Universitat de Girona

FACULTY OF MEDICINE

Active surveillance as the initial treatment of papillary thyroid microcarcinoma: a 10-years multicentric prospective study

FINAL DEGREE PROJECT

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1- ABSTRACT

TITLE: Active surveillance as the initial treatment of papillary thyroid microcarcinoma: a 10-years multicentric prospective study.

BACKGROUND: Papillary thyroid microcarcinoma has extensively been proved to have an excellent prognosis. The results of autopsy series and mass-screening studies suggest that a significant percentage of population have this disease, but its behaviour is mostly indolent. However, when an incidental microcarcinoma is diagnosed, aggressive surgical treatment is the current recommendation. Two hospitals in Japan started treating these patients with active surveillance, following them with periodic control visits and only recommending surgery after demonstrated disease progression. Even though the results with this conservative strategy are promising, there is no study that specifically compares both managements.

OBJECTIVE: The objective of this study is to determine whether active surveillance is an appropriate alternative to initial surgery in the management of patients with papillary microcarcinoma of the thyroid with good prognostic factors.

METHODS: This will be a longitudinal, prospective, non-randomized, controlled trial. It will be set in the CeCAT consortium hospitals, with the Hospital Universitari Josep Trueta as the reference center. The participants will be 191 patients diagnosed with papillary thyroid microcarcinoma in the CeCAT centers, using a consecutive non-probabilistic sequential sampling. The patients will be separated in 2 groups, according to the treatment decision, in "active surveillance group" and "initial surgery group", and then followed with periodic control visits during 10 years. Progression of the disease will be the dependent variable, and will be measured using ultrasonographic criteria. Progression will be defined either by the appearance of cervical lymph nodes, the enlargement of the primary microcarcinoma or the reappearance of lesions in the thyroid bed. Percentages, means +/- standard deviation, χ^2 test and logistic regression will be performed to analyze and describe the results of the study.

KEYWORDS: Papillary microcarcinoma of the thyroid, thyroid carcinoma, papillary carcinoma, active surveillance, conservative management

2- ABBREVIATIONS

ATA → American Thyroid Association

CeCAT → Consorci per a l'Estudi del Càncer de Tiroides

CT → Computed tomography

FNAC → Fine needle aspiration cytology

LN → Lymph node

MHz → Megahertz

MRI → Magnetic resonance imaging

PET → Positron emission tomography

PTMC → Papillary thyroid microcarcinoma

PTC → Papillary thyroid carcinoma

SEEN → Sociedad Española de Endocrinología y Nutrición

T4l → Free thyroxine

Tg → Thyroglobulin

TgAb → Anti-thyroglobulin antibodies

TSH → Thyroid stimulating hormone

US → Ultrasonography

3- INTRODUCTION

3.1. Thyroid papillary carcinoma

Thyroid carcinoma is the most common malignancy originating from the endocrine organs, and papillary thyroid carcinoma (PTC) is the most common type of thyroid carcinoma. It accounts for 88% of the total of thyroid cancer, is generally mild and grows slowly (1).

Papillary cancer is defined as a malignant epithelial tumor with papillary structures. As possible cytological features, Psammoma bodies, nuclei with a ground-glass appearance or cleaved nuclei with an "orphan-Annie" appearance caused by large nucleoli might appear (2).

The incidence of thyroid cancer in the United States is 14.2 per 100.000 individuals, and PTC accounts for 12.3 per 100.000 (3). In our population, the incidence of PTC accounts for 8.5 x 100.000 individuals.

Local symptoms are related to size, and they generally appear in cancers larger than 5 cm. The most common are dysphagia, dyspnea, dysphonia and orthopnea (1). PTC can be multifocal and invade through the thyroid capsule, and has propensity to spread via the lymphatic system. It can also metastasize hematogenously, particularly to bone and lung (2).

Most papillary cancers are identified in the early stages (> 80% stages I or II) and have an excellent prognosis, with survival curves similar to expected survival (99% survival at 20 years) (2).

TNM classification of thyroid cancer is described in FIGURE 1. If the carcinoma is diagnosed as a T1a (<1cm), it is known as a papillary thyroid microcarcinoma (PTMC).

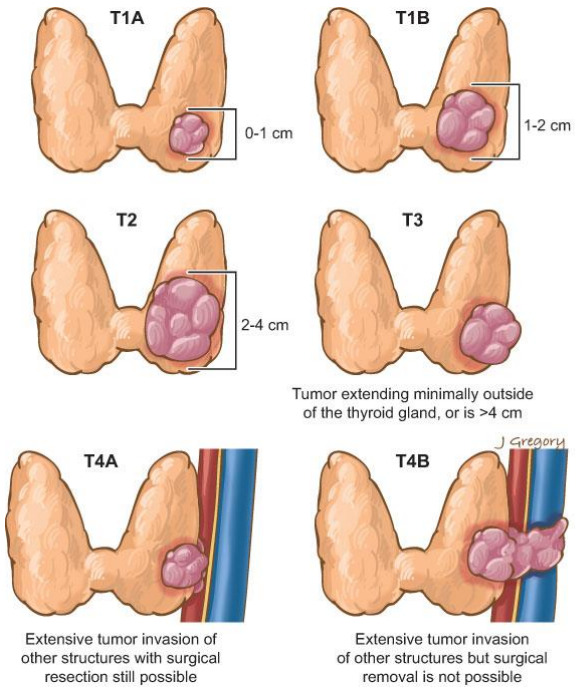


FIGURE 1: TNM classification of thyroid cancer (1)

(1) FIGURE 1: http://headandneckcancerguide.org/wp-content/uploads/2013/02/78_thyroid_Tstage2.jpg

3.2. Thyroid papillary microcarcinoma

3.2.1- Introduction

Papillary thyroid microcarcinoma is defined by the World Health Organization as a papillary thyroid carcinoma measuring ≤ 10 mm in maximum diameter (4). It is the most common subtype of PTC (5). The mean age at diagnosis has been reported to be 41.9-55 years, with a range of 4-85 years, and affects women more than men with a ratio of 4.85/1 (6). It is thought that they have different tumor biology than larger lesions, and for this reason they can remain indolent with minimal morbidity for decades (7).

Currently, almost 90% of PTMC are diagnosed incidentally, without previous symptomatology. Incidental PTMC is typically diagnosed using exploration techniques for other pathologies, while non-incidental is diagnosed due to the appearance of clinical symptoms or the identification of nodal metastasis. Incidental PTMC has different clinical characteristics and a much lower recurrence rate than non-incidental PTMC (8). They have an excellent prognosis and there is nearly no risk of recurrence or death (9). On the contrary, the non-incidental diagnosis of PTMC has been significantly associated with more aggressive tumor features, including extrathyroidal extension and disease recurrence (10,11).

It has been suggested that management protocols should be re-considered and that incidentally and non-incidentally diagnosed PTMCs should be differently managed regarding their distinct clinical features and prognosis (8).

3.2.2- Epidemiology

Autopsy prevalence

There have been a remarkable number of autopsy series in different countries trying to assess the prevalence of PTMC (6,12–17). PTMC have been found to be surprisingly prevalent, with an autopsy prevalence ranging from 5% to 35.6% of the total.
In a meta-analysis of 24 autopsy series, the average PTC prevalence calculated was 7.6%, and up to 12% when excluding series with slice thickness more than 3mm and not examining the entire thyroid gland (18).

Autopsy series have demonstrated that there is a large reservoir of PTMC (19). For this reason, it has been suggested that most of them are indolent and that PTMC does not require surgery. The first paper to suggest it was an autopsies series done in Finland, in 1985 (13). Based on this supposition, an observation trial was started in 1993 in Kuma Hospital, in Japan, to describe the natural evolution of incidental PTMC without initial surgery (20).

Clinical prevalence

PTMC accounts for 23-43% of the total of thyroid malignant diseases (6,16,20,21). In a retrospective study done in our territory, 30.1% of the differentiated thyroid carcinomas were PTMC (22).

A mass screening study done in Japan with US and US-guided FNAC showed that 2,6% of otherwise healthy women aged ≥ 30 years had thyroid carcinoma, and 56,8% were ≤ 1.0 cm (23). According to this study, the prevalence of thyroid carcinoma would be 2600 per 100.000 females. With this data, the estimated subclinical reservoir in the United States would be between 8 and 25 million of Americans (24).

However, previous studies from various countries demonstrated that the prevalence of clinical papillary carcinoma is only 1.9 – 11.7 per 100.000 females (25).

Discrepancy

The marked difference between autopsy and clinical prevalences, as well as the difference between mass-screening and clinical diagnosis strongly suggest that PTMC incidentally detected by US would rarely become clinically apparent (26). According to the previous data, it seems that only 1 of 1000 papillary carcinomas becomes clinically apparent and requires therapy. For this reason, it has been suggested that most low-risk PTMC are harmless and immediate surgery for all of them is definitely an overtreatment (23,27).

Increase of incidence

Studies done in many territories show that, in the last decades, it has been a huge increase of the incidence (28–30), suggesting that this increase has happened everywhere (9). In the USA population, it has been a 2.9 fold increase in the incidence of thyroid cancer between 1975 and 2009, and virtually the entire increase was attributable to the diagnosis of PTMC using US and US-guides FNAC (3). About this fact, it is important to note that the routine use of neck US has increased by 80% in endocrinological services over the past few decades (19).

An epidemiologic report from the USA shows that, although the incidence of thyroid carcinoma has increased a 441% between 1973 and 2002, its mortality has remained stable (1,31).

Given the known high prevalence of PTMC at autopsy, this fact suggests that the increase of PTMC is mainly due to an increment of diagnostic scrutiny (specially evaluations of the carotid artery) rather than a real increase of the incidence of PTMC (31,32). This, known as "overdiagnosis", is the identification of a disease which, if left undetected, would not cause symptoms or death for that patient during his or her lifetime (24). If not recognized, overdiagnosis generally leads to overtreatment, which is potentially harmful because it leads to unnecessary surgery, with the possible long-term consequences (the need of lifelong thyroid replacement) and a small but significant risks of complication (33).

To sum up, it is clear that the autopsy prevalence of PTMC is much higher than the clinical prevalence. The results of the mass screening and the fact that the diagnosis of PTMC is increasing, suggests that indolent PTMC, which remained undetected in the past, are being diagnosed more frequently. This overdiagnosis leads to overtreatment, and this can be harmful for the patient (34).

3.2.3- Diagnosis

Nowadays, more patients receive a diagnosis of thyroid cancer after the evaluation of an incidentally found thyroid nodule than after evaluating a symptomatic non-incidental palpable nodule (19). Typically, incidental PTMC is either diagnosed via ultrasonography guided fine needle aspiration cytology (US-guided FNAC) or during thyroidectomy in patients previously not known of having malignancy (5).

Ultrasound evaluation (US) with fine-needle aspiration cytology (FNAC) is the gold standard technique for thyroid cancer diagnosis (35). When performed by skilled operators, it is a very accurate diagnostic procedure, capable of detecting nodules measuring ≥3 mm in diameter (26,36,37). In some institutions, up to 89% of PTMC are diagnosed using this technique, without needing previous surgery (21).

A thyroid nodule is considered of high suspicion if the criteria described in TABLE 1 are met (38):

TABLE 1: CARACTERISTICS OF A HIGHLY SUSPICIOUS THYROID NODULE

Sonographic pattern	US features	Estimated risk of malignancy
High suspicion	• Solid hypoechoic nodule *or* • Cystic nodule with a solid component *with one or more of:* - Irregular margins - Microcalcifications - Taller than wide shape - Rim calcifications with small extrusive soft tissue component - Evidence of extrathyroidal extension	> 70 – 90 %

Other ways of incidentally diagnosing a PTMC are: neck or chest computed tomography (CT), magnetic resonance imaging (MRI), PET and simple palpation (39).

At initial diagnosis, we can also detect the presence of cervical lymph node metastasis (40). It is useful to evaluate the biological aggressiveness of the PTMC and to decide the treatment (41). These lymph nodes are ≥ 5 mm in their short axis in the cervical levels III-IV, and ≥ 8 mm in the levels I-II. The features considered predictive of nodal malignant involvement are described in the TABLE 2 (38):

TABLE 2: FEATURES PREDICTIVE OF MALIGNANT INVOLVEMENT IN THE LYMPH NODE

Sign	Reported sensitivity %	Reported specificity %
Microcalcifications	5 – 69	93 – 100
Cystic aspect	10 – 34	91 – 100
Peripheral vascularity	40 – 86	57 – 93
Hyperechogenicity	30 – 87	43 – 95
Round shape	37	70

If a lymph node is suspicious, a US-guided FNAC is performed (42). In addition, a measurement of the thyroglobulin in the wash-out of the needle is done, using 0.5-1 ml of physiologic solution, and defining the result of thyroglobulin level > 10 ng/ml as positive. This technique increases the sensitivity of the diagnosis of metastasis to an 81.4% (43,44).

3.2.4- Risk factors of recurrence and progression

The most important predictor of outcome is whether the tumor was incidentally or non-incidentally diagnosed (45). Considering the incidentally diagnosed, the presence of lymph node metastasis at diagnosis is the most important risk factor of progression (26).

According to a retrospective study that evaluated the possible risk factors, after a multivariate analysis, only lymph node metastasis at diagnosis was an independent predictive factor of recurrence (5). Other risk factors that have been proposed but on which there is no consensus are described in TABLE 3 (21,25,27,45–52):

TABLE 3: OTHER PROPOSED RISK FACTORS

Age	Solid pattern
Gender	Dietary iodine status
Primary tumor size	Chronic thyroiditis
Tumor multifocality	Concomitant Grave's disease
Extrathyroid extension	Bilateral involvement
Capsular invasion	Post-operative Tg level
Absence of capsule	Family history of thyroid cancer
Vascular invasion	TSH level

Cervical lymph node metastases appear in 13.5% to 64.1% of patients (10,11,26,42,53–55). They can be diagnosed in the cervical lateral compartment or in the cervical central compartment.

The incidence of cervical LN metastasis can be high, but it is important to differentiate between LN metastasis identified at diagnosis using US + FNAC, and latent LN metastases not visible with US. Studies suggest that PTMC cases with US-identified LN metastasis are much more aggressive, with a greater tendency to progress, than those showing only pathologically confirmed LN metastasis (41,42). In an autopsy study done in Spain, 14% of incidental PTMC had latent LN metastasis, but without any other sign of progression (17).

This results indicate that latent LN metastasis occur early and often in the natural history of PTMC, yet seldom develop into clinically significant disease. However, when they do it, LN metastasis identified at initial diagnosis is a significant risk factor of progression and recurrence (56).

In an American study utilizing the SEER database, patients with histology of tall cell or diffuse sclerosing variants had more risk of progression (57). Tumors with these variants are considered high-grade papillary thyroid carcinoma (58). Columnar cell, solid and hobnail variants have also been related with more unfavorable outcomes (38).

Some mutations have been suggested as possible risk factors. TERT promoter mutation (59) and BRAFV600E (7) are being investigated as possible predictors of worse prognosis.

3.2.5- Treatment

There is a lot of controversy in the treatment of PTMC, with a wide variety of practice patterns (50). The treatment of PTMC currently range from total thyroidectomy with central and lateral compartment neck dissection and TSH-suppressive therapy after surgery (54) to active surveillance without initial surgery (20).

Surgery

As it has been stated, the diagnosis of PTMC could happen in an incidental or in a non-incidental way. If an aggressive non-incidental PTMC is diagnosed, a radical therapeutic approach is desirable (60). However, if the diagnosis is incidental, the recommendations of the last American Thyroid Association Guidelines are much less aggressive.

The 2015 American Thyroid Association Management Guidelines for Adult Patients say that, if surgery is chosen for patients with thyroid cancer ≤1 cm without extrathyroidal extension and cN0, the initial surgical procedure should be a thyroid lobectomy, unless there are clinical indications to remove the contralateral lobe.
Therapeutic central and lateral node compartment should only be performed if biopsy-proven metastatic lymph nodes are involved.
The Guidelines also state that, while surgery is generally recommended for biopsy proven thyroid cancer, an active surveillance management approach can be considered as an alternative to immediate surgery in patients with very low risk tumors (38).

Complications of surgery:

Thyroid surgery carries a small but significant risk of complications. The most severe of them are permanent hypoparathyroidism, which can cause hypocalcaemia, and damage to the recurrent laryngeal nerve, which can result in chronic aspiration and compromised voice quality (1). It also can result in hematoma formation or infection (34).

In the literature, complications range from 1% to 24.1% of patients. The most relevant are described in TABLE 4 (19,40,42):

TABLE 4: THE MOST RELEVANT COMPLICATIONS OF THYROID SURGERY

Complication	Frequency of appearance
Temporary vocal cord paralysis	1 – 3.5 %
Permanent vocal cord paralysis	1 – 5.8 %
Transient hypoparathyroidism	1 – 16.2 %
Permanent hypoparathyroidism	1 – 15.2%

The percentage of complications depends on the experience of the surgeon. High volume surgeons [>99 surgeries/year] performing the operation is associated with better patient outcomes (61). However, approximately half of the thyroid operations in the United States are done by low-volume thyroid surgeons [<9 surgeries/year] (56).

When nodal recurrence is detected, reoperation is recommended (26). Unfortunately, the incidence of postoperative complications usually increases markedly with a second surgery (62).

Active surveillance

Results from the American SEER database, which includes 32 years of data, showed no significant difference in the death rate from thyroid cancer in patients who received immediate surgery compared with those who did not (63).

According to this fact and taking into account all the evidence of the excellent prognosis of most PTMCs, active surveillance has been proposed as an alternative therapeutic option. Active surveillance is a conservative observational management strategy that is currently being offered to properly selected patients with other low-risk cancers, such as prostate cancer, urethral cancer, and some non-Hodgkin lymphomas (34).

This strategy consists in periodic controls with US to try to detect the few cases of disease progression. In patients being followed with active surveillance, definitive therapy is not recommended until there is evidence of disease progression. Because of the relatively indolent nature of these malignancies, deferring definitive diagnosis and therapy until documented disease progression has no impact on disease specific survival (34,56).

This strategy has been performed in Kuma Hospital during more than 20 years, and it is also being offered to patients in the Cancer Institute Hospital from Tokyo since 1995, both of them with excellent outcomes (20,39). As a result, active surveillance was adopted in the Japanese guideline for the management of PTMC in 2011 (64).

There is uncertainty about the harms and benefits of the immediate treatment of PTMC, and for this reason clinicians should try to engage patients in shared decision making, taking into account their preferences.

At the beginning of their study, the investigators of the Kuma Hospital reported that 78% of patients preferred surgical treatment rather than active surveillance (20). However, from 2005 to 2013, thanks to the great results they were obtaining with this new management, more than 50% of the new patients chose active surveillance over initial surgery [1179 from a total of 2153 patients] (65).

3.2.6- Follow-up

Only periodical observation of the patients can distinguish the harmless PTMCs accounting for the majority from the few progressive PTMCs (25). The follow-up after treatment (both initial surgery and active surveillance) is done with periodic physical examination, neck US (+/- fine-needle aspiration cytology) and measurement of serum thyroglobulin levels (19,21).

During the follow-up, we focus on the examination of the thyroid bed if the patient has undergone initial surgery, and on the progression of the primary PTMC during active surveillance. In both cases, we also look for cervical LN metastasis.

Recurrence

In the literature, it is reported a lymph node recurrence after surgery from 1.7 to 16.7%. Most studies show a disease recurrence rate lower than 5%, while a few report 6-16.7% (10,36,40,66). In a study from the Mayo Clinic of 900 patients who underwent surgery, 4.8% of recurrence was developed after 10 years of follow-up, and 6.5% at 20 years (54).

From the 1235 patients of the Kuma Hospital active surveillance study, 6.7% of PMTC enlarged by 3 or more mm in diameter during 5 years follow-up, and nodal metastases became detectable in 1,7% patients overall (26). In the same cohort of patients, during a 10-years follow-up, the incidence of tumor enlargement was 8%, and new lymph node metastasis appeared in 3.8% of the patients (32). In the Cancer Institute Hospital study, 230 patients chose non-surgical observation. After a mean follow-up of 5 years, 7% PTMC increased in size, and 1% of patients developed cervical LN metastases (39).

Due to the slow physiopathology of PTMC, recurrence can appear several years after the initial diagnosis and treatment, even 30 years after primary surgery (21).

3.2.7- Prognosis

The prognosis of patients diagnosed with PTMC is excellent, with nearly a 100% survival, and a life expectancy not significantly different from the normal population (54,66).

The organ to which papillary carcinoma most frequently shows recurrence is the cervical lymph node. When recurrence to the node is confirmed, reoperation is desirable (27).

Despite this excellent prognosis, PTMC is capable of causing mortality (16). Distant metastases are the main cause of cancer-specific mortality in these patients, and this risk is between 0 and 1% (5,7,67). In a meta-analysis done in 2008, cancer-related death occurred in the 0.34% of patients with PTMC (6). However, PTMC only represents a life-threat for a tiny minority of patients, and those patients usually present LN metastasis at the initial diagnosis (54).

From the group of patients being treated with active surveillance in Kuma Hospital, none of them developed distant metastasis or died of PTMC. Importantly, even the patients that suffered disease progression and had to be treated with thyroid surgical management after following the conservative treatment were effectively treated (34). These facts suggest that active surveillance in properly selected patients has no impact on the disease-specific survival.

3.3. Consorci per a l'Estudi del Càncer de Tiroides

The "Consorci per a l'Estudi del Càncer de Tiroides" (CeCAT) is a platform that includes most of the Hospitals of Catalunya and the biobank of IDIBGI, in Girona. The consortium has the goal to improve the integral management of the patient with thyroid carcinoma and to expand the knowledge of this disease. This platform integrates all the professionals that play a role in the management of thyroid cancer, including endocrinologists, pathologists, radiologists, surgeons and oncologists.

The CeCAT consortium was created in 2013 to encourage the investigation of thyroid cancer and to facilitate the coordination between Hospitals. Nowadays, it is constituted by 20 Hospitals and Clinics from all Catalunya, including Hospital Clínic and Vall d'Hebron from Barcelona, Hospital Josep Trueta from Girona, Hospital Joan XXIII from Tarragona and Hospital Arnau de Vilanova from Lleida.

The consortium has a webpage, which can be accessed with a password (68). This website has made possible the creation of a database of the thyroid cancers occurred in Catalunya from 1998 to 2012, and the results have been published (22).

Biannual meetings take place to show results of ongoing research and to propose investigation projects. In these meetings, the professionals can present new projects that might be investigated and, if necessary, a multicentric team is assembled to investigate them with the CeCAT logistical support.

CeCAT has shown to be a very valuable tool for the study of thyroid cancer, making possible to perform studies in a larger, more coordinated way.

4- JUSTIFICATION

PTMC has been shown to be very prevalent in autopsy series (1-35.7%). It has also been found to be remarkably prevalent in mass-screening of women > 30 years (2-3%). However, its clinical incidence is 1000 times lower than which should be according to these results (2-3 x 100.000).

The studies also show that the PTMC incidence is increasing. Nevertheless, this increase has not been associated with an increase of the mortality, which suggests that the "extra" cases of PTMC are due to overdiagnosis more than a real increase of this disease.

With these facts we must assume that the "extra" cases of PTMC are incidental microcarcinomas that are diagnosed due to the major use of ultrasonography and other image diagnosis techniques, but which in the past remained undiagnosed and untreated. Because of this, controversy appeared on whether these microcarcinomas have to be aggressively treated (initial surgery), or if a more conservative strategy (active surveillance) would be enough.

Historically, a more aggressive surgical strategy was used, but with time a tendency for a less radical surgical treatment was implemented. The proven benign prognosis of PTMC continued, even with a much more conservative strategy. In addition, the surgical treatment results in complications for a significant percentage of patients (1-24%).

Due to all this factors, and in an attempt to implement the "*primum non nocere*" principle, two Japanese studies started using only active surveillance in patients with PTMC and good prognostic factors. After more than 15 years of follow-up, their results are very promising, with a really low percentage of disease progression and without the surgical complications. In the few cases of disease progression, surgery was performed and no worse results were obtained than with initial surgery. With all of these, we can conclude that active surveillance seems to be an acceptable initial management for low risk PTMC.

However, no study comparing directly the results of active surveillance and initial surgery has been started, and this therapy has never been systematically implemented in our population. This fact gives us the opportunity to perform a study in our population, as it is suggested in the 2015 American Thyroid Association Management Guidelines for Adult Patients. These guidelines, which are the most recent, confirm the huge controversy on the treatment of

PTMC and strongly encourage the decision to perform more trials using conservative treatment.

With all of this, we have proposed to perform this study, which will be the first to use active surveillance in the European population, and the first to compare directly both treatments. The CeCAT consortium enables us to do a multicentric study at a Catalan level, simplifying the coordination and the data collection. If the results are which we expect, it would result in a better treatment strategy for the patients, with fewer complications, and with a lower economic cost for the National Health System.

5- HYPHOTESIS

Active surveillance is an appropriate alternative to initial surgery in the management of patients with papillary microcarcinoma of the thyroid with good prognostic factors.

6- OBJECTIVE

To determine whether active surveillance is an appropriate alternative to initial surgery in the management of patients with papillary microcarcinoma of the thyroid with good prognostic factors.

We will determine it comparing the appearance of disease progression between the group that follows active surveillance and the group that choses initial surgery. We will do it during a follow-up of 10 years.

7- METHODOLOGY

7.1- Study design

Due to the physiopathology of this disease, it is necessary a long follow-up to assess properly the appearance of disease progression. As we have seen before, a study is necessary to determine if active surveillance should be proposed as an initial alternative therapy for papillary thyroid microcarcinoma in patients with good prognostic factors, as it is suggested in the most recent thyroid guidelines.

The best way to confirm or refuse our hypothesis, according to the existing data and the limitations of this topic, would be a multicentric, longitudinal, prospective, non-randomized, controlled trial.

The study will be conducted in the hospitals that integrate the CeCAT consortium, and the Hospital Universitari Josep Trueta will be the reference center.

In each of the centers we will assign an investigator (an endocrinologist), and a reference radiologist and pathologist who will perform and analyze the necessary US-guided FNACs.

7.2- Study subjects

To know which patients are going to participate in this study, we have to define our population of interest. The study subjects will be the patients diagnosed with papillary microcarcinoma of the thyroid in the CeCAT consortium hospitals that fulfil the inclusion and exclusion criteria.

7.2.1 Inclusion criteria

- Patients with ≤ 1.0 cm thyroidal nodules identified with ultrasonography.
- FNAC of the thyroid nodule with pathologically confirmed Bethesda V or VI papillary thyroid carcinoma (Bethesda classification in ANNEX 4).
- Minimal age of 18.
- Ability to understand and the willingness to sign the informed consent.

7.2.2 Exclusion criteria

- FNAC findings suggesting poorly differentiated or high-grade papillary thyroid carcinoma (tall cell, columnar cell, diffuse sclerosing or hobnail variants)
- Central or lateral neck lymph-node metastasis at initial diagnosis, identified with US and confirmed using US-guided FNAC
- Unfavorable nodule location:
  - Near the dorsal surface (close to recurrent laryngeal nerve)
  - Adjacent to the trachea (risk of cartilage invasion)
  - Near the thyroid capsule (risk of extrathyroidal invasion)
- History of radiation to the neck

If the patient has one of the described exclusion criteria, immediate surgery will be recommended, as it is the standard of treatment. Patients with PTMC and US detectable cervical LN metastasis at diagnosis also have to be evaluated for the presence of distant metastasis using computer tomography (CT).

7.3- Sample selection

The sampling method will be a consecutive non probabilistic sequential sampling. The subjects diagnosed with PTMC in the CeCAT consortium hospitals that fulfill the above-mentioned criteria will be asked to participate in this study.

All the potential participants will be given an information sheet and an informed consent (ANNEX 1 and 2). They will be considered recruited for the study only after reading and signing these documents.

7.4- Sample size

To calculate the sample size the online free application GRANMO was used.

According to the existent bibliography, we estimated that the risk of disease progression with initial surgery (appearance of new LN metastasis or thyroid bed recurrences) is 0.05 at 10

years. With active surveillance, it has been described a risk of progression (appearance of new LN metastasis or enlargement of the PTMC ≥3 mm) of 0.12 after 10 years of follow-up (25).

As the active surveillance group will not suffer an initial (and may be unnecessary) surgery with all the possible complications (up to 24.1% in some series), and the fact that is easier to perform a first neck surgery instead of a reoperation, we have assumed that a slightly higher level of disease progression in the observational group is acceptable. We have defined this acceptable higher risk as 0.07, and done our calculations. As with initial surgery, considered the reference treatment, the risk of progression is 0.05, we have considered an acceptable total risk of progression with active surveillance of 0.05 + 0.07 = 0.12.

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral contrast, we need 191 patients to demonstrate a difference equal or higher than 0.07 unities. It has been anticipated a drop-out rate of 20%, taking into account the percentage of people in previous studies who change their mind and decide to undergo surgical treatment after primarily choosing active surveillance.

7.4.1 Estimated time of recruitment

As we calculated before, 191 patients are needed for this study.

According to the existent bibliography and the actual incidence of this disease, we calculated that around 180 patients per year are diagnosed with PTMC with good prognostic factors in the hospitals in the CeCAT consortium. Considering that 10% of patients may not want to participate, we will need around 14 months to recruit these 191 patients.

Based on the existent bibliography, we assumed that the incidence of PTC in our population is 8.5 x 100.000. According to the previous data registered in Hospital Josep Trueta, 35% of the total of PTCs are PTMCs. Of those, the most of them accomplish the criteria to be included in our study (only a 20% would not fulfil the inclusion and exclusion criteria). Taking this into account, the 28% of the total of PTCs of our territory could be included in our study (an incidence of 2.4 x 100.000). Assuming that the population covered by the hospitals of the CeCAT is ≈ 7.500.000 people, we calculated that 180 patients will be suitable to join our study per year.

7.5- Procedures

Every patient seen or referred to the endocrinology department of the hospitals involved in this study which meet the inclusion and not exclusion criteria will be ask to participate in this study. The patient must agree and give their written consent after reading the information sheet (ANNEX 1 and 2).

The patients will arrive to us after the incidental discovery of a thyroid nodule. This discovery may have been made by an endocrinologist during the routine control of other thyroid diseases or by other specialists during a cervical examination. The nodule will then be studied by a radiologists specialized in thyroid examination, using US (both the B-mode [with a ≥10 MHz transducer] and the color-Doppler US). A US-guided FNAC will be performed, and the pathological diagnosis will be made by a pathologist specialized in the thyroid.

We will consider the first visit when the patient comes to our consulting room after we have the results of the US-guided FNAC.

- **1st visit**

The patient will come to our consulting room after the incidental diagnosis of a PTMC.

In the first visit, we will have the results of the US and the US-guided FNAC. If the initial FNAC is not conclusive, we will ask the radiologist to repeat it.

A clinical exploration of the neck will be performed, as well as a US exploration of the thyroid gland and the cervical lymph nodes. Thyroglobulin (Tg), antithyroglobulin antibodies (TgAb), free thyroxine (T4l) and TSH levels will be determined in a blood test. If the patient fulfills the criteria to be admitted in the study, we will present him the two management options: active surveillance or surgical treatment.

The patient will be given an information sheet about the strengths and weakness of each management (ANNEX 1). After that, he will be asked to enter the study and sign the informed consent (ANNEX 2). The decision of which treatment will be followed will be made according to the patient preferences, as it is suggested in the 2015 ATA Guidelines, and according to the existent information about the 2 therapies. The endocrinologist should advise the patient and

resolve the doubts that he might have. The patient will only be considered recruited for the study after signing the written informed consent.

Once the treatment is decided, we will record the baseline data and co-variables (age, gender, family history of thyroid carcinoma, presence of other thyroid conditions, tumor size, presence of multifocality, and TSH, T4l, Tg and TgAb levels), and the patient will be considered a part of the "active surveillance group" or the "initial surgery group". All factors that have to be tested in the first visit and in the following control visits will be written in a document that will be given to the endocrinologists that take part in the study (ANNEX 3).

The subsequent management will be different depending on which group is chosen:

- Patients who chose active surveillance will undergo periodical follow-up with physical exploration of the neck, a cervical US and a blood test twice per year. If no progression is detected for 2 years, the follow-up visits will then be programed only once per year.
- If the patient chooses initial surgery, he will be sent to the surgery department to prepare the operation. The recommended surgery will be a lobectomy of the affected thyroid lobe. If both lobes are affected, a total thyroidectomy will be performed. We will program a control 1-2 months after surgery to check the results of the operation and identify the possible complications. After that, the follow-up visits will start, in the same way than with the active surveillance group.

To obtain the maximum evidence on this topic we should randomize the patient before deciding which treatment should be followed. However, as it is an oncologic disease with good prognosis and a long follow-up, and as there is not enough strong evidence to decide one treatment or the other, it is currently recommended to choose the treatment taking into account the preferences of the patient (38).

The most recent publications suggest that with the existing evidence about the 2 therapies, more or less 50% of patients choose active surveillance while the other 50% choose initial surgery. In a study published in 2015, from 2153 patients who were offered the 2 options, 1179 opted for active surveillance [54%], and 974 for initial surgery [46%] (65).

INITIAL SURGERY GROUP

- **2nd visit**

A second visit 1-2 months after surgery will be programed. In this visit, some items will be checked:

- The pathologic results of the surgical piece
- The presence of possible complications (hypoparathyroidism, lesion of the laryngeal recurrent nerve, hematoma and infection of the surgical wound)
- The post-surgery thyroid function

A blood test with the calcium, PTH and protein levels will be demanded to check the function of the parathyroid gland and detect a possible hypoparathyroidism. The thyroid function will also be tested with the thyroid hormones levels, and a physical exploration of the voice will be performed to check the condition of the laryngeal recurrent nerve. If any complication with the voice is detected, the othorrinolaringology department will be consulted.

The TSH level will be useful to determine whether the patient needs treatment to have an adequate thyroid function. If the TSH level after lobectomy is > 2 mUI/L, it will be considered as a high level, and treatment with thyroxine will be necessary. We will start with levothyroxine at 1 microgram/kg, and will adjust the dose in the following control visits. If the surgical treatment was a total thyroidectomy, the starting dose will be 2.2 microgram/kg, and it will be adjusted during the following control visits, to achieve a TSH level < 2mUI/L.

After this visit, we will start with the follow-up.

- **Control visits**

A control visit will take place every 6 months. If the disease remains stable for 2 years, then we will program them annually. They will last for 10 years after the initial treatment.

The first control visit will be used to assess the response to surgery. In this visit, the first measure of the Tg level will take place. The results will have to be analyzed depending on the surgery performed. After a lobectomy, the Tg level should be lower than 30 ng/ml, because of the less amount of thyroid cells producing this protein. If higher, this Tg level may suggest an

incomplete resection or an increasing thyroid volume. After a total thyroidectomy, the levels of Tg should be lower than 0.2 ng/ml.

If the TgAb are positive (> 4.11 UI/ml), the level of Tg will not be useful. In this situation, the stability or reduction of the TgAb levels will be used to control the disease evolution, as a surrogate indicator of the Tg level. An increase of the TgAb levels or the Tg levels during the follow-up might indicate that the disease is progressing.

In all the control visits, including in the first, a clinical exploration of the neck, a cervical US and a blood test will be performed. With the US we will investigate the thyroid bed and the possible new appearance of LN metastases. In the blood test we will determine the serum Tg, TgAb, T4l and TSH levels to monitor the thyroid function and the disease evolution.

If the US shows signs of progression, a US-guided FNAC will be performed. If confirmed, PTMC that show signs of progression will be advised to undergo surgery at that point. If the patient requires surgery, he will be referred to the surgery department.

Progression signs consist mainly in 2 factors: the novel appearance of lymph node metastasis and/or thyroid bed recurrence.

ACTIVE SURVEILLANCE GROUP

- **Control visits**

The management of the active surveillance group will be similar to the one described for the initial surgery group. The control visits will take place every 6 months, until 2 years of disease stability. Then, they will be performed annually. This control visits will last for 10 years.

In these visits a physical exploration and a US of the neck will be performed. A blood test with the serum Tg, TgAb, T4l and TSH levels will be examined.

If TSH level is > 2 mUI/L, we will start medical treatment with 25 micrograms of levothyroxine, and we will adjust the dose to achieve a TSH level < 2 mUI/L during the following control visits. This is done to avoid the possible stimulating effect of the TSH in the PTMC growing (38).

In this group, we will compare the Tg levels with the previous measurement, to make sure that it is not progressing. During the follow-up of the active surveillance group, if the Tg levels duplicate during a year, surgical treatment should be suggested (69).

In the same way than in the initial surgery group, PTMC that show signs of progression will be evaluated with a US-guided FNAC. If confirmed, the patient will be advised to undergo surgery at that point, and will be referred to the surgery department. Progression signs will consist in the novel appearance of LN metastasis and/or in tumor size enlargement. To minimize the observer variation, the tumor size enlargement has to be confirmed with 2 different measures separated by 6 months.

If the patient decides to change the management and undergo surgery after a period of active surveillance, he will be send to the surgery department. After that the protocol that will be followed is the same that has been described for the initial surgery group, with 2nd visit after surgery and then follow-up.

If a patient changes his mind and decides to undergo surgery after being part of the active surveillance group, the data collected until that point will be used, but after the surgery the patient will no longer be considered a part of the study. This is because the data we would obtain would not be comparable because of a matter of follow-up time. The data from people that change their mind will be described differently from that obtained from the patients who have completed the follow-up, in a 3rd group, with a mean of the time followed and their results.

Even though in previous studies the number of patients changing their management was very low [3.5% in the Kuma Hospital study and 7% in the one from the Cancer Institute Hospital (39,69)], when doing the sample calculation we have considered a 20% drop-out rate. This percentage is possibly higher than the one that we would require, but we have done it this way to avoid the chance of this fact interfering in our results.

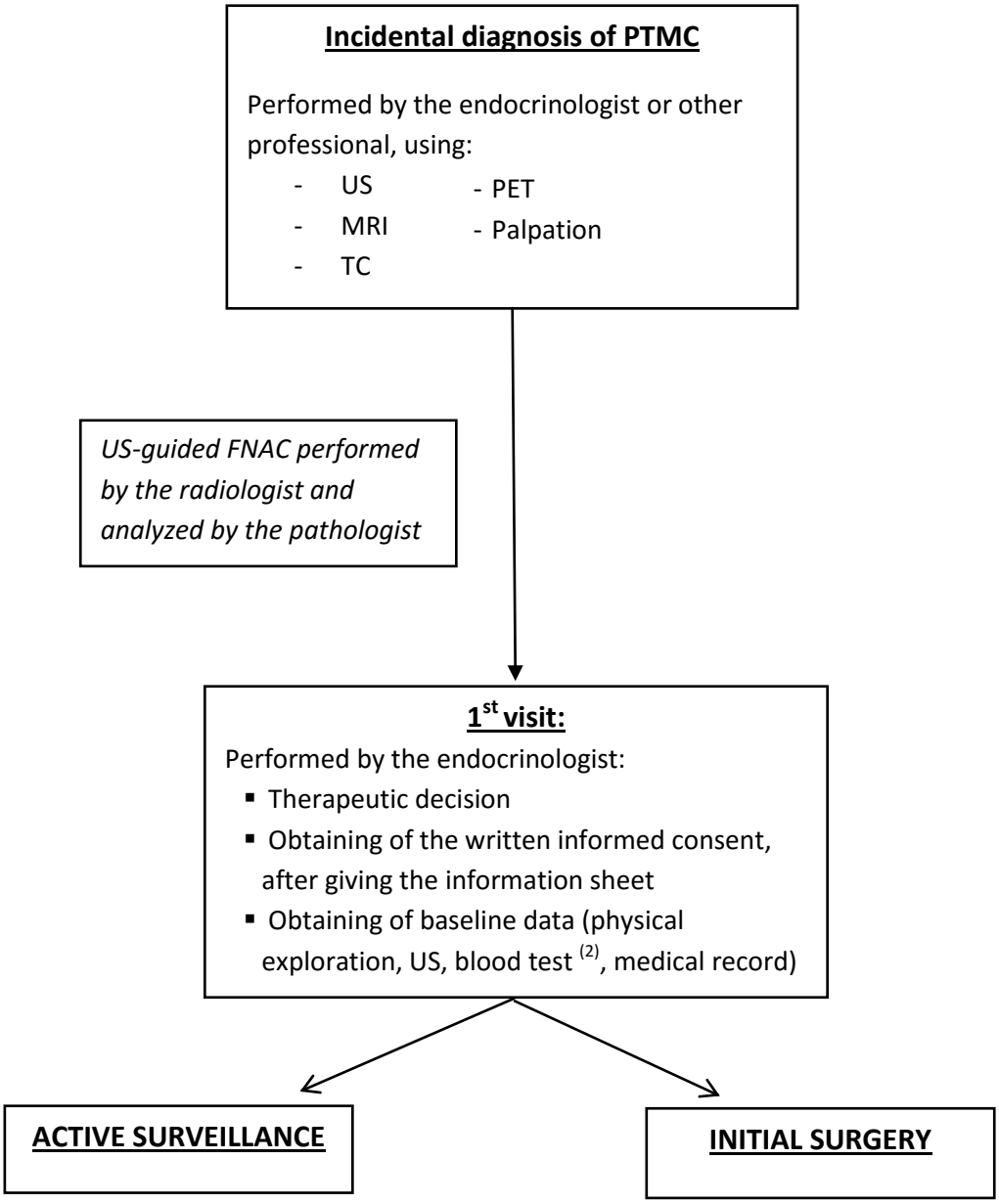


FIGURE 2: Flow Chart of therapeutic decision

(2) TSH, T4l, Tg and TgAb levels will be checked.

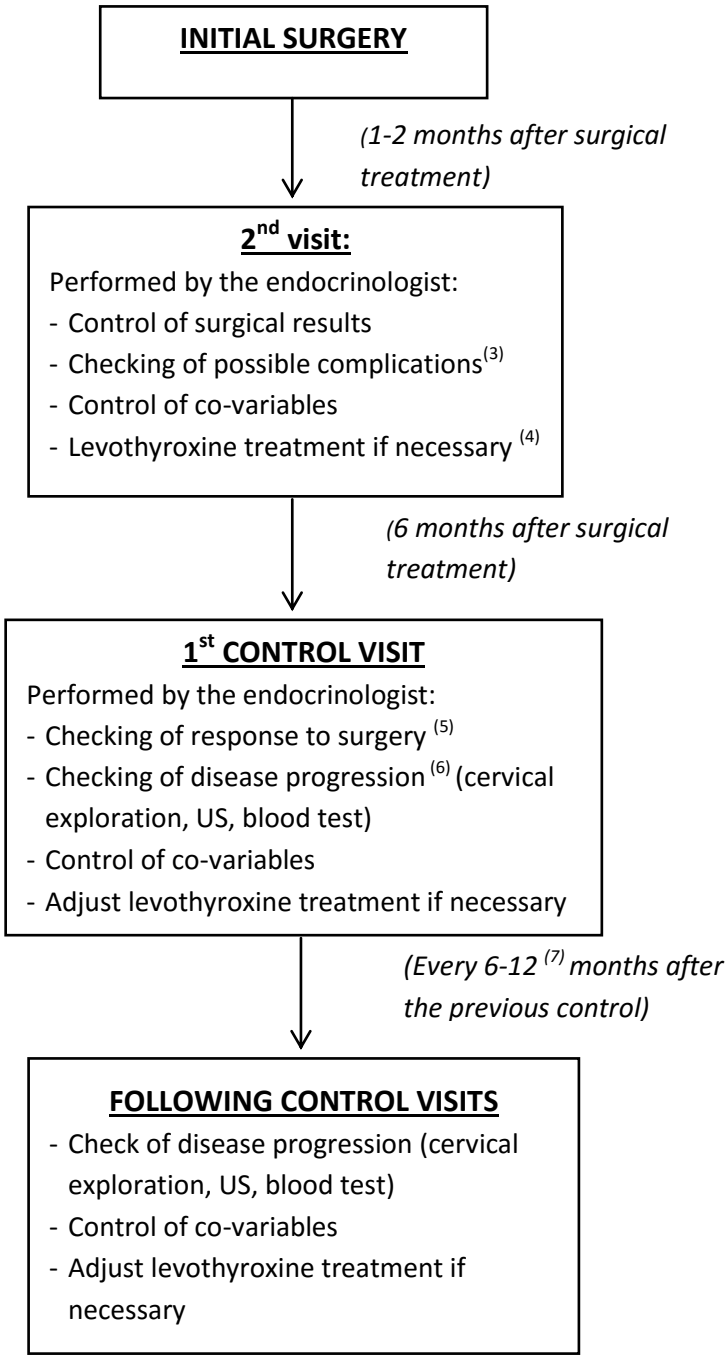


FIGURE 3: Flow Chart of initial surgery

(3) Hypoparathyroidism, lesion of the laryngeal recurrent nerve, hematoma and infection of the surgical wound

(4) If TSH > 2 mUI/L; 1 microgram/kg after lobectomy, 2.2 microgram/kg after total thyroidectomy

(5) Using Tg level: after lobectomy (excellent response, incomplete response), after total thyroidectomy (excellent response, indeterminate response, incomplete response)

(6) US examination of thyroid bed and the possible new appearance of LN metastasize. If progression is suspected, US-guided FNAC will be performed. If confirmed, the patient will undergo surgery. If not, scheduled control visits will continue.

(7) Every 6 months until 2 years of disease stability. After that, every 12 months.

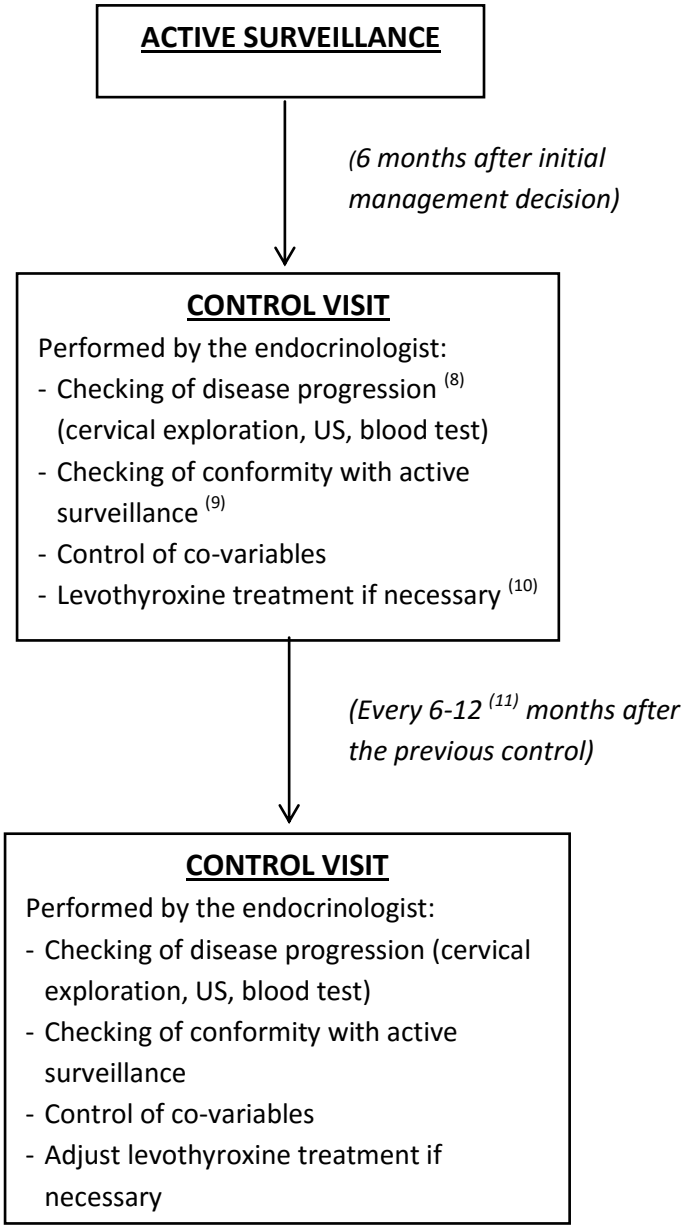


FIGURE 4: Flow Chart of active surveillance

(8) US looking for tumor size enlargement or the new appearance of LN metastasize. If progression is suspected, US-guided FNAC will be performed. If confirmed, the patient will undergo surgery. If not, scheduled control visits will continue.

(9) If the patient decides to change the management and undergo surgery, it will be performed at that point. After surgery, the patient will no longer be considered part of the study.

(10) If TSH > 2 mUI/L; 25 micrograms and adjust in the following control visits

(11) Every 6 months until 2 years of disease stability. After that, every 12 months

7.6- Study variables

Independent variable:

- **Treatment chosen by the patient: active surveillance or initial surgery**

This is a dichotomous nominal qualitative variable. It will be expressed by a percentage of people who chose active surveillance and people who chose initial surgery. The two different interventions and follow-up managements are explained above.

Dependent variable:

- **Appearance of disease progression after the initial treatment and during a 10 years follow-up**

Disease progression will be defined as one of the following:

- **Appearance of cervical lymph-node metastasis identified with US and confirmed with FNAC, and diagnosed as related to the primary PTMC.**

The cervical LN metastasis will be diagnosed using US and following the criteria of malignancy, previously described in TABLE 2. When suspicious of malignancy, a US-guided FNAC will be performed to confirm the origin of the LN, with a thyroglobulin measurement of the washout of the needle.

- **In the active surveillance group, an increase of the primary tumor size ≥ 3 mm, confirmed in two control visits separated by 6 months.**

We define tumor enlargement when the size of the tumor increases ≥ 3 mm compared with the size at the beginning of the observation. We establish the limit in ≥ 3 mm because in previous studies a 2 mm difference has been attributed in a significant number of cases to US inter-examiner difference (20,32). In addition, to minimize the observer variation, this increase has to be confirmed in 2 different measures separated by 6 months (70).

- **In the initial surgery group, reappearance of lesions in the thyroid bed suggestive of malignancy by US, and confirmed by FNAC.**

We will compare the US image in each control visit with the previous US from the patient, and look for a difference in size. If the image is suggestive of progression, a US-guided FNAC will be performed. The criteria of reappearance are described in TABLE 5 (69)**:**

TABLE 5: CRITERIA OF REAPPEARANCE OF LESIONS IN THE THYROID BED

Major criterion	**Minor criteria**
• New lesion in the thyroid bed ≥ 8 mm *+ one or more of the minor criteria:*	- Hypoechoic characteristics - Microcalcifications - Irregular borders - Abnormal vascularity - Taller than wide shape

We will collect this information as "patient with progression" or "patient without progression" during every control visit. It will be expressed by a percentage and, due to this fact, it will be considered a dichotomous nominal qualitative variable. In addition, it will be specified the reason of this progression, to enable future analysis of the results.

Co-Variables:

- Age (years)
- Gender (man or woman)
- Multifocality of the primary PTMC (yes or not)
- Family history of thyroid carcinoma (yes or not)
- Tumor size (> 5 mm or ≤ 5 mm)
- Presence of other thyroid conditions:
  - Graves' disease (yes or not)
  - Hashimoto's thyroiditis (yes or not)
  - Other (yes or not)

- TSH level:
  - Low [<0.5 mUI/L]
  - Low limit of normality [0.5 – 2 mUI/L]
  - High limit of normality [2 – 4.2 mUI/L]
  - High [>4.2 mUI/L])
- Thyroglobulin level:

  If active surveillance: (ng/ml)

  If initial surgery:
  - Total thyroidectomy (Excellent response [<0.2 ng/ml], indeterminate response [0.2 – 5 ng/ml], incomplete response [≥ 5 ng/ml])
  - Lobectomy (Excellent response [<30 ng/ml], incomplete response [≥30 ng/ml])
- Antibodies anti-Tg: (positive [>4.11 UI/ml] or negative [<4.11 UI/ml])
- Free T4 level: (ng/dl)

If surgery is the treatment chosen:

- Extension of the performed surgery:
  - Lobectomy
  - Total thyroidectomy
- Experience of the surgeon:
  - High volume surgeon [>99 surgeries/year]
  - Intermediate volume surgeon [99 - 10 surgeries/year]
  - Low volume surgeon [<10 surgeries/year]

All items evaluated are qualitative variables, and will be expressed by a percentage, with the exception of *age*, *thyroglobulin level* and *free T4 level*, which are continuous variable and will be expressed by the *mean +/- standard deviation.*

7.7- Data collection

Our dependent variable will be evaluated in each control visit using US, and US-guided FNAC if necessary. The investigators will have a case report form in which all the co-variables and relevant information that has to be collected in each control visit will appear, in order to

simplifier the data collection (ANNEX 3). The baseline data will be recorded in the 1st visit, and during the control visits the dependent variable and some co-variables will be noted.

The information will be updated to the CeCAT web page, and it will be recorded in two anonymized tables known as "active surveillance group" and "initial surgery group". A web designer will be contracted to create and maintain this webpage.

7.8- Measuring instruments

Our dependent variable will be measured using a ≥10 MHz lineal ultrasound with B-mode and color-Doppler. The US will be performed by the endocrinologist and the reference radiologist of each hospital. The confirmation of the malignancy will be done using a fine-aspiration aspiration cytology (FNAC), performed by the radiologist. The criteria to identify a suspicious nodule have been described previously (TABLE 1), as well as the criteria used to identify a cervical LN metastasis (TABLE 2).

After the FNAC, the reference pathologist will examine the sample. The Bethesda classification (ANNEX 4) will be the criteria used, identifying the grades V and VI as relevant for the study.

For some of the co-variables, the medical record and the interview with the patient will be used to identify them (*age, gender, familiar history of thyroid carcinoma, other thyroid conditions)*.

Tumor size and *presence of multifocality* will be checked using ultrasonography, with a ≥10 MHz lineal transducer equipped with color-Doppler mode.

In each control visit a blood test will be required, to assess the *level of TSH, Tg, TgAb* and *T4l*. Thyroglobulin levels will be measured using a immunometric chemiluminescent Sandwich type method (Immulite2000®), and the TgAb levels using a non-competitive chemiluminescence immunoassay (Architect®). TSH and T4 levels are measured using electrogenerated chemiluminescence.

8- STATISTICAL ANALYSIS

The sample size calculation has been described in the Sample size section.

The statistical analysis will be done using the SPSS software.

Univariate Analysis

The results will be expressed as percentages for categorical variables and as mean +/- standard deviation or median for continuous variables depending on whether or not they are normally distributed.

Bivariate Analysis

Proportions will be compared with the χ^2 test.

Multivariate Analysis

Multivariate analysis will be performed to see the possible contribution of the co-variables, using a logistic regression model.

A p value of < 0.05 will be considered statistically significant.

9- ETHICAL AND LEGAL CONSIDERATIONS

Before carrying out the study, the research protocol will be presented to the Clinical Research Ethics Committee (CEIC) of Hospital Universitari Josep Trueta. If accepted, we will ask permission to perform it to the direction of the center and to the direction of the other Hospitals involved in the study.

Since we will not depart from a previously constructed database, we will need the acquiescence of the patients to participate in the study. At the time of the inclusion, all potential participants will be informed of the purpose of the research. They will be given an information sheet (ANNEX 1) with all the necessary information and an informed consent (ANNEX 2). They will only be a part of the study once they sign the written informed consent.

Patients at all time have the right to leave the study with no impact on the quality of the health care that they will receive. Patients being followed with active surveillance can decide to undergo surgical treatment at any time, as it is the standard of treatment.

The medical record information, names and surnames will remain anonymous when publishing the results, according to the Ley Orgánica 15/1999, del 13 de Diciembre, de Protección de Datos de Carácter Personal.

This study will be conducted according to the national and international ethics guidelines and laws:

- Ley Orgánica 15/1999, del 13 de Diciembre, de Protección de Datos de Carácter Personal
- Ley 14/2007, del 3 de Julio, de Investigación Biomédica
- WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, June 1964. Last revision, October 2013.

The investigators of this project declare that there are no conflicts of interests, and that they do not receive any economic compensation to collaborate in the study.

10- STUDY LIMITATIONS

The results of this study could provide benefits and improve the treatment of the patients with PTMC, but it has some limitations that have to be explained before interpreting the results.

First of all, an important limitation is the impossibility to randomize the patients of the study. We will try to minimize the effects of a possible confounding bias by defining the plausible confounding factors described in the literature as co-variables, and with the use of a multivariate analysis. The method chosen will be a logistic regression model.

The sampling method will be a consecutive non-probabilistic, which has its own limitations. This type of sampling is useful for small sample sizes, and it is the best for uncommon pathologies, but it might not be representative of the whole population.

As is impossible to blind the patient or the examiner, we are at risk of an information bias. To try to avoid it, both active surveillance and initial surgery groups will be examined using the same technique, the US +/- US-guided FNAC, which has proven to be the gold standard in the follow-up of PTMCs. In addition, an independent blinded statistician will do the analysis of the information.

To minimize the interviewer bias, the endocrinologists attending the patients will use a case report form in each visit (ANNEX 3). Training on how to perform the control visits will also be provided before starting this study, in order to minimize the inter-observer variability. All US images will be recorded and examined by the same professional in each hospital, expert in thyroid examination.

Another problem is due to the fact that this study is a prospective cohort, and a long follow-up is required. This may account for a high drop-out rate, either by death, geographical reasons or lack of attendance. However, it is important to note that the follow-up of this study does not differ from the habitual clinical practice, so no extra effort from the patients is required. In addition, we have calculated a sample size with a 20% drop-out rate, higher than the percentage that we would require according to previous data, to avoid this fact to possibly interfere with our results.

11- IMPACT OF THE STUDY ON THE HEALTH SYSTEM

Despite the fact that active surveillance has been tested for more than 20 years and the results suggest that it is a valid alternative to initial surgery, there are not studies that properly compares both managements.

This study will provide new evidence about this controversial topic, and help to identify the best approach for this disease. Most of the cases of PTMC account for indolent disease, which are treated the same way as aggressive tumors. With these surgeries, there comes a significant risk of complications, specially hypoparathyroidism and injury to the laryngeal recurrent nerve, which could be avoided. As it has been shown, the incidence of PTMC is increasing, so this problem will become more and more important in the future.

The change in treatment that we propose would reduce the unnecessary surgical complications that these patients suffer, and would avoid them the unnecessary need to go through a surgical operation, which would improve their quality of life. As it has been proven, it would also generate an economic benefit for the Health System, avoiding unnecessary and expensive surgeries and their possible complications, and replacing them for cheaper US follow-up (71).

This is a multicentric study, so we will be able to generalize the results. We also have the opportunity to perform with study with the CeCAT consortium, which has experience conducting studies at a Catalan level.

If the results are interesting, we will have the opportunity to continue widening our understanding of this disease with longer-term studies. This trial will also provide us with a database useful for retrospective analysis.

At the time of the present protocol, there has not been published any study that compares directly active surveillance with initial surgery. It would be the first study testing active surveillance in Europe. With all this factors in mind, it would be a step forward in the treatment of this disease.

12- WORK PLAN

Principal investigators: Marc Puig, Josefina Biarnés

Collaborators: In each of the Hospitals involved, we will assign an investigator (an endocrinologist specialized in thyroid pathologies, to advise the patient and do the follow-up), a radiologist expert in neck examination (to perform the US-guided FNACs) and a pathologist (to examine the FNAC samples). Also a statistician will be hired to help analysing the data.

The study will require a long time to be performed because of the long physiopathology of this disease. The study will be completed in 12 years (144 months). It will be a multicentric study with the collaboration of the CeCAT consortium hospitals, and the Hospital Universitari Josep Trueta will be the reference hospital.

This study has been designed in 6 phases:

1. **Preparation phase** (1 month): Prior to the first meeting, it will have been conducted a literature research to check the current knowledge about PTMCs. In this phase the protocol will be written.

   → *Performed by the principal investigators*

2. **Coordination phase** (3 months): It will include:
   - Selection of the centres involved from the CeCAT consortium and the collaborators of each centre (investigator, radiologist and pathologist).
   - First meeting of the study**.**
   - Identification of problems and elaboration of the definitive protocol.

   The first meeting will be done in this phase, with all the investigators involved in the study. In this meeting the endocrinologists will be trained on how to perform the patient's follow-up. The protocol will be detailed to the collaborators, corrected if necessary and then evaluated by the CEIC of Hospital Universitari Josep Trueta.

   → *Performed by all the investigators*

3. **Field research**(134 months)
   - **Sample collection** (14 months): Patients will be recruited when consulting to the endocrinology service, and the treatment strategy will be decided. Inclusion period previewed will be 14 months (it can be prolonged in case we do not achieve the predefined sample).
   - **Follow-up visits** (120 months): They will start when the first patient is recruited. Every patient will be followed 10 years. Visits will initially be performed each 6 months. After 2 years of disease stability, they will be performed annually.

   → *Performed by all the investigators, radiologists and pathologists of each centre involved*

4. **Data collection and processing database** (134 months): Simultaneously with the study development, data will be registered in the CeCAT website, in a database made by a web designer. Once a year, during the data collection, all data registered in the database will be analysed using the appropriate statistical test.

   →*Performed by all the investigators and the statistician consultant*

   - Annual meetings will be planned to coordinate the study, check the project evolution and verify that the protocol is being followed.

5. **Statistical analysis** (3 months): A final analysis of the data will be performed.

   →*Performed by the principal investigators and the statistician consultant*

6. **Result interpretation and publication** (3 month): An interpretation, a discussion and a conclusion of the outcomes will be written. An article will be edited, published in two journals and presented in the CeCAT, SEEN and International congresses.

   →*Performed by the principal investigators*

13- BUDGET

A prospective study is usually time consuming and expensive, but in this case the costs are not too high.

This is because the surgery is included in the National Health Service provisions, and to perform the active surveillance we only need a US and a blood test. If the patient is suspected of showing recurrence, an US-guided FNAC is required.

We will hire a qualified statistician to do the statistical analysis. He will be paid 40€ per hour, with an estimated time for this work of 250 hours, so the total cost will be 10000 €. A website designer will be hired. He will create (500 €) and update (150 € per year) a database in the CeCAT website to introduce the data, with a total cost of 2300 €.

The investigators and doctors involved in this study will not receive economic compensation for their collaboration. Software such as SPPS and Microsoft Access© are not included in the budged because they are either available to the statistician or free of charge.

At the material section, the documents necessary to perform this study are budgeted. They include 200 copies of the informed consent and the information sheet, at 0.3 € per unit, with a total of 60 €. As it is difficult to calculate the precise number of case report forms that we will need, we have estimated 20 per patient, with a cost of 0.1 € per unit. As a total, we will need 400 € to print the necessary number of case report forms.

Annual meetings will be performed to coordinate the study and to check the project evolution. During the 12 years that this study will be performed, 12 coordination meetings will take place. As it is a Catalan-level study, we have calculated approximately 400 € per meeting. For the 12 meetings required, a total of 4800 € is budgeted.

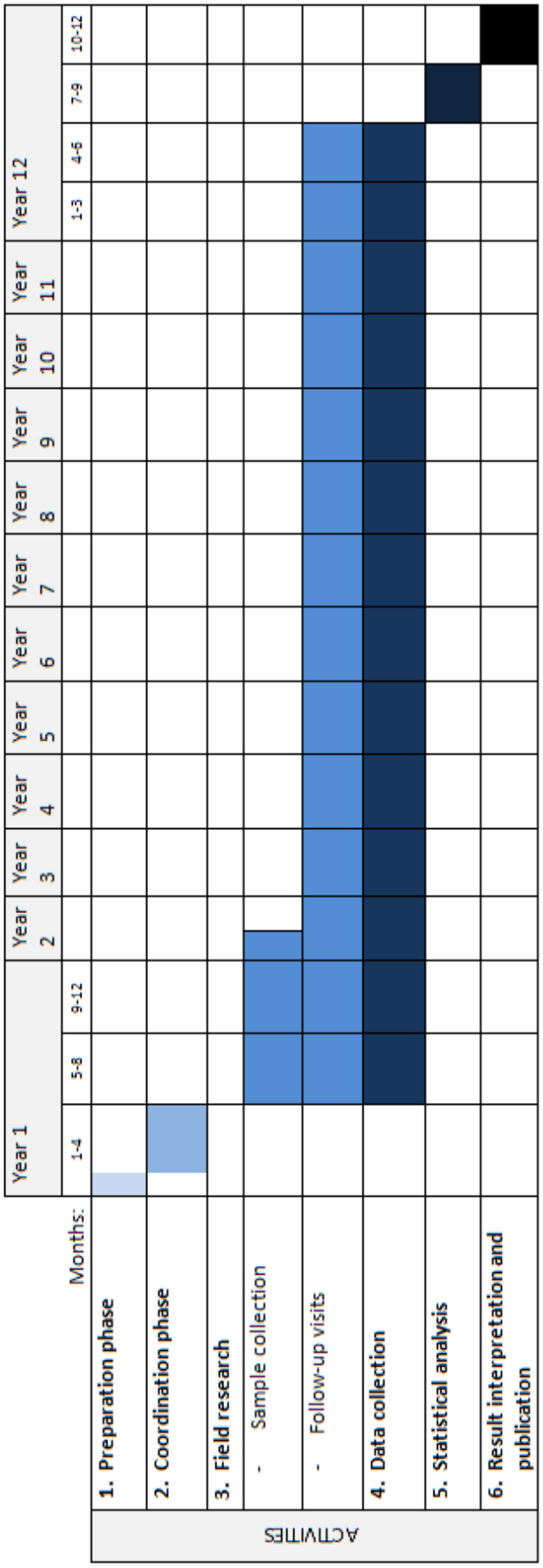
We are planning to publish the results of this study in 2 journals, with a cost of 1000 € per publication.

In the budget there are included two congresses where we plan to explain our results, the SEEN congress and an international one. Taking into account that it is 2 people per meeting, we have calculated the costs of the flights, approximately 150 € for the national and 500 € for the international. For the accommodation, we propose a 4 stars hotel for 4 nights for both

meetings and 2 people per meeting. The accommodation will cost a maximum of 250 € per person for the national congress, and 300 € per person for the international.

PERSONNEL COSTS		
Statistician	40€/hour x 250 hours	10000 €
Web designer	500€ + (150€ x 12 years)	2300 €
		SUBTOTAL: 12300 €
MATERIAL		
Information sheet and informed consent printing	0.30 €/unit x 200 participants	60 €
Case report forms printing	0.10 €/unit x 200 participants x 20 for each patient	400 €
		SUBTOTAL: 460 €
MEETING EXPENSES		
Coordination meetings	1 per year (x 12) -> 400 € x 12	4800 €
		SUBTOTAL: 4800 €
PUBLICATION and DISSEMINATION		
Publication	1000 € (per each publication) x 2	2000 €
Congresses		
▪ National (SEEN)		
- *Inscription fee*	500 € x 2	1000 €
- *Travel*	150 € x 2	300 €
- *Accommodation*	250 € x 2	500 €
▪ International		
- *Inscription fee*	600 € x 2	1200 €
- *Travel*	500 € x 2	1000 €
- *Accommodation*	300 € x 2	600 €
		SUBTOTAL:6600 €
		TOTAL AMOUNT: 24160 €

14- CHRONOGRAM



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16 – ANNEXES

ANNEXE 1: FULL D'INFORMACIÓ PER AL PACIENT

Títol de l'estudi:

Active surveillance as the initial treatment of papillary thyroid microcarcinoma: a 10-years multicentric prospective study

Benvolgut/da,

Aquest document està pensat per donar tota la informació rellevant i ajudar a prendre la decisió terapèutica més adequada en cada cas.

El càncer de tiroides és el càncer més freqüent dels òrgans endocrins. D'aquest, el tipus papil·lar és el més comú, i quan aquest fa menys d'1 cm, se l'anomena microcarcinoma papil·lar de tiroides. Aquest càncer ha demostrat tenir molt bon pronòstic, amb una mortalitat inferior a 1% i amb una expectativa de vida igual a la població sana. Tot i així, té un risc destacable de reaparèixer, i per això fa falta fer un seguiment després del tractament inicial.

En molts estudis fets en autòpsies s'ha demostrat que un gran nombre de persones tenen microcarcinomes (d'un 5% a un 35,6%), però en la immensa majoria de casos, aquests passen desapercebuts. Quan s'ha realitzat una cerca amb ecografia en la població sana, s'ha vist que fins al 2% de les dones sanes majors de 30 anys tenen aquest tipus de càncer, però que la majoria no donen símptomes i no es detecten. Degut a tot això, s'ha arribat a la conclusió que un número molt important de microcarcinomes són indolents, i que no caldria que els tractéssim, perquè no causen problemes. Amb tot, el nombre de casos de microcarcinoma ha augmentat molt en els darrers anys. Això s'ha associat a què ara es fan més proves d'imatge (ecografies de coll, TACs, RMs i PETs), i que els casos que abans passaven desapercebut i no donaven problemes, ara es detecten i es tracten amb cirurgia.

- **Objectiu de l'estudi**

Actualment, el tractament recomanat per els càncers de tiroides és la cirurgia. Aquesta ha mostrat molt bons resultats, però va associada a un cert risc de complicacions després de l'operació, com poden ser problemes a la veu o alteracions en el control del calci. Per aquest

motiu i, degut al bon pronòstic dels microcarcinomes i als fets exposats anteriorment, s'ha proposat un tractament alternatiu, que consisteix en fer un seguiment actiu d'aquesta malaltia i només operar si aquesta empitjora.

L'objectiu de l'estudi és comprovar si aquest tractament més conservador (anomenat vigilància activa) és una bona alternativa a la cirurgia inicial.

- **En què consistiria la seva participació**?

La seva participació en l'estudi consistirà en decidir, amb tota la informació que li facilitarem i amb el consell del seu metge, quin tractament decideix seguir, d'acord amb les seves preferències. En la primera visita, se li realitzarà una història clínica per recollir tota la informació que necessitem per poder començar l'estudi. Se li preguntaran antecedents personals i familiars.

Després d'això, i un cop decidit el tractament, se li realitzarà el mateix seguiment que es fa en qualsevol altre cas d'aquesta malaltia. Per tant, la seva participació a l'estudi no requerirà cap esforç extra per part seva.

- **Tractaments proposats, amb els seus punts a favor i en contra**

Cirurgia inicial

Punts a favor:

- És el tractament de referència, realitzat des de fa molt temps i amb molta experiència
- Dóna molt bons resultats, amb una supervivència superior al 99%

Punts en contra:

- *Vistos els resultats de les autòpsies i de la cerca en gent sana, és molt possible que moltes operacions siguin innecessàries.*
- *La cirurgia comporta un risc de complicacions, que segons els estudis poden anar de l'1% al 24,1% dels pacients. Entre aquestes destaquen hipoparatiroïdisme transitori o permanent, i lesions del nervi laringi recurrent, amb possible alteració de la veu.*
- *La cirurgia no evita haver de fer un seguiment posterior*
- *En cas de recidiva de la malaltia, fer una segona operació comporta més risc de complicacions.*

Vigilància activa

Punts a favor:

- No requereix una operació inicial, que pot ser innecessària
- El seguiment és el mateix que en els pacients que han estat operats
- La supervivència és la mateixa que seguint cirurgia inicial
- Ha estat provat durant més de 20 anys a Japó amb molt bons resultats, i a l'última guia sobre càncer de tiroides apareix com a una prometedora alternativa terapèutica

Punts en contra:

- *No hi ha tanta experiència com amb la cirurgia*
- *El percentatge de progressió de la malaltia és superior que amb la cirurgia (després de la cirurgia és d'un 4,8 % als 10 anys, mentre que seguint vigilància activa és del 11,8% als 10 anys)*
- *El possible estrès que suposa tenir un tumor que no ha estat extirpat*

- **Per a què fer un seguiment de 10 anys?**

Els estudis de seguiment aporten molta evidència científica quan el que es busca és conèixer les conseqüències d'algun esdeveniment. Els microcarcinomas papil·lars han demostrat que poden reaparèixer al cap de molt temps, fins i tot després de 30 anys. Per tant, per tenir dades fiables sobre si el tractament conservador és eficaç, necessitem fer un seguiment llarg, de 10 anys. Aquest seguiment, però, també es realitza fora d'aquest estudi, en la pràctica clínica diària.

- **Després de decidir el tractament inicial, què hauria de fer?**

Un cop decidit el tractament inicial, es faran visites de control per comprovar l'estat de la malaltia.

Si segueix *cirurgia inicial*, es realitzarà una visita de control després de l'operació, i després un control als 6 mesos. En aquesta es demanarà una analítica de sang, es farà una exploració física del coll i una ecografia de la tiroides. Controls iguals es realitzaran cada 6 mesos, fins a demostrar-se durant 2 anys que la malaltia es manté estable. Després es faran anualment.

Si segueix *vigilància activa*, es realitzarà el mateix seguiment que en la cirurgia inicial, sense la visita de control post-operatòria. Es farà la primera visita als 6 mesos amb analítica, exploració física i ecografia. Es realitzaran cada 6 mesos, fins a 2 anys d'estabilitat, i després anualment.

En qualsevol dels 2 casos, si es detecta que la malaltia progressa (el tumor augmenta en la vigilància activa, reapareix una massa després de cirurgia, o apareixen metàstasis als nòduls limfàtics cervicals en els 2 casos) es farà una punció-aspiració amb agulla fina (PAAF). Si es confirma que la malaltia progressa, en els 2 casos es farà cirurgia.

- **Confidencialitat**

Les dades obtingudes dels participants són estrictament confidencials. Es registraran en una base de dades on només hi tindran accés els investigadors de l'estudi i el personal autoritzat. Totes les dades obtingudes s'usaran exclusivament amb propòsits de recerca. L'estudi seguirà la normativa de la llei Orgànica 15/1999 del 13 de desembre de Protecció de dades de Caràcter Personal.

- **Canvi d'opinió**

La participació en l'estudi és voluntària i, per tant, els participants poden canviar d'opinió i abandonar l'estudi en qualsevol moment, sense necessitat de donar cap explicació i sense que això repercuteixi en la qualitat del tractament proporcionat.

De la mateixa forma, si els participants que segueixen vigilància activa decideixen canviar de tractament i prefereixen operar-se, ho podran fer en qualsevol moment, ja que la cirurgia és el tractament estàndard per aquesta patologia.

- **Més informació**

En cas que tingui qualsevol dubte o vulgui més informació, pregunti al seu metge o contacti a través de l'adreça de correu electrònic que ell li proporcionarà.

Amb tot això, el convidem a participar en el nostre estudi. Els resultats que se n'obtinguin poden permetre millorar el tractament de futurs casos d'aquesta patologia, i resultar en un benefici directe per a nous pacients que es trobin en la seva situació actual.

ANNEXE 2: FORMULARI DE CONSENTIMENT INFORMAT

Títol de l'estudi:

Active surveillance as the initial treatment of papillary thyroid microcarcinoma: a 10-years multicentric prospective study

Jo (nom i cognoms), ..., confirmo que:

- He rebut i llegit el full d'informació per al pacient que se m'ha entregat
- He pogut fer preguntes sobre l'estudi i els meus dubtes han estat resolts
- He rebut suficient informació sobre l'estudi
- Entenc que les meves dades seran tractades de forma estrictament confidencial
- Entenc quin serà el meu paper com a participant de l'estudi
- Comprenc que la meva participació és voluntària i que puc retirar-me de l'estudi quan vulgui, sense que això repercuteixi en la meva atenció sanitària futura

En conseqüència, dono la meva conformitat a participar en l'estudi: "*Active surveillance as the initial treatment of papillary thyroid microcarcinoma: a 10-years multicentric prospective study*"

Firma del participant: Firma de l'investigador:

_____ _____

Data: __ __ / __ __ / __ __ Data: __ __ / __ __/ __ __

ANNEXE 3: QUADERN DE RECOLLIDA DE DADES

Primera visita – Dades basals

Participant número: _____

Nº Història clínica: _____ Data: ___ / ___ / ____

TRACTAMENT ESCOLLIT: **VIGILÀNCIA ACTIVA** ☐ **CIRURGIA INICIAL** ☐

Edat: _____

Gènere: Home ☐ Dona ☐

Història familiar de carcinoma de tiroides: Sí ☐ No ☐

Presència d'altres patologies de tiroides? No ☐

Sí ☐

- Malaltia de Graves ☐
- Tiroiditis de Hashimoto ☐
- Altre ☐

Mida del tumor segons criteris ecogràfics: > 5mm ☐ ≤ 5 mm ☐

Presència de multifocalitat: Sí ☐ No ☐

Anàlisi de sang:

Nivell de TSH: Baix [<0,5 mUI/L] ☐

Límit baix de normalitat [0,5 – 2 mUI/L] ☐

Límit alt de normalitat [2 – 4,2 mUI/L] ☐

Alt [>4,2 mUI/L] ☐

Nivell de T4 lliure: _____ ng/dL

Presència d' anticossos anti-tiroglobulina: Positiu (>4.11 UI/ml) ☐ Negatiu (<4.11 UI/ml) ☐

Nivell de Tiroglobulina: Valorable ☐ → _____ ng/ml No valorable ☐

Segona visita *(només si CIRURGIA INICIAL)*

Participant número: _____

Nº Història clínica: _____ Data: ___ / ___ / ____

Anàlisi de sang:

Nivell de TSH: Baix [<0,5 mUI/L] ☐

Límit baix de normalitat [0,5 – 2 mUI/L] ☐

Límit alt de normalitat [2 – 4,2 mUI/L] ☐

Alt [>4,2 mUI/L] ☐

Nivell de T4 lliure: _____ ng/dL

Presència de complicacions després de cirurgia:

No ☐

Sí ☐

- Hipoparatiroidisme ☐
- Lesió del nervi laringi recurrent ☐
- Hematoma ☐
- Infecció de la ferida quirúrgica ☐

Cirurgia seguida:

- Lobectomia ☐
- Tiroidectomia total ☐

Experiència del cirurgià:

- Cirurgià "d'alt volum" [>99 operacions/any] ☐
- Cirurgià de "mitjà volum" [99 – 10 operacions/any] ☐
- Cirurgià de "baix volum" [<10 operacions/any] ☐

Visita de seguiment (CIRURGIA INICIAL)

Participant número: _____

Nº Història clínica: _____ Data: ___ / ___ / ____

Visita de seguiment número:_____

Període de temps després de cirurgia inicial: _____ mesos

Presència de progressió de malaltia:

No ☐

Sí: ☐

- Aparició de metàstasis en nòduls limfàtics cervicals ☐
- Aparició de recurrència en el llit tiroïdal ☐

Anàlisi de sang:

Nivell de TSH: Baix [<0,5 mUI/L] ☐

Límit baix de normalitat [0,5 – 2 mUI/L] ☐

Límit alt de normalitat [2 – 4,2 mUI/L] ☐

Alt [>4,2 mUI/L] ☐

Nivell de T4 lliure: _____ ng/dL

Presència d' anticossos anti-tiroglobulina: Positiu (>4.11 UI/ml) ☐ Negatiu (<4.11 UI/ml) ☐

Nivell de Tiroglobulina: No valorable ☐

Valorable: ☐

- Lobectomia: Resposta excel·lent (< 30 ng/ml) ☐

  Resposta incompleta (≥ 30 ng/ml) ☐

- Tiroidectomia total: Resposta excel·lent (< 0,2 ng/ml) ☐

  Resposta indeterminada (0,2 – 5 ng/ml) ☐

  Resposta incompleta (≥ 5 ng/ml) ☐

Visita de seguiment (VIGILÀNCIA ACTIVA)

Participant número: _____

Nº Història clínica: _____ Data: ___ / ___ / ____

Visita de seguiment número:_____

Període de temps seguint vigilància activa: _____ mesos

Presència de progressió de malaltia:

No ☐

Sí: ☐

- Aparició de metàstasis en nòduls limfàtics cervicals ☐
- Increment del tumor primari ≥ 3 mm ☐

Anàlisi de sang:

Nivell de TSH: Baix [<0,5 mUI/L] ☐

Límit baix de normalitat [0,5 – 2 mUI/L] ☐

Límit alt de normalitat [2 – 4,2 mUI/L] ☐

Alt [>4,2 mUI/L] ☐

Nivell de T4 lliure: _____ ng/dL

Presència d' anticossos anti-tiroglobulina: Positiu (>4.11 UI/ml) ☐ Negatiu (<4.11 UI/ml) ☐

Nivell de Tiroglobulina: Valorable ☐ → _____ ng/ml No valorable ☐

El pacient està conforme amb la vigilància activa i declara voler seguir amb aquest maneig:

Sí: ☐

No, prefereix canviar i realitzar cirurgia: ☐

El pacient porta ≥ 2 anys sense progressió de la malaltia:

Sí → programar visita de control en 12 mesos ☐

No → programar visita de control en 6 mesos ☐

ANNEX 4: BETHESDA CLASSIFICATION

Table 1
The Bethesda System for Reporting Thyroid Cytopathology: Recommended Diagnostic Categories*

I.	**Nondiagnostic or Unsatisfactory**
	Cyst fluid only
	Virtually acellular specimen
	Other (obscuring blood, clotting artifact, etc)
II.	**Benign**
	Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc)
	Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context
	Consistent with granulomatous (subacute) thyroiditis
	Other
III.	**Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance**
IV.	**Follicular Neoplasm or Suspicious for a Follicular Neoplasm**
	Specify if Hürthle cell (oncocytic) type
V.	**Suspicious for Malignancy**
	Suspicious for papillary carcinoma
	Suspicious for medullary carcinoma
	Suspicious for metastatic carcinoma
	Suspicious for lymphoma
	Other
VI.	**Malignant**
	Papillary thyroid carcinoma
	Poorly differentiated carcinoma
	Medullary thyroid carcinoma
	Undifferentiated (anaplastic) carcinoma
	Squamous cell carcinoma
	Carcinoma with mixed features (specify)
	Metastatic carcinoma
	Non-Hodgkin lymphoma
	Other

* Adapted with permission from Ali and Cibas.[3]

Available from*:*
Cibas ES, Ali SZ 2009 The Bethesda System For Reporting Thyroid Cytopathology. Am J Clin Pathol. 2009;132(5):658-665