Universitat de Girona
Facultat de Medicina

SARCOPENIA AS A PREDICTIVE FACTOR FOR PHARYNGOCUTANEOUS FISTULA AFTER TOTAL LARYNGECTOMY

A prospective cohort study

FINAL DEGREE PROJECT

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1. ABBREVIATIONS

AJCC	American Joint Committee on Cancer
CAD	Coronary atherosclerotic heart disease
CEIC	Comitè Ètic d'Investigació Clínica
COPD	Chronic obstructive pulmonary disease
CSA	Cross-sectional muscle area
CT	Computed tomography
CTX	Chemotherapy
C3	Third cervical vertebra
EAROL-HNS	European Academy of Otorhinolaryngology – Head and Neck surgery
ENE	Extranodal extension
EWGSOP	European Working Group on Sarcopenia in Older People
FLN	Flexible fibreoptic nasolaryngoscopy
HNC	Head and neck cancer
HPV	Human papillomavirus
L3	Third lumbar vertebra
MRI	Magnetic resonance imaging
PCF	Pharyngocutaneous fistula
RT	Radiotherapy
SCC	Squamous cell carcinoma
SEORL	Sociedad Española de Otorrinolaringología
SMI	Skeletal muscle index
SMM	Skeletal muscle mass
TL	Total laryngectomy

2. ABSTRACT

BACKGROUND: laryngeal cancer is the most prevalent type of head and neck cancer. A significant part of them is diagnosed at locally advanced stages, in which total laryngectomy remains one of the main treatment options. Pharyngocutaneous fistula is the most frequent complication following total laryngectomy, which increases the need for hospital stay, delays the start of adjuvant therapy, and lowers quality of life. The risk factors of pharyngocutaneous fistula have not been yet thoroughly established, and sarcopenia has drawn more attention in the past few years. Patients with laryngeal cancer may experience loss of skeletal muscle mass due to tumour characteristics. Low skeletal muscle mass has been associated with postoperative complications and longer hospital stay in surgical oncology.

OBJECTIVES: the aim of this study is to assess whether sarcopenia is an independent predictive factor for the development of pharyngocutaneous fistula after primary total laryngectomy in patients with locally advanced laryngeal and hypopharyngeal carcinoma. When it comes to secondary objectives, number of hospitalization days will be assessed.

DESIGN AND SETTING: the study is designed as a multicentre observational prospective cohort study with a 3-week follow-up performed among five reference hospitals of Catalonia.

PARTICIPANTS: adult patients with new diagnosis of locally advanced laryngeal or hypopharyngeal squamous cell carcinoma who are treated with a primary total laryngectomy.

METHODS: 74 patients will be recruited with a consecutive non-probabilistic sample method. Recruitment of patients will last 2 years. They will be divided into two groups depending on their exposure to sarcopenia. Sarcopenia will be assessed using CT scans at the level of the third cervical vertebra. Patients will be followed during a 3-week postoperative period in order to assess pharyngocutaneous fistula occurrence and number of hospitalization days.

KEYWORDS: *sarcopenia*, *pharyngocutaneous fistula*, *total laryngectomy*, *laryngeal carcinoma, hypopharyngeal carcinoma, computed tomography*

3. INTRODUCTION

3.1. Hypopharynx and larynx anatomy

The larynx is an organ responsible for speech and airway protection. It is in the anterior part of the neck at the heigh of C3 – C6 and it is formed by a cartilaginous skeleton, composed of 9 cartilages, which is held together by ligaments and muscles. Inferiorly, the larynx is continuous with the trachea, and the superior region connects to the inferior part of the pharynx. Its posterior wall is in touch with the hypopharynx (1).

The **hypopharynx** is the portion of the pharynx where the cavity separates anteriorly into the larynx and posteriorly into the oesophagus. It is located between the superior border of the epiglottis and inferior border of the cricoid cartilage (2). It has three anatomic subsides (3):

- Posterior pharyngeal wall: it consists of mucosa and the constrictor muscle.
- Pyriform sinuses: they are two recesses formed by the invagination of the larynx into the hypopharynx. Medially to pyriform sinuses are located the aryepiglottic folds.
- Post-cricoid area: it is the anterior wall of the hypopharynx at the level of the cricoid. It extends from the cricoarytenoid joints to the lower border of the cricoid cartilage.

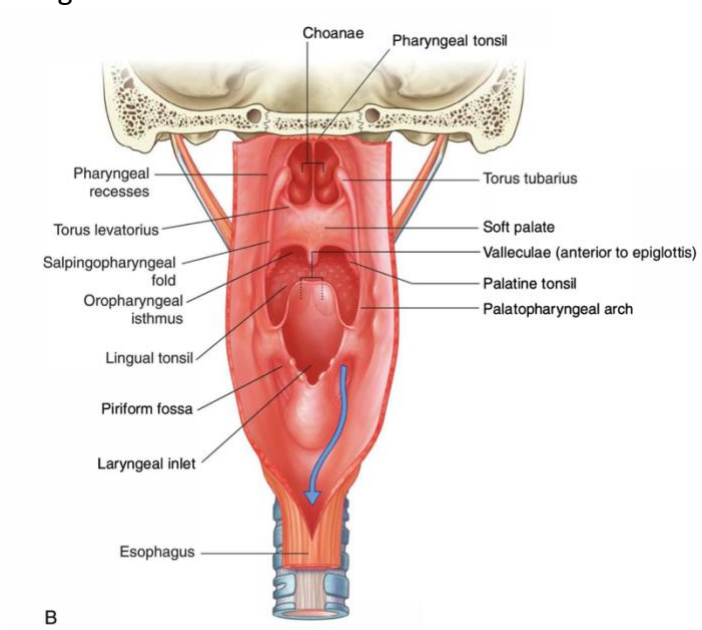

Figure 1. Posterior view with the pharyngeal wall opened (4).

The **larynx** is anatomically divided in three regions (5):

- Supraglottis: it consists of the epiglottis, aryepiglottic folds, arytenoids, and ventricular bands (false vocal cords).
- Glottis: it is composed of the true vocal cords and the anterior and posterior commissures.
- Subglottis: the region from the lower border of the glottis to the lower border of the cricoid cartilage.

This organ has several important functions, including phonation, the cough reflex and protection of the lower respiratory tract.

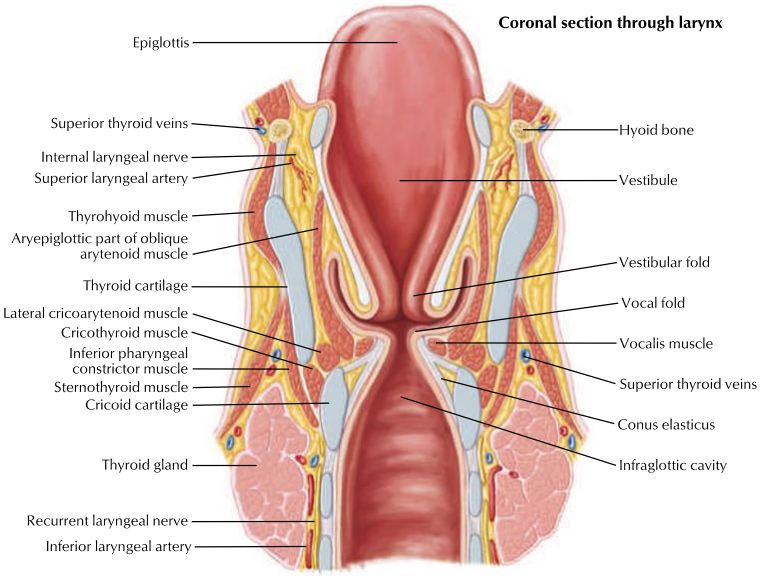

Figure 2. Coronal section through larynx (6)

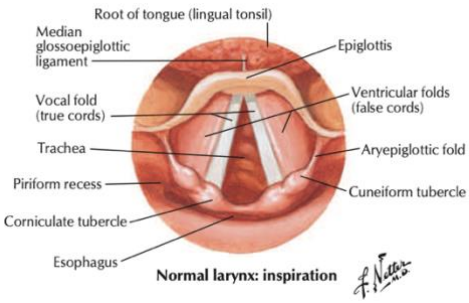

Figure 3. Normal larynx: inspiration (6)

3.2. Laryngeal cancer

3.2.1. Epidemiology

Head and neck cancer (HNC) is a heterogeneous group of upper aerodigestive tract malignancies (7). They are the seventh most common cancer globally, accounting for more than 660.000 new cases and 325,000 deaths annually worldwide during 2020 according to GLOBOCAN (8,9).

Laryngeal cancer is the second most common location in HNC, accounting for 211,000 new cases and 126,000 deaths each year worldwide (10). Larynx cancer is very common in Europe, being Spain the country with the highest incidence in the world, followed by Italy and France (11).

Larynx cancer usually appears in the sixth and seventh decade of life and it is related to tobacco and alcohol consumption (10). It is most common in men, but as the number of smoking women has increased over the past years, the ratio between men and women has decreased (12).

The most common histological type is squamous cell carcinoma (SCC), accounting for 95% of laryngeal carcinomas (11). About the regions of the larynx affected by cancer, their distribution is not uniform across the world. In Spain, supraglottic cancer is the most frequent, while in Italy or England predominates the glottic cancer. Subglottic tumours are the least common in all the countries (12).

3.2.2. Risk factors

Several risk factors have been associated with the development of laryngeal carcinoma (13).

- **Tobacco** and **alcohol** consumption are the most significant risk factors for larynx SCC. The risk is proportional to the intensity and duration of consumption, and it gradually decreases after quitting but does not return to the baseline rate for at least 20 years. Tobacco and alcohol act synergistically, and combined they have a multiplicative effect on the risk of laryngeal cancer. Alcohol is more related to the risk for supraglottic carcinoma, whereas smoking tobacco is strongly associated with glottic carcinoma (14).
- **Occupational toxins**: exposure to occupational toxins, such as asbestos, polycyclic aromatic hydrocarbons, and textile and wood dust, have been also associated with an increasing risk of larynx SCC (13).
- Human papillomavirus (HPV) infection: **HPV type 16** infection is recognized as a risk factor for HNC, especially for oropharyngeal cancers (15). In respect of the larynx, the presence of HPV and/or the marker p16 has been demonstrated in a minority of laryngeal tumours (13)
- **Genetic susceptibility**
- **Diet**: a higher intake of red meat and fat increases the risk of laryngeal cancer, while a diet varied in fruit and vegetables potentially has a protective effect (13,14).

3.2.3. Clinical presentation

The symptoms of laryngeal SCC depend on the site from which the primary tumour originates.

The principal symptom of glottic tumours is **dysphonia**, which develops early in the natural history of disease. Therefore, patients with glottic SCC are, in general, diagnosed in early stages. In advanced-stage disease, patients can present dyspnoea and stridor (14,16).

Glottic tumours stay localized in the glottis for a prolonged time because of the natural barriers to tumour spread (ligaments, membranes, and cartilages) and the lack of glottic lymphatic drainage (14).

Supraglottic tumours may cause non-specific symptoms, in consequence they are usually diagnosed in advanced stages of the disease. Patients can present symptoms such as **foreign body feeling**, **pharyngeal paraesthesia**, clearing throat, non-specific cervical soreness, otalgia, and mild dysphagia. Only when the tumour spreads to vocal cords appears dysphonia (16).

Supraglottic larynx has a rich lymphatic drainage, so it is common that patients with supraglottic SCC may also present metastatic cervical adenopathy as the first symptom (14).

Subglottic tumours are very infrequent occurring in isolation. In general, they are diagnosed in advanced-stage disease (16) and the most common symptoms are **dyspnoea** and **stridor** (14).

3.2.4. Diagnosis

At the presence of any of the symptoms explained above, it is important to carry out a detailed **clinical history** by going deeply into the symptomatology and asking about exposure to risk factors for laryngeal cancer such as tobacco and alcohol consumption.

After the interview, a full **head and neck examination** is performed, which must always include a cervical lymph node palpation. It is also performed a direct **flexible fibreoptic nasolaryngoscopy** (FLN) in order to observe the larynx and mucosal surfaces, and possible lesions. It is useful to have an idea about the location of the tumour, its

extension, and the mobility of vocal cords. In case of suspected malignancy, a **biopsy** should be taken for anatomopathological study of the lesion.

Radiological imaging is imperative in the evaluation of a patient of laryngeal SCC. Both computed tomography (CT) scan and magnetic resonance imaging (MRI) are useful techniques to evaluate larynx tumours. However, **neck CT scan** with intravenous contrast is the most used radiological study.

Once the diagnosis of laryngeal cancer is obtained, an extension study should be done with a thoracic CT (12–14).

3.2.5. Staging

Laryngeal tumours are staged according to **TNM classification** system described by the American Joint Committee on Cancer (AJCC). The TNM system considers the extension of the tumour, the presence of metastases to cervical lymphadenopathy and the existence of distant metastases (5,17). Complete TNM classification for laryngeal cancer can be seen in *Annex 1.*

Table 1. Laryngeal cancer stage groups according to AJCC 8th edition.

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1-3	N1	M0
Stage IVA	T4a	N0-1	M0
	T1-4a	N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

3.2.6. Treatment

Larynx cancer treatment depends on stage of the tumour and its location (glottis, supraglottis or subglottis). The main treatments are surgery, radiotherapy (RT), and chemotherapy (CTX). The following treatment is based on *Institut Català d'Oncologia* and *Sociedad Española de Oncología Médica* guideliness (18,19).

1. ***Early stage***: it includes stages I and II (T1-2 N0 M0). Conservative laryngeal surgery is preferred rather than open surgery. RT will be considered in case extensive surgical resection is required. The first-line treatment varies according to location:
   - Glottis: transoral laser resection is elected in T1aN0 and T2, while in T1bN0 is preferred RT.
   - Supraglottis: transoral laser resection and functional neck dissection.
   - Subglottis: RT to the tumour and lymph node areas II, III, IV and VI.
2. ***Resectable locally advanced***: it includes stages III and IVA (T3-4a N0-2 M0). The best treatment option for each patient must be determined through a multidisciplinary assessment. Surgery or RT are the primary treatments:
   - Surgical treatment: total versus partial laryngectomy and neck dissection followed by adjuvant RT. In cases of extracapsular lymph node extension and/or affected margins, CTX is added. This option is specially indicated in T4a and subglottic tumours.
   - Organ preservation treatment: induction CTX with TPF (Cisplatin, Docetaxel, and 5-Fluorouracil) for 3 weeks. According to the response it will be followed by:
     - Adjuvant RT if complete response of the primary tumour (without lymph node progression).
     - RT or RT + Cisplatin/Cetuximab if partial response (50% reduction of primary tumour without lymph node progression).
     - Total laryngectomy including neck dissection followed by RT or chemoRT if stable disease or progression.
3. ***Unresectable locally advanced***: unresectable tumours are T4b or any T with unresectable N. There are different treatment options depending on the tumour size and patient's conditions. The options are induction CTX with TPF, chemoRT + Cisplatin or RT + Cetuximab.

4. ***Recurrent and metastatic disease***: Platin + 5-Fluorouracil + Cetuximab or Paclitaxel. The treatment should be individualised depending on the previous treatments they have received.

3.3. Hypopharyngeal cancer

Hypopharyngeal tumours account for 6% of all HNC. The most common location is **pyriform sinus**, followed by posterior pharyngeal wall and post-cricoid area. The SCC is the most common histology identified in 95% of the cases (20).

The prognosis of this cancer is worse due to 75% of them are usually diagnosed in advanced stages, with 5-year survival rates in early stages of 40-70% and 35% in advanced stages (20).

As for all other HNC, **tobacco** and **alcohol** are the most important risk factors, which have a synergic effect. Other risk factors include exposition to toxics and Plummer-Vinson syndrome (21).

The main symptoms in hypopharyngeal tumours are **dysphagia** and **odynophagia** However, initially they usually are **asymptomatic** and the only complaint the patient may have is simple discomfort when swallowing or a foreign body sensation in the pharynx (20).

A similar study to the one for larynx cancer is carried out once hypopharyngeal cancer is suspected, in order to confirm the diagnosis. **Nodal metastasis** occurs relatively early, approximately 70% of patients will have an affected lymph node at the time of diagnosis. Therefore, examination of the neck is especially important (21).

The treatment depending on the stage (21):

- ***Early stage*** (T1-2): RT or conservative surgery followed by RT.
- ***Advanced stage*** (T3-4): resectable tumours can be treated with total laryngectomy with partial pharyngectomy and selective neck dissection followed by CTX, while the treatment of unresectable tumours is RT or RT in combination with CTX.

3.4. Total laryngectomy

Total laryngectomy (TL) is a surgical procedure which involves the complete removal of the larynx, and it leads to interruption of the airway. Respiration is then performed through a tracheal stoma created by moving the trachea close to the skin in the lower, anterior, cervical region (22).

This complete and permanent separation between the superior and inferior part of the airway after a TL results invoice and smell loss (22).

According to the intentionality of the surgery, TL can be classified as (23):

- **Primary TL**: a first-line treatment indicated in patients with advanced disease, especially if there is invasion of the cartilage and/or the extralaryngeal soft tissue of the neck, and extensive involvement of the base of tongue.
- **Salvage TL**: it is indicated in patients with recurrent or persistent disease after RT ± chemotherapy, as a rescue therapy.

This surgery is primarily intended to treat advanced laryngeal cancer, but it may also be used to treat posttraumatic laryngeal stenosis resistant to other treatments or benign, extensive tumours with malignancy potential (recurrent laryngotracheal papillomatosis) (22).

3.4.1. Indications

The main indications for TL are as described below (14,22):

- Advanced larynx or hypopharynx tumours with thyroid or cricoid cartilage destruction and anterior extra laryngeal invasion, with damage larynx (laryngeal dysfunction, airway obstruction, or severe aspiration) which will not likely function again even if preserved anatomically.
- Posterior commissure or bilateral arytenoid/cricoarytenoid joint tumour involvement.
- Circumferential submucosal disease with or without bilateral vocal cord paralysis.
- Subglottic extension with extensive invasion of the cricoid cartilage.
- Failed response to radiotherapy or chemoradiotherapy.

- Hypopharyngeal tumour originating at or spreading to the postcricoid mucosa.
- Histopathological subtypes of tumours that are resistant to radiotherapy: soft tissue sarcomas, chondrosarcomas, melanomas, adenocarcinomas, large cell neuroendocrine tumours, tumours of the minor salivary glands.
- Extensive pharyngeal or tongue base resections in patients with high risk for aspiration problems.
- Radiation necrosis of the larynx with no response to adequate conservative management.
- Severe laryngeal trauma that does not allow functional reconstruction of the organ.
- Non-oncological diseases predisposing to chronic aspiration.
- Recurrent laryngeal papillomatosis with a high risk of tracheal invasion.

3.4.2. Preoperative assessment

Currently, in patients diagnosed with laryngeal carcinoma who are candidate for TL, some questionnaires are performed preoperatively with the aim to detect those patients who are subject to develop negative outcomes after surgery. The following questionnaires can be seen in *Annex 2*:

- G8 Screening Tool
- Karnosfky Performance Scale Index
- Barthel Index for Activities of Daily Living

These questionnaires are a complementary tool in the decision of whether a patient can undergo the surgery or not. Moreover, it allows to identify patient's condition and optimize it, if needed, before surgery, to improve postoperative outcomes.

It is known as prehabilitation or making patient fit for surgery, and it has a multimodal approach. It includes exercise, nutritional support with dietary advice, protein and vitamin supplementation, and mental support (24).

3.4.3. Relevance of surgical technique

A TL involves the excision of all laryngeal structures and a section of the upper trachea. It results in a disconnection of the airway so a tracheostoma is performed (25).

Once the incision and flap elevation are made, dissection of adjacent structures must be performed so the larynx is freed up. Then, as a means to remove the larynx, entering into the pharynx is required.

After removal of the larynx, the resulting defect of the pharynx must be repaired, creating the **neopharynx**. When it is possible, primary closure is the first option for neopharynx reconstruction. However, if primary closure is not feasible because there is not enough pharyngeal mucosa remnant, reconstruction methods such as pedicled flaps (e.g., pectoralis major myocutaneous flap) or free vascularized flaps (e.g., free radial forearm flap) can be used (25).

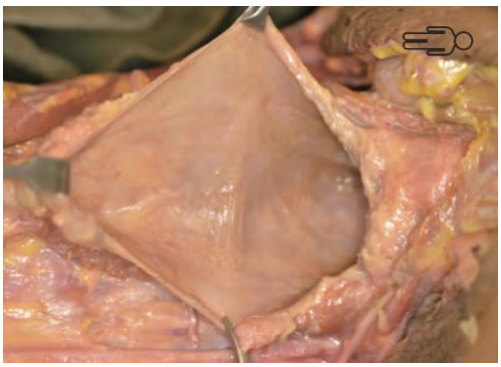

Figure 4. Preserved pharyngeal mucosa wide enough to avoid dysphagia after primary closure (26).

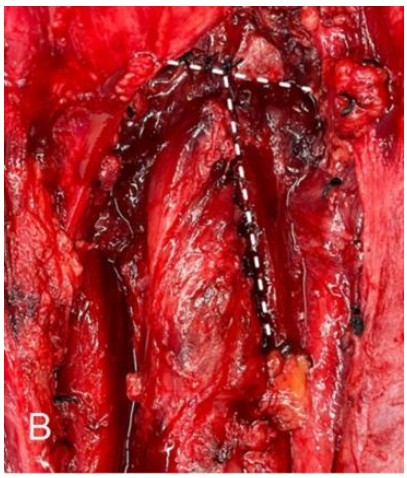

Figure 5. The mucosal layer of the neopharynx. T-shape closure (25).

The suturing technique for mucosal closure is crucial, as it must ensure a properly closure without too much tension. If sutures are too tight, the mucosa may tear or develop necrosis, while if they are too loose, a **fistula** or dehiscence may occur (22).

3.4.4. Postoperative management

In addition to standard postoperative care, early postlaryngectomy patients also receive the following monitoring: checking the wound drain vacuum and the neck flap viability, tracheostomy tube and suture line care, and nasogastric tube feeding.

Drains are removed when output is less than 25 mL/day in 2 consecutive days. Oral feeding is usually resumed 7 days after primary surgery, and after 12-14 postoperative days in previously radiated patients (14).

3.4.5. Complications

Early complications after TL mostly occur during the patient's postoperative hospitalization. It includes bleeding, drain failure, hematoma, seroma, infection of the wound and/or adjacent tissue, pharyngotracheal or pharyngocutaneous fistulas and wound dehiscence (14,22) .

Late complications include pharyngoesophageal stenosis, stoma stenosis and hypothyroidism (14).

3.5. Pharyngocutaneous fistula

Pharyngocutaneous fistula (PCF) is an abnormal communication between the pharynx and the cervical skin, resulting in a saliva leak emerging from the cutaneous orifice after swallowing. The communication usually occurs around the surgical incision or, less frequently, around the tracheostoma (27). Its development is due to a failure in the pharyngeal repair following a malignant neoplasm resection (28).

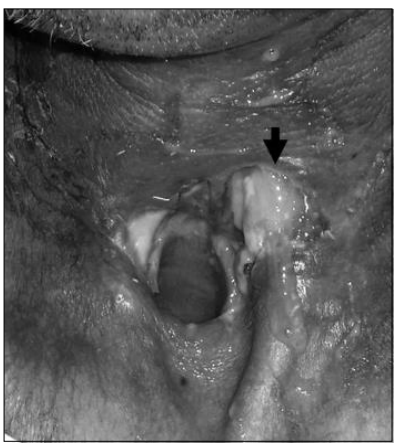

Figure 6. Pharyngocutaneous fistula situated at the level of the surgical incision to the left of the tracheostoma. The arrow points to the saliva outflow point (27).

It is the most common complication following TL. Most cases usually occur in the early postoperative period, from 7 to 10 days after surgery (29). It is rarely that PCF occur later than 30 days after surgery (30).

The reported incidence of PCF varies from 3 to 65%, depending on the study (29), with an average of 22.3% (31). Its incidence also changes depending on the type of TL, being 14.3% for primary TL and 27.6% for salvage TL (32).

PCF represents an increase of morbidity, hospitalization stay and treatment costs, and it is also associated with a delay in adjuvant therapy which can lead to a delay of oral feeding onset and voice rehabilitation (33). In addition, it has a negative impact on patients' psychological state, as well as it reduces their quality of life (34).

The complications associated with the persistence of this abnormal communication are wound infection, aspiration pneumonia and, rarely, carotid artery and jugular vein rupture if inflammation spreads nearby these vessels (28).

3.5.1. Risk factors

Numerous risk factors have an impact on PCF development after TL. However, even though exists literature about the risk factors of PCF, some of them are still controversial. Therefore, studies claim the need to do more research to figure out the most important risk factor.

According to systematic reviews and meta-analysis, the patients **aged > 60 years**, **smokers**, with **comorbidities** like diabetes, chronic obstructive pulmonary disease (COPD) and coronary atherosclerotic heart disease (CAD), and with **low preoperative albumin** (≤3.5 g/dL) **and haemoglobin levels** (≤12.5 g/dL) have more risk of PCF. The T-stage and the site of the tumour are also important, being **T3/T4** and **supraglottic tumours** more likely to develop a PCF. With regard to the treatment, the likelihood of PCF occurrence is higher in patients who have received **previous radiotherapy**, undergone a **salvage surgery** or with **positive surgical margins** (35–39).

Table 2. Potential risk factors of PCF.

Patient characteristics	Tumour characteristics	Treatment characteristics

- Age
- Smoking
- Preoperative albumin level
- Preoperative haemoglobin level
- Comorbidities
  ○ Diabetes
  ○ CAD
  ○ COPD
	- T-stage
	- Tumour site
		- Previous RT
		- Salvage surgery
		- Positive surgical margins

3.5.2. Diagnosis

The diagnosis of PCF is simple, and it is based on **clinical features**: fever, wound erythema, drainage, and the appearance of saliva at wound after swallowing about 7 to 11 days after laryngeal surgery.

The first signs of fistula are the appearance of erythema and/or cervical oedema. PCF can be identified by their cutaneous opening (salivary or purulent leakage), which in most cases is located laterally at the level of the skin incision or medially near the tracheostoma (40).

In addition to that, fever in the first 48 hours after surgery has been shown to be an excellent predictor for early recognition of PCF development (29). As said before, diagnosis of PCF is mainly clinical. However, there are some tests like methylene blue dyed water or videofluoroscopic evaluation which can be used to exclude PCF (30). Even then, there is no gold standard test for an early diagnosis of PCF. A barium swallow test is also useful to rule out a fistula and initiate oral diet (40).

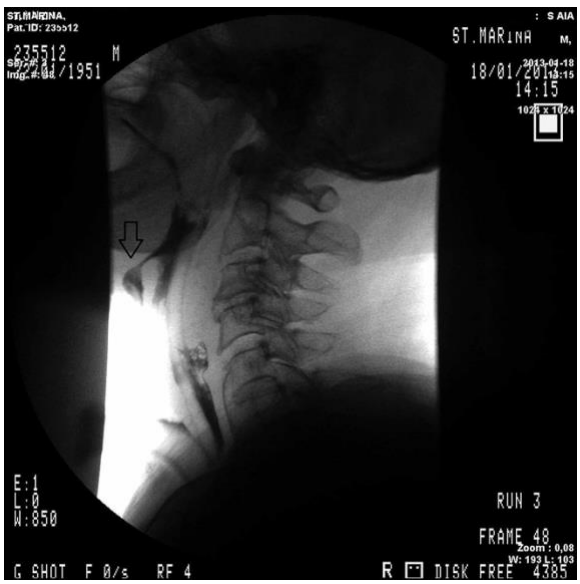

Figure 7. Barium swallow radiographs. On sagittal view fistula between the neopharynx and the skin at the C2-C4 level is visualized. A nasogastric tube is in place (41).

3.5.3. Treatment

Once PCF is diagnosed, the initial management is conservative because almost 80% of cases heal spontaneously. This conservative treatment consists in compressive

dressings, daily local wound cleaning, antibiotics coverage and suspension of oral feeding with position of a nasogastric tube or parenteral nutrition (42).

When conservative measures fail, surgical closure of PCF is required since the continuous leak of saliva expose the patient to risk of infection, aspiration, not to mention vessels exposure or rupture (32).

We can talk about major fistula when it persists despite 4 weeks or more of conservative management, and it requires surgical treatment. It is especially associated with previous radiotherapy (43).

To close the fistula, different surgical options can be used such as primary closure, pedicled muscle flaps or free flaps. The choice of the technique depends on the diameter of the fistula, history of previous RT, amount of residual pharyngeal mucosa and condition of soft tissue (32).

3.6. Sarcopenia

The term sarcopenia is derived from the Greek words “sarx” meaning flesh and “penia” meaning lack of.

In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) defined sarcopenia as a progressive and generalized skeletal muscle disorder which is associated with increased risk of negative events such as falls, fractures, physical disability and mortality (44).

In 2018, the working group met again and EWGSOP2 updated the original definition using low muscle strength as the principal determinant of sarcopenia instead of low muscle mass. According to 2018 definition (44):

- Sarcopenia is **probable** when low muscle strength is detected.
- Sarcopenia diagnosis is **confirmed** by the presence of low muscle quantity or quality.
- Sarcopenia is **severe** when low muscle strength, low muscle quantity or quality and low physical performance are all detected.

As muscle function is rarely measured, whereas muscle quantity can be easier to retrospectively determine, terms of sarcopenia and low skeletal muscle mass (SMM) are frequently used indistinctly in literature (45).

3.6.1. Types of sarcopenia

When sarcopenia is attributed to age and no other specific causes are identified, it is considered **primary**. On the other hand, sarcopenia is **secondary** when it occurs due to a systemic disease, especially when inflammatory processes are involved, like malignancy or organ failure. Physical inactivity, either by sedentary lifestyle or disability, and malnutrition can also develop sarcopenia (44).

3.6.2. Measurement of sarcopenia

The EWGSOP has defined multiples techniques and questionaries to identify and classify sarcopenia. Technique selection depends on the patient, healthcare centre resources and the purpose of testing. Cruz-Jentoft et al. explain the different tools to recognise sarcopenia in clinical practice and research (44):

- Muscle strength:
    - **Grip strength** using a calibrated handheld dynamometer.
    - **Chair stand test**: this test assesses leg strength and endurance (quadriceps muscle group). It measures the amount of time the patient needs to sit and stand up five times from a chair without using his/her arms. There is a variation which counts the number of times the patient stands up for 30 seconds.
- Muscle quantity:
    - **Dual energy X-ray absorptiometry** (DXA): it uses two X-ray beams with different energy levels to determine body composition based on the absorption of these X-rays by muscle mass, fat, and bone.
    - **Bioelectrical impedance analysis** (BIA): it estimates muscle mass based on body electrical conductivity. The impedance is inversely related to total body water. While an alternating current passes through a patient, the different impedance between tissues is used to determine total

muscle mass. This technique can be influenced by the hydration status and body fat distribution of the patient (46).

- **Cross-sectional muscle area** (CSA) **by computed tomography** (CT) **scan or magnetic resonance imaging** (MRI): although CT/RMI are considered gold standards for non-invasive analysis of muscle quantity, these tools are not usually used in primary care due to its high costs and the necessity for highly qualified personnel to use the equipment. In cancer patients, CT scan is a convenient tool for detecting sarcopenia because it is commonly used to stage and monitor the disease. The CSA measured on CT at L3 vertebra level is highly associated with total body muscle mass (46).

- Physical performance:
  - **Gait speed**: the time a patient needs to walk 4 metres is measured. A cut-off speed ≤0.8 m/s is advised by EWGSOP2 as an indicator of severe sarcopenia.
  - **Short Physical Performance Battery**: 3 tests are involved: gait speed, balance test, and chair stand test. The maximum score is 12 points and a score of ≤8 indicates poor physical performance. More detail about this can be seen in *Annex 3.*
  - **Timed-Up and Go test**: patients must be sited in a chair, and they are asked to stand up, walk 3 metres, turn around and walk back and sit down again.

All the techniques described above are used to assess, confirm, and define the severity of sarcopenia.

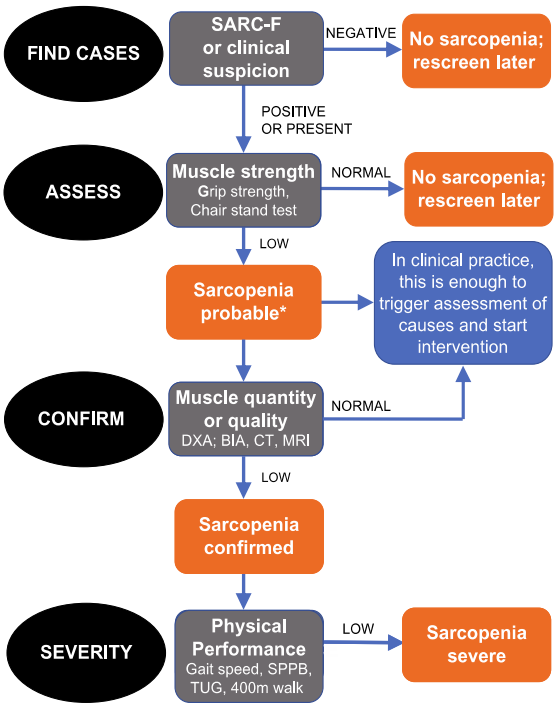

Figure 8. Sarcopenia: EWGSOP2 algorithm for case-finding, making a diagnosis and quantifying severity in practice. The steps of the pathway are represented as Find-Assess-Confirm- Severity or F-A-C-S. *Consider other reasons for low muscle strength (e.g. depression, stroke, balance disorders, peripheral vascular disorders) (44).

3.6.3. Sarcopenia in patients with HNC

Patients with HNC are at risk of developing secondary sarcopenia due to the tumour location in the upper airway and digestive tract, which can cause dysphagia and difficulty of swallowing, resulting in malnutrition and catabolic state (45). Moreover, HNC patients frequently abuse alcohol and tobacco, which also leads to malnutrition (47).

The precise prevalence of sarcopenia in these patients is unknown. It varies significantly within a range of 6 to 77% among the reported studies (48). Surov i Wienke meta-analysis shows that sarcopenia affects 42% of HNC patients (47).

In cancer patients, loss of SMM has been related to various negative clinical outcomes. Low SMM is associated to a higher incidence of postoperative complications, worse outcome after surgery, prolonged hospital stay and decreased disease-free and overall survival. Sarcopenia is also associated with increased treatment-related toxicity (49,50).

Although the questionaries explained before (*section 3.3.*5) used to evaluate physical and mental patients' condition are fundamental, they just give information about frailty and do not provide an accurate assessment of body composition and SMM.

Among the various techniques described above to evaluate body composition, and therefore sarcopenia, **CT scan** is the most suitable one in oncological patients since it is performed during diagnostic work-up to stage the tumour (51). As said above, CT scan is a tool which allow us the assessment of SMM quantity.

In cancer patients, SMM is usually assessed on abdominal CT scan at the level of the third lumbar vertebra (L3). However, abdominal CT imaging is not routinely performed in patients with HNC (52).

As neck and thoracic CT scans are carried out in HNC diagnosis and staging, an alternative method to SMM assessment at L3 was studied with the aim of avoiding the additional radiation that unnecessary abdominal CT imaging implied. Swartz et al. (53) demonstrated there was a strong correlation between SMM measured at the level of the third cervical vertebra (C3) and L3.

This technique is described in more detail in the section *Variables and measurements,* but basically, it consists in measuring the muscle area of both sternocleidomastoid and paravertebral muscles on the axial CT image at C3 level and then correlating it to L3 SMM using a formula (51).

4. JUSTIFICATION

Laryngeal cancer is the second most frequent cancer between all the head and neck malignancies. Although some larynx carcinomas are diagnosed in early stages, there are many of them which are diagnosed in locally advanced disease, especially supraglottic ones, which are the most common location in our region.

Total laryngectomy is still the surgical option in the management of advanced laryngeal and hypopharyngeal cancers. It can be performed as primary treatment or as second-line treatment when organ-preserving options have failed (43).

The occurrence of pharyngocutaneous fistula is the most common and feared complication of total laryngectomy and it is associated with a prolonged hospital stay, a delayed in adjuvant therapy and a decrease in quality of life. Although numerous studies have been carried out to identify and assess the risk factors of pharyngocutaneous fistula, there are some differences in which of these factors are the best predictors of this complication (35).

Over last years, sarcopenia and its impact on complications related to treatment in oncological patients have attracted research attention (54). Because of the location and metabolic characteristics of head and neck carcinomas, the loss of skeletal muscle mass is frequent in these patients.

Sarcopenia has been related to higher rates of complications after surgery in some malignant tumours such as colorectal, oesophageal and renal cancer (55). Although various previous studies have focused on the role of sarcopenia in the outcomes after total laryngectomy, identifying low skeletal muscle mass as a possible risk factor for pharyngocutaneous fistula, researchers encourage the need of further studies in order to have more evidence.

The aim of this study is to provide more evidence about sarcopenia as a predictive factor of pharyngocutaneous fistula. If this association is proved, the assessment of sarcopenia before total laryngectomy could become a meaningful prognostic tool into clinical practice. We would be able to perform an intervention with preoperative exercise and nutritional support in those patients who have sarcopenia to optimize their status prior to surgery and reduce their risk of developing a pharyngocutaneous fistula.

Since most of the literature which have evaluated the association between sarcopenia and pharyngocutaneous fistula were retrospective, this study is going to be prospective so better quality of evidence is provided. Moreover, as it is an observational study no great expense will be incurred.

Once there is strong evidence between this association, further studies could be carried out to determine whether intervention prior to surgery to improve physical status really improves postoperative outcomes.

5. HYPOTHESIS

5.1. Main hypothesis

Sarcopenia in patients with locally advanced laryngeal and hypopharyngeal squamous cell carcinoma undergoing primary total laryngectomy is a significant **predictor of pharyngocutaneous fistula** formation.

5.2. Secondary hypothesis

Sarcopenia in patients with locally advanced laryngeal and hypopharyngeal squamous cell carcinoma undergoing primary total laryngectomy is associated with **more hospitalization days**.

6. OBJECTIVES

6.1. Main objective

The main objective is to evaluate sarcopenia as an **independent predictive factor** for the **development of pharyngocutaneous fistula** after primary total laryngectomy in patients with locally advanced laryngeal and hypopharyngeal squamous cell carcinoma.

6.2. Secondary objective

To determine if patients with locally advanced laryngeal and hypopharyngeal squamous cell carcinoma undergoing total laryngectomy have **more hospitalization days** due to sarcopenia.

7. METHODOLOGY

7.1. Study design

This study is designed as a **multicentre observational prospective cohort study** with a 3-week follow-up.

The cohort will be defined based on the selection criteria. We will study its exposure to the risk factor that we are studying, so it will be divided in **two groups**:

- Exposed group: it will include individuals undergoing primary TL diagnosed with sarcopenia.
- Non-exposed group: it will include people undergoing primary TL who are not diagnosed with sarcopenia.

7.2. Study setting

This study is designed to be multi-centric. The hospitals participating in this study are:

- Hospital Universitari Doctor Josep Trueta (Girona)
- Hospital Universitari Germans Trias i Pujol (Badalona)
- Hospital Universitari de Bellvitge (Hospitalet de Llobregat)
- Hospital Universitari Vall d'Hebron (Barcelona)
- Hospital Universitari de Tarragona Joan XXII (Tarragona)

The reference centre of this study will Hospital Universitari Doctor Josep Trueta. One researcher will be designated as the representant and coordinator from each hospital to ensure a good communication and coordination between all the participant centres.

7.3. Study population

The population of this study will be patients diagnosed with locally advanced larynx or hypopharynx carcinoma who undergo a primary TL in the hospitals mentioned before.

All patients must meet all the inclusion criteria without having any exclusion criteria.

7.3.1. Inclusion criteria

- Age ≥18 years old
- Diagnosis of locally advanced laryngeal or hypopharyngeal SCC (stage III and IV)

- Primary TL as the treatment option
- Accepted and signed informed consent form (*Annex 5*)

7.3.2. Exclusion criteria

- Salvage TL as the treatment option
- Requirement of radical neck dissection (≥ 3 areas of cervical lymph node drainage)
- Necessity of pharyngeal mucosa reconstruction after TL
- Neck radiation therapy prior to surgery
- Unresectable tumours (T4b)
- Disseminate disease (M1)
- Non-availability of neck CT images 3 weeks before TL
- Patients with several dental artifacts at level of C3 which do not allow an accurate assessment of SMM
- History of allergy to barium contrast
- Patients not able to undergo a surgery due to frailty or anaesthetic risk

7.3.3. Withdrawal

- Request of the patient (*Annex 6*). Patients may leave the study at any time by notifying the research team.
- Patient lost to follow up. A participant should be considered lost to follow up when they do not show up for scheduled appointments despite repeated attempts to contact them.
- Death of the patient.

7.4. Sampling

7.4.1. Sample size

In a two-sided test, with an alpha of 5%, a statistical power of 80% and assuming a high risk of developing PCF into sarcopenic patients we will need 31 subjects in each group (sarcopenic and non-sarcopenic). Assuming a drop-out rate of 20% we will finally need 37 subjects per group, in total **74 subjects**.

We have assumed a high risk based on Brit et al. and Casasayas et al. studies (48,52), which RR were 1.75 and 2.84, respectively.

Computations were carried out with the Prof. Dr. Marc Saez' software based on the package 'pwr' of the free statistical environment R (versió 4.2.2).

7.4.2. Sample selection

Our sample will be recruited through a **consecutive non-probabilistic sampling** method, as patients are diagnosed. The patients will be recruited in the hospitals mentioned above.

All patients who meet inclusion criteria and none of the exclusion criteria will be informed about the study objectives and those who are interested will be given the opportunity to voluntarily participate. They will receive the information document (*Annex 4*) and the informed consent (*Annex 5*). The informed consent must be signed if they are willing to participate.

Patients recruited in each hospital will be proportional to the number of eligible cases.

7.4.3. Estimated time for sample recruitment

As calculated before, 74 subjects are required to carry out the study.

According to non-official information of Hospital Universitari Doctor Josep Trueta, we estimate 10 patients per year would be tributary of entering in the study. As for the other centres, the approximate number of patients per year will be: 20 in Badalona, 20 in Hospitalet, 20 in Barcelona and 10 in Tarragona.

Estimated time to achieve the sample size will be **2 years**. If the sample size is not achieved in this period, the recruitment time will be extended.

7.5. Variables and measurements

7.5.1. Independent variable

The independent variable of this study is **sarcopenia**. It is a qualitive nominal dichotomous variable that will be categorised as "present" or "not present".

To define sarcopenia, considered as low SMM, we will use the lumbar skeletal muscle index (SMI). It will be assessed for each patient by calculating the CSA at the level of C3 using the CT images obtained preoperatively for the staging of the tumour (≤3 weeks prior to TL).

The axial slice corresponding to C3 will be selected according to the method described by Swartz et al.: the first CT-slide to completely show the entire vertebral arc and the transverse and spinous processes (53).

In CT scan, the radiodensity range for skeletal muscle is between -29 and +150 Hounsfield units (HU), so the cross-sectional area of pixels within this radiodensity range can be extracted to define the CSA at C3 (52).

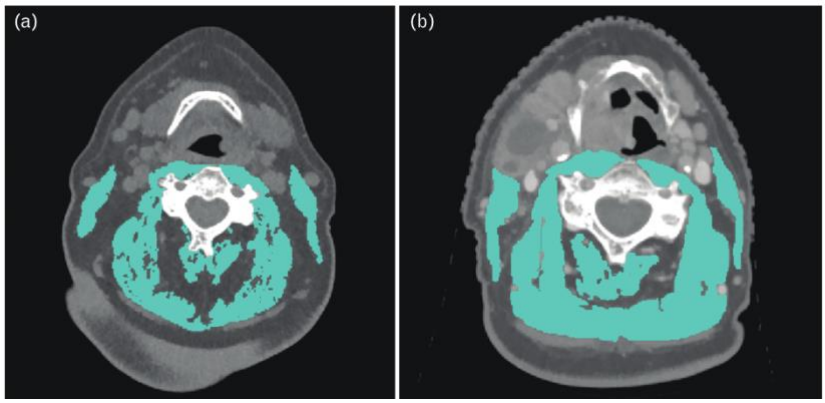

Figure 9. Examples of segmentation of skeletal muscle mass tissue (paravertebral and sternocleidomastoid muscles) at level C3: (a) low and (b) normal skeletal muscle mass (45).

Once CSA at C3 is calculated, CSA at level of L3 will be estimated using the formula published by Swartz et al. (53):

$$\text{CSA at L3 (cm}^2\text{)} = 27.304 + 1.363 * \text{CSA at C3 (cm}^2\text{)} - 0.671 * \text{Age (years)} + 0.640 * \text{weight (kg)} + 26.442 * \text{Sex}$$

Use value “1” for female sex and “2” for male sex.

According to the literature reviewed, the estimated CSA at L3 is then normalized for height to calculate lumbar SMI:

$$\text{Lumbar SMI (cm}^2\text{/m}^2\text{)} = \text{CSA at L3 / height (m}^2\text{)}$$

There is a lack of consensus on which cut-off point should be used to define sarcopenia. Although there are various cut-off points values for sarcopenia published, none of them

are definitive yet. In this study, we will use Casasayas Plass M. (51) cut-off point as the outcome of her study was also PCF according to lumbar SMI. Based on this cut-off point, sarcopenia will be defined as a **lumbar SMI ≤47.67 cm^2/m^2**. Thereby two groups will be defined depending on the results:

- Sarcopenic group if lumbar SMI ≤47.67 cm^2/m^2
- Non-sarcopenic group if lumbar SMI >47.67 cm^2/m^2

The images will be analysed using a software called Image J (software v1.44p), which is a free available platform for medical image analysis. This software has been used in other studies like the study from Casasays Plass M., who has developed a guide to assist CSA measurement using this software (51). This guide can be found in *Annex 8.*

Radiologists involved in this study will learn how to use this software by attending to a workshop.

7.5.2. Dependent variable

7.5.2.1. Main outcome

The main dependent variable is the development of a **PCF**.

In clinical practice, PCF is usually identified by clinical features like direct visualisation of saliva leakage. However, to complement the clinical diagnosis and with the purpose of having an objective diagnosis of PCF, it will be confirmed by a barium swallow test. This test will be performed at 7^{th}, 14^{th} and 21^{st} postoperative days.

A barium swallow test is a special type of imaging test which uses barium and X-rays to create images of the upper gastrointestinal tract. It will allow us to evaluate the neopharynx and to exclude any fistulous tract, seen as the contrast extravasation out of the gastrointestinal tract.

It is a qualitive nominal dichotomous variable categorised as yes or no.

7.5.2.2. Secondary outcome

The secondary outcome is **hospitalization days**. It is defined as the time between the date of TL and date of first hospital discharge. It will be expressed in number of days. It will be collected in the patient's clinical chart.

It is a quantitative continuous variable, but it is asymmetrically distributed.

7.5.3. Covariables

Other variables may have an impact on the results, therefore they will be measured and taken into consideration when the results are analysed.

- **Age**: expressed in years. The age from of the patient will be consulted from the ID card or any other official document facilitated to the investigator. Even though it is a quantitative continuous variable, it is a qualitative dichotomous variable because we are going to categorize it.
    - ≥60 years
    - <60 years
- **Sex**: it is a dichotomous nominal qualitative variable. It will be expressed in terms of "male" or "female". This variable will be collected from the ID card, or any other official document facilitated to the investigator.
- **Tobacco**: it is a qualitative polytomous nominal variable. It will be asked to the patient and collected into the data collection form (*Annex 7*).
    - No use
    - Moderate use (<20 cigarettes/day)
    - Heavy use (≥20 cigarettes/day)
- **Tumour staging**: it will be assessed according to the TNM staging system of laryngeal cancer. It is a qualitative polytomous ordinal variable.
    - Stage III
    - Stage IVA
    - Stage IVB
- **Tumour site**: the location of the tumour will be assessed by the investigators according to physical examination, FNL and imaging techniques. It is a qualitative polytomous nominal variable.
    - Supraglottic
    - Glottic
    - Subglottic
    - Hypopharynx

- **Preoperative albumin level**: it is expressed in g/dL. It will be measured with a preoperative blood test. Although it is a quantitative continuous variable, we will categorize it as:
    - ≤3.5 g/dL
    - >3.5 g/dL

  Now, the variable is a qualitative dichotomous variable.

- **Preoperative haemoglobin level**: it is expressed in g/dL. It will be measured with a preoperative blood test. Despite the fact it is a quantitative continuous variable, since we will categorize it, it is a qualitative dichotomous variable.
    - ≤12.5 g/dL
    - >12.5 g/dL
- **Comorbidities**: the comorbidities we will consider are diabetes, COPD and CAD. They will be assessed by checking the patient's medical records. They are qualitative dichotomous variables, categorized as yes or no.
- **Socioeconomic status**: it will include social classes I to V (56) taking into account the patient's education level (qualitative polytomous ordinal variable) and occupation (qualitative polytomous nominal variable). It will be asked to the patient and the information will be gathered on the data collection form (*Annex 7*).
- **Hospital**: It will be registered into the data collection form (*Annex 7*). It is a qualitative polytomous nominal variable.

Table 3. Covariables summary.

	Measurement	**Description**	**Categories**
Age	Data collection form (*Annex 7*)	Qualitative dichotomous	- ≥60 years - <60 years
Sex	Data collection form (*Annex 7*)	Qualitative nominal dichotomous	Male / Female
Tobacco	Data collection form (*Annex 7*)	Qualitative nominal polytomous	- No use - Moderate use (<20 cigarettes/day)

				- Heavy use (≥20 cigarettes/day)
Tumour staging			TNM staging system	Qualitative ordinal polytomous	- Stage III - Stage IVA - Stage IVB
Tumour site			Direct visualization and imaging techniques	Qualitative nominal polytomous	- Supraglottic - Glottic - Subglottic - Hypopharynx
Preoperative albumin level			Blood test	Qualitative dichotomous	- ≤3.5 g/dL - >3.5 g/dL
Preoperative haemoglobin level			Blood test	Qualitative dichotomous	- ≤12.5 g/dL - >12.5 g/dL
Comorbidities	**Diabetes**		Data collection form (*Annex 7*)	Qualitative nominal dichotomous	Yes / No
	COPD		Data collection form (*Annex 7*)	Qualitative nominal dichotomous	Yes / No
	CAD		Data collection form (*Annex 7*)	Qualitative nominal dichotomous	Yes / No
Socioeconomic status			Education level and occupation	Qualitative ordinal polytomous	Social class I to V
Hospital			Data collection form (*Annex* 7)	Qualitative nominal polytomous	- H.U. Dr Josep Trueta - H.U. Germans Trias i Pujol - H.U. de Bellvitge - H.U. Vall d'Hebron - H.U. de Tarragona Joan XXII

7.6. Data collection

Since this is a prospective study, the data needed to initiate the study will be collected as the study goes along.

Once the patient has been diagnosed with a locally advanced laryngeal or hypopharyngeal SCC and the multidisciplinary committee of the Head and Neck Functional Unit decides that the best option of treatment for him/her is a primary TL, the patient is cited at the consultation where the otolaryngologist communicates the definitive diagnosis and the treatment option. This is the **baseline visit** in which the doctor should explain the study to the patient after making sure he/she meets the inclusion criteria and does not meet none of the exclusion ones.

If after reading the information document (*Annex 4*) the patient agrees to participate in the study, he/she must sign the informed consent form (*Annex 5*).

During this first visit, the otolaryngologist will perform an interview to collect the clinical information in the clinical data collection form (*Annex 7*). In order to anonymize the information in the study database, a numerical code will be assigned to the patient.

From 3 weeks before the patient undergoes the TL, a protocollary neck CT scan will be performed to re-staging the tumour, necessary for the surgery. This image will be analysed by an expert radiologist and will be also used to assess whether the patient has sarcopenia or not. Not having a neck CT from ≤3 weeks prior to surgery is a reason for exclusion.

The patient will also have scheduled a preoperatory visit with an anaesthesiologist, in which a blood test will be done, and a visit with the nurse, in which frailty questionnaires (*Annex 2*) will be performed. Therefore, the patient's frailty and anaesthetic risk will be defined.

The **follow-up** will take place during the 3 weeks postoperative period. All patients will be hospitalized in the otolaryngology unit after the surgery, so they can be daily evaluated with the aim to exclude any serious acute complication. In addition to this regular clinical evaluation, on the 7^{th} postoperative day, the barium swallow test will be performed to determine if a PCF has been developed:

- In case a PCF is detected, we will have the diagnosis of PCF and the data will be collected.
- In case the test does not show a fistula, the barium swallow test will be repeated on the 14th postoperative day, following the same pattern as above.
- In those patients who have not shown a fistula yet, a barium swallow will be performed again on the 21st postoperative day, so PCF development can be ruled out. Before the patient leaves the hospital, he/she will be explained the warning signs of PCF (e.g., appearance of saliva after swallowing and erythema), so he/she can consult the otolaryngologist if necessary.

Once the patient is finally discharged, the day of first discharge will be included into the patient's clinical chart, so we are able to collect this data and analyse the number of hospitalization days.

All data collected will be anonymized and included in the study database.

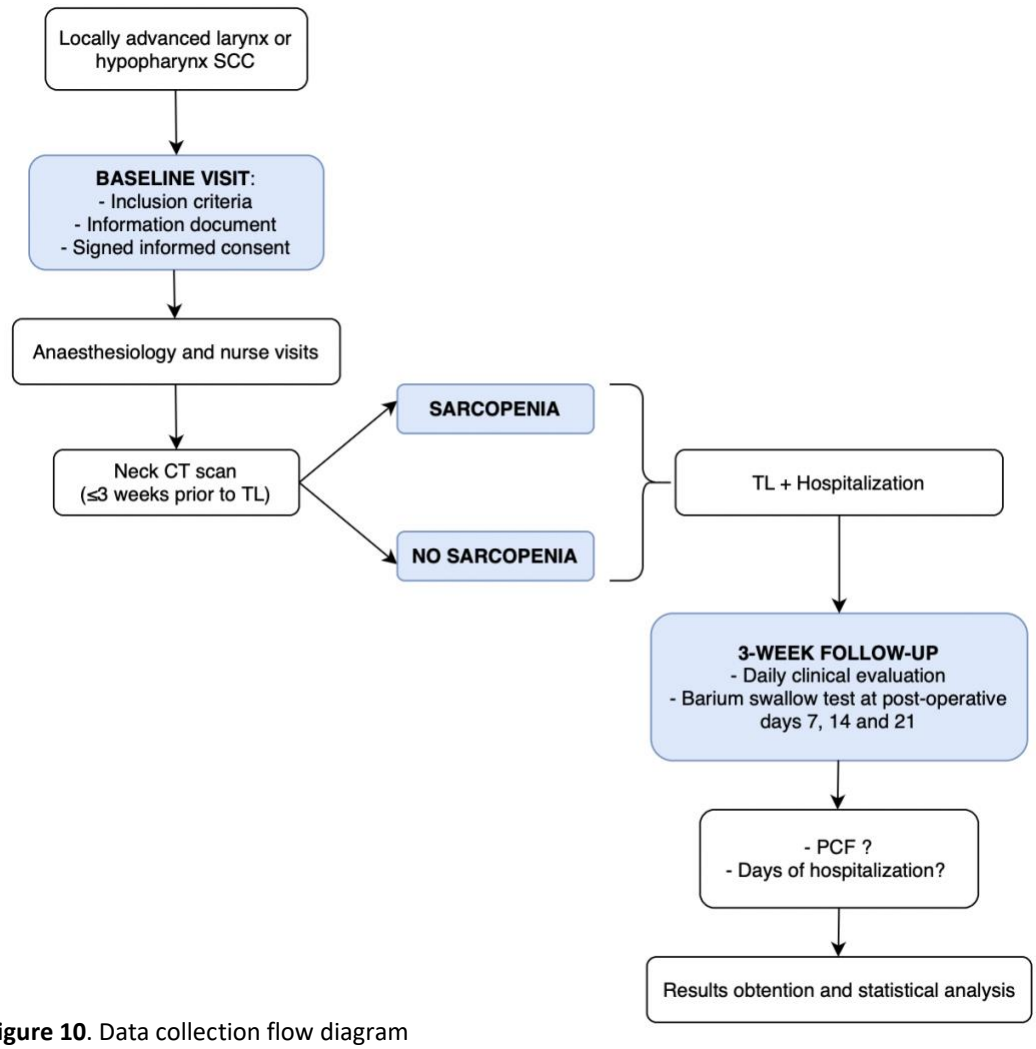

Figure 10. Data collection flow diagram

8. STATISTICAL ANALYSIS

The statistical analysis will be performed by the statistical analyst. It will be done using the Statistical Package for Social Sciences (SPSS) software version 28.1.

We will consider a value of $p<0.05$ as statistically significant, defining a confidence interval of 95% for all analyses.

8.1. Descriptive analysis

To summarize the PCF, we will use proportions.

Days of hospitalization will be summarized using medians and interquartile range (IQR), because although it is a continuous variable, it is asymmetrically distributed.

We will repeat these analyses for the groups of sarcopenia and no sarcopenia.

We will also stratify by the covariables.

8.2. Bivariate inference

The difference of proportions of PCF between sarcopenic and non-sarcopenic groups will be tested using the Chi-square and the Fisher's exact test, in case that in any cell the expected number of cases will be lower than 5.

The difference of medians of days of hospitalization between sarcopenic and non-sarcopenic groups will be tested using the Mann-Whitney's U test.

Kaplan-Meier curves will be estimated for this last variable (days of hospitalization) stratified by the sarcopenic and non-sarcopenic groups, and log-rank test.

8.3. Multivariate analysis

To assess the association of sarcopenia in the development of PCF we will use a logistic regression controlled for the covariates.

The effect of the occurrence of sarcopenia on days of hospitalization will be assessed by means of a Cox regressions, controlling for the covariates.

9. ETHICAL AND LEGAL CONSIDERATIONS

Main investigators and collaborators guarantee that the study will be conducted in accordance with 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",* revised in October 2013:

- **Autonomy**: all participants will receive an information document which explains all the study information (*Annex 4*). In case they voluntary agree to participate, an informed consent must be sign (*Annex 5*). At all times they will have the right of withdrawal if they wish so.
- **Non-maleficence**: this principle is expected to be respected, so no harm will be caused to the patient, given the observational nature of the study.
- **Beneficence**: the aim of this study is to know the predictive value of sarcopenia in PCF, so a better preoperative management can be done in order to avoid this complication.
- **Justice**: all patients meeting the inclusion criteria and none of the exclusion criteria and want to participate may enter to the study, avoiding any discrimination.

This research protocol will be evaluated by *the Comitè Ètic d'Investigació Clínica* (CEIC) of Hospital Universitari Doctor Josep Trueta and the other participating hospitals. In case of any objections, modifications will be done to achieve their conditions. Only after receiving their approval, the study will begin.

All the personal data from the patients included at the study database will be confidential according to Regulation (EU) 2016/679 of the European Parliament and of the Council of April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and the "*Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los derechos digitales*".

As a means to maintain confidentiality of the data, all patients will have assigned an identification number that will be recorded in the database for analysing the information in an anonymous way. The data will only be accessible to the researchers

responsible of the study. Data will only be used for the purpose of the study. Participants will also have the right to access and remove their personal data form the database at any time.

All data will be published with transparency, including any unfavourable events.

The researchers declare that there are no conflicts of interest in this study.

10. STUDY LIMITATIONS

- In this study, a consecutive non-probabilistic sampling method will be used, which implies the risk of selecting a non-representative sample leading to a **selection bias**. To minimize this bias, the inclusion and exclusion criteria have been designed with the purpose of having the target population well defined.

- Being a **multicentre study**, the interpretation of the results may imply interobserver variability. To avoid this, at the beginning of the study professionals will be trained on how to collect the data and how to assess the images properly, so homogeneity between the participant hospitals is ensured. During the study there will be some meetings to make sure the study is being well developed.

- As it is an observational study, we expect **confusion bias** to occur. To reduce potential confusion, both bivariate and multivariate analysis will be carried out with all potential confounding factors.

- As a prospective study design, there is a risk that subjects are **lost** due to participation withdrawal or others. However, this risk has been assessed when calculating the sample size with a drop-out rate of 20%. All withdrawals and situations where the patient's follow-up is not possible will be registered.

- Regarding the independent variable, the cut-off value that we will use to define sarcopenia in patients is **not sex-specific** and has only been used in one study. However, after reviewing the literature and realising there is not a consensus on which one should be used, we decided to use this cut-off value due to the similarity of the target patients and the outcome.

- Another concern about the independent variable is that there is a possibility that patients' SMM could **change** while they are waiting for TL. However, the CT scan we will use to assess SMM will be the one done only 3 weeks before TL.

- In relation to **inclusion and exclusion criteria**, only candidates to primary TL will be selected for the study, so the protocol will not be applicable to salvage TL. As our main outcome is PCF occurrence, these patients would influence our results.

11. WORK PLAN AND CHRONOGRAM

11.1. Team members

The research team that will conduct this study will be composed by the following members:

- **Principal investigator**: responsible for the elaboration of the protocol, writing the conclusions and publication of the results.
- **Study coordinator**: responsible for the supervision of the study.
- **Co-investigators**: in each participant hospital will have one investigator responsible for coordinating and supervising his/her team. The co-investigators will meet once a year with the principal investigator and study coordinator.
- A **data manager**: responsible for the collection of the data, the anonymisation process and creating a database.
- A **statistical analyst**: responsible for the statistical analysis.
- **Collaborators**: otolaryngology team and radiology team.

11.2. Working plan and chronogram

The period of patient recruitment will be 2 years, with a follow-up period of 3 weeks for each patient. This study is expected to last around **3 years**. The activities that will take place in this study are detailed below:

STAGE 0: STUDY DESIGN (November 2022 – January 2023)

- **First meeting** (November 2022): the study coordinator and the principal investigator meet to agree in developing this project.
- **Bibliographic research**: research about laryngeal and hypopharyngeal SCC including its management and treatment options, PCF presentation and management, and current situation about sarcopenia in HNC patients. The research has been performed in books and PubMed publications.
- **Protocol elaboration**: objectives, hypotheses, variables, and methodology.

The principal investigator and study coordinator are the main responsible.

STAGE 1: ETHICAL EVALUATION AND STUDY APPROVAL (January 2023 – March 2023)

- **Presentation to CEIC**: this protocol will be presented to the *Comitè Ètic d'Investigació Clínica* (CEIC) at Hospital Universitari Doctor Josep Trueta for its approval. Simultaneously, the protocol will be sent to the other participant hospitals Ethical Committee. If necessary, adjustments to the protocol will be made.

The principal investigator and study coordinator are the main responsible.

STAGE 2: COORDINATION (March 2023)

- **Co-investigators selection**: each hospital's research team will meet and choose a co-investigator. During the study, he/she will be in charge of communicating and coordinating with the other centres.
- **First meeting of the research team**: the principal investigator and each centre's co-investigators will meet for the first time to discuss their organization and address any issues they could have.
- **Training workshop**: all the radiologists involved in the study will meet at Hospital Universitari Doctor Josep Trueta to attend a practical workshop. The technique to measure lumbar SMI from a neck CT and to assess a PCF from a barium swallow will be reviewed. The objective is to ensure the homogeneity in the imaging analysis in order to obtain representative results.

STAGE 3: DATA COLLECTION AND FOLLOW-UP (April 2023 – May 2025)

- **Patient recruitment**: a consecutive non-probabilistic sampling method will be carried out to recruit patients in the 5 participant hospitals. It will be performed for 2 years. Only patients that meet the inclusion and none of the exclusion criteria, and that have signed the informed consent will be included in the sample. All the personal data of the patients involved will be anonymized.
- **Follow-up**: each participant of the study will be followed-up during 3 weeks after he/she has undergone the TL.

During this stage, at least once a year, the study coordinator, the principal investigator, and co-investigators of each hospital will meet telematic via videoconference, to evaluate if the protocol is being well fulfilled.

Specialists will record all the information collected during this stage and it will be delivered to the data manager who will register and anonymize it into a database.

STAGE 4: DATA ANALYSES AND INTERPRETATION (June 2025 – September 2025)

- **Statistical analyses** (June 2025 – July 2025): once all data is obtained, a subcontracted statistician will process it performing a descriptive analysis, bivariate and multivariate analysis.
- **Statistical interpretation** (August 2025 – September 2025): the final statistical analysis will be interpreted by the principal investigator and coordinators of each participant hospital in a telematic meeting. Afterwards, discussion and conclusion of the study will be elaborated.

STAGE 5: PUBLICATION AND DISSEMINATION OF THE RESULTS (September 2025 – January 2026)

- **Paper elaboration**: a paper to present the study's findings will be written by the principal investigator.
- **Presentation of the results**: the results will be presented to *Sociedad Española de Otorrinolaringología* (SEORL) and *European Academy of Otorhinolaryngology, Head and Neck surgery* (EAROL-HNS) congresses.
- **Publication of the results**: publication of the results on scientific journals.

The principal investigator and study coordinator will be the main responsible.

Table 4. Chronogram

		2022	2023								2024					2025						2026
		Nov	Dec	Jan	Feb	Mar	Apr - May	Jun - Jul	Aug - Sep	Oct - Nov	Dec	Jan - Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan - Feb	Mar - Apr	May	Jun - Jul	Aug - Sep	Oct - Dec	Jan
STAGE 0	First meeting																					
	Bibliographic research																					
	Protocol elaboration																					
STAGE 1	CEIC																					
STAGE 2	Coordinators selection																					
	First meeting research team																					
	Training workshop																					
STAGE 3	Patient recruitment																					
	Follow-up																					
STAGE 4	Statistical analyses																					
	Statistical interpretation																					
STAGE 5	Paper preparation																					
	Congress presentation																					
	Publication																					

12. BUDGET

PERSONNEL EXPENSES

Since the main research team is formed of physicians who are employed by the hospitals included in the study and their time is included in the usual clinical practice, they will not suppose an additional cost.

We will hire a data manager to collect the data and create the database. The approximate salary will be 40€/hour and we estimate approximately 100 hours of work, so it will have a total cost of 4.000€.

A statistician expert will be also hired to perform the statistical analysis from the data collected. The approximate salary will be 40€/hour and we estimate approximately 40 hours of work, so the estimation cost is 1.600€.

EXECUTION EXPENSES

As it is an observational study protocol, the tests and procedures performed to carry out this study are part of the daily clinical practice undergoing this pathology, therefore these expenses will not be included in the budget.

The only technique which is not routinely performed is the barium swallow test. Each patient will undergo a minimum of 1 and maximum of 3 this test, resulting a total of 222 tests. Every barium swallow test costs 78€.

The information document, the informed consent form and the data collection sheet must be printed for each participant. The printing costs 0.05€/page.

TRAVEL AND COORDINATION EXPENSES

All the meetings between the principal investigator, the study coordinator and the coordinators of each participant hospital will be telematic via videoconference. Therefore, no travel expenses are expected.

However, there will a face-to-face training workshop. The radiologist expert of each participant hospital will have to go to Hospital Universitari Doctor Josep Trueta in Girona where the practical 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 320€ (considering that the radiologist from Girona will have no additional travel costs).

CONFERENCE EXPENSES

The study coordinator and principal investigator will attend to a national congress (SEORL) and international congress (EAORL-HNS) to disseminate the findings to the rest of the scientific community. Their admission fee is 500€ and 800€, respectively. Travel costs, accommodation and diets must be added. Therefore, we estimate a total cost of 1.000€ per person for the national congress and 1.800€ per person for the international one.

PUBLICATION EXPENSES

Once the study has ended and the results have been interpreted, it will be published as a journal article. We will need an English correction (500€) and preparation of the open access (1.800€), so the estimated cost of the study publication is 2.300€.

All the expenses are summarized in the following table:

Table 5. Budget summary

ITEM	QUANTITY	COST	SUBTOTAL
PERSONNEL EXPENSES			
Data manager	100 hours	40€/hour	4.000€
Statistician	40 hours	40€/hour	1.600€
EXECUTION EXPENSES			
Barium swallow	222	78€/test	17.316€
Printing costs	450	0,05€/page	22,5€
TRAVEL AND COORDINATION EXPENSES			
Workshop	4	80€/person	320€
CONFERENCE EXPENSES			
SEORL	2	1.000€/person	2.000€
EAORL-NHS	2	1.800€/person	3.600€
PUBLICATION EXPENSES			
English correction		500€	500€
Open access		1.800€	1.800€
		TOTAL	31.158,5€

13. IMPACT

HNC is a significant group of tumours regarding to its incidence, with larynx cancer being the most prevalent. TL remains one of the main treatment options for locally advanced laryngeal and hypopharyngeal SCC, with PCF as the main complication.

Despite numerous studies, there is still debate about the risk factors of PCF and, in the last years, sarcopenia has gained attention.

The principal objective of this study is to calculate the predictive value of sarcopenia in the occurrence of PCF following primary TL. To determine the association between sarcopenia and days of hospitalization is also an objective.

The accomplishment of this first objective will have an impact on the preoperative strategies to improve the SMM of these patients. Moreover, measuring sarcopenia with CT scan may set up as an available tool used for individualised preoperative assessment in clinical practice.

To date, most of the studies published are retrospective, while this study is prospective, so more evidence is provided.

In the future, If the hypothesis proves right, this could also provide an opportunity to design further studies to determine whether a properly preoperative management of sarcopenia would reduce the incidence of PCF.

Moreover, if sarcopenia was shown to result in more hospitalization days after TL, the management of sarcopenia could reduce the hospital stay and, therefore, total costs of these patients.

14. FEASIBILITY

We believe this study to be feasible considering the following aspects.

This study will be carried out in five different Catalan hospitals, which have the resources and appropriate facilities to conduct the study. All the professionals who will be part of the research team are already part of these hospitals' staff, so no additional hiring is required. In fact, the only people who will need to be hired are the data manager and the statistician.

All the resources needed in the study are included in the usual clinical practice of patients with laryngeal and hypopharyngeal cancer undergoing TL management, so they will be accessible and easy to carry out by the otolaryngologists and radiologists who are part of the team. An exception is the assessment of sarcopenia using a CT scan, but they will assist a workshop to homogenize its execution.

The study is designed to be multicentric in order to avoid making the recruitment period longer than 2 years. The whole study will not take more than 3 years, so financing is a possibility. Nevertheless, the study is not particularly expensive.

Because the patient participation is relatively short, many patients will be prevented from being lost during the period between study inclusion, sampling, and evaluation of PCF occurrence.

To summarise, we believe that this study meets all the criteria for being conducted, taking into account the study's locations, the associated costs, and the number of patients required.

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16. ANNEXES

16.1. ANNEX 1: TNM CLASSIFICATION

American Joint Comitee of Cancer (AJCC) 8th edition TNM Staging system for larynx cancer.

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	The tumour invades the mucosa of more than one adjacent subsite of the supraglottis or glottis or a region outside the supraglottis (e.g., the mucosa of the base of the tongue, the vallecula, the medial wall of the piriform sinus) without fixation of the larynx.
T3	Tumour limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid are, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage.
T4	Moderately advanced or very advanced. - **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 cords(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 the thyroid cartilage.

T4	Moderately advanced or very advanced. - **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, cricoid cartilage, 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. - **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 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.

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 or smaller in greatest dimension and ENE (-).
N2	- N2a: Metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE (-). - N2b: Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE (-). - N2c: Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE (-).
N3	- N3a: Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE (-). - N3b: Metastasis in any lymph node(s) with clinically overt ENE (+).

Distant Metastasis (M)

M0	No distant metastasis.
M1	Distant metastasis.

16.2. ANNEX 2: FRAILTY QUESTIONNAIRES

G8 SCREENING TOOL *(The Oncologist 21:188-195, 2016)*

	Items	Possible response (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = severe decrease in food intake
		1= moderate decrease in food intake
		2 = no decrease in food intake
B	Weight loss during the last 3 months?	0 = weight loss >3 kg
		1 = does not know
		2 = weight loss between 1 and 3 kg
		3 = no weight loss
C	Mobility?	0 = bed or chair bound
		1 = able to get out of bed/chair but does not go out
		2 = goes out
E	Neuropsychological problems?	0 = severe dementia or depression
		1 = mild dementia
		2 = no psychological problems
F	BMI? (weight in kg)/(height in m^2)	0 = BMI <19
		1 = BMI 19 to <21
		2 = BMI 21 to <23
		3 = BMI ≥23
H	Takes more than three prescription drugs per day?	0 = yes
		1 = no
P	In comparison with other people the same age, how does the patient consider his/her health status?	0.0 = not as good
		0.5 = does not know
		1.0 = as good
		2.0 = better

	Age	0: >85
		1: 80-85
		2: <80
	Total score	0-17

KARNOFSKY PERFORMANCE SCALE INDEX

Score	Description
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort, some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most of his personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospital admission is indicated although death not imminent
20	Very sick; hospital admission necessary; active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

BARTHEL INDEX FOR ACTIVITIES OF DAILY LIVING:

Feeding	10 = independent
	5 = needs help cutting, spreading butter, etc., or requires modified diet
	0 = unable
Bathing	5 = independent (or in shower)
	0 = dependent
Grooming	5 = independent face/hair/teeth/shaving (implements provided)

	0 = needs to help with personal care
Dressing	10 = independent (including buttons, zips, laces, etc.)
	5 = needs help but can do about half unaided
	0 = dependent
Bowels	10 = continent
	5 = occasional accident
	0 = incontinent (or needs to be given enemas)
Bladder	10 = continent
	5 = occasional accident
	0 = incontinent, or catheterized and unable to manage alone
Toilet use	10 = independent (on and off, dressing, wiping)
	5 = needs some help, but can do something alone
	0 = dependent
Transfers (bed to chair and back)	15 = independent
	10 = minor help (verbal or physical)
	5 = major help (one or two people, physical), can sit
	0 = unable, no sitting balance
Mobility (on level surfaces)	15 = independent (but may use any aid; for example, stick) > 50 yards
	10 = walks with help of one person (verbal or physical) > 50 yards
	5 = wheelchair independent, including corners, > 50 yards
	0 = immobile or < 50 yards
Stairs	10 = independent
	5 = needs help (verbal, physical, carrying aid)
	0 = unable

16.3. ANNEX 3: SHORT PHYSICAL PERFORMANCE BATTERY

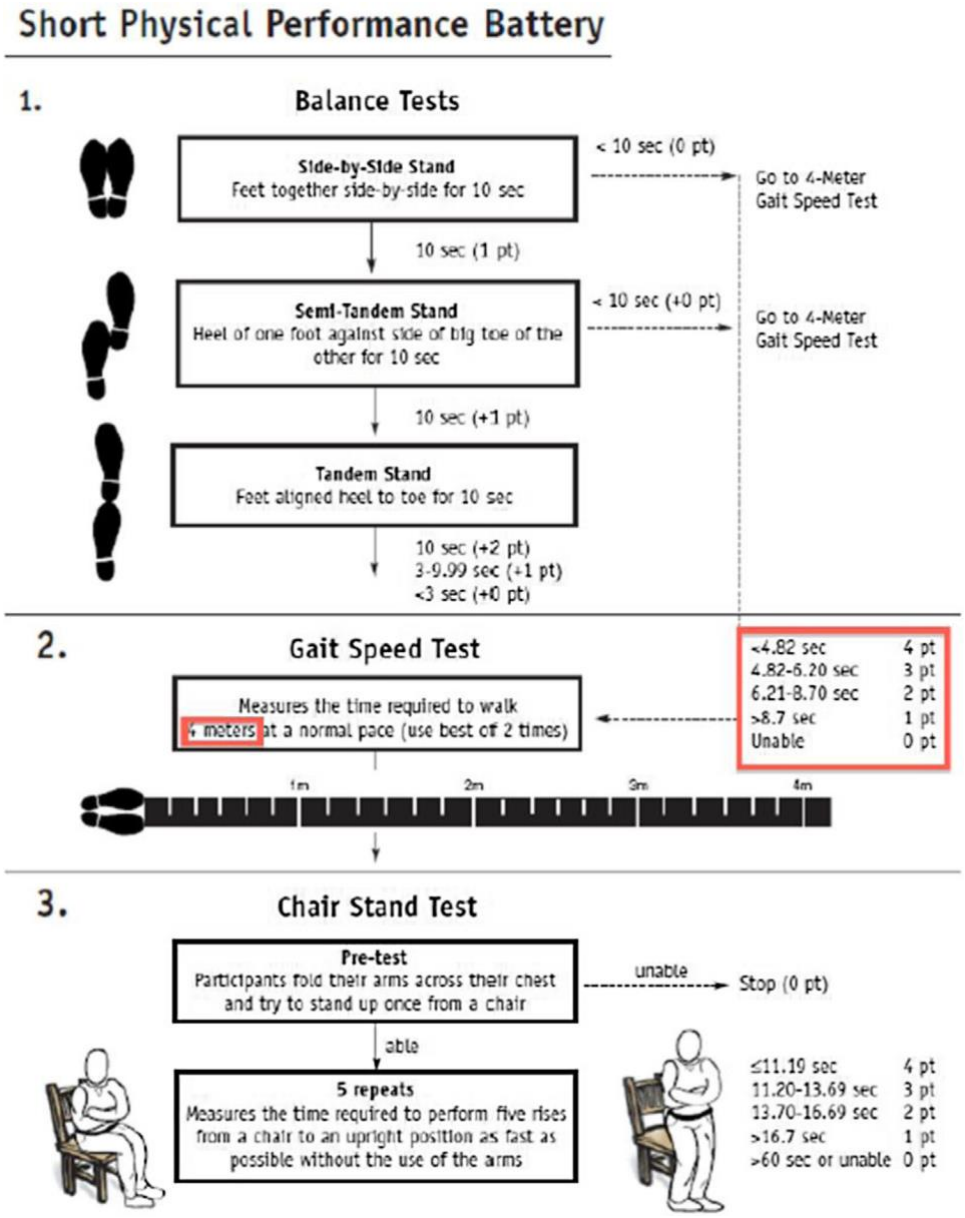

Figure 9. Short Physical Performance Battery (55).

16.4. ANNEX 4: INFORMATION DOCUMENT

FULL D'INFORMACIÓ PER AL PACIENT

Nom de l'estudi: Sarcopènia com a factor predictiu de la fístula faringocutània després de la laringectomía total

Centre assistencial:

Investigador/a principal:

Benvolgut/da,

Ens dirigim a vostè per proposar-li participar, de forma totalment voluntària, en un estudi d'investigació dut a terme als serveis d'Otorrinolaringologia de diferents hospitals de referència de Catalunya. Aquest estudi ha sigut aprovat per el Comitè d'Ètica i Investigació clínica dels hospitals corresponents i per l'Agència Espanyola del Medicament i Producte sanitari.

La nostra intenció és que vostè entengui el motiu pel qual es realitza aquest estudi i què significa formar-ne part, per tal de poder decidir si desitja participar-hi. Li preguem que llegeixi aquest document atentament i qualsevol consulta o aclariment no dubti a consultar-nos-ho.

DESCRIPCIÓ I OBJECTIU DE L'ESTUDI

Els càncers de laringe localment avançats sovint requereixen per a la seva curació una intervenció quirúrgica anomenada laringectomia total. Una de les principals complicacions d'aquesta cirurgia és l'aparició d'una fístula faringocutània que pot suposar un endarreriment en el tractament adjuvant i la rehabilitació de la veu.

En els últims anys, s'ha començat a plantejar la sarcopenia com a factor de risc pel desenvolupament de la fístula faringocutània. Els pacients amb càncer de laringe, per les característiques del tumor, solen patir malnutrició i pèrdua de massa muscular.

L'objectiu d'aquest estudi és valorar l'associació entre la sarcopènia i l'aparició d'una fístula faringocutània en pacients amb càncer de laringe després d'una laringectomia

total, per poder oferir un maneig preoperatori més adequat i aconseguir reduir la incidència d'aquesta fístula.

L'estudi es realitzarà en el seu centre de salut durant un període de 3 setmanes. És un estudi observacional, de manera que no es realitzarà cap intervenció addicional i el maneig hospitalari no serà gaire diferent al d'un/a pacient que no participi en l'estudi.

Durant l'ingrés hospitalari després de la laringectomia total, se li realitzarà una valoració clínica diària de la ferida quirúrgica. Com a mínim al 7è dia, i si escau, als dies 14 i 21 després de la operació se li realitzarà una prova d'imatge amb contrast (trànsit esofagogàstric baritat). A més a més, també es valorarà el número de dies d'ingrés.

BENEFICIS I RISCOS DE L'ESTUDI

L'estudi està enfocat a proporcionar un benefici general als pacients amb sarcopènia que tenen indicació de laringectomia total. No s'obtindrà un benefici directe personal per la seva participació.

Com que és un estudi observacional, els procediments realitzats són els mateixos que s'utilitzen habitualment i, per tant, la seva participació no comporta un risc afegit.

CONFIDENCIALITAT I PROTECCIÓ DE DADES

Des de l'inici de l'estudi, totes les dades personals recollides es gestionaran i emmagatzemaran amb total confidencialitat, tenint en compte la legislació actual *Llei Orgànica 3/2018, de 5 de desembre, de Protecció de Dades Personals i Garantia dels drets digitals*" i als reglaments 2016/679 del Parlament i Consell Europeu.

Per garantir la màxima confidencialitat, a l'inici de l'estudi se li assignarà un codi numèric mitjançant el qual s'identificaran les seves dades i informació personal. L'accés a les dades de caràcter personal quedarà restringit a l'equip investigador. No es publicarà informació personal, i les dades sempre seran utilitzades amb finalitats d'investigació.

D'acord a el que s'estableix en la legislació vigent, vostè pot exercir els drets a l'accés rectificació, oposició i cancel·lació de les dades; en cas de desitjar-ho haurà de posar-se en contacte amb l'equip investigador.

PARTICIPACIÓ I COMPENSACIÓ ECONÒMICA

L'equip d'investigació responsable d'aquest assaig clínic no obté cap benefici econòmic. Com a pacient, la seva participació es totalment voluntària i no obtindrà cap compensació econòmica. En cas de no voler participar a l'estudi, podrà tractar-se amb l'equip d'especialistes sense cap canvi en la seva atenció mèdica. Per participar, haurà de firmar el consentiment informat que li facilitarem conforme ha llegit la fulla d'informació per al pacient i vol participar a l'estudi. Vostè està en el seu dret de sortir de l'estudi durant el transcurs d'aquest si així ho desitja. Preguem que si és el cas, informi a l'equip investigador. Abans de decidir si vol formar part de l'estudi, està en el seu dret de demanar segones opinions a altres professionals si ho desitja.

CONTACTE

En cas de qualsevol dubte o si necessita més informació, pot posar-se en contacte amb l'equip investigador de l'hospital corresponent mitjançant:_____

Gràcies per la seva atenció.

16.5. ANNEX 5: INFORMED CONSENT

CONSENTIMENT INFORMAT

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

- He rebut una copia de la fulla de informació per al pacient.
- He llegit i comprès tota la informació facilitada en la fulla de informació per al pacient. He pogut platejar qualsevol dubte que m'ha sorgit, i aquest ha sigut resolt adequadament.
- Estic conforme amb la quantitat d'informació facilitada.
- Comprenc que la meva participació en aquest estudi és voluntària i no remunerada.
- Comprenc els beneficis i riscos que comporta participar en aquest estudi.
- Comprenc que les meves dades personals seran confidencials i que puc sol·licitar la retirada i eliminació d'aquestes en qualsevol moment de l'estudi.
- Autoritzo que les meves dades i la meva història clínica pugui ser utilitzada per l'equip investigador per a fins relacionats amb l'estudi.
- He entès que puc revocar el meu consentiment informat sobre la participació a l'estudi, sense necessitat d'especificar el motiu i sense que aquest fet afecti a la meva assistència.

En conseqüència,

- Dono lliurament la meva conformitat a participar en l'estudi *Sarcopènia com a factor predictiu de la fístula faringocutània després de la laringectomía total*

☐ Sí ☐ No

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

Data: _____

16.6. ANNEX 6: WITHDRAWN CONSENT

REVOCACIÓ DEL CONSENTIMENT INFORMAT

Jo, _____ amb document d'identificació personal (DNI/NIE) _____, revoco el consentiment informat per a la participació en l'estudi: *Sarcopènia com a factor predictiu de la fístula faringocutània després de la laringectomía total.*

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

Data: _____

16.7. ANNEX 7: DATA COLLECTION FORM

Fulla de recollida de dades de les variables demogràfiques i epidemiològiques dels pacients participants a l'estudi.

Hospital: _____

Data: _____

Marcar amb una creu l'opció que millor s'adeqüi:

1. **Codi numèric assignat**: _____
2. **Data de naixement** (dia/mes/any): __/__/_____
3. **Sexe**:

   ☐ Home ☐ Dona

4. **Estatus socioeconòmic**:

   ☐ Classe I: Directius de l'Administració i de les empreses (excepte els inclosos a la classe II). Alts funcionaris. Professionals liberals. Tècnics superiors.

   ☐ Classe II: Directius i propietaris-gerents del comerç i dels serveis personals. Altres tècnics (no superiors). Artistes i esportistes.

   ☐ Classe III: Quadres i càrrecs intermitjos. Administratius i funcionaris, en general. Personal dels serveis de protecció i seguretat.

   ☐ Classe IV: Treballadors manuals qualificats o semiqualificats de la indústria, comerç i serveis; així com del sector primari.

   ☐ Classe V: Treballadors no qualificats.

5. **Hàbit tabàquic**:

   ☐ No fumador

   ☐ Fumador moderat (<20 cigarrets/dia)

   ☐ Fumador sever (≥20 cigarrets/dia)

6. **Antecedents mèdics:** _____

16.8. ANNEX 8: PRACTICAL GUIDE FOR CALCULATING CSA

This guide has been extracted from the study carried out by Casasayas Plass M. (51).

Guía práctica para el cálculo de áreas de sección mediante el programa Image J

Descargar el programa Image J de la página web: https://imagej.nih.gov/ij/download.html

1. Abrir en pantalla el corte seleccionado (Figura 15.A): *File → Open*. Es recomendable crear un duplicado usando el comando (*Control+Shift+D*) o mediante la opción que aparece al clicar el botón derecho.

Si se desconoce el corte específico, es posible importar toda la serie y seleccionar la imagen adecuada: *File → Import → Image Sequence*.

2. Determinar la escala a la que se encuentra la imagen para saber así el tamaño de cada pixel en milímetros: *Analyze → Set scale.*
3. Ampliar o reducir la imagen con las tecla + o - .
4. Con el fin de resaltar un tipo de tejido, es necesario delimitar unos umbrales. Éstos se definen mediante: *Image → Adjust → Threshold → Set Upper and Lower thresholds.* Éstos corresponden a las Unidades Hounsfield que definen cada tipo de tejido. Para resaltar el tejido muscular, se limitan los umbrales a -29 y +150 UH. (Figura 15.B)
5. Antes de empezar a delimitar las regiones de interés, es necesario indicar al programa que calcule el área de los pixels resaltados. *Analyze → Set measurement* → Marcar la casilla "*Limit to threshold*". En este panel de opciones también reduciremos los decimales a 0.
6. Para delimitar la zona de interés debemos usar la herramienta *"Free hand selection"*.
7. Debemos añadir cada una de las regiones de interés delimitadas a un directorio de almacenamiento: *Analyze→ Tools → ROI Manager.* ROI corresponde a "Region of interest". (Figura 15.C)
8. Para eliminar una selección: *Edit → Selection → Select none*.
9. Para modificar y ajustar un área delimitada se debe usar la herramienta *"Brush Selection Tool"*. Tras haberla seleccionado en el panel de control *"ROI Manager"*, se puede redefinir el área según las siguientes indicaciones:
    a. Presionando la tecla *"Shift"* y dibujando por fuera de la selección actual se crea nuevo contenido.
    b. Presionando la tecla *"Alt"* y dibujando por dentro de la selección actual se elimina contenido previamente seleccionado.
10. Determinar qué valores queremos medir y calcular. *Set → Measurements*
11. Seleccionar todas las áreas clicando *"Show all"* en el comando de *"ROI Manager"* y finalmente *"Measure"* para efectuar los cálculos. (Figura 15.D)