OBESE PATIENTS WITH THYROID CANCER: A DANGEROUS SURGERY?

Final degree project

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Mentor: José Ignacio Rodríguez Hermosa
Me gustaría agradecer al Servicio de Cirugía General del Hospital Trueta por haberme acogido siempre, y en especial a los Drs. Gironès y Rodriguez por haber invertido tanto tiempo y conocimiento en mí, mostrándome el maravilloso mundo de la cirugía con sus más y sus menos.

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I. Abstract

**Background**: Thyroid cancer is the most common endocrine cancer and its incidence has increased intensely in recent decades. In the same period, there has been an epidemic of obesity in both developed and developing countries. Having epidemiological data that obesity is associated independently with thyroid cancer, there is a lack of studies comparing endocrine specific postoperative complications of thyroidectomy and lymph node dissection between normal weight and obese patients with thyroid cancer.

**Aim**: To analyze the postoperative complications between thyroid cancer patients with a BMI ≥30, compared with those having a BMI below 30.

**Design**: An ambispective cohort study carried out in a tertiary referral hospital in Girona within an Endocrinology Surgery Unit.

**Participants**: Patients operated of thyroid cancer at Hospital Universitari Dr. Josep Trueta, separated into two groups depending on their BMI: ≥30 or <30.

**Key Words**: Obesity, thyroid cancer, thyroidectomy, central lymph node dissection, complications.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>TC</td>
<td>Thyroid cancer</td>
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<td>PTC</td>
<td>Papillary thyroid cancer</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>TT</td>
<td>Total Thyroidectomy</td>
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<td>CLND</td>
<td>Central Neck Lymph Node Dissection</td>
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<td>ASA</td>
<td>American Society of Anesthesiology Classification</td>
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<tr>
<td>HIS</td>
<td>Hospital Information Systems</td>
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<td>CEIC</td>
<td>Comitè Etic de Investigació Clínica</td>
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<tr>
<td>RLN</td>
<td>Recurrent Laryngeal Nerve</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<td>ACS NSQIP</td>
<td>American College of Surgeons National Surgery Quality Improvement Program</td>
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III. Introduction

a. Background

- **EPIDEMIOLOGY OF THYROID CANCER**

During the past decades, the incidence of thyroid cancer has increased worldwide\(^{(1,2)}\), with the majority of the growth occurring in the past 15 years\(^{(3)}\). Even though this type of cancer is rather rare (less than 2% of all cancers in males and approximately 1-5% in females), it is the most common endocrine malignancy\(^{(4,5)}\). This tendency is present on every continent except Africa, where detection is feasibly insufficient. Also in a few countries (Norway, Sweden) thyroid cancer incidence has decreased. However, in countries like the USA, thyroid cancer went from 2.4% to 6.6% in both genders, and in Italy for example it is the second most frequent cancer in women below 45 years of age\(^{(1)}\).

Following the WHO classification, thyroid cancer is composed of four major types\(^{(6)}\) (ANNEX 1):

- Papillary thyroid carcinoma
- Follicular thyroid carcinoma
- Anaplastic thyroid carcinoma
- Medullary thyroid carcinoma

Literature documents that this increase in thyroid cancer, has been basically entirely attributed to trends in papillary thyroid cancer incidence\(^{(4)}\).
EPIDEMIOLOGY OF OBESITY

Coinciding with the increase of PTC incidence, is an epidemic of obesity (4,7). Obesity is commonly defined as body mass index (BMI), expressed as weight in kilograms divided by height in meter squared-equal or greater than 30kg/m².

During the last 20 years, obesity has quickly become a global pandemic health problem: The WHO predicted that in 2015, 700 million of adults will be obese (5). Catastrophic data come from developed countries such as the USA, where 35% of the population is obese. In Europe, the prevalence of obesity in men ranged from 4.0% to 28.3% and in women from 6.2% to 36.5% (8). This is an example of obesity in Spain:

This graph shows the evolution of the prevalence of obesity depending on sex, of the adult Spanish population (+18 years old) from 1987 until 2014. It equally shows the prevalence of the combination of obesity and overweight during the same period.
The implications of obesity in health concluded that it is a risk factor for a wide range of diseases and health problems, including hypertension, hypercholesterolemia, diabetes, coronary disease and some types of cancer.

The prevalence of obesity in adults reaches 16.91% in 2014, keeping the high levels reached in 2009 (16,0%) and 2011 (17,03%), following the increase of the last 25 years (ENSE 1987-2014) and now slightly higher in men than in women.

Since 1987, obesity in women went from 8% to 16.1% in 2014. In men, the increase has been even higher, going from 7% in 1987 until 17.1% in 2014. (9)

- **RELATIONSHIP BETWEEN OBESITY AND THYROID CANCER**

From all this we can extract the conclusion that more obese patients also undergo other surgical procedures apart from bariatric surgery. Some studies have shown a correlation between high BMI and morbidity or mortality (10). More patients with elevated BMI are undergoing cervical procedures than ever before, and there seems to be a relationship between high BMI and some thyroid and parathyroid disorders. Despite the controversy in the literature, obesity is associated to an increased incidence of thyroid cancer (5,11–13). The following examples illustrate this statement:

- As shown in some cohorts (3,7,14–16). A pooled analysis of prospective cohort studies found a combined hazard ratio of 1.53 for thyroid cancer in obese men and women).
- A meta-analysis confirmed an association between BMI and thyroid cancer (17).

The “increasing incidence of thyroid cancer has paralleled a rising prevalence of obesity over the past 3 decades. Some studies show that a high BMI and body fat percentage had the strongest association with PTC risk specifically” (PTC risk in obese subjects was
approximately four times that of normal-weight subjects) (4, 13, 18), and also found increased risks of follicular thyroid cancer. Regarding the medullary thyroid cancer risk, obesity showed an inverse association with it. This result indicates that obesity may have a different effect on the pathogenesis and occurrence of thyroid cancer in different histologies. (17)

It is important to contemplate certain factors that should be considered when trying to interpret studies of TC risk in obese individuals. This are confounders which could influence the association between obesity and thyroid cancer:

- **Sex:** It is likely that sex influences the association of obesity status with TC, as several studies have found such associations only in women. (11)
- **Age:** The incidence of cancer is highest among those over age 65 years. (3)
- **Smoking:** Convincing evidence of its association with both weight and thyroid cancer risk. (18)
- **Type of obesity:** The longer the time period in the obese state, the higher the TC risk appeared to be. (11)

Detailed analysis of the cofounders is made in the “Variables” chapter.

### THYROIDECTOMY AND THE INTEREST ON ITS COMPLICATIONS

It is generally accepted that total thyroidectomy and central lymph node dissection is indicated in thyroid cancer treatment, even though the indications for elective central lymph node dissection remain controversial. (19)

Thyroidectomy, first introduced in the 12th century, is a common surgery being practiced widely. (ANNEX 3)

The operative technique is, in general lines:

Ultrasound vascular in contact with the glandular parenchyma or installing metal clips, capsular dissection of parathyroid glands and their vascularization, identification, if possible, of the superior laryngeal nerve in the cricothyroid space and/or the upper
pole, and identification of lower laryngeal nerves (recurrent nerve) until laryngeal penetration point. Monitoring of the inferior laryngeal nerve is used depending on its availability at the hospital where the surgery is performed (10). Lymph node dissection was performed in the territories VI and VII. (ANNEX 4)

This procedure has a very low mortality rate but a specific morbidity (10). Based on the literature, this are the most relevant complications of this surgical procedure (10,14,20–23).

- Postoperative permanent hypocalcemia: It is the most common complication after thyroidectomy. The literature shows that the incidence for permanent hypocalcemia after surgical interventions for thyroid cancer was around 3.3%
- Recurrent permanent laryngeal nerve palsy: Is the most important complication because it deeply influence the patient’s social life.
- Hematoma

We also highlighted secondary endpoints to evaluate between the obese and the non-obese patients:

- Operative time: The literature reports a mean operative time of 97 minutes (10).
- Mean duration of hospital stay

Hypothyroidism is considered an expected result. Hence is not a complication if we consider that total thyroidectomy has its own logic. Infections in thyroid surgery are rare and have a low incidence. Death is a rare and unexpected event (21,22).

The complications are furtherly developed in the “Variables” section.

Focusing mainly in the permanent complications, as this are the ones that have a higher impact in the patient’s life, literature reports that the rate of complications was of 7.1% (22).
Before any surgical operation patients must be accurately informed of the magnitude of their pathology, the indications for surgical treatment, the potential alternative therapies, the advantages provided by the operation, and the possible complications and their remedies. They must be especially cautiously informed of the complications and their incidence. Only after this information is given, can patients accept to or refuse the operation(22).

b. Justification

As of today, an increasing number of patients with a high BMI undergo surgical procedures, and there is growing interest in understanding predictors of patient outcomes. “Some studies have reported that high BMI is a risk factor for postoperative morbidity or mortality, whereas others have reported inconsistent associations between different degrees of obesity and postoperative outcomes”.(14) A rarity of literature exists on outcomes after thyroidectomy in patients with high BMI. “A few studies have focused primarily on procedural/anesthetic approaches to the obese patient or have measured the BMI of patients, but no studies have assessed obesity as an independent variable” (10,14).

Because epidemiological data on BMI in relation to thyroid cancer and its postsurgical complications are limited(18), we will perform an investigation of this issue in a cohort study that will include 450 patients.

Most often, it is regarded among surgeons that patients with “high BMI would present more often with postoperative complications when compared with patients having a normal BMI”. However this idea is not supported by the existing literature and the relationship between obesity and outcomes after any type of surgery remains controversial. “Studies comparing endocrine-specific complications of endocrine surgery between obese patients and others are rare”. There are no studies comparing endocrine-specific complications of thyroidectomy.(10) This study will be the first to
compare endocrine specific postoperative complications of thyroidectomy and lymph node dissection between normal weight and obese patients with thyroid cancer.

c. Implications

The impact of this study varies depending on whether causality between obesity and the outcomes of thyroid surgery will be proved or not.

1. If causality is proved:

The impact of this proposed study will be multi layered. Given apparent prevalence of TC, the development of the obesity epidemic and the risks described here above, it is important to take into consideration the management of said risks to have safer surgical procedures, enhance the general quality of health and distribute the consequent profits to hospitals and health systems.

Managing the elevated risks linked to obese patients will have a waterfall effect throughout society. A safer thyroidectomy decreases the surgical complications, which(11):

- Increases the health of the patient: shorter procedure time, less anesthesia time and quantity, shorter post-op hospitalization time, quicker recovery, fewer and faster post-op appointments etc.
- Awareness campaigns of the dangers of TC and its surgery could help physicians and patients put in place efficient prophylaxis programs. These programs could decrease the risk of both TC and all obesity related diseases.
- The combination of shorter surgical procedures, usage of less materials, less medications and hospital & health system resources will generates large economies from safer surgeries and better health in general, that can then be better used or redistributed.

2. If causality is not proved:

If the outcome of our study doesn’t show a causality relation between obesity and post-operative complications: thyroidectomy could be performed safely in obese individuals.
This could help inform surgeons and patients regarding appropriate risks and expectations of thyroid procedures.(14)
IV. Bibliography


V. Hypothesis

a. Primary hypothesis

In the surgery of thyroid cancer, the obese patients have more complications than those non-obese.

VI. Objectives

a. Main objective

To analyze the postoperative complications between patients with a BMI ≥30 with TC, compared with those having a BMI below 30 with TC.

b. Secondary objective

To describe which specific subtype of TC presents more often among obese individuals.
VII. Methodology

a. Study design
A cohort, longitudinal, observational, analytic, ambispective study will be performed. The retrospective part of the study will be from 2010 to 2015 and the prospective from 2016 until 2018.

b. Study population
This study will include all adults diagnosed with TC and eligible for TT and CLND between 2010 and 2018 at the Hospital Universitari Josep Trueta of Girona. Following the WHO guidelines (further explained in “Variables”), the patients will be divided into two groups: one group (A) will include patients with a BMI ≥30 (obese) and the other (B) will include patients with a BMI 18.5-29.9 (normal weight and overweight individuals) in a 1:1 ratio.

i. Inclusion criteria
- Patients diagnosed of TC confirmed by pathological or histological examinations who underwent total thyroidectomy + central lymph node dissection at our hospital
- Patients between 18 and 75 years of age.
- Patients operated under general anesthesia.

ii. Exclusion criteria
- Patients with benign thyroid pathology
- Patients who underwent parathyroidectomy
- Patients who underwent partial thyroidectomy or TT without CLND
- Smoker patients
- Patients with history of previous hypocalcemia
- Patients taking anticoagulant treatment
- Patients who underwent previous neck surgical procedures
- ASA ≥ IV patients
- Patients older than 75 years old
- Patients younger than 18 years of age (as thyroid cancer in this group is very rare)(3)
- Underweight patients (BMI ≤ 18.5 kg/m²)
- Patients operated of total thyroidectomy but without CLND
VIII. Sampling

a. Sample selection

A consecutive, non-probabilistic sampling will be performed as patients are diagnosed of TC and tributary of TT and CLND. The sample recruitment will be done through the informatics program SAP HIS from 2010 until 2018.

Since this is a program of the hospital, it is confidential so informed consent won’t be needed, as all the patients have previously signed the consent for the surgery. Also, when a doctor/researcher wants to access a patient’s medical records, a reason of why they are doing it must be entered in the programmed and it is recorded.

b. Sample size

The sample size and power calculator GRANMO was used to achieve our sample size. Using the POISSON approximation, and accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 208 exposed subjects and 208 in the non-exposed are necessary to recognize as statistically significant a relative risk greater than or equal to 2.4. The proportion in the non-exposed group has been estimated to be 0.071 (20,22). It has been anticipated a drop-out rate of 10%.

We assumed that the event rate in exposed is 0.171 because by clinical criteria, we established that the obese (exposed) will complicate (event appearance) 10% more than those non-obese (non-exposed), and the non-exposed/exposed ratio is 1.

It is estimated that at our hospital approximately 50 TT with CLND surgeries might take place within a year. Since we will need 208 non-obese patients and 208 obese who will have this surgery, with a generous estimation it will be possible for the sample selection to be carried out in 8 years (around 450 patients).
IX. Variables and measurement instruments

a. Independent variable

**Obesity:** The WHO states obesity as excessive fat accumulation that might impair health (24) It is defined by a BMI equal or greater than 30.

Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m$^2$).

The definition of the WHO is:

- A BMI greater than or equal to 25 is overweight
- A BMI greater than or equal to 30 is obesity.
- A BMI of 18.5-24.9 is normal weight.
- A BMI of less than 18.5 is underweight.

BMI provides the most useful population-level measure of overweight and obesity as it is the same for both sexes and for all ages of adults. However, it should be considered a rough guide because it may not correspond to the same degree of fatness in different individuals.

This is a qualitative and dichotomous variable (yes/no)

As mentioned before, we divided the patients into two groups: obese (BMI ≥30) or non-obese (BMI <30).
b. Dependent variable

**Complications:** There are several postoperative complications of the surgery for thyroid cancer, but stating the most common ones, we defined this variable as (10,14,22,23):

- **Postoperative permanent hypocalcemia:** Is the most frequent complication after thyroidectomy for cancer plus CLND(23). Postoperative hypocalcemia can be defined as a serum calcium level below 8mg/dl. Hypocalcemia was considered permanent when calcium and vitamin D replacement was necessary for over than 6 months. Patients will have their blood tested before the surgery, 1 hour post-surgery, 3 months and 6 months after the surgery.

- **Permanent RLN palsy:** This is the most important complication because it deeply influences the patient’s social life. Postoperative vocal cord palsy or paresis were defined as the presence of immobility or decreased movement of the vocal cords. A persisting vocal cord dysfunction after 6 months was considered permanent(23). Palsies that resulted from inferior laryngeal nerve resection because of neoplastic involvement were classified as sequelae and not computed as complications.(20)

- **Superior laryngeal nerve lesions:** are relatively frequent and often underestimated. They manifest as a lowered voice tone, vocal fatigue, and difficulty singing note intonation. If the homolateral LRN lesion is present, dysphagia for liquids often occurs. It is caused by impaired coordination of glottis closure by the epiglottis, which determines liquid inhalation in the airway. Any recurrent laryngeal nerve palsy that was persistent at 6 months was considered as permanent palsy.

- **Post-operative hematoma:** Hemorrhage within a thyroidectomy wound usually occurs within 24 hours of operation, with most significant hematomas
becoming apparent with 6 to 8 hours. Acute respiratory embarrassment is potentially lethal unless surgically relieved as an emergency procedure. Tracheostomy is infrequently required in those with insidious hemorrhage. This complication endangers the life of the patient (23).

- **Operative time (minutes):** We dichotomized this variable as normal operative time (90-120 minutes) and prolonged (>120 minutes) based on the mean time that this surgery takes.

- **Mean duration of hospital stay (days):** This variable was dichotomized into regular (0-2 days) and extended (>2 day) based on the overall median duration of stay for thyroidectomy found in prior ACS NSQIP surgical outcomes literature (14).

This is a qualitative and dichotomous variable (yes/no). It is important to mention that all patients included had the same surgical technique (total thyroidectomy and central lymph node dissection) and underwent general anesthesia.

Also, we must highlight that the date of occurrence of the complications will be documented, by seeing the patients 6 months after the surgery, and comparing their condition with that of a few hours after the surgery. This is important for the complications of permanent hypocalcemia and permanent RLN palsy.

c. **Covariates**

The covariates of this study are the following:

- **Surgeon (1/2):** At the surgery department of our hospital, there are two attending surgeons mainly performing the thyroidectomies, so each of them will be assigned a number (surgeon number 1, or surgeon number 2). Resident surgeons will collaborate in the surgery always by helping the attending

- **Sex (male/female)**
- Age (measured in years)
- Smoking (yes/no)
- Type of obesity (young adulthood 18-20 years old, or adulthood >20 years old).
- Subtype of thyroid cancer (Papillary, Follicular, Medullary, Poorly differentiated, Anaplastic)
- Ethnicity: Caucasian, African, Asian
- ASA classification 1-2 and 3 (ANNEX 2)

d. Data collection

For data collection, the surgeons of the endocrinology surgery department will inform the rest of the members of the unit about the study that is being carried out.

The data will be collected from the electronic medical records (SAP HIS for Windows Database) of the patients who fit the inclusion criteria and will be included in a database made specifically for this study. This database will have the patient’s information codified, so to fill ethical obligations and avoid biases.
X. Statistical analysis

a. Descriptive-univariate analysis

The results will be expressed as percentages (proportions) for categorical variables, such as the dependent and the independent variables.

For quantitative continuous variables, assuming a normal distribution, the mean ± the typical deviation (SD) will be estimated. If not possible to assume a normal distribution, the median (quartiles) will be estimated.

b. Bivariate analysis

Comparisons of results for major variables will be performed using $\chi^2$ (Chi-square) test and represented on a frequency table, as both the dependent and independent variables are qualitative.

c. Multivariate analysis

In order to detect possible confusion caused by the specific covariates that may explain the relationship found between the independent and dependent variables, a multivariate analysis will be performed. Considering that our variables take into account the time, a Cox proportional hazard regression model will be used.

A descriptive analysis of the variables will be performed using IBM SPSS Statistics version 22, 2014 (IBM, Armonk, NY, US). The data set will be thoroughly screened prior to commencing analyses, and double-checking all entries and screening for the presence of missing data will ensure the accuracy of the information.
XI. Ethical considerations

This protocol will be sent to the CEIC Department of The Hospital Universitari Josep Trueta, in order to be evaluated and accepted.

The principle of the World Health Association Declaration of Helsinki of Ethical Principles for Medical Research Involving Human Subjects (Last revision in 64th General Assembly, Fortaleza, Brazil, October 2013), will be followed in the current study. Also, we will take into consideration the Spanish Organic Law 14/2007, de Investigación Biomédica, that regulates biomedical investigation involving human beings in Spain.

According to “Ley Orgánica 15/1999, 13 de Diciembre, Protección de Datos de Carácter Personal”, clinical history information, names and surnames will remain anonymous when collecting data from the database and publishing results. This way, the researcher will only know the patients by a code, and the real information will be stored somewhere else.

The investigators of this project declare that there are no conflicts of interests.
XII. Study limitations

- The first limitation that may be considered is the typical of a cohort study, including the long duration of the study (8 year follow-up).

- Taking into consideration that the present study will be carried out in a single-institution center, additional research will be required to confirm our findings. Also, our study was performed in an area which is not racially diverse, so the results might not be applicable to the general population, nor to ethnicities other than Caucasians.

- Obesity is the result of various genetic, metabolic and environmental factors. Therefore, it is very difficult to control independently each one of these variables and clarify its possible contribution to the TC relation (4,11).

- There are certain factors that should be considered when trying to interpret studies of TC risk in obese individuals. It is possible that confounders (sex, age) may explain the lack of uniformity in the findings (4,11).

- To minimize the information (observer) bias, the obese/non-obese data should be codified so researchers aren’t influenced while they work with the data. During the statistical analysis phase, the main hypothesis should equally be hidden from the biostatistician.

- To take into account the non-differential misclassification bias, we should consider that some of the patient’s data will be incomplete. On the other hand, these patients will not be excluded from the study because the influence of the missing data (mainly covariates) does not have transcendence in the outcome of the results. However, to avoid this, doctors of the endocrinology surgery
department will be strongly encouraged to collect complete data relevant for the study.

- The percentage of complications in the non-exposed group (non-obese) was found in the literature previously referenced. This percentage also includes obese people as it does not distinguish between obese or non-obese. Hence, this could inhibit the accuracy of the study as it will affect the sample size.

- Some studies show that BMI index is not the most accurate measurement of obesity. Further measurements should be carried out on this topic, and should use other tools to measure obesity, such as waist circumference, waist-to-hip ratio or Body fat percentage(4,14).

- Almost all the literature available mentions the use of the laryngoscope to monitor the function of the inferior laryngeal nerve. This technology is not available yet at Hospital Dr.Josep Trueta de Girona, so we will be incapable of checking the integrity of the nerve post-surgery(14).

- One of the main problems of the study is the use of a non-probabilistic consecutive sampling, which has its own limitations. It is hardly representative of the entire population. Therefore, it may not enable us to draw definitive conclusions concerning the outcome of the association of obesity and postsurgical complications.

- Confounding bias: the relationship is difficult to control due to co-variables. This limitation will be minimized by the use of a multivariate analysis.
XIII. Feasibility

a. Work plan and chronogram scheme

Hereunder is located the proposed chronogram (ANNEX 5) depicting the tasks, the personnel required and the timeline of the study.

The protagonists of this study are the participating endocrine surgeons, the researchers as well as the contracted biostatistician. The study is projected to take 4 years, from 2015 to 2018, and look at 8 years of data (2010 – 2018).

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- **Planning**: this phase is carried out by the researches along with the surgeons and will take place during the first month of the study.
- **Bibliography Research**: will be carried out by the researchers for the most part as well as by the surgeons.
- **Database Creation**: will be done by the researchers with MS Excel, with the collaboration of the surgeons. Help from technical consultants will be available if needed. 1 month will be needed for this phase.
- **Retrospective Data Collection**: During the first year, the surgeons will use the SAP patient management system to collect the relevant patient data from the year 2010 to 2014 and transmit it to the researchers.
- **Prospective Data Collection**: The surgeons will continue to collect and transmit the relevant data to the researchers until the end of 2018.
- **Database Entry**: From 2015 to 2018 the researchers will enter the patients’ information into the MS Excel database and codify it for further analysis.
• **Statistical Analysis:** At the of the data collection & entry phase, all the data will be given to the contracted biostatistician who will have 30 hours during the month of January 2018 to perform the statistical analysis.

• **Interpretation & Redaction:** From February to May, the researchers will have 4 months to interpret the statistical analysis and write the conclusions of the study.

• **Publication, Congresses & Press:** The last 6 months of 2018 will be dedicated to the publication of the article and presented at selected congresses.

b. **Availability of means**

The project will take place at Hospital Universitari Dr. Josep Trueta, where they will provide all means for developing the study, including the informatics equipment suitable for processing database for the study development without additional cost. However, the biostatistician will be paid by the project.

The investigators and the doctors working for the program will not receive a compensation for their work in this study.

Software such as SPSS and Microsoft Access© are not included because they are either available to the statistician or free of charge.
### XIV. Budget

<table>
<thead>
<tr>
<th>Item</th>
<th>Quantity</th>
<th>Cost per unit</th>
<th>Cost</th>
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<tr>
<td><strong>Personnel</strong></td>
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<tr>
<td>Biostatistician</td>
<td>30 hours</td>
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<td><strong>Goods and services</strong></td>
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<td>Literature review: payment</td>
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<td>articles and other literature material</td>
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<td>Publication fees: International Journal of Endocrinology</td>
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<td><strong>Travel and subsistence</strong></td>
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<td>arrangements**</td>
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<td>Dissemination of the results:</td>
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<td>Conferences</td>
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<td>- Inscriptio fee: Congreso</td>
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<td>of Asociación Española de</td>
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<td>Cirujanos (AEC)</td>
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<td>- Travel (AVE BCN-MAD)</td>
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<td><strong>TOTAL COST</strong></td>
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XV. Annexes


| Table 1: Thyroid tumors by world health organization (2004). |
|-------|-----------------|
| I. Primary | 2. Non-epithelial |
| 1. Epithelial | - Primary lymphoma and plasmacytoma |
| A. Follicular cell derived | - Angiosarcoma |
| 1) Benign | - Teratoma |
| - Follicular adenoma | - Smooth muscle tumors |
| 2) Uncertain malignant potential (UMP) | - Peripheral nerve sheath tumors |
| - Thyroplastic tumor | - Paraganglioma |
| 3) Malignant | - Papillary carcinoma |
| - Papillary carcinoma | - Solitary fibrous tumor |
| - Follicular carcinoma | - Follicular dendritic cell tumor |
| - Poorly differentiated carcinoma | - Langerhans cell hystiocytosis |
| - Undifferentiated (Anaplastic) carcinoma | - Rous-Dorfman disease |
| B. C cell derived | - Granular cell tumor |
| - Medullary carcinoma | |
| C. Mixed follicular and C cell derived | |
| - Mixed medullary and follicular carcinoma | |
| - Mixed medullary and papillary carcinoma | |
| D. Epithelial tumors of different or uncertain cell derived | |
| - Micropapillary carcinoma | |
| - Sarcomatous micropapillary carcinoma with eosinophilia | |
| - Squamous cell carcinoma | |
| - Mucoepidermoid carcinoma | |
| - Spindle cell tumor with thymus-like differentiation | |
| (SETTLE) | |
| - Carcinoma showing thymus-like differentiation | |
| (CASTLE) | |
| - Ectopic thymoma | |
| II. Secondary | |

# Annex 2: ASA Classification

**ASA Physical Status Classification System**

ASA PHYSICAL STATUS CLASSIFICATION SYSTEM

Last approved by the ASA House of Delegates on October 15, 2014

Current definitions (NO CHANGE) and Examples (NEW)

<table>
<thead>
<tr>
<th>ASA PS Classification</th>
<th>Definition</th>
<th>Examples, including, but not limited to:</th>
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<tbody>
<tr>
<td>ASA I</td>
<td>A normal healthy patient</td>
<td>Healthy, non-smoking, no or minimal alcohol use</td>
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<tr>
<td>ASA II</td>
<td>A patient with mild systemic disease</td>
<td>Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30 &lt; BMI &lt; 40), well-controlled DM/HTN, mild lung disease</td>
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<tr>
<td>ASA III</td>
<td>A patient with severe systemic disease</td>
<td>Substantive functional limitations; One or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA &lt; 60 weeks, history (&gt;3 months) of MI, CVA, TIA, or CAD/stents</td>
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<tr>
<td>ASA IV</td>
<td>A patient with severe systemic disease that is a constant threat to life</td>
<td>Examples include (but not limited to): recent (&lt; 3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis</td>
</tr>
<tr>
<td>ASA V</td>
<td>A moribund patient who is not expected to survive without the operation</td>
<td>Examples include (but not limited to): ruptured abdominal/thoracic aeurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction</td>
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<tr>
<td>ASA VI</td>
<td>A declared brain-dead patient whose organs are being removed for donor purposes</td>
<td><em>The addition of “E” denotes Emergency surgery; (An emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part)</em></td>
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</table>

These definitions appear in each annual edition of the ASA Relative Value Guide®. There is no additional information that will help you further define these categories.

Source: ASA PHYSICAL STATUS AND CLASSIFICATION SYSTEM [Internet]. USA; 2015 [cited 2015 Dec 3]. Available from: https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system
Annex 3: Anatomy of the thyroid gland and its surroundings

Source: Image provided by Dr. Rodríguez
Annex 4: Cervical lymph node territories

Source: Image provided by Dr. Rodríguez
### Annex 5: Chronogram

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<th>Task</th>
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<td>Planning</td>
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<td>Database Creation</td>
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