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FINAL DEGREE PROJECT

ENHANCING QUALITY OF LIFE IN LOCALLY ADVANCED LARYNGEAL AND HYPOPHARYNGEAL CANCER TREATMENT THROUGH COGNITIVE BEHAVIOURAL THERAPY IMPLEMENTATION

A MULTICENTRE, SINGLE-BLINDED, RANDOMIZED CLINICAL TRIAL

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"To cure sometimes,

to relieve often,

to comfort always."

Edward Livingston

Al doctor Antoni Borés, per retrobar-me amb la part més bonica de la medicina.

A en Xavier Castells, per guiar-me i aconsellar-me durant aquest camí.

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TABLE OF CONTENTS

1. ABBREVIATIONS AND ACRONYMS 6

2. ABSTRACT 7

3. INTRODUCTION 8

3.1. Definition and classification of head and neck cancer 8

3.2. Epidemiological and aetiological trends in head and neck cancer 9

3.3. Laryngeal and hypopharyngeal risk factors 11

3.3.1. Tobacco and alcohol consumption 11

3.3.2. HPV infection 12

3.3.3. Socioeconomic status 12

3.3.4. Social support and interpersonal relations 14

3.3.5. Bile reflux 15

3.3.6. Occupational toxic agents 15

3.4. Laryngeal and hypopharyngeal cancer and its treatment comorbidities 16

3.4.1. Body image distress 16

3.4.2. Depression 16

3.4.3. Suicide 17

3.4.4. Substance dependence and abuse 18

3.4.5. Pain 18

3.4.6. Dysphagia 18

3.5. Staging 18

3.5.1. Locally advanced laryngeal cancer stages 19

3.5.2. Locally advanced hypopharyngeal cancer stages 24

3.6. Laryngeal and hypopharyngeal locally advanced cancer treatment 25

3.7. Psychosocial interventions in HNC patients 27

3.7.1. Cognitive behavioural therapy 27

4. JUSTIFICATION 28

5. HYPOTHESIS 29

5.1. Primary hypothesis 29

5.2. Secondary hypothesis 29

6. OBJECTIVE 29

6.1. Primary objective 29

6.2. Secondary objectives 29

7. METHODOLOGY 30

7.1. Study design 30

7.2. Population 31

7.2.1. Inclusion criteria 31

7.2.2. Exclusion criteria 31

7.2.3. Withdrawal criteria 32

7.3. Sample 32

7.3.1. Sample selection 32

7.3.2. Sample size 32

7.3.3. Randomization 33

7.4. Variables and measuring methods 34

7.4.1. Independent variable 34

7.4.2. Dependent variable 34

7.4.3. Covariates 35

7.5. Measuring instruments 37

7.5.1. EORTC QLQ-C30 questionnaire 37

7.5.2. EORTC QLQ-H&N43 questionnaire 38

7.6. Study intervention 38

7.7. Patient journey 43

7.8. Data collection 44

7.9. Statistical analysis 44

8. WORK PLAN 46

8.1. Participating centers 46

8.2. Research team members 46

8.3. External contractors 46

9. CHRONOGRAM 47

9.1. Study stages 47

9.2. Chronogram 49

10. BUDGET 50

10.1. Not included costs 50

10.2. Included costs 50

11. ETHICAL AND LEGAL CONSIDERATIONS 53

12. LIMITATIONS AND STRENGHTS 55

12.1. Limitations 55

12.2. Strengths 55

13. IMPACT ON THE HEALTH SYSTEM AND FUTURE RESEARCH 57

14. FEASIBILITY 58

15. BIBLIOGRAPHY 59

16. ANNEXES 66

16.1. ANNEX 1 – AJCC stages classification for laryngeal and hypopharyngeal cancers 66

16.2. ANNEX 2 – Informative document 74

16.3. ANNEX 3 – Informed consent document 78

16.4. ANNEX 4 – Withdrawn consent 79

16.5. ANNEX 5 – Data collection sheet 80

16.6. ANNEX 6 – EORTC QLQ-C30 QUALITY OF LIFE QUESTIONNAIRE 85

16.7. ANNEX 7 – EORTC QLQ-C30 QUALITY OF LIFE SCORING 88

16.8. ANNEX 8 – EORTC QLQ-H&N43 QUALITY OF LIFE QUESTIONNAIRE 89

16.9. ANNEX 9 – EORTC QLQ-H&N43 QUALITY OF LIFE SCORING 92

INDEX OF TABLES

Table 1: Anatomical locations of head and neck cancers based on ICD-10.

Table 2: Interaction between ever-smoking cigarettes and SES variables.

Table 3: Interaction between ever-drinking alcohol and SES variables.

Table 4: Locally advanced supraglottic laryngeal cancer stages.

Table 5: Locally advanced glottis laryngeal cancer stages.

Table 6: Locally advanced subglottic laryngeal cancer stages.

Table 7: Locally advanced hypopharyngeal cancer stages.

Table 8: Characteristics of hospitals included in the study: location, geographical area of care and basic population.

Table 9: Hospitals participating in the study estimated number of patients of interest according to their basic population.

Table 10: Summary table of independent and dependent variables.

Table 11: Summary table of covariates.

Table 12: Weekly themes and main content of CBT sessions.

Table 13: Budget details of the study.

INDEX OF FIGURES

Figure 1: World age-standardized rates for incidence of head and neck cancer for both sexes and all group of ages.

Figure 2: Figure 2: Locally advanced laryngeal and hypopharyngeal cancer treatment strategies.

Figure 3: Flow diagram of the study

Figure 4: Patient journey diagram

1. ABBREVIATIONS AND ACRONYMS

AJCC	American Joint Committee on Cancer
BID	Body image distress
BRIGHT	Building a Renewed Image after Head and neck cancer Treatment
CBT	Cognitive behavioural therapy
CEIC	Comitè Ètic d'Investigació Clínica
CEORL-HNS	Confederation of European Otorhinolaryngology and Head and Neck Surgery
CT	Computed tomography
EORTC	European Organization for Research and Treatment of Cancer
HNC	Head and neck cancer
HNTFU	Head and neck tumour functional unit
HPV	Human papillomavirus
HRQoL	Health-related quality of life
ICD	International Classification of Diseases
ICS	Institut Català de la Salut
INHANCE	International Head And Neck Cancer Epidemiology
MDD	Major depressive disorder
OPSCC	Oropharyngeal squamous cell cancer
QoL	Quality of life
SCC	Squamous cell carcinoma
SCCHN	Squamous cell carcinoma of the head and neck
SEORL-CCC	Sociedad Española de Otorrinolaringología y Cirugía de Cabeza y Cuello
SES	Socioeconomic status
WHO	World Health Organisation

2. ABSTRACT

BACKGROUND: Laryngeal cancer is the most prevalent among all the head and neck cancers. Typically, both laryngeal and hypopharyngeal cancers are diagnosed in a locally advanced stage, requiring aggressive and potentially mutilating treatments. This may result in significant comorbidities such as depression or chronic and severe pain, having a great impact in patients' quality of life. Despite cognitive behavioural therapy has demonstrated remarkable benefits in enhancing quality of life and emotional wellbeing for patients with other cancers, its effectivity in patients with locally advanced laryngeal and hypopharyngeal cancer remains unexplored. This absence of literature in this particular population emphasizes the necessity of exploring the potential impact that cognitive behavioural therapy may have in improving quality of life, reducing comorbidities and potentially increasing survival rates of these patients.

OBJECTIVE: The main objective is to study the efficacy of incorporating cognitive behavioural therapy to the standard treatment for improving quality of life among patients diagnosed with locally advanced laryngeal or hypopharyngeal cancer, in comparison with the standard treatment alone. Secondary objectives of this trial are to evaluate if incorporating cognitive behavioural therapy in the treatment plans results in an improvement of 1-year survival rates and a reduction on the amount of comorbidities in this population, compared to those only receiving the standard treatment.

DESIGN AND SETTING: This study is designed as a multicentre, prospective, single-blinded, randomized clinical trial. It will be conducted in 8 different hospitals from Catalunya.

PARTICIPANTS AND METHODS: 246 individuals newly diagnosed with locally advanced laryngeal or hypopharyngeal squamous cell carcinoma will be enrolled over a 20-months period through a non-probabilistic consecutive sampling. Patients will be randomly divided in two groups: an intervention group, receiving cognitive behavioural therapy sessions, and a control group, with control psychological sessions without a therapeutic goal. The amount and time of sessions will be the same in both groups: 15 sessions in 6 months. Throughout this period, 2 questionnaires will be answered 6 times in order to assess quality of life and potential comorbidities. Survival rates will be evaluated 1 year after diagnosis.

KEYWORDS: Locally advanced laryngeal and hypopharyngeal cancer, cognitive behavioural therapy, quality of life, survival, post treatment comorbidities.

3. INTRODUCTION

3.1. Definition and classification of head and neck cancer

Head and neck cancer (HNC) refers to a group of malignant tumours located in the paranasal sinuses, the nasopharynx, the oropharynx – which includes tonsils, soft palate and base of tongue-, the hypopharynx, the larynx, the oral cavity –which includes oral mucosa, gum, hard palate, tongue and floor of the mouth-, the tongue and the salivary glands. (1) They represent the seventh most common cancer globally, with more than 660,000 new cases and 325,000 deaths annually. (2) All these cancers combined represent the 5% of all tumours in humans. (1)

Although most of HNCs are histologically similar, with approximately 90% of them being squamous cell carcinoma (SCC) (1), notable differences can be appreciated in terms of epidemiology, aetiology, symptoms and even in their treatment and prognosis depending on the anatomical tumour site. It is for this reason that they are considered separate entities and they can be categorised according to their anatomical location in different groups. The most common used classification is the International Classification of Diseases (ICD) from the World Health Organisation (WHO) (Table 1)

Table 1: Anatomical locations of head and neck cancers based on ICD-10

Anatomical locations	ICD-10 code
Malignant neoplasm of lip	C00.0-C00.6, C00.8-C00.9
Malignant neoplasm of base of tongue	C01
Malignant neoplasm of other and unspecified part of tongue	C02.0-C02.4, C02.8-C02.9
Malignant neoplasm of gum	C03.0-C03.1, C03.9
Malignant neoplasm of floor of mouth	C04.0-C04.1, C04.8-C04.9
Malignant neoplasm of palate	C05.0-C05.2, C05.8-C05.9
Malignant neoplasm of other and unspecified parts of mouth	C06.0-C06.2-C06.8-C06.9
Malignant neoplasm of parotid gland	C07
Malignant neoplasm of other and unspecified major salivary glands	C08.0-C08.1, C08.8-C08.9
Malignant neoplasm of tonsil	C09.0-C09.1, C09.8-C09.9
Malignant neoplasm of oropharynx	C10.0-C10.4, C10.8-C10.9
Malignant neoplasm of nasopharynx	C11.0-C11.3, C11.8-C11.9
Malignant neoplasm of piriform sinus	C12

Malignant neoplasm of hypopharynx	C13.0-C13.2, C13.8-C13.9
Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx	C14.0-C14.2, C14.8
Malignant neoplasm of nasal cavity and middle ear	C30.0-C30.1
Malignant neoplasm of accessory sinuses	C31.0-C31.3, C31.8-C31.9
Malignant neoplasm of larynx	C32.0-C32.3, C32.8-C32.9
Malignant neoplasm of other and ill-defined sites	C76.0

ICD: International Classification of Diseases

3.2. Epidemiological and aetiological trends in head and neck cancer

Historically, in the last years of the 20th century the global incidence for HNC was decreasing in concordance with a reduction of tobacco consumption and alcohol intake. Even so, nowadays incidence of HNC continues to rise, with a predicted 30% increase by 2030 according to GLOBOCAN.(2–4)

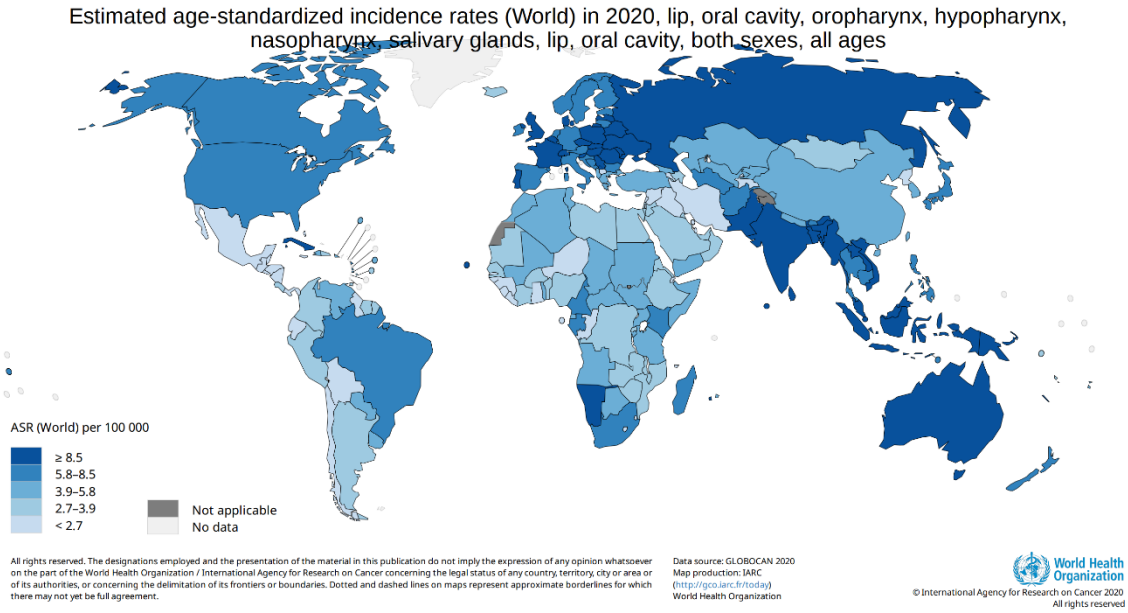

Figure 1: World age-standardized rates for incidence of head and neck cancer for both sexes and all group of ages.

Map generated with GLOBOCAN website (4) (https://gco.iarc.fr/today/online-analysis-map)

ASR: Age-standardised rates.

These trend changes may be explained by new aetiological agents related with HNC in the last decades, which also explains higher incidences for specific HNC entities in concrete geographical areas. For example, some Southeast Asia and Asia-Pacific regions have a higher incidence of oral cancer related with chewing of areca nut, whereas in Europe and the USA the increasing incidence of HNC has been related with oropharyngeal cancer and its association with human papillomavirus (HPV) infection. (2)

HNC affects men two to four times more than women, with the majority of cases being diagnosed over 50 years. Low education and low household income –in conclusion: low socioeconomic status (SES)- were also linked with a higher risk of HNC. Survival and prognosis for HNC are poor, with a global five-year survival average of 50% and huge comorbidities for those who survive, which have a heavy impact on their quality of life (QoL) such as eating, speech and physical appearance. (1–3,5–8). In fact, Spain was the European country with the highest mortality rate of laryngeal cancer in men in 2008, with 3280 new larynx cancers diagnosed and 1640 deaths, (9) and is actually ranked in sixth place in mortality from cancer in men. (1)

The increasing tendency in HNC incidence is mostly explained by the irruption of HPV as a cause of oropharyngeal squamous cell cancer (OPSCC). From 1988 to 2004 OPSSC associated to HPV has increased a 225% and is expected to surpass the incidence of cervical cancer as the most common malignancy tumour caused by HPV. This change in the aetiological trends has been reflected as an epidemiological shift, giving birth to a “new” HNC patient in contrast with the “traditional” one. The new HNC patients are younger, mainly male and have none or low exposure to tobacco and alcohol. In contrast, this new patient profile has more sexual partners, specifically oral sex. Physical presentation characteristics have also changed, being smaller primary tumours with more advanced neck disease, yet they have a better response to treatment. (10)

The epidemiology of laryngeal and hypopharyngeal cancer is similar to the HNC in general, being a SCC the most common diagnosis, in males older than 40-years-old. The highest incidence for laryngeal cancer is in Southeast and Eastern Europe countries (Spain, France, Italy, Serbia and Poland), Latin America (Brazil and Argentina) and West Asia (Pakistan and Turkey). In Spain, the supraglottic cancer is more common than the glottic cancer, being the subglottic cancer the less frequent site for laryngeal cancer. The highest incidence for hypopharyngeal cancer is found in France, India and Pakistan. (9)

The 5-year relative survival rate for laryngeal cancer is 64%. This percentage vary depending on the primary tumour's anatomical site, being 47% for supraglottic carcinoma, 79% for glottic carcinoma and 40% for subglottic carcinoma. (11) The 5-year relative survival rate for hypopharyngeal cancer is 37%, being the lowest among all the HNC. (12)

3.3. Laryngeal and hypopharyngeal risk factors

Many studies have extensively described a great range of risk factors for HNC, being the main risk factors tobacco smoking and alcohol consumption. High-risk HPV, especially HPV type 16, and the consumption of chewed areca nut in some regions of Asia are also a major risk factor for oropharyngeal cancer and oral cavity cancer, respectively. A large list of other risk factors considered as *minor risk factors* should be taken into account: SES, HNC family history, oral hygiene, chronic inflammatory processes like chronic laryngitis, gastroesophageal reflux or gastritis, occupational exposition to carcinogens, other infections such as Epstein-Barr Virus, genetic susceptibility… (2,3,5,6,9)

Most of these risk factors have been demonstrated thanks to the International Head and Neck Cancer Epidemiology (INHANCE) consortium. INHANCE is a collaboration of different research groups around the world, pooling 35 studies and data from 25,500 patients with HNC and 37,100 controls. This pooling data allows a more precise estimation of risk and a major precision on detecting possible confounding factors. Even so, one of the biggest limitations of INHANCE is the lack of studies from regions with a high HNC incidence such as some South-East Asia regions like India or the whole African continent. (6)

3.3.1. Tobacco and alcohol consumption

The classic major risk factors for HNC are tobacco smoking and alcohol intake, especially when used in combination. (2)

Tobacco is the most common aetiology for larynx SCC, causing mainly glottic cancer. Alcohol is the second most important risk factor when talking of laryngeal cancer, especially for supraglottic cancer. In fact, over the 90% of laryngeal cancers could be prevented if tobacco and alcohol were avoided. (9,13)

Similar trends are stablished in hypopharyngeal cancer main risk factors, with alcohol consumption as the first main cause and tobacco smoking as the second. (14)

3.3.2. HPV infection

As mentioned before, high-risk HPV (specially serotype 16) is strongly related to oropharyngeal cancer and, with less strength, to hypopharyngeal cancer. HPV is the main cause of the increasing incidence of HNC. Additionally, recent studies have demonstrated the presence of HPV infection and/or p16 marker in a minority of laryngeal tumours. (15) Even though, more studies will be necessary to elucidate the real link between HPV infection and larynx cancer as it remains unclear.

3.3.3. Socioeconomic status

Independently of the primary tumour site, general increased odds of squamous cell carcinoma of the head and neck (SCCHN) are seen in population with lower income and fewer years of education. Individuals who haven't completed high-school education have almost 4 times the odds for SCCHN than those who completed college or more. (16)

A systematic review and meta-analysis conducted by Conway et al (17) showed that low SES was significantly associated with increased oral cancer risk, no differences between high and low-income countries, across the world. They found a significant association between oral cancer and low income, low occupational social class and low educational attainment.

In fact, Conway et al and other authors related major behaviour risk factors (smoking, alcohol, diet and sexual history –related with HPV infection-) with inequality itself. In other words, people with a low SES are more likely to develop these behaviours. This manifest, on the one hand, that part of the HNC associated with low SES may be explained by major behaviour risk factors but, on the other hand and more importantly, this relation sets up a deeper role for social determinants of health, not only being a cause for the disease, but also a cause for other aetiologies of HNC. (17)

Going further with this, there is statistically significant evidence of the interaction between SES –defined as household income, education and insurance type- and smoking or drinking status. Results can be seen in Table 2 and Table 3, adapted from: I*nteraction between known risk for head and neck cancer and socioeconomic status: the Carolina Head and Neck Cancer Study*. (16)

Table 2: Interaction between ever-smoking cigarettes and socioeconomic status variables				
	Never-smoker OR (95% CI)	Ex-smoker OR (95% CI)	Current smoker OR (95% CI)	p interaction
Income				**<0.001**
>$50.000	1 (Ref)	1.17 (0.84-1.50)	2.47 (1.69-3.25)	
$20.000-$50.000	0.83 (0.52-1.14)	1.28 (0.94-1.62)	3.77 (2.77-4.78)	
<$20.000	0.84 (0.43-1.24)	2.11 (1.39-2.85)	5.11 (3.61-6.61)	
Education				**0.009**
Some college and above	1 (Ref)	1.30 (0.98-1.62)	2.49 (1.85-3.12)	
High school graduate	0.93 (0.55-1.30)	1.53 (1.10-2.00)	4.45 (3.14-5.78)	
Less than high school	0.91 (0.38-1.44)	2.09 (1.36-2.81)	7.38 (5.03-9.73)	
Insurance type				**0.011**
Private	1 (Ref)	1.30 (0.93-1.67)	2.68 (1.92-3.45)	
Medicaid/Medicare	0.47 (0.26-0.67)	1.09 (0.76-1.42)	3.26 (2.27-4.26)	
None	1.03 (0.19-1.88)	1.40 (0.37-2.43)	2.05 (1.25-2.85)	
Other	0.89 (0.46-1.32)	1.03 (0.67-1.40)	4.36 (2.43-6.29)	

As shown in Table 2, current smokers with an annual income lower than $20.000 have more than five times the odds of SCCHN than never-smokers with an annual income higher than $50.000. Instead, current smokers with >$50.000 income have almost 2.50 times the odds of SCCHN compared to never-smokers with the same annual income.

When talking of education, current smokers who haven't ended high school studies have more than seven times the odds of SCCHN compared to never smokers with some college education or above. Similar to annual income, current smokers who ended college studies or more have nearly 2.5 times the odds of SCCHN compared to never-smokers with college education or more.

Table 3: Interaction between ever-drinking alcohol and socioeconomic status variables				
	Never-drinker OR (95% CI)	Ex-drinker OR (95% CI)	Current drinker OR (95% CI)	p interaction
Income				**0.069**
>$50.000	1 (Ref)	2.16 (1.37-2.95)	2.47 (1.69-3.25)	
$20.000-$50.000	1.25 (0.75-1.75)	1.71 (1.24-2.17)	1.62 (1.24-1.99)	
<$20.000	1.21 (0.66-1.76)	2.11 (1.39-2.85)	2.91 (2.05-3.78)	
Education				**0.027**
Some college or above	1 (Ref)	1.65 (1.17-2.14)	1.04 (0.82-1.26)	
High school graduate	0.82 (0.46-1.18)	1.66 (1.11-2.19)	1.78 (1.33-2.27)	
Less than high school	1.29 (0.66-1.91)	2.19 (1.52-2.87)	2.69 (1.80-3.58)	
Insurance type				**0.149**
Private	1 (Ref)	1.91 (1.28-2.54)	1.56 (1.17-1.95)	
Medicaid/Medicare	0.93 (0.53-1.33)	1.72 (1.21-2.22)	1.37 (0.99-1.75)	
None	1.04 (0.20-2.06)	0.87 (0.40-1.35)	1.97 (1.15-2.80)	
Other	1.24 (0.54-1.94)	2.34 (1.33-3.34)	1.51 (1.04-2.00)	

Table 3 manifests the interaction between alcohol consumption and SES factors: current drinkers with incomes <$20.000 have almost 3 times the odds of SCCHN in comparison with never drinkers and income >$50.000, which represents a higher risk than current drinkers with high income.

The main conclusion for all the information collected in Table 2 and Table 3 is that there is significant evidence of the interaction between SES, smoking and drinking status: those individuals with lower annual income and less years of education have higher odds of SCCHN in current smokers and drinkers than those with greater level of SES.(16)

3.3.4. Social support and interpersonal relations

Social support is an important factor in mitigating emotional distress and social dysfunction experimented by patients. (18) It is independently associated with improved health-related quality of life (HRQoL) before and after treatment, better adherence to treatment and better and sooner rehabilitation. On top of that, social support significantly reduces HNC-specific mortality, and it has been seen to give a survival benefit even larger than chemotherapy. (8)

Although limited research has been done, social support seeking behaviours are described as the most prevalent strategy for coping in HNC patients, including both laryngeal and hypopharyngeal cancer. (19) Loneliness, isolation and lack of social network is well described in literature as an important factor for poor health. These factors are associated with a higher incidence of cancer and cancer related mortality, which is in part explained by the fact that individuals who are socially isolated and lonely use less and have worse access to healthcare and have poorer health-related behaviours. (20)

In contrast with that, social networks are related with several elements linked with a decreased cancer incidence and mortality, such as less depressive symptoms, better health behaviours and decreased stress related with physiological processes, including immunological resistance to infections. (20) Higher levels of social support reported by patients are significantly related with better HRQoL outcomes in speech, aesthetics, social disruption, depressive symptoms and mental general health status. (19)

A meta-analysis which integrated 87 studies analysed the relation between cancer mortality and three social network indicators (perceived social support, network size and marital status) concluded that individuals showed a reduced relative risk of mortality by 25% when the level of perceived support increased by one standard deviation unit, by 20% when the network size increased by one standard deviation and by 12% when individuals were married compared with those unmarried. (21) In concordance with this information, some studies carried out on adults with cancer showed that those unmarried or lacking social support had a shorter overall survival and worse treatment response in contrast with married people. (22)

3.3.5. Bile reflux

Laryngopharyngeal reflux, a variant of gastro-oesophageal reflux disease has been described in the last decade as an independent risk factor for hypopharyngeal cancer due to its carcinogenic effect. Its pathogenic mechanism is related with conjugated bile acids promoting DNA damage as well as histological changes in hypopharynx mucosa. (23)

3.3.6. Occupational toxic agents

Some toxics like asbestos, wood dust, coal dust, cement dust or polycyclic aromatic hydrocarbons have been associated with laryngeal cancer, even though some of them stay controversial. (13)

Asbestos is also considered an independent risk factor for hypopharyngeal cancer. Additionally, the habit of chewing of areca nut, prevalent in South Asia and East Africa, is strongly associated with this cancer too. (24)

3.4. Laryngeal and hypopharyngeal cancer and its treatment comorbidities

Treatment of locally advanced laryngeal and hypopharyngeal cancer has evolved in recent years to organ-preservation protocols, which include concurrent chemo-radiation therapy rather than classic radical surgeries. These new treatment protocols target are to decrease morbidity associated with surgery and postoperative oncological treatment. Although it has demonstrated increased disease-free intervals, organ-preserving treatments have other serious treatment-related effects and the 5-year survival rate has not changed and remains in approximately at 50%. (18)

Treatment of these cancers usually results in aesthetic, structural and functional deficits which lead into complications in everyday vital needs like eating, swallowing, breathing or speech. (8,25) It has also been described as the most emotionally traumatic and psychologically distressing of all cancers. (7,8)

All these comorbidities explain the fact that outcomes related to appearance, voice or pain are as much as important as survival for patients. (8)

3.4.1. Body image distress

3 out of 4 laryngeal and hypopharyngeal cancer survivors manifest image concerns and nearly 30% have clinically significant body image-related distress (BID). Likewise, BID is related with huge psychosocial morbidity, including alarming increases in moderate-severe depressive and anxiety symptoms, a reduced QoL and higher rates of suicide mortality compared to other cancer survivors. (18,26)

3.4.2. Depression

Major depressive disorder (MDD) diagnosis is disproportionately higher in these patients in comparison with other cancers. Depression is both cause and consequence of many other psychosocial issues including inadequate social support, dissatisfaction with the medical team and information provided by them, substance abuse, or struggles with self-image. (8,18) Depression in patients with HNC is also correlated with male gender, being unmarried, being younger, low education, smoking, or low physical functioning. (18)

Depression is also linked to a large list of comorbidities: delays and interruption in radiation treatment, poorer treatment response, prolonged hospitalizations, tobacco and alcohol use,

lower HRQoL in terms of speech, eating, aesthetics and social functioning, malnutrition… and is also independently associated to 30-40% relative survival disadvantage. (8,18,27,28) Nearly 70% of patients will experience an interruption in treatment, and those suffering from depression have three times a higher risk of noncompliance with medical treatment recommendations. (27)

A relation has also been stablished between depression and biological pathways which promote tumour progression. For example, depression is linked with systemic inflammation and higher levels of C-reactive protein and proinflammatory interleukin 1 and 6. Depression has also been related with a hypothalamic-pituitary-adrenal axis dysregulation and cortisol hormone excessive and dysfunctional secretion. All together, these anomalies contribute to cancer progression and lower survival taxes in multiple cancer types as they reduce patients' immune system capacity to fight tumours effectively and lowering response to medical treatment. (27)

3.4.3. Suicide

HNC patients have higher taxes of substance abuse and pain issues, both directly linked with an increased risk of suicide. In fact, HNC has the second highest rate of suicide (63.4 cases per 100,000 person-years) only behind pancreas cancer (86.4 cases per 100,000 person-years) in comparison with general cancer population (23.6 per 100,000 person-years). (3,7)

Suicide attempts are three times higher in these patients than in general population. (8,29) Moreover, those patients with loco-regionally advanced or metastatic disease, primary tumours of hypopharynx or larynx or cancers treated only with radiotherapy are more likely to attempt and complete suicide. (8)

As seen in depression, many other comorbidities are correlated and increase the risk of suicidal ideation and attempt: alcoholism and nicotine use, pain, psychosocial and psychosomatic issues related to primary tumour site and radiation… (8)

A study carried by Nosayaba et al titled *"Suicide risk among cancer survivors: head and neck versus other cancers"* (7) exposed that many HNC survivors face economic issues and financial stress as a result of medical treatment costs. Indeed, an article (30) cited by Nosayaba placed HNC as the most expensive cancer to treat. Moreover, approximately 50% of HNC survivors become functionally disabled and are unable to work after treatment, which explains cancer as the first cause of medical-related bankruptcy in the United States. Likewise, bankruptcy is directly related with depression and suicide, as well as with higher mortality taxes as financial speculation can limit access to treatment. (7)

3.4.4. Substance dependence and abuse

According to evidence exposed above, tobacco and alcohol use are two of the main risk factor with a synergic effect. Even though, the use and/or abuse of these substances stay in approximately 45% of users after diagnosis. Patients who keep this behavioural risk factors have worse survival, higher recurrence taxes and nearly a 50% chance of a second primary cancer. (8)

3.4.5. Pain

Pain is related with both the disease itself and as a consequence of therapy. Nociceptive pain appears as a consequence of destructive lesions and direct bone and soft tissue involvement, whereas neuropathic pain arises due to invasion of nerves and as a treatment toxicity. In fact, 80% of laryngeal and hypopharyngeal patients undergoing radiotherapy treatment experienced pain, which can be explained by the numerous side effects associated with radiotherapy in these cancers: dermatitis, mucositis, tongue pain, laryngeal radionecrosis, dysphagia… (31,32)

Pain is also related with smoking, depression and fatigue, which is not surprising as several studies have shown this correlation in several cancer types. This connection can be explained by the significant emotional shift a cancer diagnosis represents and may also be related with inflammatory changes associated with cancer and its treatment. (33)

3.4.6. Dysphagia

Dysphagia is the main determinant factor for having a functional larynx. Severe late dysphagia (defined as the appearance of swallowing difficulties at least 90 days after treatment) affects nearly 20% of patients treated for laryngeal or hypopharyngeal cancer, no matter the treatment approach applied. (34)

Dysphagia is an important cause of malnutrition, dehydration, weight loss, chronic aspiration and aspiration pneumonia. These complications may lead to not only health issues and death, but also result in depression, social isolation and negatively impact the QoL of these patients. (34,35)

3.5. Staging

Tumours are classified following the TNM System (1), which is composed of 3 elements:

- T: Extension of the primary tumour
- N: Absence or presence and extension of loco-regional lymph node metastasis
- M: Absence or presence of distant metastasis

After the values of the T, N and M have been set on, they are combined and assigned to an overall stage. For the majority of cancers (including larynx and hypopharynx), stages go from I to IV, with stage I being the less advanced and stage IV being the most advanced stage. Usually stages are subdivided using capital letters; in this case, stage IV is divided in IVA, IVB, and IVC for both laryngeal and hypopharyngeal cancer.

Stages can also be grouped depending on the spreading magnitude of the primary tumour in local, regional or advanced disease. Localized disease is defined as a cancer which has not spread outside the main organ (in this case, the larynx or the hypopharynx). When the cancer has invaded adjoining structures or lymph nodes we talk about regional or locally advanced disease. Finally, distant disease is considered when malignant cells has spread to distant parts of the body like the lungs. (36)

When talking about laryngeal and hypopharyngeal cancer, we consider stages I and II of the American Joint Committee on Cancer (AJCC) staging as local disease, stages III, IVA and IVB (without distant metastasis) as regional or locally advanced disease and stage IVC (presence of distant metastasis) as advanced disease. (36)

3.5.1. Locally advanced laryngeal cancer stages (36)

3.5.1.1. Supraglottic laryngeal cancer

Table 4: Locally advanced supraglottic laryngeal cancer stages

AJCC stage	Stage grouping	Stage description
III	T3 N0 M0	The tumour is still only in the larynx, but it has caused a vocal cord to stop moving, OR the tumour is growing into nearby areas such as the postcricoid area, paraglottic space, pre-epiglottic tissues, or the inner part of the thyroid cartilage (firm tissue that separates the thyroid gland from the front of the larynx) (T3). The cancer has not spread nearby to lymph nodes (N0) or distant parts of the body (M0).
	T1 to T3 N1 M0	The tumour might or might not have grown into structures just outside the larynx, and it might or it might not have affected a vocal cord (T1 to T3). The cancer has spread to a single lymph node on the same side of the neck as the tumour, which is no larger than 3 cm across (N1). The cancer has not spread to distant parts of the body (M0).

IVA	T4a N0 or N1 M0	The tumour has grown through the thyroid cartilage and/or is growing into tissues beyond the larynx (such as the thyroid gland, trachea, oesophagus, tongue muscles or neck muscles) (T4a). The cancer has not spread to nearby lymph nodes (N0), or it has spread to a single lymph node on the same side of the neck as the tumour, which is no larger than 3 cm across (N1). The cancer has not spread to distant parts of the body (M0).
	T1-T4a N2 M0	The tumour might or might not have grown into structures outside the larynx, and it might or might not have affected a vocal cord (T1 to T4a). The cancer is N2: - It has spread to a single lymph node on the same side of the neck as the tumour, which is larger than 3 cm but no larger than 6 cm across, OR - It has spread to more than one lymph node on the same side of the neck as the tumour, none of which is larger than 6 cm across, OR - It has spread to at least one lymph node on the other side of the neck, none of which is larger than 6 cm across. The cancer has not spread to distant parts of the body (M0).
IVB	T4b Any N M0	The tumours is growing into the area in front of the spine in the neck (the prevertebral space), surrounds a carotid artery or is growing down into the space between the lungs (T4b). The cancer might or might not have spread to nearby lymph nodes (any N). It has not spread to distant parts of the body (M0).
	Any T N3 M0	The tumour might or might not have grown into structures outside the larynx, and it might or might not have affected a vocal cord (any T). The cancer has spread to at least one lymph node that is larger than 6 cm across, OR it has spread to a lymph node and then grown outside of the lymph node (N3). It has not spread to distant parts of the body (M0).

3.5.1.2. Glottic laryngeal cancer

Table 5: Locally advanced glottis laryngeal cancer stages		
AJCC stage	**Stage grouping**	**Stage description**
III	T3 N0 M0	The tumour is still only in the larynx, but it has caused a vocal cord to stop moving, OR the tumour is growing into the paraglottic space, OR the tumour is growing into the inner part of the thyroid cartilage (firm tissue that separates the thyroid gland from the front of the larynx) (T3). The cancer has not spread nearby to lymph nodes (N0) or distant parts of the body (M0).
	T1 to T3 N1 M0	The tumour might or might not have grown into structures just outside the larynx, and it might or it might not have affected a vocal cord (T1 to T3). The cancer has spread to a single lymph node on the same side of the neck as the tumour, which is no larger than 3 cm across (N1). The cancer has not spread to distant parts of the body (M0).
IVA	T4a N0 or N1 M0	The tumour has grown through the thyroid cartilage and/or is growing into tissues beyond the larynx (as such as the thyroid gland, trachea, cricoid cartilage, oesophagus, tongue muscles or neck muscles (T4a). The cancer has not spread to nearby lymph nodes (N0), or it has spread to a single lymph node on the same side of the neck as the tumour, which is no larger than 3 cm across (N1). The cancer has not spread to distant parts of the body (M0).
	T1-T4a N2 M0	The tumour might or might not have grown into structures outside the larynx, and it might or might not have affected a vocal cord (T1 to T4a). The cancer is N2: - It has spread to a single lymph node on the same side of the neck as the tumour, which is larger than 3 cm but no larger than 6 cm across, OR - It has spread to more than one lymph node on the same side of the neck as the tumour, none of which is larger than 6 cm across, OR - It has spread to at least one lymph node on the other side of the neck, none of which is larger than 6 cm across. The cancer has not spread to distant parts of the body (M0).

IVB	T4b Any N M0	The tumour is growing into the area in front of the spine in the neck (the prevertebral space), surrounds a carotid artery or is growing down into the space between the lungs (T4b). The cancer might or might not have spread to nearby lymph nodes (any N). It has not spread to distant parts of the body (M0).
	Any T N3 M0	The tumour might or might not have grown into structures outside the larynx, and it might or might not have affected a vocal cord (any T). The cancer has spread to at least one lymph node that is larger than 6 cm across, OR it has spread to a lymph node and then grown outside of the lymph node (N3). It has not spread to distant parts of the body (M0).

3.5.1.3. Subglottic laryngeal cancer

Table 6: Locally advanced subglottic laryngeal cancer stages

AJCC stage	Stage grouping	Stage description
III	T3 N0 M0	The tumour is still only in the larynx, but it has caused a vocal cord to stop moving, OR the tumour is growing into the paraglottic space, OR the tumour is growing into the inner part of the thyroid cartilage (firm tissue that separates the thyroid gland from the front of the larynx) (T3). The cancer has not spread nearby to lymph nodes (N0) or distant parts of the body (M0).
	T1 to T3 N1 M0	The tumour might or might not have grown into structures just outside the larynx, and it might or it might not have affected a vocal cord (T1 to T3). The cancer has spread to a single lymph node on the same side of the neck as the tumour, which is no larger than 3 cm across (N1). The cancer has not spread to distant parts of the body (M0).
IVA	T4a N0 or N1 M0	The tumour is growing through the cricoid or thyroid cartilage and/or is growing into structures beyond the larynx (such as the thyroid gland, trachea, oesophagus, tongue muscles or neck muscles) (T4a).

		The cancer has not spread to nearby lymph nodes (N0), or it has spread to a single lymph node on the same side of the neck as the tumour, which is no larger than 3 cm across (N1). The cancer has not spread to distant parts of the body (M0).
	T1-T4a N2 M0	The tumour might or might not have grown into structures outside the larynx, and it might or might not have affected a vocal cord (T1 to T4a). The cancer is N2: - It has spread to a single lymph node on the same side of the neck as the tumour, which is larger than 3 cm but no larger than 6 cm across, OR - It has spread to more than one lymph node on the same side of the neck as the tumour, none of which is larger than 6 cm across, OR - It has spread to at least one lymph node on the other side of the neck, none of which is larger than 6 cm across. The cancer has not spread to distant parts of the body (M0).
IVB	T4b Any N M0	The tumour is growing into the area in front of the spine in the neck (the prevertebral space), surrounds a carotid artery, or is growing down into the space between the lungs (T4b). The cancer might or might not have spread to nearby lymph nodes (any N). It has not spread to distant parts of the body (M0).
	Any T N3 M0	The tumour might or might not have grown into structures outside the larynx, and it might or might not have affected a vocal cord (any T). The cancer has spread to at least one lymph node that is larger than 6 cm across, OR it has spread to a lymph node and then grown outside of the lymph node (N3). It has not spread to distant parts of the body (M0).

3.5.2. Locally advanced hypopharyngeal cancer stages (12)

Table 7: Locally advanced hypopharyngeal cancer stages		
AJCC stage	**Stage grouping**	**Stage description**
III	T3 N0 M0	The tumour is larger than 4 cm across, OR the tumour is affecting the movement of the vocal cords, OR the tumours has grown into the oesophagus (T3). The cancer has not spread nearby to lymph nodes (N0) or distant parts of the body (M0).
	T1 to T3 N1 M0	The tumour can be any size and might or might not have grown into structures outside the hypopharynx, and it might or might not have affected a vocal cord (T1 to T3). The cancer has spread to a single lymph node on the same side of the neck as the tumour, which is no larger than 3 cm across (N1). The cancer has not spread to distant parts of the body (M0).
IVA	T4a N0 or N1 M0	The tumour has grown into the thyroid or cricoid cartilage, the hyoid bone, the thyroid gland, or nearby areas of muscle or fat (T4a). The cancer has not spread to nearby lymph nodes (N0), or it has spread to a single lymph node on the same side of the neck as the tumour, which is no larger than 3 cm across (N1). The cancer has not spread to distant parts of the body (M0).
	T1-T4a N2 M0	The tumour can be any size and might or might not have grown into structures outside the hypopharynx, and it might or might not have affected a vocal cord (T1 to T4a). The cancer is N2: - It has spread to a single lymph node on the same side of the neck as the tumour, which is larger than 3 cm but no larger than 6 cm across, OR - It has spread to more than one lymph node on the same side of the neck as the tumour, none of which is larger than 6 cm across, OR - It has spread to at least one lymph node on the other side of the neck, none of which is larger than 6 cm across. The cancer has not spread to distant parts of the body (M0).

IVB	T4b Any N M0	The tumour is growing into the area in front of the spine in the neck, surrounds a carotid artery, or is growing down into the space between the lungs (T4b). The cancer might or might not have spread to nearby lymph nodes (any N). It has not spread to distant parts of the body (M0).
	Any T N3 M0	The tumour can be any size and might or might not have grown into structures outside the hypopharynx, and it might or might not have affected a vocal cord (any T). The cancer has spread to at least one lymph node that is larger than 6 cm across, OR it has spread to a lymph node and then grown outside of the lymph node (N3). It has not spread to distant parts of the body (M0).

All stages of laryngeal and hypopharyngeal cancer can be seen in Annex 1.

3.6. Laryngeal and hypopharyngeal locally advanced cancer treatment (37)

The treatment algorithm for these cancers is divided depending on the feasibility of surgery:

If the tumour is **resectable** there are 2 possible options:

1- Surgery followed by adjuvant treatment. Adjuvant treatment consists in:
   a. Chemo-radiotherapy in patients with major risk factors (extracapsular invasion, affected margins)
   b. Radiotherapy in patients with minor risk factors (lymph node affectation without extracapsular invasion, vascular/lymphatic/perineural invasion and primary tumour pT3-pT4)
2- Organ-preservation strategies:
   a. Radical concomitant chemo-radiotherapy
   b. Neoadjuvant (or induction) chemotherapy followed by loco-regional treatment, which may vary depending on the response to chemotherapy and consists in a combination of radiotherapy, cisplatin, cetuximab and surgery.

If the tumour is **non-resectable**, different treatment options are available:

1- Concomitant chemo-radiotherapy
2- Chemotherapy
3- Neoadjuvant chemotherapy followed by loco-regional treatment with chemo-radiation

In any of these 3 cases, cervical lymph-node dissection is recommended in case of complete local response (demonstrated by a negative PET-CT) with residual lymph-node disease.

Radiotherapy regimen consists in 33 sessions administered daily from Monday to Friday, which means a total of six weeks and three days, with a total dose of 70 Gy. The most common chemotherapy protocol used is three cycles of TPF, which consists in a combination of paclitaxel, cisplatin and 5-fluorouracil. Cetuximab is a monoclonal antibody with the epidermic growth factor receptor as target which is used in patients that present severe toxicity to chemotherapy or an important deterioration of their general status. (37,38)

Note that all these treatments are conditioned by other factors such as patient age, comorbidities presented, Performance Status, tumour subtype and location…

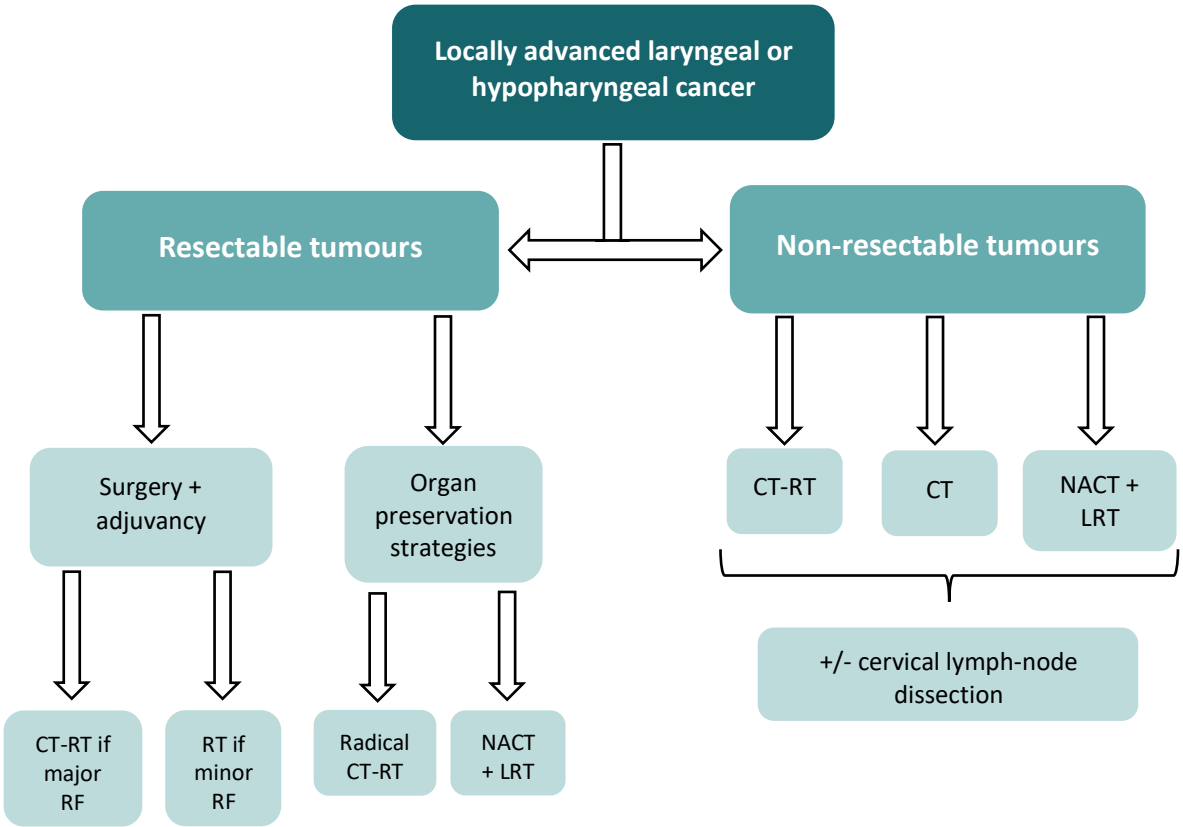

Figure 2: Locally advanced laryngeal and hypopharyngeal cancer treatment strategies.
CT: Chemotherapy; RT: Radiotherapy; RF: Risk factors; NACT: Neoadjuvant chemotherapy; LRT: Loco-regional treatment

3.7. Psychosocial interventions in HNC patients

In concordance with the influence it has been attributed to psychosocial factors in the laryngeal and hypopharyngeal cancer patient journey –from the risk factors associated with the development of the disease to the side effects related with treatment and its comorbidities-, implementing useful psychosocial interventions has been a major concern in the prevention and treatment of these patients in recent years.

Furthermore, evidence-based psychosocial treatments have high potential to complement biomedical treatment efficacy. (27) In long-term breast cancer survivors, psychological intervention has been associated with positive outcomes not only on the emotional status of patients but also on symptoms related to disease and treatment, being reflected on a decreased morbidity and higher QoL scores. (22) Additionally, early psycho-social intervention post-diagnosis of advanced cancer can have beneficial effects in terms of QoL and reduce comorbidities such as depression or anxiety. (28)

3.7.1. Cognitive behavioural therapy

Cognitive behavioural therapy (CBT) is an evidence-based psychological approach focused on helping individuals to identify, analyse and modify existing patterns of thinking, emotional reactions and behaviour via an assessment of current difficulties, and to try out new approaches progressively, monitoring and evaluating effects in all three areas. (39)

Despite CBT can be offered in different modes (individualized, group therapy, for home use without therapist…), the preferred mode of patients is the one-to-one therapy. In the same way, professionals also consider individualized CBT as their preferred option. (40)

CBT has been studied in HNC patients with BID in an intervention known as BRIGHT (Building a Renewed ImaGe after Head and neck cancer Treatment), with positive outcomes and demonstrated feasibility, acceptability and preliminary efficacy, even though further research is needed. (26)

4. JUSTIFICATION

HNC include some of the most traumatic and psychologically distressing cancers and have huge comorbidities which affect every-day patients' life. (1–3,5–8) Laryngeal and hypopharyngeal cancers are anatomically related and have common risk factors, which allow an integrated study of both sites. In fact, hypopharyngeal cancer is frequently diagnosed in advanced stages and usually leads to a wrong diagnosis as laryngeal cancer. (9)

Quality of life is a difficult concept to define and quantify as it includes many aspects and is inherently based in the subjective experience of individuals. (41) The WHO defines QoL as "an individual's perception of their position in life in context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns."(42)

Previously, survival was the exclusive goal of cancer treatment. However, there is an increasing recognition of QoL as an important outcome, and it has been even associated with predicting survival. (41) In accordance with this, laryngeal and hypopharyngeal cancer patients are treated by a multidisciplinary team which includes surgical and oncological specialists, HNC specialized nurses who educate patients to become competent and autonomous in changing their laryngeal cannula, speech pedagogues, nutritionists and others. Even so, psychological support provided by a psycho-oncologist expert during the cancer journey is not still part of the standard treatment.

As previously mentioned, laryngeal and hypopharyngeal cancer patients have traditionally been described as individuals with low SES, poor or lack of a social network and multiple behavioural risk factors and comorbidities such as tobacco and alcohol consumption, drug dependence and abuse, depression or anxiety. All these factors combined make these patients the perfect profile for a CBT intervention, given the potentially positive impact and benefit they can take out. Moreover, research on the role of CBT as a complementary treatment in this patient population can provide new knowledge on how it influences not just in short-term well-being, but also on survival rates and long-term comorbidities.

Limited research has been done about how psycho-social interventions can improve these patients QoL, and most of the studies conducted in this area showed inconclusive results and/or had several limitations. However, there is consensus in one point: further investigation is needed to set up strong evidence regarding the relationship between psychosocial interventions and a QoL improvement among locally advanced laryngeal and hypopharyngeal cancer patients.

5. HYPOTHESIS

5.1. Primary hypothesis

- The addition of CBT sessions to the standard treatment is an effective strategy for improving the QoL in patients diagnosed with locally advanced laryngeal or hypopharyngeal cancer, compared to the standard treatment alone.

5.2. Secondary hypothesis

- The addition of CBT sessions to the standard treatment is an effective strategy for improving the 1-year survival rates in patients diagnosed with locally advanced laryngeal or hypopharyngeal cancer, compared to the standard treatment alone.
- The addition of CBT sessions to the standard treatment is an effective strategy for reducing the amount of comorbidities in patients diagnosed with locally advanced laryngeal or hypopharyngeal cancer, compared to the standard treatment alone.

6. OBJECTIVE

6.1. Primary objective

- The purpose of this trial is to study the efficacy of the addition of CBT sessions to the standard treatment on improving QoL among patients diagnosed with locally advanced laryngeal or hypopharyngeal cancer, in comparison with the standard treatment alone.

6.2. Secondary objectives

Other objectives of this study are:

- To study the efficacy of the addition of CBT sessions to the standard treatment on improving 1-year survival rates among patients diagnosed with locally advanced laryngeal or hypopharyngeal cancer, in comparison with the standard treatment alone.
- To study the efficacy of the addition of CBT sessions to the standard treatment on reducing the amount of comorbidities among patients diagnosed with locally advanced laryngeal or hypopharyngeal cancer, in comparison with the standard treatment alone.

7. METHODOLOGY

7.1. Study design

A **multicentre, prospective, single-blinded, randomized clinical trial** will be performed at the Head and Neck Tumours Functional Unit (HNTFU) of 8 different hospitals from the Institut Català de la Salut (ICS), in a 3 years and 4 months period:

- Hospital Universitari Doctor Josep Trueta
- Hospital Universitari de Bellvitge
- Hospital Universitari Vall d'Hebron
- Hospital Universitari Germans Trias i Pujol
- Hospital Universitari Arnau de Vilanova
- Hospital Universitari Joan XXIII
- Hospital de Tortosa Verge de la Cinta
- Hospital de Viladecans

These hospitals have been chosen as all them offer public service, they are all directed by ICS and they are all referral hospitals in their respective geographic areas. More information about hospitals included in the study can be seen in Table 8. (43–45)

Methodology will consist in randomly assigning every patient in one of the two groups: the control group and the intervention group. In the **intervention group,** patients will receive the standard treatment based on patients' and tumour characteristics, with the addition of multiple CBT sessions with a psycho-oncologist. Meanwhile, in the **control group**, the same standard treatment will be applied, also complemented with multiple sessions with a psycho-oncologist but without a therapeutic goal.

Table 8: Characteristics of hospitals included in the study: location, geographical area of care and basic population

Hospital	Location (Geographical area of care)	Basic population
Hospital Universitari de Girona Doctor Josep Trueta	Girona (Alt Empordà, Baix Empordà, Garrotxa, Gironès, Pla de l'Estany, Selva, Ripollès, Cerdanya oriental)	750,000 inhabitants

Hospital Universitari de Bellvitge	Hospitalet de Llobregat (Hospitalet de Llobregat, Prat de Llobregat)	200,000 inhabitants
Hospital Universitari Vall d'Hebron	Barcelona (Horta-Guinardó, Nou Barris and Sant Andreu districts, Montcada i Reixac)	400,000 inhabitants
Hospital Universitari Germans Trias i Pujol	Badalona (Barcelonès Nord, Maresme)	800,000 inhabitants
Hospital Universitari Arnau de Vilanova	Lleida (Lleida, Alt Pirineu, Aran, Aragonese fringe)	400,000 inhabitants
Hospital Universitari Joan XXIII (Tarragona)	Tarragona (Alt Camp, Conca de Barberà, Baix Camp, Baix Penedès, Tarragonès, Priorat)	800,000 inhabitants
Hospital de Tortosa Verge de la Cinta	Terres de l'Ebre (Baix Ebre, Montsià, Terra Alta, Ribera de l'Ebre)	200,000 inhabitants
Hospital de Viladecans	Viladecans (Castelldefels, Viladecans, Gavà, Begues, Sant Climent de Llobregat)	200,000 inhabitants

7.2. Population

The study population includes individuals aged 18 years or older who have been newly diagnosed of locally advanced laryngeal or hypopharyngeal SCC, and are undergoing treatment at any of the 8 hospitals participating in this trial.

7.2.1. Inclusion criteria

- Individuals aged 18 years or older.
- Individuals newly diagnosed of locally advanced SCC of larynx or hypopharynx.
- Individuals who have signed the informed consent (Annex 3).

7.2.2. Exclusion criteria

- Individuals with presence of metastatic disease or other fatal conditions at the diagnosis.
- Individuals diagnosed of tumours with histological patterns that differ from SCC.
- Individuals with an inadequate level of awareness nor ability to collaborate throughout the process.
- Individuals who have participated in CBT session in the last 6 months.

7.2.3. Withdrawal criteria

- Individuals who revoke of informed consent.
- Individuals who flagrantly fail to comply with the study procedures.

7.3. Sample

7.3.1. Sample selection

All patients diagnosed of locally advanced SCC of larynx or hypopharynx in any of the 8 hospitals participating in the trial will be informed about the aim of the study and will be invited to voluntarily join. They will receive an informative document about what implies joining the study (Annex 2) and the informed consent (Annex 3) that needs to be signed to participate.

A **non-probabilistic consecutive sampling** will be applied to patients meeting all the inclusion criteria and none of the exclusion criteria.

7.3.2. Sample size

The sample size of this study has been calculated with GRANMO application.

Accepting an alpha risk of 5% and a statistical power of 80% in a two-sided test, **123 subjects will be needed in each group (a total of 246 subjects)** in order to detect a difference of 9 units or more. A common standard deviation of 23 is assumed. It has been estimated a drop-out rate during the follow-up period of 20%.

The common standard deviation value is extracted from the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 reference values. (46) The 9 units established as the minimum difference to detect is based on expecting a low-moderate impact in this trial, which stands for a 0.4 standard deviation.

According to data collected from Registre Hospitalari del Càncer a Girona, 268 new cases of laryngeal and 44 of hypopharyngeal SCC were diagnosed in the period from 2013 to 2017 in the province of Girona (in a population of 742,528 individuals). (47)

Other studies observed that 35% of laryngeal cancers and 78% of hypopharyngeal cancers are diagnosed in a locally advanced stage. (48,49) If this percentage is applied to the data extracted from Registre Hospitalari del Càncer a Girona, we can conclude that from 2013 to 2017 94 new cases of laryngeal cancer and 34 of hypopharyngeal cancer were diagnosed at a locally advanced stage. That means that, **annually, 19 new cases of laryngeal cancer and 8 of hypopharyngeal cancer (27 cases in total) are diagnosed in the province of Girona in a locally advanced stage.**

This same estimation is applied and summarized for every participating hospital and their basic population information in Table 9.

Table 9: Hospitals participating in the study estimated number of patients of interest according to their basic population		
Hospital	**Basic population**	**Estimated number of locally advanced laryngeal or hypopharyngeal cancer diagnosed annually**
Hospital Universitari de Girona Doctor Josep Trueta	750,000 inhabitants	27 patients
Hospital Universitari de Bellvitge	200,000 inhabitants	8 patients
Hospital Universitari Vall d'Hebron	400,000 inhabitants	15 patients
Hospital Universitari Germans Trias i Pujol	1,000,000 inhabitants	37 patients
Hospital Universitari Arnau de Vilanova Lleida	400,000 inhabitants	15 patients
Hospital Universitari Joan XXIII (Tarragona)	800,000 inhabitants	29 patients
Hospital de Tortosa Verge de la Cinta	200,000 inhabitants	8 patients
Hospital de Viladecans	200,00 inhabitants	8 patients
TOTAL		**147 patients**

As seen in Table 9, 147 patients will be recruited in 12 months from the 8 participating hospitals. So, **to reach the 246 needed patients for this trial, 20 months of recruitment will be needed.**

7.3.3. Randomization

Computerized randomization will be used to identify and balance any potential confounder, and in this way, a potential confusion bias is avoided. Randomization will also avoid subject assignment bias.

Participants will be randomly assigned to the intervention or control group in a 1:1 ratio using an independent computerized randomization system. While the independent statistician in charge of analysing the data and the patients will be blinded, the psycho-oncologist and physicians will know whether the technique has been performed or not, so they will not be blinded. In conclusion, this trial will be **a single-blinded study**.

7.4. Variables and measuring methods

7.4.1. Independent variable

The independent variable of this study is the **CBT sessions**, which will be categorized as applied or not applied. Thus, it is a dichotomous, nominal and qualitative variable.

More information about the duration and procedure of CBT sessions can be seen in *7.7. Study intervention* section.

7.4.2. Dependent variable

1. Primary dependent variable:

   The main dependent variable of this study is the **QoL**, which will be measured by 2 questionnaires: the **EORTC QLQ-C30 questionnaire** (Annex 6) and the complementary **EORTC QLQ-H&N43 questionnaire** (Annex 8).

   Scores on these questionnaires are ranged from a maximum of 298 to a minimum of 73. In order to simplify the scores obtained through questionnaire and to ease results comparisons, results are transformed into means, scoring from 0 to 100. Thus, this variable will be categorized as the score obtained in the item **"global health status/QoL" in a scale from 0 to 100,** which is a discrete, ordinal variable.

   More details about questionnaires items, scoring and results can be seen in *7.6. Measuring instruments* section.

2. Secondary dependent variables:
   a. Overall **survival at 1-year after diagnosis** in patients with locally advanced larynx or hypopharynx SCC, defined in two groups: alive or dead. Thus, it is a dichotomous, nominal and qualitative variable.
   b. The **number of comorbidities** will be assessed by the 2 questionnaires mentioned before. A score equal or higher than 50 (in a scoring range from 0 to 100) will be considered as the presence of the symptom evaluated by the item. It will be categorized as the number of comorbidities presented, so it will be a simple discrete variable.

Table 10: Summary table of independent and dependent variables				
	VARIABLES	**DESCRIPTION**	**MEASUREMENT**	**CATEGORIES**
INDEPENDENT VARIABLE	**CBT sessions**	Dichotomous, nominal and qualitative variable	Attendance to sessions with a psycho-oncologist	Applied / Not applied
MAIN DEPENDENT VARIABLES	**QoL**	Discrete ordinal variable	EORTC QLQ-C30 questionnaire	0 to 100
SECONDARY DEPENDENT VARIABLES	**Survival**	Dichotomous, nominal and qualitative variable	Clinical history patients' check	Alive / Dead
	Amount of comorbidities	Simple discrete variable	EORTC QLQ-C30 and EORTC QLQ-H&N43 questionnaires	Number of comorbidities presented

CBT: Cognitive behavioral therapy; QoL: Quality of life; EORTC: European Organization for Research and Treatment of Cancer.

7.4.3. Covariates

All covariates will be collected in the computerized data collection sheet (Annex 5)

Patients' covariates:

- **Age**: It is a quantitative variable measured in years but categorized in intervals, resulting in a qualitative polytomous ordinal variable. The intervals are as follow:
    - 18-39 years
    - 40-59 years
    - 60-79 years
    - 80 or more years
- **Gender**: It is a categorical nominal variable categorized as male, female or non-binary.
- **Socioeconomic status**: It is a qualitative ordinal variable that will be divided from I to V taking into account the patient's occupation and education level according to the work of Domingo et al. (50)

- **Tobacco smoking:** Tobacco is a risk factor for developing a primary laryngeal or hypopharyngeal tumour and also increases the risk of relapse. It is for this reason that it can be a potential confounding factor. It is evaluated with packages/year index:

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

  Results are classified as a quantitative discrete variable in low risk (≤20), moderate risk (21-40) and high risk (≥41).
- **Alcohol consumption:** As tobacco, is a main risk factor for developing primary laryngeal or hypopharyngeal tumour or relapses. It will be classified as a quantitative discrete variable in four groups depending on the grams of alcohol consumed daily: non-consumers, low consumers (<20g for women and <50g for men), moderate consumers (20-40g for women and 50-60g for men) and high consumers (>40g for women and >60g for men).

Disease-related covariates

- **HPV infection**: it has been demonstrated that pharyngeal (and especially oropharyngeal) SCC positive for HPV (especially p16) has a different evolution and prognosis compared to those related with tobacco and alcohol consumption. Although it is still unclear the role that HPV plays in laryngeal and hypopharyngeal cancer, it should be taken as a possible confounding. A HPV PCR will be done to every patient and will be classified as a qualitative dichotomous variable in two groups: positive or negative.
- **Treatment received**: Different treatment strategies can be applied in larynx and hypopharynx locally advanced cancer patients depending on both tumour and patient characteristics. As treatments can notably differ and be related with multiple and a huge variation of comorbidities, it is necessary to take it into account as a possible confounding. They will be categorised as a qualitative nominal dichotomous variable depending on if the patient has received surgery or not.
- **Staging**: As treatment options and prognosis may vary depending on the stage at the diagnosis moment, patients will be divided in 3 groups: stage III, IVA or IVB.

Table 11: Summary table of covariates			
COVARIATES	**DESCRIPTION**	**MEASUREMENT**	**CATEGORIES**
Age	Qualitative polytomous ordinal variable	Self-refereed	18-39 years / 40-59 years / 60-79 years / 80 or more years
Gender	Categorical nominal variable	Self-refereed	Male / Female / Non-binary
SES	Qualitative ordinal variable	Occupational and educational level	Class I to V
Tobacco smoking	Quantitative discrete variable	Packages/year index	Low / Moderate / High risk
Alcohol consumption	Quantitative discrete variable	Grams of alcohol consumed daily	Non consumer / Low consumer / Moderate consumer / High consumer
HPV infection	Qualitative nominal dichotomous variable	p16 determination in biopsy or HPV PCR	Positive / Negative
Treatment received	Qualitative nominal dichotomous variable	Head and neck specialized physician criteria	Surgery / No surgery
Staging	Qualitative ordinal variable	TNM and AJCC staging classifications	III / IVA / IV B

SES: Socioeconomic status; HPV: Human papillomavirus; AJCC: American Joint Committee on Cancer

7.5. Measuring instruments

7.5.1. EORTC QLQ-C30 questionnaire

It is a **30-item cancer-specific questionnaire, patient based measure designed for self-administration that evaluates patients' quality of life**. It has cross-cultural validity and its psychometric properties are considered satisfactory. The items are distributed in 3 different groups:

1. Functional scales: physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning.

2. Symptom scales/items: fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties.
3. Global health status/QoL: global health status/QoL.

All scales and items are measured from 1 to 4 except global health and global QoL which are measured from 1 to 7. In order to give standardized results to facilitate comparisons they can be recalculated in a 0 to 100 scoring range: **a high score for functional scales and global health status reflect a high level of functioning and QoL, whereas high scores for symptom scales represent a higher level of symptoms and a lower QoL**.

All questions can be consulted in Annex 6.

The EORTC QLQ-C30 scoring manual will be used to calculate the final scorings (Annex 7).

7.5.2. EORTC QLQ-H&N43 questionnaire

This is a **supplementary questionnaire which is used in combination with the QLQ-C30 questionnaire to measure QoL in HNC patients**. This questionnaire is the renewed version of the EORTC QLQ-H&N35 and QLQ-H&N37; it has been already validated and it is being used broadly all over the world. This new version includes new items which consider symptoms that come up from new treatment strategies in HNC that are emerging in recent years.

The QLQ-H&N43 consists in 43 items, distributed in 6 multi-item and 13 single-item symptom subscales, which evaluate pain, swallowing, senses (taste and smell), speech, social eating, social contact, sexuality, teeth, dry mouth and sticky saliva, body image, shoulder pain, skin problems, anxiety, opening mouth, coughing, lymphedema, wound healing, weight loss and neurological problems.

All questions can be seen in Annex 8.

Scoring is identical to the QLQ-C30 questionnaire, scoring from 1 to 4 and then it can be recalculated in a 0 to 100 range, where **higher scores represent higher levels of symptoms and lower QoL**.

The EORTC QLQ-H&N43 scoring manual will be used to calculate the final scorings (Annex 9)

7.6. Study intervention

It is important to note that patients will be informed of the aim of the study as to be "**evaluating the influence on patients' wellbeing of therapeutic tools which are not used in the standard treatment of the disease**", but not describing nor giving extra information about any factor knowing it may be susceptible of producing bias by a changing of behaviour. In addition, data

analysts will also be blinded. Contrary, physicians will recruit suitable patients for the study and psycho-oncologists will be in charge of developing CBT sessions (which will have different objectives in the intervention and control group) and so they must necessarily know to which group every patient belongs.

Consequently, **patients and data analysers will be blinded** to QoL changes related to CBT as being the subject of study, but **physicians and psycho oncologists won't be able to be blinded**. Thus, **this trial will be a single-blinded study.**

Any patient who visits a HNTFU of any of the participating hospitals that meet inclusion and exclusion criteria will be informed about the existence and the aim of this study and will be given one week to read all the information and decide whether they want to participate or not. All the patients interested in joining the study must sign the informed consent (Annex 3) to be included, and relevant data will be registered in the data collection sheet (Annex 5) by a head and neck expert physician.

A **HPV PCR** test will be performed on every patient before randomization and it will be registered in the data collection sheet (Annex 5). HPV infection, especially p16 serotype, has been demonstrated as an independent risk factor for hypopharyngeal cancer (although with less strength compared to oropharyngeal cancer) and its relation with laryngeal cancer remains unclear. HPV it is a well-known prognosis factor, as HNC associated with HPV are usually diagnosed at later stages, with smaller primary tumours and more advanced neck disease but, contrary, these cases have better treatment response.

After that, all patients will be **randomly assigned** to one of the two groups explained.

Patients participating in the **intervention group will undergo multiple CBT sessions** with the following structure:

The **first CBT session** will be scheduled the day that the patient returns the signed informed consent. This first session will take place on the same day as the beginning of treatment, whether it is surgery, chemotherapy or radiotherapy, and it will be conducted immediately before treatment starting, in order to stablish an idea of the **baseline QoL** of patients prior to any treatment.

Future sessions will be scheduled once a week for the first two months. As part of the patients will have to come to the hospital for daily radiotherapy treatment, CBT sessions will be scheduled before or after treatment if possible, reducing the number of times that patients have to come and trying to minimize a possible attrition bias. After eight weeks, patients will be asked

to come once every two weeks for two months and then once a month for two months, being **a total of 15 CBT sessions in a 6-month period**.

The same psycho-oncologist will give to every patient, before the beginning of sessions, the **QoL questionnaires** (Annex 6 and 8) **to answer 6 times during this 6-month period**: within the first CBT session and once a month for the whole intervention time.

Every session will be conducted by an expert psycho-oncologist properly trained and will last between 45 minutes and 1 hour. The content and main themes of CBT sessions are summarized in Table 12, adapted from: *Effects of Cognitive Behavioral Therapy for Depression and Anxiety, Response Rates and Adverse Events in Patients with Locoregional Advanced Nasopharyngeal Carcinoma.* (51)

Table 12: Weekly themes and main content of CBT sessions.

CBT session	Weekly theme
1	Introduction session - Introducing to each other and begin to build a relationship - Introducing to CBT model: what it is, what to expect and how it will be conducted through sessions - Interrogate and know better the patients' background: family structure, SES, education and working status, comorbidities such as depression or anxiety, toxic habits… - Explaining the patient possible adverse effects that can happen during treatment.
2-9	Associating thoughts, emotions or feelings and behaviour sessions - Identifying of automatic thoughts through different strategies: questioning, case discussion, role play… - Understanding the automatic thoughts and emotional and behavioural reflection associated with their disease.
10-14	Cognitive restructuring sessions - Changing unreasonable cognition and generate alternative thoughts - Strengthening positive cognitive style - Teaching relaxation skills such as mindfulness meditation, abdominal breathing, progressive muscle relaxation training…

15	Closing session - Sharing attitudes and experiences before and after the sessions - Sharing experiences of applying cognitive-restructuring skills - Establish long-term personal goals and ending the treatment relationship

CBT: Cognitive behavioural therapy; SES: Socioeconomic status.

Patients participating in the **control group** will also attend to follow-up sessions and will fill the QoL questionnaires (Annex 6 and 8) with a psycho-oncologist at the same frequency as the intervention group. Unlike the intervention group, these sessions won't have a therapeutic objective. Instead, they will mainly consist of informational sessions where the patient and the psycho-oncologist will discuss about the patient's illness, the treatment they have received/are receiving and potential complications that may occur.

Psycho-oncologists will be in charge of ensuring all questionnaire are answered properly and to calculate final scores (ranging from 0 to 100) for every item of both questionnaires. After every session where questionnaires have to be filled, the psycho-oncologist will record the scores in the data collection sheet (Annex 5) to prevent any information loss. When necessary, they will also include notes after every CBT session about the topics discussed and the resulting outcomes.

6 months after the end of the intervention (1 year after diagnosis) **survival will be evaluated**, determining in every patient if they're alive or not by checking their clinical history. After that, all data will be collected by the hospital coordinator and send it to the main investigator to be entered on the database.

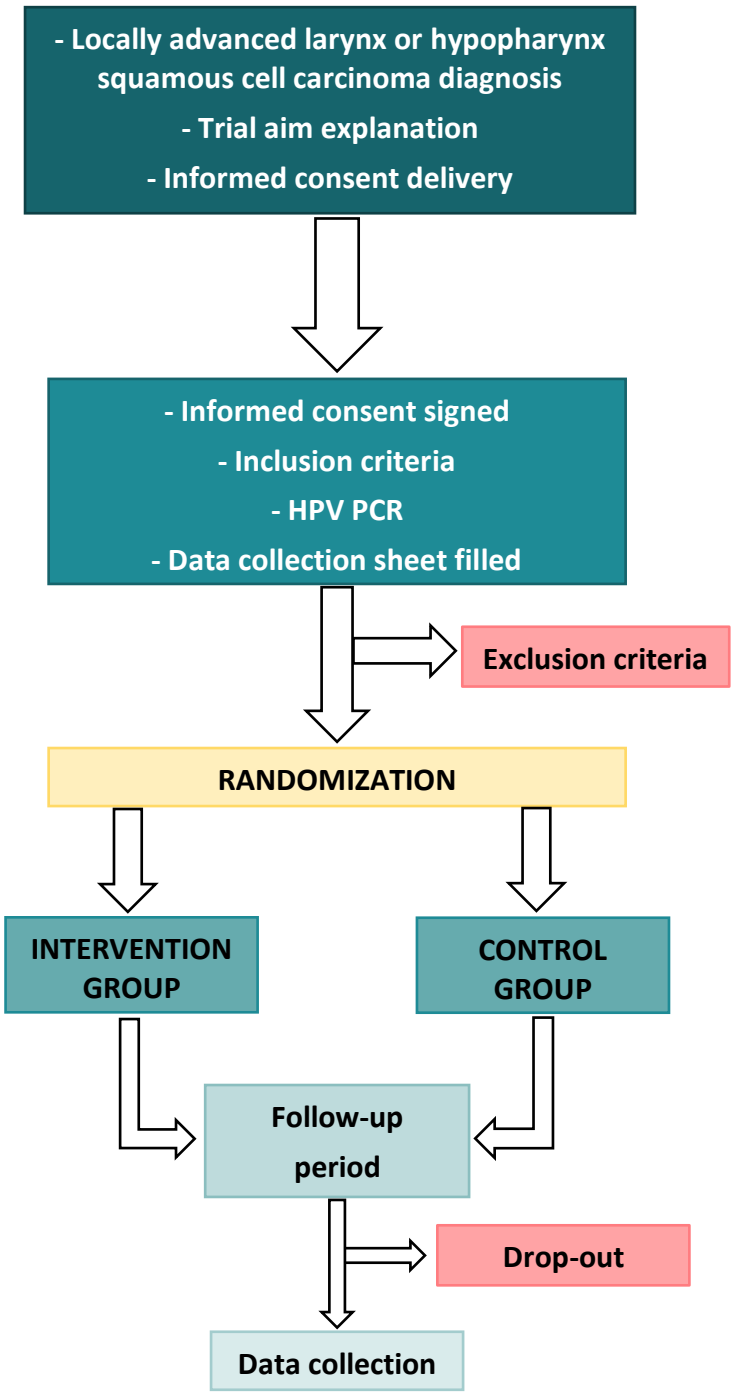

Figure 3: Flow diagram of the study
HPV: Human papillomavirus

7.7. Patient journey

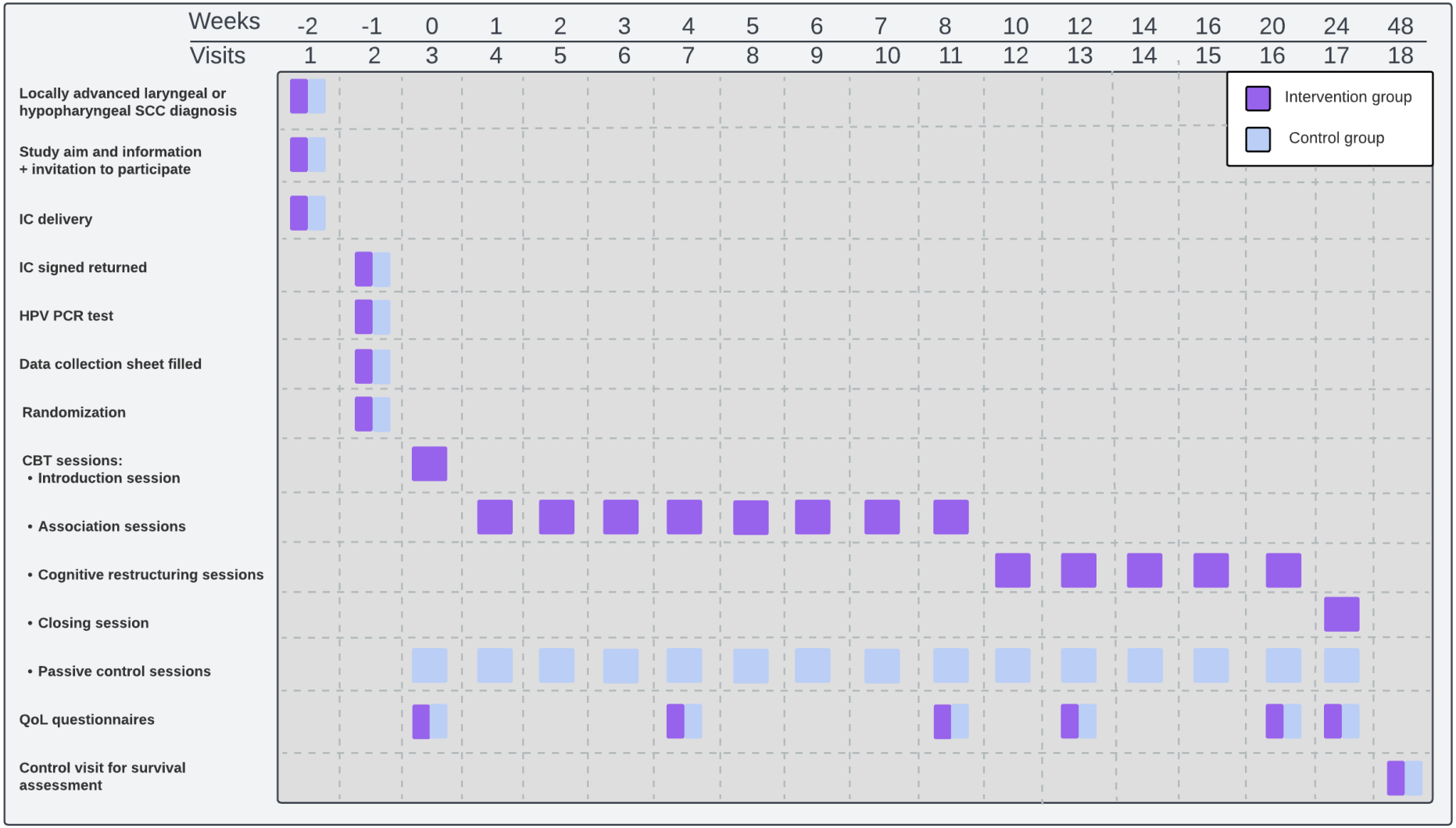

Figure 4: Patient journey diagram

IC: Informed consent; HPV: Human papillomavirus; CBT: Cognitive behavioural therapy; QoL: Quality of life

7.8. Data collection

A computer database will be created in order to collect all data from patients, always maintaining anonymity. This database will be fundamental to facilitate posterior data analysis.

All head and neck expert physicians involved in the study will be trained on how to fill the data collection sheet (Annex 5) in the first visit with patients in aim to avoid possible confusion about which information is necessary and how should be registered.

All psycho-oncologists participating in the study will be trained on how to direct CBT sessions and which are the main themes to treat in each session in order to apply homogenous criteria. They will also be trained on how to properly fill QoL questionnaires to avoid mistakes in scoring items and calculating final scores.

7.9. Statistical analysis

A statistical analyst will be in charge to analyse all data obtained. They will be blinded to ensure final results are not interfered. A p-value <0.05 will be considered as statistically significant, defining a 95% confidence interval for all analyses. The software used will be *Statistical Package for Social Sciences (SPSS)*.

We will evaluate quantitative variables to know their distribution: if there is a normal distribution they will be expressed with mean and standard deviation, whereas they will be expressed with median if its distribution is atypical. Qualitative variables will be expressed in proportions. The sample of this study will be examined and characterized using sociodemographic information.

QoL will be assessed by comparing scores of the "*Global Health Status/QoL"* item of the EORTC QLQ-C30 in both the intervention and the control group separately before the beginning and after the end of the intervention. Results between the two groups will also be compared in order to provide a comprehensive and integrative analysis of the impact of the intervention.

We will calculate **survival** rates at 1 year after diagnosis in both groups and compare them.

In order to assess **comorbidities**, we will compare every individual item of both QoL questionnaires before the beginning and after the end of CBT sessions in each group. Furthermore, we will compare the results between the two groups.

QoL, survival rates and comorbidities will be also analysed for different **subgroups**, considered as covariates, which may influence the outcomes: age, sex, SES, alcohol intake, tobacco consumption, HPV infection, stage and treatment strategy.

In order to avoid a possible attrition bias, we will perform an **intention-to-treat analysis**, imputing lost data during the intervention and follow-up with last observation carried forward technique.

8. WORK PLAN

8.1. Participating centers

The centers proposed to carry out the study are as follow:

- Hospital Universitari de Girona Doctor Josep Trueta
- Hospital Universitari de Bellvitge
- Hospital Universitari Vall d'Hebron
- Hospital Universitari Germans Trias i Pujol
- Hospital Universitari Arnau de Vilanova
- Hospital Universitari Joan XXIII
- Hospital de Tortosa Verge de la Cinta
- Hospital de Viladecans

8.2. Research team members

A multidisciplinary team will be needed for this project. The team will be composed by:

- **Main investigator:** The person who will lead the study, will be in contact with the coordinators of every hospital participating in the study and will try to make everything go as planned.
- **Hospital coordinators:** There will be a hospital coordinator in every participating centre. Their role will consist in collecting all the data at the end of the intervention and ensure the protocol is being properly applied.
- **Psycho-oncologist:** They will be the persons in charge to develop the CBT sessions, to give patients the QoL questionnaires and to collect them in order to be analysed.
- **Health care professionals:** Here it is included any other worker that will have contact with patients participating in the study, mainly head and neck physician and nurses that visit and treat patients suitable for the study.

8.3. External contractors

- **Independent statistician:** The person who will perform database control, data analyses and interpret the results obtained.
- **Quality data controller:** Foreign person hired to guarantee all data collected from each hospital in the study agrees with the database information and the final results.
- **Computer engineer:** A computer engineer will be hired to create a computer data collection sheet and database in order to store all the information of the study.
- **Linguistic proofreader:** This person will be hired to revise and correct any errors.

9. CHRONOGRAM

The whole study will have an estimated duration of 40 months, which is the same as **3 years and 4 months**. Several steps will be successively done in this trial, grouped in 6 stages:

9.1. Study stages

Stage 1: Protocol elaboration and study design (2 months: January-February 2024)

1. First meeting (January 2024): The aim of this session is to share ideas about this project and its area of study.
2. Bibliographic research and protocol elaboration (January-February 2024): Exhaustive bibliographic research needs to be done in order to compile the latest evidence and studies about topics of interest for the project, as well as to have a solid basis for the protocol redaction.
3. Data collection sheet creation (January-February 2024): A computerized answer-filling prototype will be created by a computer engineer to enter all the relevant information of the patient, any CBT session outcomes and QoL questionnaires scores.
4. Hospitals participating contact (February 2024): The main investigator will get in contact with every hospital selected in the study and will invite them to join.

Stage 2: Ethical approval (3 months: February-April 2024)

5. Ethical evaluation and approval: The main investigator will present the protocol to the "Comitè Ètic d'Investigació Clínica (CEIC)" of every hospital participating in the study for their ethical approval. Any suggestion pointed by CEICs will be analysed and modifications will be considered.

Stage 3: Coordination and health professional training (1 month: April 2024)

6. Meeting with each hospital: The main investigator will meet every hospitals' research team and will designate a coordinator for each hospital in the study.
7. Formation sessions: An online session will be organized for all hospital coordinators, health and neck specialized physicians and psycho-oncologists participating in the study to learn how to use and fill properly the **data collection sheet** (Annex 5). In addition, a rigorous standardized training program for psycho-oncologists, directed by an expert in the field will be taught in order to apply a homogenous criteria in **CBT sessions** to ensure the quality and uniformity of this research.

Stage 4: Sample recruitment, intervention, follow-up and data collection (33 months: May 2024-January 2027)

8. Sample recruitment (May 2024-December 2025): Patients who meet all the inclusion criteria and none of the exclusion criteria will be recruited by a HNC specialized physician. All patients must sign the informed consent to join the study. Recruitment will finish when each group is formed by 123 patients, which will last 20 months.
9. Intervention (May 2024-June 2026): As the intervention lasts 6 months for each patient, it will start in May 2024, with the first patient recruited, and will end in June 2026, 6 months after the last patient recruited.
10. Follow-up (May 2025-December 2026): Follow-up consists in a control visit for each patient 6 months after the intervention. It is a protocol visit which is eventually performed in the standard treatment, and it will be used as the moment to evaluate survival rates at 1 year after diagnosis.
11. Post-intervention data collection (January 2027): The hospital coordinator of every hospital will be in charge of collecting all the information from the data collection sheet and send it to the main investigator.

Stage 5: Data analysis and results interpretation (2 months: January-February 2027)

12. Creation of a computer database (January 2026): A computer engineer will be hired to create a database where all the anonymous data will be registered.
13. Statistical analysis and quality data control (January 2026): An independent statistician will be hired to analyse, interpret and compare all data collected.
14. Results interpretation and conclusions (January-February 2027): Results will be presented by the statistician to the research team, who will discuss the outcomes and end up with conclusions.

Stage 6: Results publication and dissemination (2 months: March -April 2027)

15. Article writing and publication (March 2027): The main investigator will write the final article, which will be revised by a linguistic proofreader and finally published.
16. Dissemination (April 2027): The study will be published as a journal article and will be presented to the Sociedad Española de Otorrinolaringología y Cirugía de Cabeza y Cuello (SEORL-CCC) National Congress and to the Confederation of European Otorhinolaryngology and Head and Neck Surgery (CEORL-HNS) International Congress.

9.2. Chronogram

STAGES AND ACTIVITIES	STAFF	YEARS																																					
		2024												2025												2026												2027			
		J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A
STAGE 1 –PROTOCOL ELABORATION AND STUDY DESIGN																																									
1. First meeting	MI	■																																							
2. Bibliographic research and protocol elaboration		■	■																																						
3. Data collection sheet creation	CE	■	■																																						
4. Hospitals participating contact	MI		■																																						
STAGE 2 – ETHICAL APPROVAL																																									
5. Ethical evaluation and approval	CEIC		■	■	■																																				
STAGE 3 – COORDINATION AND HEALTH PROFESSIONALS TRAINING																																									
6. Meeting with every participating hospital	MI, HC, HCP, PO				■																																				
7. Formation sessions					■																																				
STAGE 4 – SAMPLE RECRUITMENT, INTERVENTION, FOLLOW-UP AND DATA COLLECTION																																									
8. Sample recruitment	HCP					■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■																
9. Intervention	HCP, PO					■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■										
10. Follow-up																		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■				
11. Post-intervention data collection	HC																																					■			
STAGE 5 – DATA ANALYSIS AND RESULTS INTERPRETATION																																									
12. Creation of database	CE																																					■			
13. Statistical analysis and quality data control	S, QDC																																					■			
14. Results interpretation and conclusions	S, MI, HC, HCP, PO																																					■	■		
STAGE 6 – RESULTS PUBLICATION AND DISSEMINATION																																									
15. Article writing, revision and publication	MI, LP																																							■	
16. Dissemination	MI																																								■

MI: Main investigator; CE: Computer engineer; CEIC: Comitè Ètic d'Investigació Clínica; HC: Hospital coordinator; HCP: Healthcare professionals; PO: Psycho-oncologists; S: Statistician; QDC: Quality data controller; LP: Linguistic proofreader

10. BUDGET

10.1. Not included costs

- **Staff:** All the personnel participating in the research team won't be payed, as it is considered that their reason for joining this trial is the scientific prestige and gained knowledge, and shouldn't be boosted by an economic reward. The staff participating are: the main investigator, hospital coordinators, psycho-oncologists and all the head and neck expert physicians and nurses (health care professionals) from every participating hospital.
- **Materials:** The only material needed to develop CBT sessions is an adequate hospital meeting room, so it will not be considered in the study budget.
- **Liability insurance:** as this trial does not count with any invasive procedure and it is considered to have low intervention level, no insurance will be hired in this study.

10.2. Included costs

Personnel costs

- **Training session on data collection sheet:** An online session will be organized for all hospital coordinators, health and neck specialized physicians and psycho-oncologists participating in the study to learn how to use and fill properly the data collection sheet. The person in charge of the session will be paid 30€/h and the session is expected to last for an hour and a half, which make a total expense of 45€.
- **Psycho-oncologists training program:** A rigorous standardized training program directed by an expert in the field will be taught in order to apply a homogenous criteria in CBT sessions to ensure the quality and uniformity of this research. The expert trainer will be paid 80€/h and the program will be taught in 10h, which make a total expense of 800€.

Subcontracted services

- **Statistical analysis:** The statistician who will analyse all data will be paid 30€/h for an estimated work of 80h, which make a total expense of 2,400€.
- **Creation of a computerized data collection sheet and database:** A computer engineer will be hired to create an intuitive and accessible data collection sheet and a database. This service will cost 40€/h and will take 100h of work, which make a total expense of 4,000€.
- **Quality data control:** A quality data controller will be hired to guarantee all data collected from each participating hospital in the study agrees with the database

information and the final results. The person hired will be paid 40€/h and the expected workload is approximately of 500h, due to the high number of participants and the volume of patients' data that needs to be analysed. The work is budgeted at 20,000€.

Material costs

- **HPV PCR:** A PCR for HPV will be done to each patient at the beginning of the study. Each PCR costs 100€ and there are a total of 246 patients, so in total it is budgeted for 24,600€.
- **Printing costs:** Informative document (Annex 2), informed consent document (Annex 3) and withdrawn consent document (Annex 4) will be printed and given to each patient so they can read all documents calmly. This is a total of 6 pages for each patient. The printing cost is 0.03€/page and the sample size needed in this trial is of 246 participants, which makes a total expense of 44.28€.

Travel expenses and diets

- **Meetings:** The main coordinator will meet every hospitals' research team once the ethical approval is given by every hospitals' CEIC to introduce him/herself and to designate a hospital coordinator in each centre. There will be a total of 7 travels (1 per hospital) and each travel is budgeted at 100€, so in total it will be 700€.

Dissemination costs

- **Publication fees:** Main results and conclusions of this trial are expected to be published in a journal article. It is assumed 1,500€ for publication fees.
- **Linguistic correction:** A linguistic proofreader will be hired before the article publication in order to rectify any errors. It is budgeted at 200€.
- **National and international congresses:** The main investigator will present the trial results and conclusions at both national (SEORL) and international congresses (CEORL-HNS) with dissemination purposes. The congress registration fees are 500€ and 800€, respectively. Meals and accommodation will also be provided, with an additional cost of 500€ and 1,000€, respectively. Therefore, the total cost will be of 2,800€.

Table 13: Budget details of the study				
	ITEM	**HOURS OR UNITS**	**HOUR OR UNIT COST**	**SUBTOTAL**
PERSONNEL COSTS	Training session on data collection sheet filling	1.5h	30€/h	45€
	Psycho-oncologists training program	20h	80€/h	800€
				Subtotal: 845€
OUTSOURCED SERVICES	Statistical analysis	80h	30€/h	2,400€
	Creation of computerized data collection sheet and database	100h	40€/h	4,000€
	Quality data controller	500h	40€/h	20,000€
				Subtotal: 26,400€
FUNGIBLE COSTS	HPV PCR	246 units	100€/unit	24,600€
	Printing costs	1476 pages	0,03€/page	45€
				Subtotal: 24,645€
TRAVEL EXPENSES AND DIETS	Main investigator meetings with each hospital	7 meetings	100€/meeting	700€
				Subtotal: 700€
DISSEMINATION COSTS	Article publication fees	1 publication	1,500€	1500€
	Linguistic correction	1 publication	200€	200€
	National SEORL-CCC congress	1 congress	1000€	1000€
	International CEORL-HNS congress	1 congress	1800€	1800€
				Subtotal: 4,500€
				TOTAL COST: 57,290€

HPV: Human papillomavirus; SEORL-CCC: Sociedad Española de Otorrinolaringología y Cirugía de Cabeza y Cuello; CEORL-HNS: Confederation of European Otorhinolaryngology and Head and Neck Surgery

11. ETHICAL AND LEGAL CONSIDERATIONS

This study will be carried out according to the requirements established by the Medical World Association in the Declaration of Helsinki of Ethical Principles for Medical Research Involving Humans Subjects, established in 1964 and last revised in October 2013.

This trial obeys the Principles of Biomedical Ethics from Beauchamp and Childress, more commonly known as the four fundamental ethical principles: Beneficence, non-maleficence, autonomy and justice.

The **beneficence** principle is based on the moral duty to act for the well-being of others. In this study beneficence will be respected as all patients will receive one of the standard treatments for locally advanced laryngeal or hypopharyngeal cancer, which may include surgery, radiotherapy, chemotherapy or a combination of them.

The **non-maleficence** principle is honoured as all patients will receive the standard and adequate treatment for their condition, independently in which group they are assigned. Furthermore, as CBT is considered as a harmless intervention, patients in the intervention group are not assuming any additional risk by participating in this study.

The **autonomy** principle will be fully respected as patients will voluntarily join this study and only those who sign the informed consent will be able to participate. Patients will also receive an information document with all the details of the study, so they can freely decide if they're interested in participating.

Finally, the **justice** principle is guaranteed as every person meeting all the inclusion criteria and none of the exclusion criteria will be offered to participate in the study, without any kind of discrimination.

As mentioned before, an **informative document** (Annex 2) with an easily comprehensive and understandable language will be given to every potential participant to ensure complete awareness about this study. Obtaining a signed **informed consent** (Annex 3) from every participant is indispensable to participate. Every patient is free to refuse participating in the study and can **withdraw** (Annex 4) at any time without any prejudice. The decision whether or not to participate in the study will be respected according to the *Ley 41/2002, de 14 de*

noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica.

The **confidentiality and privacy** of all patients is assured with the *Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los Derechos Digitales*, as well as *Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data*. All data and clinical information collected from every patient throughout this study will be anonymous and confidential as each patient will be represented by a randomized code in both the computerized data collection sheet and the database. Furthermore, all data collected will be only accessible for the research team and will be only used for research purposes.

The study will be presented to the **CEIC** of every participating hospital, and their approval is mandatory for the trial to start. All suggestions proposed by any CEIC will be taken into consideration. This trial has been developed in accordance with the Spanish legal precepts of *Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios* Clínicos and Ley *14/2007, de 3 de julio, de Investigación Biomédica.*

No conflicts of interest are declared by the investigators in charge of this study. The main objective of this trial is to develop generalizable knowledge to improve human health and quality of life. All data will be transparently published and unfavourable results or outcomes will not be excluded.

12. LIMITATIONS AND STRENGHTS

12.1. Limitations

The primary disadvantage of this study is that a high cooperation from patients will be needed as they will have to attend to multiple CBT sessions over a long period of time. This may result in a notable drop-out rate and, in consequence, potentially committing an **attrition bias**. In order to correct it, we will employ an **intention-to-treat analysis**, imputing lost data using the last observation carried forward technique.

Given the impossibility to mask psycho-oncologists, a **detection bias** may occur. To minimize this potential bias, **blinding** will be implemented for both the patients and the statistician in charge of analysing the final results.

Furthermore, as this trial is designed as a multicentre study and the intervention –CBT sessions- is professional-dependent, there is a chance of **inter and intra variability** between both hospitals and professionals. With the intention to minimize this variability, all professionals will be properly **trained** by the same expert. However, this fact can also be a strength because multicentre studies have higher external validity than single-site studies.

12.2. Strengths

CBT and psycho-social interventions are **gaining power** as a powerful complementary therapeutic tool to conventional treatment, and its benefits have been proven in several pathologies and clinical conditions. The latest publications in HNC and specifically in larynx and hypopharynx cancer agree in the **need of more studies** evaluating this field due to both the lack of literature and great limitations in the few studies existing.

Hypopharynx and larynx cancers have treatments with important comorbidities such as mutilating surgeries, notable pain after radiotherapy or breathing and swallowing disorders. Patients usually have poor social networks and low SES that, in combination with this type of cancer and its treatment, potentially leads to a poor QoL and an increased risk to suffer from depression, anxiety or other disorders. It is because of all these arguments that the aim of this study can suppose a **huge benefit for this population**.

As this will be a randomized study, there is **no risk of a potential confusion bias** so all potential confounding variables (whether considered or not in this study) will be balanced between both groups through chance.

CBT can potentially **reduce healthcare costs** by improving patient adherence and well-being, which may lead to a reduced number of complications, rehospitalizations and additional medical treatments.

13. IMPACT ON THE HEALTH SYSTEM AND FUTURE RESEARCH

HNC represent an important group of tumours in terms of incidence, comorbidities and mortality rates. Among these, laryngeal cancers are the most prevalent, and usually hypopharyngeal cancers are often misdiagnosed as laryngeal cancer due to the combination of 2 factors: their anatomical relation and a lately diagnosis. Unfortunately, the majority of hypopharyngeal cancers and approximately 35% of laryngeals cancers are diagnosed in a locally advanced stage, resulting in poor survival rates and treatments with huge sequelae, leading to a poor QoL and potentially causing significant comorbidities such as depression, chronic pain, drug dependence, and many others.

The present study tries to put on focus of treatment the person and not the disease they suffer by implementing CBT sessions to a group of patients diagnosed with locally advanced laryngeal or hypopharyngeal cancer. We aim to assess their QoL during and after the intervention.

In this same line, CBT has demonstrated significant benefits in a large number of pathologies and medical conditions, both in terms of improving QoL and survival rates. Still, limited research has been done investigating the potential profit CBT might offer in laryngeal and hypopharyngeal cancer as part of a multidisciplinary treatment approach.

In summary, outcomes obtained in this trial may lead to an integration of psychological support and therapy into daily clinical practice for patients diagnosed of locally advanced carcinoma of larynx or hypopharynx.

14. FEASIBILITY

This study will be carried out in 8 different public hospitals from Catalunya, all of which count with a specialized head and neck service where our target population can be diagnosed recruited. With all this centres participating in the study, it is feasible to reach the required sample size in 20 months, which is an **acceptable period of time**.

Since CBT is a **non-invasive procedure**, it is believed that patients will not be reluctant to participate as they do not face any additional risk compared to the standard treatment they will receive, whether they are in the control or intervention group.

Every member of the research team will receive the **necessary training** in order to be capable of developing their roles in the study's intervention. Consequently, head and neck specialized physicians will be formed on how to correctly fill the data collection sheet (Annex 5) while psycho-oncologists will receive training on conducting CBT sessions, what is expected to be worked in each session, to ensure patients fill properly the QoL questionnaires (Annexes 6 and 8) and how to calculate final scores of questionnaires (Annexes 7 and 9).

The study is budgeted at 57,290€, which is considered **not expensive**. This economical budget is achievable because all the participating hospitals already count with all the material and equipment necessary to carry out the intervention. Additionally, the majority of the personnel required will already be part of the research team.

Taking all this information into account, it is concluded that this study has a feasible realisation.

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16. ANNEXES

16.1. ANNEX 1 – AJCC stages classification for laryngeal and hypopharyngeal cancers

Supraglottic cancer stages (36)

AJCC stage	Stage grouping	Stage description
0	Tis N0 M0	The tumour is only in the top layer of cells lining the inside of the larynx and has not grown any deeper (Tis). The cancer has not spread nearby to lymph nodes (N0) or distant parts of the body (M0).
I	T1 N0 M0	The tumour has grown deeper, but it is only in one part of the supraglottis, and the vocal cords move normally (T1). The cancer has not spread nearby to lymph nodes (N0) or distant parts of the body (M0).
II	T2 N0 M0	The tumour has grown deeper, and it has grown into more than one part of the supraglottis (or glottis), and the vocal cords move normally (T2). The cancer has not spread nearby to lymph nodes (N0) or distant parts of the body (M0).
III	T3 N0 M0	The tumour is still only in the larynx, but it has caused a vocal cord to stop moving, OR the tumour is growing into nearby areas such as the postcricoid area, paraglottic space, pre-epiglottic tissues, or the inner part of the thyroid cartilage (firm tissue that separates the thyroid gland from the front of the larynx) (T3). The cancer has not spread nearby to lymph nodes (N0) or distant parts of the body (M0).
	T1 to T3 N1 M0	The tumour might or might not have grown into structures just outside the larynx, and it might or it might not have affected a vocal cord (T1 to T3). The cancer has spread to a single lymph node on the same side of the neck as the tumour, which is no larger than 3 cm across (N1). The cancer has not spread to distant parts of the body (M0).
IVA	T4a N0 or N1 M0	The tumour has grown through the thyroid cartilage and/or is growing into tissues beyond the larynx (such as the thyroid gland, trachea, oesophagus, tongue muscles, or neck muscles) (T4a).

		The cancer has not spread to nearby lymph nodes (N0), or it has spread to a single lymph node on the same side of the neck as the tumour, which is no larger than 3 cm across (N1). The cancer has not spread to distant parts of the body (M0).
	T1-T4a N2 M0	The tumour might or might not have grown into structures outside the larynx (as far as moderately advanced disease), and it might or might not have affected a vocal cord (T1 to T4a). The cancer is N2: - It has spread to a single lymph node on the same side of the neck as the tumour, which is larger than 3 cm but no larger than 6 cm across, OR - It has spread to more than one lymph node on the same side of the neck as the tumour, none of which is larger than 6 cm across, OR - It has spread to at least one lymph node on the other side of the neck, none of which is larger than 6 cm across. The cancer has not spread to distant parts of the body (M0).
IVB	T4b Any N M0	The tumour is growing into the area in front of the spine in the neck (the prevertebral space), surrounds a carotid artery, or is growing down into the space between the lungs (T4b). The cancer might or might not have spread to nearby lymph nodes (any N). It has not spread to distant parts of the body (M0).
	Any T N3 M0	The tumour might or might not have grown into structures outside the larynx, and it might or might not have affected a vocal cord (any T). The cancer has spread to at least one lymph node that is larger than 6 cm across, OR it has spread to a lymph node and then grown outside of the lymph node (N3). It has not spread to distant parts of the body (M0).
IVC	Any T Any M M1	The tumour might or might not have grown into structures outside the larynx, and it might or might not have affected a vocal cord (any T). The cancer might or might not have spread to nearby lymph nodes (any N). The cancer has spread to distant parts of the body (M1).

Glottic cancer stages (36)

AJCC stage	Stage grouping	Stage description
0	Tis N0 M0	The tumour is only in the top layer of cells lining the inside of the larynx and has not grown any deeper (Tis). The cancer has not spread nearby to lymph nodes (N0) or distant parts of the body (M0).
I	T1 N0 M0	The tumour has grown deeper, but it is only in the vocal cords, and they move normally (T1). The cancer has not spread nearby to lymph nodes (N0) or distant parts of the body (M0).
II	T2 N0 M0	The tumour has grown deeper, into the supraglottis or subglottis, and/or the vocal cords do not move normally (T2). The cancer has not spread nearby to lymph nodes (N0) or distant parts of the body (M0).
III	T3 N0 M0	The tumour is still only in the larynx, but it has caused a vocal cord to stop moving, OR the tumour is growing into the paraglottic space, OR the tumour is growing into the inner part of the thyroid cartilage (firm tissue that separates the thyroid gland from the front of the larynx) (T3). The cancer has not spread nearby to lymph nodes (N0) or distant parts of the body (M0).
	T1 to T3 N1 M0	The tumour might or might not have grown into structures just outside the larynx, and it might or it might not have affected a vocal cord (T1 to T3). The cancer has spread to a single lymph node on the same side of the neck as the tumour, which is no larger than 3 cm across (N1). The cancer has not spread to distant parts of the body (M0).
IVA	T4a N0 or N1 M0	The tumour has grown through the thyroid cartilage and/or is growing into tissues beyond the larynx (such as the thyroid gland, trachea, cricoid cartilage, oesophagus, tongue muscles or neck muscles) (T4a). The cancer has not spread to nearby lymph nodes (N0), or it has spread to a single lymph node on the same side of the neck as the tumour, which is no larger than 3 cm across (N1).

		The cancer has not spread to distant parts of the body (M0).
	T1-T4a N2 M0	The tumour might or might not have grown into structures outside the larynx, and it might or might not have affected a vocal cord (T1 to T4a). The cancer is N2: - It has spread to a single lymph node on the same side of the neck as the tumour, which is larger than 3 cm but no larger than 6 cm across, OR - It has spread to more than one lymph node on the same side of the neck as the tumour, none of which is larger than 6 cm across, OR - It has spread to at least one lymph node on the other side of the neck, none of which is larger than 6 cm across. The cancer has not spread to distant parts of the body (M0).
IVB	T4b Any N M0	The tumour is growing into the area in front of the spine in the neck (the prevertebral space), surrounds a carotid artery, or is growing down into the space between the lungs (T4b). The cancer might or might not have spread to nearby lymph nodes (any N). It has not spread to distant parts of the body (M0).
	Any T N3 M0	The tumour might or might not have grown into structures outside the larynx, and it might or might not have affected a vocal cord (any T). The cancer has spread to at least one lymph node that is larger than 6 cm across, OR it has spread to a lymph node and then grown outside of the lymph node (N3). It has not spread to distant parts of the body (M0).
IVC	Any T Any M M1	The tumour might or might not have grown into structures outside the larynx, and it might or might not have affected a vocal cord (any T). The cancer might or might not have spread to nearby lymph nodes (any N). The cancer has spread to distant parts of the body (M1).

Subglottic cancer stages (36)

AJCC stage	Stage grouping	Stage description
0	Tis N0 M0	The tumour is only in the top layer of cells lining the inside of the larynx and has not grown any deeper (Tis). The cancer has not spread nearby to lymph nodes (N0) or distant parts of the body (M0).
I	T1 N0 M0	The tumour has grown deeper, but it is only in the subglottis (T1). The cancer has not spread nearby to lymph nodes (N0) or distant parts of the body (M0).
II	T2 N0 M0	The tumour has grown deeper, into the vocal cords, which might or might not move normally (T2). The cancer has not spread nearby to lymph nodes (N0) or distant parts of the body (M0).
III	T3 N0 M0	The tumour is still only in the larynx, but it has caused a vocal cord to stop moving, OR the tumour is growing into the paraglottic space, OR the tumour is growing into the inner part of the thyroid cartilage (firm tissue that separates the thyroid gland from the front of the larynx) (T3). The cancer has not spread nearby to lymph nodes (N0) or distant parts of the body (M0).
	T1 to T3 N1 M0	The tumour might or might not have grown into structures just outside the larynx, and it might or it might not have affected a vocal cord (T1 to T3). The cancer has spread to a single lymph node on the same side of the neck as the tumour, which is no larger than 3 cm across (N1). The cancer has not spread to distant parts of the body (M0).
IVA	T4a N0 or N1 M0	The tumour is growing through the cricoid or thyroid cartilage and/or is growing into structures beyond the larynx (such as the thyroid gland, trachea, oesophagus, tongue muscles, or neck muscles) (T4a). The cancer has not spread to nearby lymph nodes (N0), or it has spread to a single lymph node on the same side of the neck as the tumour, which is no larger than 3 cm across (N1). The cancer has not spread to distant parts of the body (M0).

	T1-T4a N2 M0	The tumour might or might not have grown into structures outside the larynx, and it might or might not have affected a vocal cord (T1 to T4a). The cancer is N2: - It has spread to a single lymph node on the same side of the neck as the tumour, which is larger than 3 cm but no larger than 6 cm across, OR - It has spread to more than one lymph node on the same side of the neck as the tumour, none of which is larger than 6 cm across, OR - It has spread to at least one lymph node on the other side of the neck, none of which is larger than 6 cm across. The cancer has not spread to distant parts of the body (M0).
IVB	T4b Any N M0	The tumour is growing into the area in front of the spine in the neck (the prevertebral space), surrounds a carotid artery, or is growing down into the space between the lungs (T4b). The cancer might or might not have spread to nearby lymph nodes (any N). It has not spread to distant parts of the body (M0).
	Any T N3 M0	The tumour might or might not have grown into structures outside the larynx, and it might or might not have affected a vocal cord (any T). The cancer has spread to at least one lymph node that is larger than 6 cm across, OR it has spread to a lymph node and then grown outside of the lymph node (N3). It has not spread to distant parts of the body (M0).
IVC	Any T Any M M1	The tumour might or might not have grown into structures outside the larynx, and it might or might not have affected a vocal cord (any T). The cancer might or might not have spread to nearby lymph nodes (any N). The cancer has spread to distant parts of the body (M1).

Hypopharyngeal cancer stages (12)

AJCC stage	Stage grouping	Stage description
0	Tis N0 M0	The tumour is only in the top layer of cells lining the inside of the larynx and has not grown any deeper (Tis). The cancer has not spread nearby to lymph nodes (N0) or distant parts of the body (M0).
I	T1 N0 M0	The tumour has grown deeper, but it is only in one part of the hypopharynx, and it is no more than 2 cm across (T1). The cancer has not spread nearby to lymph nodes (N0) or distant parts of the body (M0).
II	T2 N0 M0	The tumour has grown into more than one part of the hypopharynx, OR it has grown into a nearby area, OR it is larger than 2 cm but no larger than 4 cm across and has not affected the vocal cords (T2). The cancer has not spread nearby to lymph nodes (N0) or distant parts of the body (M0).
III	T3 N0 M0	The tumour is larger than 4 cm across, OR the tumour is affecting the movement of the vocal cords, OR the tumours has grown into the oerophagus (T3). The cancer has not spread nearby to lymph nodes (N0) or distant parts of the body (M0).
	T1 to T3 N1 M0	The tumour canbe any size and might or might not have grown into structures outside the hypopharynx, and it might or might not have affected a vocal cord (T1 to T3). The cancer has spread to a single lymph node on the same side of the neck as the tumour, which is no larger than 3 cm across (N1). The cancer has not spread to distant parts of the body (M0).
IVA	T4a N0 or N1 M0	The tumour has grown into the thyroid or cricoid cartilage, the hyoid bone, the thyroid gland, or nearby areas of muscle or fat (T4a). The cancer has not spread to nearby lymph nodes (N0), or it has spread to a single lymph node on the same side of the neck as the tumour, which is no larger than 3 cm across (N1). The cancer has not spread to distant parts of the body (M0).

	T1-T4a N2 M0	The tumour can be any size and might or might not have grown into structures outside the hypopharynx, and it might or might not have affected a vocal cord (T1 to T4a). The cancer is N2: - It has spread to a single lymph node on the same side of the neck as the tumour, which is larger than 3 cm but no larger than 6 cm across, OR - It has spread to more than one lymph node on the same side of the neck as the tumour, none of which is larger than 6 cm across, OR - It has spread to at least one lymph node on the other side of the neck, none of which is larger than 6 cm across. The cancer has not spread to distant parts of the body (M0).
IVB	T4b Any N M0	The tumour is growing into the area in front of the spine in the neck, surrounds a carotid artery, or is growing down into the space between the lungs (T4b). The cancer might or might not have spread to nearby lymph nodes (any N). It has not spread to distant parts of the body (M0).
	Any T N3 M0	The tumour can be any size and might or might not have grown into structures outside the hypopharynx, and it might or might not have affected a vocal cord (any T). The cancer has spread to at least one lymph node that is larger than 6 cm across, OR it has spread to a lymph node and then grown outside of the lymph node (N3). It has not spread to distant parts of the body (M0).
IVC	Any T Any M M1	The tumour can be any size and might or might not have grown into structures outside the hypopharynx, and it might or might not have affected a vocal cord (any T). The cancer might or might not have spread to nearby lymph nodes (any N). The cancer has spread to distant parts of the body (M1).

16.2. ANNEX 2 – Informative document

FULL D'INFOMRACIÓ AL/LA PARTICPANT

Nom de l'estudi: Enhancing quality of life in locally advanced laryngeal and hypopharyngeal cancer treatment through cognitive behavioural therapy implementation.

Centre assistencial:

Investigador/a principal:

INTRODUCCIÓ

Benvolgut/da,

En primer lloc, l'equip investigador vol agrair el seu interès en el projecte. Ens dirigim a vostè per informar-lo sobre un estudi d'investigació al que el volem convidar a participar el qual s'està desenvolupant en diversos serveis d'otorinolaringologia d'hospitals de referència de Catalunya.

L'estudi en qüestió ha estat aprovat pel Comitè d'Ètica i Investigació Clínica (CEIC) de tots els hospitals participants, d'acord amb la legislació vigent i respectant els principis enunciats en la Declaració de Hèlsinki i les guies de bona pràctica clínica.

La nostra intenció és que rebi la informació correcta i suficient per entendre el motiu pel que es realitza l'estudi i quines implicacions té formar-ne part, amb l'objectiu que pugui decidir si vol o no participar. És per aquest motiu que li preguem llegir aquest full informatiu amb atenció i ens pregunti tots els dubtes que li puguin sorgir.

DESCRICIPCIÓ DE L'ESTUDI

Per què és necessari aquest estudi i quin és el seu objectiu?

Els tumors localment avançats de laringe i hipofaringe requereixen d'una combinació de tractaments (quirúrgic, quimioteràpic i/o radioteràpic) complexa i amb potencials efectes adversos que condicionen la quotidianitat i la qualitat de vida de les persones que ho pateixen.

La motivació darrere d'aquest projecte d'investigació és demostrar l'eficàcia d'eines terapèutiques no utilitzades en el tractament estàndard de la malaltia, i com aquestes poden representar una millora en el benestar i supervivència de les persones que ho pateixen.

Les eines terapèutiques a avaluar no s'especifiquen ni se'n dóna més detall per tal d'evitar el possible biaix que podria suposar el seu coneixement pel fet d'influir en la forma d'actuar, expressar-se i comunicar-se, reduint així la validesa de l'estudi.

Quants centres hi participen i quina durada té?

Un total de 8 centres d'arreu de Catalunya participaran en aquest estudi: Hospital Universitari Josep Trueta (Girona), Hospital Universitari de Bellvitge (Barcelona), Hospital Universitari Vall d'Hebron (Barcelona), Hospital Universitari Germans Trias i Pujol (Badalona), Hospital Universitari Arnau de Vilanova (Lleida), Hospital Universitari Joan XXIII (Tarragona), Hospital de Viladecans i Hospital de Tortosa Verge de la Cinta.

L'estudi està previst que tingui una durada de 3 anys i 4 mesos, tot i que el temps que vostè participarà serà 1 any.

Qui pot participar en l'estudi?

Tota persona major d'edat, diagnosticada d'un carcinoma escamós de laringe o hipofaringe en estadi localment avançat opta a participar en aquest estudi.

En què consisteix la meva participació en l'estudi?

Si vostè compleix amb les característiques per participar en l'estudi i està interessat/da en formar-ne part és imprescindible que a la propera visita al servei d'otorinolaringologia entregui firmat el document de Consentiment Informat que se li entrega juntament amb aquesta informació.

Una vegada hagi decidit que vol participar i hagi entregat el consentiment informat, es recollirà informació bàsica sobre vostè i la seva història clínica i se l'assignarà aleatòriament en 1 dels 2 grups que conformaran l'estudi.

A partir d'aquí, se li farà un seguiment des del dia que inicii el tractament (independentment de quin sigui) durant 6 mesos, on realitzarà les següents activitats:

- Se li programaran un total de 15 sessions amb un/a psico-oncòleg/oga per a fer seguiment.
- En 6 d'aquestes 15 sessions se li demanarà que contesti dos qüestionaris amb preguntes en relació a la seva malaltia i el seu estat de salut i d'ànim.

Finalment, 1 any després de l'inici de la seva participació en aquest projecte, serà citat per fer una nova visita de control, moment en el que vostè haurà conclòs la seva participació en l'estudi.

Beneficis i riscos de l'estudi

Amb la seva participació en aquest estudi ajudarà a ampliar el coneixement científic sobre el tema d'estudi, ajudant així a que en un futur es puguin optimitzar els tractaments i els pacients es puguin beneficiar de noves eines terapèutiques.

Per altra banda, considerem que formar part d'aquest estudi no implica cap risc afegit, donat que l'eina avaluada és una teràpia no invasiva i no tindrà cap repercussió negativa en la seva evolució.

Confidencialitat i protecció de dades personals

Tota informació referent a vostè recollida durant l'estudi serà introduïda a una base de dades amb un codi que garanteixi l'anonimat per al seu anàlisis. El seu nom ni cap altra manera en la que pugui ser identificat apareixerà en cap document públic, i l'ús comercial d'aquestes dades està prohibit.

Tota la informació és guardada i gestionada de manera segura i confidencial, d'acord amb la Llei Orgànica 03/2018, del 5 de desembre i del Reglament (UE) 2016/679 del Parlament Europeu de 27 d'abril de 2016 de protecció de dades.

Ningú excepte les persones que formen part de l'equip de recerca d'aquest estudi tindran accés a les seves dades. Aquestes dades podran ser compartides amb investigadors d'altres centres exclusivament amb finalitat investigadora.

En qualsevol moment de l'estudi té dret a exercir els drets d'oposició, accés, rectificació i anul·lació en l'àmbit reconegut per RGPD. Té dret a sol·licitar una còpia de les dades que ha facilitat per l'estudi, així com reclamar el canvi de dades que siguin incorrectes.

L'equip investigador té l'obligació de conservar les dades recollides un mínim de 25 anys després de la finalització de l'estudi. Passat aquest període de temps, la seva informació personal només es conservarà amb la finalitat de vetllar per la seva salut, i per altres fins d'investigació científica si vostè ho hagués autoritzat i així ho permetés la llei i els requisits ètics.

Les dades no es podran eliminar encara que deixi de participar en l'estudi per tal de garantir la validesa de la investigació.

Difusió del resultats

Un cop hagi finalitzat l'estudi, els resultats seran publicats en revistes de divulgació científica, amb l'objectiu que altres centres assistencials i els seus pacients es puguin beneficiar del coneixement generat i els resultats extrets. Com s'ha esmentat abans, cap dada personal apareixerà en aquestes publicacions.

Compensació econòmica

Cap membre de l'equip de recerca d'aquest estudia rebrà cap tipus de benefici econòmic.

La participació per part dels pacients és totalment voluntària i, per tant, tampoc serà remunerada. Tanmateix, tampoc li suposarà cap despesa addicional.

Contacte

En cas de dubtes abans, durant o després de la realització d'aquest estudi, no dubti en posar-se en contacte amb l'equip investigador a través del següent correu: _____

Moltes gràcies per la seva col·laboració.

Atentament,

L'equip investigador.

Signatura de/la pacient

Signatura de l'investigador/a

Nom:

Data:

Nom:

Data:

16.3. ANNEX 3 – Informed consent document

FULL DE CONSENTIMENT INFORMAT DEL/LA PACIENT

TÍTOL DE L'ESTUDI: Enhancing quality of life in locally advanced laryngeal and hypopharyngeal cancer treatment through cognitive behavioural therapy implementation.

Jo, (nom i cognoms) _____, amb DNI _____, i a data (DD/MM/AAAA) _____ declaro que:

- He llegit i entès el document informatiu que se m'ha entregat
- He pogut realitzar totes les preguntes que m'han sorgit i han estat respostes satisfactòriament
- He rebut la informació suficient i necessària sobre l'estudi
- La meva participació en l'estudi és voluntària i que puc retirar-me de l'estudi en qualsevol moment, sense necessitat de cap explicació i sense que repercuteixi en el seguiment i tractament de la meva malaltia.
- Consenteixo que les dades personals i clíniques recollides siguin emmagatzemades en una base de dades automatitzada i que aquesta informació pugui ser utilitzada únicament amb finalitats científiques.

D'acord amb el que estableix el Reglament (UE) 2016/679 del Parlament i del Consell, de 27 d'abril de 2016, relatiu a la protecció de les persones físiques pel que fa al tractament de dades personals i a la lliure circulació d'aquestes, declaro haver estat informat/da de:

- L'existència d'una base de dades on s'inclouran la meves dades personals
- De la finalitat de la seva recollida i dels destinataris de la informació
- Del procés de codificació de les dades
- De la disponibilitat d'exercir els drets d'accés, rectificació i cancel·lació dirigint-me per escrit a l'equip investigador de l'estudi.

Dono lliurement la meva conformitat per participar en l'estudi.

Firma del pacient Firma de l'investigador/a

16.4. ANNEX 4 – Withdrawn consent

FULL DE REVOCACIÓ DEL CONSENTIMENT INFORMAT DEL/LA PACIENT

Jo, (nom i cognoms) _____, amb DNI _____, a data (DD/MM/AAAA) _____ revoco el consentiment informat prèviament firmat en l'estudi "Enhancing quality of life in locally advanced laryngeal and hypopharyngeal cancer treatment through cognitive behavioural therapy implementation".

Firma del pacient

16.5. ANNEX 5 – Data collection sheet

FULL D'INFORMACIÓ CLÍNICA DEL/LA PACIENT

DADES IDENTIFICATIVES

Codi participant:

Hospital:

Data:

DADES PERSONALS

Data de naixement (DD, MM, AAAA): _____ / _____ / _____

Edat:

Gènere: Home ☐ Dona ☐ No-binària ☐

DADES SOCIODEMOGRÀFIQUES

Estatus socioeconòmic:

- ☐ Classe I: Directius de l'administració i les empreses (excepte els inclosos a la classe II). Alts funcionaris. Professionals liberals. Tècnics superiors.
- ☐ Classe II: Directius i propietaris-gerents del comerç i dels serveis personals. Altres tècnics (no superiors). Artistes i esportistes.
- ☐ Classe III: Càrrecs intermitjos. Administratius i funcionaris, en general. Personal dels serveis de protecció i seguretat.
- ☐ Classe IV: Treballadors manuals qualificats o semiqualificats de la indústria, comerç i serveis, així com del sector primari.
- ☐ Classe V: Treballadors no qualificats.
- ☐ Classe VI: Altres casos, mal especificats o desconeixement.

Hàbit tabàquic:

- No fumador ☐
- Ex-fumador (si fa més de 6 mesos que no fuma) ☐
- Fumador (o fa menys de 6 mesos que ha deixat de fumar)
    - Índex paquets/any:
        - Baix risc (≤20) ☐ Risc moderat (21-40) ☐ Alt risc (≥ 41) ☐

Consum d'alcohol:

- ☐ No consum
- ☐ Consum lleu (<20g/dia en dones, <50g/dia en homes)
- ☐ Consum moderat: (20-40g/dia en dones, 50-60g/dia en homes)
- ☐ Consum elevat: (>40g/dia en dones, >60g/dia en homes)

Consum d'altres drogues (sí/no):

Altres malalties o trastorns concomitants (trastorns neurològics, malalties infeccioses cròniques, trastorns cardiovasculars o altres –especifiqui quin-):

Infecció pel virus del papil·loma humà tipus 16 (sí/no):

Tipus de tractament rebut:

- ☐ Quirúrgic
- ☐ No quirúrgic

Estadi de la malaltia:

- ☐ IIII
- ☐ IVA
- ☐ IVB

ANOTACIONS PSICO-ONCOLOGIA

SESSIÓ	ANOTACIONS
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	

RESULTATS DELS QÜESTIONARIS

1. QÜESTIONARI QLQ-C30:

	Item	Valor (0-100)					
		Q1	Q2	Q3	Q4	Q5	Q6
GLOBAL HEALTH STATUS / QOL	Global Health status / QoL						
FUNCTIONAL SCALES	Physical functioning						
	Role functioning						
	Emotional functioning						
	Cognitive functioning						
	Social functioning						
SYMPTOM SCALES / ITEMS	Fatigue						
	Nausea and vomiting						
	Pain						
	Dyspnoea						
	Insomnia						
	Appetite loss						
	Constipation						
	Diarrhoea						
	Financial difficulties						

2. QÜESTIONARI QLQ-H&N43

	Item	Valor (0-100)					
		Q1	Q2	Q3	Q4	Q5	Q6
MULTI-ITEM SCALES	Pain in the mouth						
	Swallowing						
	Problems with teeth						
	Dry mouth and sticky saliva						
	Problems with senses						
	Speech						
	Body image						
	Social eating						
	Sexuality						
	Problems with shoulder						
	Skin problems						
	Fear of progression						
SINGLE ITEMS	Problems opening mouth						
	Coughing						
	Social contact						
	Swelling in the neck						
	Weight loss						
	Problems with wound healing						
	Neurological problems						

16.6. ANNEX 6 – EORTC QLQ-C30 QUALITY OF LIFE QUESTIONNAIRE

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in:

- Your initials: _ _ _
- Your birthdate (Day, Month, Year): _ _ / _ _ / _ _ _ _
- Today's date (Day, Month, Year): _ _ / _ _ / _ _ _ _

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4

10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions, please circle the number between 1 and 7 that bestapplies to you:

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

16.7. ANNEX 7 – EORTC QLQ-C30 QUALITY OF LIFE SCORING

	Scale	Number of items	Item range*	**Version 3.0** Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.
† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

For all scales, the *RawScore*, *RS*, is the mean of the component items:

$$RawScore = RS = (I_1 + I_2 + ... + I_n)/n$$

Then for **Functional scales**:

$$Score = \left\{1 - \frac{(RS - 1)}{range}\right\} \times 100$$

and for **Symptom scales / items** and **Global health status / QoL:**

$$Score = \{(RS - 1)/range\} \times 100$$

Examples:

Emotional functioning

$$RawScore = (Q_{21} + Q_{22} + Q_{23} + Q_{24})/4$$
$$\text{EF } Score = \{1 - (RawScore - 1)/3\} \times 100$$

Fatigue

$$RawScore = (Q_{10} + Q_{12} + Q_{18})/3$$
$$\text{FA } Score = \{(RawScore - 1)/3\} \times 100$$

16.8. ANNEX 8 – EORTC QLQ-H&N43 QUALITY OF LIFE QUESTIONNAIRE

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
31. Have you had pain in your mouth?	1	2	3	4
32. Have you had pain in your jaw?	1	2	3	4
33. Have you had soreness in your mouth?	1	2	3	4
34. Have you had pain in your throat?	1	2	3	4
35. Have you had problems swallowing liquids?	1	2	3	4
36. Have you had problems swallowing pureed food?	1	2	3	4
37. Have you had problems swallowing solid food?	1	2	3	4
38. Have you had problems swallowing?	1	2	3	4
39. Have you had problems swallowing with your teeth?	1	2	3	4
40. Have you had problems because of losing some teeth?	1	2	3	4
41. Have you had problems opening your mouth wide?	1	2	3	4
42. Have you had a dry mouth?	1	2	3	4
43. Have you had sticky saliva?	1	2	3	4
44. Have you had problems with your sense of smell?	1	2	3	4
45. Have you had problems with your sense of taste?	1	2	3	4

46. Have you had problems with coughing?	1	2	3	4
47. Have you had problems with hoarseness?	1	2	3	4
48. Have you had problems with your appearance?	1	2	3	4
49. Have you felt less physically attractive as a result of your disease or treatment?	1	2	3	4
50. Have you felt dissatisfied with your body?	1	2	3	4
51. Have you had problems eating?	1	2	3	4
52. Have you had problems eating in front of your family?	1	2	3	4
53. Have you had problems eating in front of other people?	1	2	3	4
54. Have you had problems enjoying your meals?	1	2	3	4
55. Have you had problems talking to other people?	1	2	3	4
56. Have you had problems talking on the telephone?	1	2	3	4
57. Have you had problems talking in a noisy environment?	1	2	3	4
58. Have you had problems speaking clearly?	1	2	3	4
59. Have you had problems going out in public?	1	2	3	4
60. Have you felt less interest in sex?	1	2	3	4
61. Have you felt less sexual enjoyment?	1	2	3	4
62. Have you had problems raising your arm or moving it sideways?	1	2	3	4
63. Have you had pain in your shoulder?	1	2	3	4
64. Have you had swelling in your neck?	1	2	3	4
65. Have you had skin problems (e.g. itchy, dry)?	1	2	3	4

66. Have you had a rash?	1	2	3	4
67. Has your skin changed color?	1	2	3	4
68. Have you worried that your weigh is too low?	1	2	3	4
69. Have you worried about the results of examinations and tests?	1	2	3	4
70. Have you worried about your health in the future?	1	2	3	4
71. Have you had problems with wounds healing?	1	2	3	4
72. Have you had tingling or numbness in your hands or feet?	1	2	3	4
73. Have you had problems chewing?	1	2	3	4

16.9. ANNEX 9 – EORTC QLQ-H&N43 QUALITY OF LIFE SCORING

The QLQ-HN43 module is a revised and updated version of the Head and Neck Cancer Module QLQ-H&N35 (Björdal et al. 2000). It is a supplementary questionnaire module to be employed in conjunction with the QLQ-C30. The QLQ-HN43 incorporates twelve Multi-item scales to assess Pain in the mouth (PA), Swallowing (SW), Problems with teeth (TE), Dry mouth and sticky saliva (DR), Problems with senses (SE), Speech (SP), Body image (BI), Social eating (SO), Sexuality (SX), Problems with shoulder (SH), Skin problems (SK) and Fear of progression (ANX). In addition, seven Single items assess Problems opening the mouth (OM), Coughing (CO), Social contact (SC), Swelling in the neck (SN), Weight loss (WL), Problems with wound healing (WO) and Neurological problems (NE). The scoring approach for the QLQ-HN43 is identical in principle to that for the Symptom scales of the QLQ-C30. All scoring information specific to the QLQ-HN43 is presented in Table 1. Interpretation: All of the Multi-item scales and Single-item measures range in score from 0 to 100. A high score represents a high level of symptomatology or problems.

	Number of items (n)	Item range *	QLQ-HN43 item numbers (I_1, I_2, ..., I_n)
Multi-item scales			
Pain in the mouth	4	3	31 - 34
Swallowing	4	3	35 - 38
Problems with teeth	3	3	39, 40, 73
Dry mouth and sticky saliva	2	3	42, 43
Problems with senses	2	3	44, 45
Speech	5	3	47, 55 - 58
Body image	3	3	48 - 50
Social eating	4	3	51 - 54
Sexuality	2	3	60, 61
Problems with shoulder	2	3	62, 63
Skin problems	3	3	65 - 67
Fear of progression	2	3	69, 70
Single items			
Problems opening mouth	1	3	41
Coughing	1	3	46
Social contact	1	3	59
Swelling in the neck	1	3	64
Weight loss	1	3	68
Problems with wound healing	1	3	71
Neurological problems	1	3	72

* "Item range" is the difference between the possible maximum and the minimum response for individual items. All items are scored 1 to 4, giving range = 3.

How to score

1) **Raw score**

For each Multi-item scale, calculate the average of the corresponding items.

$$Raw\ Score = RS = \left\{\frac{(I_1 + I_2 + \ldots + I_n)}{n}\right\}$$

For each Single-item measure, the score of the concerning item corresponds to the raw score.

2) **Linear Transformation**

To obtain the Score S, standardize the raw score to a 0 – 100 range using the following algorithm:

$$S = \left\{\frac{(RS - 1)}{range}\right\} \times 100$$