POSTOPERATIVE OUTCOMES AFTER APPLYING INTEGRA® DERMAL REGENERATION TEMPLATE ON PHARYNGECTOMIZED PATIENTS.

A RANDOMIZED CLINICAL TRIAL

FINAL DEGREE PROJECT

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1 LIST OF ABBREVIATIONS

AEMPS – Agencia Española de Medicamentos y Productos Sanitarios

ASIR – Age-Standardized Incidence Rate

CT – Computed Tomography

ENT – Oto-rhino-laryngological

HNC – Head and Neck Cancer

HHV – Human Herpes Virus

HPV – Human Papilloma Virus

HUDJT – Hospital Universitari Doctor Josep Trueta

IMRT – Intensity Modulated Radiotherapy

IT® – Integra® Dermal Regeneration Template

MECV-V – Método de Exploración Clínica Volumen-Viscosidad

MRI – Magnetic Resonance Imaging

OP-SCC – Squamous Cell Carcinoma of the Oropharynx

RT – Radiation Therapy

SCC – Squamous Cell Carcinoma
POSTOPERATIVE OUTCOMES AFTER APPLYING INTEGRA®DERMAL REGENERATION TEMPLATE ON PHARYNGECTOMIZED PATIENTS.

SPSS – Statistical Package for the Social Sciences

TLM – Trans-Oral Laser Microsurgery

TNM – Tumour Node Metastases

TORS – Trans-Oral Robotic Surgery

TOUSS – Trans-Oral UltraSonic Surgery

VAS – Visual Analogue Scale
2 ABSTRACT

**Background:** Patients with squamous cell carcinoma of the oral cavity or the oropharynx who undergo a surgical excision, and whose resection is not deep enough to require a reconstruction with a myocutaneous flap, have been usually left to heal by secondary intention. Nevertheless, this results in an unacceptable pain (grades of pain over 50mm in the visual analogue scale (VAS)), long use of nasogastric feeding tube, long hospitalizations and with prolonged dysphagia. M. Tobed and A. Borés have recently developed a new reconstructive technique using Integra® Template (IT®) which aims to improve the postoperative outcomes.

**Hypothesis and objectives:** The reconstruction of the oral cavity and oropharyngeal defects after tumour resections with IT® will improve the postoperative outcomes by mainly reducing the pain. The aim of this study is to register and compare the grade of pain and the outcomes in both techniques (the conventional and IT® reconstruction).

**Design and setting:** This is a randomized, controlled, open-label clinical trial which will be carried out in Hospital Universitari Doctor Josep Trueta from January 2017 until March 2022.

**Methods:** 36 patients, 18 per group, will be needed for the study. They will be recruited using a consecutive non-probabilistic method and they will be randomly assigned to two intervention groups. Those patients who undergo a surgical resection of an oral cavity or oropharyngeal tumour and who do not need a reconstruction using a myocutaneous flap will be offered to enter the study. T-student’s test will be used to prove statistical association between the different techniques and the grade of postoperative pain and a confidence interval of 95% will be assumed.

**Intervention:** The intervention consists on applying IT® over the wound bed once the tumour has been completely resected (intervention group). To do so, Integra® Dermal Regeneration Template 2in x 2in and Ethicon Securestrap™ will be used. The control group will not receive any additional reconstruction after the excision of the tumour and their wound will be left to heal by secondary intention.

**Key words:** Integra®, oropharyngeal cancer, oral cavity cancer, reconstructive surgery, pain, outcomes.
3 INTRODUCTION

3.1 ANATOMY AND HISTOLOGY

The pharynx is a fibromuscular tube that is semi-circular in cross section and is situated directly anterior to the vertebral column. It extends from the skull base to the lower border of the cricoid cartilage. Six muscles are predominantly responsible for the voluntary actions of the pharynx: three pharyngeal constrictor muscles that are roughly circularly layered on top of one another and three vertically oriented muscles (stylopharyngeus, salpingopharyngeus, and palatopharyngeus). These muscles aid in the act of swallowing.

The pharynx is divided in 3 sections depending on the location called nasopharynx, oropharynx and hypopharynx (fig. 3-1).

The oropharynx is the middle part of the pharynx directly below the soft palate that communicates anteriorly with the oral cavity proper by the isthmus of the fauces, also known as the oropharyngeal isthmus. Specifically, the oropharyngeal isthmus is bound superiorly by the soft palate, laterally by the palatoglossal arches, and inferiorly by the posterior third of the tongue. The posterior root of the tongue exhibits numerous follicles that contain lymphatic tissue, which are known collectively as lingual tonsils. In close proximity, the lingual surface of the epiglottis curves anteriorly and is attached to the posterior tongue at the midline and lateral edges, forming the median and lateral glossoepiglottic folds. The depressions created between the median and lateral glossoepiglottic folds are termed epiglottic valleculae.
The most prominent feature of the oropharynx is the two folds that are termed the pillars of the fauces, the palatoglossal arch and the palatopharyngeal arch. The palatoglossal arch contains the palatoglossus muscle and travels anteroinferiorly from the soft palate to the lateral aspect of the tongue.

Posterior to the palatoglossal arch, the palatopharyngeal arch, that contains the palatopharyngeus muscle and travels posteroinferiorly from the soft palate to the lateral part of the pharynx. Due to the insertion points and direction of the pharyngeal arches, they create a triangular space known as the tonsillar fossa, which contains lymphoid tissue called palatine tonsil. The arches are used as anatomic landmarks for the purposes of palatine tonsillar evaluation, manipulation, and surgery(2).

Figure 3-1 Opened posterior view of the interior of the pharynx. Source: Netterimages.com
A structure with a great importance located in the hypopharynx is the piriform recess. The piriform recess is a depression lying lateral to the orifice of the larynx and bounded laterally by the thyroid cartilage and medially by the cricoid and the arytenoid cartilages. Is the most common site where squamous cell carcinoma occurs in the hypopharynx(3).

3.2 EPIDEMIOLOGY

Head and Neck cancers (HNCs) are the ninth most common malignancy in the world, with unacceptably high mortality rates in the developing countries. More than 90% of these cancers are squamous cell carcinomas (SCCs).

Globally, the estimated age-standardised incidence rate (ASIR) per 100,000 p.a. for all ages and both genders for oropharynx and hypopharynx cancers is 1.9 (fig. 3-2). Worldwide, 5-year prevalence rates in proportion by 100,000 for both genders for oropharynx and hypopharynx are 6.0. In the southern Europe, the ASIR per 100,000 p.a. is estimated around 3.4 in males and 1.0 in females (GLOBOCAN 2012)(4).

Specifically in Spain, 6,632 new cases were diagnosed in 2014(5).

The global incidence and mortality trends show an increase in both developed as well as developing countries, with only the USA showing falling mortality rates. According to GLOBOCAN 2012, the global projected burden of oropharynx and hypopharynx cancer is estimated to increase among males and females by 17.3 and 15.5% in developed countries by 2030(4).
To conclude, the annual incidence shown in Girona for oral cavity, oropharyngeal and hypopharyngeal cancers is of 31 for men and 7 for women during 2010, 2011 and 2012(6).

Figure 3-2 Estimated ASIR for cancer of the tonsils (C09) and oropharynx (C10) by gender and world area (age 0 to 75+ years). Source: GLOBOCAN 2012.

3.3 RISK FACTORS

The wide variation in the worldwide incidence and mortality from HNC is mainly attributed to variations in exposure to the major environmental and behavioural risk factors. These risk factors include tobacco consumption (both smoked and ‘smokeless’), the chewing of areca nut (betel nut), heavy consumption of any form of alcoholic beverage(7–9) and sustained infection with ‘high-risk’ genotypes of the human papillomavirus (HPV) family (particularly HPV-16 and HPV-18, for neoplasms originating in the tonsils, base of the tongue and elsewhere in the oropharynx), as well as some human herpes-viruses (HHVs) (HHV-4, better known as Epstein-Barr virus with nasopharyngeal carcinoma, which is biologically a distinct disease). Susceptibility to these agents may be genetic, which is compounded by various
cultural dietary products high in nitrous compounds and volatile nitrosamines such as salted fish, hot spices and certain preserved foods(10). These environmental agents are more potent in subjects with diets deficient in antioxidants and in free radical-scavenging macro- and micro- nutrients, typically derived from fresh fruits and vegetables(11,12).

3.4 CLINICAL PRESENTATION

Squamous cell carcinoma of the oropharynx(OP-SCC) develops most frequently in the tonsillar region and base of the tongue, often appearing as an ulcerated mass, fullness, or irregular erythematous mucosal change(13). Such tumours often present at a more advanced stage than the ones of the oral cavity because of their ability to grow undetected and their propensity for metastasis. The most common chief complaints are the presence of a neck mass (from metastatic disease), sore throat, and dysphagia. However, significant differences are noted with respect to the HPV status of the tumour(14). In patients with HPV-related OP-SCC, the most common complaint is development of a neck mass (51%), followed by sore throat (28%), and dysphagia (10%). It is not unusual for a patient to present with significant metastatic neck disease yet to have a small primary tumour that remains hidden or undetectable. In contrast, the most common symptom in HPV-negative OP-SCC is sore throat (53%), followed by dysphagia (41%), and neck mass (18%) (15).

Because HPV-positive OP-SCCs have a better prognosis than HPV-negative tumours, HPV tumour status is routinely assessed at most institutions for patients who have oropharyngeal carcinoma or metastatic head and neck carcinoma with an unknown primary site. Upon histopathologic examination, HPV-related OP-SCC tends to be non-keratinizing with a somewhat basaloid appearance recapitulating tonsillar crypt epithelium(16). Methods for
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evaluating HPV tumour status include quantitative reverse-transcriptase polymerase chain reaction for high-risk HPV E6 and E7 mRNA, DNA or RNA in situ hybridization-based methods, and p16 immunohistochemistry(17).

3.5  DIAGNOSIS

Imaging aids in determining the extent of the primary tumour, regional lymph node spread, and distant metastasis. Because the oral cavity and oropharynx are amenable to visual examination (either trans-orally or endoscopically), initial diagnosis and staging may rely primarily on clinical examination. However, for tumours that are not visible or palpable (e.g., OP-SCC arising in a tonsillar crypt), imaging studies are especially important(15).

Advanced clinical examination by an otolaryngologist/head and neck surgeon or head and neck surgical oncologist typically includes fiber-optic endoscopic examination of the nasopharynx, oropharynx, hypopharynx, and larynx. A computed tomography (CT) scan or magnetic resonance imaging (MRI) of the primary tumour and neck typically is indicated for accurate loco-regional staging. Cystic lymph node metastases are not unusual for HPV-related tumours(18). Furthermore, according to recent studies, ultrasound may be a useful adjunct, not only for guiding fine-needle aspiration biopsy of lymph nodes but also for the identification of unknown primary tumour sites in patients with metastatic lymph node disease of the head and neck region(19,20).

HPV testing of cytopathologic samples from cervical lymph nodes may aid in determining the ethiology and predicting the location of unknown primary tumours; the use of liquid-phase
cytologic assays for HPV determination is especially promising but requires further studies for clinical validation(17,21,22).

### 3.6 STAGING

The 2010 tumour node metastases (TNM) staging system of the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC) is used to classify oropharyngeal carcinoma.

Patients with early (stage I and II) disease are those whose tumours are under 4 cm in greatest dimension without invasion into surrounding structures and with no clinical or radiographic evidence of lymph node involvement(23).

TNM tables can be found in the annex (annex 1 and 2).

### 3.7 TREATMENT

#### 3.7.1 Early stage cancers

Early squamous cell carcinomas of the oropharynx can be treated with either primary surgery or definitive radiation therapy (RT) as a single modality. Definitive RT and primary surgery have yielded similar rates of local control and survival in retrospective studies, although there are no prospective randomized trials comparing the two approaches. The morbidity associated with each treatment approach is an important factor in making treatment decisions.

RT is used more commonly, but surgery may be preferred in selected situations. Minimally invasive techniques, such as trans-oral laser microsurgery (TLM) and trans-oral robotic
surgery (TORS), have made resection of carefully selected early oropharyngeal cancers both feasible and well tolerated (24).

The risk of occult neck metastases in a patient with early (T1/T2) oropharyngeal cancer and a clinically negative neck is relatively high. Thus, elective treatment of the neck should be strongly considered. Elective treatment of the neck can be accomplished with either nodal dissection or RT.

Early tonsil cancers without soft palate or base of tongue involvement are considered lateralized primaries, and elective nodal treatment can involve either selective neck dissection (levels two to four) in patients undergoing primary surgery (trans-oral or open) or ipsilateral elective nodal dissection in patients undergoing definitive RT (Annex 3).

However, it is important to address both sides of the neck for base of tongue, soft palate, and posterior pharyngeal wall primary tumours as these are considered midline structures, which can have bilateral lymphatic drainage. For patients with midline tumours managed with definitive RT, bilateral neck irradiation is recommended. For patients who initially undergo primary surgery of midline tumours, bilateral selective neck dissection including levels two to four is recommended (25, 26).

Depending on the specific site of the tumour the preferred treatment differs:

- **Soft palate:** Patients with early cancers of the soft palate are usually treated with RT to the primary tumour and to the bilateral neck. Nevertheless, primary surgery is generally associated to greater functional impairment, particularly velopharyngeal
insufficiency. If primary surgery of the soft palate is performed, then rehabilitation with a free flap or obturator is necessary in most of the cases(27).

- **Tonsillar cancer:** early tonsillar cancers can be treated with either primary surgery or RT with similar outcomes. Small tumours confined to the tonsil can be treated with radical tonsillectomy but in tumours that extend beyond the tonsil itself, the pharyngeal wall and/or soft palate should be included in the resection(28).

Trans-oral approaches have largely replaced open procedures for early stage oropharyngeal primary tumours due to the lower morbidity associated and the improved outcomes(29,30).

- **Base of tongue:** in squamous cell carcinomas arising at the base of tongue the risk of occult lymph node metastasis is higher than for other oropharyngeal subsites ranging from 21 to 45 percent(31). Hence, elective RT to the lymph nodes or lymph node dissection is recommended.

Surgery for early unilateral base of tongue cancer consists of hemiglossectomy, which can be done with a trans-pharyngeal approach avoiding the potential complications of the traditional mandibular osteotomy. With the advent of TORS an TLM, primary surgery and definitive RT are now equivalent options in properly selected patients(32).

Compared with conventional open surgery, TLM minimizes the risk of fistula, flap failure, abscess or osteoradionecrosis and is associated with a shorter hospital stay. However postoperative haemorrhage occurs in 5 to 10 percent of cases(33).
3.7.2 Advanced stage cancers

Locally advanced oropharyngeal cancers include T3 or T4 primary tumours without lymph node involvement and T1 or greater tumours with cervical node involvement but without distant metastases (17).

There are two different approaches which may be appropriate to treat this stages of oropharyngeal cancers: The surgical approach followed by RT and the combination of chemotherapy plus RT.

- **Organ preservation approaches:** For patients with unresectable (T4b) disease, a combined modality approach that includes chemotherapy plus RT, given either sequentially or concurrently, is used. Nevertheless, this kind of approach is also used for patients with potentially resectable disease.
Platinum-based chemotherapy and once daily fractionation with intensity modulated radiotherapy (IMRT) and image-guided RT (IGRT) is the standard of care for regimens combining chemotherapy and RT(34).

The most common complication in patients who receive RT to treat oropharyngeal cancers is dysphagia although some data suggest that IMRT might reduce the risk of this complication(35).

• **Surgery:** TORS and TLM approaches have emerged that allow adequate visualization and exposure of oropharyngeal primary tumours without the morbidity of mandibulotomy and lip split approaches. These approaches are most feasible for early T stage tumours of the oropharynx and become more challenging with advanced T stages, particularly for those tumours with mandibular involvement.

Excellent overall survival and swallowing results have been reported using TLM as primary treatment for advanced stage oropharyngeal cancer in a multicentre study. Those who received adjuvant RT reduced the risk of death by 50 percent(36). Similarly, TORS achieves excellent functional and oncologic outcomes when combined with risk-based adjuvant treatment in patients with early T stage tumours(37).

When early primary stage is accompanied by advanced nodal staging, controversy exists over the best treatment approach. Since many of these patients will require adjuvant chemo-radiation for their advanced nodal stage disease, the question arises whether trans-oral approaches add benefit to those patients who may be cured by chemo-radiation alone and which approaches offer the best functional results(35). The management of the neck in patients with head and neck cancer is complex and
the choice of treatment will depend upon the extent of disease, the treatment modality used to treat the primary tumour and the response to therapy.

3.7.3 Trans-oral UltraSonic Surgery (TOUSS)

TOUSS consists in a new endoscopic alternative to TORS for approaching pharyngeal and laryngeal tumours based on ultrasonic scalpel as a resection tool.

Many papers have been published about the safety, utility and advantages of the ultrasonic scalpel. It has been used routinely in surgical settings such as laparoscopic surgery and open abdominal and thoracic procedures in the last two decades. Specifically in head and neck surgery, it has been widely used in the last decade for open and minimally invasive thyroidectomy, and showing its potential for other open head and neck procedures like glossectomy, tonsillectomy or laryngopharyngectomy. Its superior haemostasis allows clean and bloodless procedures, and the lower temperature and heat diffusion to surrounding tissue improve the safety compared with electrocautery. Trans-oral endoscopic approach can be a step forward, and the endoscope represents a real alternative to microscope for minimally invasive approach of

Figure 3-4 TOUSS applied to a tumour involving base of tongue and oropharynx. Source: Author
upper aero-digestive tract lesions. Nevertheless, TORS is unreachable for most of ENT departments and there is not even evidence of its cost-effectiveness. Therefore, TOUSS has been designed as a “robotless” endoscopic trans-oral procedure, inspired in laparoscopic setup, in order to get, at least, the same output as reported for TORS.(38)

3.8 RECONSTRUCTION SURGERY

An important issue related to treatment and outcomes in head and neck oncology is reconstruction and rehabilitation. Because cancers of the oral cavity and oropharynx can have a direct impact on function of the teeth, tongue, mandible, palate, and pharynx, patients often present with disruption of their abilities to eat, drink, chew, and swallow(39). In addition, surgical and radiation treatments of these cancers may result in further loss of function and major cosmetic changes, which often require extensive reconstruction and/or rehabilitation(40).

The goals of reconstruction for the oropharynx include restoring continuity to the aero-digestive tract and replacing the volume of the tongue base in order to maintain swallowing function without aspiration(41).

Defects of the tonsillar fossa and pharyngeal walls can be reconstructed with a skin graft or allowed to heal by secondary intention when they are small and superficial. Deep wounds, such as those that result in communication with the neck contents, require a flap for closure. These defects are typically closed with thin flaps such as the antero-lateral thigh (in non-obese patients) or the radial forearm fasciocutaneous flap to avoid obstructing the airway or interfere with swallowing. Isolated base of tongue defects can sometimes be closed
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primarily. Partial defects, including those occurring in continuity with a tonsillar or retro-molar trigone resection, are best reconstructed with a thin to moderate thickness fasciocutaneous free flap(42).

Figure 3-5 Radial forearm free flap harvest for a right oropharyngeal defect. Source: M. Hanasono

3.9 COMPLICATIONS

Despite a good organ preservation rate, concomitant chemo-radiotherapy with curative intent is associated with important early and late morbidities(43). Long-term swallowing dysfunction is not rare, and adapted nutrition or a feeding tube is often required, impairing social life. Although functional open surgery for selected pharyngeal or pharyngo-laryngeal tumours has oncological outcomes that are similar to those of more destructive surgical procedures, it requires a temporary tracheotomy and the use of a nasogastric tube for several weeks, as well as a relatively long hospital stay(44). For these reasons, new, less invasive techniques such as TLM are warranted. Several advantages have been reported in comparison to open functional surgery: tracheotomy can be avoided in most cases; feeding tubes are not
systematically required; the risk of aspiration pneumonia is reduced; and the hospital stay is shorter. Also, TLM, in contrast to open surgery, better spares sensory pharyngeal nerve branches and thus improves the capability of protecting the airway during swallowing(45).

According to the results of J. Kutter et al, postoperative complications can be expected in 29% of cases. In their study, using 55 patients with pharyngeal and pharyngolaryngeal tumours, there were 16 early postoperative complications:

- 7 patients (13%) presented with a recurrent aspiration pneumonia.
- 3 patients (5%) required a secondary tracheotomy for laryngeal obstruction due to oedema.
- 2 patients (4%) needed a second general anaesthesia for haemostasis (endoscopic coagulation) of severe post-operative bleeding.
- 4 patients (7%) presented with cervical emphysema that resolved spontaneously.

The total median hospitalization stay (including a possible second hospitalization stay for neck dissection) was 13 days (range, 1-88 days) for all patients and 15 days (range, 4-88 days) for patients with neck dissection. Pain was a major factor during the first week, with a median score of 40 of 100 on the analogue pain scale (range, 0-70 of 100), and regressed after 4 weeks to a median of 0 of 100 (range, 0-20 of 100). Despite early swallowing rehabilitation, that was started on postoperative day 1 (range, 0-13), in most patients (37 patients (67%)) additional alimentation through a feeding tube was required. Feeding tubes were removed after a median period of 7 days (range, 0-679 days)(46).
Pain

Acute pain is related to the type of surgical procedure, its duration and to the occurrence of operative complications.

Concerning the prevalence of postoperative acute pain after head and neck surgery, the studies available show a great heterogeneity in relation to the number of patients involved, surgical procedures performed, established approach to analgesia and methods adopted for pain evaluation. However, in major surgical procedures, the prevalence of acute pain is estimated between 30 and 70% (47). A Swedish study conducted on 191 patients showed that 76% of the patients experienced moderate to severe postoperative pain after major surgery (48), whereas a recent study with a larger sample (1736 patients), showed a postoperative prevalence of pain (Numerical Rating Scale/NRS > 4) of 28.5 % immediately after general anaesthesia (49).

According to M. Sommer et al, around 50% of the patients who underwent oral and oropharyngeal surgery presented unacceptable pain (understood as VAS score over 40mm) during the first four postoperative days (50).

3.10 INTEGRA® DERMAL REGENERATION TEMPLATE (IT®)

Integra® Dermal Regeneration Template is a bilaminar synthetic dermal substitute, composed of a porous bovine collagen based dermal analogue of glycosaminoglycan and chondroitin-6-sulphate matrix covered by a temporary epidermal substitute made of silicone. This silicone layer must be removed in approximately 3 weeks, after the dermis regeneration (51).
Integra® artificial skin was introduced in 1981 and its use in acute surgical management of burns is well established, but Integra® has also been used in patients undergoing reconstructive surgery and repair of surgical defects caused by tumour resection(52). However, there are disadvantages to its use; it is relatively expensive (956€ for the smaller 2-in x 2-in sheet), difficult to use, and prone to infection. One of the major advantages of Integra is considered to be the improved scar cosmetic appearance and elasticity when compared to split thickness skin graft alone applied to burns(53).

Use of Integra® template is contraindicated in patients with known hypersensitivity to bovine collagen or chondroitin materials and should not be used on clinically diagnosed infected wounds.
Most common complications are (54):

- **Haematoma**: Haematomas usually develop in the first 48 hours. Haematomas need to be removed and any bleeding/drainage must be stopped to allow cellular ingrowth into the matrix.

- **Fluid accumulation**: In unmeshed Integra® Dermal Regeneration Template sheets, clear or amber fluid may accumulate under the matrix. Although fluid drainage is a normal part of the healing process, fluid accumulation can lead to infection and/or formation of granulation tissue and should therefore be removed. Fluid accumulation appears during the first 5 postoperative days.

- **Purulence and infection**: Infection is the most common cause for loss of Integra template. Common sources are non-viable tissue in the wound bed, or contamination through seams or staple holes. If purulence and infection are promptly dealt with, loss of Integra template sheets can be avoided. Nevertheless, if aggressive treatment (aspiration or evacuation, treatment with topical antimicrobials, culture and initiation of systemic antibiotic therapy) of purulence is not successful as evidenced by increasing purulence, non-take of Integra® template or silicone separation, then the affected area needs to be removed. Purulence and infection is most likely to occur during the first 12 postoperative days.

- **Areas of incomplete Integra® template take**: Areas of incomplete take or detachment of the Integra template can result from mechanical dislodgement (due to shear or improper splinting), infection, haematoma, premature silicone separation or damaged matrix.
This complication may appear 5 days after the application of the Integra® template.

- **Premature silicone separation**: The silicone layer can be left in place for extended periods without detriment to the underlying neodermis. Premature separation of the silicone is not a problem if it stays in contact with the neodermis.
4 JUSTIFICATION

An important issue related to treatment and outcomes in head and neck oncology is reconstruction and rehabilitation (39). Patients with an oropharyngeal or an oral cavity cancer who undergo a surgical procedure, depending on the defect caused during the operation, may need a reconstruction using a flap (those with deeper defects) or in other cases can be left to heal by secondary intention (those with small and superficial defects) (42). Nevertheless, limits between those patients with the need of a huge reconstruction using flaps and those who may benefit of other kind of procedures such as skin grafts, Integra® Template or heal by secondary intention, still must be established. That is to say, some studies are required to define the exact indications of reconstructive surgery after squamous cancer resections.

Patients who undergo a partial pharyngectomy often present with disruption of their abilities to eat, drink, chew, and swallow (39). Apart from that, heavy pain has been recorded in patients of Hospital Universitari Doctor Josep Trueta (HUDJT) achieving levels of pain of 70 and 80 out of 100 in the visual analogue scale (VAS) for pain.

A new technique, never applied before, is being undergone nowadays in HUDJT by doctors Marc Tobed and Antoni Borés. This technique consists in applying Integra® Dermal Regeneration Template over the resected area of the pharynx or the oral cavity. Its aim is to reduce the pain and improve the postoperative outcomes of those patients without indication of surgical reconstruction. The limits they have defined are patients whose resections do not include the styloglossus and/or stylohyoid muscles. According to their own experience, with
this technique pain can be reduced from levels of 70 and 80 to levels under 40 and almost none of the patients need a feeding tube for a long period, while according to J. Kutter et al, rates of 67% of additional feeding through a tube can be found with the traditional technique (heal by secondary intention)(46). Nevertheless, no studies have been done to validate these results so there is a need of further investigation to see and compare the exact outcomes of the application of Integra® Template in patients who have previously received a surgical treatment for a squamous cell carcinoma of the oral cavity or the oropharynx.

Therefore, our intention is to undergo an open randomised clinical trial to compare and evaluate the pain and postoperative outcomes, assessed as the grade of dysphagia and the need of a feeding tube, in patients who receive Integra® Template and in those who are allowed to heal by secondary intention.
5 HYPOTHESIS AND OBJECTIVES

5.1 HYPOTHESIS

Patients who undergo trans-oral pharyngeal reconstruction with Integra® Dermal Regeneration Template (IT®) have better postoperative outcomes (lower pain and fewer complications) compared to those who receive no treatment after the pharyngectomy.

5.2 OBJECTIVES

5.2.1 Primary objective

The primary aim of the study is to register and compare the grade of pain (using VAS) in patients treated with a trans-oral pharyngeal reconstruction using IT® compared to those who do not receive any treatment after the pharyngectomy.

5.2.2 Secondary objectives

- To register and compare the complications (haemorrhage and infection) of both techniques during the postsurgical period.
- To register and compare the number of days that nasogastric feeding tube is needed with both techniques.
- To register and compare the amount of days of hospitalization with both techniques.
- To register and compare the grade of dysphagia with both techniques one week, one month and one and two years after the surgery using the MECV-V test.
6 MATERIAL AND METHODS

6.1 STUDY DESIGN

We propose a randomized controlled open-label clinical trial to compare the pain and other postsurgical outcomes, including local complications in patients who undergo a trans-oral Integra® reconstruction (intervention group) and in those who do not receive any additional treatment (control group) after the pharyngectomy.

Patients will be randomly assigned to 2 groups. The first one, the intervention group, will get a trans-oral Integra® reconstruction, while the control group, will not receive any type of reconstruction.

The study will be performed entirely in Hospital Universitari Doctor Josep Trueta.

6.2 STUDY POPULATION

Our target population will be those patients who have squamous pharyngeal cancer or a cancer involving the posterior third of the oral cavity and will undergo a surgical procedure needing a pharyngectomy and without the need of a traditional myocutaneous flap reconstruction.

We will stratify our patients according to their TNM and if they have previously received chemo-radiation.
6.2.1 **Inclusion criteria**

- Patients over 18 years old.
- Either gender.
- Patients diagnosed of squamous carcinoma of the oropharynx or the posterior third of the oral cavity. All stages can be included in this study.
- Patients who will undergo a pharyngectomy as the therapy of his/her pharyngeal or oral cavity squamous carcinoma.
- Patients who have read the information sheet (Annex 5) for participants and have signed the informed consent forms (Annex 4 and 6).

6.2.2 **Exclusion criteria**

- Patients who need a traditional reconstruction with a myocutaneous flap.
- Patients whose styloglossus muscle has been resected during the pharyngectomy.
- Patients whose stylohyoid muscle has been resected during the pharyngectomy.
- Patients with known hypersensitivity to bovine collagen or chondroitin materials.
- Pregnancy.
- Patients with any other chronic condition, such as neurological, metabolic, gastrointestinal, respiratory or cardiovascular chronic diseases.
- Patients taking any chronic medication for any known or unknown condition.
- Patients who are not able to understand the surgical procedure that will undergo.
6.2.3 **Participant withdrawal or termination**

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if the patient meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

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

6.3 **SAMPLE**

6.3.1 **Patient selection**

Our sample will be obtained from the “Hospital Universitari Doctor Josep Trueta” with a non-probabilistic consecutive sampling method. It will take between a year and a half and two years to obtain the number of patients necessary to go on with the study.

Patients with a squamous cancer of the oropharynx or oral cavity and that fit the inclusion criteria will be offered to enter the study previously to the surgery.

6.3.2 **Sample size**

To calculate our sample size, we have used the power calculator GRANMO. According to the already registered cases, the average VAS for pain expected after a pharyngectomy is around 67mm and the standard deviation is 19mm (n=13 subjects; unpublished results). In the patients who will be operated using Integra®, we expect to find a minimum difference of a standard deviation in the VAS score compared to those operated using the traditional
POSTOPERATIVE OUTCOMES AFTER APPLYING INTEGRA®DERMAL REGENERATION TEMPLATE ON PHARYNGECTOMIZED PATIENTS.

technique which would result in an average pain under 50 units in the VAS score. Finally, to calculate the sample size we have decided to accept an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test. A 10% of drop-out rate has been anticipated.

Using these data previously mentioned, the number of patients necessary to do the study would be 18 per group.

A standard deviation is the minimum difference we have expected to find, as it is the variation that we would consider as clinically relevant.

6.3.3 Estimated time of recruitment

According registered cases from last year, in the head and neck department of Hospital Universitari Doctor Josep Trueta, 26 patients received surgical treatment due to oropharyngeal and oral cavity tumours. From these 26 patients, 20 met the inclusion criteria to enter our study. Hence, we expect that approximately two years will be needed to recruit the necessary number of patients for this study.

6.3.4 Randomization method

A statistician specialist will perform a randomization sequence using statistical software that will assign a code to every patient that fits the criteria to enter the study. Then, the patients will be randomly distributed with a proportion of 1:1 into two groups.

Marc Tobed is going to be the person who will receive the code of each patient and will be the responsible to proceed with the treatment of the patient. He will not be aware of the
group assigned to each patient until the resection of the tumour has been performed to avoid possible bias.

At the end of the data collection, another statistician, different from the first one, will be the responsible of analysing the data due to the need to blind this part of the study.

Once all the sample has been randomized, a univariate analysis will be undergone to confirm the randomization has been successful.

6.3.5 Masking techniques

Due to the inherent limitations of the surgical procedures, there is no option to do a triple-blinded study. The patients and the doctor will be aware of the surgical techniques assigned to every case. Therefore, the only possibility to reduce the bias of the study is to blind the person who will analyse the statistics.

6.4 VARIABLES

6.4.1 Independent variable

The independent variable of our study will be whether our patients receive a pharyngeal reconstruction with Integra® Dermal Regeneration Template (intervention group) or they have no added surgical treatment (control group) after the pharyngectomy for his/her squamous cell carcinoma.

6.4.2 Main dependent variable

Our main dependent variable is the grade of pain of our patients during the postsurgical hospitalization. To measure the pain, we will use the visual analogue scale (VAS) (Annex 7).
The pain VAS is a unidimensional measure of pain intensity, which has been widely used in diverse adult populations(55). It is self-completed by the respondent, who is requested to mark a line perpendicular to the VAS line at the point that represents his/her pain intensity(56,57). VAS is a horizontal line, 100mm length, and for pain intensity, the scale is most commonly anchored by “no pain” (score of 0mm) and “very severe pain” or “worst possible pain” (score of 100mm). To avoid clustering of scores around a preferred numeric value, numbers or verbal descriptors at intermediate points are not recommended(58). Using a ruler, the score is determined by measuring in millimetres from the left hand end of the line to the point that the patient marks(59).

To analyse the results, we will take into account the grade of pain at days 3, 4 and 5 after the procedure and the mean value will be used for the statistical analysis. We will use the mean value of three days to avoid possible bias that could appear in a single measure. Apart from that, days 3, 4 and 5 were chosen to skip the first two days where the patient may not be already stabilised after the surgery.

This is a quantitative continuous variable.

6.4.3 Secondary dependent variables

- **Complications:** we will register separately the presence of local haemorrhage or infection. We have chosen these two complications as they are the most important and the ones that affect the most the postoperative outcomes.

  Haemorrhage will be considered as a complication when a surgical intervention is required to solve the episode. Haemorrhage may appear even more than 10 days after
surgery. Therefore, is important to stay aware of it although the patient has overcome the first days without any complication.

Infection will be considered according to clinical (presence of purulence), analytic (PCR and VSG elevation) and microbiological (detection of any type of bacteria in a culture) signs at any point. All three criteria must be accomplished.

Both are dichotomous variables (YES/NO).

- **Grade of dysphagia**: we will register the grade of dysphagia a week, a month and one and two years after the procedure. To measure it, we will use the MECV-V test (Annex 8 and 9). This test evaluates how the patient swallows different viscosities and different quantities. This evaluation is performed with the patient in sedestation and continuous monitoring of oxygen saturation (pulse oximeter). Three boluses of 5, 10 and 20 ml are administered and nectar, pudding and liquid (water) viscosities are used. It begins with nectar viscosity in low volume, which is gradually increased, followed by the same procedure for water and finally for pudding viscosity. On each occasion, it is registered if there are any signs of disturbance of safety (cough, lower basal saturation of oxygen greater than a 5% and changes in the voice) and/or the effectiveness (insufficient lip seal, oral or pharyngeal residuals and discontinuous swallowing). If any safety compromise sign is detected, higher volumes and/or lower viscosity will not be tested. We will conclude that our patient presents no dysphagia if all the stages of the test are passed without any safety or effectiveness disturbance signs. This is a quantitative discrete variable with the following values:
  - 0: No dysphagia detected.
  - 1: Liquid dysphagia.
o 2: Semiliquid (nectar) dysphagia.

o 3: Total dysphagia.

- **Days of nasogastric feeding tube:** The need of a nasogastric feeding tube represents a great limitation for the patient and increases the days and the costs of hospitalization.

  All our patients will be provided a nasogastric feeding tube at the end of the surgical procedure to improve the immediate postoperative outcomes and the need of maintaining the feeding tube will be evaluated daily. Once the pain and the grade of dysphagia allows the patient to get all his/her nutritional needs by oral intake, the feeding tube will be removed.

  This is a quantitative discrete variable.

- **Days of hospitalization:** hospitalization in a level 3 hospital (HUDJT) costs 723€ per day. Moreover, long hospitalization is related with an increased risk of infection and with lower satisfaction of the patients. Therefore, it would be important to determine the mean hospitalization related to both groups.

  Hospitalization will be concluded once the patient’s feeding tube has been removed, and the patient presents no acute complications such as haemorrhage or infection needing medical support.

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

### 6.4.4 Covariates

Covariates are defined as those factors that may influence the results of the study. In our case, we have two main factors that can change the outcomes of the surgical techniques:
• **TNM**: an advanced stage will require a more aggressive surgery. Therefore, the outcomes will be lower in those who undergo an aggressive operation.

• **Previous treatment received by the patient**: when patients receive radiotherapy previously to the surgery the difficulty of the intervention increases as there are many changes caused by the radiation in the mucosae. Thus, lower outcomes may be found on the patients who have received previous radiotherapy. We will classify the patients as: No previous treatment or previous radiotherapy received.

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

### 6.5 DATA COLLECTION

A summary of all the process can be found in the annex section (Annex 11).

For the process of the data collection, all the head and neck cancer department of HUDJT must be aware about the study to enter every patient who fits the inclusion criteria. Therefore, Marc Tobed is going to be the responsible to explain to the rest of the members of the department our study. Another important point will be the collaboration with the nursery department and specifically with the nurses that will be in charge of the patients during their hospital stay.

Our patients will be also correctly informed (Annex 5) before entering the study and will sign the consent form (Annex 4 and 6). They will also play an important role during the hospitalization to register their level of pain with the VAS and during the following two years to register the evolution of their possible dysphagia.
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Trial entry

Patients with an OC-SCC or an OP-SCC who have the indication of a surgical treatment will be informed about the possibility of entering the trial. Nevertheless, just those who fit all the inclusion criteria after the tumour resection will be able to enter to it.

Patients will be either informed orally and with an information sheet (Annex 5). If they agree to engage in, we will proceed to collect all data needed for our study.

We will use the TNM staging system to classify the tumour of our patients and it is also important to note if our patients have previously received any treatment (radiotherapy).

During the hospitalization

The most important data for our study will be obtained during the early post-operative period.

Pain will be registered every day during the hospital stay using the VAS. Nevertheless, in our study we will compare the grade of pain 3, 4 and 5 days after the procedure. We will use the mean value of the three days.

Special attention must be paid in order to detect any sign of infection or haemorrhage so nurses must be informed about it and they will check periodically the status of our patients.

Finally, the grade of dysphagia must be defined one week after the procedure. In case the patient has already left the hospital, he will be asked to come to the outpatients’ clinic to check it and register it. The need of a feeding tube during the hospitalization also must be noted down.
Integra® Template withdrawal

Those patients who undergo a reconstruction with IT® will be asked to go to the outpatients’ clinic 21 days after the operation to remove the silicone layer of the IT®.

Follow up

We will follow up our patients along two years after the surgery. During this period the most important variable to assess and the one that will change the outcome of our patients is the dysphagia.

We will date our patients one, three and six months, one year and two years after the resection of their tumours. To precise the grade of dysphagia one month and one and two years after the surgery, the MECV-V test will be used. The responsible for applying this test to our patients will be Núria Pons, our nutritionist.

6.6  INTERVENTION

As mentioned before, once the patients have signed the informed consent (annex 4 and 6) and have been correctly randomized they will enter the study. During the surgical procedure, all of them will have their tumours resected. Trans-oral techniques combining TOUSS and electrocautery will be applied to reduce the morbidity and improve the general outcomes.

After having resected the tumour, starts the aim of study of this project.

The control group will undergo the conventional therapy which consists in leaving the wound after the surgical excision to heal by secondary intention. Therefore, in these cases no more surgical procedures will be needed.
The intervention group will undergo a reconstruction using Integra® Dermal Regeneration Template. To place the Integra® we will follow the next steps:

1. The exact area to be covered must be first determined. To do so, we will use a sterile ruler.

2. Once we have measured the area that must be covered, we will then decide the product size. There are two options available: 2in x 2in (5cm x 5cm) and 4in x 5in (10cm x 12.5cm).


4. Wound bed preparation:
   a. The wound bed may be prepared with a surgical wound cleaner.
   b. Meticulous haemostasis needs to be achieved to prevent haematomas or excessive fluid accumulation. To achieve it, electrocautery or other topical haemostats may be used.
c. Uniform and flat wound bed to ensure intimate contact with the Integra® Template.

Figure 6-2 Wound bed prepared to receive the Integra® Template. Source: Author

5. Application of the Integra® Template:
   a. The collagen layer must be in direct contact with the prepared wound bed, starting at the edge. To avoid any confusion, the silicone layer is identified by the black threads and must be placed out, away from the wound bed.
   b. Make sure the Integra® Template lays flat with no wrinkles or bubbles.
   c. Cut or trim the Integra® Template to size and select sheet fixation method. Integra Template should be secured using sutures and/or staples (Ethicon Securestrap™). If more than one sheet is needed, gaps and overlaps must be avoided.
Once the Integra® Template has been applied, the patient will be hospitalized.

When the neodermis formation has been completed, approximately 21 days after its application, the silicone layer will be removed. To do so, we will first remove the staples and/or sutures. Then, we will gently take the silicone layer, by using forceps, lifting from the edges and peeling it back carefully.

Normally, the silicone layer can be easily separated and removed. Difficult separation may indicate that neodermis has not fully matured.
6.7 SAFETY

IT® has been previously applied with other indications and systematic reviews have already demonstrated the safety of the procedure.

Major postoperative complications, such as haemorrhage and infection, have already been considered in this research protocol. These complications, however, are related to the surgical operation rather than the intervention herein described. Nevertheless, these complications will be registered and analysed in our study.

Other minor complications observed are fluid accumulation, premature silicone separation and areas of incomplete IT® take.
6.8 STATISTICAL ANALYSIS

All statistical analysis will be performed with Statistical Package for the Social Sciences (SPSS) for Windows®.

As mentioned before, data of all patients who enter the study will be analysed even if they withdraw without completing the study as we will therefore use an intention to treat analysis.

Univariate analysis

In our study, we will work with three categorical variables (type of procedure, haemorrhage and infection), one quantitative discrete variable (grade of dysphagia) and two quantitative continuous variables (grade of pain and the days of nasogastric feeding tube).

For quantitative continuous variables, if a normal distribution could be assumed, we will use mean and standard deviation; whereas if a normal distribution cannot be assumed, the median and the quartiles will be estimated. For categorical variables and the quantitative discrete variable, the results will be expressed in percentages.

Bivariate analysis

For our primary objective, the independent variable (type of procedure) is categorical and the dependent one (grade of pain) is a quantitative continuous one. Therefore, the Student’s T test will be used to analyse the data and perform the comparison between them.

To analyse the relation between our independent variable and the grade of dysphagia, defined as a quantitative discrete variable, Mann-Whitney U test will be used.
Finally, to analyse the other secondary dependent variables in relation to our independent variable we will need two different tests. For the categorical variables (haemorrhage and infection), we will use the $\chi^2$ (Chi-Square), and for the days of nasogastric feeding tube the Student’s T test will be used.

**Multivariate analysis**

A multivariate analysis will be accomplished to adjust our variables for covariates, thus we will try to avoid potential confounders that could modify the results. To do so, we will use a multiple lineal regression model in case the dependent variable is a continuous variable or a quantitative discrete one (grade of pain, days of nasogastric feeding tube and grade of dysphagia) and a multiple logistic regression model in case the dependent variable is a dichotomous one (haemorrhage and infection).

A confidence interval of 95% will be assumed and $p<0.05$ will be considered statistically significant.

**6.9 WORK PLAN AND CHRONOGRAM**

This study will take approximately 5 years and 3 months. All the activities will be organized in 4 phases detailed below:

1- **Preparation and coordination phase (4months)**

During the first part of the study a detailed protocol will be elaborated. This will take from December 2016 until January 2017. This protocol will contain a detailed explanation of the variables and the objectives proposed for the study and the design and chronogram will also be explained.
All investigators, collaborators, nursing staff, administrative staff and statisticians will meet and all tasks will be assigned at this moment. It is important to ensure that everybody taking part in this study knows its task and the way to perform it. Once the protocol is ready, it will be presented to the Ethical Committee for its evaluation and approval. All changes suggested will be taken into account.

2- **Field work and data collection (4 years)**

The sample recruitment will take 2 years. Patients who undergo a surgical excision of a tumour involving the oral cavity or the oropharynx and meet the inclusion criteria will be randomized into two groups. Along 2016, 20 patients met the inclusion criteria. Hence, two years will be enough to recruit the 36 patients needed for our study.

Patients who are assigned to the intervention group will receive the Integra® Template and all complications suffered during the early postoperative period will be correctly registered and treated. Patients assigned to the control group will proceed with the conventional way and their complications will also be registered and treated.

To conclude, all patients will be followed up during two years after the surgical excision of their tumours. While the trial is taking place, the data collected from each patient will be registered in our database, and it will be periodically analysed by the statistician to control if the protocol is being followed.
3- Statistical analysis and interpretation (5 months)

After processing the database, all data will be analysed using the appropriate statistical test by a statistician. For this phase of the study, a blinded statistician will be used.

Data will be analysed in two different phases:

I. Once all patients of the study have been treated and all data regarding to postoperative early outcomes (pain, days of nasogastric feeding tube, days of hospitalization and early complications) has been correctly processed.

This will allow us to publish the first data obtained from our study and explain the new technique.

II. After all data (including the follow up) has been collected.

The following step will be the interpretation of the results and the elaboration of the articles.

Two months will be needed for the statistical analysis and three more for the interpretation of the results and the elaboration of the articles.

4- Publication and dissemination (6 months)

After writing and editing the scientific papers, the researchers will publish the results and will attend conferences to disseminate the findings.

Chronogram may be found at the annex section (Annex 13).
7 ETHICAL ASPECTS

This study protocol will be evaluated by the Clinical Research Ethics Committee of Hospital Universitari Doctor Josep Trueta and will not be applied unless it has its approval. This committee shall ensure that the study respects the ethical principles for medical research involving human subjects established by Helsinki’s Declaration, and that the privacy of all the participants is protected and confidential as well as their personal information according to Ley Orgánica 15/1999 de Protección de Datos de Carácter Personal. To maintain confidentially of personal data, an identification number will be used instead of the patient’s name.

Any further recommendation from the Clinical Research Ethics Committee will be considered to improve the procedure.

Prior to the inclusion, the information sheet (Annex 5) will be provided to all our candidate patients to enter the study. All risks, benefits and alternatives to the procedures will be detailed using the best update data available at that point to ensure the patients perfectly understand the study before they sign the informed consent (Annex 4 and 6). Thus, the principle of autonomy will be respected.

The subjects will participate voluntarily in the study after giving their informed consent. In the case that a potential research subject could not give us the permission to include him or her in our study, we will seek informed consent from the legally authorized representative. If the representative is not available, we will proceed without informed consent and obtain the consent to remain in the research as soon as possible from the subject or a legally authorized representative.
This study includes an invasive procedure in the intervention group. Therefore, the Spanish law 14/2007 of the 3rd December about Biomedical Investigation will be respected. Particularly section II, where it specifies the basic principles, requirements, authorization and safety of studies in which a human being undergoes an invasive procedure.

This study also includes the application of a health product (Integra® Template) in the intervention group. Therefore, the Spanish law RD 1090/2015, related to the clinical investigation using health products, will be respected. This study will be registered in EudraCT and the authorisation of the AEMPS (Agencia Española de Medicamentos y Productos Sanitarios) will be asked.

The Spanish Constitution of 1978, in the article 43, talks about the right of health protection, and this is undoubtedly preserved on this trial.

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

The main limitation of our study is related to the sample size. No other studies relating pharyngectomy and pain have been done before, therefore no objective data could be obtained from our research to define the exact pain expected after the surgery. To minimize this limitation, we used the data from M. Tobed’s registered cases to obtain the mean value of postoperative pain and the standard deviation. For this reason, these values may differ from other centres and other professionals and could also differ from the ones we will finally find in our study. If important differences are found in the beginning of our study, the sample size will be readjusted to the new values.

The second limitation is the extrapolation of the results to other centres and populations. The outcomes of oral cavity and oropharyngeal surgeries are strongly related to operator experience, which means that our results will be valid for our population but may differ when applied to other populations.

An additional limitation of our study is related to the open-label design. Because the intervention consists in a surgical procedure, there is no option to blind the participants, the doctors and the research team. This could cause an ascertainment bias. To overcome this limitation, the statistician who analyses the data will be blind.

Another limitation related to the design of our study is the recruitment method. The consecutive recruitment is a non-probabilistic recruitment and may not obtain the best representative population, so a selection bias may occur. Nevertheless, to minimize this bias, very few exclusion criteria has been set.
To conclude with the limitations of our study, the extra cost that supposes the application of the IT® (1341€ per patient) could result in a great amount of money at the end of the year, 26820€ in our centre. Nevertheless, this cannot be analysed as an isolated datum. We expect that IT® will reduce the hospital stay of our patients and according to “Diari Oficial de la Generalitat de Catalunya” and specially the article “SLT/30/2013”, where the public costs of the Catalan Health System are specified, the cost of the hospitalization in our hospital is 723€ per day. Hence, if IT® could prove a decrease of 2 or more days of hospitalization compared to the control group, the use of IT® would result in a decrease of the healthcare patient’s costs.

The main strength of our study is that it will be all performed in HUDJT and all the surgeries will be done by M. Tobed. By avoiding a multicentre design or using more than one surgeon we will avoid possible bias affecting our studies. Apart from that, due to the randomization process, both groups will be similar and comparable to each other.
9 FEASIBILITY

This study will take place exclusively in Hospital Universitari Doctor Josep Trueta from Girona, where all the means necessaries for its development will be available and provided.

The whole entorhinal service, the head and neck committee, the nutritionist and the nurse staff are all well trained and will work together to achieve the marked objectives.

The hospital will provide all the necessary means such as personnel salaries, operation rooms, cures and follow up. Computer devices and programs to elaborate the database and to carry out the statistical analysis will also be provided.

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

In HUDJT around 26 patients undergo surgical procedures related with oropharynx and oral cavity cancers every year. Therefore, within two years, we will have our sample completed.
10 BUDGET

This study will be carried in HUDJT and the research team is already employed by the institution and no extra hours will be needed. For this reason, this services will not be included in our budget. A part from that, the first part of the surgical procedure which includes the tumour resection is part of the normal procedure used in the clinical practice as well as the follow up of our patients.

The evaluation of the complications, the grade of pain and the grade of dysphagia also form part of the routine activity related to these patients and will not suppose an extra cost.

Extra services

A statistician will be needed in order to create a data base, randomize the patients, collect the data and perform the statistical analysis. We expect that 60 hours will be needed and the salary of our statistician is 25€/hour.

Material

To go on with our study we will need some extra material for our intervention group. An Integra® Dermal Regeneration Template (2in x 2in) and Ethicon Securestrap™ to fix the Integra® will be used for every patient. No other extra material will be needed.

Insurance

An insurance policy will be hired for our 36 patients with an extra cost of 4000€.
Publication and dissemination

The approximate cost for the publication of our results will be 2500€.

We will also attend to the Spanish, the European and the World entorhinal congress. We will attend twice to all of them, first to present our initial results and in second term to present the final results of our study.

The costs of attending the National congress will be:

a. Registration: 360€
b. Meals and accommodation: 240€
c. Flights: 150€
d. Total: 750€

The costs of attending the European Congress will be:

a. Registration: 580€
b. Meals and accommodation: 450€
c. Flights: 250€
d. Total: 1280€

The costs of attending the world congress will be:

a. Registration: 690€
b. Meals and accommodation: 450€
c. Flights: 400€
d. Total: 1540€
### BUDGET PROPOSAL

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*Table 10-1 Budget proposal. Source: Author*
11 IMPACT

Patients with an oropharyngeal cancer or a cancer of the oral cavity who undergo a surgical excision have poor postoperative outcomes. These patients usually spend long periods hospitalised due to the need of feeding tube and suffer from unacceptable grades of pain (most of them over 50mm in the VAS test). For all these reasons a solution must be found to improve the postoperative outcomes and allow our patients to get more rapidly back to their normal lives.

The new reconstructive technique, applying Integra® Template to the wound bed after the tumour excision, aims to mainly reduce the grade of pain of our patients. This would lead to an early recover of the oral nutrition and, therefore, to shorter hospital stays.

It will also be important to determine the safety and complications related to this new technique to be confident with its implementation.

If our study shows relevant positive results and our hypothesis is validated, we would be able to implement this new technique on our centre and publish the results to let other centres start using this new procedure, even though results may differ depending on the surgeon.

As a whole, it will suppose a great change in the management of these patients and a great improve on their early postoperative outcomes leading to an earlier recover.
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Eur Arch Otorhinolaryngol [Internet]. 2005 Apr 14 [cited 2017 Jan
10];262(4):302–6. Available from:


POSTOPERATIVE OUTCOMES AFTER APPLYING INTEGRA®DERMAL REGENERATION TEMPLATE ON PHARYNGECTOMIZED PATIENTS.

Jun;2(2):175–84.


14 ANNEXES

ANNEX 1: TNM Definitions for Oral Cavity and Oropharyngeal Carcinoma according to the American Joint Committee on Cancer, 7th Edition

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumor (T)</td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor more than 2 cm but not more than 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Oral cavity: Tumor more than 4 cm in greatest dimension</td>
</tr>
<tr>
<td></td>
<td>Oropharynx: Tumor more than 4 cm in greatest dimension or extension to lingual surface of epiglottis</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced local disease</td>
</tr>
<tr>
<td></td>
<td>Oral cavity: Tumor invades adjacent structures only (eg. through cortical bone [mandible or maxilla] into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face)</td>
</tr>
<tr>
<td></td>
<td>Note: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumor as T4</td>
</tr>
<tr>
<td></td>
<td>Oropharynx: Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible</td>
</tr>
<tr>
<td></td>
<td>(Note: mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of larynx)</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced local disease</td>
</tr>
<tr>
<td></td>
<td>Oral cavity: Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery</td>
</tr>
<tr>
<td></td>
<td>Oropharynx: Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base, or encases carotid artery</td>
</tr>
<tr>
<td>Regional lymph node involvement (N)</td>
<td></td>
</tr>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>Distant metastasis (M)</td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>
ANNEX 2: Staging and TNM Classification for Oral and Oropharyngeal Carcinoma according to the American Joint Committee on Cancer, 7th Edition

<table>
<thead>
<tr>
<th>STAGE</th>
<th>TNM CLASSIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>Tis N0 M0</td>
</tr>
<tr>
<td>I</td>
<td>T1 N0 M0</td>
</tr>
<tr>
<td>II</td>
<td>T2 N0 M0</td>
</tr>
<tr>
<td>III</td>
<td>T3 N0 M0 &lt;br&gt;T1 N1 M0&lt;br&gt;T2 N1 M0&lt;br&gt;T3 N1 M0</td>
</tr>
<tr>
<td>IV</td>
<td>IVA &lt;br&gt;T4a N0 M0 &lt;br&gt;T4a N1 M0 &lt;br&gt;T1 N2 M0&lt;br&gt;T2 N2 M0&lt;br&gt;T3 N2 M0&lt;br&gt;T4a N2 M0</td>
</tr>
<tr>
<td></td>
<td>IVB &lt;br&gt;T4b Any N M0 &lt;br&gt;Any T N3 M0</td>
</tr>
<tr>
<td></td>
<td>IVC &lt;br&gt;Any T Any N M1</td>
</tr>
</tbody>
</table>
ANNEX 3: Lymph node levels of the neck
Este documento informativo pretende explicar, de forma sencilla, la intervención quirúrgica denominada **EXTIRPACIÓN DE UNA TUMORACIÓN FARÍNGEA**, así como los aspectos más importantes del período postoperatorio y las complicaciones más frecuentes que, como consecuencia de esta intervención, puedan aparecer.

**BREVE DESCRIPCIÓN DEL PROCEDIMIENTO QUIRÚRGICO:**

Las tumoraliones faríngeas pueden tener una naturaleza, un tamaño y una localización muy distinta, dentro de la faringe. En dependencia de estas circunstancias, el especialista le aconsejará una u otra técnica quirúrgica.

En general, la intervención se lleva a cabo mediante anestesia general. Hay casos en los que se puede realizar a través de la abertura bucal. En otras ocasiones esta abertura debe de ser ampliada mediante la sección del labio e incluso de la mandíbula inferior. Hay casos, por último, en los que la vía de abordaje se inicia desde el cuello.

En muchos casos, esta intervención exige la realización de una traqueotomía, que es una técnica quirúrgica que consiste en la apertura de la tráquea a nivel del cuello, con objeto de establecer una comunicación, un orificio, entre ésta y el exterior, permitiendo la respiración a través de dicha comunicación.

En otras ocasiones, se requiere la colocación de una sonda de alimentación, que suele introducirse a nivel de la nariz y alcanzar el esófago, para facilitar la alimentación del paciente. Esta sonda suele ser temporal. En algunas situaciones concretas, el especialista puede disponer la realización de un orificio en el abdomen que comunica, mediante una sonda, el estómago con el exterior, para facilitar la alimentación del paciente intervenido.

Además, en la mayor parte de las ocasiones, se requiere la realización de un vaciamiento ganglionar cervical. El vaciamiento ganglionar cervical consiste en la extirpación de la mayor parte de los ganglios linfáticos del cuello de un solo lado (unilateral), o de los dos (bilateral). Se realiza a través de una incisión que se practica en el cuello, en uno o ambos lados. Su finalidad es impedir que la enfermedad se extienda a otras partes del cuerpo.

El cuello es zona de paso de grandes vasos –arterias y venas que riegan la cabeza y el cuello–, de importantes nervios que, desde el cerebro, se dirigen hacia las diferentes zonas y órganos del resto del cuerpo y, además, contiene músculos y estructuras glandulares. A veces, al practicar un vaciamiento cervical puede ser necesario sacrificar alguna de estas estructuras, siempre con fines curativos. Por otra parte, en el transcurso de la intervención pueden resultar lesionadas alguna de estas estructuras.

Dependiendo de cada caso, es posible que el paciente permanezca ingresado en la U.C.I. para su mejor control postoperatorio durante las primeras 24 horas tras la intervención. Al día siguiente puede pasar a la planta, donde continuará su recuperación.

El paciente llevará unos pequeños tubos de drenaje en uno o ambos lados del cuello, que se retiran a los 2 ó 3 días. En los primeros días después de la intervención, pueden aparecer hemorragia o infecciones que obliguen a reintervenir, prolongando la estancia hospitalaria.
Después de la intervención, si se ha realizado una traqueotomía, se coloca un tubo, en el oriﬁcio practicado, llamado cánula traqueal. A través de dicho tubo se respira y se expulsan las secreciones. Es muy importante mantenerlo limpio para que no se obstruya. Por ello es imprescindible aspirar las secreciones y humedecerlo para que éstas no se sequen en su interior. Esta cánula deberá ser empleada durante días o semanas. En algunos casos la cánula debe llevarse de forma deﬁnitiva.

Tras la intervención, aparecen molestias dolorosas en el momento de tragar, que suelen ser intensas e irradiarse hacia los oídos, prolongándose a lo largo de diez o quince días, debiendo, por ello, administrarse calmantes. Puede notarse, durante las primeras horas, la saliva teñida de sangre o, incluso, aparecer vómitos de sangre oscura, ya digerida, y que están en relación con la sangre deglutida durante la intervención. También pueden ser normales las heces oscuras, en los días inmediatos, por el mismo motivo.

Durante los primeros días puede percibirse mal aliento. Al principio, la alimentación suele realizarse a través de una sonda, como ya hemos dicho, y, después, es posible que se realice a través de la boca. Inicialmente consistirá sólo en líquidos y, posteriormente, alimentación blanda hasta completar la cicatrización.

La duración del ingreso hospitalario es variable, dependiendo de las molestias, la evolución, etc. Durante los mismos se controlará la presencia de fiebre y hemorragia, así como el proceso de cicatrización de la herida.

El período de cicatrización dura, aproximadamente, 7 días, parte de los cuales deberá permanecer ingresado en el hospital y, posteriormente, acudir a las consultas externas del Servicio para las revisiones o curas que sean necesarias.

En determinados casos, para el correcto tratamiento de la enfermedad será necesario la administración de radioterapia y/o quimioterapia tras la intervención.

En caso de NO EFECTUARSE ESTA INTERVENCIÓN, si no se realizan otros tratamientos hay que suponer que la naturaleza de la tumoración justiﬁque su crecimiento inexcusable que acabará produciendo profundos trastornos de la alimentación y de la respiración e, incluso, la extensión del tumor a otras zonas más distantes del organismo.

BENEFICIOS ESPERABLES: Curación de la enfermedad.

PROCEDIMIENTOS ALTERNATIVOS: Pueden ser la radioterapia y la quimioterapia, con menor probabilidad de éxito que la cirugía, en la mayoría de los casos.

RIESGOS ESPECÍFICOS MÁS FRECUENTES DE ESTE PROCEDIMIENTO: Cabe la posibilidad de que se produzca una hemorragia de cierta intensidad durante el periodo posterior a la intervención. Si esta hemorragia postoperatoria fuera muy intensa o no se tratara con corrección podría aparecer una anemia e incluso un shock –llamado hipovolémico– por la pérdida del volumen de sangre. Por ello, si se produjera, su tratamiento podría requerir una nueva intervención o una transfusión. Cabe la posibilidad de que, accidentalmente, pueda pasar la sangre que procede de la herida operatoria hacia las vías respiratorias; a esta posibilidad se la conoce como hemoaaspiración y puede llegar a obstruir las vías aéreas produciendo, incluso, una parada cardiorrespiratoria.

Es posible que se produzca la infección de la herida quirúrgica o del aparato respiratorio, y disfagia –dificultades para tragar– que pueden ser definitivas y quedar como secuela.

Pueden aparecer, también, fístulas faríngeas –comunicaciones de la garganta con el exterior del cuello–, entesema cervical o mediastínico –pequeñas burbujas de aire en el cuello o en el tórax–, necrosis –destrucción– de las partes blandas del cuello, recidiva –reaparición– de la enfermedad, temprana o tardíamente.

Pueden aparecer alteraciones del olfato y del gusto, limitaciones en la motilidad de la lengua o del labio y una cicatriz antiestética o dolorosa.
En el caso de la realización de una traqueotomía, pueden aparecer tapones mucosos en la tráquea o los bronquios.

En el caso de que se precise un vaciamiento cervical, puede aparecer una hemorragia a nivel del cuello, que puede requerir una nueva intervención quirúrgica y una transfusión. En ocasiones, esta hemorragia puede ser la causa del llamado «hematoma sofocante del cuello», que pudiera requerir la realización de una traqueotomía si es que no se ha realizado con anterioridad.

Pueden aparecer diferentes complicaciones cardiovasculares, tales como el shock hipovolémico –llamado así por la pérdida del volumen de sangre–, la embolia gaseosa –penetración de aire en el interior de los vasos–, la trombosis venosa –formación de un coágulo en el interior de una vena–, la embolia pulmonar –enclavamiento de un coágulo en el interior de los vasos que llegan al aparato respiratorio– y el paro cardíaco.

Cabe la posibilidad de que aparezcan alteraciones encefálicas, generalmente por isquemia (disminución del riego) cerebral, tales como ceguera, hipoacusia neurosensorial –sordera– y vértigo; hemiplejía –es decir parálisis de la mitad del cuerpo– y, incluso, el fallecimiento del paciente. Se puede producir un edema –inflamación– de la laringe, y dificultades respiratorias que puedan requerir traqueotomía, si no se ha realizado antes.

Además, hay que considerar, entre las complicaciones, la posibilidad de que se produzca una movilización anormal, la fractura o la edentación –pérdida de alguna pieza dental– de manera accidental, la fisura del paladar, la aparición de una voz nasalizada que llamamos rinolalia y la insuficiencia del velo del paladar para ocluir las fosas nasales en su parte posterior, durante la deglución.

El stress del paciente puede justificar una úlcera gastroduodenal y una depresión.

Además, las complicaciones propias de toda intervención quirúrgica y las relacionadas con la anestesia general. El riesgo vital es poco frecuente, aunque puede producirse en todo acto médico que incluye anestesia: se ha descrito un caso de muerte cada 15.000 intervenciones con este tipo de anestesia.

En general, el riesgo quirúrgico aumenta en relación con la edad, la cantidad y la gravedad de las enfermedades padecidas

**RIEGOS RELACIONADOS CON SUS CIRCUNSTANCIAS PERSONALES Y PROFESIONALES:**

- ...
- ...
- ...

**OBSERVACIONES Y CONTRAINDICACIONES:**

- ...
- ...
- ...

Documento de consentimiento informado recomendado por la Sociedad Española de Otorrinolaringología y Patología Cervico-Facial

Edición 1.ª - Año 2003

— 3 —
DECLARACIONES Y FIRMAS

Declaro que he sido informado, por el médico, de los aspectos más importantes de la intervención quirúrgica que se me va a realizar, de su normal evolución, de las posibles complicaciones y riesgos de la misma, de sus contraindicaciones, de las consecuencias que se derivarían en el caso de que no me sometiera a la mencionada intervención y de las alternativas a esta técnica quirúrgica.

Estoy satisfecho de la información recibida. He podido formular todas las preguntas que he creído convenientes y me han sido aclaradas todas las dudas planteadas.

Declaro, además, no haber ocultado información esencial sobre mi caso, mis hábitos o régimen de vida, que pudieran ser relevantes, a los médicos que me atienden.

Sé, por otra parte, que me intervendrá el facultativo que, dentro de las circunstancias del equipo médico en el día de la intervención, sea el más adecuado para mi caso.

Tras todo ello, DOY MI CONSENTIMIENTO PARA SER OPERADO, así como para que, durante la intervención, el cirujano tome las muestras biológicas que considere necesarias para el estudio de mi proceso, o las imágenes precisas para la adecuada documentación del caso.

En el caso de que, durante la intervención, el cirujano encuentre aspectos de mi enfermedad que le exijan o le aconsejen modificar el procedimiento inicialmente proyectado, podrá hacerlo de la manera que mejor convenga a mi salud, advirtiéndoselo a mi familia o, en su ausencia, tomando la decisión por él mismo. Conozco, por otra parte, mi derecho a revocar esta autorización en cualquier momento.

Firma del paciente Firma del médico

TUTOR LEGAL O FAMILIAR

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

Firma del tutor o familiar

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

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

Firma del paciente o representante legal Fecha: / /
INFORMATION SHEET FOR PARTICIPANTS

PROJECT: POSTOPERATIVE OUTCOMES AFTER APPLYING INTEGRA® DERMAL REGENERATION TEMPLATE ON PHARYNGECTOMIZED PATIENTS. A RANDOMIZED CLINICAL TRIAL

Investigators: Marc Tobed Secall and Xavier Carreras Castañer

Location: Hospital Universitari Doctor Josep Trueta

You are being invited to take part in a research study.

Please take time to read the following information about the study carefully. It is important for you to understand why the research is being done and what it will involve. Ask us if there
is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

**What is the purpose of the study?**

The primary aim of the study is to register and compare the grade of pain (using VAS) and the postoperative outcomes in patients treated with a trans-oral pharyngeal reconstruction using Integra® Dermal Regeneration Template (IT®) compared to those who do not receive any treatment after the pharyngectomy.

We also want to assess the complications related to the application of the Integra® Template and see if the use of IT® is related to a shorter hospital stay.

Our goal is to improve the postoperative outcomes of pharyngectomized patients by using IT® and reducing the grade of pain.

**Description of the study**

In this study, two treatment options are proposed. The first one, which is the conventional treatment, is to allow the wound to heal by secondary intention. The second option consists in applying IT® to the wound bed during the same procedure of the excision of the tumour.

Patients will be randomly distributed into two groups.

In the cases that IT® is applied, the removal of the silicone layer will be done 21 days after the initial surgery. This procedure will not need anaesthetics and will be done in the outpatients’ clinic.
POSTOPERATIVE OUTCOMES AFTER APPLYING INTEGRA®DERMAL REGENERATION TEMPLATE ON PHARYNGECTOMIZED PATIENTS.

All patients taking part in our study will be followed up during 2 years after the tumour resection and their grade of dysphagia and complications will be registered. They will be dated 1, 3, 6 months and 1 and 2 years after the surgery on the outpatients’ clinic.

**Why have you been invited?**

You will undergo an oral cavity or oropharyngeal tumour excision meeting the criteria to enter our study.

**Voluntary Participation**

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change.

If you choose not to participate in this research project, you will be offered the conventional procedure, which consists on leaving the wound to heal by secondary intention, offered in this hospital.

You may change your mind later and stop participating even if you agreed earlier.

You may also be excluded from the study if the investigators consider it strictly necessary because you may meet the exclusion criteria at one point. In any case, you will receive a proper explanation why have you been withdrawn from the study.
What are my responsibilities if I take part in the study?

- To go to all the study’s appointments and other appointments asked by the study team.
- To follow all the study’s instructions.
- To inform about any problem or doubt during the study.

What are the possible benefits of taking part?

The information we get from this study may help us to treat future patients with a similar condition better. However, it is not guaranteed that your condition will be better as a consequence of participating in the study.

What are the possible risks of taking part?

Some complications may occur due to the application of the IT®. The major complications would be the infection or a haematoma formation. Other minor complications would be the fluid accumulation, the premature silicone separation or areas of an incomplete IT® take.

What happens when the research study stops?

Once the study has finished, you will receive the medical care you need depending on your condition without affecting having or not participated in the study.

Responsibility and insurance

You are insured for any damage you may suffer as a result of your participation on this trial, in accordance with the law.
Confidentiality

All patients’ data is recorded on a password protected computer database. The information will be confidential according to the Spanish Organic law (15/1999) on personal data protection.

Only the researchers and collaborators will be able to access this information and data collected during the study. Your personal identification will not be disclosed.

Sharing the results

The knowledge that we get from doing this research will be shared with you through community meetings before it is made widely available to the public. Confidential information will not be shared. There will be small meetings in the community and these will be announced. After these meetings, we will publish the results in order that other interested people may learn from our research.

Economic compensation

Your participation in the study will not be associated with any economic compensation. Nevertheless, you will not pay the treatments received during this study.

Right to refuse or withdraw

You do not have to take part in this research if you do not wish to do so and refusing to participate will not affect your treatment at this clinic in any way. You will still have all the benefits that you would otherwise have at this clinic. You may stop participating in the
research at any time that you wish without losing any of your rights as a patient here. Your treatment at this clinic will not be affected in any way.

Who can I contact to for Further Information, doubts or problems?

If you have any questions about your rights as a research subject, about your participation in the study or any complaints about the study, please contact with your research doctor.

Hospital Universitari Dr. Josep Trueta

Av/ de França, s/n. 17007 – Girona

Thank you for reading this. Try to keep this information sheet until your participation in the study is finished. Any queries, questions or doubts do not hesitate to ask us.
ANNEX 6: Consent form to enter the trial

<table>
<thead>
<tr>
<th>Hospital Dr. Josep Trueta, Av. França s/n 17007 Girona</th>
<th>INFORMED CONSENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>POSTOPERATIVE OUTCOMES AFTER APPLYING INTEGRA® DERMAL REGENERATION TEMPLATE ON PHARYNGECTOMIZED PATIENTS. A RANDOMIZED CLINICAL TRIAL</td>
<td></td>
</tr>
</tbody>
</table>

WRITTEN INFORMED CONSENT FOR THE PATIENT

TITLE OF THE STUDY: POSTOPERATIVE OUTCOMES AFTER APPLYING INTEGRA® DERMAL REGENERATION TEMPLATE ON PHARYNGECTOMIZED PATIENTS. A RANDOMIZED CLINICAL TRIAL

I... ..............................................................................................................................................................................................................................................................................................

Confirm that: have been informed by the investigator about the purpose of the study.

- I have read and understood the information sheet.
- I have had time to think and consider this information.
- I have had the opportunity to ask any questions and be answered.
- I understand that my participation is entirely voluntary and I can withdraw this study any moment I wish, for any reason and without any consequences for the healthcare I receive.
- I give permission to collect my data and analyse it. I have been informed that all my data will be kept confidential.
POSTOPERATIVE OUTCOMES AFTER APPLYING INTEGRA®DERMAL REGENERATION TEMPLATE ON PHARYNGECTOMIZED PATIENTS.

I have spoken with (name of the investigator / head and neck surgeon /nurse):

........................................................................................................................................................................

In consequence,

I give my conformity to enter this study.

Yes  No

I allow the personnel of this study to consult my clinical history with the aim of verification of the data.

Yes  No

I allow the use of the gathered data for further investigation in the head and neck surgery department.

Yes  No

Signature of the participant:  Signature of the investigator:

Date: __ __ / __ __ / __ __
ANNEX 7: Visual Analogue Scale (VAS)

How severe is your pain today? Place a vertical mark on the line below to indicate how bad you feel your pain is today.

No pain | | Very severe pain

ANNEX 8: Material, preparation and method used for MECV-V test

<table>
<thead>
<tr>
<th>MATERIAL</th>
<th>PREPARATION</th>
<th>METHOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>300ml of water</td>
<td>1 glass with 100ml of water</td>
<td>Patient in sedestation position</td>
</tr>
<tr>
<td>13’5gr of thickener</td>
<td>1 glass with 100ml of water + 4’5grs of thickener – nectar viscosity</td>
<td>Pulse oximeter monitoring of the patient’s oxygen saturation</td>
</tr>
<tr>
<td>50ml needle</td>
<td>1 glass with 100ml of water + 9grs of thickener – pudding viscosity</td>
<td>Explain the procedure to the patient</td>
</tr>
<tr>
<td>3 glasses</td>
<td></td>
<td>Ask the patient to say his/her name to check the quality of his/her voice</td>
</tr>
<tr>
<td>1 pulse oximeter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 depressor or spoon</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ANNEX 9: MECV-V test
ANNEX 10: Variables summary table

<table>
<thead>
<tr>
<th>Type</th>
<th>Units</th>
<th>Measure method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure</td>
<td>Dichotomous variable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No reconstruction • IT® reconstruction</td>
<td>No measuring method needed</td>
</tr>
<tr>
<td>Grade of pain</td>
<td>Quantitative continuous variable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Usually expressed in millimetres (or cm).</td>
<td>Visual Analogue Scale for pain (VAS)</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>Dichotomous variable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Yes • No</td>
<td>No measuring method needed</td>
</tr>
<tr>
<td>Infection</td>
<td>Dichotomous variable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Yes • No</td>
<td>Clinic, analytic and microbiological signs</td>
</tr>
<tr>
<td>Grade of dysphagia</td>
<td>Quantitative discrete variable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 0: No dysphagia • 1: Liquid dysphagia • 2: Nectar dysphagia • 3: Total dysphagia</td>
<td>MECV-V test</td>
</tr>
<tr>
<td>Days of nasogastric feeding tube</td>
<td>Quantitative continuous variable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amount of days using feeding tube</td>
<td>No measuring method needed</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>Quantitative continuous variable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amount of days remaining at the hospital</td>
<td>No measuring method needed</td>
</tr>
<tr>
<td>TNM stage</td>
<td>Categorical ordinal variable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I-IV TNM stages</td>
<td>Clinic, radiologic and pathologic diagnostic</td>
</tr>
<tr>
<td>Previous treatment received</td>
<td>Dichotomous variable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Yes • No</td>
<td>No measuring method needed</td>
</tr>
</tbody>
</table>
## ANNEX 11: Data collection summary table

<table>
<thead>
<tr>
<th>-15 days: Pre-entry</th>
<th>During these days, patients with recently diagnosed tumours will be informed and they will accept the consent form (Annex 4, 5 and 6).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1: Trial entry</td>
<td>Once the resection is done, all patients who fit the inclusion criteria will enter the trial. At this point (during the same procedure), those randomly assigned to the intervention group will undergo Integra® Template reconstruction.</td>
</tr>
</tbody>
</table>
| Day 1-15: Hospitalization | The grade of pain and the complications will be registered during the hospitalization. The days of hospitalization will vary depending on the patients’ status.  
Also, dysphagia will be tested one week after the intervention and the amount of days the patient needs a feeding tube will also be registered. |
| Day 21: Integra® Template withdrawal | 21 days after the reconstruction, the silicone layer will be removed. |
| Days 21-730: Follow up | Grade of dysphagia will be followed up (1 month and 1 and 2 years after the intervention) and late complications will be registered.  
Patients will be dated 1-3-6 months and 1-2 years after the intervention. |
ANNEX 12: Integra® preparation

- Open the outer pouch
- Fill a basin with 1 liter of sterile saline
- Product Preparation

**Using aseptic technique, place the inner pouch into the sterile field**

**While holding the tab, peel off both polyethylene sheets from the Integra® template**

**Remove the product from the inner pouch using the attached center tab**

**Carefully remove the Integra® template from the tab**

**Rinse Integra® template for a minimum of 1-2 minutes. Keep the Integra template in the saline bath until application.**

**Note: Integra® template is packaged between 2 polyethylene sheets and an attached center tab. Using the center tab, place the product into a basin containing the sterile saline solution.**
ANNEX 13: CHRONOGRAM