Functional outcomes of immunotherapy induction treatment and transoral robotic surgery therapeutic approach for oropharyngeal squamous cell carcinoma

AN INTERVENTION STUDY BASED ON A PROSPECTIVE COHORT
I would like to express my sincere gratitude to otorhinolaryngology department of Hospital Universitari Doctor Josep Trueta for giving me the opportunity to learn at their side and for making me feel part of the team.

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ABSTRACT

Background
Therapeutic approach of locally advanced oropharyngeal squamous cell carcinoma (SCC) is based in treatment strategies which result in poor functional outcomes, mainly in distinct grades of dysphagia, leading to impaired quality of life for these patients. Therefore, minimally invasive surgeries, like transoral robotic surgery (TORS), are been used to achieve less postoperative morbidity. Moreover, there is an increasing interest in induction treatment strategies, such immunotherapy, which might play a role in achieving less intensive primary surgeries.

Objective
The aim of this study is to analyse if in the therapeutic approach of locoregional advanced SCC of the oropharynx, immunotherapy as an induction treatment together with TORS can obtain an improvement in functional outcomes, with the same adequacy of surgical margins and local control of disease, compared with current treatment strategies.

Design
A multicentre non-randomized intervention study based on a prospective cohort will be carried out during 9 years and 11 months at Hospital Universitari de Girona Doctor Josep Trueta (Girona), Hospital Germans Trias i Pujol (Badalona) and Hospital Universitari de Bellvitge (L'Hospitalet de Llobregat).

Methods
Using a non-probabilistic consecutive sampling, patients who have had histologically confirmation of SCC of the oropharynx, in a locally advanced stage, with surgical indication, who express biomarkers to undergo immunotherapy induction treatment and meet all other inclusion and exclusion criteria will be recruited to perform this study. To do so, 216 patients will be assigned into two groups. Intervention group will receive immunotherapy induction treatment followed by TORS. Control group will receive conventional treatment (TORS). Both groups will be followed up in order to assess functional outcomes, mainly the grade of dysphagia by functional videoendoscopy. The main dependent variable, the grade of dysphagia, will be categorized by: absence or minor defect, and major defect. Once categorized, a logistic regression on the intervention’s variable controlling all covariates will be estimated.

Key words
**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AEMPS</td>
<td>Agencia Española de Medicamentos y Productos Sanitarios</td>
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<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
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<td>ASIR</td>
<td>Age-standardised incidence rate</td>
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<td>CPG</td>
<td>Clinical practice guidelines</td>
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<td>CRT</td>
<td>Chemoradiotherapy</td>
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<td>CR</td>
<td>Crude rate</td>
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<td>CT</td>
<td>Computed tomography</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FUHNT</td>
<td>Functional Unity of Head and Neck Tumours</td>
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<td>HNSCC</td>
<td>Head and neck squamous cell carcinoma</td>
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<td>HPV</td>
<td>Human papillomavirus</td>
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<td>HUDJT</td>
<td>Hospital Universitari Doctor Josep Trueta</td>
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<tr>
<td>ICO</td>
<td>Institut Català d’Oncologia</td>
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<td>ICS</td>
<td>Institut Català de la Salut</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>OS</td>
<td>Overall survival</td>
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<tr>
<td>PEG</td>
<td>Percutaneous endoscopic gastrostomy</td>
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<tr>
<td>PD-1</td>
<td>Programmed cell death protein 1</td>
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<tr>
<td>PD-L1</td>
<td>Programmed death-ligand 1</td>
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<tr>
<td>RS</td>
<td>Relative survival</td>
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<td>RT</td>
<td>Radiotherapy</td>
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<tr>
<td>SCC</td>
<td>Squamous cell carcinoma</td>
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<tr>
<td>SEORL</td>
<td>Sociedad Española de Otorrinolaringología</td>
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<tr>
<td>TLM</td>
<td>Transoral laser microsurgery</td>
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<tr>
<td>TNM</td>
<td>Tumour – node – metastasis</td>
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<td>TORS</td>
<td>Transoral robotic surgery</td>
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<tr>
<td>US</td>
<td>United States</td>
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<td>VAS</td>
<td>Visual analogue scale</td>
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<td>WHO</td>
<td>World Health Organization</td>
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1 INTRODUCTION

1.1 ANATOMY AND FUNCTION OF PHARYNX

The pharynx is a muscular and membranous tube which constitutes the crossing point between the respiratory and digestive pathways. It is located posterior to the nasal and oral cavities, extending inferiorly past the larynx. The pharynx extends from the cranial base to the beginning of oesophagus, approximately at the level of the inferior border of the cricoid cartilage from anterior, and the inferior border of the C6 vertebra from posterior. The flat posterior wall of the pharynx lies against the prevertebral layer of deep cervical fascia (1).

The wall of the pharynx is exceptional for the alimentary tract, because it has a muscular layer composed of voluntary muscle. These muscles are organized into two layers: there are longitudinal muscles internal to a circular layer of muscles. This differs from most of the alimentary tract (which is composed of smooth muscle, with a layer of longitudinal muscle external to a circular layer). The external circular layer of pharyngeal muscles consists of three pharyngeal constrictors: superior, middle and inferior. The internal longitudinal muscles consist of the palatopharyngeus, stylopharyngeus and salpingopharyngeus. Besides, there are two more muscles that work jointly with those previous muscles, the tensor veli palatini muscle and the levator veli palatini. All these muscles elevate the larynx and shorten the pharynx during swallowing and speaking (2).

On its interior, the pharynx is divided into three parts: the nasopharynx (behind the nose and superior to the soft palate), the oropharynx (behind the oral cavity) and the laryngopharynx or hypopharynx (from inferior to the epiglottis and to where the common pathway diverges into the respiratory and digestive pathways).

The nasopharynx has a respiratory function, as it is the posterior extension of the nasal cavities. The nasal cavity opens into the nasopharynx through two choanae. The roof and posterior wall of the nasopharynx lie inferior to the body of the sphenoid bone and the basilar part of the occipital bone (1).

The oropharynx has a digestive function. It is bounded by the soft palate superiorly, the base of the tongue inferiorly, and the palatoglossal and palatopharyngeal arches laterally. It extends from the soft palate to the superior border of the epiglottis. Anatomical structures that constitute the oropharynx are (1):

- Soft palate
- Palatine tonsil
- Palatine arches (palatoglossal or anterior arch, and palatopharyngeal or posterior arch)
- Pharynx walls
- Base of tongue (lingual tonsils)
- Valleculae

Deglutition is the complex process that transfers a food bolus from the mouth through the pharynx and oesophagus into the stomach. Solid food is masticated and mixed with saliva to form a soft bolus that is easier to swallow. Deglutition occurs in three stages (3):

- **Stage 1: oral phase.** The bolus is prepared, compressed against the palate and pushed from the mouth into the oropharynx, mainly by movements of the muscles of the tongue and soft palate. Deglutition is voluntary in this stage, so it is influenced by superior cerebral functions.

- **Stage 2: pharyngeal phase.** The soft palate is elevated, sealing off the nasopharynx from the oropharynx and laryngopharynx, functionally separating the airway from the digestive tract. When velopharyngeal and laryngeal sphincters close, the pharynx widens and shortens to receive the bolus of food as the suprathyroid muscles and longitudinal pharyngeal muscles contract, elevating the larynx. The bolus is propelled through pharynx, and superior oesophageal sphincter opens. This stage finishes when laryngopharynx descends, and straightening of epiglottis and opening of laryngeal sphincter happen. This phase is involuntary and rapid (it lasts one second).

- **Stage 3: oesophageal phase.** Sequential contraction of all three pharyngeal constrictor muscles creates a peristaltic movement that forces the food bolus inferiorly into the oesophagus. The bolus reaches the stomach thanks to
peristaltic movement (more slowly than pharyngeal peristalsis) of oesophagus. This phase is also involuntary.

The abundant lymphoid tissue in the pharynx forms an incomplete tonsillar ring around the superior part of the pharynx called Waldeyer’s lymphatic ring. The lymphoid tissue is aggregated in certain regions to form masses called tonsils. The palatine, lingual and pharyngeal tonsils form this tonsillar ring. The antero-inferior part of the ring is formed by the lingual tonsil in the posterior part of the tongue. Lateral parts of the ring are formed by the palatine and tubal tonsils, and posterior and superior parts are formed by the pharyngeal tonsil. The palatine tonsils are located on each side of the oropharynx between the palatine arches, on the tonsillar sinus (fossa), but do not fill the whole tonsillar sinus in adults (1).

![FIGURE 3.3. Lymphoid tissue in tongue and pharynx. Source: Moore’s Clinically Oriented Anatomy (7th edition).](image-url)
laryngopharynx is related to the bodies of the C4–C6 vertebrae. Its posterior and lateral walls are formed by middle and inferior pharyngeal constrictor muscles. Internally, the wall is formed by palatopharyngeus and stylopharyngeus muscles. The laryngopharynx communicates with the larynx through the laryngeal inlet on its anterior wall (1).

1.2 OROPHARYNGEAL CANCER

1.2.1 EPIDEMIOLOGY

Head and neck cancers include a group of malignant tumours located in several areas of the upper aerodigestive tract: paranasal sinuses, nasopharynx, oropharynx (tonsil, soft palate and base of tongue), laryngopharynx, larynx, oral cavity (oral mucosa, gums, hard palate, tongue and floor of the mouth) and salivary glands (4).

Head and neck cancers are the sixth most common malignancy worldwide accounting for about 600,000 new cases per year. Head and neck squamous cell carcinomas (HNSCC) constitute approximately 7% of all tumours diagnosed in adult population worldwide (5). According to GLOBOCAN project, worldwide the estimated age-standardised incidence rate (ASIR) per 100,000 person-years in 2018, for all ages and both genders is (6):

- For all head and neck cancers (including larynx, hypopharynx, lip, oral cavity, nasopharynx, oropharynx and salivary glands): 130.4 person-years.
- For oropharynx cancers: 20.4 person-years.

![FIGURE 1.4. Estimated ASIR (World) in 2018, oropharynx cancer, both sexes, all ages. Source: GLOBOCAN 2018.](image)
Worldwide, 5-year prevalence rate in proportion per 100,000 habitants for both genders for oropharynx carcinoma is 3.7 (7).

According to data from Red Española de Registros de Cáncer (REDECAN), the new estimated cases of lip, oral cavity and pharynx cancer in Spanish men during 2015 were 4,980 (crude rate, CR, of 21.9 cases per 100,000 men-years). In Spanish women, at 2015 the new cases diagnosed with cancer of lip, oral cavity and pharynx were 1,690 (CR: 7.2) (8). According to GLOBOCAN project, from the total of cancers diagnosed in the Spanish population, cancers of the oral cavity (lip, tongue and mouth), pharynx (oropharynx, nasopharynx and hypopharynx) and larynx represent the sixth most frequent cause of cancer, and the fifth in case of men (9). In total, the global incidence of head and neck cancers in Spanish population is 32.1 cases per 100,000 person-years at CR (8).

Regarding the survival, in Spain, according to results from EUROCARE-5 project published in 2014, the overall survival rate (OS) and the relative survival rate (RS) at 5 years in men diagnosed with oropharyngeal cancer was 32.6% and 35.7%, respectively, and in women was 48.5% and 53.5% (8).

1.2.2 RISK FACTORS

The incidence of head and neck cancers is related to predisposing factors such as toxic habits, the ageing of the population, the lack of hygiene and control of oral cavity and the presence of human papillomavirus (HPV) or Epstein-Barr virus infection (10).

The two main risk factors for head and neck cancer, where oral cavity and pharynx cancers are included, are tobacco and alcohol consumption (8). Several studies have demonstrated the synergic effect between these both toxic habits, up to the point that the risk of developing a head and neck cancer in those patients is estimated to be thirty times superior compared with non-drinkers and non-smokers (6). It is estimated that, in the United States (US), the alcohol consumption combined with tobacco is responsible for 75-85% cancers of oral cavity, pharynx, larynx and oesophagus. The risk is seven times superior in smokers than in non-smokers (11).

However, what it has been observed is that, although smoking rates are steady or even slightly decreasing, the incidence of oropharyngeal squamous cell carcinomas (SCC) is increasing in the US, specifically in males and young adults, and besides, HPV positivity rates in oropharyngeal SCCs are also increasing (12). This has led to an increase in the overall incidence of HPV-positive head and neck cancers, whereas the incidence of
HPV-negative cancers (primarily caused by tobacco and alcohol) has continued to decrease (10).

Oropharyngeal SCC is now recognized as distinct because of its strong association with high risk HPV. Conventional head and neck SCC is strongly associated with smoking, smokeless tobacco use and/or heavy alcohol use, while HPV-related oropharyngeal SCC is associated with higher numbers of sex partners and higher oral sex exposure (13). A strong causal relationship has been established between oral HPV type 16 infection and an increased risk of oropharyngeal cancer. Other HPV types that are also risk factors for developing oropharyngeal cancer are HPV types 18, 31 and 33 (10).

For all these stated above, nowadays is well accepted that HPV infection is a cause of SCC of the oropharynx, especially for the tonsils and base of the tongue. Specifically, some studies show that HPV is responsible for more than 60% of cancers of the oropharynx in the US, and more than 90% of the cases in Sweden. This increase on the incidence of cancers of the oropharynx, caused by HPV infection, and the simultaneous decrease in other locations (due to a decrease in alcohol and tobacco consumption), might be the tendency in coming years, mostly in countries with a high prevalence of this virus infection (4).

Conventional HNSCC (HPV-negative cancer) commonly occurs in middle aged to older men without a significant race predilection, while HPV-related oropharyngeal SCC occurs in slightly younger patients, is even more common in men than women, is associated with lower smoke exposure and is more common in Caucasians (13).

It has been seen that patients with locally advanced HPV-positive head and neck cancers have improved outcomes compared with those with HPV-negative tumours. HPV-related oropharyngeal SCC is biologically distinct, because these tumours are less genetically complex, have less frequently p53 mutations and show different genetic expression profiles compared to HPV-negative oropharyngeal SCC. For this reason, HPV-status is considered a prognostic factor (10,13).

1.2.3 HISTOLOGICAL TYPES

The oral cavity, oropharynx, larynx and hypopharynx are lined by squamous epithelium. Therefore, most cancers arising from these regions are squamous in origin. These squamous cell cancers are often referred to as HNSCC, and they comprise the majority of head and neck cancers. Verrucous carcinoma is a type of SCC that is low grade and rarely metastasizes. Head and neck cancers can also begin in the salivary glands, but salivary gland cancers are relatively uncommon. Minor salivary glands found throughout
the oral cavity and the oropharynx can give rise to adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma and polymorphous low-grade carcinoma. Finally, lymphoma has to be particularly considered for tumours of the tonsillar fossa (14,15).

The majority of oropharyngeal cancers originate from the base of the tongue and the tonsils and more than 90% are SCC (16). Upon histopathologic examination, HPV-related oropharyngeal SCC tends to be nonkeratinizing with a somewhat basaloid appearance recapitulating tonsillar crypt epithelium (17).

1.2.4 PATHOGENESIS OF HEAD AND NECK CANCER

Neoplasms arise clonally from transformed cells that have undergone specific genetic alterations in protooncogenes or tumour-suppressor genes. There are critical genetically changes in each step of the progression of head and neck cancer, which allow the conversion from a preneoplastic lesion to an invasive cancer. This fact has allowed to determinate a model of molecular progression of these cancers (16). Some of the genetic changes that could be found are:

- Loss of chromosomal region 9p21. This is the most common of all genetic changes and occurs early in the progression of these tumours (17). The main effect of this loss is the inactivation of the p16 gene, an inhibitor of cyclin-dependent kinase (CDK) that is important in regulating the cell cycle (18). This early inactivation is consistent with the finding that keratinocytes in culture often lose p16 function and thus escape senescence (19).
- Mutation of p53 gene. Approximately half of all head and neck cancers contain a mutation of the p53 gene located at 17p13. The loss of p53 function due to a mutation results in a progression from preinvasive to invasive lesions and increases the likelihood of further genetic progression (20).
- Amplification of the oncogene cyclin D1. This constitutively activates cell cycle progression, and it is seen in about a third of all tumours. It is usually associated with invasive disease (21).
- Loss of other tumour-suppressor genes. Other tumour-suppressor genes have not been isolated or characterized for most of the regions that are commonly lost in these tumours (22).

The model of the molecular progression of HNSCC demonstrates that tissue with a normal or benign appearance (for instance, minimal dysplasia) can also contain clonal genetic changes. Some patients present with cervical nodal metastasis from clinically
occult primary mucosal lesions. Many of those occult primary tumours are later found in Waldeyer's ring, especially in the tonsils and the base of the tongue. Clonal genetic changes could be detected in more than a half of the cases performing directed biopsies in patients with this presentation. These data give support to the fact that pathologically benign mucosa patches of clonal cells can give rise to metastatic lesions of SCC (16).

Finally, an important issue related with the pathogenesis of oropharyngeal SCC is its relation with HPV infection. As the result of infection with HPV, a clinically, genomic and immunologically distinct subgroup of tumours arise from the epithelium of the tonsil and the base of tongue (23). While HPV-negative tumours are characterized by tobacco-associated mutations in genes including TP53 and CDKN2A, in HPV-positive HNSCC integration of viral genome from HPV (HPV E6 and E7 oncogenes) into the host cellular genome leads to the expression of the E6 and E7 viral oncoproteins, with the consequent degradation of the tumour-suppressor protein p53 and functional inactivation of retinoblastoma protein, respectively, which results in the development of cancer (24).

1.2.5 CLINICOPATHOLOGIC PRESENTATION

Oropharynx SCC develops most frequently in the tonsillar region and base of the tongue. Clinically, early mucosal lesions appear as an indurated nodule, or as an irregular erythematous mucosal change or a shallow ulcer with poorly defined margins (15). Oropharynx tumours often present at an advanced stage because of their ability to grow undetected and their propensity for lymph node metastasis (17).

These tumours may become exophytic or infiltrative, expanding rapidly into underlying muscles, which results in difficulty with speech or eating. The signs and symptoms of benign and malignant lesions of the oral cavity and the oropharynx include bumps on the lip or mouth and white or red patches in the oral cavity. Other symptoms suggesting a malignant growth include a non-healing ulcer on the lip or mouth, unusual pain or bleeding in the mouth, difficulty or pain with chewing, swallowing, or speech, a change in the fit of dentures, a change in voice, referred ear pain and neck masses (15).

Mainly, patients tend to complain about a neck mass (which implies there is already metastatic disease), sore throat and dysphagia. However, there are significant differences depending on HPV-status of the tumour. In patients with HPV-related oropharyngeal SCC, the most common complaint is the 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, even though having a small primary tumour that remains hidden or undetectable. In contrast, the most common symptom in
HPV-negative oropharyngeal SCC is sore throat (53%), followed by dysphagia (41%) and neck mass (18%) (17).

Oropharyngeal tumours are frequently associated with nodal metastasis at the time of diagnosis. The extensive lymphatic vessels in this region drain primarily to the jugulodigastric basins. However, retropharyngeal nodes are also at risk with oropharyngeal cancers (15).

Distance metastasis are rarely seen, but lung, liver and bone are the common metastatic sites for oral cavity and oropharyngeal cancers (15).

1.2.6 IMAGING AND CLINICAL ASSESSMENT FOR OROPHARYNGEAL CANCER

Head and neck cancers are potentially curable if are detected at early stages, although, unfortunately, two thirds of cases are still diagnosed at locoregional advanced stage (tumours at III, and mostly IV M0 stage) (4).

Patients with oropharyngeal SCC usually attend to the specialist to evaluate an enlarged cervical lymph node. The physical examination is then followed by a fine-needle aspiration biopsy, and further clinical evaluation may be appropriate, as well as a directed anamnysis to find out possible risk factors. The advanced clinical examination performed by an otolaryngologist/head and neck surgeon includes a fiberoptic endoscopic examination of the nasopharynx, oropharynx, hypopharynx and larynx. Furthermore, a computed tomography (CT) scan or a magnetic resonance imaging (MRI) of the primary tumour and neck typically is indicated for accurate locoregional staging. In some cases, an ultrasound of the lymph nodes may be useful in order to guide the fine-needle aspiration biopsy, and also for the identification of unknown primary tumour site in patients consulting for metastatic lymph node disease of the head and neck region (15,17).

Because HPV-positive oropharyngeal SCCs have better prognosis than HPV-negative tumours, it is useful to assess HPV tumour status. This is done by HPV testing of cytopathologic samples from tumour or cervical lymph nodes. This way, it is possible to determinate the etiology and also to predict the location of unknown primary tumours. Methods for evaluating HPV tumour status include: quantitative reverse transcriptase polymerase chain reaction for high risk HPV E6 and E7 mRNA, methods based on DNA or RNA in situ hybridization and p16 immunohistochemistry.
1.2.7 STAGING

In order to determine the stage of HNSCC, CT and MRI have been universally accepted as vital tools for clinical staging. Besides, newer imaging approaches, including positron-emission tomography (PET) and the identification of sentinel nodes, show promise.

The concept of molecular staging has also been introduced. This is based on the fact that genetic alterations can be used to detect rare cancer cells in samples with normal histological appearance at first, including lymph nodes and tissue margins at the periphery of the tumour. The molecular analysis of tissues of HNSCC is useful to predict the likelihood of tumour recurrence and also to determine the relationship between the primary lesion of HNSCC and the subsequent lesions. This may assist clinicians in determining whether to treat a secondary lesion aggressively (with curative intent), or to take a palliative approach (as in the case of distant metastatic disease) (16).

The Union for International Cancer Control (UICC) tumour node metastasis (TNM) project has published the 8th edition of the TNM classification of malignant tumours that comes into effect on January 1st, 2017. This TNM classification is as well used by the American Joint Committee on Cancer (AJCC). With this newer version of the TNM classification, a different classification and prognosis stage has been introduced according to the HPV tumour status, due to the globally better prognosis of oropharyngeal SCC HPV-positive tumours.

According to the 8th edition TNM classification, locoregional advanced SCC of the oropharynx corresponds to prognostic stages III and IV without distance metastasis, this means, T3 and T4a.

TNM tables can be found in the Annex 1.

1.2.8 THERAPEUTIC APPROACH

Treatment of head and neck cancers is complex. The specific site of disease, stage and pathologic findings guide the therapeutic approach. For oropharyngeal SCC at an early stage, a single modality treatment consisting in either radiotherapy (RT) alone or surgery is well indicated, though for advanced stages it is typically required combinations of either surgery followed by RT, or initial concomitant chemoradiotherapy (CRT), according to the newest version of National Comprehensive Cancer Network (NCCN) guidelines (version 2.2018). Making a decision on which combined strategy should be performed might be difficult, because functional and curative outcomes have to be predicted before treatment, and current evidence gives support to both strategies (25).
As said before, in order to treat oropharyngeal SCC in locally advanced stages, the two basic treatment modalities available are surgery and RT. In general, nonsurgical therapy is recommended when the expected functional or cosmetic outcome of surgery could result in higher morbidity or lower quality of life. Examples of such situations include bilateral involvement of the base of tongue, extensive soft palate disease or limited surgical access.

Whenever radiation therapy is performed, either intensity modulated radiation therapy (IMRT) or 3-dimensional conformal radiation therapy (3DCRT) is recommended (17).

Regarding surgery, several surgical techniques are available, including open resection, transoral robotic surgery (TORS) and transoral laser microsurgery (TLM). The general surgical principle remains the same for all techniques: removal of the entire cancer with at least 1 cm margins. Nowadays there is a trend away from open surgical procedures, and toward transoral approaches minimizing external incisions.

Neck dissections typically are performed when there is clinically evident lymph node disease or a significant risk for occult metastasis. This is particularly important, as the findings of the neck dissection can lead to upstaging or downstaging the tumour and help to determine the need for adjuvant treatment.

In our closest field, the therapeutic approach for oropharyngeal SCC is performed in each case following the newest version (from 2017) of Institut Català d’Oncologia (ICO) and Institut Català de la Salut (ICS) clinical practice guidelines (CPG), under which oropharyngeal SCC have different approaches depending on its TNM classification and prognosis stage (4).

1.2.8.1 Oropharyngeal SCC, early stage disease (T1-T2N0)

Single modality treatment involving surgery or RT is generally recommended for 30% to 40% of patients presenting with early stage disease (stages I and II). This two modalities, surgery and RT, result in similar survival rates in patients with early stage disease. The choice of surgery or RT is often based on local institutional expertise or perceived relative morbidity of these treatment options (10).

ICO-ICS CPG recommend performing radical RT on the tumour and surrounding areas at risk. A possible alternative to this might be surgery of the primary tumour followed by unilateral or bilateral lymph node dissection, depending on the localization of primary tumour, and later evaluating complementary RT according to risk factors in pathological anatomy findings. Novel surgical techniques such TORS offer a local control of disease of 96.3% and a OS of 95.0% in T1-T2 cancers (4).
1.2.8.2 Oropharyngeal SCC, locally advanced disease (stage III and IV, without distant metastasis)

It is usual to diagnose a patient with HNSCC in an already locally advanced disease, often with prominent involvement of lymph nodes. Nowadays, conventional treatments for locally advanced disease are multimodal, consisting in combinations of surgery, RT and chemotherapy (25). This combined modality therapy is generally recommended for approximately 60% of patients with locally advanced disease at diagnosis (10). These therapeutic strategies result in significant short term and long term morbidity, and are curative in only about 50% of patients (14). Even though, current treatment guidelines still recommend surgery with postoperative adjuvant therapy (depending on the surgical pathology findings and the final pathologic stage) or definitive CRT as the standard of care for those patients. Adverse features that are indication of undergoing adjuvant treatment may include: extranodal extension, positive margins, nodal disease in levels IV or V, perineural invasion, vascular embolism and lymphatic invasion (10).

ICO-ICS CPG (4) consider stages III and IV without distant metastasis as resectable locally advanced disease, taking into account that, from those patients presumably considered resectables, most of them have low likelihood of cure with surgery, and the others prefer to preserve the organ functionality. In those cases, it is especially relevant the role of chemotherapy and RT. Following the current recommendations, for patients with resectable locally advanced disease participation in clinical trials is a preferred or recommended treatment option that has to be considered at first.

The treatment that nowadays is given is radical surgery, including bilateral cervical lymphadenectomy, followed by a scheme of RT and cisplatin (level of evidence IA). If there is a contraindication to chemotherapy, RT and cetuximab should be given (level of evidence IA). If there is large lymphatic node involvement (N2b and N3) or fast growth is observed, induction chemotherapy with docetaxel, cisplatin and fluorouracil (TPF) scheme should be considered (level of evidence III). It is also recommended to determinate the HPV-status, as HPV-positive tumours have changed the latest edition of TNM classification. Cervical lymphadenectomy after non-surgical local treatment is recommended if residual disease is found (level of evidence IVD) (4).

1.2.8.3 Oropharyngeal SCC, locally advanced unresectable disease

Prognosis of this group of patients is still adverse, with survival times lower than 20-24 months. Less than 15% of patients with unresectable head and neck cancer treated with exclusive RT are still alive at 5 years. Relapse pattern is basically locoregional (60-70%),
followed by distant metastasis (20-30%), without forgetting the incidence of secondary tumours (4).

Following ICO-ICS CPG, in every particularly case treatment should be individualized, or supportive therapy should be carried. In general, schemes based on CRT followed by cisplatin or cetuximab are given (4).

1.2.8.4 Unresectable recurrent or metastatic disease

Approximately 10% of patients with head and neck cancer are diagnosed with metastatic disease. Besides, nearly 50% of patients treated for locoregional advanced disease develop recurrences, and of this subset of patients, only 15-30% can be treated with rescue treatment with radical intent (26).

As systemic treatment in recurrent disease has a palliative intent, when a patient presents with local or ganglionic recurrence (or both of them), the first-line therapeutic option is salvage surgery, if a multidisciplinary committee considers this option viable. Furthermore, in low volume and local recurrences, RT could be given again if approved by committee (4).

Even so, in patients that cannot be treated with salvage surgery nor RT, or in patients with initial metastatic disease, the therapeutic approach of choice is chemotherapy, whenever patient’s functional impairment allows it (Karnofsky Performance Scale Index >50% or Performance Status of 0-2). According to ICO-ICS CPG, combinations of drugs may include platinum-based antineoplastic agents, fluorouracil (5-FU), cetuximab, paclitaxel or methotrexate (MTX) (4). The median survival time of this patients with chemotherapy palliative systemic treatment is between 6 and 9 months (27).

1.2.9 RECONSTRUCTION AND REHABILITATION

An important issue related to treatment and outcomes in head and neck oncology is reconstruction and rehabilitation. After the surgical procedure it might be necessary to restore the structure of areas where the tumour was removed. Patients often present with disruption of their abilities to eat, drink, chew and swallow. In addition, surgery and RT of these cancers may result in a loss of function and cosmetic changes, which often require extensive reconstruction and rehabilitation.

When tumours are small, the narrow edge of normal tissue removed along with the tumour is usually small enough that reconstructive surgery isn’t needed. When defects are small, healing typically occurs secondarily. However, for larger defects, a piece of muscle with or without skin may be rotated from an area close by, such as the chest
(pectoralis major pedicle flap) or the upper part of the back (trapezius pedicle flap). Free tissue transfer with soft tissue flaps (for instance, radial forearm free flap or anterolateral thigh flap) may be an option too. If defects are large or involve the soft palate, then velopharyngeal insufficiency may occur, which may require reconstruction with palatoplasty, velopharyngoplasty and/or a palatal obturator (28,29).

Surgeries to restore body function that can be performed include tracheostomies and feeding tubes. If excessive swelling is expected in the airway after tumour is removed, a short-term tracheotomy might be performed to allow the patient breathe more easily. It stays in place for a short time, and is then removed when it is no longer needed. A permanent tracheostomy is needed after a total laryngectomy. As cancers in oropharynx and oral cavity may keep the patient from swallowing, a feeding tube may be necessary. If swallowing problem is likely to be only short-term, it is possible to place a nasogastric feeding tube. Nevertheless, if the problem will last long term, a percutaneous endoscopic gastrostomy (PEG) might be necessary (16).

1.2.10 COMPLICATIONS RESULTING FROM CURRENT TREATMENT

Concomitant CRT is currently the standard of care for non-surgical approach of locally advanced oropharyngeal SCC (30). Even though the introduction of intensity modulated radiotherapy in treatment of this cancers, which has significantly decrease the rate of xerostomia resulting in an improvement in the patient’s quality of life (15), the side effects due to CRT remain significant (31). This fact has led to and increasing interest in less intensive treatments for oropharyngeal SCC, particularly those associated with HPV infection which have better prognosis, so clinical trials are been held to reduce either RT dose or even substitute CRT for more targeted agents (such cetuximab) for HPV-positive tumours, while intensifying therapy for high risk HPV-negative tumours (32).

Besides, minimally invasive surgical approaches to treat oropharyngeal SCC, such TORS, are gaining interest because traditionally surgical resection in oropharyngeal SCC has been associated with poor cosmetic outcomes, whereas patients treated with TORS have superior pharyngeal preservation with excellent survival outcomes (33–35). Improvements in surgical techniques, especially in reconstruction with microvascular free flaps (to facilitate the rehabilitation of these patients) and advances in robotic surgery, have made oropharyngeal region more accessible, implying less morbidity (33).

Most common complications resulting from current treatment are the following ones:

- **Radical surgery complications.** Oropharyngeal SCC is often diagnosed in advanced stages, and therefore has a poor prognosis. In addition, functional
outcomes are also poor because several basic activities may be affected by the surgery, specifically speech and swallowing, requiring significant lifestyle change (33). The complications of surgery include: infection, weight loss, facial swelling, difficulty with speech, difficulty with phonation, difficulty with swallowing, velopharyngeal insufficiency and loss of speech or swallowing capability (15,17). Surgical treatment for oropharyngeal SCC can be performed with a low-risk of postoperative mortality, but with a risk of long term use of tracheostomy and feeding tubes (33).

- **(Chemo)-radiotherapy related complications.** Patients treated with RT (with or without chemotherapy), experience significant acute and late toxicities such as mucositis, dysphagia, xerostomia (dryness of mouth), soft tissue fibrosis and neutropenia. Moreover, other complications might include fatigue and weight loss, dermatitis, dysgeusia (loss of taste), erythema and moist desquamation of skin and laryngeal oedema, causing hoarseness. Rare, but severe, complications of radiation include possible hearing loss, osteoradionecrosis, trismus, pharyngoesophageal stricture and carotid artery rupture (15,30,35–37).

1.3 NOVEL THERAPIES FOR OROPHARYNGEAL CARCINOMA

1.3.1 Immunotherapy

Current treatment guidelines recommend surgery with post-operative adjuvant therapy or definitive CRT as standard of care in locoregional advanced HNSCC. Despite these intensive multimodality treatments, recurrence of disease persists. This is an important cause of treatment failure. Recurrent disease is especially problematic in HPV-unrelated HNSCC (38).

Preclinical models and early observations with the use of immunotherapics as adjuvant treatment in other types of solid tumours, together with the fact that immunotherapics have established efficacy in HNSCC advanced stages, has led to a renewed interest in neoadjuvant approaches previously to definitive surgery for HNSCC. The concept of a neoadjuvant immunotherapy approach is especially relevant, because immunotherapy might have potential benefits such as tumour downsizing, early systemic therapy to address the risk of distant metastatic spread, conversion to resectable disease and early selection of responders (38).

The mechanism of action of immunotherapy is based on the immune microenvironment of HNSCC. This is characterized by changes in immune cell populations, immune checkpoints and tumour or microenvironment factors. These changes alter the balance
of the immune environment in favour of immunosuppression, allowing tumour evasion and escape from immune surveillance. Immune therapies, in particular those targeting the programmed cell death protein 1 (PD1) receptor or its ligand programmed death-ligand 1 (PD-L1), including nivolumab, pembrolizumab, durvalumab and atezolizumab, have shown significant efficacy in subsets of patients with HNSCC (14).

PD1 is a receptor protein on the surface of cells, mainly T cells, that binds two ligands, PD-L1 and PD-L2. This receptor acts as an immune checkpoint, as it has a role in regulating the immune system's response to other cells of human body by down-regulating the immune system and promoting self-tolerance by suppressing T cell inflammatory activity. Nivolumab is a monoclonal antibody (human immunoglobulin G4 type), that has been designed to recognise and attach to receptor PD-1. Cancer cells can produce proteins (PD-L1 and PD-L2) that attach to this receptor and switch off the activity of T cells, preventing them from attacking the cancer. By attaching to the receptor, nivolumab prevents PD-L1 and PD-L2 from switching off the T cells, increasing the ability of the immune system to kill cancer cells (14).

Nivolumab is authorised for use in the European Union. It is currently indicated for treatment of HNSCC that has recurred or metastasized, despite treatment with platinum-based chemotherapy. In 2016, Food and Drug Administration (FDA) approved nivolumab in monotherapy for treatment of patients with recurrent or metastatic HNSCC after having received chemotherapy with platinum-based antineoplastic drugs. The National Comprehensive Cancer Network (NCCN) recommends nivolumab for patients with this indication as a category 1 recommendation, based on high-quality evidence (10).

Ferris RL et al. (39) assessed nivolumab’s efficacy in patients with recurrent or metastatic HNSCC that had progressed in less than 6 months from receiving platinum. They did not found differences in progression-free survival (PFS), but found a 20% of gain in OS at a year. Regarding the PD-L1 expression analysis, they found that when expression is greater than 1%, 5% and 10%, the hazard ratio (HR) is nearly 0.50 and is significant in case of 1% and 5% expression. Regarding toxicity, the rate of adverse effects was similar in both groups, but the proportion of grade 3 and 4 treatment related adverse events was inferior in nivolumab group (13.1% of patients), compared with those who received standard therapy (35.1% of patients). In nivolumab group, rash, pruritus and endocrine processes such hypothyroidism were more frequent than in standard, single-agent systemic therapy (methotrexate, docetaxel or cetuximab) group, meanwhile in standard treatment group, gastrointestinal adverse effects were more common.
These results indicate that nivolumab prolongs survival in patients with recurrent or metastatic HNSCC that has progressed after platinum-based chemotherapy, compared with patients who receive standard single-agent systemic therapy (39).

1.3.2 Transoral robotic surgery

TORS is defined as the surgical procedure performed through oral cavity with utilization of robotic arms. It was first developed by Gregory S. Weinstein and Bert W. O’Malley Jr., at the Hospital of University of Pennsylvania (40). First experimental research were started at 2004 and at 2006 first clinical trials’ outcomes on patients were published (41). Nowadays, the most commercialized robotic surgery system is da Vinci® Surgical System (Intuitive Surgical Inc. Sunnyvale, California). FDA approved at 2000 the clinical application of da Vinci® and at 2009 its use in otorhinolaryngologic transoral surgical procedures. The multicentre study which provided feasibility and security evidence allowing the FDA approval was later published (40).

Appropriate primary management options for treating oropharyngeal SCC are RT with or without chemotherapy or transoral surgery, which includes TLM and TORS. Transoral surgery offers clear advantages because lesions that otherwise would need a wider approach, even a transcervical approach that could imply a mandibulotomy, can be managed less aggressively. As transoral approaches are minimally invasive, in most patients there is no need of later reconstruction of oropharynx. All this has led to a reduced morbidity, reduced surgical time, less days of hospitalization, faster functional recovery, and thus, a reduction in treatment related costs for these patients. Da Vinci® system allows optimization of minimally invasive surgical procedures, as it provides magnified 3D high definition view and allows the surgeon’s hand movements to be translated into precise movements of tiny instruments inside the patient’s body. For this reason, da Vinci® allows to perform the same transoral conventional surgical procedures, with more technical advantages. According to this fact, there has been a recent interest in TORS over TLM for oropharyngeal SCC management, as it improves several factors, including: enhanced endoscopic images over microscopes, superior visualization of the tongue base with angled endoscopes, manoeuvrability of surgical instruments and an apparently improved ability for trainees to be taught and adopt the technique (42).

The focus of surgical innovation during the past years has been on the conservation of organ function and more effective ways of reconstruction. There are several published series (43–46) which confirm that oncological outcomes using TORS are comparable at alternative surgical and CRT approaches, but obtaining enhanced improvements in
functionality, mainly in swallowing. That is why robotic surgery in head and neck surgery improves efficiency of other surgical options.

Primary surgical management of oropharyngeal SCC with TORS and neck dissection provides an accurate pathological staging, which can lead to an appropriate selection of subsequent adjuvant postoperative therapy, without compromising the survival (47). The problem is that applying the available evidence to the clinical setting is particularly difficult, because there are many differing (C)RT protocols and reports of functional outcomes. An increasing recognition that combined CRT protocols have greater side-effects than RT alone has emerged, as well as the popularization of transoral surgery techniques. For patients with oropharyngeal SCC, compared to definitive RT, TORS results in similar OS outcomes and is also associated with decreased adjuvant chemotherapy and RT use (30). Furthermore, HPV-positive oropharyngeal SCC represents a group of younger patients, who present with less comorbidity and less typical risk factors of head and neck cancer. Consequently, research has increasingly focused on the potential for treatment de-escalation (42).

Weinstein et al. (40) determined the safety, feasibility and the adequacy of surgical margins for treatment of head and neck cancers using TORS. According to this study, surgical adverse outcomes and complications resulting from TORS might be:

- **Positive surgical margins.** Of 161 patients with malignant tumours, positive surgical margins were detected in only 7 patients (4.3%), demonstrating the adequacy of surgical margins for patients undergoing TORS for malignant lesions. The rates of positive margins by anatomic site were 3.8% for oropharyngeal tumours and 8.0% for laryngeal tumours. None of the 7 study subjects with hypopharynx or oral cavity tumours had positive surgical margins.
- **Haemorrhage.** Any participant required a transfusion due to intra-operative blood loss.
- **Tracheostomy.** In the peri-operative period, elective tracheostomy was performed in 22 patients (12.4%), with subsequent removal in 18/22 patients. 2 of these patients had undergone tracheotomy prior to consideration for TORS. For this reason, only 4 (2.3%) of the total 177 patients who underwent a TORS procedure still had a tracheostomy at 12 months follow-up.
- **Compromise of swallowing function and PEG dependence.** Overall, 12 patients (12/177; 6.7%) needed a PEG tube when assessed at an average follow-up of 345 days after TORS. However, 3 of these patients had undergone full-dose RT (and 1 patient with chemotherapy) prior to surgical salvage with TORS.
Thus, for patients undergoing TORS without previous therapy, the PEG rate was 5.0%.

- **Dysphagia.** In the immediate postoperative period of 30 days, 16 patients had postoperative dysphagia.

In conclusion, based on this multicentre study, no serious adverse event was judged to be directly related to the robotic device itself, and TORS appeared to be safe, feasible, and useful in the multidisciplinary management of head and neck cancer (40).

To sum up, TORS is a safe procedure with minimal complications and acceptable clinical and functional outcomes (40,48,49). Patients with oropharyngeal SCC treated with TORS have superior pharyngeal preservation with excellent survival outcomes (35). Besides, recent single institution studies on the impact of TORS on oncologic outcomes seem to indicate similar OS and disease-free survival (46,48).
2 JUSTIFICATION

In Spain, the estimated number of new diagnosed cases of oropharyngeal SCC in 2015 was 6,670 (8). Results from EUROCARE-5 project (2014), show a RS at 5 years in men and woman of 35.7% and 53.5%, respectively (4). According to this data, it can be said that oropharyngeal SCC has relevant incidence and mortality rates. Given the rise in oropharyngeal SCC incidence and the changing demographics of the patient population (who tend to be younger), swallowing impairment and its effect on quality of life must be a key consideration for health professionals.

The problem is that the ideal treatment for this cancer remains controversial, as RT and surgery are equally effective in the treatment of patients with early-stage disease, and the same happens for CRT or the combination of surgery with postoperative CRT for advanced stage cancers. For this reason, there is not a clear preference of treatment. In addition to this, current treatment strategies result in poor functional outcomes, mainly in distinct grades of swallowing impairment. Moreover, in most cases of cancer recurrence, current treatments do not allow to perform a reintervention on the same area.

Radiation therapy, with or without chemotherapy, preserves the anatomical structure more than conventional radical surgical treatment options, and has thus become the standard treatment for many oropharyngeal cancers. However, despite the better organ preservation, the function of the oropharynx can still be affected. Because of this, transoral laryngopharyngeal surgery has emerged with the aim of reducing morbidity, compared with CRT. Nevertheless, patients may still not avoid morbidity, because most still require adjuvant CRT after transoral cancer surgery. In this area is where TORS can play an important role, by further improving functional outcomes compared with other transoral surgical techniques. TORS has demonstrated the possibility of maximizing functional preservation, together with limiting anatomical structures’ destruction in patients (50).

Already available evidence suggests that TORS is more efficient, not only than alternative surgical procedures, but also than other possible non-surgical therapeutic approaches, and promotes a surgical indication based on significant reduction in functional outcomes (43,51–53). Besides, TORS can provide adequate local control of disease in selected patients, resulting in a short hospital stay, as well as low rates of tracheostomy and feeding-tube dependence (40,50).
Taking into account those facts and in order to perform less aggressive primary therapeutic strategies, the aim should also be on implementing effective neoadjuvant approaches prior to definitive surgery.

Major changes are currently taking place in the world of oncologic therapeutic strategies with the introduction of new drugs and therapeutic targets. Immunotherapy treatments have established efficacy in advanced HNSCC, so there is a renewed interest on its possible neoadjuvant use. Furthermore, preclinical models and early observations with the use of adjuvant immunotherapy in other solid tumours have contributed too to this increasing interest in neoadjuvant approaches to treatment. Immunotherapy based strategies may have potential benefits such as tumour downsizing, early systemic therapy to address the risk of distant metastatic spread, conversion to resectable disease and early selection of responders. It is important to notice that nowadays there are trials been held using this neoadjuvant immunotherapeutic approach to confirm both safety and initial efficacy, so in the meantime, the question of whether immunotherapy neoadjuvant treatment has a critical role to play in HNSCC remains open (38).

In this context, the intention of this non-randomized intervention study based on a prospective cohort is to assess if a better improvement in functionality after treatment in patients diagnosed with locoregional advanced oropharyngeal SCC is possible. Immunotherapy as an induction treatment followed by TORS will be compared with current therapeutic strategies based on TORS and adjuvant CRT, in order to know if patients could have better functional outcomes, and therefore, an improvement on their quality of life.
3 HYPOTHESIS

In the therapeutic approach of locoregional advanced squamous cell carcinoma of the oropharynx, immunotherapy as an induction treatment followed by transoral robotic surgery can obtain an improvement in functional outcomes, with the same adequacy of surgical margins and local control of disease, compared with current treatment strategies.

4 OBJECTIVES

4.1 PRIMARY OBJECTIVE

The aim of this study is to evaluate if in the therapeutic approach of locoregional advanced squamous cell carcinoma of the oropharynx, immunotherapy as an induction treatment followed by transoral robotic surgery can obtain an improvement in functional outcomes.

Functional outcomes will be mainly evaluated by the grade of dysphagia, assessed by functional videoendoscopy following Sociedad Española de Otorrinolaringología (SEORL) criteria. Other secondary variables that are going to be considered in order to evaluate functional outcomes are days depending on nasogastric feeding tube, as well as further complications (including postoperative haemorrhage and pain).

4.2 SECONDARY OBJECTIVES

Other secondary objectives are:

- To determine if immunotherapy based induction treatment followed by transoral robotic surgery can obtain the same local control of disease than current therapeutic approaches in locally advanced squamous cell carcinoma of the oropharynx.
- To determine if immunotherapy based induction treatment followed by transoral robotic surgery can obtain the same adequacy of surgical margins than current therapeutic approaches in locally advanced squamous cell carcinoma of the oropharynx.
To determine if immunotherapy based induction treatment followed by transoral robotic surgery can obtain the same survival rates, compared with current therapeutic strategies, in locally advanced squamous cell carcinoma of the oropharynx.
5 MATERIALS AND METHODS

5.1 STUDY DESIGN

A non-randomized intervention study based on a prospective cohort will be performed at the Functional Unity of Head and Neck Tumours (FUHNT) of Hospital Universitari de Girona Doctor Josep Trueta (HUDJT). In order to recruit enough participants, it will be necessary to involve other hospitals of ICO with TORS platform. Therefore, a multicentre study will be performed involving HUDJT, Hospital Germans Trias i Pujol from Badalona and Hospital Universitari de Bellvitge from L'Hospitalet de Llobregat. Thus, recruitment will take around 2 years.

In order to compare functional outcomes of two possible therapeutic interventions for locally advanced stage oropharyngeal SCC, patients who can undergo a surgical approach and express immunotherapy biomarkers will be assigned into two groups.

Patients at the intervention group will receive immunotherapy induction treatment followed by TORS. By pathological anatomy criteria, patients will receive postoperative adjuvant treatment (RT, and if necessary chemotherapy may be added) or not.

Patients at the control group will receive the current therapeutic approach, which consists in TORS followed by postoperative adjuvant therapy if needed (RT, and if necessary chemotherapy may be added).

5.2 STUDY POPULATION

Eligible individuals will be those patients with oropharynx SCC undergoing diagnose and treatment management at the FUHNT of HUDJT, as well as in the other hospitals of ICO with TORS platform mentioned above, with an indication of surgical treatment and expression of immunotherapy biomarkers.

There are participants’ baseline characteristics which might potentially influence on dependent variables, so covariates are going to be contemplated and it will be necessary to stratify participants.

As dysphagia is the main dependent variable, it will be necessary to assess if patients have had any previous grade of dysphagia before the therapeutic procedure is performed. This will be done by functional videoendoscopy.
5.2.1 Inclusion and exclusion criteria

Inclusion criteria:

- Patients over 18 years old.
- Both genders.
- Patients diagnosed of squamous cell carcinoma of the oropharynx, in a locally advanced stage (stages III and IV without distant metastasis).
- Indication of surgical treatment.
- Indication of immunotherapy induction treatment (expression of PD-L1 at levels of 1% or more in a minimum of 100 tumour cells evaluated).
- Patients who have read the information sheet for participants and have signed the informed consent forms.

Exclusion criteria:

- Previous chemoradiotherapy treatment on the area.
- Previous head and neck mucosal surgeries undergone (with the exception of tonsillectomy).
- Unresectable tumour.
- Previous therapy targeting T-cell costimulating or immune-checkpoint pathways.
- Patients with any other chronic condition (neurological, cardiovascular, metabolic, gastrointestinal, respiratory, previous psychiatric disorders... among others).
- Patients taking any chronic medication for any known or unknown condition.
- Patients who are not able to understand the therapeutic procedure that will undergo.

5.2.2 Participant withdrawal or termination

Participants are free to withdraw from participation in the study at any time upon request. When withdrawing from the study, the participant should let the research team know that he/she wishes to withdraw, in order to be given a variety of instructions on how to safely stop using the study's medication, as well as on who to contact if there were any questions or concerns that arise after having completed the study. The research team may need to have the participant return so that he/she can be monitored for any future adverse effects from the study treatments, procedures or interventions.
An investigator may terminate participation in the study if the patient meets any exclusion criteria (either newly developed or not previously recognized) that preclude further study participation.

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

5.3 SAMPLE

5.3.1 Sample selection

The sample will be obtained from HUDJT from Girona, Hospital Germans Trias i Pujol from Badalona and Hospital Universitari de Bellvitge from L'Hospitalet de Llobregat. As it will be sought to include all accessible subjects as part of sample, it will take 2 years to obtain the necessary number of participants to carry on the study.

A consecutive non-probabilistic sampling will be carried out in patients who have had histologically confirmation of SCC of the oropharynx, in a locally advanced stage, with surgical indication, who express biomarkers to undergo immunotherapy induction treatment and meet all other inclusion and exclusion criteria.

5.3.2 Sample size

In a bilateral contrast with a level of significance (α) of 5%, a statistical power of 80%, assuming a 10% of drop-out rate (as follow-up will be at short-term) and anticipating a moderate effect of the intervention, there will be needed 216 patients.

This computations have been carried out with the Prof. Marc Saez's software based on the library ‘pwr’ of the free statistical environment R (version 3.5.1).

5.3.3 Estimated time of recruitment

According to expert opinion, the number of patients diagnosed with oropharyngeal SCC, expressing immunotherapy biomarkers and meeting the other inclusion and exclusion criteria at FUHNT of HUDJT last year was approximately 20 patients.

Therefore, taking into account the necessary number of patients, it is expected that approximately 2 years will be needed in order to recruit the amount of participants for this study. For this reason, it will be necessary to undergo a multicentre study, as HUDJT will not be able to provide enough participants.
5.3.4 Masking techniques

Due to the inherent limitations of treatment strategies, 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.

5.4 DATA COLLECTION

A summary of all the process can be found in the Annex section (Annex 2).

To perform the data collection, all the head and neck cancer department of HUDJT must be aware about the conduction of the trial to enlist every patient who fit the inclusion and exclusion criteria. The same consideration has to be taken into account for the other hospitals taking part in the study. Moreover, all the participant professionals of all centres will be trained about what they have to enquire and how to collect information. It is important to ensure that everybody taking part in this study knows its task and the way to perform it, so data collection could be similar in all participating centres.

Besides, it has to be considered the importance of collaboration with nursery department, specifically with nurses in charge of study’s participants during their hospitalization.

Patients will be also correctly informed (Annex 3) before entering the study and will sign the consent forms (Annexes 4 and 5). It is important to explain participants the importance of not withdrawing from the study during the follow-up period, in order to correctly assess the outcomes. Nevertheless, all patients who entry the study will be included in the statistical analysis so no substitutive patients will be added to the study in cases of withdrawal or termination.

5.4.1 Constitution of the cohort

Patients diagnosed with oropharyngeal SCC at locally advanced stage, who fit in all inclusion and exclusion criteria, will be informed about the possibility of participating in the study. Participants will be either informed orally and with an information consent sheet (Annex 3). If they agree to engage in, all data collection needed for the study will start.

Only those patients expressing immunotherapy biomarkers and tributaries to surgery will be considered to enter the study.
An important issue that has to be taken into account is if participants have had any previous grade of dysphagia, to allow outcome comparison. According to expert opinion (as there are not published results yet), the average grade of dysphagia after TORS with postoperative adjuvant therapy (which is the current treatment), assessed by functional videoendoscopy (following SEORL criteria), is the following:

- At 0 months (previously to treatment): 3 points.
- At 3 months after treatment: 10 points.
- At 6 months after treatment: 7 points.
- At 12 months after treatment: 6 points.

5.4.2 During hospitalization

Special attention must be paid in order to detect any sign of haemorrhage or pain, so nurses must be informed about it and check periodically the status of the patients. The need of a PEG tube during the hospitalization also must be taken into account.

5.4.3 Follow-up

Participants will be followed up along a totally of 5 years after the intervention. At HUDJT, the first year follow-up will be performed at FUHNT. Between the first and the fifth year, the follow-up will be done at the head and neck surgery outpatient clinic.

The main dependent variable to assess is the grade of dysphagia, so patients will be followed up by functional videoendoscopy at 0, 3, 6 and 12 months after undergoing TORS. The other secondary dependent variables will be also assessed.

Clinical control (consisting in physical examination and videoendoscopy) of the outcomes will be assessed as follows: the two first years, every 3 months; the third and fourth year, every 6 months; and at the fifth year, one last control.

Radiological control (involving MRI scan of the neck, and CT scan of the head and neck and thorax), will be assessed as follows: the first control will be at first 3 months; during two first years, every 6 months; finally, from the third year to the end, annually controls will be performed.
5.5 VARIABLES AND MEASUREMENT METHODS

5.5.1 Independent variable
The independent variable of this study is the procedure performed in the intervention, that is, whether if patients receive induction treatment with immunotherapy followed by TORS, or only TORS.

5.5.2 Main dependent variable
As the aim of the study is to compare functional outcomes using distinct therapeutic approaches, the main dependent variable that is going to be used is the grade of dysphagia. In order to determine it, the grade of dysphagia will be assessed with functional videoendoscopy (3) previously to undergoing treatment, and at 3 months, at 6 months and at 12 months after intervention.

5.5.2.1 Grade of dysphagia
Dysphagia is a symptom which states the difficulty in transport of endogenous secretions or food bolus through the superior digestive tract. As mentioned before, deglutition occurs in three phases: oral, pharyngeal and oesophageal phase.

In order to assess the grade of dysphagia, SEORL criteria for deglutition disorders (Annex 6) will be followed, giving three gradient points (0: absence of defect; 1: minor defect; 2: major defect) for each item in each phase (3). Functional videoendoscopy will be used as the diagnose method to assess these deglutition disorders. It will be performed at 0 months (previously to therapeutic intervention), at 3 months, at 6 months and at 12 months.

Functional videoendoscopy is a technique which consists in assessing directly, using a nasofibroendoscopy, patients’ deglutition capacity. It allows an anatomic as well as a functional assessment.

- **Anatomic assessment.** Before starting the intervention, local anaesthesia may be applied in a nostril. Evaluation of structures will be performed, including: velopharyngeal sufficiency, pharynx, base of tongue and larynx. Breathing, phonation and airway protection (which constitute the laryngeal competence, by closure of vocal cords, effectiveness coughing and right ascension of larynx when swallowing) will be also evaluated. Patients’ ability to swallow secretions will be observed too, as this might be a potential risk of aspiration. Sensitivity of anatomic structures will be also assessed applying soft pressure with the fibroendoscopy.
- **Deglutition assessment.** Patients will be given food of distinct consistency and volumes (starting from easiest textures and gradually increasing the difficulty) coloured with methylene blue. Observation of food retention or aspiration will be done, as well as identification of in which deglutition phase might this happen. Musculature movements and its correct coordination will be assessed during deglutition in oral and pharyngeal phase. Also, it has to be taken into account if residual food accumulation occurs or if retrograde reflux appears, as this might increase the risk of aspiration.

Grade of dysphagia is, therefore, a quantitative discrete variable.

### 5.5.3 Secondary dependent variables

Other secondary variables that are going to be assessed are:

- PEG tube dependence
- Adequacy of surgical margins
- Local control of disease
- Five-year disease-free survival

#### 5.5.3.1 Percutaneous endoscopic gastrostomy tube dependence

To evaluate possible functional outcomes, apart from dysphagia, PEG tube dependence at 3, 6 and 12 months will be also assessed. As evaluation of this variable depends on facultative criteria, it is therefore considered as a secondary dependent variable.

PEG tube has become a preferred option for long-term nutritional support device for patients with dysphagia (54), although there is a considerable debate about quality of life of these patients and real benefit in terms of nutritional gain.

A PEG tube will be placed in patients after the intervention, and will be removed when dysphagia or pain allow oral intake of nutrients.

PEG tube dependence is a categorical dichotomous variable.

#### 5.5.3.2 Adequacy of surgical margins

Adequacy of resection margins is of extreme importance in order to make decisions regarding postoperative treatment and prediction of prognosis in patients with oropharyngeal SCC. It has been indicated that failure to achieve a clear surgical margin results in an increased risk of local recurrence and a subsequently reduced chance for survival (55).
During surgical removal, the palpable or visible tumour will be resected with a margin of normal tissue to make sure complete removal of tumour is done. This mainly will depend on surgeon’s clinical judgment, interpretations of imaging investigations and preoperative planning of the extent of resection. After this, resected specimens of tumour will be submitted to surgical pathologist, who will examine the entire specimen grossly and microscopically to comment whether the tumour is completely excised or if residual tissue remains in situ. Examination of the resected specimen by a surgical pathologist will be done postoperatively as routine pathological examination. In order to assess adequacy of surgical margins, pathological anatomy criteria will be the following ones:

- Free margins: ≥ 0.5 mm
- Optimal margins: > 0.2 mm and > 0.5 mm
- Close margins: ≤ 0.2 mm
- Affected margins: lesional cells at the margins

Adequacy of surgical margins is a categorical ordinal variable.

5.5.3.3 Local control of disease

Local control of disease refers to the total and permanent disappearance of the disease from primary site. Therefore, it is a major goal of cancer therapeutic strategies.

The local control of disease will be evaluated at 3, 6 and 24 months after intervention with clinical and radiological control.

It is a categorical dichotomous variable.

5.5.3.4 Five-year disease-free survival

Disease-free survival refers to the percentage of people in a trial who are alive and cancer free (without any signs or symptoms of cancer) after a specified number of years from the end of primary curative (when no disease can be detected) cancer treatment.

In a clinical trial, measuring the disease-free survival is one way to see how well a new treatment works.

Disease-free survival at five years follow-up will be assessed by clinical and radiological control.

It is a categorical dichotomous variable.
5.5.4 Safety variables

In order to assess complications resulting from TORS, haemorrhage and grade of pain are going to be determined.

No relevant complications (grade 3 or 4 events) are expected from immunotherapy treatment.

5.5.4.1 Grade of pain

Pain is a subjective experience influenced by culture, previous experiences and meaning to the individual. Therefore, quantifying it to determine appropriate treatment presents a challenge for clinicians. The most common tool used to quantify pain in clinical settings is the visual analogue scale (VAS). However, using this scale presents some limitations, mostly a ceiling effect, which can lead to an impossibility to quantify variation in the intensity of severe pain and cause compression of all intensity ratings. Furthermore, the levels of the VAS are not well defined, leaving room for misinterpretation, bias and confusion. For these reasons levels of the VAS have limitations to report pain (56)(57), so the grade of pain in this study will be assessed by the requirement of analgesic drugs, following WHO’s recommendations for cancer pain relieving. WHO has developed a three step ladder for cancer pain relief in adults. If pain occurs, there should be prompt oral administration of drugs in the following order:

- Nonopioids (aspirin and paracetamol).
- Then, as necessary, mild opioids (codeine).
- Then, strong opioids such as morphine, until the patient is free of pain.

FIGURE 5.1. World Health Organization’s pain relief ladder.
Source: World Health Organization
To calm fears and anxiety, additional drugs (adjuvants) should be used. To maintain freedom from pain, drugs should be given every 3-6 hours, rather than on demand. This three step approach of administering the right drug in the right dose at the right time is inexpensive and 80-90% effective, according to WHO's recommendations.

Grade of pain is a categorical ordinal variable.

5.5.4.2 Postoperative haemorrhage

Transoral resection of oropharyngeal carcinoma is safe, and severe life-threatening haemorrhage is rare (58). Nevertheless, perhaps the most concerning complication resulting from TORS is the risk of life-threatening oropharyngeal haemorrhage in the acute post-operative period. In contrast to post-operative haemorrhage in other locations in the body, oropharyngeal haemorrhage may be particularly life-threatening, because even a relatively modest amount of blood loss can result in aspiration and subsequent airway asphyxiation (59).

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 TORS. Therefore, is important to stay aware of it although the patient has overcome the first days without any complication.

Presence of haemorrhage is a categorical dichotomous variable.

5.5.5 Covariates

Covariates are participants’ baseline characteristics which potentially may influence on dependent variables. For this reason, participants will be stratified according to these covariates, which are:

- **HPV-status**: HPV-related oropharyngeal SCC occurs in slightly younger patients, is even more common in men than women, is associated with lower smoke exposure and is more common in Caucasians (13). It has been seen that patients with locally advanced HPV-positive head and neck cancers have improved outcomes compared with those with HPV-negative tumours (10). HPV-related oropharyngeal SCC is biologically distinct, and for this reason, HPV-status is considered a prognostic factor (10). HPV-status will be evaluated by HPV testing of cytopathologic samples.

- **Age**: age may influence on patients’ postoperative incidence of complications and recovery. Thus, lower functional outcomes may be found in elderly patients.
- **Gender**: even though evidence on literature regarding if gender may affect functional outcomes has not been found, it will be considered anyway.
- **Socio-economic factors** (proxied by education and occupation): socio-economic factors might influence in an indirect way through the lack of control of some patients’ comorbidities.

In addition to the stated above, all the covariates will be controlled for in a multivariate analysis.

A table summarizing all variables can be found in the Annex section (Annex 7).

### 5.6 INTERVENTION

Those patients diagnosed with locally advanced oropharyngeal SCC, tributaries to surgery, expressing immunotherapy biomarkers (tumour PD-L1 membrane expression) and fitting all other inclusion and exclusion criteria will be considered to enter the study.

Tumour PD-L1 membrane expression will be evaluated by means of immunohistochemical testing (with the use of antihuman PD-L1 antibody). If expression levels are 1% or more in a minimum of 100 tumour cells that could be evaluated, it will be considered that patients express immunotherapy biomarkers. If there is not presence of immunotherapy biomarkers, patients will not be able to participate in the study.

Once participants sign the informed consents and information sheet (Annexes 3, 4, and 5) they will enter the study. They will be distributed into two groups.

Control group will receive conventional treatment, consisting on surgery (tumour resection performed with TORS and cervical lymphadenectomy) with postoperative adjuvant therapy as needed.

The participants in intervention group will receive immunotherapy induction treatment, which consists in nivolumab (OPDIVO®) at a dose of 15 mg/Kg every 15 days, completing 3 – 4 doses. After having completed induction treatment, patients’ disease stage will be evaluated again (as induction treatment can lead to upstaging or downstaging the tumour). If there is still locally advanced stage disease, patients will then undergo TORS and cervical lymphadenectomy, followed by adjuvant therapy as needed. If there is a change in disease stage patients will be asked to terminate the study, and they will be treated according to usual clinical practice.
Functional outcomes of immunotherapy induction treatment and transoral robotic surgery therapeutic approach for oropharyngeal squamous cell carcinoma

Technical specifications sheet of nivolumab can be found in the Annex section (Annex 8). Further relevant information about this drug can be found at Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) website (60).

5.7 SAFETY

Both techniques, immunotherapy treatment as well as TORS, have been performed previously with other indications and systematic reviews have already demonstrated its safety and feasibility.

Surgical adverse outcomes and complications resulting from TORS, such local haemorrhage and pain, would not be directly related to the robotic device itself. Besides, no serious adverse event is expected due to surgical procedure. Nevertheless, presence of local haemorrhage and/or pain will be registered and taken into account in the study.

Possible adverse effects resulting from nivolumab treatment are not expected to be serious, as nivolumab is authorised for use in the European Union and has demonstrated its safety usage.

5.8 STATISTICAL ANALYSIS

All statistical analysis will be executed with Statistical Package for the Social Sciences (SPSS) version 25 (IBM, Armonk, NY, US) for Windows®.

In this study there are seven qualitative variables, which are: procedure performed, PEG tube dependence, adequacy of surgical margins, local control of disease, five-year disease-free survival, grade of pain and postoperative haemorrhage. The grade of dysphagia is a quantitative discrete variable. Follow-up periods for each variable are:

- Grade of dysphagia: at 0-3-6-12 months.
- PEG tube dependence: at 3-6-12 months.
- Adequacy of surgical margins: at immediate postoperative period.
- Local control of disease: at 3-6-24 months.
- Five-year disease-free survival: at 5 years.
- Grade of pain: at postoperative period.
- Postoperative haemorrhage: at postoperative period.
- Covariates: will be assessed at the beginning of the study and follow-up will not be required.
5.8.1 Descriptive analysis

The dependent quantitative variable (the grade of dysphagia) will be summarized using median and interquartile range (IQR), stratifying patients by received intervention and at the follow-up periods stated above.

Dependent qualitative variables, as well as qualitative covariates, will be summarized using proportions, once again stratifying patients by received intervention (induction immunotherapy followed by TORS, or only TORS) at each follow-up time.

For five-year disease-free survival secondary dependent variable, survival curves following Kaplan-Meier estimator will be estimated and represented, stratifying by received intervention.

5.8.2 Bivariate inference

Difference of medians of the main dependent variable (the grade of dysphagia) between the intervention groups and the control group will be contrasted by Student's T test and Mann-Whitney U test, respectively.

Difference on proportions of qualitative variables between intervention groups and control group will be contrasted by χ² test (Chi-Square test) and Fisher's exact test when expected frequencies will be less than five.

Difference in survival curves of intervention groups and control group will be contrasted by log-rank test.

5.8.3 Multivariate analysis

A multivariate analysis will be accomplished to adjust variables for covariates, thus potential confounders that could modify the results will try to be avoided. Covariates that will be contemplated in this study are: HPV-status, age, gender and socio-economic factors.

Only for the multivariate analysis, the main dependent variable (grade of dysphagia) will be categorized by: absence or minor defect, and major defect. Once categorized, a logistic regression on the intervention’s variable controlling all covariates will be estimated.

In all other variables, except for five-year disease-free survival, this type of logistic regressions will be also performed.

Five-year disease-free survival will be estimated with a Cox regression with intervention’s variable and adjusted for covariates.
In all cases, a confidence interval of 95% will be assumed and p<0.05 will be considered statistically significant.

5.9 WORK PLAN AND CHRONOGRAM

The whole study will take approximately 9 years and 11 months (from November 2018 to October 2028). All the activities will be organized in five phases detailed below:

1) Preparation and coordination phase (5 months).
   a. Study setting-up. In this first period, the principal investigator and co-workers will perform a draft of the initial idea of the protocol. They will make a review of the literature, suggest objectives and hypothesis, select the participating hospitals…
   b. First informative meeting. A first meeting will take place with all the investigators of the hospital in order to present the protocol draft, with an explanation of the project design and the execution plan. Collaborators could decide if they agree with the organization of the study.
   c. Final project design and redaction.
   d. CEIC (“Comitè d’ètica d’investigació clínica”) revision and approval. Protocol will be given to CEIC for its revision and approval. All changes suggested will be taken into account.
   e. Second informative meeting. With the purpose of homogenizing a standardized method, a second informative meeting will be scheduled after the CEIC approval. All the participant professionals will be trained about what they have to enquire and how to collect information. It is important to ensure that everybody taking part in this study knows its task and the way to perform it.

2) Fieldwork (patients’ inclusion and evaluation) and data collection (7 years)
   a. Subjects’ recruitment. During the first 2 years, patients diagnosed with locally advanced oropharyngeal SCC tributaries to surgery who meet the inclusion and exclusion criteria will be recruited as the sample of the study. Information sheet (Annex 3) and informed consents (Annexes 4 and 5) will be facilitated to patients before including them into the study.
   b. Subjects’ evaluation. This period will start at the same time as patients’ recruitment, and will finish 5 years from the inclusion of the last participant. Therefore, each patient will be followed during 5 years.
c. Data collection. While the study is taking place, data collected from each patient during the follow-up will be registered in a database. The creation of the database, the entrance of information and controls of quality of this database will be performed by a data manager. This period will finish at the end of the follow-up of the last patient.

d. Face-to-face meetings. To ensure the quality and homogeneity of data, the main investigator will motivate all the participating staff remembering them the training received previously.

3) Data analysis and interpretation (4 months).

   After processing the database, all data will be analysed (each analysis will take 1 month) in two different phases:

   a. Statistical analysis monitoring. In order to control the progress of the study, statisticians will perform 3 statistical along the 7 years of the previous phase. This will allow to publish the first data obtained from the study regarding early postoperative outcomes (including adequacy of surgical margins, grade of pain and postoperative haemorrhage, as well as first assessment of grade of dysphagia, PEG tube dependence and local control of disease).

   b. Final data analysis. After having collected all data (including the long term follow-up variables, such later grade of dysphagia, later PEG tube dependence, later local control of disease and five-year disease-free survival), statisticians will proceed to analyse it and perform a final statistical analysis.

4) Results and final report writing (5 months)

   a. Interpretation of the results. Investigators will analyse and discuss the final results in order to elaborate definitive conclusions.

   b. Final report elaboration

5) Publication and dissemination (6 months)

   a. Publication of the results. The results will be presented to specific conferences and meetings.

   b. Dissemination of the report. The report will be disseminated to congresses, meetings, conferences and scientific journals among others.

The study chronogram may be found at the Annex section (Annex 9).
6 ETHICAL ASPECTS

Main investigators and collaborators guarantee that the study will be conducted in accordance to the human rights and the ethical considerations gathered in the World Medical Association Declaration of Helsinki of “Ethical Principles for Medical Research Involving Human Subjects”, revised in 2013.

This study includes an invasive procedure in the intervention group. Therefore, “Ley 14/2007, de 3 de julio, de Investigación biomédica”, particularly section II, where it specifies the basic principles, requirements, authorization and safety of studies in which a human being undergoes an invasive procedure, will be respected. The present study will also be designed in accordance to the “Real Decreto 1090/2015, de 24 de julio” for the rational use of drugs in clinical trials. This study protocol will be registered in the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database for drugs and health products. It will be evaluated by a Clinical Research Ethics Committee and will not be applied unless it has its approval. Any further recommendation from the Clinical Research Ethics Committee will be considered to improve the procedure. It will be also necessary the approval of the direction of each authorized centre. The protocol has to be also approved by AEMPS, and a specific insurance will be needed.

The present study will also be designed to ensure that privacy of all participants is protected as well as confidential, according to “Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales”. Personal and clinical information will be used just for the purpose of the research. To maintain confidentiality, an identification number will be used instead of the patient's name for analysing the information in an anonymous way. Data will only be accessible for the responsible researchers of the project. Prior to the inclusion on the study, all information about the study and its purposes will be explained to each patient. Patients will be invited to read an information sheet (Annex 3) where all risks, benefits and alternatives to the procedures will be detailed using the best update data available, at that point to ensure they perfectly understand the study before they sign the informed consents (Annexes 4 and 5). Thus, the principle of autonomy and “Ley Orgánica 41/2002, de 14 de Noviembre, de Autonomía del Paciente y de Derechos y Obligaciones en Materia de Información y Documentación Clínica” will be respected. Patients will participate voluntarily in the study after giving their informed consent. In the case that a potential research subject could not give the permission to include him or her in the study, seek of informed consent from the legally authorized representative will be done. If the representative is not available, the study will proceed without the informed consent and the consent to remain in the
research will be obtained as soon as possible from the subject or a legally authorized representative.

The Spanish Constitution of 1978, in the article 43, alludes to the right of health’s protection, and this will be 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 trained for their assigned tasks, so the principle of non-maleficence will be respected.

The authors declare that they do not have any conflict of interest.
7 STRENGTHS AND LIMITATIONS

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

- As in the study an intervention will be performed, it will be necessary to work with a non-randomized sample instead of a whole population, so a selection bias may occur. It will not be possible to randomize participants, because only those patients expressing immunotherapy biomarkers and tributaries to surgery will be considered to enter the study. This is the main limitation of the study. Therefore, results from the study will be adjusted by all potential confounding variables, and a multivariate analysis will be accomplished to adjust variables for these covariates.

- It is an intervention study based on a prospective cohort. Hence, it is defined as observational, and one of the main limitations of this type of studies is the large duration of it, in this case 9 years and 11 months (involving 2 years of recruitment and 5 years of follow-up per each patient). This amount of time causes a high proportion of losses during the follow-up which may alter the results of the study. On the other hand, the cost of the follow-up in the study is not much higher in itself because, despite of the large duration, nearly all of the follow-up requirements are included in the usual following of these type of patients.

- Other limitations are related to the questionnaires used to assess variables, as the ones that have been used are not validated. No other studies relating the grade of dysphagia assessed by functional videoendoscopy and TORS have been performed before, therefore no objective data could be obtained for this research to define the exact grade of dysphagia expected after transoral surgery. To minimize this limitation, data from expert opinion has been used to obtain the mean value of postoperative grade of dysphagia and the standard deviation. For this reason, these values may differ from other centres and other professionals, and could also differ from the ones that will be finally found in this study. If important differences are found at the beginning of the study, sample size will be readjusted to the new values.

- This study is planned to be a multicentre study. Therefore, interpretation of endpoints involves some degree of inter-observer variability. For this reason all the participant professionals of all centres will be trained about what they have to enquire and how to collect information. It is important to ensure that everybody
taking part in this study knows its task and the way to perform it, so data collection could be similar in all participating centres.

- Another limitation related to the design of this 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.

- This study does not provide long-term tumour specific survival data, as the follow-up will be stopped at 5 years.

- After having completed immunotherapy induction treatment, patients’ disease stage may vary (as induction treatment can lead to upstaging or downstaging the tumour). Therefore, if there is a change in disease stage, patients may be asked to terminate the study, so sample may be reduced.

By contrast, the main strength of this multicentre study is that it will have more external validity than if it was only performed in a single centre, as the sample will be more representative because it involves patients of a larger area. To ensure this, it is important that all the participant professionals of all centres are trained so data collection could be similar. Anyway, if significant differences on outcomes are found between the intervention and the control groups, a next study with a larger sample will be necessary, in order to validate this study findings and get definitive conclusions.
8 BUDGET

Investigators
The research team participating at this study is already employed by the centres where it will be carried, and no extra hours will be needed. For this reason, this services will not be included in the budget. Evaluation of complications is also part of the routine activity related to these patients and will not suppose an extra cost. However, a statistician and a data manager will be hired in order to create a database, collect the data and perform the statistical analysis.

Medical resources
The surgical procedure which includes the tumour resection by TORS is part of the normal procedure used in the clinical practice of the centres participating at the study, as well as the follow-up of the patients, so no extra budget will be needed. Nevertheless, to go on with the study some extra material will be necessary for the intervention group. Among these material intravenous nivolumab medicine, as well as other medical devices (syringes, needles...), are included. Nivolumab is not funded by the National Health System so there will be need to use extra budget to pay for it. The expenditure due to nivolumab induction treatment would be:

_Intravenous nivolumab: 59,280.00€/patient x 108 patients = 6,402,240.00 €_

*The price has been consulted with the hospital pharmacy*

Functional videoendoscopy assessment will be performed to compare functional outcomes, as well as radiologic controls (by MRI scan and CT scan) that usually are performed in habitual clinical practice. This assessment is performed in the routine management of these patients, so any extra budget will be needed.

Insurance
An insurance policy will be hired covering all participants.

Publication and diffusion
The approximate cost for the publication of the results will be 2,500€.
Meetings, conferences and congresses will be attended twice, first to present the initial results and in second term to present the final results of the study.
### Table 8.1. Budget proposal. Source: Author.

It has to be taken into account that studies receive financing up to 3 years. Therefore, as this study will last nearly 10 years, at the second year additional financing for next 3 years will be asked for.
9 FEASIBILITY

This non-randomized intervention study based on a prospective cohort will be developed in three ICO hospitals which have TORS platform implemented: HUDJT (Girona), Hospital Germans Trias i Pujol (Badalona) and Hospital Universitari de Bellvitge (L'Hospitalet de Llobregat).

All of otorhinolaryngologic carcinomas detected in the province of Girona have as a reference centre HUDJT, being intended to FUHNT. According to expert opinion, in HUDJT around 40 patients every year are diagnosed with SCC of the oropharynx in a locally advanced stage. From those, around 20 patients can undergo a surgical procedure and fit immunotherapy biomarkers criteria. Therefore, in 2 years the sample will be completed, taken into account the participation in the study of the other two centres mentioned above.

All three centres are totally equipped medically and technologically to accomplish the objectives of the study. The centres participating in the study will provide all the necessary means such as personnel salaries, operation rooms, cures and follow-up equipment. In case of presenting any complication that requires re-intervention, operating rooms will be available.

The whole otorhinolaryngology services, the head and neck committees and nursery staff have enough knowledge and experience and are all well trained to achieve the assigned objectives.

Computer devices and programs to elaborate the database and to carry out the statistical analysis will also be provided.

For all these mentioned above, this protocol is feasible to be brought out in our area, regarding availability of the sample, the professionals and the equipment.
10 CLINICAL AND HEALTHCARE IMPACT

Oropharyngeal cancers have relevant incidence and mortality rates. Nowadays the therapeutic approach of locally advanced oropharyngeal SCC is based in treatment strategies which result in poor functional outcomes, mainly in distinct grades of dysphagia, leading to impaired quality of life for these patients.

Given the rise in oropharyngeal SCC incidence and the changing demographics of the patient population (who tend to be younger), swallowing impairment and its effect on quality of life must be a key consideration for health professionals. Therefore, obtaining better functionality without compromising oncological outcomes should be a priority.

For this reason research has increasingly focused on the potential for treatment de-escalation using less intensive treatments for oropharyngeal SCC. In this context, minimally invasive surgical approaches, such as TORS, have turned out in less morbidity.

An important issue to consider is that, in order to perform less aggressive primary therapeutic strategies, the aim should also be on implementing effective neoadjuvant approaches prior to definitive surgery. Because of this, a possible neoadjuvant immunotherapy approach has a special relevance.

If strong evidence is found in this study, the daily clinical practice management of oropharyngeal SCC will improve. Consequently, the inherent morbidity related to its therapeutic approach may decrease and, therefore, National Health System resources used to solve this clinical condition might also be reduced. As a whole, results in this study may trigger a great clinical impact for treatment strategies of locally advanced carcinomas of oropharynx.
11 BIBLIOGRAPHY


Functional outcomes of immunotherapy induction treatment and transoral robotic surgery

therapeutic approach for oropharyngeal squamous cell carcinoma


Functional outcomes of immunotherapy induction treatment and transoral robotic surgery
therapeutic approach for oropharyngeal squamous cell carcinoma


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381–5.


12 ANNEXES

12.1 ANNEX 1. Staging and TNM classification for oropharyngeal carcinoma

AJCC (8th edition) TNM categories and definitions for HPV-associated (p16+) oropharyngeal SCC:

<table>
<thead>
<tr>
<th>T Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No primary tumor identified</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor size ≤ 2 cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor size &gt; 2 cm but ≤ 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor size &gt; 4 cm in greatest dimension or extension to lingual surface of epiglottis</td>
</tr>
<tr>
<td>T4</td>
<td>Moderately advanced tumor invading larynx, extrinsic tongue muscles, medial pterygoid, hard palate, or mandible or beyond</td>
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</table>

<table>
<thead>
<tr>
<th>Clinical N Category</th>
<th>Criteria</th>
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<tr>
<td>Nx</td>
<td>Regional nodes cannot be assessed</td>
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<tr>
<td>N0</td>
<td>No regional nodal metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis to one or more ipsilateral nodes, ≤ 6 cm</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis to contralateral or bilateral lymph nodes, &lt; 6 cm</td>
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<td>N3</td>
<td>Metastasis in any cervical lymph node &gt; 6 cm</td>
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<table>
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<td>pN0</td>
<td>No regional nodal metastasis identified</td>
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<tr>
<td>pN1</td>
<td>Metastasis to 4 or fewer lymph nodes</td>
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<tr>
<td>pN2</td>
<td>Metastasis to 5 or more lymph nodes</td>
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<th>M Category</th>
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<tr>
<td>M0</td>
<td>Absence of distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Presence of distant metastasis</td>
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</table>

*Clinical and pathologic T classification schemes are similar.*
AJCC (8th edition) prognostic stage groups for HPV-associated (p16+) oropharyngeal SCC (clinical):

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<thead>
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<th>T Category</th>
<th>N Category</th>
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<tr>
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<td>M0</td>
<td>I</td>
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<td>M0</td>
<td>II</td>
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<td>T3</td>
<td>N0, N1, or N2</td>
<td>M0</td>
<td>II</td>
</tr>
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<td>T0, T1, T2, T3, or T4</td>
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<td>M0</td>
<td>III</td>
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<td>T4</td>
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<td>Any N</td>
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AJCC (8th edition) prognostic stage groups for HPV-associated (p16+) oropharyngeal SCC (pathologic):

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<th>N Category</th>
<th>M Category</th>
<th>Stage Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0, T1, or T2</td>
<td>N0, N1</td>
<td>M0</td>
<td>I</td>
</tr>
<tr>
<td>T0, T1, or T2</td>
<td>N2</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td>T3 or T4</td>
<td>N0, N1</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td>T3 or T4</td>
<td>N2</td>
<td>M0</td>
<td>III</td>
</tr>
<tr>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>IV</td>
</tr>
</tbody>
</table>
Functional outcomes of immunotherapy induction treatment and transoral robotic surgery therapeutic approach for oropharyngeal squamous cell carcinoma

AJCC (8th edition) TNM categories and definitions for non-HPV-associated (p16−) oropharyngeal SCC:

<table>
<thead>
<tr>
<th>T Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor size ≤ 2 cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor size &gt; 2 cm but ≤ 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor size &gt; 4 cm in greatest dimension or extension to lingual surface of epiglottis</td>
</tr>
<tr>
<td>T4</td>
<td>Moderately advanced or very advanced tumor</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced tumor involving larynx, extrinsic tongue muscles, medial pterygoid, hard palate, or mandible</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced tumor involving lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encasement of the carotid artery</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical N Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>Regional nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional nodal metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis to single ipsilateral node, ≤ 3 cm and ENE-negative</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in a single ipsilateral lymph node &gt; 3 cm but ≤ 6 cm in greatest dimension and ENE-negative or metastases in multiple ipsilateral lymph nodes, ≤ 6 cm in greatest dimension and ENE-negative or metastases in bilateral or contralateral lymph nodes, ≤ 6 cm in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in a single ipsilateral lymph node &gt; 3 cm but ≤ 6 cm in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastases in multiple ipsilateral lymph nodes, ≤ 6 cm in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, ≤ 6 cm in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node &gt; 6 cm in greatest dimension and ENE-negative or metastasis in any lymph nodes and clinically overt ENE-positive</td>
</tr>
<tr>
<td>N3a</td>
<td>Metastasis in a lymph node &gt; 6 cm in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N3b</td>
<td>Metastasis in any lymph node(s) and clinically overt ENE-positive</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathologic N Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>Regional nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional nodal metastases</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis to single ipsilateral node, ≤ 3 cm and ENE-negative</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis to single ipsilateral node, ≤ 3 cm and ENE-positive or metastasis in a single ipsilateral lymph node &gt; 3 cm but ≤ 6 cm in greatest dimension and ENE-negative or metastases in multiple ipsilateral lymph nodes, ≤ 6 cm in greatest dimension and ENE-negative or metastases in bilateral or contralateral lymph nodes, ≤ 6 cm in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis to single ipsilateral node, ≤ 3 cm and ENE-positive or metastasis in a single ipsilateral lymph node &gt; 3 cm but ≤ 6 cm in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastases in multiple ipsilateral lymph nodes, ≤ 6 cm in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastases in bilateral or contralateral lymph nodes, ≤ 6 cm in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node &gt; 6 cm in greatest dimension and ENE-negative or metastasis in multiple ipsilateral lymph nodes, ≤ 6 cm in greatest dimension and ENE-positive or metastases in bilateral or contralateral lymph nodes, with any ENE-positive</td>
</tr>
<tr>
<td>N3a</td>
<td>Metastasis in a lymph node &gt; 6 cm in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N3b</td>
<td>Metastasis in a single ipsilateral lymph node &gt; 3 cm in greatest dimension and ENE-positive or metastases in multiple ipsilateral, contralateral, or bilateral lymph nodes, with any ENE-positive or a single contralateral node ≤ 3 cm and ENE-positive</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>Absence of distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Presence of distant metastasis</td>
</tr>
</tbody>
</table>

*Clinical and pathologic T classification schemes are similar.*
AJCC (8th edition) prognostic stage groups for non-HPV-associated (p16−) oropharyngeal SCC:

<table>
<thead>
<tr>
<th>T Category</th>
<th>N Category</th>
<th>M Category</th>
<th>Stage Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
<td>0</td>
</tr>
<tr>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>I</td>
</tr>
<tr>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>III</td>
</tr>
<tr>
<td>T1, T2, T3</td>
<td>N1</td>
<td>M0</td>
<td>III</td>
</tr>
<tr>
<td>T4a</td>
<td>N0, N1</td>
<td>M0</td>
<td>IVA</td>
</tr>
<tr>
<td>T1, T2, T3, T4a</td>
<td>N2</td>
<td>M0</td>
<td>IVA</td>
</tr>
<tr>
<td>AnyT</td>
<td>N3</td>
<td>M0</td>
<td>IVB</td>
</tr>
<tr>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
<td>IVB</td>
</tr>
<tr>
<td>AnyT</td>
<td>Any N</td>
<td>M1</td>
<td>IVC</td>
</tr>
</tbody>
</table>
### 12.2 ANNEX 2: Data collection summary table

<table>
<thead>
<tr>
<th>Time</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>-15 days: pre-entry</td>
<td>During these days, patients diagnosed with locally advanced oropharyngeal SCC will be informed about the possibility of entering the study, and they will accept the consent forms (Annexes 4 and 5). A functional videoendoscopy will be performed to assess the previous grade of dysphagia.</td>
</tr>
<tr>
<td>Day 1: study entry</td>
<td>If patient fits the inclusion and exclusion criteria, he/she will be assigned into intervention or control group, to undergo one of the two therapeutic procedures.</td>
</tr>
<tr>
<td>Day 1-15: hospitalization</td>
<td>The hospital stay may vary depending on patient’s characteristics. Complications like the grade of pain and postoperative haemorrhage will be assessed if occur. PEG tube dependency will be also taken into account.</td>
</tr>
<tr>
<td>1st year to 5th year follow-up</td>
<td>Grade of dysphagia will be assessed at 3, 6 and 12 months after intervention. Clinical and radiological control will be performed from 1st to 5th year.</td>
</tr>
</tbody>
</table>
INFORMATION SHEET FOR PARTICIPANTS

PROJECT: Functional outcomes of immunotherapy induction treatment and transoral robotic surgery therapeutic approach for oropharyngeal squamous cell carcinoma.

INVESTIGATORS: Marc Tobed Secall and Ainhoa Garcia Belerda
LOCATION: Hospital Universitari de Girona 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 functional outcomes obtained in patients diagnosed with locoregional advanced squamous cell carcinoma of the oropharynx, after immunotherapy induction treatment followed by transoral robotic surgery is performed, compared with those patients who do not receive previous immunotherapy induction treatment. We also want to assess the complications related to the intervention, as well as local control of disease, adequacy of surgical margins and survival rates for both procedures.

Description of the study
In this study, two treatment options are proposed. The first one, which is the current treatment, is performing transoral robotic surgery followed by postoperative adjuvant treatment as necessary. The second option consists in administering immunotherapy induction treatment previously to performing transoral robotic surgery, and then if necessary administering adjuvant treatment.
All patients taking part in our study will be followed up during 5 years after the tumour resection, and their grade of dysphagia and complications will be registered. They will be dated 3, 6 and 12 months for grade of dysphagia assessment, and up to 5 years since intervention to perform clinical and radiological controls at Functional Unity of Head and Neck Tumours of Hospital Universitari de Girona Doctor Josep Trueta and at outpatient clinic.

Why have you been invited?
You will undergo an 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 tumour resection with transoral robotic surgery and adjuvant treatment as necessary, 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 better future patients with similar conditions. 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 transoral robotic surgery. Uncommon complications would be: postoperative haemorrhage, compromise of swallowing function
and PEG dependence, dysphagia, need of performing a tracheostomy and persistence of positive surgical margins.

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 taking into account having or not participated in the study.

Responsibility and insurance
You will be 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 (03/2018) 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 de Girona 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. If any queries, questions or doubts do not hesitate to contact us.
12.4 ANNEX 4. Consent form to enter the trial

WRITTEN INFORMED CONSENT FOR THE PATIENT


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.

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: __ __ / __ __ / __ __
Este documento informativo pretende explicar, de forma sencilla, la intervención quirúrgica denominada CIRUGÍA ROBÓTICA TRANSORAL, así como los aspectos más importantes del periodo postoperatorio y las complicaciones más frecuentes que, como consecuencia de esta intervención, puedan aparecer.

**BREVE DESCRIPCIÓN DEL PROCEDIMIENTO QUIRÚRGICO**

Llamamos CIRUGÍA ROBÓTICA TRANSORAL a la técnica o el conjunto de técnicas quirúrgicas que tienen como finalidad la extirpación, con objetivos diagnósticos o terapéuticos, de lesiones o estructuras ubicadas en la cavidad oral, faringe o laringe, y que se realizan a través de la boca con instrumentación robótica.

Es una cirugía cuya vía de abordaje puede calificarse como mínimamente invasiva y está diseñada para disminuir las posibles secuelas de las maniobras quirúrgicas realizadas con técnicas convencionales, si bien siempre existen secuelas, que pueden variar en dependencia de la localización y la extensión del tejido extirpado.

Como en todos los procedimientos de abordaje mínimamente invasivo existe la posibilidad de que la aparición de complicaciones obligue a convertir esta vía de abordaje en otra convencional, si bien esta situación suele ser excepcional.

Igualmente, si por motivos propios de la anatomía del paciente hay una exposición insuficiente de las lesiones que limite las garantías de éxito, puede ser necesario suspender el procedimiento, o convertirlo en otro más adecuado a las circunstancias del caso.

Dependiendo de cada caso, es posible que el paciente permanezca ingresado en la U.C.I. para su mejor control postoperatorio durante los primeros días tras la intervención. Posteriormente pasará a la planta, donde continuará su recuperación.

Tras la intervención, aparecerán molestias o dolor franco, que pueden ser intensas, que pueden acentuarse en el momento de tragar, y que el paciente puede percibir en la zona de la intervención e irradiarse hacia los oídos. Estas molestias pueden prolongarse a lo largo de diez, quince o más 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.

Es frecuente que inicialmente no se pueda tragar con normalidad a través de la boca. Por ello, el médico puede decidir alimentarle a través de una sonda colocada por la nariz, o -de manera excepcional a través de una vía directa con el estómago (a esta vía se la denomina gasterostomía). La normalización de la deglución suele ser progresiva.

En ocasiones, esta técnica requiere la realización de una traqueotomía provisional (una comunicación de la tráquea –es decir, el tubo de respirar- con el exterior, mediante un orificio que se practica en el cuello) y que se mantiene abierto mediante una cánula, facilitando así la respiración. La traqueotomía puede mantenerse, si es necesario, el eventual tratamiento posterior con radioterapia o si la cicatrización de la zona intervenida no hace posible su retirada. La traqueotomía requiere cuidados específicos.

No obstante, hay que señalar que la cirugía robótica Transoral está diseñada para minimizar la necesidad de la mencionada traqueotomía, las sondas señaladas y otros problemas funcionales. A pesar de ello, tras la intervención pueden quedar secuelas, que dependerán del área concreta intervenida, y que suelen ser normalmente menores que las de los tratamientos convencionales.

La duración del ingreso hospitalario es variable, dependiendo de la evolución de cada caso, aunque la cirugía de mínimo abordaje se asocia con la reducción de tiempo de ingreso.

Durante todo el proceso se controlará la presencia de fiebre, hemorragia u otras complicaciones, así como la cicatrización de la herida operatoria. Tras el alta hospitalaria, el paciente realizará de forma ambulatoria las revisiones o curas que sean necesarias. En determinados casos, para el correcto tratamiento de la enfermedad, será necesaria la administración de radioterapia y/o quimioterapia tras la intervención.

En caso de NO EFECTUAR esta intervención

Persistirán las lesiones que la hubieran podido justificar o no se podrá disponer de los elementos de diagnóstico previstos. Si la intervención se ha recomendado por la existencia de un tumor maligno, la evolución espontánea -es decir, sin tratamiento- del mismo, ocasionará la muerte del paciente por extensión local, regional o a distancia (lo que conocemos como metástasis). Esta extensión provocará problemas para la deglución, asfixia, infecciones y hemorragias. Si el motivo del procedimiento es diagnóstico en caso de no realizarse, el médico no tendrá los elementos de diagnóstico necesarios para el mejor tratamiento de la enfermedad

BENEFICIOS ESPERALES

Curación de la enfermedad con menores secuelas mutilantes o incapacitantes
PROCEDIMIENTOS ALTERNATIVOS

Pueden ser la radioterapia y la quimioterapia, con probabilidades de éxito variables en cada caso. Existen también alternativas de tratamiento quirúrgico que son, de forma general, la cirugía abierta o el abordaje Transoral con otra instrumentación (incluido el láser). En la actualidad, las tres formas de tratamiento suelen combinarse para optimizar los resultados. Su médico, asesorado por un comité de especialistas, le aconsejará sobre la mejor conducta a seguir.

RIESGOS ESPECÍFICOS MÁS FRECUENTES DE ESTE PROCEDIMIENTO

Puede producirse una hemorragia que pueda requerir una nueva intervención, una transfusión e, incluso, complicaciones cardiovasculares.

Puede producirse una infección de la herida quirúrgica, o del aparato respiratorio, tales como traqueitis, bronquitis y neumonitis.

Pueden producirse acúmulos de moco seco, lo que se denomina tapones mucosos, en la cánula de traqueotomía (si es que ésta se ha realizado), en la tráquea o los bronquios, lo que podría determinar una disnea (dificultad respiratoria). Puede producirse un edema, es decir una inflamación, de la laringe, una estrechez de la laringe (que llamamos estenosis laringea), o la aparición de una sienquias (bridas cicatriciales). Estas circunstancias podría determinar también la aparición de una dificultad respiratoria. Dicha dificultad respiratoria requeriría la prescripción de un tratamiento médico, la realización de una traqueotomía (si es que ésta no se hubiera realizado previamente), e incluso, la imposibilidad de retirar la cánula de la traqueotomía (si es que ésta existiera). Pueden, asimismo, aparecer disfagia (dificultades para tragar) y falsas rutas en la deglución (atraquagamientos), generalmente temporales, pero que pueden quedar como secuela.

Pueden aparecer fistulas cutáneas (comunicaciones de la garganta o la boca con el exterior del cuello), que pueden precisar tratamientos prolongados e incluso una reintervención. Es excepcional, pero puede aparecer, una pericondritis (inflamación de los cartílagos de la laringe), una osteitis (inflamación de los huesos) o necrosis (destrucción) de las partes blandas del cuello. Puede aparecer un enfisema cervical o mediastínico (pequeñas burbujas de aire en el cuello o en el tórax).

Es posible que aparezca, por el stress, una úlcera gastroduodenal y una depresión.

Aunque no se han descrito, potencialmente el sistema robótico utilizado puede producir lesiones mecánicas o quemaduras en la cara, boca o en la vía aérea, tras la combustión de los tubos de intubación anestésica o la rotura de los manguitos protectores. Puede producirse, asimismo la ignición del oxígeno y gases anestésicos. Asimismo, los dispositivos de exposición Transoral pueden producir lesiones dentarias. Cabe la posibilidad de una recidiva (reaparición) de la enfermedad, temprana o tardíamente.

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

RIESGOS RELACIONADOS CON SUS CIRCUNSTANCIAS PERSONALES Y PROFESIONALES

OBSERVACIONES Y CONTRAINDICACIONES

DECLARACIONES Y FIRMAS

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

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

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

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

Acepto que, durante la intervención, el cirujano pueda tomar las muestras biológicas que considere necesarias para el estudio de mi proceso, o las imágenes precisas para la adecuada documentación del caso.

Comprendo que, a pesar de las numerosas y esmeradas medidas de higiene del equipo asistencial que me atiende, el acto quirúrgico y la estancia en el hospital son un factor de las llamadas infecciones hospitalarias, que son excepcionales, pero posibles.
En el caso de que, durante la intervención quirúrgica, el cirujano descubra aspectos de mi enfermedad, o de otras enfermedades que pudiera padecer, que le exijan o le aconsejen modificar, de forma relevante, el procedimiento terapéutico inicialmente proyectado, consultará la decisión a tomar con la persona autorizada por mí a este respecto. Únicamente cuando las eventualidades acaecidas durante la intervención quirúrgica pongan en riesgo mi vida autorizo al cirujano para que adopte la decisión más conveniente para mi salud.

Entiendo que es posible que el cirujano finalice la intervención sin haber completado los objetivos inicialmente planteados, al enfrentarse a circunstancias no previstas que pudieran requerir mi consentimiento expreso para ser resueltas.

Entiendo que, en este documento, se me informa de los riesgos y complicaciones más frecuentes y relevantes de la intervención quirúrgica. No obstante, si yo lo precisara, el médico podría facilitarme información complementaria sobre todos los riesgos y complicaciones posibles de este procedimiento quirúrgico. En resumen, considero que la información ofrecida por el médico y la contenida en el presente documento resultan suficientes y adecuadas para comprender todos los aspectos de la intervención a la que voy a ser sometido y asumir sus riesgos y posibles complicaciones.

Tras todo ello, DOY MI CONSENTIMIENTO PARA SER SOMETIDO A ESTA INTERVENCIÓN, entendiendolo, por otra parte, mi derecho a revocar esta autorización en cualquier momento.

En _____________, a _____ de _____________ de 20__

Fdo.: _____________________ Fdo.: _____________________

El paciente El facultativo

TUTOR LEGAL O FAMILIAR

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

En _____________, a _____ de _____________ de 20__

Fdo.: _____________________

El representante legal
REVOCACIÓN DEL CONSENTIMIENTO

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

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

En ________________, a ____ de ________________ de 20___

Fdo.: ___________________________

El paciente/representante legal
### 12.6 ANNEX 6. SEORL criteria for deglutition disorders

<table>
<thead>
<tr>
<th>Fase</th>
<th>Alteraciones</th>
<th>Signos</th>
<th>Tratamiento</th>
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<td>Oral</td>
<td>Defecto cierre labial</td>
<td>Babeo</td>
<td>Rehabilitación muscular oral</td>
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<td></td>
<td>Debilidad facial</td>
<td>Retención de alimento en cavidad oral</td>
<td>Presentar alimento por el mejor lado</td>
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<td>Debilidad masticación</td>
<td>Masticación dificultosa</td>
<td>Modificaciones de consistencia del alimento</td>
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<td>Debilidad lingual</td>
<td>Deglución fraccionada por alteración propulsión y retraso inicio de deglución</td>
<td>Rehabilitación muscular lingual Mniobra de deglución forzada</td>
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<td></td>
<td>Insuficiencia de cierre palatogloso</td>
<td>Paso prematuro a faringe y aspiración predeglución</td>
<td>Rehabilitación reflejo deglución</td>
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<td>Faringea</td>
<td>Insuficiencia velopalatina</td>
<td>Reflujo oronasal</td>
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<td>Reflejo deglutorio retrasado</td>
<td>Aspiración predeglución</td>
<td>Rehabilitación reflejo deglución Deglución supraglótica</td>
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<td>Alteración peristalsis faringea</td>
<td>Degluciones múltiples, residuo faringeo y aspiración postdeglución</td>
<td>Mniobra de deglución forzada</td>
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<td>Disminución de elevación laringea</td>
<td>Aspiración durante la deglución</td>
<td>Mniobra de Mendelsohn</td>
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<td>Alteración del cierre laringeo</td>
<td>Aspiración durante la deglución</td>
<td>Rehabilitación cierre glótico Deglución super-supraglótica</td>
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<td>Disfunción apertura cricofaringea</td>
<td>Residuo hipofaringeo y aspiración postdeglutoria</td>
<td>Deglución super-supraglótica</td>
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<td>Esofágica</td>
<td>Alteración motilidad</td>
<td>Aspiración postdeglutoria</td>
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12.7 ANNEX 7. Variables summary table

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<tr>
<th>VARIABLE</th>
<th>TYPE OF VARIABLE</th>
<th>MEASURE METHOD</th>
<th>UNITS</th>
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<tr>
<td>Procedure</td>
<td>Categorical</td>
<td>No measuring method needed</td>
<td>- Immunotherapy + TORS - Current treatment (TORS)</td>
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<td>Grade of dysphagia</td>
<td>Quantitative</td>
<td>SEORL criteria for dysphagia, using functional videoendoscopy (at 0-3-6-12 months)</td>
<td>Points given for each item in all three phases of deglutition: - 0: absence of defect - 1: minor defect - 2: major defect</td>
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<td>PEG dependence</td>
<td>Categorical</td>
<td>At 3-6-12 months</td>
<td>- Yes - No</td>
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<td>Adequacy of surgical margins</td>
<td>Categorical</td>
<td>Pathological anatomy criteria</td>
<td>- Affected - Close: ≤ 0,2cm - Optimal: &gt; 0,2cm → &gt; 0,5cm - Free: ≥ 0,5cm</td>
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<td>Local control of disease</td>
<td>Categorical</td>
<td>At 3, 6 and 24 months</td>
<td>- Yes - No</td>
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<td>Five-year disease-free survival</td>
<td>Categorical</td>
<td>At 5 years</td>
<td>- Yes - No</td>
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<td>Postoperative haemorrhage</td>
<td>Categorical</td>
<td>No measuring method needed</td>
<td>- Yes - No</td>
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<td>Variable</td>
<td>Type</td>
<td>Description</td>
<td>WHO’s three-step ladder:</td>
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<td>Grade of pain</td>
<td>Categorical ordinal variable</td>
<td>Requirement of analgesic drugs</td>
<td>- nonopioids</td>
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<td>- mild opioids</td>
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<td>- strong opioids</td>
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<tr>
<td>HPV-status</td>
<td>Categorical dichotomous variable</td>
<td>HPV testing of cytopathologic samples</td>
<td>- HPV-positive patients</td>
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<td>- HPV-negative patients</td>
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<td>Age</td>
<td>Quantitative continuous variable</td>
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<td>Years</td>
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<td>Gender</td>
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<td>- Male</td>
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<td>- Female</td>
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<td>Socio-economic factors</td>
<td>Quantitative continuous variable</td>
<td>No measuring method</td>
<td>Education years</td>
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</table>
12.8 ANNEX 8. Drug relevant information

Relevant information about nivolumab (60).

Name of the product:

OPDIVO® 10 mg/ml concentrado para solución para perfusión.

Qualitative and quantitative composition:

- Active ingredient: each ml of concentrate contains 10 mg of nivolumab
- Excipients:
  - Sodium citrate dihydrate
  - Sodium chloride
  - Mannitol (E421)
  - Pentetic acid (diethylenetriaminepentaacetic acid)
  - Polysorbate 80
  - Sodium hydroxide (for pH adjustment)
  - Hydrochloric acid (for pH adjustment)

Pharmaceutical form:

Concentrate for solution for perfusion (sterile concentrate).

Indications:

- Treatment of melanoma
- Adjuvant treatment of melanoma
- Treatment of non-small cell lung cancer
- Treatment of renal cell cancer
- Treatment of classic Hodgkin lymphoma
- Treatment of head and neck squamous cell carcinoma
- Treatment of urothelial carcinoma

Oropharyngeal squamous cell carcinoma posology and instructions for its administration:

The recommended dose of OPDIVO® at monotherapy is nivolumab 240 mg each 2 weeks during 30 minutes.

OPDIVO® only can be administrated through intravenous perfusion. The total needed dose of OPDIVO® can be perfused directly or as a solution of 10 mg/ml, or can be diluted with a sodium chloride solution for injectable preparations at a concentration of 9 mg/ml
(0.9%) or a glucose solution for injectable preparations at a concentration of 50 mg/ml (5%).

No dose adjustments are required for special populations (elderly patients, chronic kidney failure and liver failure). There are no data about paediatric population.

**Contraindications:**

- Hypersensitivity to active ingredient or to any excipient.

**General adversences and precautions:**

Patients undergoing treatment with OPDIVO® should receive the information card for the patient and should be informed about the risks of OPDIVO®.

OPDIVO® must be suspended permanently in the following cases:

- Recurrent Grade 4 or Grade 3 adverse reactions.
- Persistent Grade 2 or Grade 3 adverse reactions despite their management.

Depending on the severity of the adverse reactions, treatment with nivolumab should be suspended, and corticosteroids or even immunosuppressants should be administered.

Patients should be monitored continuously (at least 5 months after the last dose) as there may be adverse reactions with nivolumab at any time during or after suspending treatment.

**Adverse reactions:**

- Infections: superior airway infection, pneumonia...
- Hematologic disorders: neutropenia, eosinophilia.
- Immune system disorders: hypersensitivity, related to perfusion reaction.
- Immuno-related adverse reactions:
  - Immuno-related pneumonitis.
  - Immuno-related colitis.
  - Immuno-related hepatitis.
  - Immuno-related nephritis and renal failure.
  - Immuno-related endocrinopathies (hypothyroidism, hyperthyroidism, suprarenal insufficiency, hypophysitis, diabetes mellitus, diabetic ketoacidosis).
  - Immuno-related skin adverse reactions.
- Nutrition disorders: loss of appetite, dehydration...
Central nervous system disorders: peripheral neuropathy, headache, dizziness...
Cardiac disorders: tachycardia, pericardial disorders, arrhythmias, myocarditis...
Vascular disorders: hypertension, vasculitis.
Respiratory disorders: pneumonitis, dyspnoea, cough...
Gastrointestinal disorders: diarrhoea, nausea, vomiting, colitis, abdominal pain, constipation, xerostomia...
Skin and subcutaneous tissue disorders: skin rash, pruritus, vitiligo, dry skin, erythema, alopecia...
Musculoskeletal and connective tissue disorders: musculoskeletal pain, arthralgia, arthritis, Sjögren syndrome...
Renal and urinary disorders: tubulointerstitial nephritis, renal failure...
General and injection site disorders: fatigue, pyrexia, oedema, pain...

Overdose:
No notified cases of overdose have been notified at clinical trials.

Interactions:
Nivolumab is a human monoclonal antibody, and therefore no studies of pharmacokinetic interactions have been conducted. Since monoclonal antibodies are not metabolized by cytochrome P450 (CYP) enzymes or other drug-metabolizing enzymes, neither the inhibition nor the induction of these enzymes by drugs co-administered is expected to affect the pharmacokinetics of nivolumab.

Other forms of interaction may include systemic immunosuppression. The use of systemic corticosteroids and other immunosuppressants should be avoided before starting treatment with nivolumab, due to its potential interference with pharmacodynamic activity. However, systemic corticosteroids and other immunosuppressants may be used after beginning treatment with nivolumab to treat the immuno-related adverse reactions.

Fertility, pregnancy and breastfeeding:
The use of nivolumab during pregnancy or in women of childbearing age who are not using effective contraceptive methods is not recommended, unless the clinical benefit outweighs the possible risks. Effective contraception should be used at least 5 months after the last dose of nivolumab.
A decision must be made about stopping breastfeeding or discontinuing nivolumab treatment, taking into account the benefit of breastfeeding for the child and the benefit of the treatment for the mother.

The effect of nivolumab on male and female fertility is unknown.
12.9 ANNEX 9. Study chronogram

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<th>2019</th>
<th>2020</th>
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Functional outcomes of immunotherapy induction treatment and transoral robotic surgery therapeutic approach for oropharyngeal squamous cell carcinoma