both laryngeal and alaryngeal voice, being capable of assessing the quality and functionality of the voice by asking about 3 domains: functional, physical and emotional (66,67). The questionnaire consists of 10 items per domain, and patients rate the perception they have of their voice about each item from 0 (never) to 4 (always), giving a possible total score of 120 (68). As it is a numbered scale, the variable is considered quantitative discrete.

Values above 60 indicate severe disability, between 30 and 60 moderate disability and less than 30 mild to no disability (66).

VHI-30 is a questionnaire widely used all over the world, so it has the great advantage of having been validated in many languages, including Spanish (69).

SECONDARY OUTCOMES

- Acute complications rate (Qualitative dichotomous variables categorised as yes or no):
    - **Pharyngocutaneous fistula rate**: measured by the direct visualisation of saliva and/or water leaking outside the pharynx through a defect in the pharyngeal mucosa lining. It shall subsequently be objectively confirmed by a methylene blue swallowing test or a Gastografin® swallow radiography.
    - **Wound dehiscence rate:** Visualization of the wound healing failure, causing a partial or total separation of the previously approximated wound edges.

- Late complications rate (Qualitative dichotomous variables categorised as yes or no):
  - **Stomal stenosis rate**: measured by clinical presentation and exploration.
  - **Pharyngoesophageal stenosis rate**: measured by clinical presentation and exploration with the addition of direct visualisation by video-endoscopy or scan.
- **Time** to reintroduce oral feeding: determined by the days required to begin enteral nutrition since the surgery (quantitative discrete variable, measured by days).
- Presence of **dysphagia** after reintroducing oral feeding (qualitative dichotomous variable categorised as yes or no): determined by swallowing video endoscopy if the patient refers dysphagia symptoms. It will be considered that dysphagia is the presence of food's residue remaining in the mouth or pharynx structures.

7.6.3- COVARIABLES

The covariables are those factors that can influence the relation between the independent and the dependent variable, so it is important to take them into account in order to see if they have any effect on the results. All covariables will be measured through the data collection sheet *(Annex 5).*

	VARIABLE	DESCRIPTION	MEASURMENT	CATEGORIES
COVARIABLES	Gender	Qualitative nominal dichotomous	Self-refereed	Male / Female
	Age	Quantitative discrete	Self-refereed	≤70 years old >70 years old
	Socioeconomic status	Qualitative ordinal	Education level and occupation	Class I to V (70)
	Ethnicity	Qualitative nominal non-dichotomous	Self-refereed	- Caucasian - African - Asian - Latin-American - Other
	Adjuvant chemotherapy	Qualitative nominal dichotomous	Adjuvant chemotherapy indications	Yes / No

Table 4. Covariables assigned in the trial.

7.7- INTERVENTION

Once the TL has been carried out it is necessary to reconstruct the pharynx in the same surgical act according to the technique assigned to the patient, dividing the procedure into three possible different groups:

GROUP A (n=30)

The reconstruction using the PMMF is carried out by following the next steps (71–74):

1. Surface markings of the vascular pedicle
    - Two lines must be drawn to find the vascular pedicle. The first one goes from the shoulder to the xiphoid apophysis. The second will be a vertical one starting from the mid-clavicle in the direction of crossing the first line (Figure 13).

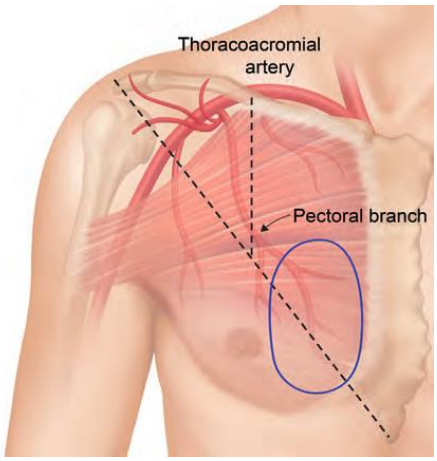

Figure 13. PM pedicle location and surface markings (74).

2. Skin paddle design and elevation of skin paddle
    - To ensure an adequate pedicle's length, it has to be measured that the distance between the top of the skin paddle and the inferior edge of the clavicle is at least as long as the distance between the recipient site for the flap and the inferior edge of the clavicle. After confirming the measures, the skin paddle is drawn.
    - Two incisions must be done. A first incision is made around the skin paddle and another one is made from the peripheral margin of the skin paddle along the anterior axillary fold following the drawn line. Then the paddle's dissection is extended to the surface of the PMM (Figure 14).
    - The skin paddle must be tracked to the underlying muscle to avoid damaging the myocutaneous perforators.

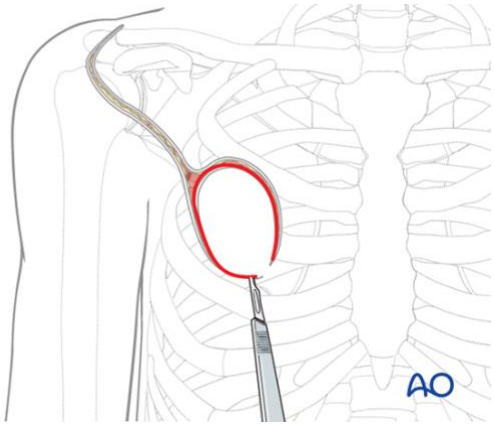

Figure 14. Both skin incisions (73).

3. Exposure of pectoralis major muscle

    - With the dissection extended to the muscle, the skin and breast tissue above the skin paddle is elevated from the PM up to the clavicle with a skin hook, exposing the Pectoralis major muscle (Figure 15).

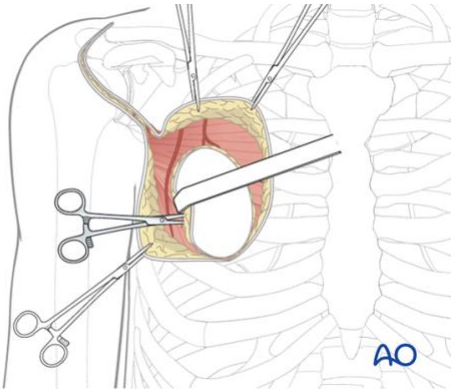

Figure 15. Pectoralis major exposure and raising (73).

4. Elevation of the pedicle

    - Using a cautery, the Pectoralis major muscle is incised medially and inferiorly to the skin paddle and it is dissected from the ribs, the intercostal muscles and the sternum. It is very important to not divide the muscle superiorly to the skin paddle since It could divide the vascular pedicle (Figure 15).
    - By dissecting through the lateral border of the Pectoralis major muscle you can find the dissection plane between the pectoralis minor and major muscles and the vascular pedicle. Once this plane has been totally identified, the PM and its pedicle can be easily freed by stripping with a finger towards the clavicle (Figure 16).

- Once the PM is totally free, the pedicle can be seen inside the muscle fascia on its deep surface. While keeping in view the pedicle in order to avoid injuring it, the branches from the lateral thoracic artery and the branches of the medial pectoral nerve, which enter into the deep surface of the flap, are divided (Figure 17).

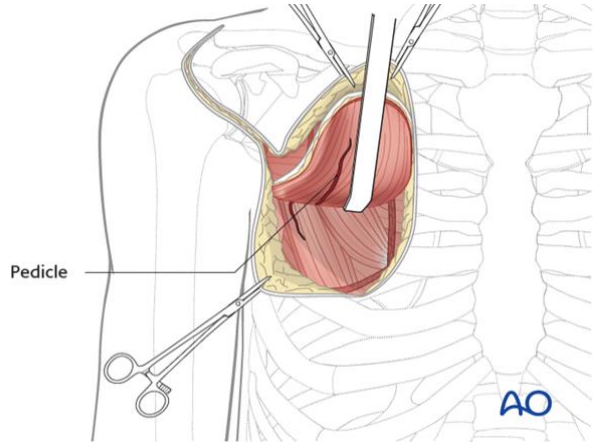

Figure 16. PM pedicle visualization in the plane between both pectoralis muscles (73).

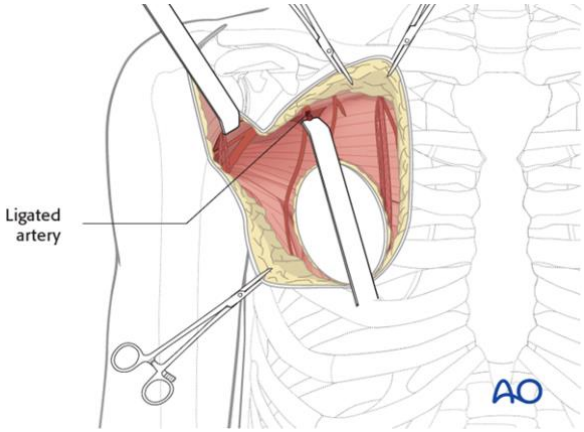

Figure 17. Lateral thoracic artery ligation (73).

5. Skin tunnel over the clavicle

- The flap is passed into the neck through a subcutaneous tunnel superficial to the clavicle (Figure 18). This tunnel must be wide enough to allow the delivery of the flap without strangling the vascular pedicle.
- A scalpel can be used to divide the subdermal connective tissue fibres of the skin above the tunnel to gain some additional space. The flap has to pass to the neck without being twisted.

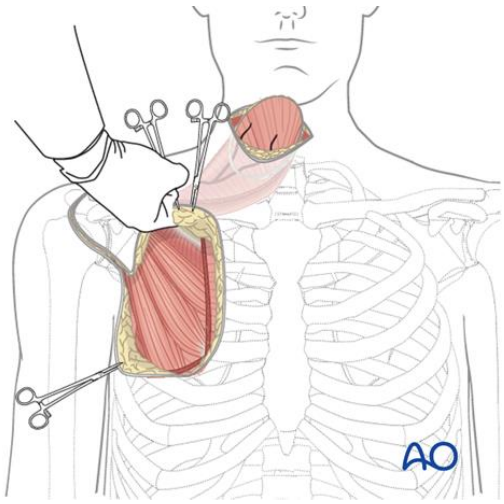

Figure 18. Pedicle passing through the subcutaneous tunnel (73).

6. Placement of the flap at the recipient site
    - The pharynx is closed with the muscle of the flap.
    - The flap' skin is used to close the surface defect of the neck

7. Closure of the donor site defect
    - The donor site can be closed primarily in layers. Use absorbable sutures for deep dermis and staples for skin.
    - Before full closure, one or two large drains are inserted.

GROUP B (n=15)

In this group, two surgical teams must work simultaneously: while one team performs the total laryngectomy, the other group prepares the lifting of the radial forearm flap.

The reconstruction using the RFFF is carried out by following these steps (75–78):

1. Arm selection and preparation
    - In case both arms are good potential donors of the flap, it is preferable to have the operating arm table on the opposite side to the resection surgeons in order to create enough space for both teams. The patient's preference will also be taken into account.
    - The arm must be placed on an arm table, avoiding hyperextension or hyperabduction of the shoulder.
    - Shave the arm.
    - Apply a tourniquet to the upper arm. The arm has to be raised and then the tourniquet is inflated, setting the pressure at 250mmHg. The ischemic time must be recorded from this moment.
2. Surface markings (Figure 19)
    - Palpate and mark the radial artery at the wrist (between *brachioradialis* and *flexor carpi radialis* tendons) and proximally (marking its path to the medial ulnar fossa).
    - Draw the superficial veins in the medial and lateral forearm.
    - Mark the flap design on the forearm, which will be carried out centred above the radial artery. Its design has to include the lateral intermuscular septum and a superficial vein (cephalic vein in most cases).

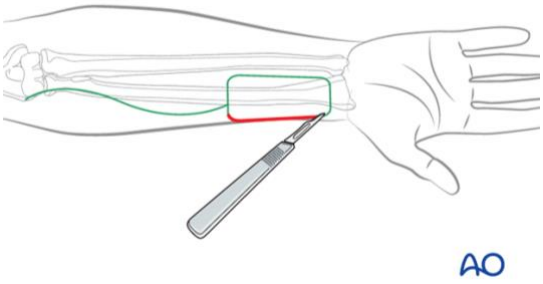

Figure 19. Flap design and scalpel skin incision following the lines, starting laterally (78).

3.2- Lateral and proximal elevation

- The flap is elevated with a scalpel from the lateral in a deep subcutaneous plane until you can see the cephalic vein lying into the subcutaneous fat (Figure 20). The cephalic vein has to be elevated and skeletonised proximally to the flap. Later it has to be separated without its surrounding soft tissue.
- Next to the cephalic vein you can see the lateral antebrachial cutaneous nerve. There is no need to elevate it as the planned flap is not innervated.

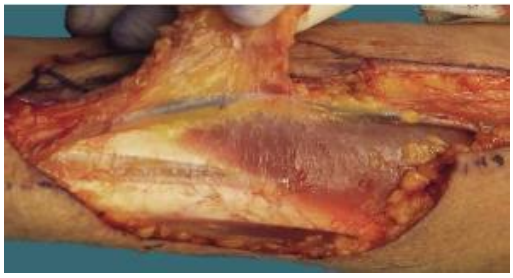

Figure 20. Cephalic vein exposure in deep subcutaneous plain (75).

- Elevate the lateral flap's aspect in a subfascial plane above the extensor and abductor tendons. At this point, the superficial branch of the radial nerve should be identified medial to the *extensor pollicis brevis* and *abductor pollicis longus* muscles and lateral to the *brachioradialis* muscle. Extend this dissection medially above the epitenon covering the tendons and the radial nerve until you can see the flat tendon of the *brachioradialis* muscle (Figure 21).
- Continue the dissection over the *brachioradialis* tendon until its sharp medial edge. Then, the assistant must retract the *brachioradialis* muscle from the radial site of the arm with skin hooks while the main surgeon releases the medial edge of the muscle off the underlying lateral intermuscular septum using a sharp dissection.

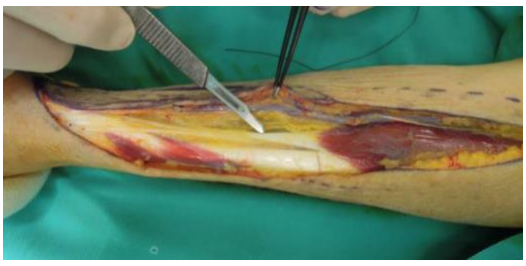

Figure 21. Scalpel pointing the brachioradialis tendon (75).

- To find the radial artery, which lies just below the *brachioradialis* tendon, dissect and elevate the tendon superiorly until its musculotendinous junction (Figure 22). At this point, change the scalpel blade angle to a horizontal plane to cut along the under surface of the tendon. Be careful you do not damage the perforators arteries around the tendon's medial edge during this step.
- With the medial edge retracted, release the muscle fascia laterally to the vascular pedicle. It will leave the brachioradialis muscle fully mobilised, allowing you to see the full length of the radial artery (Figure 23). Ligate and divide the larger muscle perforators with clips and coagulate the small ones with the bipolar forceps.

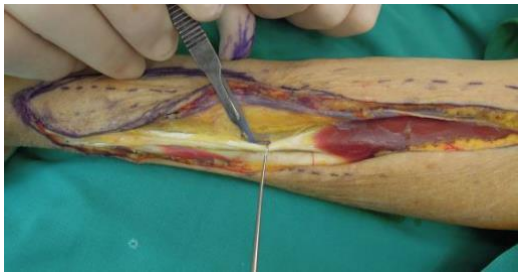

Figure 22. Brachioradialis tendon dissection (75).

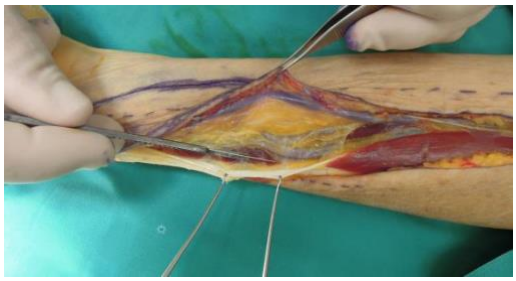

Figure 23. Radial artery exposure after brachioradialis muscle mobilisation (75).

3.3- Medial and distal elevation

- Next step is to elevate the medial side of the flap. This will be done by cutting the epimysium covering the wrist flexor muscles with a scalpel and elevating the deep fascia over the tendons preserving, as it has been done before, the epitenon covering the tendons (Figure 24). Then, incise the fascia over the radial artery and isolate, ligate and cut the radial artery and its *venae comitantes* (Figure 25).
- Proceed with the dissection in a distal to proximal direction. Divide the side-branches of the radial artery until a good vessel length is achieved to reach the recipient vessels in the neck (Figure 26).

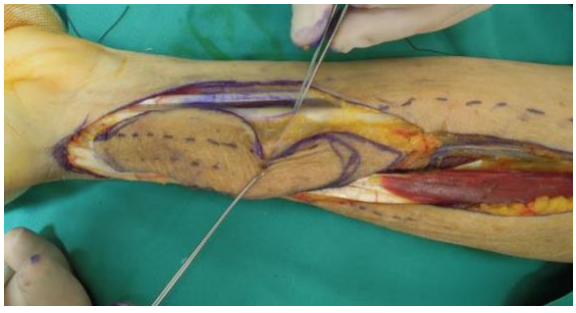

Figure 24. Deep fascia elevation over the tendons (75).

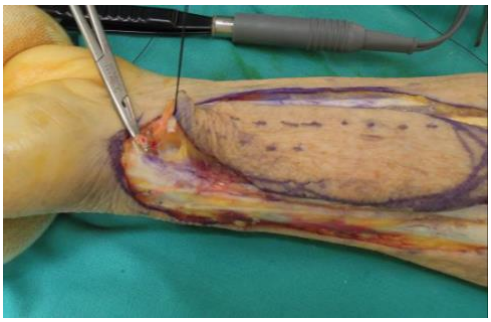

Figure 25. Radial artery divided (75).

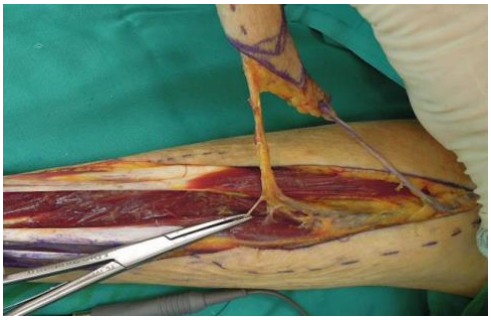

Figure 26. Side branches of the radial artery being divided reaching a good artery length (75).

3. Preparation of the donor site pedicle

- Apply topical lignocaine to the perforator pedicle continuously.
- Keep veins intact until you decide what vessels are going to be used for the anastomosis. Once the decision is made, ligate all the other veins. The cephalic vein can be divided at any point of its course, but it is typically dissected at the level of the ulnar cavity.
- Separate carefully the vein and artery from each other to allow both anastomoses to be placed at some distance from each other if needed.
- Mark the anterior edge of the pedicle with ink.
- Deflate the tourniquet. While waiting for the reperfusion of the flap vasculature, the surgeon prepares the recipient vessels in the neck. Meanwhile, leave the flap attached by its vascular pedicle.

4. Preparation of the recipient site

- The recipient artery is selected according to the size. The most commonly used is the facial artery.
    - Place a micro clap proximally on the artery.
    - Divide the artery with micro-scissors.
    - Remove excess adventitia.

- Irrigate the lumen with heparin/saline solution. Then inspect the lumen artery and remove fibrin (if found) with a micro forceps.
- Dilate the arterial lumen with the rounded tip of a micro needle holder.
- Irrigate again the arterial lumen with the solution.

- The venous anastomosis is performed by preparing the internal jugular vein.
  - Select the segment of vein you will use for the anastomosis.
  - Separate any remaining adventitia over the vein using hydro dissection with a heparin/saline solution. Then remove this adventitial layer with micro scissors.

5. Placement of the flap at the recipient site

- Once the recipient vessels are prepared, divide and ligate the flap's vascular pedicle.
- Flush the vein and the artery with the heparin/saline solution.
- Suture the flap to neck's mucosa and skin to avoid applying traction to the microvascular anastomoses. Do not suture the entire skin yet.
- Do not rotate de vascular pedicle. You can use the ink mark done before to orientate the pedicle and avoiding twisting it.
- The vessel anastomose should be performed with a continuous suture technique using nylon.
  - The arterial micro-anastomosis is done first. As the diameters of both arteries are similar, an end-to-end anastomosis should be performed.
  - The venous anastomosis is done end-to-side to the internal jugular vein.
- To revascularize the flap, ask the anaesthetist to raise the arterial blood pressure to the normal range and release the vascular clap on the internal jugular vein.
  Check for bleedings from the anastomosis. Later release the clamp on the artery and check for arterial distension or bleedings.
- Once the anastomosis is performed, complete the skin and mucosa flap suture.

6. Forearm closure

- Once the flap is elevated, close the forearm in layers. Use absorbable sutures for deep dermis and staples for skin.
- It may be necessary to use a skin graft in the donor defect.

GROUP C (n=15)

As in group B, two surgical teams must work simultaneously: while one team performs the total laryngectomy, the other group prepares the lifting of the anterolateral thigh flap.

The reconstruction using the ALT flap is carried out by following the next steps (76,77,79,80):

1. Preparation
    - Rotate the leg internally by elevating the ipsilateral hip off the bed.
    - Expose the thigh from the inguinal ligament until below the knee. You must be able to work in the anterior, medial and lateral thigh.
    - Shave the thigh.
2. Tentative flap design: Identify where do the perforators enter the skin.
    - Draw a straight line from the anterior iliac spine to the patella's lateral border and locate its midpoint. Then make a mark 2cm lateral to it (Figure 27). The perforators are usually found in a 3cm radius around this point.
    - Use the Doppler locate the perforators and mark them on the skin (Figure 28).
    - The flap design is going to be based on the location of the perforators, but it can be later modified depending on where they are found during the surgery.

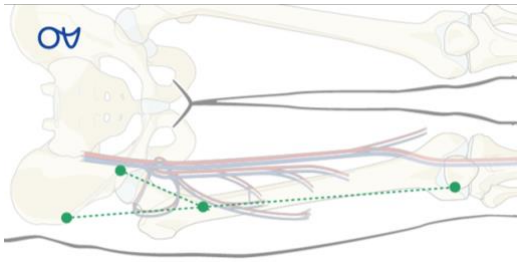

Figure 27. Straight line from the iliac spine to the patella's lateral border and key points to find the perforators (80).

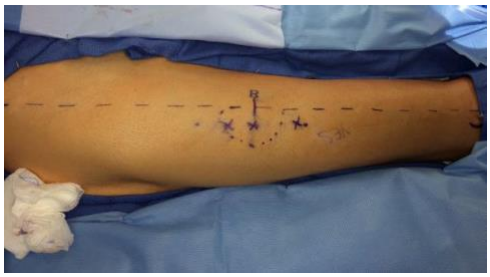

Figure 28. Dopplered mapped perforators (79).

3. Flap dissection
    - Medial elevation:
        - Perform a medial incision with a scalpel and extend the subcutaneous dissection medially (Figure 29). Check for the vessels running laterally before you make an incision of the deep fascia on the *rectus femoris* surface.
        - Extend this incision longitudinally.
    - Perforators localization: Look for the perforators coming out of the thigh and entering the fascia and skin.

- While the assistant elevates the lateral fascia with skin hooks, the main surgeon retracts the muscles medially and incise the fascia above the *rectus femoris*.
- Skeletonise the muscle laterally using a scalpel to find perforators (Figure 30). If you do not find any septocutaneous perforators, divide the fascia above *vastus lateralis* and skeletonise laterally over that muscle.
- You have to look for more perforators proximally, distally and laterally.
- Once you have located all the perforators, and you can be sure that there are no more left, proceed in the pedicle localization.

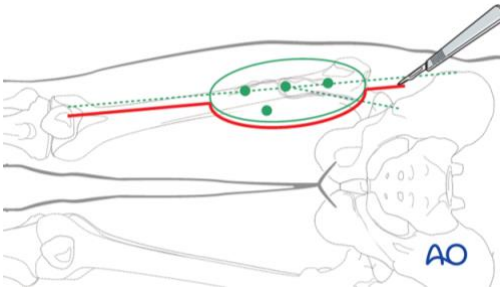

Figure 29. Skin incision following the drawn lines (80).

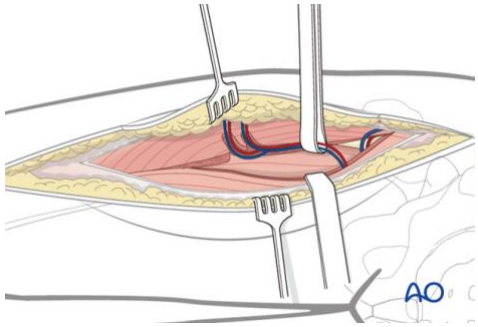

Figure 30. Skeletonization of perforators after retracting the muscle (80).

- Pedicle localization
  - Make an incision of the thin fascia surrounding the *rectus femoris* and open this plane with your finger.
  - Retract the rectus femoris and the sartorius medially. This will allow you to see the pedicle running above the *vastus intermedius*.
- Perforator dissection
  - While the assistant retracts nearby muscles with a skin hook, the main surgeon dissects through the muscle following the perforator until the pedicle is found. This dissection is performed with fine, blunt tipped scissors, staying always on the vessel surface and keeping always in sight the vessel course (Figure 31).
  - Complete this de-roofing with all the perforators.
  - Skeletonise the perforators with great care, from distal to proximal.
  - In case you come across with some small side branches you can use bipolar coagulation on them, keeping always a safe distance from the perforators. On larger branches small clips should be used.

- Vascular pedicle dissection
    - Follow the pedicle proximally until a you find an artery and vein of decent calibre (Figure 32).
    - Keep in mind that there are significant variations in the vascular anatomy, specially of the veins.
    - Using a soft blunt dissection, separate the *fascia lata* from the *vastus lateralis* ubicated lateral to the perforators.

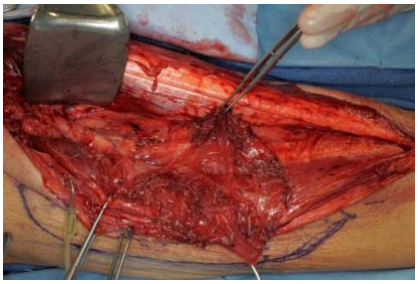

Figure 31. Perforator dissection. It should be done with blunt tipped scissors (79).

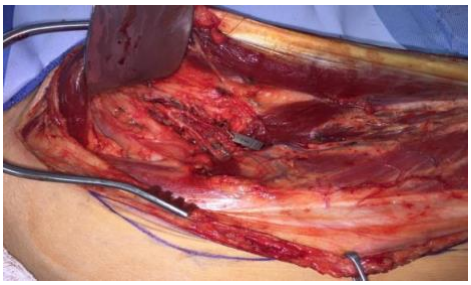

Figure 32. Pedicle exposure (79).

- Lateral incision
    - Make a downward incision from the skin and subcutaneous tissue to the *fascia lata* (Figure 33).
    - Incise the *fascia lata* while you protect the perforators by placing a finger in the tunnel lateral to the perforators.
    - Dissect the inside of the fascia, as no muscle is needed for this reconstruction.
    - Continue the back-dissection while protecting the pedicle.
    - Use staples to secure the flap to the donor site to avoid traction injury to the pedicle while preparing the neck vessels.

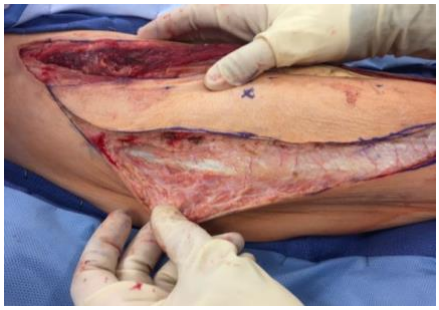

Figure 33. Incision down to fascia lata (79).

4. Preparation of the recipient site

- The recipient artery is selected according to the size. The most commonly used is the facial artery.
    - Place a micro clap proximally on the artery.
    - Divide the artery with micro-scissors
    - Remove excess adventitia.
    - Irrigate the lumen with heparin/saline solution. Then inspect the lumen artery and remove fibrin (If found) with a micro forceps.
    - Dilate the arterial lumen with the rounded tip of a micro needle holder.
    - Irrigate again the arterial lumen with the solution.
- The venous anastomosis is performed by preparing the internal jugular vein.
    - Select the segment of vein you will use for the anastomosis.
    - Separate any remaining adventitia over the vein using hydro dissection with a heparin/saline solution. Then remove this adventitial layer with micro scissors.

5. Flap harvest and thigh closure
    - Once the neck vessels are prepared, ligate the artery and vein with suture ligatures and harvest the ALT flap.
    - Insert a closed suction drain. Then close the leg in layers. Use absorbable sutures for deep dermis and staples for the skin.

6. Placement of the flap at the recipient site

- Flush the vein and the artery with the heparin/saline solution.
- Place the ALT flap on the pharynx and suture it to neck's mucosa and skin to avoid applying traction to the microvascular anastomoses. Do not suture the entire skin yet.
- The vessel anastomose should be performed with a continuous suture technique using an 8/0 nylon suture.
    - The arterial microanoastomosis is done first. As the diameters of both arteries are similar, an end-to-end anastomosis should be performed.
    - The venous anastomosis is done end-to- side to the internal jugular vein.
- To revascularize the flap, ask the anaesthetist to raise the arterial blood pressure to the normal range and release the vascular clap on the internal jugular vein. Check for bleedings from the anastomosis. Later release the clamp on the artery and check for arterial distension or bleedings.

7.8- SAFETY

All the surgical techniques performed in this study have been previously applied and various systematic reviews have proven them to be safe. Even though, they are not exempt from risks.

The main complications of the surgical intervention derive from the total laryngectomy, in which it is worth highlighting due to its possible vital complications: haemorrhage, pneumonia and the possibility of death (1/15.000) (81). It should be noted that death often occurs in patients with other serious medical complications. Other complications of TL are explained in more detail in the section *3.4.3- Main complications.*

As far as flaps are concerned, the main serious complications to be highlighted are cervical hematoma, haemorrhage and vascular flap failure with necrosis, although the most frequent complication is of a mild nature: the incomplete healing of the skin graft placed to cover the donner side in the RFFF, while in ALT and PMMF non-serious complications are very rare.

Shall be considered major surgical complications and therefore **criteria for withdrawal** from the study death of the patient or flap necrosis. These complications should be recorded and reported to the principal investigator.

7.9- DATA COLLECTION

FIRST VISIT

Once the patient has been diagnosed with a locally advanced larynx or hypopharynx SCC, he or she is cited at the ENT consultations to be communicated the definitive diagnosis. This moment is when the doctor has to explain the study.

If the patient agrees to participate in the study, he or she has to sign the informed consent after reading the patient's information document (*Annexes 6 and 7*). Then the doctor will perform an interview, a physical examination and an Allen's test (see figure 34) in order to rule out any disease or pathology included in the exclusion criteria. Allen's test will be considered normal, and therefore that there is an adequate ulnar circulation, if the usual colour returns to the palm in less than 10 seconds (82).

If the patient does not comply with any contraindication to the study, he or she must complete several questionnaires to find out his or her basic functional status and whether he or she is capable of enduring the rehabilitation needed after a total laryngectomy (*Annex 3*).

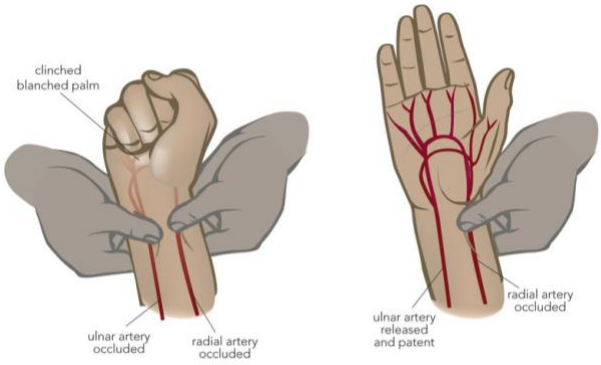

Figure 34. Allen's Test procedure (82).

INTERVENTION AND HOSPITALISATION

- **Anaesthesiology visit**. Before the surgical procedure the patients must be visited by an anaesthesiologist, who will decide if the patient can be operated depending on the patient's risk according to the ASA stages (*Annex 2*).
- **Randomization**. The patients will be randomly assigned to one of the three intervention groups of the study (*See 7.5.4-Randomization*).
- **Intervention**. The patient will be operated following the steps explained previously in section *7.7-Intervention*.
- **Hospitalisation**. All patients must be hospitalized in the otolaryngology unit for at least 15 days. During this stay the patient will be evaluated daily, ruling out acute complications.
  The patient will be fed through a nasogastric tube while the wound in the oesophagus and pharynx heals.
- **Adjuvant treatment**. Patients will be treated with adjuvant radiotherapy ± chemotherapy following the latest treatment guidelines depending on the stage of the tumour and its anatomopathological characteristics (26). Chemotherapy will be necessary in those patients with affected surgical margins around the primary tumour (<1mm) and/or extracapsular invasion of lymph nodes or if deemed necessary by the head and neck committee. In all cases adjuvant treatment will last three months.

CLINICAL FOLLOW-UP

Once the patient is discharged, he or she has to visit the otorhinolaryngologist on several occasions to check on his or her general condition and on the absence of late complications:

- After 7 days: Clinical check-up.
- After 14 days: Clinical check-up.
- After one month: Clinical check-up.
- After 3 months: Clinical and radiological (neck-CT scan) check-up.

VOICE PROSTHESIS INSERTION

If the control at 3 months from the hospital discharge is good, the wound has healed well without presence of pharyngoctuaneous fistula at the time, and no anomalies are seen in the CT such as a very severe stenosis, the patient will be seen the following week to have the voice prosthesis inserted through a **wire-guided balloon catheter puncture technique**. This technique has been chosen even though it is not the standardised one in all the participant hospitals because it has proved to be a minimally invasive option, much safer than other conventional techniques and which greatly reduces the anatomical limitations that other techniques have, such as trismus or bad exposure (83).

In the case that the patient is still not a candidate for TEP due to some altered finding during the 3-month scan, the patient should be re-evaluated in one month.

VOICE EVALUATION

Although with the wire-guided balloon catheter puncture technique most patients start speaking immediately, it may take some time to learn how to phonate well with the prosthesis, so the first voice evaluation will be taken one month later. All the evaluations will be performed by an otorhinolaryngologist and a speech therapist. During the visit the patient must fill in the VHI-30 questionnaire.

Throughout a whole year, a speech therapist, in addition to the otolaryngologist, will carry out regular check-ups with each patient besides the voice functionality check-up visits.

This voice check-up procedure will be repeated three more times:

- 3 months after the TEP placement.
- 6 months after TEP placement.
- 12 months after TEP placement.

These determinations over time will allow us to detect if there is any modification in the voice functionality as the patient adapts to the voice prosthesis.

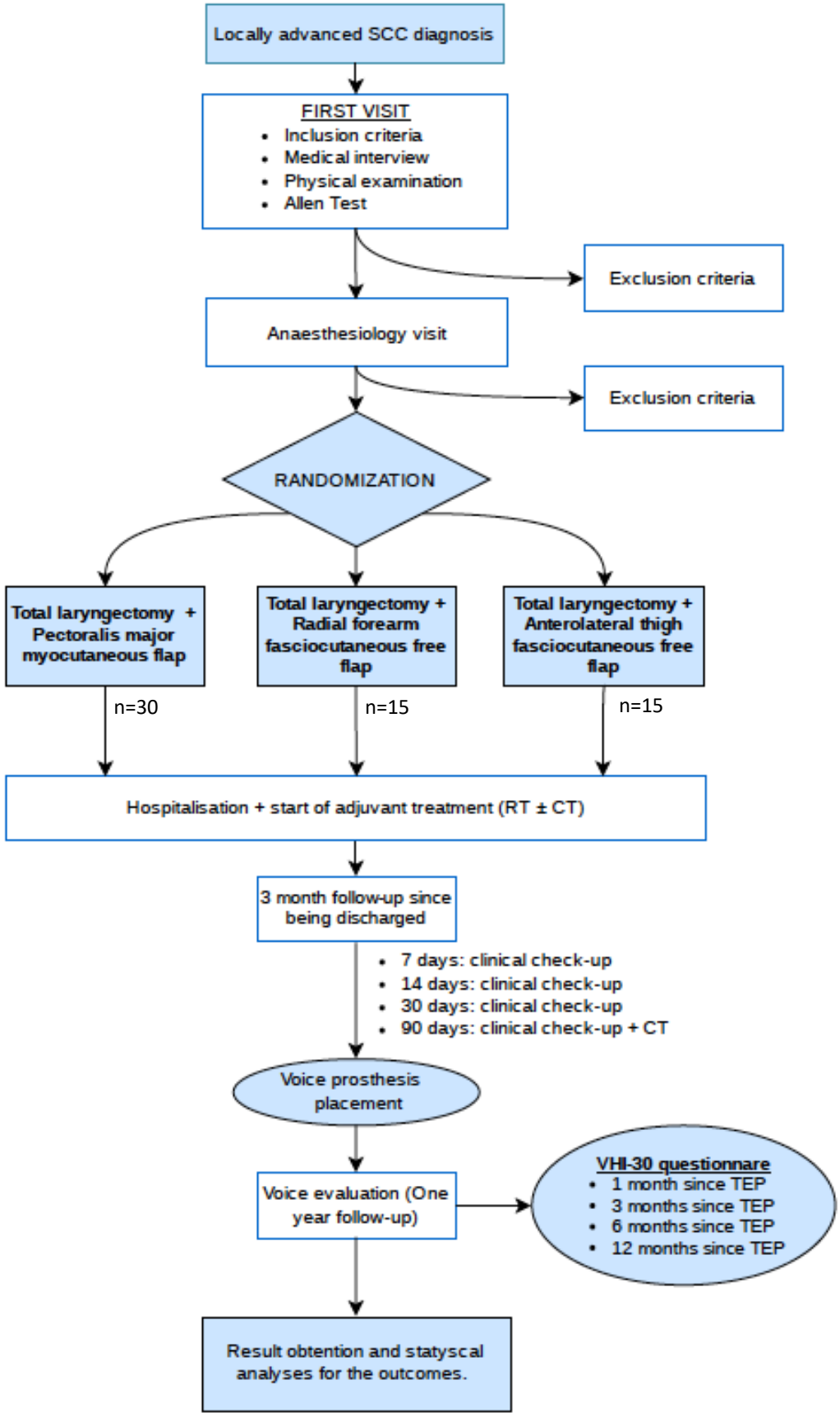

Figure 35. Data collection flow diagram.

8. STATISTICAL ANALYSIS

Statistical analysis will be performed using IBM Statistical Package for Social Sciences (SPSS) available for the Windows program. The statistician in charge of the analysis will be blinded to the study groups.

For all analyses, a value of $p<0.05$ will be considered as statistically significant, defining a confidence interval of 95%.

All the variables have been defined as quantitative or qualitative. The type of variable in which everyone has been classified can be seen in 7.*6- Study Variables*.

8.1- UNIVARIANT ANALYSIS

The univariate analysis will be used for the analytical description of the sample:

Quantitative variables with a normal distribution will be expressed by an arithmetic mean as a central trend measure, with the standard deviation as the dispersion measure, while quantitative variables without a normal distribution will be expressed by a median as a central trend measure, with interquartile ranges as the dispersion measure.

Qualitative variables will be expressed in percentages with a confidence interval of 95%.

The curves of survival will be estimated and represented with the Kaplan-Meier method.

All results are going to be classified by the three surgical techniques.

8.2- BIVARIATE ANALYSIS

Although there are three intervention groups, these are divided into two categories of flaps when analysed: the muscle flaps group (A) and the fasciocutaneous flaps group (B and C), and therefore the difference in the voice quality and functionality, known from the score on the VHI-30, between the different intervention groups will be analysed with the **ANOVA test** as the analysis will be performed with the data obtained from the questionnaires at 4 different times in order to progressively assess the voice quality and functionality: after 1 month, 3 months, 6 months and 12 months of placing the voice prothesis.

The comparation of time to reintroduce the oral feeding between the two groups will be analysed with the contrast **Log-rank test**.

The presence of dysphagia after reintroducing oral feeding and both acute and late complications rate will be analysed using **Chi-square test**. We will use the exact Fisher's test when the expected number of counts in any cell of the table of contingency is lower than five.

8.3- MULTIVARIATE ANALYSIS

Because randomization we expect our groups to be balanced in terms of age, gender, ethnicity or any other variable, so there should not be any cofounding. Even though, if cofounding is suspected during the statistical analysis, we will adjust the associations between the outcome and the independent variables for the confounders covariables.

The effect of the intervention on the voice quality and functionality will be measured with a **General Linear Model (GLM) for repeated measurements**, adjusted for possible confounders such as gender, age, socioeconomic status, ethnicity and adjuvant chemotherapy.

The time to reintroduce the oral feeding will be adjusted by the same covariables using a **Cox regression**.

For the complications rate and the dysphagia presence a **logistic regression** will be used, adjusting the results for the same covariables as before.

9. ETHICAL AND LEGAL CONSIDERATIONS

This clinical trial 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 reviewed on 2013)* about the ethical principles for medical research involving human subjects.

All basic ethical principles are compiled in this trial:

- Principle of autonomy. The study preserves the patient's freedom through the patient's information document and informed consent (*Annexes 6 and 7*). Patients will be informed about all the protocol details after reading the patient's information document and will have to sign the informed consent if they agreed to participate, as stated on the "*Ley 41/2002, de 14 de noviembre, Básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica*". The patient is guaranteed confidentiality and privacy in accordance with *Regulation (EU) 2016/679 of parliament and the European Council, April 27, 2016, concerning the protection of natural people with regard to the processing of personal data* and "*ley Orgánica 3/ 2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los Derechos Digitales (LOPD-GDD*)".

- Principle of beneficence. One of the main treatments for locally advanced larynx and hypopharynx SCC is total laryngectomy, a technique that will be performed on all patients in this study. Also, all the pharyngeal wall reconstruction techniques used in the study have proven to be effective, with a totally functional pharynx in all of them.

- Principle of non-maleficence. All patients with locally advanced larynx or hypopharynx SCC will receive the pertinent treatment for their disease through TL with flap reconstruction whether or not they decide to participate in the study. Furthermore, all the reconstructive surgical techniques used have proven to be equally safe, so no patient will be at more risk for any complication from being part of one group or another.

- Principle of justice. All patients who meet the inclusion criteria without meeting any of the exclusion criteria will be offered to participate in the study without any kind of discrimination.

Before beginning this study, the project will be submitted and introduced to the European Clinical Trials Database to get a registration number. Then it will be evaluated by the Clinical Research Ethical Committee (CEIC) of *Hospital Universitari Doctor Josep Trueta* (Girona) for its

review and approval. After all the ethical committees' approval, the protocol will be sent to the director of each participant hospital in order to get their approval.

Only after the approval from all the mentioned entities the study will be carried out. In addition, all suggestions given by the CEIC will be taken into account and added to the protocol.

All members from the research team in every participating hospital will have to sign a statement which will indicate their approval of the final protocol with their acceptance of the ethics aspects of research.

All data will be published with transparency without excluding any unfavourable events.

Since this clinical trial is a research project with invasive procedure, it must comply with the *"Ley 14/2007"* and the *"Real Decreto 1716/2011" for research on biological samples and the "Real Decreto 1090/2015" for clinical research with sanitary products.*

10. LIMITATIONS

1. This protocol is designed to be applied to those patients who require a flap for the pharynx reconstruction in the same intervention as the TL. This allows us to evaluate the voice functionality released by a flap in its most optimal situations, since the neck would not have received any injury by any external agent before such as previous TL surgical complications or previous neck radiotherapy, but this situation, at the same time, limits the study sample and the **target population** since it leaves out of the trial several patients in whom a flap pharynx reconstruction after TL is also indicated and who will therefore have a voice derived from the flap through a VP.
2. The consecutive non-probabilistic recruitment method used in this trial may not obtain a representative sample, so there may occur a **selection bias**. Furthermore, due to the higher incidence of SCC among males, a low number of female participants is expected. Nevertheless, to minimize this bias, the exclusion criteria we designed have been focused on the contraindications of the different reconstructive interventions, which as they are not very common, they are not expected to significantly modify the typical population of total laryngectomy. In addition, the intervention assignation is going to be random, making the three treatment groups equivalent. Finally, being a multicentric study composed by hospitals from several provinces of Catalunya implies that, if significant results are achieved, they could be easily more generalized.
3. The impossibility of **masking** the patient and the doctor from the intervention to be performed may lead to a **detection bias.** To minimize this, the statistical expert in charge of evaluating the results will not know to which group each patient belonged.
4. Being a multicentric trial in which the main intervention is a surgery (operator-dependent) we have to take into account that there is a risk of **variability** in the interventions between different surgical teams. In order to avoid this, all surgeons participating in the study will undergo a preparation in a workshop before the study starts so that everyone can perform the interventions in the same way.
5. As the surgery is operator-dependent, the personal experience and the **learning curve phenomenon** may be an issue that could affect the study results. To avoid this situation, all hospitals selected for this study have a head and neck team of surgeons who are experts in reconstructive neck surgery and who often perform the trial's interventions, so this learning curve phenomenon will be imperceptible in our study.

6. In a study in which the patient must be followed-up for a long time once he or she is completely cured, there is always a risk of **withdrawals**. To minimize the losses, this possible effect has been taken into account when determining the sample needed for the trial. In addition, there is also the possibility to replace the losses during the recruitment period, as the sampling method in this study is consecutive.

11. WORK PLAN AND CHRONOGRAM

The activities developed in this study will be carried out in the following way:

STAGE 0: STUDY DESIGN (November 2020- February 2021)

- Activity 1. Bibliographic research about surgical management of locally advanced larynx and hypopharynx SCC, pharyngeal surgical reconstruction techniques and voice quality and functionality measurement procedures. The research has been performed in PubMed.
- Activity 2. Protocol elaboration including hypothesis, objectives, variables and methodology.

The principal investigator (PI) will be the main responsible.

STAGE 1: ETHICAL EVALUATION AND APPROBATION (February – March 2021)

- Activity 3. The protocol will be presented to the CEIC of the *Hospital Universitari Doctor Josep Trueta,* Girona. Once it gets the approbation, this protocol will be shared with the other services and direction of the other participant hospitals to obtain their approval.
- Activity 4. Contracting an insurance.

The PI will be the main responsible.

STAGE 2: COORDINATION (March 2021 – April 2021)

- Activity 5 (March 2021). The research team of each hospital will meet and select their coordinator. He or she will be the responsible of coordinating with the other centres during the duration of the study and of the task organization from his or her hospital.
- Activity 6 (March 2021). The first meeting of the coordinators of each centre will be carried out to discuss their organization and to solve any problems they could have.
- Activity 7 (April 2021). All the surgeons involved in the study will meet at *Hospital Universitari Doctor Josep Trueta* to participate in a practical workshop in which the 3 surgical techniques that constitute the independent variables of the study will be reviewed. The objective of this training session will be to ensure the homogeneity of the surgical technique in all the centres in order to obtain more representative results.

Hospital coordinator, the principal investigator (PI) and investigators will be all responsible.

STAGE 3: DATA COLLECTION AND FOLLOW-UP VISITS (May 2021- September 2024)

- Activity 8 (May 2021 – May 2023). Patient recruitment will be done by a consecutive sampling in the 5 hospitals participants in the trial. In order to be included in the sample, a patient must meet all the inclusion criteria and must not meet any of the exclusion criteria.

Then they will be randomly assigned to one of the intervention groups and the total laryngectomy will be performed. The flap for the reconstruction of the pharynx will be performed according to the assigned intervention group during the same surgery.

- Activity 9 (May 2021 – September 2024). Follow-up visits will be performed periodically. During the first 3 months after having been discharged the patient will be visited 4 times to make a clinical assessment. The last one will also include a neck-CT. A week after the last check-up a visit is scheduled to insert the voice prosthesis. From this point on, 4 visits will be carried out, in which the patient must fill in the VHI-30 questionnaire in order to obtain an assessment of voice functionality and quality. These visits will be scheduled after one month, three months, six months and twelve months from the VP insertion date.
- Activity 10 (May 2021 – September 2024): The specialists will record all the data collected of the different variables in the database.

During this stage, the coordinators will meet at least once a year to discuss and comment on the current status of the trial and about possible problems that may have arisen.

Investigators, coinvestigators and coordinators will be all responsible.

STAGE 4: DATA ANALYSIS AND INTERPRETATION (October 2024-April 2025)

- Activity 11 (October 2024): the statistical analysis will be performed by a subcontracted statistician who will be masked for the intervention groups. He or she will perform the analysis once all the data has been collected.
- Activity 12 (November 2024-April 2025): The data will be interpretated by the main investigator and coordinators. After this step, the discussion and conclusion will be elaborated.

Coordinators, PI and the statistic will be all responsible.

STAGE 5: RESULTS PUBLICATION AND DISSEMINATION OF THE RESEARCH FINDINGS (April-June 2025)

- Activity 13: The principal investigators will generate a paper to show the study results and conclusions.
- Activity 14: Presentation of the results on *the Sociedad Española de Otorrinolaringología* (SEORL).
- Activity 15: Presentation of the results on the European Academy of Otorhinolaryngology, Head and Neck surgery (EAROL-HNS).
- Activity 16: publication of the results on scientific journals.

PI and coordinators will be all responsible.

TASK		2020	2021					2022	2023		2024			2025			
		Nov -Dec	Jan	Feb	Mar	Apr	May - Dec	Jan-Dec	Jan-May	Apr-Dec	Jan-Sep	Oct	Nov-Dec	Jan-Mar	Apr	May	Jun
STAGE 0	A1: Bibliographic research																
	A2: Protocol elaboration																
STAGE 1	A3: CEIC																
	A4: Insurance contracting																
STAGE 2	A5: Coordinators selection																
	A6: First meeting																
	A7: Surgical workshop																
STAGE 3	A8: Recruitment and intervention																
	A9-10: Follow-up and data collection																
STAGE 4	A11: Statistical analysis																
	A12: Statistical interpretation and discussion																
STAGE 5	A13: Paper preparation																
	A14-15: Congress presentation																
	A16: Publication																

Figure 36. Chronogram.

12. FEASIBILITY

The medical team for this study will be composed by otorhinolaryngologic specialists, plastic surgeons, radiologists, radiotherapists, oncologists and nurses, all of them experienced enough to attend the necessities of the included patients and to execute the study's procedures. All the hospitals included in this trial have this medical team in their stuff, so no additional employment will be necessary. The one person that will indeed be necessary to recruit is the statistical analyser who processes all the data and interpret the results.

All the procedures and interventions to be carried out in the trial are part of the usual clinical practice, so no extra material or preparation will be required other than a workshop for each procedure to homogenize its execution in the different hospitals. The only exception is the TEP through a wire-guided balloon catheter puncture technique, which is not a standard procedure in all the participant hospitals, but all teams are capable of performing it. The extra material required for this technique has been taken into account when calculating the budget for the study (*See 13. Budget*).

As it concerns the treatment of the patient's cancer, surgical removal is included in this protocol and the adjuvant treatment required is well set out in the ICO guidelines, in order that the same treatment can be carried out in all centres without any problem.

With regard to patient's follow-up, all the participant centres dispose from the necessary means to proceed with the right follow-up, so all the study phases will be performed in all the participant hospitals.

13. BUDGET

PERSONNEL EXPENSES

The whole research teams are employed by the hospitals included in the study, and how there is no need to employ additional clinicians, this will not suppose any additional cost.

As it is a multicentre study, we will hire a Contract research organization (CRO) in order to ensure a global coordination and to provide and supervise an appropriate rate of patients' inclusion and data collection in all the hospitals. It will approximately cost 20.000€. Moreover, to facilitate the data recording from all centres, we will hire an investigation assistant under partial time. His or her job will take approximately 80h, so paying about 20€ per hour makes a total of 1.600€.

We will also hire a statistical expert to randomize and code patients and to perform the statistical analysis from the data collected. The approximate salary will be 35€/hour with an estimated cost of 1050€ (30 hours).

LIABILITY INSURANCE

As invasive procedures are performed, it is necessary to hire an insurance to cover any possible adverse effect that patients included in the study could suffer attributable to their participation on it. The estimated cost is 36.000 € (600€ per patient).

EXECUTION EXPENSES

Material for bibliographic research has not represented any additional expense.

The 3 reconstructive surgical interventions to be compared in the trial are common procedures in the centres participating in the study, so their implementation will not involve additional costs as they are all included in our National Health System (NHS).

Post-operation care and the follow-up of the first months will be the same as the one usually carried out in laryngectomized patients, so there is no extra cost in this part.

Extra follow-up visits for voice assessment only require the patient interview and completion of the VHI-30 questionnaire, without the need to request any additional complementary tests, so there are no additional expected costs besides the printing of the questionnaires.

Therefore, the execution expenses are composed by:

- Printing of all documents necessary for each patient over the course of the study: the fragility and functionality questionnaires (*Annex 3*), the patient's protocol information document (*Annex 6*), the informed consent (*Annex 7*), the data collection document (*Annex 5*) and 4 copies of the VHI-30 *(Annex 4*). 11 sheets will be required per patient, of a total of 60 patients, the cost will be 165€ for all the documents needed.
- The procedure of placing the voice prosthesis through a wire-guided balloon catheter puncture is not a standard procedure in all participating hospitals, so it will be necessary to acquire one oesophageal wire-guided balloon dilatation catheter (CRE ™ Wireguided) per patient in order to perform the tracheoesophageal puncture. Each unit has a cost of 350€, so the total cost will be 21.000€.
- We will need to pay IMB SPSS Statistics license for the statistical analysis for one year which will cost 300€.

TRAVEL AND COORDINATION EXPENSES

All meetings between the coordinators of the different hospitals can be telematic via videoconference, so no travel expenses are expected.

The only session that will need to be held in person is the surgical workshop. Two members of the surgical team from each participating hospital (an otolaryngologist and a plastic surgeon) will have to go to the *Hospital Universitari de Girona Doctor Josep Trueta*, where the workshop will take place. We estimate a cost of 80€ per researcher in terms of travel and diets, so the expenses for the workshop will be 640€ (Counting that the participants from Girona will not have any extra travel expenses).

CONFERENCE EXPENSES

In order to disseminate the results to the rest of the scientific community we will attend national and international congresses. Two researchers will participate in the national congress (SEORL) with the final analyses. The admission fee is estimated on 500 € per person and per congress, in which should be added travel and accommodation costs, which will be approximately 500€ per person and per congress. Therefore, we calculate a global cost of 2.000 €.

Scientific results will also be presented in an international congress (EAROL-HNS) by two researchers only when final results and analyses are obtained.

The admission fee is approximately 800 € per person and the costs of travel and accommodation are estimated to be 1.000 € per person. Therefore, this will be budgeted on 3.600 €.

PUBLICATION EXPENSES

Once the study is finished and we have extracted and interpretated the results, we will publish it as a journal article. For this we must have into account the English correction (500 €) and preparation of the open access (1.800 €), so the estimated subtotal of the publication costs is budgeted on 2.300 €.

All the expenses are summarized in the following table:

ITEM	QUANTITY	COST	SUBTOTAL
PERSONNEL COSTS			
Research team	Provided by the NHS (included in each hospital stuff)		
Investigation assistant	80h	20€/h	1.600€
Statistician	30h	35€/h	1050€
INSURANCE POLICY			
Trial policy	60 patients	600€	36.000€
MATERIAL AND EXECUTION			
Flaps intervention material	60 patients	Provided by the NHS	
Hospital care and first follow-up	60 patients	Provided by the NHS	
Document sheets	660 sheets	0.15€	99€
CRE ™ wire guided	60 units	350€	21.000€
IMB SPSS license	1 year	300€	300€
CRO contracting	-	20.000€	20.000€
TRAVELS AND COORDINATION			
Surgical workshop	8 attendants	80€	640€
PUBLISHING EXPENSES AND DISSEMINATION OF RESULTS			
SEORL (national congress)	2 inscriptions fees	500€ pp	2.000€
	2 travels and accommodations	500€ pp	
EAORL-HNS (international congress)	2 inscriptions fees	800 € pp	3.600€
	2 travels and accommodations	1.000€ pp	
Article publication expenses	English correction	500€	2.300€
	Open Access	1.800€	
TOTAL: 88.589€			

Table 5. Budget summary.

14. IMPACT ON THE NATIONAL HEALTH SYSTEM

Head and neck SCC is an important group of tumours in terms of incidence, mortality and comorbidities. From this group, larynx cancer is the most prevalent and incident one. For this reason, several important studies have been carried out all around the world in order to find a curative treatment that is the least aggressive possible for the patient.

Even with this great efforts, total laryngectomy still remains a very significant pillar in the management of locally advanced larynx and hypopharynx SCC, so it must be a priority to seek the treatment that allows the patient to have the best possible quality of life despite the degree of mutilation resulting from such surgery. At this point is where this trial gets important, as this is **one of the first studies**, **if not the first**, to evaluate and compare voice functionality after flap pharynx reconstruction in TL in an experimental clinical trial.

Based on our hypothesis, the PMMF will allow the patient to achieve a better quality and functionality voice. If this hypothesis turns out to be truth it would allow to totally change the **current management of the totally laryngectomized patients**, since a reconstruction technique would have demonstrated superiority over the others in terms of voice functionality, so surgical teams could focus on performing this muscle flap in the first instance and use the free fasciocutaneous flaps as alternatives after the failure of the PMMF instead of the current trends, in which surgical teams perform one flap or another depending on their comfort and their technical skills. In this way, the patient will be cured of his illness and would also have a voice quality very similar to the one before the intervention, a situation that we believe is fundamental, since giving the best possible **quality of life** to the patients should be the goal of current medicine.

In this trial, the comparison of the flaps is made in its most optimal form, as no patients with any previous external factors that might modify the functionality of the flap (such as previous neck radiotherapy or chemotherapy) have been included. Therefore, if the hypothesis is confirmed with significant results, a door would be opened where the flaps could be studied and compared in other situations of their use, as for example in the rescue after the failure of the organ preservation, which is another major indication of LT and the use of reconstructive flaps, that has been excluded from this study because these organ preservation protocols are based on chemoradiotherapy.

15. BIBLIOGRAPHY

1. García-Porrero JA, Hurlé JM. Aparato Respiratorio. In: García-Porrero JA, Hurlé JM, editors. Anatomía humana. Madrid: McGraw Hill Interamericana; 2005. p. 438–88.

2. Drake RL, Vogl AW, Mitchell AWM. Cabeza y cuello. Anatomía regional: Faringe. In: Gray anatomía para estudiantes. 2nd ed. Barcelona: Elsevier; 2010. p. 985–96.

3. Fernández AI, Delgado N, Dominguez E, Martínez M, Alegre N. Hypopharynx and larynx anatomy. In Madrid: European Society of Radiology; 2016.

4. Gilroy AM. Oral cavity & pharynx. In: Gilroy AM, MacPherson BR, editors. Atlas of anatomy. 3rd ed. New York: Thieme; 2016. p. 598–617.

5. Netter FH. Thyroid Gland and Larynx. In: Hansen JT, Benninger B, Brueckner-Collins J, Hoagland TM, R. Shane Tubbs M, editors. Atlas of human anatomy. 7th ed. Philadelphia, PA: Elsevier; 2019. p. 87–93.

6. Gilroy AM. Neck. In: Gilroy AM, MacPherson BR, editors. Atlas of anatomy. 3rd ed. New York: Thieme; 2016. p. 618–44.

7. Drake RL, Vogl AW, Mitchell AWM. Cabeza y cuello. Anatomía regional: Laringe. In: Gray anatomía para estudiantes. 2nd ed. Barcelona: Elsevier; 2010. p. 997–1009.

8. Weidenbecher M. MetroHealth Medical Center [Internet]. Cleveland voice and sleep: anatomy & physiology. [cited 2021 Jan 15]. Available from: http://www.clevelandvoiceandsleep.com/anatomy--physiology.html

9. 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. 2018;68(6):394–424.

10. Armstrong WB, Vokes DE, Maisel RH. Malignant Tumors of the Larynx. In: Flint PW, Haughey BH, Lund VJ, Niparko JK, Mark A. Richardson, Robbins KT, et al., editors. Cummings Otolaryngology Head & Neck Surgery. 5th ed. Philadelphia, PA: Elsevier; 2010. p. 1482–511.

11. Concus AP, Tran T-PN, Sanfilippo NJ, DeLacure MD. Malignant Laryngeal Lesions. In: Lalwani AK, editor. Current Diagnosis & Treatment in otolaryngology - Head & Neck Surgery. 2nd ed. New York: McGraw Hill; 2008. p. 437–55.

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

13. Sociedad Española de Oncología Médica. Las cifras del cáncer en España 2020. Soc Española Oncol Médica. 2020;5–36.

14. Chang S, Ha P. Biology of Head and Neck Cancer. In: Flint PW, Haughey BH, Lund VJ, Niparko JK, Richardson MA, Rob KT, et al., editors. Cummings Otolaryngology Head & Neck Surgery. 5th ed. Philadelphia, PA: Elsevier; 2010. p. 1015–29.

15. Paleri V, Winter S, Fox H, Palaniappan N. Tumours of the larynx. In: Watkinson JC, Clarke RW, editors. Scott-Brown's Otorhinolaryngology Head and Neck Surgery Volume 3. 8th ed. Boca Raton, FL: CRC Press; 2019. p. 237–62.

16. Licitra L, Bernier J, Grandi C, Locati L, Merlano M, Gatta G, et al. Cancer of the larynx. Crit Rev Oncol Hematol. 2003;47(1):65–80.

17. 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.

18. 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;33:541–50.

19. Steuer CE, El-Deiry M, Parks JR, Higgins KA, Saba NF. An update on larynx cancer. CA Cancer J Clin. 2017;67(1):31–50.

20. Alter BP, Giri N, Savage SA, Rosenberg PS. Cancer in dyskeratosis congenita. Blood. 2009;113(26):6549–57.

21. Ülger Z, Karaca B, Dikbaş O, Işik M, Altundağ K, Güler N. Fanconi's anemia and squamous cell carcinoma of the larynx. Ann Hematol. 2003;82(5):321–2.

22. Rinaldo A, Coca-Pelaz A, Silver CE, Ferlito A. Paraneoplastic Syndromes Associated with Laryngeal Cancer. Adv Ther. 2020;37(1):140–54.

23. Bootz F. Guideline on diagnosis, treatment, and follow-up of laryngeal cancer. HNO. 2020;68(10):757–62.

24. 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.

25. Grupo Español de Tratamiento de Tumores de cabeza y cuello. Guias de Práctica Clínica para el Tratamiento del Cáncer de Cabeza y Cuello. Clin Transl Oncol. 2010;18–23.

26. Institut Català d'Oncologia. Praxis para el tratamiento médico y con irradiación del cáncer de orofaringe, hipofaringe, laringe y nasofaringe. In: Tratamiento médico y con irradiación del cáncer de cabeza y cuello. Barcelona: Institut Català d'Oncologia, Institut Català de la Salut; 2017. p. 12–90.

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

28. Patel SA, Qureshi MM, Dyer MA, Jalisi S, Grillone G, Truong MT. Comparing surgical and nonsurgical larynx-preserving treatments with total laryngectomy for locally advanced laryngeal cancer. Cancer. 2019;125(19):3367–77.

29. Singh Badwal J. Total Laryngectomy for Treatment of T4 Laryngeal Cancer: Trends and Survival Outcomes. Polish J Surg. 2019;91(1):1–10.

30. Rassekh CH, Haughey BH. Total Laryngectomy and Laryngopharyngectomy. In: Flint PW, Haughey BH, Lund VJ, Niparko JK, Richardson MA, Rob KT, et al., editors. Cummings Otolaryngology Head & Neck Surgery. 5th ed. Philadelphia, PA: Elsevier; 2010. p. 1563–76.

31. Pai PS, Nair D, Laskar SG, Prabhash K. Management of hypopharyngeal cancer. In: Watkinson JC, Clarke RW, editors. Scott-Brown's Otorhinolaryngology Head and Neck Surgery Volume 3. 8th ed. Boca Raton, FL: CRC Press; 2019. p. 273–94.

32. Uppaluri R, Sunwoo JB. Neoplasms of the Hypopharynx and Cervical Esophagus. In: Flint PW, Haughey BH, Lund VJ, Niparko JK, Richardson MA, Robbins KT, et al., editors. Cummings Otolaryngology Head & Neck Surgery. 5th ed. Philadelphia, PA: Elsevier; 2010. p. 1421–40.

33. Hutton CF. Hypopharyngeal carcinoma developing in Plummer-Vinson syndrome. Br J Radiol. 1962;35(February):143–4.

34. Eckel HE, Bradley PJ. Natural History of Treated and Untreated Hypopharyngeal Cancer. Adv Otorhinolaryngol. 2019;83:27–34.

35. Eckel HE, Bradley PJ. Treatment Options for Hypopharyngeal Cancer. Adv Otorhinolaryngol. 2019;83:47–53.

36. University of Iowa Health Care [Internet]. Total Laryngectomy | Iowa Head and Neck Protocols. Iowa City: University of Iowa. 2019 [cited 2020 Dec 31]. Available from: https://medicine.uiowa.edu/iowaprotocols/total-laryngectomy

37. Fagan J. Total laryngectomy [Internet]. Open access atlas of otolaryngology, head & neck operative surgery. Cape Town: University of Cape Town. 2016 [cited 2021 Jan 15]. Available from: http://dx.doi.org/10.15641/0-7992-2534-1

38. Patel D, Kuriakose MA, Iyer S. Reconstruction of the laryngopharynx. Indian J Plast Surg. 2007;40:44–51.

39. Liu M, Liu W, Yang X, Guo H, Peng H. Pectoralis Major Myocutaneous Flap for Head and Neck Defects in the Era of Free Flaps: Harvesting Technique and Indications. Sci Rep. 2017;7:1–9.

40. Gonzalez-Orús Álvarez-Morujo R, Martinez Pascual P, Tucciarone M, Fernández Fernández M, Souviron Encabo R, Martinez Guirado T. Salvage total laryngectomy: is a flap necessary? Braz J Otorhinolaryngol. 2020;86(2):228–36.

41. Sousa AA, Castro SM de O, Porcaro-Salles JM, Soares JMA, de Moraes GM, Carvalho JR, et al. The usefulness of a pectoralis major myocutaneous flap in preventing salivary fistulae after salvage total laryngectomy. Braz J Otorhinolaryngol. 2012;78(4):103–7.

42. Gabrysz-Forget F, Tabet P, Rahal A, Bissada E, Christopoulos A, Ayad T. Free versus pedicled flaps for reconstruction of head and neck cancer defects: A systematic review. J Otolaryngol - Head Neck Surg. 2019;48(1):1–31.

43. Hanasono MM, Corbitt CA, Yu P, Skoracki RJ. Success of sequential free flaps in head and neck reconstruction. J Plast Reconstr Aesthetic Surg. 2014;67(9):1186–93.

44. Hasan Z, Dwivedi RC, Gunaratne DA, Virk SA, Palme CE, Riffat F. Systematic review and meta-analysis of the complications of salvage total laryngectomy. Eur J Surg Oncol. 2017 Jan 1;43(1):42–51.

45. Wax MK, Touma BJ, Ramadan HH. Management of tracheostomal stenosis. Laryngoscope. 1999;109(9):1397–401.

46. Hakeem AH, Hakeem IH, Garg A. Rehabilitation after total laryngectomy. Otorhinolaryngol Clin An Int J. 2010;2(3):223–9.

47. Edels Y, Clarke P. Rehabilitation after total laryngectomy. In: Watkinson JC, Clarke RW, editors. Scott-Brown's Otorhinolaryngology Head and Neck Surgery Volume 3. 8th ed. Boca Raton, FL: CRC Press; 2019. p. 9.

48. Hilgers FJM, Brekel MWM van den. Vocal and Speech Rehabilitation Following Laryngectomy. In: Flint PW, Haughey BH, Lund VJ, Niparko JK, Richardson MA, Rob KT, et al., editors. Cummings Otolaryngology Head & Neck Surgery. 5th ed. Philadelphia, PA: Elsevier; 2010. p. 1594–610.

49. Zenga J, Goldsmith T, Bunting G, Deschler DG. State of the art: Rehabilitation of speech and swallowing after total laryngectomy. Oral Oncol. 2018;86(August):38–47.

50. Grigore R, Oancea ALA, Simion-Antonie C, Popescu B, Nitu L, Bejenaru P, et al. The quality of life in patients with total laryngectomy. Arch Balk Med Union. 2020;55(1):87–97.

51. Lorenz KJ. Rehabilitation after total laryngectomy-A tribute to the pioneers of voice restoration in the last two centuries. Front Med. 2017;4(JUN):1–12.

52. Penagos Vélez AM, López Álvarez F, Núñez Batalla F. Rehabilitación del paciente laringectomizado. In: Libro virtual de formación en ORL. Madrid: SEORL Sociedad Española de Otorrinolaringología y Patología Cérvico-Facial; p. 1–13.

53. 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;70(3):169–74. Available from: https://doi.org/10.1016/j.otorri.2018.01.003

54. Speech & swallow therapy, THANC guide [Internet]. [cited 2021 Jan 19]. Available from: https://thancguide.org/cancer-basics/after-treatment/rehabilitation/speech-swallow-therapy/

55. Laryngectomy | Tracheostomy Education [Internet]. [cited 2021 Jan 7]. Available from: https://tracheostomyeducation.com/laryngectomy/

56. Dragičević D, Jović RM, Kljajić V, Vlaški L, Savović S. Comparison of Voice Handicap Index in Patients with Esophageal and Tracheoesophageal Speech after Total Laryngectomy. Folia Phoniatr Logop. 2020;72(5):363–9.

57. Moon S, Raffa F, Ojo R, Landera MA, Weed DT, Sargi Z, et al. Changing trends of speech outcomes after total laryngectomy in the 21st century: A single-center study. Laryngoscope. 2014;124(11):2508–12.

58. Arenaz Búa B, Pendleton H, Westin U, Rydell R. Voice and swallowing after total laryngectomy. Acta Otolaryngol [Internet]. 2018;138(2):170–4. Available from: https://doi.org/10.1080/00016489.2017.1384056

59. 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.

60. Ackerberg T. Nutritional management after total laryngectomy. South African J Clin Nutr. 2011;24(2):107–8.

61. Moerman M, Martens JP, Dejonckere P. Application of the voice handicap index in 45 patients with substitution voicing after total laryngectomy. Eur Arch Oto-Rhino-Laryngology. 2004;261(8):423–8.

62. Attieh AY, Searl J, Shahaltough NH, Wreikat MM, Lundy DS. Voice restoration following total laryngectomy by tracheoesophageal prosthesis: Effect on patients' quality of life and voice handicap in Jordan. Health Qual Life Outcomes. 2008;6:1–10.

63. Torrejano G, Guimarães I. Voice Quality After Supracricoid Laryngectomy and Total Laryngectomy With Insertion of Voice Prosthesis. J Voice. 2009;23(2):240–6.

64. Schindler A, Mozzanica F, Ginocchio D, Invernizzi A, Peri A, Ottaviani F. Voice-related quality of life in patients after total and partial laryngectomy. Auris Nasus Larynx. 2012;39(1):77–83.

65. van Sluis KE, van der Molen L, van Son RJJH, Hilgers FJM, Bhairosing PA, van den Brekel MWM. Objective and subjective voice outcomes after total laryngectomy: a systematic review. European Archives of Oto-Rhino-Laryngology. 2018;11–26.

66. Cocks H, Dwivedi RC, Waters AMI. Measures of treatment outcomes. In: Watkinson JC, Clarke RW, editors. Scott-Brown's Otorhinolaryngology Head and Neck Surgery Volume 3. 8th ed. Boca Raton, FL: CRC Press; 2019. p. 461–72.

67. Hurren A, Miller N. Voice outcomes post total laryngectomy. Curr Opin Otolaryngol Head Neck Surg. 2017;25(3):205–10.

68. McGlashan JA. Evaluation of the voice. In: Watkinson JC, Clarke RW, editors. Scott-Brown's Otorhinolaryngology Head and Neck Surgery Volume 3. 8th ed. Boca Raton, FL: CRC Press; 2019. p. 925–42.

69. Núñez-Batalla F, Corte-Santos P, Señaris-González B, Llorente-Pendás JL, Górriz-Gil C, Suárez-Nieto C. Adaptación y validación del índice de incapacidad vocal (VHI-30) y su versión abreviada (VHI-10) al español. Acta Otorrinolaringol Esp. 2007 Nov 1;58(9):386–92.

70. Domingo A, Macros J. Propuesta de un indicador de la clase social basado en la ocupación. 1988. p. 3(10):320–6.

71. Fagan J. The pectoralis major flap [Internet]. Open access atlas of otolaryngology, head & neck operative surgery. Cape Town: University of Cape Town. 2016 [cited 2021 Jan 15]. Available from: http://dx.doi.org/10.15641/0-7992-2534-1

72. Gilbert RW, Watkinson JC. Pedicled flaps in head and neck reconstruction. In: Watkinson JC, Clarke RW, editors. Scott-Brown's Otorhinolaryngology Head and Neck Surgery Volume 3. 8th ed. Boca Raton, FL: CRC Press; 2019. p. 1283–98.

73. AO Surgery reference [Internet]. Ong HS, Ji T, Zhang CP. Pectoralis myocutaneous pedicle flap. Davos: AO Foundation. 2017 [cited 2020 Dec 28]. Available from: https://surgeryreference.aofoundation.org/cmf/reconstruction/basic-technique/pectoralis-myocutaneous-pedicle-flap

74. Pectoralis major flap, the Chinese University of Hong Kong [Internet]. [cited 2021 Jan 19]. p. 634. Available from: http://www.ent.cuhk.edu.hk/images/publication/head-and-neck-dissection-and-reconstruction-manual/16_PECTORALIS-MAJOR-FLAP.pdf

75. Zyl O van. Radial free forearm flap (RFFF): Surgical Technique [Internet]. Open access atlas of otolaryngology, head & neck operative surgery. Cape Town: University of Cape Town. 2016 [cited 2021 Jan 15]. Available from: http://dx.doi.org/10.15641/0-7992-2534-1

76. Watkinson JC, Gilbert RW. Reconstructive microsurgery in head and neck surgery. In: Watkinson JC, Clarke RW, editors. Scott-Brown's Otorhinolaryngology Head and Neck Surgery Volume 3. 8th ed. Boca Raton, FL: CRC Press; 2019. p. 1299–320.

77. Zyl O van, Fagan J. Free tissue transfer flaps in head & necj reconstruction: microvascular anastomosis technique [Internet]. Open access atlas of otolaryngology, head & neck operative surgery. Cape Town: University of Cape Town. 2016 [cited 2021 Jan 15]. Available from: http://dx.doi.org/10.15641/0-7992-2534-1

78. AO Surgery reference [Internet]. Ong HS, Ji T, Zhang CP; Radial forearm fasciocutaneous flap. Davos: AO Foundation. 2017 [cited 2020 Dec 28]. Available from: https://surgeryreference.aofoundation.org/cmf/reconstruction/basic-technique/radial-forearm-fasciocutaneous-flap#introduction

79. Pipkorn P, Zyl O van. Anterolateral thigh (ALT) free flap for head and neck reconstruction [Internet]. Open access atlas of otolaryngology, head & neck operative surgery. Cape Town: University of Cape Town. 2016 [cited 2021 Jan 15]. Available from: http://dx.doi.org/10.15641/0-7992-2534-1

80. AO Surgery reference [Internet] [Internet]. Ong HS, Ji T, Zhang CP; Anterolateral thigh. Davos: AO Foundation. 2017 [cited 2020 Dec 28]. Available from: https://surgeryreference.aofoundation.org/cmf/reconstruction/basic-technique/anterolateral-thigh

81. Herranz J, Sarandeses A, Fernandez MF, Barro CV, Vidal JM, Gavilán J. Complications after total laryngectomy in nonradiated laryngeal and hypopharyngeal carcinomas. Otolaryngol - Head Neck Surg. 2000;122(6):892–8.

82. Peripheral arterial access in neonates requiring intensive care, Better Safer Care [Internet]. [cited 2021 Jan 19]. Available from: https://www.bettersafercare.vic.gov.au/clinical-guidance/neonatal/peripheral-arterial-access-in-neonates-requiring-intensive-care#goto-modified-allens-test

83. 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.

16. ANNEXES

16.1- ANNEX 1: TNM CLASSIFICATION

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

PRIMARY TUMOUR (T)

Tx	Primary tumour cannot be assessed
Tis	Carcinoma *in situ*
	SUPRAGLOTTIS
T1	Tumour limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumour 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	Tumour 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. Tumour 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 oesophagus). - T4b: Very advanced local disease. Tumour invades prevertebral space, encases carotid artery, or invades mediastinal structures
	GLOTTIS
T1	Tumour limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility: - T1a: tumour limited to one vocal cord - T1b: Tumour involves both vocal cords.
T2	Tumour extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3	Tumour 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 disease: - T4a: Moderately advanced local disease. Tumour 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 oesophagus). - T4b: Very advanced local disease. Tumour invades prevertebral space, encases carotid artery, or invades mediastinal structures.
	SUBGLOTTIS
T1	Tumour limited to the subglottis.
T2	Tumour extends to vocal cord(s) with normal or impaired mobility.
T3	Tumour 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 disease: - T4a: Moderately advanced local disease. Tumour 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 oesophagus). - T4b: Very advanced local disease. Tumour 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	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	N3a: Metastasis in a lymph node >6cm in greatest dimension and ENE (–) N3b: Any metastasis in a lymph node ENE(+)

DISTANT METASTASIS (M)

MO	No distant metastasis
N1	Distant metastasis

16.2- ANNEX 2: AMERICAN SOCIETY OF ANESTHESIOLOGY PHYSICAL STATUS (ASA PS) CLASSIFICATION SYSTEM

ASA PS CLASIFICATION	DEFINITION
ASA I	A normal healthy patient.
ASA II	A patient with mild systemic disease.
ASA III	A patient with severe systemic disease.
ASA IV	A patient with severe systemic disease that is a constant threat to life.
ASA V	A moribund patient who is not expected to survive without the operation.
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes.

16.3- ANNEX 3: FRAGILITY AND FUNCIONALITY QUESTIONNAIRES

ESCALA G-8 *(The Oncologist 21:188-195, 2016)*

A: Ha disminuido la ingesta de alimentos durante los últimos 3 meses debido a la pérdida de apetito, problemas digestivos, dificultades para masticar o tragar	0: Disminución severa
	1: Disminución moderada
	2: Ausencia de disminución
B: Perdida de peso durante los últimos 3 meses.	0: > 3kg
	1: No lo sabe
	2: Entre 1 y 3 kg
	3: No ha perdido peso
C. Mobilidad	0: En cama o atado a la silla
	1: Capaz de salir de la cama pero no sale
	2: Sale de la cama
D. Problemas neuropsiquiatricos	0: Severa demencia o depresión
	1: Demencia leve
	2: Sin problemas
E. Peso y talla	0: IMC <19
	1: IMC: 19-21
	2: IMC 21-23
	3: IMC > 23
F. Toma más de tres medicamentos con receta al día?	0: Si
	1: No
G. En comparación a otras personas de su misma edad, ¿cómo considera el paciente su estado de salud?	0: Peor
	0,5: No lo sabe
	1: Buena
	2: Mejor
Edad	0: ≥85 años
	1: 80-85 años
	2: <80 años
RESULTADO TOTAL (0-17):	

ESCALA DE VALORACIÓN FUNCIONAL DE KARNOFSKY

100	Normal: Sin quejas ni indicios de enfermedad.
90	Actividades normales, pero con signos y síntomas leves de enfermedad
80	Actividad normal con esfuerzo, con algunos síntomas de enfermedad
70	Capaz de cuidarse, pero incapaz de llevar a término actividades normales o trabajo activo.
60	Requiere atención ocasional, pero puede cuidarse de si mismo.
50	Requiere gran atención, incluso médica. Encamado <50% del día.
40	Inválido, incapacitado, necesita cuidados y atenciones especiales. Encamado > 50% del día.
30	Inválido grave, severamente incapacitado, tratamiento de soporte.
20	Encapado por complete, paciente muy grave, necesita hospitalización y tratamiento activo.
10	Moribundo.
0	Fallecido.

MENTAL ADJUSTMENT TO CANCER SCALE, MINI-MAC *Watson et al. (1994)*

A continuación encontrará una serie de frases que describen las distintas reacciones que la gente experimenta cuando está enferma. Por favor, marque con una cruz el número situado a la derecha de cada frase que indique en qué medida se aplica su estado actual correspondiendo que:

- Número 1: la frase no tiene NADA que ver con usted.
- Número 2: La frase solo tiene ALGO que ver con usted.
- Número 3: La frase tiene BASTANTE que ver con usted.
- Número 4: La frase tiene MUCHO que ver con usted.

1. Vivo mi vida día a día.	1	2	3	4
2. Me tomo mi enfermedad como un reto.	1	2	3	4
3. Me he puesto en manos de Dios.	1	2	3	4
4. Me he dado por vencido/a.	1	2	3	4
5. Siento mucha rabia por lo que me ha sucedido.	1	2	3	4
6. Me siento completamente pedido cuando intento pensar qué puedo hacer.	1	2	3	4
7. Es un sentimiento devastador	1	2	3	4
8. Valoro lo que tengo	1	2	3	4
9. Me preocupa que la enfermedad vuelva a aparecer o empeore.	1	2	3	4
10. Intento luchar contra la enfermedad	1	2	3	4
11. Intento distraerme cuando me vienen a la cabeza pensamientos sobre mi enfermedad	1	2	3	4
12. No puedo manejar esta situación.	1	2	3	4
13. Me siento aprensivo/a	1	2	3	4
14. No tengo muchas esperanzas puestas en mi futuro.	1	2	3	4
15. Siento que no hay nada que yo pueda hacer para ayudarme a mi mismo/a	1	2	3	4
16. Creo que esto es el fin del mundo.	1	2	3	4
17. No pensar en mi enfermedad me ayuda a hacerle frente.	1	2	3	4
18. Me siento muy optimista.	1	2	3	4
19. He tenido una buena vida, lo que viva a partir de ahora es un regalo.	1	2	3	4
20. Siento que no hay esperanza en mi vida.	1	2	3	4
21. No puedo afrontar esta situación.	1	2	3	4
22. Pensar en mi enfermedad me altera.	1	2	3	4
23. Estoy decidido/a a vencer esta enfermedad.	1	2	3	4
24. Desde que me han diagnosticado mi enfermedad me doy cuenta lo valiosa que es la vida y estoy sacándole el máximo partido.	1	2	3	4
25. Me cuesta creer que esto me haya sucedido a mi.	1	2	3	4
26. Me esfuerzo mucho en no pensar en mi enfermedad.	1	2	3	4
27. Deliberadamente me quito de la cabeza cualquier pensamiento sobre mi enfermedad	1	2	3	4
28. Me encuentro muy nervioso/a por mi enfermedad.	1	2	3	4
29. Estoy asustado/a.	1	2	3	4

16.4- ANNEX 4: VOICE HANDICAP INDEX 30 (VHI-30)

Marque con una X la casilla con la que más se sienta representado/a, yendo desde nunca (0) hasta a siempre (4):

	PARTE I o F: Subescala funcional	0	1	2	3	4
1	La gente oye con dificultad mi voz					
2	La gente me entiende con dificultad en sitios ruidosos					
3	Mi familia no me oye si la llamo desde el otro lado de la casa					
4	Uso el teléfono menos de lo que desearía					
5	Tiendo a evitar la conversación en grupo debido a mi voz					
6	Hablo menos con mis amigos y familiares debido a mi voz					
7	La gente me pide que repita lo que digo al hablar cara a cara					
8	Mis problemas con la voz alteran mi vida personal y social					
9	Me siento desplazado de las conversaciones por mi voz					
10	Mi problema de voz me hace perder dinero					
		Puntuación total:				

	PARTE II o O: Subescala orgánica:	0	1	2	3	4
11	Noto que pierdo aire por la boca cuando hablo					
12	Mi voz suena diferente a lo largo del día					
13	La gente me pregunta “¿qué te pasa con la voz?”					
14	Mi voz suena ronca y seca					
15	Siento que necesito tensar la garganta para producir voz					
16	Nunca sé como va a ser mi voz cuando voy a hablar					
17	Trato de cambiar mi voz para que suene mejor					
18	Me esfuerzo mucho para hablar					
19	Mi voz empeora por la tarde					
20	Mi voz se altera, o “se me va” en mitad de una frase					
		Puntuación total				

	PARTE III o E: Subescala emocional	0	1	2	3	4
21	Estoy tenso cuando hablo con los demás debido a mi voz					
22	La gente parece irritada por mi voz					
23	Creo que la gente no comprende mi problema de voz					
24	Mi voz me molesta					
25	Progreso menos debido a mi voz					
26	Mi voz me hace sentir discapacitado					
27	Me siento molesto cuando me piden que repita una frase					
28	Me siento avergonzado cuando me piden repetir una frase					
29	Mi voz me hace sentir incompetente					
30	Estoy avergonzado de mi problema con la voz					
		Puntuación total:				

PUNTUACIÓN FINAL	

16.5- ANNEX 5: DATA COLLECTION DOCUMENT

Hoja de recogida de datos de las variables demográficas y epidemiológicas en los pacientes participantes del estudio. Marcar con una cruz la opción que mejor se adecue.

HOSPITAL: _____

FECHA: _____ / _____ / _____

Nª HISTORIA CLÍNICA: _____

FECHA DE NACIMIENTO (Día / Mes / Año): ____ / _____ / _____

GÉNERO

☐ Mujer ☐ Hombre

ESTATUS SOCIOECONÓMICO

☐ Clase I ☐ Clase II

☐ Clase III ☐ Clase IV

☐ Clase V

ETNIA

☐ Caucásica ☐ Africana

☐ Asiática ☐ Latinoamericana

☐ Otra

DIAGNÓSTICO

- Localización: _____
- Estadio T:

T1 ☐ T2 ☐

T3 ☐ T4a ☐

T4b ☐

- Estadio N:

N0 ☐ N1 ☐

N2 ☐ N3 ☐

¿REQUERIRÁ ADJUVANCIA CON QUIMIOTERAPIA?

☐ Sí

☐ No

FECHA DE INTERVENCIÓN ____ / _____ / _____

16.6- ANNEX 6: PATIENT'S PROTOCOL INFORMATION DOCUMENT

HOJA DE INFORMACIÓN SOBRE EL ENSAYO CLÍNICO

Nombre del estudio: Comparison of voice quality and funcionality between muscle and fasciocutaneous flaps used for pharyngeal reconstruction after a total laryngectomy.

Centro asistencial:

Investigador/a principal:

Bienvenido/a,
Nos dirigimos a usted para invitarle a participar en un estudio de investigación, llevado a cabo por los Servicios de Otorrinolaringología de varios hospitales de referencia en Cataluña. Este estudio ha sido aprobado por el Comité de Ética e Investigación Clínica del Hospital Universitari Doctor Josep Trueta y por la Agencia Española del Medicamento y Productos Sanitarios

Nuestra intención es que usted comprenda el motivo por el cuál se está realizando este estudio i qué implica formar parte de él para que así pueda decidir de forma voluntaria si finalmente desea participar o no. Es por eso por lo que le rogamos que se tome el tiempo necesario para leer detenidamente y comprender este resumen informativo sobre nuestro estudio.
No tiene por qué decidir hoy acerca de su participación; cualquier duda que surgiese, nuestro equipo le responderá y pondrá a su disposición toda la información necesaria.

DESCRIPCIÓN Y OBJECTIVO DEL ESTUDIO

Los tumores de laringe y de hipofaringe localmente avanzados requieren en muchos casos, para su curación, de una intervención quirúrgica llamada laringectomía total. En esta cirugía se extirpa toda la laringe junto al tumor, con las grandes consecuencias directas que tiene esta intervención: respiración mediante una traqueostomía y pérdida de la voz.

Una vez superados los primeros meses después de la cirugía, los pacientes son capaces de volver a hablar a través de una protesis traqueoesofágica que se coloca de forma ambulatoria.

Durante la cirugía de la laringectomía total, en algunas situaciones, como es su caso al haber sido escogido para participar en este ensayo, debido a las características del tumor, hace falta extirpar una gran parte de faringe junto a la laringe, con la necesidad de reconstruir esa zona a partir de la transposición de tejido de otra parte del cuerpo mediante un colgajo.
Hay muchas técnicas efectivas para realizar estos colgajos y todas ellas permiten al paciente volver a hablar de forma funcional.

El objectivo de este ensayo es comparar 3 de las técnicas de reconstrucción de colgajos más utilizadas actualmente para ver si la calidad de voz desprendida es mejor en alguna de estas técnicas.

METODOLOGÍA E INTERVENCIÓN

En teste estudio participarán un total de 60 pacientes. Cada uno será distribuido aleatoriamente en uno de los 3 grupos del estudio de igual tamaño (A, B y C). En todos los grupos se tratará el tumor mediante la misma técnica quirúrgica: la laringectomía total, difiriendo en la técnica quirúrgica con la que se reconstruirá su faringe.

- A los pacientes del grupo A se les reconstruyen la pared faríngea con un colgajo pediculado del músculo pectoral mayor.
- A los pacientes del grupo B se les reconstruyen la pared faríngea con un colgajo libre fasciocutaneo radial de antebrazo
- A los pacientes del grupo C se les reconstruyen la pared faríngea con un colgajo libre fasciocutaneo del muslo.

Después de la intervención quirúrgica, todos los pacientes independientemente del grupo al que pertenezcan completarán su tratamiento con radioterapia sola o quimio-radioterapia según las características de su tumor y serán seguidos de la misma forma por el equipo de otorrinolaringología. De esta forma, todos los pacientes que participen en el ensayo serán tratados del cáncer de la misma forma, sin diferencias entre los distintos grupos.

BENEFICIOS Y RIESGOS DEL ESTUDIO

En todos los pacientes participantes se les reconstruirá la faringe mediante un colgajo. Todos los colgajos utilizados han demostrado ser buenas opciones, ya que actualmente los pacientes pueden volver a hablar con una voz muy funcional indistintamente del colgajo que se le haya realizado. El principal beneficio que usted va a recibir si participa en el estudio es tener un seguimiento extra que no se hace de rutina en los pacientes laringectomizados. A partir de que se le coloque la prótesis traqueoesofágica, si usted decide participar en el estudio será citado varias veces a la consulta de su equipo de otorrinolaringología en la que se le realizará una valoración de la funcionalidad de la voz a través de un cuestionario.

Los riesgos a los que está sometido el paciente en este ensayo derivan de las posibles complicaciones quirúrgicas, por lo que no hay más riesgos en este ensayo clínico que en el tratamiento actual estándar, ya que en todos los casos la cirugía sería la misma.

ALTERNATIVAS AL PROCEDIMIENTO

Si el paciente elige no participar en el ensayo clínico será tratado mediante la misma técnica quirúrgica (laringectomía total) y la pared faríngea será reconstruida con la técnica quirúrgica que el equipo quirúrgico escojan de forma consensuada, sin ningún tipo de aleatorización. En cualquier caso, la técnica usada será alguna de las 3 que se realiza en el ensayo.

En referencia al seguimiento, los pacientes que no participen en el estudio recibirán igualmente la misma atención que los que participen, con la única diferencia que los que escojan no participar no acudirán a las visitas extras de valoración de la voz después de que se les haya colocado la prótesis de voz traquoeoesofágica.

CONFIDENCIALIDAD

Desde el comienzo de su participación en este estudio, todos los datos personales que se recojan serán gestionadas y almacenadas con total confidencialidad ajustándose a la actual legislación de la Ley Orgánica 3/2018, de 5 de diciembre, de Protección de datos personales y garantía de los derechos digitales. Dicha información será identificada con un número y será usada tan sólo con fines de investigación.
El acceso a ella estará sólo a disponibilidad a investigadores y otras autoridades sanitarias. Usted dispone el derecho de poder consultar la información recopilada y corregirla en caso de error. Le garantizamos que ninguna información personal será publicada.

DIFUSIÓN DE LOS RESULTADOS

Cuando haya finalizado el estudio y se hayan extraído conclusiones, la intención es publicar dichos resultados en revistas científicas. De esta forma, otros centros asistenciales y pacientes con la misma afección podrán beneficiarse. Como se ha comentado anteriormente, en dichas publicaciones no aparecerá ningún dato personal.

PARTICIPACIÓN Y COMPENSACIÓN ECONÓMICA

Los investigadores que participan en este estudio no obtienen beneficio económico.
Además, debe comprender que su participación en este estudio es estrictamente voluntaria. Por lo tanto, si usted decide participar no recibirá ningún tipo de compensación económica, pero tampoco les supondrá ningún gasto. En el caso contrario, tampoco supondrá un cambio en cuanto a su atención médica por el equipo de especialistas.

Si usted decide participar, deberá firmar la hoja de consentimiento informado conforme da su aprobación. Es también su derecho poder salir del estudio si en algún momento de su transcurso así lo decide; dicho hecho tampoco alterará su atención médica, aunque le rogamos que lo comunique a alguno de los profesionales del Servicio de Otorrinolaringología de su hospital.

Antes de decidir sobre su participación, usted es libre de pedir una segunda opinión a otros profesionales médicos si así lo requiere.

RESPONSABILIAD Y ASEGURANZA

Los promotores de este estudio tienen contractada una póliza de seguro para su realización, tal como se establece en la legislación. En caso de perjuicio o de detrimento de su salud en consecuencia a la participación de su participación en este estudio, se le proporcionará la indemnización correspondiente.

CONTACTO

En caso de cualquier duda durante la realización de este estudio, podrá ponerse en contacto siempre que lo necesite con: _____

16.7- ANNEX 7: INFORMED CONSENT

DOCUMENT DE CONSENTIMENT INFORMAT DEL PACIENT

Jo, _____, amb document de identificació personal (DNI/NIE) _____ declaro que:

- He rebut una copia del full de informació per al pacient.
- He rebut i entès tota la informació que apareix en el document d'informació per al pacient.
- He pogut plantejar qualsevol dubte que m'ha sorgit, i me l'han resolt adequadament.
- Estic conforme amb la quantitat de informació que se m'ha proporcionat.
- Entenc que la meva participació és voluntària i no remunerada.
- Entenc els potencials riscos i beneficis derivats de participar en aquest estudi.
- Comprenc que les meves dades i proves seran confidencials.

A més, comprenc que tot i haver firmat el consentiment informat, puc revocar-lo en qualsevol moment i que això no suposarà un perjudici en el meu tractament i assistència sanitària.

En conseqüència,

- Dono lliurement la meva conformitat a participar en l'estudi "*Comparison of voice quality and funcionality between muscle and fasciocutaneous flaps used for pharyngeal reconstruction after a total laryngectomy.*" i estic d'acord en què la informació obtinguda en aquest assaig clínic pugui ser utilitzada en investigacions futures.
- Accepto que els investigadors del projecte puguin posar-se en contacte amb mi en un futur si es considera oportú.

☐ **Sí** ☐ **No**

Signatura del pacient **Signatura de l'investigador**

Lloc i data: _____, _____ de _____ de l'any_____

REVOCACIÓ DEL CONSENTIMENT INFORMAT

Jo, _____, amb document de identificació personal (DNI/NIE) _____, revoco el consentiment prèviament firmat per a la participación en el assaig clínic: "*Comparison of voice quality and funcionality between muscle and fasciocutaneous flaps used for pharyngeal reconstruction after a total laryngectomy".*

Signatura del pacient: Signatura de l'investigador:
Lloc i data: _____, _____ de _____ de l'any _____

DOCUMENTO DE CONSENITMIENTO INFORMADO DEL PACIENTE

Yo, _____, con documento de identificación personal (DNI/NIE) _____ declaro que:

- He recibido una copia de la hoja de información para el paciente.
- He leído y comprendido toda la información que aparece en la hoja de información para el paciente.
- He podido exponer cualquier duda que me ha surgido, y me la han resuelto adecuadamente.
- Estoy conforme con la cantidad de información que me ha sido proporcionada.
- Comprendo que mi participación es voluntaria y no remunerada.
- Entiendo los potenciales riesgos y beneficios derivados de participar en este estudio.
- Comprendo que mis datos y pruebas serán confidenciales.

Además, comprendo que aún y haber firmado el consentimiento informado, puedo revocarlo en cualquier momento y que esto no supondrá un perjuicio en mi tratamiento y asistencia sanitaria.
En consecuencia:

- Doy mi conformidad a participar en el estudio "*Comparison of voice quality and funcionality between muscle and fasciocutaneous flaps used for pharyngeal reconstruction after a total laryngectomy"*. y estoy de acuerdo en que la información obtenida en este ensayo clínico pueda ser utilizada en investigaciones futuras.
- Acepto que los investigadores del proyecto puedan ponerse en contacto conmigo en un futuro si se considera oportuno.

☐ **Sí** ☐ **No**

Firma del paciente	**Firma del investigador**

Lugar y fecha: _____, _____ de _____ del año _____

REVOCACIÓN DEL CONSENTIMIENTO INFORMADO

Yo, _____, con documento de identificación personal (DNI/NIE) _____ revoco el consentimiento previamente firmado para la participación en el ensayo clínico: "*Comparison of voice quality and functionality between muscle and fasciocutaneous flaps used for pharyngeal reconstruction after a total laryngectomy".*

Firma del paciente	**Firma del investigador**

Lugar y fecha: _____, _____ de _____ del año _____