Universitat de Girona
Facultat de Medicina

Prediction of chemoradiotherapic response on hypopharynx and larynx carcinomas by high-resolution magnetic resonance angiography

A prospective cohort study

FINAL DEGREE PROJECT

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“Medicine is a science of uncertainty

and an art of probability”

William Osler

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1. ABSTRACT:

Background: Hypopharynx and larynx carcinomas are ones of the most frequent tumours of head and neck area which are mainly composed of squamous cells. The majority part of those carcinomas are diagnosed in advanced stages when the election of the treatment is still controversial, choosing between surgery plus radiotherapy or chemoradiotherapy. One of the most important points for predicting the tumoural response to chemoradiotherapy is the exposure to hypoxia. High-resolution gadofosveset-enhanced magnetic resonance angiography is an innovative image technique that evaluates the vessels of the body, and recently there are some studies that have started using it in order to analyse the vascularization of carcinomas. Therefore, the vascular pattern could be a measure to estimate the grade of hypoxia exposure.

Objective: The aim of this study is to analyse whether there is an association between the tumoural vascular pattern obtained by high-resolution gadofosveset-enhanced magnetic resonance angiography, and clinical and radiologic response of the tumour to chemoradiotherapy, in patients with locally advanced squamous cell carcinoma of hypopharynx and larynx.

Methods: It will be an observational analytic prospective cohort study with a follow-up of 9.5 years, performed at Hospital Universitari Doctor Josep Trueta of Girona. Using a non-probabilistic consecutive sampling, patients aged 18 or more with the new diagnosis of locally advanced squamous cell carcinoma of hypopharynx or larynx will be recruited and divided into two groups depending on the vascular pattern of the tumour, that indirectly represents the tumoural exposition to hypoxia. The two groups will be followed in order to analyse clinic and radiologic response of the carcinoma to chemoradiotherapy, and consequently the overall and disease free survival during the follow-up period.

Key words: hypopharynx carcinoma, larynx carcinoma, squamous cell carcinoma, chemoradiotherapy, gadofosveset trisodium, magnetic resonance angiography

2. ABBREVIATURES:

AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
AMR	Angiography Magnetic Resonance
CEIC	Comissió d'Ètica per la Investigació Mèdica
CR	Complete Response
CRT	Chemoradiotherapy
CT	Chemotherapy
DFS	Disease Free Survival
DNI	Death national index
DP	Disease Progression
DWI	Diffusion-weighted imaging
EGFR	Epidermic Growth Factor Receptor
EMT	Epithelial-Mesenchymal Transition
FUHNT	Functional Unity of Head and Neck Tumours
HIF-1	Hypoxia Inducible Factor 1
HPV	Human Papilloma Virus
MRI	Magnetic Resonance Imaging
OS	Overall Survival
PET	Positron Emission Tomography
PF	Cisplatin plus 5-fluorouracil
PR	Partial Response
PWI	Perfusion-weighted imaging
RR	Relative Risk
RT	Radiotherapy
SD	Stable Disease
TC	Computed Tomography
TPF	Paclitaxel, cisplatin and 5-fluorouracil

3. INTRODUCTION:

3.1 Background:

3.1.1 Hypopharynx and larynx carcinomas:

Epidemiology

Head and neck squamous cell carcinoma is the **6th most common** neoplasm at world level, observing an incidence of 600.000 new cases annually and representing the 9% of the annual mortality due to cancer(1,2). The main affected areas are oral cavity, pharynx and larynx(1). Larynx and in less proportion hypopharynx, represent **more than 25%** of the cases and show a clear predominance (98%) of **squamous cell carcinoma**, mostly at a glottic or subglottic level, from a histological point of view(3).

Data concerning the highest larynx cancer incidence has been seen in South-Eastern European countries (Spain, France, Italy), Eastern European countries (Serbia and Poland), Latin-America (Brazil and Argentina) and Western Asian countries (Pakistan and Turkey); while the areas with the highest incidence of hypopharynx cancer are France, India and Pakistan(4). It has been demonstrated that Spain is the European country with the highest rated of incidence and mortality of larynx cancer in males. However, females have one of the lowest rates in Europe(3,4). So it can be said that the incidence of larynx and also hypopharynx cancer is significantly higher in men than in women, with a ratio that varies **from 4:1 to 7:1**(2–4). However, some studies have recently

shown an increase on the incidence of these neoplasms in women due to a higher exposure to risk factors(4).

Risk factors:

The main risk factors of the squamous cell carcinoma of hypopharynx and larynx are **tobacco** and **alcohol** which act in a synergistic way for tumour development on the area when presented together(4). Many studies conclude that ¾ of head and neck carcinoma are due to alcohol and tobacco consumption, although just a minority of smokers and alcoholics will develop them(2). In general, larynx cancer has a strong association with tobacco while hypopharynx cancer is more associated with alcohol consumption(4).

Smoking is detected in 97% of the patients with squamous cell carcinoma of larynx, representing a relative risk (RR) of 10-30 in smokers of 10 cigarettes/day during 10 years(3,5). However, this RR returns to its initial values after 10 years of abstinence (2). On the other hand, chronic alcoholism has a much lower relative risk that can vary depending on the affected area: RR= 4,3 in hypopharynx and supraglottis, and RR=2,1 in glottis and subglottis(5).

Other risk factors that have less impact on the carcinoma development are:

- Black ethnicity
- Virus: The most important one is human papilloma virus (HPV), especially the 16 subtype which is positive in 35% of head and neck carcinomas, being more frequent in oropharynx
- Chronic inflammatory processes, like chronic laryngitis, gastritis or gastroesophageal reflux

- Occupational exposition to nickel, asbestos, hydrocarbons, wood dust, among others, which can have a latency period of 40 years
- Genetic factors
- Nutritional deficiencies: Vitamin A and beta-carotenes which are still controversial
- Low socioeconomic level which should be discharged as a confusing factor because of its relation with a higher exposure to toxic risk factors(2,3)

Clinical symptoms and signs:

The earliest symptom and the most frequent one that is observed in patients with hypopharynx and larynx carcinoma is **dysphonia**. Every dysphonia that appears gradually and lasts for more than two weeks has to be studied as it is an indication of laryngoscopy exploration.

Other frequent symptoms that usually appear later are: dysphagia, odynophagia, dyspnoea, reflex otalgia… We also have to take into account the presence of constitutional syndrome, which is typical on patients with carcinomatous pathology, consisting in anorexia, asthenia and loss of weigh(6). If regional affection has already occurred, lymph nodes on the cervical area may be detected, mainly in areas II and III(7)(Annex 1).

Diagnose:

At any otorhinolaryngologic symptom or sign, the pathology will be studied together with the clinical history and the physical exploration of the area, always undertaking a cervical lymph node palpation. In case of possible intern

affection, we will proceed to realise an indirect or direct fibrolaryngoscopy in order to evaluate all the structures as well as identify, describe and locate the injury.

In the event of a possible lesion, image techniques will have to be carried out in order to confirm the diagnosis. A computed tomography (TC) or a magnetic resonance imaging (MRI) will be performed so as to evaluate the main characteristics of the lesion and its local and distance extension. It has to be complemented with a histologic analysis of the mass obtained by a direct laryngoscopy with local or general anaesthesia(2,6).

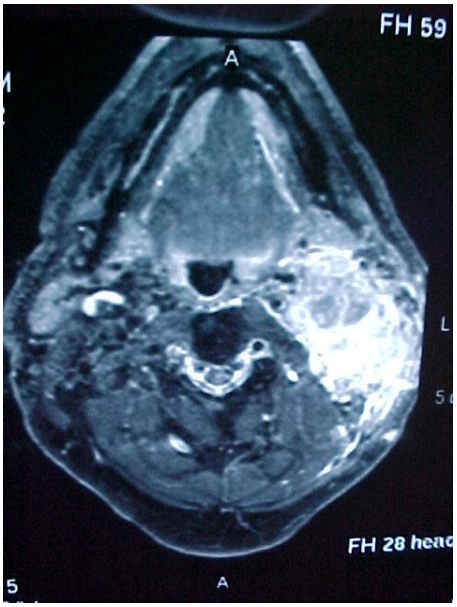

Image 1. Pharynx carcinoma with high regional affection (T1N3M0)
From Otorhinolaryngologic Department of Hospital Universitari Dr Josep Trueta

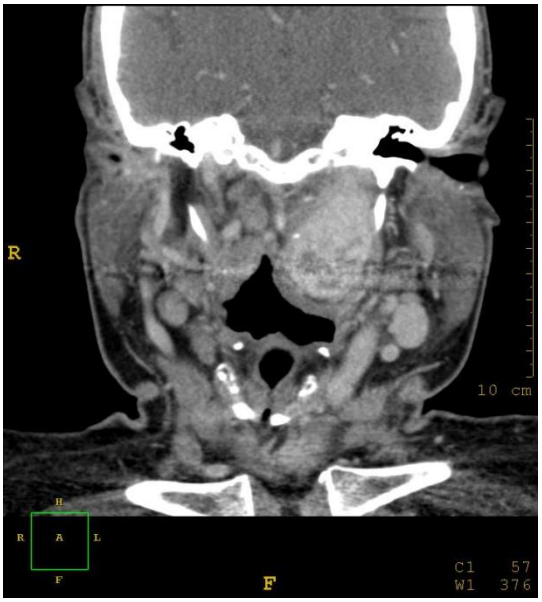

Image 2. Retropharynx lymph node
From Otorhinolaryngologic Department of Hospital Universitari Dr Josep Trueta

Staging:

The tumour will be classified according to the previously mentioned tests using TNM System which is an expression of the anatomic extent of the disease. It is based on the assessment of the following three components:

T The extent of the primary tumour
N The absence or presence and extent of regional lymph node metastasis
M The absence or presence of distant metastasis(8)

Despite the differences on how to classify the extent of the primary tumour (T), TNM classification in the hypopharynx and the larynx cancer is similar regarding the regional and distant extension (N and M). This classification is as follows:

Table 1. TNM classification for hypopharynx and larynx classification(8)

Hypopharynx

T1	Tumor limited to one subsite of hypopharynx and 2 cm or less in greatest dimension
T2	Tumor involves more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest diameter without fixation of hemilarynx
T3	Tumor measures more than 4 cm in greatest dimension or with fixation of hemilarynx
T4	Tumor invades adjacent structures (e.g., thyroid/cricoid cartilage, carotid artery, soft tissues of neck, prevertebral fascia/muscles, thyroid and/or esophagus)

Supraglottis

T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues
T4	Tumor extends through the thyroid cartilage, and/or extends into soft tissues of the neck, thyroid and/or esophagus

Glottis

T1	Tumor limited to vocal cord(s) (may involve anterior or posterior commissures) with normal mobility
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3	Tumor limited to the larynx with vocal cord fixation
T4	Tumor invades through thyroid cartilage and/or to other tissues beyond the larynx, e.g., trachea, soft tissues of neck, including thyroid, pharynx

Subglottis

T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation
T4	Tumor invades through cricoid or thyroid cartilage and/or extends to other tissues beyond the larynx (e.g., trachea, soft tissues of neck, including thyroid, esophagus)

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4	N0	M0
	T4	N1	M0
	Any T	N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Treatment:

The main objective of the treatment of squamous carcinoma of hypopharynx and larynx is to reach a balance between locoregional effective control of the carcinomatous disease and the preservation of the maximum functionality of the zone, the phonation and the swallowing, in order to preserve the highest possible quality of life (9).

The treatment depends on the tumour stage: early stages (I and II) or advanced stages (III and IV):

1. **Early stages:**

Early stages are usually treated with a single therapeutic modality, choosing between **microsurgery** with or without laser, or **radiotherapy** (RT). Both options have shown comparable results in locoregional control, larynx preservation and overall survival (OS). Thus, the election of the treatment will

depend on the characteristics of the tumour, the patient's factors and the patient's or doctors' preferences(1,10,11).

2. Advanced stages:

Treatment on stages III and IV is still controversial. Until 1990, the standard treatment was considered to be total laryngectomy, with the exception of irressecable tumours when the first option was chemoradiotherapy (CRT). Nowadays, two big branches of treatment exist: **Surgery** or **organ preservation therapy**(2,12).

2.1 Surgery plus radiotherapy:

The surgical option is based on the resection of the primary tumour associated with bilateral neck dissection if N+. Some studies conclude that approximately 59% of the patients receive total laryngectomy, 32% partial laryngectomy and, just a 9%, an isolated tumoural resection preserving the larynx and a part of its functionality. After 3-6 weeks of surgery, patients will receive conventional fractionated RT with a maximum dose of 60 Gy.

Moreover, if patients have high risk prognostic factors (positive surgical margins or affection in < 5mm, extracapsular extension, lymphatic dissemination…) they will receive concomitantly CT with cisplatin or 5-fluorouracil in a dose of 100 mg/m^2 on days 1, 22 and 43 after surgery(13,14).

2.2 Organ preservation therapy

The main aim of organ preservation therapy is to preserve the larynx function whenever a good locoregional control is reached. It has many options:

- **Fractionated conventional RT:** Irradiating the area of the primary tumour with a total dose of 70Gy, and all the cervical and supraclavicular lymph node with 50-60Gy.
- **Inductive CT plus adjuvant RT:** CT agents' protocols have been recently changed since taxanes have been studied in head and neck area and have shown a higher rate of total response (reduction of 100% of the tumour). Previously, the protocol was cisplatin plus 5-fluorouracil (PF), while now it is more common to use paclitaxel, cisplatin and 5-fluorouracil (TPF) for 3 cycles. Nevertheless, both treatments are still being used nowadays. After CT, if total or partial response of > 80% is observed, the treatment will carry on with adjuvant radiotherapy in a dose of 70Gy on the localization of the primary tumour and 50-60Gy on the cervical lymph node area, administering an irradiation of 2Gy weekly together with a dose of cisplatin or cetuximab. If minor or absent response, a rescue surgery together with a posterior RT will be considered.
- **CRT concomitant:** It consists of administering 3 CT cycles of cisplatin at days 1, 22 and 43; and RT in a dose of 70Gy on the localization of the primary tumour and 50-60Gy on the cervical lymph node area, administering an irradiation of 2Gy weekly. If a response of $\leq$ 80% is detected, a rescue surgery treatment together with a posterior RT will be considered (12–14).
- **Cetuximab:** Cetuximab is a new drug recently developed with the objective to inhibit specific molecular target. It is a quinmerac monoclonal

IgG1 antibody and has the epidermic growth factor receptor (EGFR) as target. Cetuximab gets bind to EFGR, blocking the union of endogenous ligands to this receptor and, consequently, inhibits its function(15).

Patients who received inductive CT and have presented sever toxicities or an important deterioration of their general status, cetuximab plus RT could be the first option of sequential treatment. It can also be used in concomitant CRT, substituting the place of RT in this protocol.

- **Surgery:** Surgical intervention will be kept as a second option. We will consider it if:
    - Presence of cervical lymph node $\geq$ 3cm or multiple lymph nodes on the initial stadiage, indicating a neck dissection. It will be carried out 8 weeks after finishing RT
    - There is a histologic confirmation of the persistence of tumoural disease post-treatment, absence of response after 2 cycles of CT or relapses. It will be an indication of rescue laryngectomy(12–14).

Some studies have shown that isolated conventional RT is the worst therapeutic option, due to lower larynx preservation, overall survival (OS) and disease-free survival (DFS) indexes compared to other therapeutic options. Comparing inductive CT (with PF protocol) followed by RT with concomitant CRT, similar data of OS, DFS and toxicity are found. Concomitant CRT is recommended as the first option because of its lower rates of treatment failures, better locoregional control and a significantly higher percentage of larynx preservation. It has to be taken into account that acute toxicity will be more severe because the toxicity of both CT and RT will appear together. Dysphagia to hard food

during the first 2 years after treatment will be present; however, no differences in phonation have been seen(12,16). Since taxanes have been introduced as TPF protocol of CT, other studies still consider inductive CT plus adjuvant RT as an option for treatment. They have shown a significant improve on response and organ preservation taxes, classifying it as the standard treatment. Other treatments as cetuximab in combination with RT have shown a better locoregional control and OS, than isolated conventional RT. No studies about the comparison between cetuximab plus RT and radical CRT have been performed yet(14).

2.3 Comparative of treatment:

Many studies have focused on analysing differences between the two main branches of the treatment, concluding that either surgical or organ preservation therapy show similar results in OS, locoregional control, metastasis appearance and RT toxicity (mostly dermatologic problems, nausea, vomiting, ototoxicity…) while differences in larynx preservation have been seen(2,13).

However, it's necessary to emphasize the importance of a multidisciplinary team in this field, constituted of radiologists, anatomopatologysts, oncologists and otorhinolaryngologists. This is because we have to evaluate multiple individual variables, of the patient or the tumour, in order to choose which one is the best therapeutic modality that will be adapted to the possibilities and the necessities of the patient(9,17). In hypopharynx and larynx carcinomas there are not irressecable criteria, so the decision will only depend on the

multidisciplinary team. We also have to consider the options of the institution, the surgeon experience and the evolution of reconstructive techniques(14).

Second Neoplasms:

During the last decades, there has been an improvement on locoregional control of head and neck squamous cell carcinoma, although it does not represent an improvement of the survival due to the appearance of second neoplasms or metastasis. In this case, it has been observed that a decrease of OS in 10 years from 55% in patients with good control of the disease, has turned to 22% in patients who have developed a second carcinoma(18).

If second neoplasms appear during the first 6 months of the diagnosis, they are considered to be synchronic; while the ones diagnosed after these 6 months are metachronic. 9-14% of the patients with head and neck carcinoma will present a synchronic second tumour, and 10-20% a metachronic neoplasm, mainly between 31 and 43 months from the diagnosis(2). Some studies have proven that the annual probability of developing a metachronic second neoplasm is about 4-6%, while patients that after the diagnose and treatment of the first neoplasm continue smoking present a risk 1,7 times higher, detecting a tobacco attributed incidence of 36-40%.

In 1953, Slaughter et al proposed the term of "***condemned mucosal syndrome***" indicating that the carcinogen effect of tobacco and alcohol which promoted the apparition of the first neoplasm, also act on the rest of the aerodigestive tract mucosa boosting the appearance of new neoplasms. This

fact supports more that alcohol and tobacco are important prognostic factors for head and neck squamous cell carcinomas(2,18).

The area most frequently affected by second neoplasms are head and neck or lungs, representing 42-70% and 5-26% respectively(2). Generally, when the index tumour is located on the hypopharynx, the main localization of the second neoplasm is digestive axis (hypopharynx or oesophagus); while in relation to the larynx, it usually appears on the respiratory axis (larynx or lungs). On all of these cases, second neoplasms have better prognosis if they are localized in head and neck area. This fact results in the 5-year survival index, being 49% if it is situated on head and neck, 15% on lungs and 0% on oesophagus(18).

3.1.2 High-resolution gadofosveset-enhanced AMR:

A new technique of angiography magnetic resonance (AMR) based on the usage of Gadolinium derived agents as contrast, is being used in multiple studies and even in clinical explorations at world level. It consists of the use of *Gadofosveset Trisodium* (Ablavar®) which is the first intravascular contrast agent approved on high-resolution AMR.

Gadofosveset has renal elimination and presents a high affinity for plasmatic albumin, providing a great angiographic ability. Secondly, it has a higher intravascular retention which allows us the possibility of administering it in lower doses than conventional Gadolinium, and also to perform the AMR images until 60 minutes post-administration. Characteristically it has a higher relaxation in T1(19,20). The relaxation, at AMR level, depends directly on the protein plasmatic concentration. In that way, any pathologic deviation of the protein concentration will be reflected as changes on the contrast enhancement of the AMR. For example(20,21):

So this contrast agent will represent an improvement on radiologic techniques in order to detect the quantity of proteins, mostly albumin, on the tissue. It will have utility in detecting vascularization which will be traduced into the image as a higher or lower enhancement, depending on the vascular changes that have

occurred. It also has a better contrast-to-noise, meaning a higher spatial resolution.

Gadofosveset has a good security profile for its administration as intravenous bolus with a dose of 0,03mmol/kg. Statistical significant differences between the adverse effects of *Gadofosveset* versus placebo have not been seen. However in 0.8% of the patients, symptoms of low-moderate intensity appeared, as for example:

- Nausea and vomiting
- Jaundice
- Cutaneous rash
- Limited cutaneous oedema
- Changes on blood pressure or cardiac frequency
- Flushing(19,22)

There are many diseases in which *Gadofosveset Trisodium* has demonstrated to be useful for diagnosing or treating as: atherosclerotic disease, aortic aneurisms/dissections, glioblastoma, multiple myeloma stenosis of renal artery, pulmonary embolism, deep venous thrombosis, vasculitis (Takayasu between others)… although it is just indicated for vasculopathies in order to evaluate the state of the vessels (20,21,23–25).

For example, in **glioblastomas**, the use of *Gadofosveset* as *"*off-label*",* allows for clinical physicians to determine the tumour vascularity. Knowing that hypervascularization in this tumour is a data of poor prognosis, they could correlate the AMR with poor survival and a higher grade of malignancy(25).

Otherwise, there are other studies that discard the use of *Gadofosveset*, as the one made about the response of locally advanced **rectal carcinoma** to CRT. It explains that this contrast agent is not useful to detect nodal staging and locoregional pathology, in order to know if the carcinoma has responded to CRT and to decide the type of surgery to perform(26).

3.1.3 Other tests on MRI:

There are also other tests that evaluate the vascularity of determined areas which are mainly used in the nervous central system:

- Perfusion-weighted imaging (PWI): Perfusion is physiologically defined as the steady-state delivery of blood to a tissue. It depends on blood volume and blood velocity which will affect the MRI.

  Thereby if the area is enhanced, it means that this zone is well perfused. After that we have to establish the washing time: if it is short, it will be traduced into a good connection between the vascularization and the possible presence of shunt arteriovenous; if it is large, it will imply a bad vascular net(27).

  The main role of PWI is to evaluate ischaemic conditions, neoplasms and neurodegenerative diseases.

- Diffusion-weighted imaging (DWI): Diffusion is the random motion of water molecules. DWI is a form of MRI based on measuring this movement in a tissue. The relationship between histology and diffusion is complex, however generally we detect lower diffusion coefficients in tissues with high density of cells or those with cellular swelling. In this

case, it will be represented on the image by an enhancement because the diffusion is being restricted. It is particularly useful in tumours and ischaemia(28,29).

3.2 Justification:

Referring to squamous cell carcinomas of hypopharynx and larynx, data show that **hypoxia** is a factor of poor prognosis. The rapid proliferation of malignant cells results in the formation of hypoxic areas within the solid tumour. The cells of those areas will activate protective mechanisms as migration to other areas to survive in adverse conditions. So hypoxia is known to be one of the critical characteristics of the tumour microenvironment that will profoundly affect invasion, metastasis and the response to treatment.

It is known that hypoxia up-regulate the expression of hypoxia-inducible factor-1 (HIF-1) which is involved in regulating the transcription of various target genes in response to hypoxia. Some studies have shown that an overexpression of HIF-1 plays an important role in tumour invasion, metastasis, angiogenesis and resistance to CT. Specifically in larynx, hypoxia also induces an epithelial-mesenchymal transition (EMT) phenotype and it leads to changes on the expression of EMT-related proteins (Vimentin, E-Cadherin and N-Cadherin). Less concentration of oxygen produce an increase in N-Cadherin and Vimentin, and a decrease in E-Cadherin that will modulate cell invasion and migration of the tumour(30).

Recent data indicate the possibility that hypoxia interferes on RT and CT because it reduces the tissue sensibility to these therapies, difficult the drug access and induces tolerance(31).

Nowadays, one of the main challenges of the medicine is to eradicate tumoural pathology, preserving as much as possible the patient's life quality. In locally

advanced squamous cell carcinomas of hypopharynx and larynx it has been seen that there is still controversy about the election of the treatment, and it is usually planned among all the multidisciplinary team. The two main branches of treatment are surgery ahead of CRT. Knowing that hypoxia leads to a major proportion of invasion and metastasis, and less response to CT and RT, it could be interesting to measure the grade of the lack of oxygen in order to help with the treatment election. Also, it is important to take into account the loss of quality of life that a total laryngectomy may produce when the patient would have responded to CRT; and the difficulties that the surgeon will have if he has to operate an irradiated area for a rescue surgery.

Evaluating data obtained from many studies, the suggestion would be using a high-resolution gadofosveset-enhanced AMR as an image technique with prognostic finality in squamous cell carcinomas of hypopharynx and larynx. This AMR will help us to detect the presence or the absence of tumour vascularization and, secondarily, estimate the grade of hypoxia. Moreover, we could introduce PWI and DWI techniques in order to estimate the vascular pattern of the tumour. In that way, we could analyse in detail tumour characteristics in order to guide us in the election for the best treatment for each patient in locally advanced carcinomas.

4. HYPOTHESIS:

Primary hypothesis:

Patients diagnosed of locally advanced squamous cell carcinoma of hypopharynx or larynx with a hypervascular pattern of gadofosveset-enhanced high-resolution AMR, indicating a low grade of exposition to hypoxia, have better radiologic response to CRT.

Secondary hypothesis:

- Patients diagnosed of locally advanced squamous cell carcinoma of hypopharynx or larynx with a hypervascular pattern of gadofosveset-enhanced high-resolution MRA have also a better clinical response to CRT.
- Patients diagnosed of locally advanced squamous cell carcinoma of hypopharynx or larynx with a hypervascular pattern of gadofosveset-enhanced high-resolution MRA have a higher index of OS and DFS.
- Patterns of gadofosveset-enhanced high-resolution MRA are predictive factors for inductive chemotherapy.

5. OBJECTIVE:

Primary objective:

The aim of this study is to analyse whether there is an association between the pattern of gadofosveset-enhanced high-resolution ARM, indicating higher or lower exposure to hypoxia, and the response to CRT of patients with locally advanced squamous cell carcinoma of hypopharynx and larynx. It will be evaluated by radiologic and clinical markers, and rates of OS and DFS.

Secondary objectives:

Other objectives of the study are:

- To evaluate the presence of gadofosveset-enhanced high-resolution ARM patterns that could modify organ preservation protocols.
- To analyse if ARM patterns could act as a predictive factor for evaluating the response to inductive chemotherapy.

6. MATERIALS AND METHODS:

a) Study design:

A prospective cohort study will be performed at the Functional Unity of Head and Neck Tumours (FUHNT) of Hospital Universitari de Girona Doctor Josep Trueta, in a 9.5 years period. It is a prospective longitudinal observational study.

b) Population:

The study population include adult patients with hypopharynx or larynx carcinoma, undergoing to diagnose-treatment manage at the FUHNT of Hospital Universitari de Girona Doctor Josep Trueta.

Inclusion criteria:

- ≥ 18 years of age
- Locally advanced tumour: Stages III and IV
- Squamous cell carcinoma type
- Indication of CRT treatment
- Patient's informed consent

Exclusion criteria:

- Indication of others treatments based on surgery or radiotherapy
- Usage of monoclonal antibodies as the chemotherapic agent (mainly cetuximab)
- Previous radiotherapy on the area
- RMN contraindications

- Immunosuppressed patients or receiving immunosuppressive treatment
- Presence of metastasis

c) Sample:

According to data recollected from Registre Hospitalari del Càncer de Girona, there has been detected 93 new cases of squamous cell carcinoma of hypopharynx or larynx from January of 2013 to September of 2016 in the province of Girona. Analysing it, we determine a mortality rate of 42.86% at 2-3 years from the diagnosis. Also we detect the differences shown in some studies between genders, observing a men-women ratio of 9:1.

In our study we restrict the population to patients with squamous cell carcinoma of hypopharynx or larynx that are on stages III or IV. In this register we find that 92.47% of the patients diagnosed of this type of cancer belong to stage III or IV, suggesting a backward diagnose when the tumour is already extended. As we explained previously, there is a large range of possibilities for treating the carcinoma and 37,21% of locally advanced tumours of this data has been treated with CRT, in front of 15,21% of patients treated with surgery plus RT, as the most used therapies. Other patients were treated with other treatments: RT, CT, surgery, refused treating…(32).

Sample selection:

A **consecutive non-probabilistic sampling** will be carried-out in patients undergoing to diagnose-treatment manage of larynx and hypopharynx

carcinoma, meeting the inclusion and exclusion criteria. Patients will be approached when they have the final diagnose of the neoplasm in the FUHNT of Hospital Universitari de Girona Doctor Josep Trueta, and we propose CRT as the first option of treatment.

All of the patients will be informed about the study and invited to participate voluntarily if they are interested. They will receive a document with all the information explaining what entering to this study involves (Annex 3), and the informed consent (Annex 4) that has to be signed if they are willing to participate.

Sample size:

The sample size of this cohort study has been calculated with GRANMO application. Due to the lack of information about the results of high-resolution ARM with gadofosveset in hypopharynx and larynx carcinoma and its response to CRT measured by clinic and radiologic response, we took into consideration that we will see a total response in 40% of the patients with a hypovascular pattern (conforming group 1), and in 70% of the ones with hypervascular pattern (conforming group 2), regarding to the results of some studies that show the absolute reduction of total laryngectomies due to CRT treatment.

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, **37 subjects** are necessary in the first group and **74 subjects** in the second one to detect as statistically significant a proportion difference, expected to be of 0,4 in group 1 and 0,7 in group 2. It has been anticipated a drop-out rate of 15% due to patients that will stop the treatment because of its toxicity, deaths or losses

during the following as changes of residence. It has been used ARCSINUS approximation.

d) Variables and measurement methods:

Independent variable

The independent variable is the vascular pattern of the hypopharynx and larynx carcinoma detected by gadofosveset-enhanced high-resolution ARM. Radiologists will evaluate the ARM images for the presence of tumour-associated neovascularization, classifying neoplasms as hypovascular or hypervascular, depending on whether vessels were detected.

After the diagnosis of locally advanced squamous cell carcinoma of hypopharynx or larynx, patients will have to sign an informed consent in order to perform the gadofosveset-enhanced high-resolution ARM (Annex 5). An amount corresponding to 0.03 mmol/kg body weight of gadofosveset will be administered, and after 5 minutes we will take 3D high-resolution contrast-enhanced MRA images of the entire head and neck area. It will be performed using a multishot spoiled turbo fast field echo sequence.

The image will be analysed by two expert radiologists in order to determine the presence of tumour-associated neovascularization. As there is a lack of information about the use of this type of ARM in hypopharynx and larynx cancer, the study based on the use of high-resolution gadofosveset-enhanced ARM in glioblastomas, stablishing a limit of three vessels, will be taken into consideration. Tumours with three or less vessels are classified as

hypovascular, while ones with more than three vessels are classified as hypervascular (Annex 6). Readers will have to reach a consensus before the final analysis, if there is any discordant classification(25).

Thereby we will define two groups depending on the results: hypovascular or hypervascular carcinomas. So, it is a dichotomic, nominal and qualitative variable.

Dependent variable

1. ***Primary endpoint:***

Efficacy of CRT measured by radiologic response, classifying it as: complete response, partial response, stabilization of the disease or progression.

After the treatment with CRT, patients will have to be followed in a stretched way in order to detect any change in the carcinoma. From eight to twelve weeks after finishing radiotherapy treatment, an image technique will be performed. It has to be the same as used initially to diagnose the tumour, mostly computed tomography (TC) or magnetic resonance (MRI).

The image will be analysed by two expert radiologists that have to be different to those that classified the carcinoma as hypervascular or hypovascular. That way, the analysis of the TC or MRI will be blind and any any information bias that could appear will be avoided. These experts will have to evaluate the radiologic response of the tumour in front of CRT treatment following RECIST 1.1 criteria. The response to treatment will be measured by image biomarkers which, in solid carcinomas, are based on size changes occurred before and

after the treatment. They are measured by differences between maximum diameters of the lesion or the sum of the maximum diameters of multiple lesions.

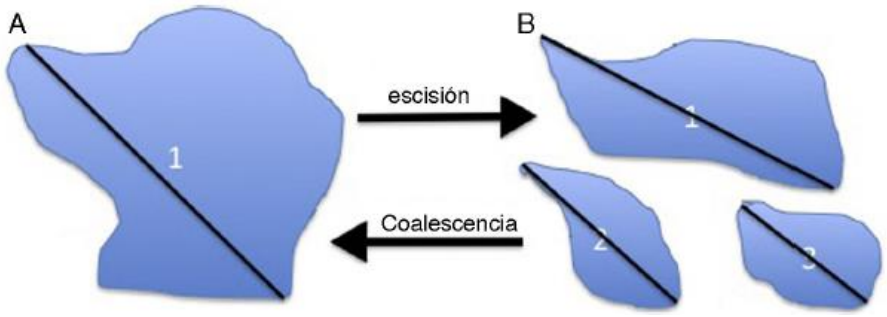

Image 3. How to measure the lesion, based on RECIST criteria(33)

During the 90s, the criteria universally used were OMS ones, evolving to RECIST in 2000 which have been updated in 2009 as RECIST 1.1. It has been shown that RECIST 1.1 criteria are the easiest, the fastest and the most reliable method to evaluate the tumour size, despide its limitations. It includes the evaluation of the size of ≥ 10mm injuries measured with TC, MRI or positron emission tomography (PET), although it does not contemplate density changes of the lesion or tumours in areas that have been irradiated previously. Therefore the next step in order to advance into the field of radiologic biomarkers would be to include:

- Morphologic parameters: Important for differentiating solid, cystic and necrotic components of the tumours.
- Functional parameters: For determining the functionality of the lesion, evaluated through perfusion or diffusion.

First of all, the target lesion that we want to follow has to be defined in order to apply RECIST 1.1 criteria, taking into account the variability or the difficulties of measurement that may appear during the process. Afterwards, radiologists will evaluate the present images comparing them with the ones at the diagnostic moment, and classifying the response as:

- **Complete response (CR):** Disappearance of 100% of valuable and measurable disease, without the appearance of new injuries for $\geq$ 4 weeks.
- **Partial response (PR):** Reduction of $\geq$ 30% of the sum of the diameters of the target lesion.
- **Disease progression (DP):** Increase of $\geq$ 20% of the lesion with one of the next characteristics:
  - Absolut increase of $\geq$ 5mm of the sum of the diameters of the target lesion
  - New metastasis
  - Progression of no-target injuries
- **Stable disease (SD):** When there is not enough reduction or increase for classifying it as PR or DP, respectively(33).

After the initial response evaluation, the measurement of the disease evolution will continue for the next 5 years.

It is an ordinal qualitative variable.

2. Secondary endpoints:

1. Efficacy of CRT measured by clinical response, classifying it as: complete response, partial response, stable disease or progression.

   From eight to twelve weeks after finishing radiotherapy treatment, as the tumour response on image techniques is evaluated, a clinical evaluation of the patients will also be carried out. The clinical response will be evaluated by two clinical physicians who will not know the results of the high-resolution gadofosveset-enhanced ARM, in order to have another blind assessment.

   It will consist of the clinical history and a physical examination.

   - **Clinical history:** The main symptoms on the area will be checked: dysphonia, dysphagia, odynophagia, coughing, hawking, foreign body sensation… The patient will also be enquired about any clinical evolution.
   - **Physical examination:** Clinical examiners will palpate cervical lymph nodes in order to evaluate if there are any new or remaining adenopathies on the area. Also, they will carry out an endoscopy with the purpose of reviewing pharynx and larynx structures in order to evaluate, from a direct image, the evolution of the carcinoma.

   Recollecting all of these data, we will classify clinical response in:

   - **CR:** Absence of symptoms and disappearance of 100% of the disease measured by endoscopy, without the appearance of new injuries for $\geq$ 4 weeks.

- **PR:** Persistent symptoms with persistent structural changes of the primary lesion as well resulting in a reduction of its size, decreasing the commitment with neighbouring structures.
- **SD:** Absence of any clinical or endoscopy improvement.
- **DP:** Persistence or increment on the symptoms associated with an increase of the size or invasion of the tumour

2. Measurement of overall survival (OS) and disease-free survival (DFS) in patients with locally advanced squamous cell carcinoma of hypopharynx and larynx, treated with CRT.

   As patients are monitored and followed up for evaluating the radiologic and clinical response, the mortality rate and the recurrences can also be evaluated. So, with these data, OS and DFS in the first year and in 5 years can be worked out.

3. Efficacy of inductive chemotherapy (CT) measured by radiologic and clinical response, before treating the patient with radiotherapy. After a month of ending inductive CT, it is important to evaluate if this therapy have worked correctly. An image technique (TC or MRI, depending on the one used for the initial diagnosis) will be performed, and RECIST 1.1 criteria will be followed for evaluating the lesion. We will classify the response in:

   - **CR:** Disappearance of 100%, or clinical absence of the disease
   - **PR:** Evaluated with a reduction of $\geq$ 50% in the 2nd cycle of CT or $\geq$ 80% in the 3rd cycle. Clinically, we will see a decrease of the symptoms accompanied with an important reduction of the objectified lesion.

- **SD:** When there is not enough reduction for classifying it as PR.
- **DP:** There is a clear evidence of a disease's progression (Annex 2).

Potential covariables

- **Patient-related covariates:** Tobacco and alcohol.
  - Tobacco: Tobacco is a risk factor to develop a primary hypopharynx and larynx carcinoma, but some studies prove that people who continue smoking after finishing the treatment have also more possibilities to relapse. For that reason, it can interfere into the evaluation of the response of the tumour to the treatment. It is evaluated with packages/year index which indirectly indicates the risk of smoking:

$$\frac{\text{(Number of cigarrets / day) x years smoking}}{20}$$

    The result is classified as:
    - Low risk $\leq$ 20
    - Moderate risk = 21 – 40
    - High risk $\geq$ 41
  - Alcohol consumption: As tobacco, it is also a risk factor for developing either primary carcinomas or relapses. It is considered if the consumption is greater than 25-30g.
- **Disease-related covariates:** Tumour Volume
  - Tumour Volume: It is known that the volume of the tumour can interfere in the prognosis of the pathology, so it can also be related with the vascular pattern of the carcinoma. It will be calculated with

the formula: $V = 3\pi R$. Staging these types of tumours, we know that data about the size of the primary lesion that change the T classification are 3 cm and 6 cm. So, we catch as radius 1,5 cm and 3 cm, respectively, getting volumes about 14 cm^3 and 28 cm^3. Thus we will classify volume of the tumour in three groups: small < 14 cm^3, mild = 14 - 28 cm^3 and large > 28 cm^3.

- **Treatment-related covariates:** Different types of chemotherapic agents and protocols of administration could interfere to the tumoural response. We will consider two groups of treatment:
    - Inductive TPF chemotherapy during 3 cycles plus adjuvant RT
    - Concomitant CRT with Cisplatin during 3 cycles

e) Data collection and study circuit:

Baseline visit:

Each patient diagnosed of locally advanced squamous cell carcinoma of hypopharynx and larynx that meet inclusion and exclusion criteria, will be informed about the existence of this study. All the patients that sign the informed consent (Annex 4) will be included in the study composing the sample, as we do a consecutive sampling. Demographic and clinical data of all of them will be obtained using a Case Report Form (Annex 7) and will be entered in the study's electronic database. It will be carried out by two expert physicians of head and neck area, and all data will be entered to the database by the data manager.

We will schedule a date to perform high-resolution gadofosveset-enhaced AMR, as soon as the patient signed the informed consent for the realization of the technique (Annex 5), in order to determine the presence of tumour-associated neovascularization. The image will be analysed by two expert radiologists with the purpose of classifying the tumour as hypervascular or hypovascular.

Next visits:

2-4 weeks after classifying the carcinoma, we will start the treatment with CRT. The patient will be followed by an oncologist that needs to plan and adapt the CRT protocol to the patient. They will be treated during 6-8 weeks, depending on the use of inductive CT, and then we will start to study the disease evolution after the treatment. There are two options of treatment:

- Inductive TPF chemotherapy protocol will be administrated during 3 cycles, in days 1, 22 and 43. A month after finishing CT we will evaluate the response: if the patient presents a CR or a PR of $\geq$ 80%, we will continue the scheme of treatment, starting RT with a dose of 70Gy on the localization of the primary tumour and 60Gy on the cervical lymph node area, administering an irradiation of 2Gy weekly together with a dose of cisplatin or cetuximab; if the response is < 80%, the option is surgery plus adjuvant RT.

- Concomitant CRT protocol is usually selected when the patient refuses surgery. It consists of administering 3 cycles of CT in days 1, 22 and 43, based on cisplatin, associated with RT administrated with the same scheme as the previous protocol of treatment.

8-12 weeks since the patient has finished RT, we will start the following. Each visit, taken by the two physicians, will consist on:

- **Clinical history:** Asking for the main symptoms on the area (dysphonia, dysphagia, coughing…) and enquiring about the possible evolution of them.
- **Physical exploration and endoscopy:** Cervical lymph node palpation associated with an intensive exploration of the oral cavity, nose, pharynx and larynx. It is important to detect any possible relapses or the remanence of strange lesions on the area.
- **Image technique** (TC or MRI, depending on the one that was used to diagnose the patient), in order to detect the response to the treatment and control its evolution. It must be evaluated by two radiologists who have to be different from the ones who evaluated the high-resolution gadofosveset-enhanced AMR.

We will perform this protocol at 8-12 weeks, 6 months, 12 months, 18 months and 24 months. After that, the following will be carried out once a year: 36 months, 48 months and 60 months. With those techniques, we will confirm mainly the radiologic response, but also clinical response, of the disease in front of the treatment and the possible remanence or relapses during 5 years.

In order to detect deaths or losses during the following, the hospital register will analyse:

- Deceased patients: Evaluated from the hospital register

- Theoretical alive patients: Patients that we do not have classified as death but they have already deceased. It depends on deaths that have occurred on the hospital and the death national index (DNI). Thereby, we will do an analysis in order to detect if there is a match between the patients into the study and the ones who died in the hospital or who are into the DNI.

- Activity on the healthcare system: We will determine if the patient is alive through the health activity during the 5 year following-up. The patient will have a minimum sanitary following during those 5 years, and this activity will be written in his clinical history. So, patients who have not had any visit during those 5 years and who are not deceased will be classified as losses during the following. These patients will be analysed as:
    - Diagnosis data plus 1 month
    - Last control data plus 1 month

7. STATISTICAL ANALYSIS:

Descriptive – Univariate Analysis:

The independent variable is the pattern of high-resolution gadofosveset-enhanced AMR, defined as hypervascular or hypovascular. So, it will be considered a nominal dichotomic qualitative variable. Interobserver agreement for vascular pattern was assessed using Kappa statistics being acceptable values ≥ 0.7

The outcomes, as radiologic response to CRT, will be statistically treated as ordinal qualitative/categorical variables, because of its possible results: CR, PR, SD or DP. Clinical response will be considered the same type of variable; while OS and DFS will be treated as continuous quantitative variables.

Qualitative or categorical variables will express the results as percentages. Quantitative variables, assuming that they are not normally distributed, will estimate median. In the case that they follow a normal distribution, arithmetic mean and typical deviation will be calculated.

The potential covariates must be statistically analysed too. Categorical ones will be expressed as relative frequencies. We do not have any quantitative variables (Annex 8).

Bivariate Analysis:

In the bivariate analysis of study outcomes, we will compare relative frequencies of radiologic (primary endpoint) and clinical (secondary endpoint)

response, during 5-year following, with the pattern of AMR using X_2 test (Annex 8).

As it is a cohort prospective study, we will have to calculate RR of hypovascular pattern in front of hypervascular one for the absence of complete response to CRT. Depending on its result:

RR > 1	Hypovascular pattern is a risk factor compared with hypervascular one
RR = 1	There is no association between the vascular pattern and the response to CRT
RR < 1	Hypovascular pattern is a protective factor compared with hypervascular one

We will also analyse OS and DFS in the 1st and 5th year after the treatment, looking for any association with the AMR pattern. It will be analysed in isolation by Kaplan-Meier method, dividing the survival in two groups: the patients with hypervascular pattern and the ones with hypovascular pattern. Then we will compare the curves of the graphics by log-rank test, in order to determinate if the OS and DFS have the same tendency inside of each group and afterwards, comparing both groups (Annex 8).

We will also perform a base-line characteristics table in order to evaluate possible influences of the potential covariables, between hypervascular and hypovascular group. We will use X_2 test for those categorical variables. The same bivariate analysis will be performed for each potential covariate and the disease's response groups (Annex 8).

Multivariate Analysis:

The analysis will have to be adjusted for those covariates that have been studied in the previous analysis, and have already shown a significant statistical difference (considered with $p < 0.05$). For that reason, we will perform a logistic regression analysis in order to adjust the study to potential confounding factors.

Statistical analysis will be performed using SPSS for Windows.

8. ETHICAL CONSIDERATIONS:

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*". 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 and health products and "*Ley 14/2007 por procedimientos invasivos*".

The research protocol will be presented to *Comissió d'Ètica per la Investigació Mèdica* (CEIC) of the Hospital Universitari de Girona Doctor Josep Trueta, for receiving its authorization before the study is initiated. CEIC will also have to approve the final report, at the end of the study. The protocol also has to be approved by the AEMPS.

According to "*Ley Orgánica 15/1999, de 13 de Diciembre, de Protección de Datos de Carácter Personal*", personal and clinical information will be strictly confidential and will just be used for the purpose of the research. To maintain confidentiality, all of the patients will have an identification number that will be included in the case data report for analyzing the information in an anonymous way. Data will only be accessible for the responsible researchers of the project. However, any patient information will be used without his previous consent. During the first visit, we will explain all the information of the study and its purposes to each patient. We will bring them an information sheet (Annex 3) and they will be invited to sign the informed consent (Annex 4) if they agree,

according to "*Ley Orgánica 41/2002, de 14 de Noviembre, de Autonomía del Paciente y de Derechos y Obligaciones en Materia de Información y Documentación Clínica*".

Participants of the study have the right to access and remove their personal data from the database of the research protocol whenever they want.

The authors declare that they do not have any conflict of interest.

9. LIMITATIONS OF THE STUDY:

Analysing the study, we detect and take into consideration the presence of some limitations that may interfere into the research. They are the following ones:

- It is a prospective cohort study, defined as observational, and one of the main limitations of this type of studies is the large duration of it, in our case 9.5 years. This amount of time causes a high proportion of losses during the following which may alter the results of the study. The cost of our study is not much higher because, despite of the large duration, all of the image techniques are included in the usual following of these types of patients.
- It is planned to be a single-centre study and consequently the patient's sample will be too small to draw any definitive conclusions about the usefulness of our findings for patient management, and it will take us 4.5 years to meet all of the sample. Also it may interfere on the external validity, because we don't know if the patients of Girona province are a representative sample comparing it with patients from other areas. Therefore, if significant differences on radiologic or clinical response are found between the two radiologic patterns, a next study with a larger sample will be necessary to validate our findings and get definitive conclusions.
- High-resolution gadofosveset-enhanced AMR is not included in routine clinical protocols, so patients will require further image studies apart the ones necessary for the diagnosis. Also, the AMR pattern

identified by radiologists won't be correlated with the findings in a histologic or molecular level, to assess the tumour-associated neovascularization.

- In order to avoid any information bias, we used blinding techniques. Radiologists and clinical physicians that evaluate the patient's response after the treatment with CRT won't know the AMR vascular pattern of the tumour. The interobserver variability in the assessment of radiologic lesions or clinical symptoms and signs will be avoided by demanding to radiologists and physicians a unified opinion, after the required discussion.

10. WORK PLAN AND STUDY CHRONOGRAM:

The whole cohort study will be carried out during 10 years and 11 months, and will be organized in 5 phases which are the following ones:

1. **COORDINATION PHASE (5 months):**
   - 1.1. 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, propose objectives and hypothesis, selection of the participating hospitals…
   - 1.2. 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.
   - 1.3. Final project design and redaction
   - 1.4. CEIC revision and approval: Protocol will be given to the CEIC for its revision and approval.
   - 1.5. 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 this information.
2. **PATIENT'S INCLUSION, EVALUATION AND DATA COLLECTION PHASE (9.5 years):**
   - 2.1. Subject's recruitment: During the first 4.5 years, patients who meet the inclusion and exclusion criteria will be recruited as the sample of our

study. We have to facilitate the information sheet (Annex 3) and the informed consent (Annex 4) to the patients before including them into the study.

2.2. Subject's evaluation: This period will start at the same time as patient's recruitment, and will finish 5 years from the inclusion of the last participant. Therefore, each patient will be followed during 5 years.

2.3. Data collection: All data recollected from the patient's during the following, will be gathered in a standardized case report sheet (Annex 7) and will be entered to 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 with the end of the following of the last patient.

2.4. 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 PHASE (4 months):

3.1. Statistical analysis monitoring: In order to control the progress of the study, statisticians will perform three statistical analyses along the 9.5 years of the previous phase (1 month/each).

3.2. Final data analysis: After collecting all data, statisticians will proceed to analyze it and to perform a final statistical analysis.

4. RESULTS AND FINAL REPORT WRITING PHASE (6 months):

4.1. Interpretation of the results: Investigators will analyze and discuss the final results in order to elaborate definitive conclusions.

4.2. Final report elaboration

5. PUBLICATION AND DISSEMINATION PHASE (6 months):

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

5.2. Dissemination of the report: The report will be disseminated to congresses, meetings, conferences, scientific journals…

STUDY CHRONOGRAM

YEAR	2016					2017	2018	2019	2020	2021	2022	2023	2024	2025	2026				2027		
Month of the year	A	S	O	N	D										J -J	J A	S O	N D	J F	M A	M J
ACTIVITY																					
1. Coordination																					
Study setting-up																					
First informative meeting																					
Final project design and redaction																					
CEIC revision and approval																					
Second informative meeting																					
2. Patient's inclusion, evaluation and data collection																					
Subjects' recruitment																					
Subjects' evaluation																					
Data collection																					
Face-to-face meetings																					
3. Data analysis																					
Statistical analysis monitoring																					
Final data analysis																					
4. Results and final report writing																					
Interpretation of the results																					
Final report elaboration																					
5. Publication and dissemination																					
Publication of the results																					
Meetings, conferences, congresses…																					

11. BUDGET:

ITEM	UNIT COST (€)	UNITS / HOURS	TOTAL COST (€)
STAFF			
Statistician	35€/hour	80 hours	2.800,00€
Data manager	40€/hour	30 hours	1.200,00€
IMAGING TECHNIQUES			
High-resolution gadofosveset-enhanced AMR + radiologic evaluation	150€ Gadofosveset 330€ AMR 20€ evaluation	111 units	55.500,00€
STUDY INSURANCE			
Risk of *Gadofosveset* injection			2.500,00€
PUBLICATION AND DIFFUSION COSTS			
Article publication charges			1.500,00€
Meetings, conferences and congresses: - Inscriptions - Transport - Food and miscellanea	 360,00€ 85,00€ 200,00€	2 physicians x 2 meetings /congresses	2.580,00€
PRINTING			
Information sheet, informed consent and case report form printing	0,25€	350 units	87,50€
		TOTAL	**66.167,50€**

Otorhinolaryngologists and radiologists are part of the FUHNT of Hospital Universitari de Girona Doctor Josep Trueta, so the added cost will be just the extra hours that they would have to do.

It also happens with the imaging techniques, because direct laryngoscopies and TC / MRI are the tests used during the normal following of those patients during 5 years.

Face-to-face meetings performed during the study will not suppose an additional expense, because each week, all the FUHNT gets reunited on the committee and we can take this meeting as a suitable moment to motivate the participants, once a year.

12. FEASIBILITY:

All of the carcinomas of the otorhinolaryngologic area detected in the province of Girona, have as a reference centre the Hospital Universitari de Girona Doctor Josep Trueta, being intended to FUHNT. According to data recollected from Registre Hospitalari del Càncer de Girona, from January of 2013 to September of 2016 there has been detected 93 new cases of squamous cell carcinoma of hypopharynx or larynx. Knowing that 92.47% of the patients diagnosed of this type of cancer belong to stage III or IV, we realize that we need approximately 4.5 years for the recruitment period, in order to achieve the number of 111 patients required.

Moreover Hospital Universitari de Girona Doctor Josep Trueta is totally equipped medically and technologically to accomplish the objectives of the study.

For all the data mentioned above, this protocol is feasible to be brought out in our province, regarding availability of the sample, the professionals and the imaging techniques.

13. CLINICAL AND HEALTHCARE IMPACT:

Hypopharynx and especially larynx carcinomas are ones of the most incident tumours of head and neck area. They are usually diagnosed in locally advanced stages (2/3 parts in stages III or IV, without metastasis), so the controversy about the treatment is one of the main discussed items in these type of patients. The two main therapies are based on surgery plus RT or CRT, and election is chosen according to the final discussion of the multidisciplinary team.

The present study would provide better knowledge about the intrinsic characteristics of the tumour in order to guide us during the treatment election process. Determining the vascular pattern of the tumour, we could predict the response to CRT. Thereby, it could be an important point for considering CRT as the first option of treatment or directly purpose to the patient the surgical option. In that way we avoid all the secondary effects of CRT that could influence to the patient's quality of life and the bad quality of the irradiated tissue if surgeons will have to perform a rescue surgery. Also it will be traduced into a decrease of the cost of the hypopharynx and larynx carcinoma's treatment, mostly in patients who need a rescue therapy.

In summary, results obtained in this study could be implemented into the daily clinical practice triggering a great clinical impact for the treatment process of locally advanced carcinomas of hypopharynx and larynx.

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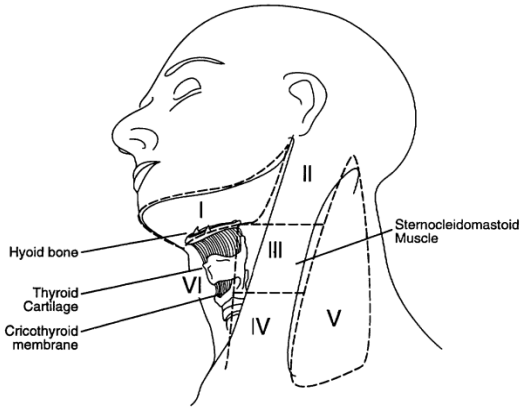
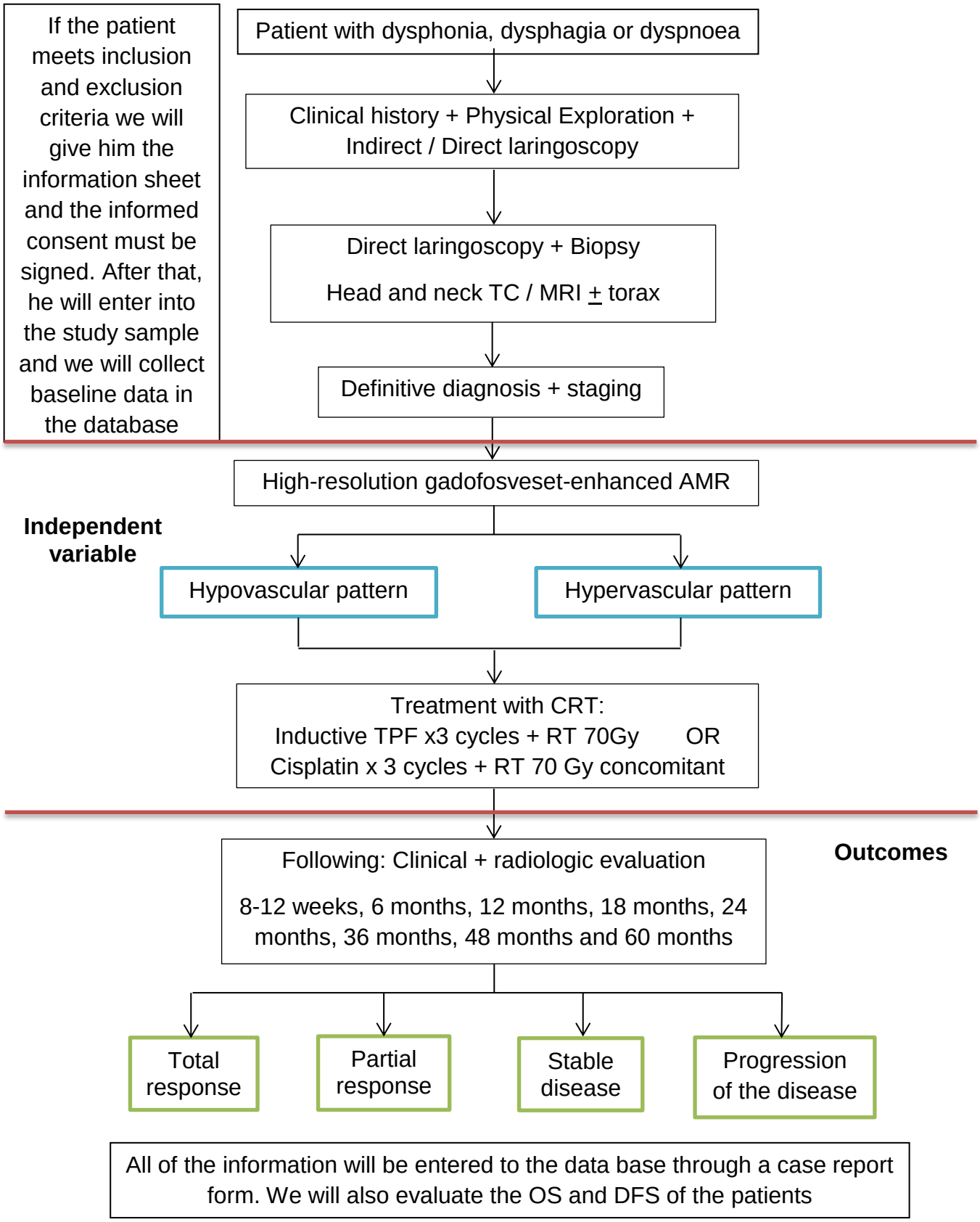
15. ANNEXES:

Annex 1. Areas of cervical lymph node drainage(7)



Level	Anatomic Name	Key Borders and Landmarks	Primary Drainage Site
I	IA = submental; IB = submandibular	Hyoid bone	Anterior oral cavity, lip, sinonasal
		Posterior margin of submandibular gland	
		IA or IB—anterior belly of digastric muscle	
II	Anterior cervical or upper jugular	Inferior margin of hyoid	Oropharynx, posterior oral cavity, supraglottic larynx, parotid gland
		Posterior margin of submandibular gland	
		Posterior margin of sternocleidomastoid	
		IIA or IIB—posterior margin of internal jugular vein	
III	Middle jugular	Inferior margin of hyoid	Glottic, subglottic, and hypopharyngeal regions
		Inferior margin of cricoid	
IV	Lower jugular	Inferior margin of cricoid	Subglottic, thyroid, and cervical esophagus
		Clavicle	
V	Posterior compartment or spinal accessory	Posterior border of sternocleidomastoid	Nasopharynx; skin carcinomas of the neck or occipital scalp
		Clavicle	
		VA or VB—inferior margin of cricoid	
VI	Visceral or central compartment	Medial margins of carotid arteries	Subglottic; thyroid and cervical esophagus
		Inferior margin of hyoid	
		Superior aspect of manubrium	
VII	Superior mediastinal	Superior aspect of manubrium	Subglottic; thyroid and cervical esophagus
		Innominate vein	
	Retropharyngeal	Medial margin of internal carotid arteries to the level of hyoid	Nasopharynx, oral cavity, sinonasal, thyroid, and pharyngeal and laryngeal tumors with posterior wall involvement
	Parotid	Within parotid gland	Skin of scalp, orbit, nasopharynx
	Supraclavicular fossa[a]	On axial images at or below the clavicle, lateral to the medial edge of the common carotid artery, and medial to clavicle; includes some level IV and V nodes	Any head and neck cancer and cancers of the thorax and abdomen, including lung, breast, esophageal, gastric, pancreatic, gynecologic, and prostate cancers

Annex 2. Study flow chart



Annex 3. Information sheet

HOJA DE INFORMACIÓN AL PACIENTE:

Predicción de la respuesta a quimioradioterapia en carcinomas de hipofaringe y laringe, a través de angiografías por resonancia magnética de alta resolución

Cohorte prospectivo monocéntrico sobre el uso del *Gadofosveset trisódico* como agente de contraste para las angiografías por resonancia magnética de alta resolución, y según su patrón radiológico poder predecir la respuesta tumoral al tratamiento con quimioradioterapia.

Código del promotor:

Promotor:

Investigadores principales:

Centro:

Nos dirigimos a usted para informarle sobre el estudio de investigación al que se le invita a participar. Este estudio ha sido aprobado por el Comité Ético de Investigación Clínica (CEIC) de este hospital i la Agencia Española del Medicamento y Productos Sanitarios (AEMPS), en cumplimieto con la legislación vigente, el "*Real Decreto 1090/2015, de 24 de Julio*", para el uso racional de medicamentos y productos sanitarios.

Antes de que se decida acerca de su participación en este estudio, es importante que reciba y comprenda correctamente la información contenida en este documento. Por ello es necesario que se tome su tiempo y lea detenidamente la siguiente información, que puede consultar con las personas que considere oportunas. Su médico le aclarará todas las dudas que puedan surgirle tras la explicación.

Condiciones de participación:

Su participación en este estudio es totalmente voluntaria y puede decidir no participar o retirarse del mismo en cualquier momento, sin dar ninguna explicación. Esta decisión nunca afectará a sus derechos legales y éticos a recibir tratamiento: usted continuará recibiendo el tratamiento más adecuado para su enfermedad.

No obstante, si usted decide retirarse de este estudio, es importante que informe a su médico. De igual forma, su médico puede decidir retirarle del estudio en caso de no cumplir con el protocolo que se establece.

Descripción del estudio:

a) Objetivos del estudio

Se le ha ofrecido participar en este estudio porque padece de un carcinoma escamoso localmente avanzado de hipofaringe o laringe y se le ha propuesto como primera opción de tratamiento la quimioradioterapia.

Este estudio tiene como objetivo valorar si hay asociación entre el patrón radiológico obtenido a través de una angiografía por resonancia magnética de alta resolución con *Gadofosveset trisódico* y la respuesta tumoral a quimioradioterapia, evaluada a través de varios parámetros: respuesta clínica, respuesta radiológica y supervivencia (global y libre de enfermedad). Su utilidad erradica en la dificultad para elegir un tratamiento en este tipo de tumores, ya que la decisión final, actualmente, se basa en el acuerdo que llega el comité multidisciplinario de tumores.

b) Procedimientos del estudio

Se prevé la participación de 111 pacientes en este estudio, todos de la provincia de Gerona, que llegan con las características previamente comentadas en el Hospital Universitario Doctor Josep Trueta.

Usted debe saber que se trata de un estudio puramente observacional, es decir, que la resonancia magnética que le vamos a realizar no va a intervenir en el curso natural de la enfermedad. Simplemente vamos a valorar su evolución al tratamiento en correspondencia al patrón radiológico observado. Se van a dividir los pacientes en 2 grupos según los patrones observados: tumores hipovasculares y tumores hipervasculares, los cuales vamos a seguir en el tiempo para evaluar si hay algún tipo de asociación entre el patrón vascular tumoral y la respuesta al tratamiento. Ni usted ni los investigadores que lo atiendan conocerán que tipo de patrón radiológico presenta su patología.

Para obtener el patrón, vamos a realizarle una angiografía por resonancia magnética antes de iniciar el tratamiento, que va a ser una prueba diagnóstica añadida a las que se hacen como protocolo actualmente. La angiografía se va a realizar con un nuevo agente de contraste, el *Gadofosveset trisódico*, que presenta una mayor resolución de imagen a nivel vascular y ha demostrado ser seguro. Este agente actualmente empieza a ganar terreno en el campo de las arteriopatias, siendo de gran importancia para la evaluación vascular. El riesgo añadido de realizar esta técnica de imagen es mínimo:

- Técnica de imagen que no utiliza las radiaciones ionizadas como base.
- Mínimos efectos adversos por parte del *Gadofosveset trisódico* (0,8% de los pacientes), que han demostrado ser similares a los producidos por el placebo

Sin embargo, este agente de contraste no tiene autorizada la indicación para utilizarse en carcinomas de hipofaringe o laringe, por lo que se utilizaría en lo que se conoce como “uso off-label”.

¿Qué deberá hacer si decide participar en este estudio?

Una vez realizado el diagnóstico del carcinoma escamoso avanzado de hipofaringe o laringe, se plantearan los posibles tratamientos. En el caso de que el más adecuado a sus necesidades sea la quimioradioterapia, usted será sometido a una angiografía por resonancia magnética con *Gadofosveset trisódico*. De este modo podremos clasificar a su tumor según el patrón vascular que hayamos visualizado vía las pruebas de imagen. A partir de aquí, usted recibirá exactamente el mismo tratamiento que habíamos planteado anteriormente, la quimioradioterapia.

Una vez finalizado el tratamiento, usted seguirá una serie de controles para garantizar un desarrollo correcto y seguro del estudio. Algunos de esos controles, como la realización de algunas laringoscopias directas y pruebas de imagen (TC o MRI), se harían igualmente en su caso aunque no participase en el estudio para el control de la evolución de la enfermedad tras el tratamiento. Estos se realizarán durante 5 años, cada vez más espaciados, en los que se le preguntará por la clínica presentada en el período de tiempo entre consulta y consulta, se les realizará una laringoscopia directa y una prueba de imagen (TC o MRI, dependiendo de la prueba de imagen utilizada inicialmente para el diagnóstico).

Usted debe garantizar el cumplimiento del tratamiento y del seguimiento. Durante el estudio usted deberá notificar cualquier otro tratamiento que esté tomando o que empiece a tomar, y notificar la aparición de cualquier síntoma característico: dificultad o dolor en tragar, sensación de ahogo, tos o carraspera…

Todas las personas que participen en este estudio, tanto hombres como mujeres, deben utilizar métodos anticonceptivos adecuados durante el período que dure el tratamiento y por un total de aproximadamente 12 meses por la toxicidad de los agentes usados en la quimioterapia.

Beneficios derivados de su participación en el estudio:

Con su participación, usted está contribuyendo a mejorar el conocimiento sobre el manejo terapéutico de este tipo de cáncer.

Riesgos derivados de su participación en el estudio:

Debe saber que únicamente el riesgo añadido debido a la participación radicará en los efectos que pueda tener la realización de esta angiografía por resonancia magnética con *Gadofosveset trisódico* en nuestro organismo.

El *Gadofosveset trisódico,* como hemos comentado anteriormente, no ha demostrado presentar diferencias significativas respecto placebo, a nivel de producir efectos adversos. Algunos estudios han evaluado los que más frecuentemente aparecen, aunque solo se vean en un total de 0,8% de los pacientes:

- Náuseas y vómitos
- Rash cutáneo
- Prurito
- Resfriado
- Edema cutáneo limitado
- Alteraciones en la presión arterial o frecuencia cardíaca

A nivel de fertilidad, embarazo y lactancia, el *Gadofosveset trisódico* no ha demostrada ningún efecto perjudicial. De todos modos, es recomendable evitar el embarazo y la lactancia durante el tratamiento por la toxicidad de los agentes quimioterápicos. Las mujeres en edad fértil deberán realizar una prueba de embarazo antes de iniciar el tratamiento, para excluir que estén embarazadas. Durante la quimioradioterapia, todos los pacientes en edad reproductiva deberán utilizar métodos anticonceptivos eficaces durante el tratamiento, aproximadamente durante 1 año.

Tratamientos alternativos:
En todos los pacientes con carcinoma escamoso localmente avanzado de hipofaringe y laringe se les propone dos opciones de tratamiento: cirugía seguida de radioterapia posterior; o quimioradioterapia. La elección del tratamiento se basa en la conclusión que se saca después de presentar el caso a un equipo médico multidisciplinar, y concordándolo siempre con el propio paciente. Si el paciente optase por la terapia basada en cirugía más radioterapia posterior, ya no se incluiría en el estudio.

Seguro:
Usted estará cubierto por una póliza de responsabilidad civil contratada por el promotor del estudio que cubre cualquier posible daño y perjuicio que pueda derivarse de la participación en el estudio, tal y como lo exige la legislación española vigente.

Confidencialidad:
La realización de técnicas de imagen, la comunicación y la cesión de los datos de carácter personal de todos los participantes del estudio se ajustará a la "*Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal"*. De acuerdo a esta ley, usted tiene derecho al acceso, modificación, oposición y cancelación de sus datos y para ello podrá dirigirse a su médico en

el estudio. Los datos que se recogerán en este estudio se identificarán mediante un código y tan solo su doctor y colaboradores podrán identificar posteriormente a los participantes. En ningún caso se transmitirán datos a terceros que contengan información que pueda identificarle directamente, como nombre y apellidos, dirección u otros.

El acceso a su información personal queda restringido a los investigadores de este estudio, autoridades sanitarias (AEMPS), CEIC y personal autorizado por el promotor del estudio, cuando se precise comprobar datos y procedimientos del estudio, pero siempre manteniendo la confidencialidad de acuerdo con la legislación vigente.

Si decide retirar su consentimiento a participar en este estudio, ningún dato se añadirá a la base de datos y usted puede exigir la destrucción de cualquier dato o muestra previamente registrados.

Compensación económica:
El promotor del estudio es el responsable de la gestión y de la financiación del mismo. Usted no tendrá que pagar por las pruebas añadidas del estudio.

Contacto con el investigador:
Para cualquier duda o información adicional sobre el estudio o sobre sus derechos como participante en un estudio de cohorte, deberá contactar con el investigador de su hospital.

Datos de contacto: _____

Annex 4. Informed Consent

FORMULARIO DE CONSENTIMIENTO INFORMADO DEL PACIENTE

Nombre y apellidos del paciente:
Fecha de nacimiento:

1. Confirmo que mi médico, el Dr/Dra _____ (nombre y apellidos del médico) me han informado de forma comprensible y con detalle sobre los objetivos y el significado de este estudio, y me ha proporcionado una hoja de información al paciente.
2. He entendido que el médico responsable del estudio es el Dr/Dra _____ y es a quien debo referirme en caso de tener algún problema.
3. He entendido la información, tanto oral como escrita, que me han proporcionado*. He tenido tiempo para reflexionar sobre qué significa el estudio para mí y he consultado todas las dudas que hayan podido surgirme con respecto a los detalles del estudio.
4. Entiendo que mi participación en este estudio es totalmente voluntaria y que puedo retirarme del mismo en cualquier momento y por cualquier motivo, sin tener que dar explicaciones, y sin que esto repercuta en ningún caso en mi atención o mis cuidados médicos.
5. Doy mi autorización para que mis datos clínicos obtenidos en este estudio sean procesados, y que estos datos podrán ser conservados y procesados electrónicamente para su evaluación científica.
6. Doy mi aprobación para que las Autoridades Sanitarias correspondientes tengan acceso a mi historia clínica para comprobar si el estudio ha sido llevado a cabo según las leyes y requisitos vigentes.
7. Declaro que presento voluntariamente mi conformidad para participar en este estudio mediante el presente documento.

** Si el paciente no puede leer o firmar el consentimiento, deberán estar presentes 2 testigos imparciales durante la discusión del consentimiento informado.*

Paciente: Nombre: Fecha: Firma:	**Declaración de los testigos:** Al firmar este documento, atestiguamos que la información fue explicada con claridad y entendida por el paciente, y que el paciente otorgó libremente su consentimiento informado. Nombres: Fecha: Firmas:

Declaración del Investigador del Consentimiento Informado del paciente

Yo, _____ he explicado en su totalidad los detalles de este estudio, tal y como se describe en la hoja de información al paciente.

Fecha:

Firma:

Annex 5. Informed consent for ARM:

Hospital Universitari de Girona Doctor Josep Trueta

Institut Català de la Salut

Primer cognom
Segon cognom
Nom
Data de naixement **Sexe**
NHC **DNI**
CIP
Episodi origen

Consentiment informat

Cognoms i nom de la persona responsable quan el pacient sigui menor o incapaç de donar el seu consentiment **DNI*** **Relació amb el/la pacient***

Nom del procediment

RM CAP I COLL

QUESTIONARI

QÜESTIONARI

Portador de:
Marcapassos: SI / NO
Aparell electrònic (estimulador vagal, epidural, implant coclear, etc.): SI / NO
Pròtesi metàl·lica o vascular: SI / NO
Pírcings, tatuatges: SI / NO

Antecedents de:
Insuficiència Renal Crònica Greu: SI / NO
Trasplantament Renal: SI / NO
Trasplantament Hepàtic: SI / NO
Reacció al·lèrgica al contrast: SI / NO

Possibilitat de:
Llimadures/metralla:
Clips quirúrgics:
Embaràs:

Pes:
Kg:

QUÈ ÉS LA RESSONÀNCIA MAGNÈTICA (RM)?

És una de les tècniques de diagnòstic per la imatge més modernes i innòcues. Mitjançant un potent imant i ones de ràdio s'obtenen imatges del cos humà.
No utilitza Raigs X ni elements radioactius.
No té efectes nocius demostrats.
Durant l'estudi d'RM, el metge i tècnic de la sala de control us parlaran i us controlaran a través d'un monitor. Disposeu d'un avisador dins de l'aparell per si necessiteu avisar al personal. Durant el procediment, el personal vetllarà al màxim pel vostre confort.

Hospital Universitari de Girona Doctor Josep Trueta
Institut Català de la Salut

Primer cognom
Segon cognom
Nom
Data de naixement **Sexe**
NHC **DNI**
CIP
Episodi origen

Consentiment informat

PRECAUCIONS
Cal que informeu sobre la necessitat o no d'estar en dejú. Especialment si és l'RM d'un nadó o nen (per si fos necessari sedar-lo) o en adults que es facin una RM abdominal.
Comuniqueu al personal sanitari si patiu al·lèrgies conegudes.
Comuniqueu al personal sanitari si sou portadors d'objectes metàl·lics o electrònics.
Entreu a la sala sense objectes metàl·lics.
Per concretar el diagnòstic pot ser necessari administrar contrast endovenós. En aquest cas us informarà prèviament.
Aporteu la màxima informació clínica de que disposeu, així com altres proves que us hagin fet (Rx, TC o RM, sobretot si s'han realitzat a altres centres).

Marcapàs i aparells electrònics
Donat el risc de lesió i de mal funcionament del propi aparell, no es pot entrar a la sala amb marcapàs cardíac, estimuladors electrònics o determinades pròtesis.
Abans d'entrar a la sala s'ha de notificar al personal si s'és portador d'aparells electrònics i es valorarà la compatibilitat amb la màquina de ressonància.

Embaràs
Tot i que no s'han demostrat efectes nocius de l'RM sobre el fetus, és recomanable que es notifiqui si la pacient està embarassada. En certes ocasions es pot valorar clínicament la idoneïtat de l'estudi.

MITJA DE CONTRAST AMB GADOFOSVESET TRISÒDIC
En determinades ocasions és necessari l'administració d'un mitjà de contrast que permetrà arribar a un diagnòstic més concloent.

Què és el contrast?
És un material (metall pesat) que en algunes patologies permet obtenir resultats més satisfactoris de l'RM, ai així detectar de forma més adient certes lesions o patologies.
S'administra en forma de líquid injectat per la vena.
En determinades ocasions l'administració de Gadofos-veset pot produir reaccions adverses lleus (cefalea, nàusees, ...)

Abans de la prova
En cas de patir insuficiència renal greu, ser portador o estar en llista d'espera de trasplantament renal o hepàtic s'ha de comunicar, per tal que en funció del risc/benefici, antecedents i dades de la funció renal es decideixi la idoneïtat d'administrar contrast.
En cas de reacció al·lèrgica prèvia comuniqui-ho, de forma que es puguin prendre les mesures adients.
En cas de lactància es recomana suspendre la mateixa durant 24 hores un cop administrat el contrast.

Hospital Universitari de Girona Doctor Josep Trueta

Institut Català de la Salut

Primer cognom
Segon cognom
Nom
Data de naixement **Sexe**
NHC **DNI**
CIP
Episodi origen

Consentiment informat

Utilització de les imatges de recerca
En determinades ocasions les imatges diagnòstiques que se li realitzaran durant l'RM sol·licitada podrien fer-se servir amb finalitat docent en la difusió del coneixement o en la recerca científica.
El personal investigador de la Unitat d'RM podria necessitar algunes de les imatges per realitzar estudis que resultin en benefici dels pacients. En el seu cas es sol·licita permís pel projecte. En cas de que accedeixi la informació passarà a arxivar-se acomplint la normativa de confidencialitat de dades vigent.
Si una vegada llegida aquesta informació té alguna pregunta, no dubti en consultar al personal especialitzat de la Unitat de Ressonància Magnètica.

AUTORITZACIÓ

Sota signant o el seu representant confirma que:
Ha estat informat/da de l'exploració de ressonància magnètica que el seu metge/ssa li ha sol·licitat.
Ha llegit el full informatiu i coneix les possibilitats alternatives de la prova.
Coneix i ha entès els possibles riscos generals i específics de la prova de Ressonància Magnètica.
Ha entès les explicacions sobre els contrast: Gadofosveset els seus efectes adversos.
Ha estat informat del dret a acceptar o denegar el procediment i les possibles alternatives, així com el dret a anul·lar parcial o totalment l'acceptació realitzada.
Aquest consentiment es formula d'acord amb el que estableix la Llei 21/2000 de 29 de desembre publicada al DOGC núm. 3303 de l'11 de gener del 2001.

Sobre la utilització de les imatges
Ha entès les explicacions sobre la utilització de les imatges per a projectes de recerca.
Ha estat informat del dret a acceptar-la o denegar-la, així com el dret a anul·lar l'acceptació realitzada.

Autoritzo la realització de la Ressonància Magnètica: SI / NO
Autoritzo l'administració de contrast endovenós Gadofosveset SI / NO
Autoritzo la utilització de les imatges per a projectes de recerca: SI / NO

NOTA LEGAL

En virtut del dipositat, en els articles 4, 5 i 6 de la Llei Orgànica 15/1999 de 13 de desembre, l'IDI posa en el seu coneixement que disposa d'un fitxer, amb dades de caràcter personal denominat FITXER DE PACIENTS DE L'IDI. La finalitat de la seva creació és el tractament mèdic-sanitari als usuaris del nostre centre, en la seva totalitat o part del mateix. Els destinataris de la informació són tots els departaments en els quals s'organitza l'IDI així com els estaments oficials públics, privats que per obligació legal o necessitat material hagin d'accedir a les dades a l'efecte de la correcta prestació de l'assistència mèdic-sanitària que constitueix la finalitat del tractament d'aquestes dades. En tot cas, vostè té dret a exercitar els drets d'oposició, accés, rectificació i cancel·lació en l'àmbit reconegut per la Llei Orgànica 15/1999 de 13 de desembre, així com el Codi Tipus de la Unió Catalana d'Hospitals al que aquest centre està adherit. El responsable de fitxer és l'IDI. Per exercitar els drets a dalt esmentats, i per a qualsevol aclariment, pot dirigir-se per escrit mitjançant instància dirigida al Responsable del Departament d'Informàtica de l'IDI en el següent domicili: Parc Sanitari Pere Virgili. C/Esteve Terradas, 30. Edifici Mestral, 2a planta, 08023 Barcelona.

Hospital Universitari de Girona Doctor Josep Trueta

Institut Català de la Salut

Primer cognom
Segon cognom
Nom
Data de naixement **Sexe**
NHC **DNI**
CIP
Episodi origen

Consentiment informat

Servei	Professional que informa	Número d'identificació
OTORRINOLARINGOLOGIA	TOBED SECALL MARC	10845543

Signatura del/la pacient o responsable **Data** **Signatura del professional**

☐ Accepta

☐ No accepta

Revocació consentiment informat.

Jo, En/Na revoco el consentiment prestat en data declaro per tant que, després de la informació rebuda, no autoritzo a sotmetre'm al procediment de RM CAP I COLL

Annex 6. High-resolution gadofosveset-enhanced ARM images

High-resolution gadofosveset-enhanced ARM technique has never been used in hypopharynx or larynx carcinomas. As we said previously, there are other studies that have already used it in order to evaluate the tumoural neovascularization. One of the most conclusive studies is the one that evaluates the relationship between OS and DFS in Glioblastomas, and the vascular pattern observed on the imaging technique(25). Some images characterizing the two main vascular patterns are as follows:

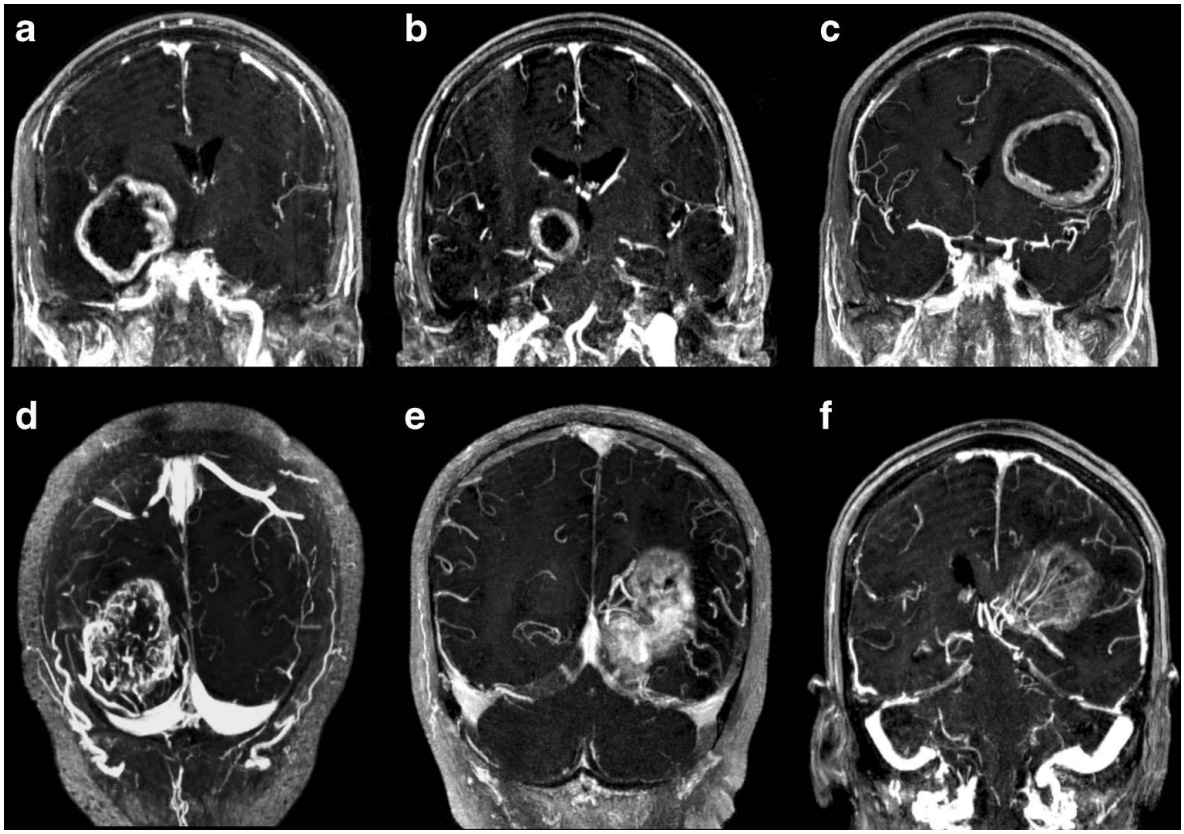


Image 4. Panel of six cases illustrating glioblastoma vascular patterns on high-resolution contrast-enhanced MRA. Hypovascular (a-c) defined as $\leq$ 3 vessels, and hypervascular (d-f) defined as > 3 vessels (25).

Annex 7. Case report form

CASE REPORT FORM

Patient identification code:

Sociodemographic and clinical data:

Age:
Gender: ☐ Male ☐ Female
Date of birth:
Race:

Personal history:

Allergies:
Toxic habits: ☐ Alcohol ☐ Tobacco ☐ Others
Quantify: _____ _____ _____
Medical conditions:
Surgery:
Current treatments:

Family history:

Otorhinolaryngologic conditions:
Other medical or surgical conditions:

Main disease:

Symptoms: Time of evolution: _____

- ☐ Dysphonia
- ☐ Odynophagia
- ☐ Dysphagia
- ☐ Dyspnea
- ☐ Coughing
- ☐ Other symptoms. Which ones? _____

Direct laryngoscopy plus biopsia:
Area affected: _____
Approximate size of the lesion: _____ cm
Analysis histologic: ☐ Squamous cell ☐ Other: _____

TC/MRI:
Area affected: _____
Maximum diameter of the lesion: _____ cm
Stage: T ____ N ____ M ____ Final stage ____

High-resolution gadofosveset-enhanced magnetic resonance angiography:

Vascular pattern: ☐ Hypovascular
☐ Hypervascular

Treatment:

CRT protocol: ☐ Inductive CT plus adjuvant RT
☐ Concomitant CRT

Following-up: After finishing treatment:

	Symptoms	**Physical Exploration**	**Direct laryngoscopy** Size of the lesion (cm)	**TC/MRI** Max. diameter (cm) and tumoural volume (cm^3)	**Toxic habits** Tobacco and alcohol
Visit 1					
Visit 2					
Visit 3					
Visit 4					
Visit 5					
Visit 6					
Visit 7					
Visit 8					

Annex 8. Statistical analysis

a) Univariate analysis:

Characteristics	%
Tobacco consumption: - Low risk - Mild risk - High risk	
Alcohol consumption	
Tumour volume: - Small - Mild - Large	
CRT concomitant	
CT induction + RT adjuvant	

b) Bivariate analysis

Chi^2 test

Variable		Hypervascular pattern (%)	Hypovascular pattern (%)	Risk Ratio (95% CI)	P value
Radiologic response	CR				
	PR				
	SD				
	DP				
Clinical response	CR				
	PR				
	SD				
	DP				

Kaplan-Meyer method: This table must be done for each of those groups: OS of hypervascular and hypovascular pattern, and DFS of hypervascular and hypovascular pattern.

Time (years)	Status	Cumulative survival	Standard error	Cumulative events	Number remaining
1					
2					
3					
4					
5					
6					

7					
8					
9					

Chi^2 test for covariables:

Covariable	Hypervascular pattern	Hypovascular pattern	Risk Ratio (95% CI)	P value
Tobacco consumption: - Low risk - Mild risk - High risk				
Alcohol consumption				
Tumour volume: - Small - Mild - Large				
CRT concomitant				
CT induction + RT adjuvant				