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FINAL DEGREE PROJECT

THYROID CANCER EPIDEMIOLOGY IN NORTHEAST SPAIN, GIRONA: A POPULATION-BASED INCIDENCE TREND STUDY 1994 – 2020

A CROSS-SECTIONAL EPIDEMIOLOGICAL STUDY

Endocrinology service

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INDEX

1. ABSTRACT

TITLE: Thyroid Cancer Epidemiology in Northeast Spain, Girona: a population-based incidence trend study 1994 - 2020

BACKGROUND: Thyroid carcinoma (TC) is the most prevalent malignant tumor within the endocrine system, experiencing a notable global incidence surge in recent decades, attributable to heightened detection of incidental tumors. Mortality rates have either decreased or remained stable, attributed to advancements in diagnostic techniques, particularly for papillary carcinoma. Techniques such as ultrasound, ultrasound-guided fine-needle aspiration and other imaging techniques for other clinical reasons have enhanced sensitivity in detecting small thyroid nodules. The epidemiological features of TCs are largely influenced by the increased identification of indolent cases, which suggests possible overdiagnosis. Therefore, our study aimed to provide an up-to-date assessment on the regional distribution of TC incidence during the period 1994 – 2020 in Girona (northeast region of Spain).

OBJECTIVE: To describe and analyze incidence and trends of TC in Girona during the period 1994 - 2020 by sex, age, histological type, and stage at diagnosis to check whether this data are similar to those observed in other countries and regions.

METHODS: This research constitutes a population-based cross-sectional study. TC cases were obtained from the population-based Cancer Registry of Girona (GCR) between 1994 and 2020. All our cases were classified into 7 subtypes: papillary, follicular, medullary, oncocytic, anaplastic and poorly differentiated, other types and non-specified. We extracted age-standardised incidence rates (ASR) per 100 000 person-year and Annual Percentage Changes (APC) of TC, as defined by the International Classification of Disease for Oncology 3rd edition (code C73), for a northeast region of Spain (Girona) by sex and 5 age groups (0-14, 15-24, 25-49, 50-69, and ≥ 70 years) from GCR database.

RESULTS: During the study period 1994 – 2020 we registered 1,149 diagnosed cases of TC in Girona province (76.85% in women). Mean age of diagnosis were 48.7 years ± 15.9. The most common

histological type was papillary (80.4%), following by follicular (8.0%), medullary (4.8%), oncocytic (2.1%), anaplastic (2.1%). Global ASR was 6.42 per 100 000 inhabitants-year (95%CI: 6.05 – 6.81), representing 9.78 (95%CI: 9.14 - 10.46) in women and 3.06 (95%CI: 2.70 – 3.45) in men. Incidence trends significantly increased in global (APC +2.23%), primarily in women (APC: +2.41%), for papillary type (APC: +2.31%) in stage I of diagnosis (APC: +2.44%). Papillary carcinoma was the most common, representing the 80.4% of total cases, follicular 10.1% and medullary carcinoma in 4.8%.

INTERPRETATION: These data showed an increasing trend in incidence of TC in Girona, especially in women between 1994 - 2020 years. Papillary carcinoma was the most common histological type. Our study is in accordance with the European trend in TC incidence and sex differences.

KEYWORDS: Thyroid cancer, epidemiology, trends, incidence, cancer registry, papillary carcinoma, Spain, Girona

2. ABBREVIATIONS AND ACRONYMS

TC	Thyroid carcinoma
DTC	Differentiated thyroid carcinoma
US	Ultrasonography
US-FNB	Ultrasound-guided fine-needle biopsy
FMTC	Familial medullary thyroid carcinoma
TSH	Thyroid stimulating hormone
WBS	Whole body scan
RLN	Recurrent Laryngeal nerve
PTC	Papillary thyroid cancer
FTC	Follicular thyroid cancer
MTC	Medullary thyroid cancer
DHGTC	Differentiated high-grade thyroid carcinoma
PDTC	Poorly differentiated thyroid carcinoma
ATA	American Thyroid Association
RAI	Radioactive iodine
Tg	Thyroglobulin
TSH	Thyrotropin

ROM	Risk of malignancy
ICD-O-3	International Classification of Diseases for Oncology, 3rd edition
WHO	World Health Organization
SEEN	Sociedad Española de Endocrinología y Nutrición
SEER	Surveillance, epidemiology and end results
AJCC	American Joint Committee on Cancer

LIST OF FIGURES AND TABLES

List of Figures

List of Tables

3. INTRODUCTION

THYROID CANCER

Thyroid cancer (TC) is the most common malignant disease of the endocrine system. Its incidence rates have rapidly increased in high income countries, and its incidence is much higher in women, with a female:male sex ratio of 3. The largest increase has been observed in South Korea (1). In Europe, thyroid cancer represented 0.7 and 2.5% of all cancer burden in men and women respectively, however it only cased death in 0.2% (males) and 0.6% (females). At the same time thyroid cancer incidence rises up, its mortality rates remain stable or are even decreasing.

Despite sex differences in incidence trends, thyroid cancer histological distribution is the same between both sexes. Papillary and follicular carcinoma represents 98% of thyroid cancer burden.

This increasing trend may be attributed partially to the improved detection of smaller tumors (< 2cm), better ultrasound detection, fine-needle aspiration biopsies and the increased pathological reports of incidental carcinomas < 1cm. The introduction of new diagnostic techniques (ultrasonography, computed tomography, and magnetic resonance imaging), combined with increased medical surveillance and access to health care services, can lead to massive increases in detection of small thyroid nodules caused by the large reservoir of asymptomatic, nonlethal disease known to exist in the thyroid gland.

Therefore, overdiagnosis it seems to be the most plausible hypothesis for the high incidence rate of thyroid cancer as the rising number of diagnoses reflects a more effective detection of a subclinical reservoir of cancers, which would not have caused symptoms or death, if left undetected.

PATOGENESIS

The pathogenesis of thyroid cancer is primarily linked to the impact of external radiation, which predisposes to chromosomal breaks, leading to genetic rearrangements and loss of tumor suppressor genes. Exposure to radiation increases the risk of benign and malignant thyroid nodules, is associated with multicentric cancers, and shifts the incidence of thyroid cancer to an earlier age group. Children seem more predisposed to the effects of radiation than adults.

Many well-differentiated thyroid cancers express Thyrotropin (TSH) receptors, maintaining responsiveness to TSH. Elevated serum TSH levels, even within the normal range, are linked to an increased risk of thyroid cancer in individuals with thyroid nodules.

Various genetic alterations have been explored in thyroid neoplasms, but the exact cause of most thyroid cancers is not yet known. However, certain mutations, such as RET/PTC and PAX8-PPARγ1 rearrangements, are relatively specific for thyroid neoplasia.

Activation of the RET-RAS-BRAF signaling pathway is seen in up to 70% of PTCs, with heterogeneous mutation types. Rearrangements involving the RET gene on chromosome 10 lead to receptor overexpression, occurring in 20 – 40% of PTCs and being more frequent in tumors developing after the Chernobyl radiation accident.

BRAF V600E mutations appear to be the most common genetic alteration in PTC. These mutations activate the kinase, which stimulates the mitogen-activated protein kinase (MAPK) cascade and are found in about 20 – 30% of thyroid neoplasms, including both PTC follicular variant and FTC.

The identification of PTC with RET or TRK1 (tyrosine receptor kinase) rearrangement has not proven useful for predicting prognosis or treatment responses, though analysis of specific mutations might aid in classification, prognosis, or choice of treatment.

Medullary thyroid cancer (MTC), when associated with multiple endocrine neoplasia (MEN) type 2, harbors an inherited mutation of the RET gene. All three phenotypes (MEN2A, FMTC and MEN2B) involve high risk for development of MTC, 25% (2,3)

RISK FACTORS

The increase probability of malignancy of the thyroid nodule are many (4): be a male sex, have history of therapeutic radiation in the head and neck region during childhood (before the age of 18); have family history of thyroid carcinoma or syndromes linked to thyroid cancer, such as Cowden disease, Familial Adenomatous Polyposis, Carney Complex or Multiple Endocrine Neoplasia type 2 (MEN2). Presence of nodules in patients either younger than 20 or older than 65 years, have a rapid enlargement of a neck mass and have symptoms like vocal cord paralysis, hoarse voice, nodules fixed to adjacent structures, and lateral cervical lymphadenopathy.

WHO 2022 THYROID CANCER CLASSIFICATION

The fifth edition (2022) World Health Organization (WHO) classification of thyroid neoplasms has been released in 2022, with updates which contains changes to nomenclature, grading and prognostication of thyroid proliferations based on pathologic features and molecular profile. Therefore its importance on its applicability in patient management and future directions in this field (5).

The majority of thyroid tumors are derived from follicular epithelial cells, while a small number arises from calcitonin-secreting C cells. Follicular cell-derived neoplasms are categorized into 3 classes: benign tumors, low-risk neoplasms, and malignant neoplasms. The classification has evolved based on histopathology and molecular pathogenesis.

Encapsulated / circumscribed thyroid tumors with a predominant follicular growth pattern often display RAS mutation molecular profile. In contrast, most papillary and/or infiltrative growth patterns and florid nuclear atypia exhibit BRAFV600E-like molecular pattern (6).

The old term ‘‘Hürthle cells’’ is replaced with ‘‘oncocytic cells’’.

Cribiform morular thyroid carcinoma (CMTC) is no longer considered PTC, now is into thyroid tumors of uncertain histogenesis.

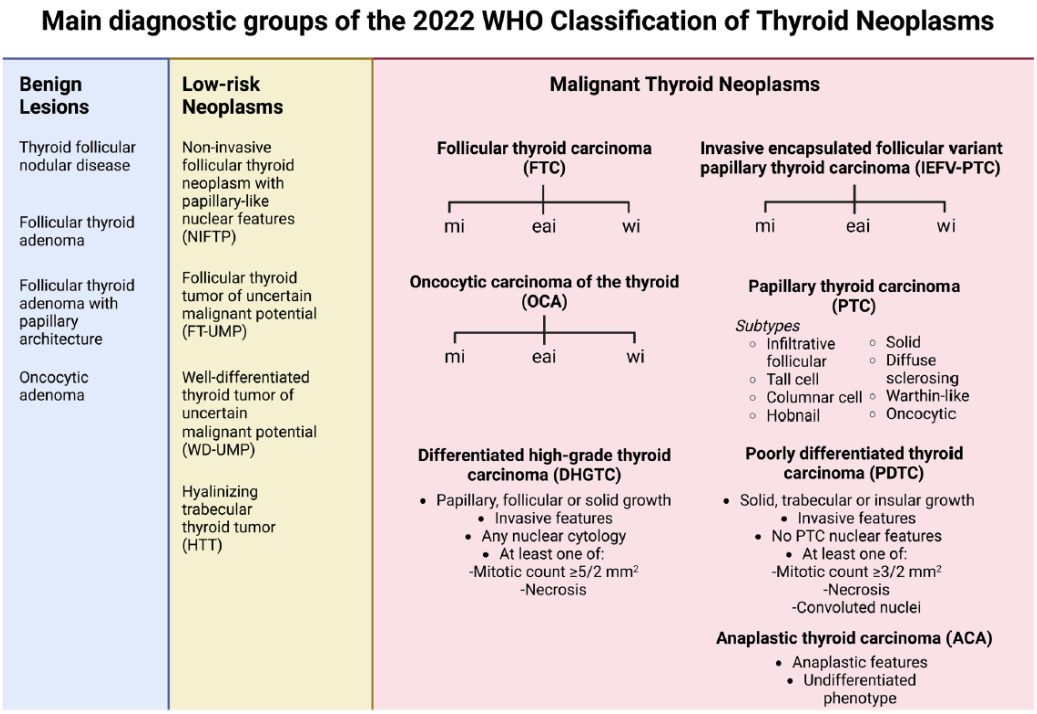


Figure 1. Overview of the main diagnostic groups of the 2022 WHO classification of thyroid tumors (5). Not included here are mixed medullary and follicular cell-derived carcinomas, salivary gland-type carcinomas of the thyroid, thyroid tumors of uncertain histogenesis, intrathyroidal thymic tumors and embryonal thyroid neoplasms. MI, minimally invasive; EAI, encapsulated angioinvasive; WI, widely invasive.

PAPILLARY CELL-DERIVED NEOPLASM (PTC)

PTC is the most common type (represents the 80 – 90%) of thyroid carcinoma from follicular epitellium. It's more prevalent in women with bimodal presentation: first pic around 20 - 30 years old and the second one around median age.

50% of PTC presents mutations in the gen BRAF, which has worst prognostic due to the association to extrathyroidal invasion and lymphatic dissemination. 60 - 80% of irradiated patients they have the activation of protooncogene RET/PTC in chromosome 10q11-2 and rearrangement of TRK

It presents as unique nodule, painless with slow growth, 30% of cases it is associated with cervical lymphadenopathies, most often through lymphatic dissemination and can invade other neighboring structures and metastases at distance.

FOLLICULAR CELL-DERIVED NEOPLASMS (FTC)

FTC represents the 10 - 15% of malign neoplasm. It's typical in women around 50 years old and more common in iodine-deficient regions. FTC is difficult to diagnose by FNA because the distinction between benign and malignant follicular neoplasms requires histology due to the nuclear features of follicular adenomas and carcinomas do not differ. Rather, follicular carcinoma is diagnosed by the presence of capsular and/or vascular invasion.

FTC tends to spread by hematogenous routes leading to bone, lung and central nervous system metastases. Mortality rates associated with angioinvasive FTC are less favorable than the PTC, in part because a larger proportion of patients present with stage IV disease.

INVASIVE ENCAPSULATED FOLLICULAR VARIANT PAPILLARY THYROID CARCINOMA (IEFV-PTC)

Invasive encapsulated follicular variant of papillary thyroid carcinoma (IEFV-PTC, RAS-like mutation profile) is now considered a separate entity and no longer a subtype of PTC (BRAFV600E-like)

ONCOCYTIC CARCINOMA OF THE THYROID (OCA)

Malignant tumor with high follicular cellularity with atypia and oncocytic change (requires > 75% of oncocytic cells). It has frequent ganglionic metastasis (30%). Women around 61 years old predominantly has this kind of tumor.

DIFFERENTIATED HIGH-GRADE THYROID CARCINOMA (DHGTC)

High-grade follicular cell-derived carcinoma has 2 histologic subtypes: poorly differentiated thyroid carcinoma (PDTC) and differentiated high-grade thyroid carcinoma (DHGTC) that includes 3 types: Papillary (PTC), Follicular (FTC) or oncocytic thyroid carcinoma (OCA) (5).

Mitotic count > 2 mm2, necrosis, Ki67 index (at least 1 of these features) are considered as a new histologic grading system to identify high-grade follicular-cell derived carcinomas (PTC, FTC and OCA) and medullary thyroid carcinomas.

DHGTC and PDTC are classified under ‘‘follicular-derived carcinomas, high-grade’’ in the new 2022 WHO classification:

- DHGTC requires presence of ≥ 5 mitoses / 2mm ± tumor necrosis
- PDTC is an FTC with areas of solid or trabecular growth, mitotic count ≥ 3 / 2mm2 and necrosis

Tumor type	Mitotic count	Tumor necrosis	Ki67 index
Poorly differentiated thyroid carcinoma[a]	≥3 mitoses per 2 mm^2	Present	Not required[b]
Differentiated high-grade thyroid carcinoma[a]	≥5 mitoses per 2 mm^2	Present	Not required[b]
Medullary thyroid carcinoma			
High grade[c]	≥5 mitoses per 2 mm^2	Present	≥5%
Low grade[d]	<5 mitoses per 2 mm^2	Absent	<5%

WHO, World Health Organization.
[a]An anaplastic thyroid carcinoma component should not be seen. Thyroid tumors with mixed histologic patterns should be classified according to their least differentiated component and highest grade; [b]The Ki67 proliferation index is not required for diagnosing poorly differentiated thyroid carcinoma and differentiated high-grade thyroid carcinoma, but these tumors usually have a Ki67 index of 10% to 30%; [c]High-grade cancers have at least one of the three high-grade features; [d]Low-grade cancers have mitotic count <5 per 2 mm^2, no tumor necrosis, and Ki67 proliferation index <5%.

Figure 2. Histopathologic Grading Scheme for Thyroid Cancer in the 2022 WHO Classification (6)

POORLY DIFFERENTIATED THYROID CARCINOMA (PDTC)

Morphologically it’s between the behavior of a well-differentiated and undifferentiated carcinoma.

It consists of solid and big tumor, quick growth with possible local extrathyroidal extension (adherences to cervical tissues) and lymph node metastasis at the moment of diagnosis. It can also metastases to bone, lung and brain.

ANAPLASTIC THYROID CARCINOMA (ACA)

ATC is a poorly differentiated and aggressive cancer. The prognosis is poor, and most patients die within 6 months of diagnosis. Because of the undifferentiated state of these tumors, the uptake of radioiodine is usually negligible.

Clinically, it can result in the following manifestations: painful neck swelling, dysphonia, dyspnea and dysphagia. Rapidly growing mass with infiltration into adjacent structures (adherence to superficial and deep planes), leading to lymphatic dissemination. Invasion of cervical lymph nodes (> 40%) and pulmonary, bone, and brain metastases at the time of diagnosis (40%); and sometimes hypothyroidism due to glandular destruction.

MEDULLARY THYROID CARCINOMA (MTC)

Medullary thyroid carcinoma (MTC) is a tumor arising from the parafollicular cells or C cells of the thyroid gland.

MTC can be sporadic or familial and accounts for about 5% of thyroid cancers. There are three fam ilial forms of MTC: MEN 2A, MEN 2B, and familial MTC without other features of MEN. Elevated serum calcitonin provides a marker of residual or recurrent disease. All patients with MTC should be tested for RET mutations, because genetic counseling and testing of family members can be offered.

OTHER THYROID NEOPLASMS

Mixed medullary and follicular cell-derived carcinomas

Salivary gland-type carcinomas of the thyroid

- Mucoepidermoid carcinoma
- Secretory carcinoma

Thyroid tumors of uncertain histogenesis

- SMECE Sclerosing mucoepidermoid carcinoma with eosinophilia

Thymic tumors within the thyroid

Embryonal thyroid neoplasms

- Malign teratoma → tiroblastoma. DICER1

DIAGNOSIS

Palpable thyroid nodules are found in about 5% of adults. Given this high prevalence rate, practitioners may identify thyroid nodules on physical examination. However, the increased usage of diagnostic medical imaging (e.g., carotid ultrasound, cervical spine MRI) has led to an increased frequency of incidental nodule detection, accounting for the majority of patients currently presenting for nodule evaluation. The main goal of this evaluation is to identify, in a cost-effective manner, the small subgroup of individuals with malignant lesions that have the potential to be clinically significant.

Nodules are more common in iodine-deficient areas, in women, and with aging. Most palpable nodules are > 1 cm in diameter, but the ability to feel a nodule is influenced by its location within the gland (superficial versus deeply embedded), the anatomy of the patient's neck and the experience of the examiner. More sensitive methods of detection, such as CT, thyroid ultrasound and pathologic studies, reveal thyroid nodules in up to 50% of glands in individuals aged > 50 years.

Most patients with thyroid nodules have normal thyroid function tests. Nonetheless, thyroid function should be assessed by measuring a TSH level, which may be suppressed by one or more autonomously functioning nodules. If the TSH is suppressed, a radionuclide scan is indicated to determine if the identified nodule is ''hot'', as lesions with increased uptake are almost never malignant and FNA is unnecessary. Otherwise, the next step in evaluation is performance of a thyroid ultrasound for three reasons: (1) Ultrasound will confirm if the palpable nodule is indeed a nodule and classify it with (EU)-TI-RADS (Annex I). (2) US will assess if there are additional nonpalpable nodules for which FNA may be recommended based on imaging features and size. (3) US will characterize the imaging pattern of the nodule, which, combined with the nodule's size, facilitate decision-making about FNA. Evidence-based guidelines from both the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists provide recommendations for nodule FNA based on sonographic patterns and size (Annex II).

Given what is known about the prevalence and generally indolent behavior of small thyroid cancers < 1 cm, the ATA guidelines do not recommend FNA for any nodule < 1cm unless metastatic cervical lymph nodes are present.

FNA biopsy performed with ultrasound guidance is the best diagnostic test when performed by physicians familiar with the procedure and when the results are interpreted by experienced cytopathologists. However, the distinction between benign and malignant follicular lesions is often not possible using cytology alone because of the absence of characteristic nuclear features in follicular carcinoma. The Bethesda System (Annex III) is now widely used to provide more uniform terminology for reporting thyroid nodule FNA cytology results.

Cytology results indicative of malignancy generally mandate surgery, after performing preoperative sonography to evaluate the cervical lymph nodes. Nondiagnostic cytology specimens most often result from cystic lesions but may also occur in fibrous long-standing nodules. Benign nodules may be monitored by ultrasound for growth, and repeat FNA may be considered if the nodule enlarges. For nodules with suspicious for malignancy cytology, surgery (lobectomy or total thyroidectomy) is recommended after ultrasound assessment of cervical lymph nodes.

The evaluation of a thyroid nodule is stressful for most patients. They are concerned about the possibility of thyroid cancer, whether verbalized or not. It is constructive, therefore, to review the diagnostic approach and to reassure patients when no malignancy is found. When a suspicious lesion or thyroid cancer is identified, the generally favorable prognosis and available treatment options can be reassuring.

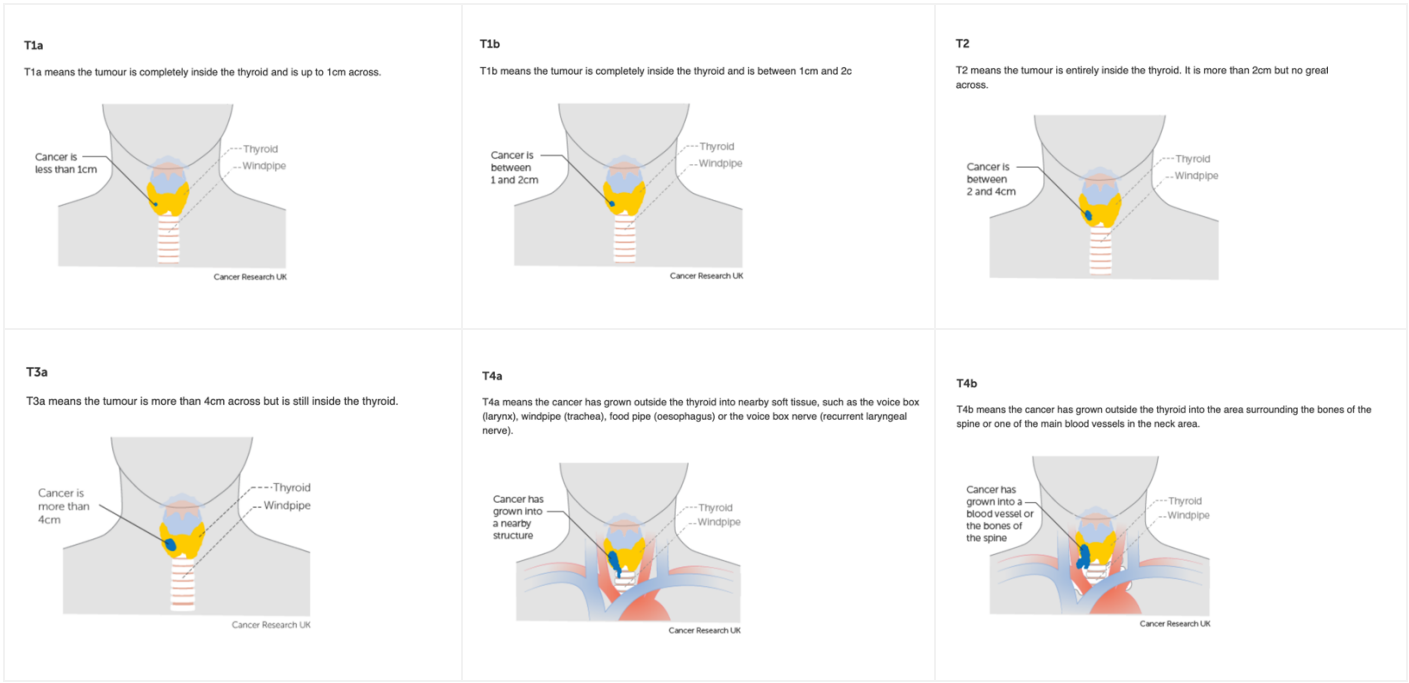
TNM 8TH EDITION AJCC (AMERICAN JOINT COMMITTEE ON CANCER) PUBLISHED IN 2017 (7)

Primary tumor (pT) for papillary, follicular, poorly differentiated, oncocytic cell and anaplastic thyroid carcinoma	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 2 cm in greatest dimension limited to the thyroid
T1a	Tumor ≤ 1 cm in greatest dimension limited to the thyroid
T1b	Tumor > 1 cm but ≤ 2 cm in greatest dimension limited to the thyroid
T2	Tumor > 2 cm but ≤ 4 cm in greatest dimension limited to the thyroid
T3 *	Tumor > 4 cm limited to the thyroid or gross extrathyroidal extension invading only strap muscles
T3a *	Tumor > 4cm limited to the thyroid
T3b *	Gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid or omohyoid muscles) from a tumor of any size
T4	Includes gross extrathyroidal extension into major neck structures
T4a	Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus or recurrent laryngeal nerve form a tumor of any size.
T4b	Gross extrathyroidal extensioni invading prevertebral fascia or encasing carotid artery or mediastinal vessels from a tumor of any size.
Primary tumor (pT) for medullary thyroid carcinomas	
Tx - T3	*Definitions are similar to the above*
T4	Advanced disease
T4a	Moderately advanced disease; tumor of any size with gross extrathyroidal extension into the nearby tissues of the neck, including subcutaneous soft tissue, larynx, trachea, esophagus or recurrent laryngeal nerve
T4b	Very advanced disease; tumor of any size with extension toward the spine or into nearby large blood vessels, invading the prevertebral fascia or encasing the carotid artery or mediastinal vessels.

Regional lymph node (pN)	
Nx	Regional lymph nodes cannot be assessed
N0	No evidence of regional lymph node metastasis
N0a *	One or more cytologic or histologically confirmed benign lymph nodes
N0b *	No radiologic or clinical evidence of locoregional lymph node metastasis
N1 *	Metastasis to regional nodes
N1a *	Metastasis to level VI or VII (pretracheal, paratracheal, prelaryngeal / delphian or upper mediastinal) lymph nodes; this can be unilateral or bilateral disease
N1b *	Metastasis to unilateral, bilateral or contralateral neck lymph nodes (levels I, II, III, IV or V) or retropharyngeal lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

***** All categories may be subdivided: (s) solitary tumor and (m) multifocal tumor (the largest tumor determines the classification)

Table 1. Thyroid cancer TNM 8th edition AJCC published in 2017



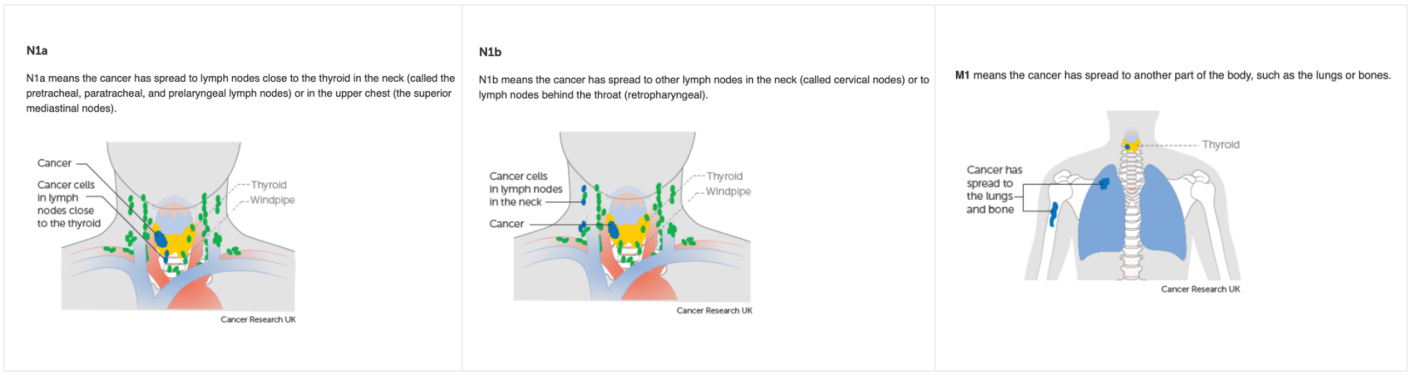


Figure 3. Thyroid cancer TNM

RISK STRATIFICATION

One of the most widely used is the tumor-node-metastasis (TNM) classification elaborated by the American Joint Committee on Cancer (AJCC), which allows to predict the risk of cancer-related death. The 8th edition of the AJCC staging system for thyroid cancer (AJCC-8) was published in 2017 and implemented on 1 January 2018 (8).

In the AJCC-8, the age threshold for high risk of disease-specific mortality is above 55 years, the median age at diagnosis in several published series. Therefore, young patients under 55 years old, whose mortality risk can be defined solely on the basis of the absence or presence of distant metastases (stages I and II, respectively) (9).

The major changes related to DTC in the AJCC 8th edition respect the previous one include the following: (1) the age-at-diagnosis cut-off used for staging increased from 45 to 55 years, (2) minor histological extrathyroidal extension was removed from the T3 classification, (3) N1 disease was down-staged to stage I or II (10). See all these differences in Annex IV.

Similarly, stage IV in the 7th edition included all patients with gross extrathyroidal extension or distant metastases at diagnoses, but also included all patients with lateral neck lymph node involvement. Conversely, stage IV in the 8th edition excludes patients with just lateral neck lymph node metastases and includes only the patients at highest risk of dying from TC ($\geq$ 55 years old with extensive gross extrathyroidal extension defined as T4b disease or distant metastases at diagnosis). As a result, the 8th classifies fewer patients as having stage IV disease, but conveys a much poorer prognosis for this category than would have been predicted using the 7th edition (9).

In addition, stage IVC no longer exists in the AJCC 8th edition for DTC.

Staging guide for thyroid cancer (AJCC 8e)

Age at diagnosis	T category	N category	M category	Stage	Expected 10-yr DSS
		Differentiated thyroid cancer			
<55 years	any T	any N	M0	**I**	98–100%
	any T	any N	M1	**II**	85–95%
≥ 55 years	T1	N0/NX	M0	**I**	98–100%
	T1	N1	M0	**II**	85–95%
	T2	N0/NX	M0	**I**	98–100%
	T2	N1	M0	**II**	85–95%
	T3a/T3b	any N	M0	**II**	85–95%
	T4a	any N	M0	**III**	60–70%
	T4b	any N	M0	**IVA**	< 50%
	any T	any N	M1	**IVB**	< 50%
		Medullary thyroid cancer			
any	T1	N0	M0	**I**	
	T2	N0	M0	**II**	
	T3	N0	M0	**II**	
	T1-3	N1a	M0	**III**	
	T4a	any N	M0	**IVA**	
	T1-3	N1b	M0	**IVA**	
	T4b	any N	M0	**IVB**	
	any T	any N	M1	**IVC**	
		Anaplastic thyroid cancer			
any	T1-T3a	N0/NX	M0	**IVA**	
	T1-T3a	N1	M0	**IVB**	
	T3b	any N	M0	**IVB**	
	T4	any N	M0	**IVB**	
	any T	any N	M1	**IVC**	

Table 2. The latest clinical staging guide for TC (AJCC 8e) published in 2017 (7)

RECURRENCE

PTC has excellent survival, however even after treatment for TC, it is possible for the primary cancer to return (called **recurrent disease**).

Recurrent thyroid cancer may occur years after the initial treatment for the disease is completed, the average time to recurrence has been reported from 6 months to decades later. Typically it occurs in the neck area, such as the lymph nodes (regional recurrence). Some other patients experience distant metastases, when the cancer has spread to other areas of the body, commonly develops firstly in the lungs and secondly in bones (11).

* true ‘‘recurrence’’ if a patient had an undetectable TG in the absence of TG antibodies and a negative neck US within one year of the previous surgery.

‘‘persistent’’ disease as having a positive TG level, an abnormal US or persisting elevated TG antibodies after treatment, which means that the disease hasn’t been cured.

Initial American Thyroid Association (ATA 2015) risk of recurrence classification (9)	
Low risk (all the following)	No local or distant metastases All macroscopic tumour has been resected No invasion of locoregional tissues Tumor does not have aggressive histology (*e.g.*: tall cell, insular, columnar cell carcinoma, oncocytic cell carcinoma, follicular thyroid cancer) No vascular invasion No ^{131}I uptake outside the thyroid bed on the post-treatment scan, if done Clinical N0 or ≤ 5 pathologic N1 micrometastases (< 0.2 cm) Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (< 4 foci) vascular invasion Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including BRAFV600E mutated (if known)
Intermediate risk (any of the following)	Microscopic invasion into the perithyroidal soft tissues Cervical lymph node metastases or ^{131}I uptake outside the thyroid bed on the post-treatment scan done after thyroid remnant ablation Tumor with aggressive histology or vascular invasion Clinical N1 or > 5 pathologic N1 with all involved lymph nodes < 3cm Multifocal papillary microcarcinoma with extrathyroidal extension (ETE) and BRAFV600E mutated (if known)
High risk (any of the following)	Macroscopic (gross ETE) invasion of tumor into the perithyroidal tissues Incomplete tumor resection Distant metastases Postoperative serum thyroglobulin suggestive of distant metastases Pathologic N1 with any metastatic lymph node ≥ 3 cm Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion)

Table 3. ATA 2015 Risk of recurrence classification

The recurrence rate of thyroid cancer may vary depending on the type, the stage at initial diagnosis, how far the cancer spread before remission was reached. In a 2021 study looked at 10 years of data with more than 4.000 participants with papillary thyroid cancer classified into 3 groups with the following recurrence rates: (12)

- **Low risk**: 1.6% recurrence rate over a 10-year period
- **Intermediate risk**: 7.4% recurrence rate over a 10-year period
- **High risk**: 22.7% recurrence rate over a 10-year period

According to research, the average recurrence rate of follicular thyroid cancer is around 13’6%.

Factors associated with a higher risk of recurrence: lymph node metastasis, histologic variant, tumor size, extra-thyroidal extension, extra-nodal extension, male sex and age above 55 years old at time of diagnosis. Therefore, the importance of following up all the patients with thyroid cancer to help detect recurrences as soon as possible, before the disease gets worse, there’s various tools available.

TREATMENT

Surgery represents the first line of treatment. In low-risk patients, surgery includes total thyroidectomy or unilateral lobectomy. While therapeutic selective neck dissection (levels IIa, III, IV, Vb, and VI) is indicated in patients with documented lymph node metastases, elective dissection of the central and lateral compartments is not indicated in low-risk patients.

All well-differentiated thyroid cancers (DTC) > 1 cm (T1b or larger) should be surgically although active surveillance may be an option for small intrathyroidal micropapillary thyroid cancers (T1a) without metastases. Surgery removes the primary lesion and allows accurate histologic diagnosis and staging. For patients at high risk for recurrence, bilateral surgery allows administration of radioiodine for remnant ablation and potential treatment of iodine-avid metastases or clinical evidence of extrathyroidal invasion (13).

The administration of I131 after surgery should be considered if Tg levels remains elevated in serum and its dose is depending on the degree of risk. For high-risk patients, surgery should include total thyroidectomy and elective central compartment neck dissection (14).

Therefore, near-total thyroidectomy is appropriate for tumors > 4cm or in the presence of metastases or clinical evidence of extrathyroidal invasion. In addition, for patients found to have a high risk tumor after lobectomy based upon aggressive pathology features (e.g., vascular invasion or a less differentiated subtype), completion surgery should be performed. Postoperative sonography should be performed in all patients to assess the central and lateral cervical lymph node compartments for suspicious adenopathy, which if present, should undergo FNA and be removed, as indicated, at surgery.

Most tumors are still TSH-responsive, **levothyroxine suppression of TSH** is a mainstay of TC treatment. The degree of TSH suppression should be individualized based on a patient's risk of recurrence. It should be adjusted over time as surveillance blood tests and imaging confirm absence of disease or, alternatively, indicate possible residual/recurrent cancer. For patients who have a low risk of recurrence, TSH levels should be maintained within the lower normal range (0.5 – 2.0 mIU/L). For individuals classified as either an intermediate or high risk of recurrence, it is recommended to keep TSH levels within the range of 0.1 to 0.5 mIU/L and < 0.1 mIU/L, respectively, if there are no

strong contraindications to mild thyrotoxicosis. For those with confirmed metastatic disease, the target TSH level should be maintained below 0.1 mIU/L.

Not all patients benefit from **radioiodine therapy**. Well-DTC often incorporates radioiodine, although less efficiently than normal thyroid follicular cells. Radioiodine uptake is determined primarily by expression of the NIS and is stimulated by TSH, requiring expression of the TSH-R. For patients at higher risk of recurrence (larger tumors > 4cm, more aggressive variants of papillary cancer, tumor vascular invasion, extrathyroidal invasion, lymph node metastases), 131I therapy may provide an adjuvant role and potentially treat residual tumor cells.

Radioiodine is administered after iodine depletion (patient follows a low-iodine diet for 1 – 2 weeks) and in the presence of elevated serum TSH levels to stimulate uptake of the isotope into both the remnant and potentially any residual tumor. To achieve high serum TSH levels, there are two approaches: (i) the patient may be withdrawn from thyroid hormone so that endogenous TSH is secreted and, ideally, the serum TSH level is > 25 mIU/L at the time of 131I therapy, but it's inconvenience is all the symptoms the patient will experience in hypothyroidism (asthenia, low metabolism, bradycardia, weakness, dry skin, constipation…), (ii) Alternatively, recombinant human TSH (rhTSH) is administered as two daily consecutive injections (0.9 mg) with administration of 131I 24 h after the second injection, the patient can continue to take levothyroxine and remains euthyroid.

The management of MTC is primarily surgical. Prior to surgery, pheochromocytoma should be excluded in all patients with a RET mutation. Unlike tumors derived from thyroid follicular cells, these tumors do not take up radioiodine (4).

For ACA, external beam radiation therapy can be attempted and continued if tumors are responsive. Recent data demonstrate survival benefit with immune checkpoint (4).

COMPLICATIONS AFTER THYROIDECTOMY

Surgical complications rates are acceptably low if the surgeon is highly experienced in the procedure. Serious complications after thyroidectomy are rare but the incidence of minor complications and their sequelae are not infrequent. Minor complications may sometimes result in prolonged

hospitalization with loss of work and may require specialized care and follow-up. The two most common early complications of thyroid surgery are hypoparathyroidism / hypocalcemia (20 – 30%) and recurrent laryngeal nerve injury (RLN 5 – 11%) (15). Other potential complications include: hemorrhage, hematoma, seroma, scarring, infection of the wound, and permanent hoarse or weak voice due to RLN injury (16–18). And the need to take thyroid hormone replacement for the rest of their life.

FOLLOW-UP

During follow-up, the tools applicable for detecting a possible recurrence are serum thyroglobulin (TG), serum anti-TG antibodies, high-resolution ultrasonography (US) for thyroid bed and neck recurrences, as well as computed tomography (CT), magnetic resonance imaging (MRI), and positron-emission tomography (PET-CT) for neck and distant metastases (14).

Thyroglobulin (TG) is a tumor marker that should be under 0.2 ng/mL in patients that have done thyroidectomy, this value should be even lower in those that have radioI131 in post-surgery. And antibodies anti-thyroglobulin, another marker that must be analyzed, has to be negative all the time, if it is positive can falsify the TG value. TG together with antibodies anti-TG must be monitored periodically along the whole life.

Radiographic studies, specifically ultrasound, have emerged as standard surveillance tools is recommended to do periodically as well. Possible abnormal US if it includes any of the following phrases: abnormal tissue in the thyroid bed, suspicious lymph nodes in the central or lateral neck, increase in growth of mass or lymph nodes, or invasion of surrounding structures. Then if the results suggest recurrence disease, it would be necessary complete the study with whole-body scan with I131 (WBS, can see the uptake for the metastases), MRI, CT and other more specific tests (11).

The WBS with low dose of ^{131}I (5 mCi) can help in detecting recurrences and metastases 6 months after treatment.

The evaluation of post-treatment responses in thyroid cancer is crucial of determining the risk of recurrence. An **excellent response**, characterized by a low recurrence rate of 1 – 4%, is indicated by imaging negative for disease recurrence and serum thyroglobulin concentration either lower than

0.2 ng/mL in the basal state or higher than 1 ng/mL under TSH stimulation. An **indeterminate response**, associated with a 15 – 20% recurrence rate, involves non-specific findings on imaging studies and serum thyroglobulin levels ranging from 0.2 to 1 ng/mL in the basal state or 1 to 10 ng/mL under TSH stimulation, with stable or decreasing thyroglobulin antibodies. A **biochemical incomplete response**, with a recurrence rate of 20%, is characterized by negative imaging for disease recurrence but elevated serum thyroglobulin concentrations, exceeding 1 ng/mL in the basal state or higher than 10 ng/mL under TSH stimulations, or an increase in thyroglobulin antibody concentrations. A **structural incomplete response**, associated with a higher recurrence rate of 50 – 85%, is determined by structural or functional evidence of disease in imaging studies, such as neck ultrasound, CT, MRI, whole-body scan, or 18F-fluorodeoxyglucose PET. Each response category plays a crucial role in guiding further management and intervention strategies based on the risk of recurrence (19).

4. JUSTIFICATION

Thyroid nodules are very common, prevalence of 60 % for each neck ultrasound. Only 5 - 15% of them are malignant, the most common is papillary carcinoma (20).

TC is the most common malignant tumor of the endocrine system (21–23). TC roughly accounted for 1% of all new malignant neoplasms in man and 3% in women (24).

According to the SEEN (Sociedad Española de Endocrinología y Nutrición) in Spain around 4,500 new cases of thyroid cancer are identified every year, which represents more than 9 cases per 100,000 population; 5 cases per year every 100,000 males; more than 13 cases per year every 100,000 females. The incidence of TC has duplicated in the last 10 years.

Studies have shown that the incidence of thyroid cancer in high-income countries has tripled over the past 25 years although mortality from thyroid cancer has remained relatively low and stable (24–27). The incidence of this disease arises from 4.9 per 100,000 inhabitants in 1975 to 14.3 per 100,000 inhabitants in 2009.

TC has significant increase in global incidence over the past decades, mostly due to increased diagnosis of incidental tumors. Since the early 1980's, an increase in incidence rates, principally concerning early papillary thyroid carcinomas, has been observed initially in very high-income countries and subsequently in some middle-income countries (27).

Mortality has either decreased or remained stable (28). This rise has been a reflection of the growing scrutiny of the thyroid gland with ultrasonography (29) and is mainly associated with improvements in diagnostic techniques. The introduction of new diagnostic techniques such as ultrasound, fine-needle aspiration guided by ultrasound and computed tomography, which can detect small thyroid nodules, are more sensitive. Also, combined with increased medical surveillance and access to health care services, can lead to massive increases in detection of small papillary lesions caused by large reservoir of asymptomatic, nonlethal disease known to exist in the thyroid gland (30).

Globally, the estimated number of new cases of thyroid cancer is 449,000 in women (10.1 cases for 100,000 habitants) and 137,000 in men (3.1 cases per 100,000), it's 3% of all cancers. New cases were diagnosed worldwide and its incidence is much higher in women, with a female:male sex ratio of 3 (28). In Europe, thyroid cancer represents 0.7 and 2.5% of all cancer burden in men and women

respectively; Spain presents a lower incidence of TC than the European Union (8.8 vs 10.0 in 2018) and a 5 year relative-survival of 90.4% (31,32).

A population-based study of TC incidence trends by histology in 25 countries (33) showed that papillary thyroid cancer was the main contributor to overall incidence of TC in all studied countries. In women, the age-standardised incidence rates for PTC ranged from 4.3 to 5.3 cases per 100,000 women in the Netherlands, the UK, and Denmark (representing approximately 70% of all cases of TC) to 143.3 cases per 100,000 person-years in South Korea (representing 96% of all cases of thyroid cancer), corresponding to a ratio of greater than 30 times between the highest and lowest observed age-standardised rate. Conversely, trends were relatively stable and incidence rates low for other histological subtypes (in women, not exceeding 3 cases per 100,000). PTC showed the largest variation, with highest rates recorded in some high-income countries, such as the South Korea, Italy, France, Canada, Australia, and the USA, as well as in socioeconomically transitioning countries in Asia (eg, Turkey and China), and Latin America (eg, Colombia), as we can see in Figure 4 (33).

Although it is generally accepted that overdiagnosis of thyroid cancer is due to increases in diagnostic and screening activities, evaluating and understanding papillary thyroid cancer incidence trends over the past decades is important.

It is important to thoroughly investigate overdiagnosis, because the diagnosis of clinically irrelevant tumors results in consequent over-treatment that exposes patients to the potential complications of thyroidectomy including hypocalcemia due to hypoparathyroidism, laryngeal nerve injury, seroma, hematoma, and more rarely, Horner's syndrome, carotid artery injury and brachiocephalic vein injury. Additionally, patients receiving thyroidectomy for tumors of little clinical relevance undergo undue stress, require extended leaves from work during postoperative recovery, require thyroid hormone replacement medication for life and require future follow-up visits to ensure no recurrence of disease (34).

As overdiagnosis of thyroid cancer is now a public health problem of global relevance, monitoring and provision of timely evidence for the evolution of the current epidemiological patterns is important. Such evidence will be key to developing tailored prevention strategies to limit overdiagnosis at the national, subnational and regional level (27).

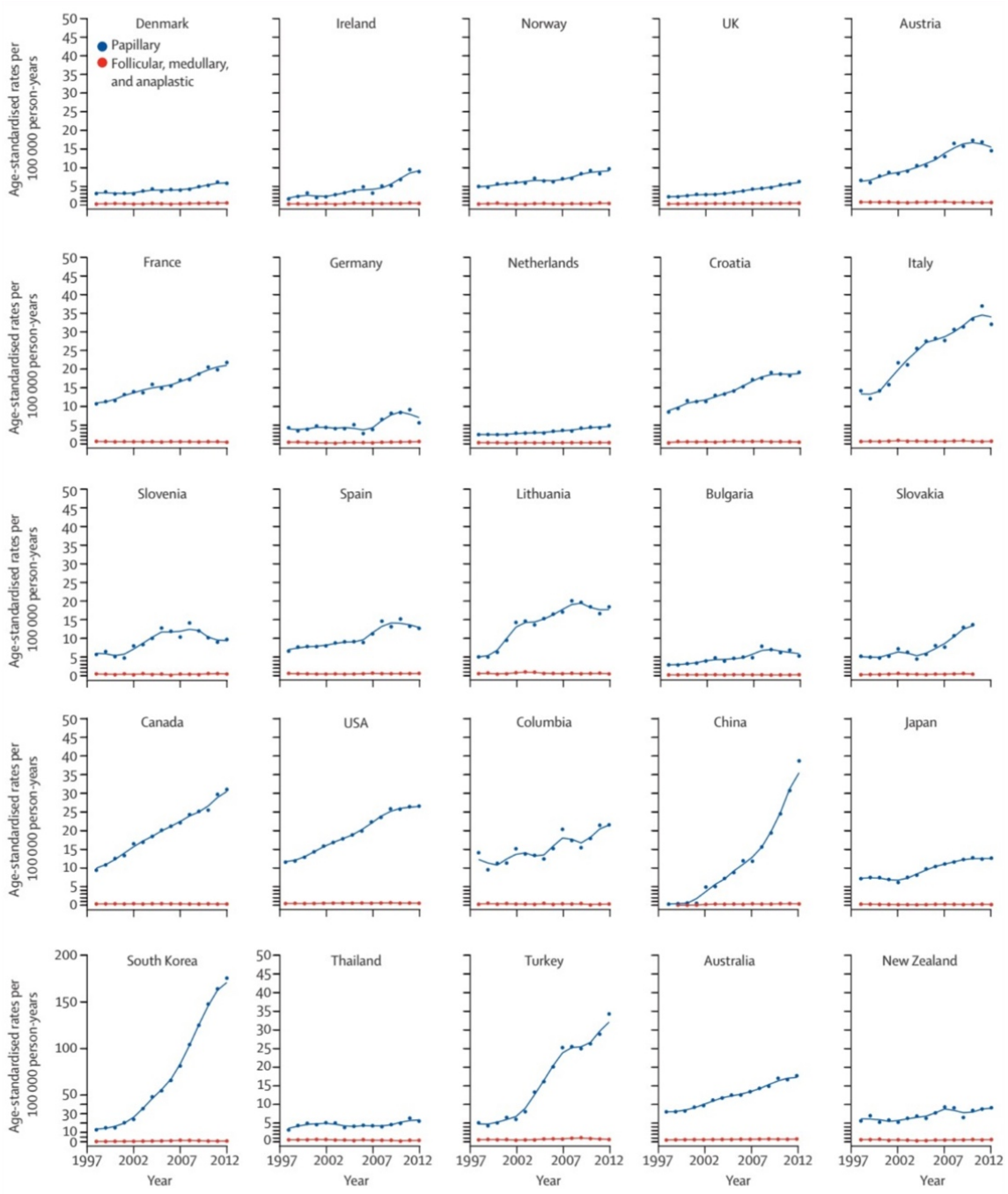


Figure 4. Time trends in age-standardized incidence rates of thyroid cancer by histological subtype in women, from 1998 to 2012 (33).

Therefore, this study aims to investigate trends of incidence from a data base of patients diagnosed with TC throughout the province of Girona. So, it provides epidemiological and demographical

evidence of TC cases from our region, involving a large number of patients treated and followed for 26 years up to nowadays when this study is conducted. Furthermore, this can contribute to resultant health and financial implications for patients, and ongoing efforts and potential strategies to combat this growing clinical and public health issue.

With all of this, the large information obtained it will help us to provide a better treatment strategy for the patients, with fewer complications, that will result in lower economic cost for the National Health System.

5. HYPOTHESIS

Incidence trends of thyroid cancer in Girona has increased during the period 1994 – 2020.

Thyroid cancer is more common in females than in males.

Papillary thyroid cancer is the main contributor to overall thyroid cancer in our country and is the histological type that have increase in recent decades.

6. OBJECTIVES

This is a population-based study providing a global assessment of the epidemiology of common thyroid cancer types in a long observation period (1994 – 2020). Our main objective is to estimate, describe and analyze incidence trends of thyroid cancer in Girona during the period 1994 - 2020 by histological type, sex and stage at diagnosis to check whether this data is similar to those observed in other countries and regions.

To analyze the changing incidence of thyroid cancer and suggest explanations for these trends. To compare our Girona results with reports from other countries.

To investigate the demographic characteristics for each group of age, histological type and sex (male or female) and see their epidemiological differences related to proportion, incidence, Age-standardized rate (ASR) and Annual Percentage Change (APC).

7. SUBJECTS AND METHODS

STUDY DESIGN

We compiled incident cases of thyroid cancers obtained from the Girona population-based Cancer Registry (GCR) collected during the period 1994 - 2020. The GCR covers the population of Girona province, located in northeastern Spain, with 777,339 inhabitants in 2020 according to the National Statistics Institute. The GCR is a member of the International Agency for Cancer Registries (IACR). Procedures for cancer registries and coding rules were used in accordance with the standards of the International Agency for Research on Cancer (IARC) standards.

The mortality data have been obtained from the Mortality Registry of the Information and Studies Service of the General Directorate of Health Resources of the Department of Health of the Generalitat de Catalunya.

Demographic characteristics of interest for this analysis included gender, race, and age at diagnosis. This information was originally abstracted from medical records.

For this study, the cases are morphologically coded according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Topography and morphology were coded according to International Classification of Diseases for Oncology, 3rd Edition, ICD-O-3.

Histological types were defined using ICD-O-3 WHO histological classification of tumors into four major types: papillary carcinoma, follicular carcinoma, medullary carcinoma, anaplastic and other / unspecified for the rest of the cases with microscopic verification. Morphology codes are grouped as follows:

- Neoplasms or unspecified carcinomas (8000, 8010)
- Squamous cell carcinomas (8070, 8071)
- Papillary carcinomas (8050, 8260, 8340, 8341, 8342, 8343, 8344, 8350, 8450 - 8460)
- Follicular carcinomas (8330, 8332, 8335, 8339)
- Oncocytic carcinomas (8290)
- Medullary carcinoma (8345, 8510-8513)

- Anaplastic carcinoma (8020-8035)
- Carcinoma, NOS (Not Otherwise Specified) (8000, 8010)
- Other types, including unspecified, poorly specified (e.g., insular) (8337, 8430, 8346, 8347, 8200, 9081)

And age at diagnosis was categorized as 0-14, 15-24, 25-49, 50-69, and ≥ 70 years old.

This study did not involve any human contact, but only record linkage analysis of health-care database.

STUDY POPULATION

This is a population-based retrospective cohort study from Girona Cancer Registry. Study subjects were all incident and fatal cases of thyroid cancer (C73 according to ICD-10) registered between 1994 and 2020 and residing in Girona Province. GCR applies standard cancer registry procedures and coding rules.

DATA COLLECTION

It is considered a case any invasive malignant tumor o unspecified (if we don't have any diagnostic confirmation available), diagnosed in individuals residing in the Girona regions at the time of diagnosis or at the time of death if the death certificate is the only source of information. In situ carcinomas and tumors of uncertain behavior are also recorded. The GCR database has provincial coverage since January 1994. Tumors are recorded, not individuals, assuming that the same individual may have two or more tumors. Therefore, incidence reflects the number of primary cancers, not the number of patients with cancer. The norms and criteria for multiplicity used are those defined in the International Rules for Multiple Primary Cancers by the International Agency for Research on Cancer, International Association of Cancer Registries, and European Network of Cancer Registries.

For the calculation and presentation of incidence results, international standard criteria defined in the joint recommendations of the European Network of Cancer Registries (ENCR), the International

Agency for Research on Cancer (IARC), and the International Association of Cancer Registries (IACR) are used. To define a case as a resident, the registry uses information from hospital and other centers databases, medical records and death certificates. In case of discrepancies between different sources, this information is actively reviewed with the medical history, and if doubt persists, residency is accepted according to the information source considered most reliable. A person is considered a resident if they have lived in the province of Girona for a minimum period of a 2 year before their cancer diagnosis.

DATA PROCESSING

Once the information is collected, the GCR processes the data to ensure the completeness of the recording, the validity of the data, and its maximum accuracy. This includes avoiding duplications, correct coding and addressing other aspects of the overall data quality. Tumors without histopathological diagnosis, relying on exploratory techniques (clinical, surgical, imaging or laboratory), are also included, provided that the clinical information allows for a high level of certainty that the pathology in question is a registrable tumor according to the registry criteria. Cases exclusively derived from the death certificate with no additional information are included in the registry as malignant tumors if the certificate specifies so.

STAGE AT DIAGNOSIS

We used to categorize all malignant thyroid cancer diagnoses into four main stages according to ACJJ risk stage stratification: I, II, III and IV (A, B, C). The patients are classified according to its edition from that moment of diagnoses.

8. STATISTICAL ANALYSIS

The analysis of the data are obtained by **statistical analyst**.

GCR presents separate analyses for men and women, as well as for the diagnostic period and tumor locations. Incidences categorized using groupings based on ICD-10 codes and descriptions used for cancer incidence. All calculations have been performed by querying the GCR database until 2020.

Age-specific incidence rates per 100 000 person-year were created for 4 groups: < 25, 25-49, 50-69 and > 69 years. Analysis was done at the level of sex, age, histological type and year of diagnoses.

We calculated incidence rates using direct standardization (namely, the age-standardized rate) using the European population as a reference, per 100,000 person-years. The results are presented by age and sex aggregated in tables.

European age-standardized incidence rates were calculated by multiplying the age-specific incidence rates with the European standard population respectively and expressed per 100,000 person-year.

To assess the trend and significance of the observed change during the period, the Annual Percentage Change (APC) is calculated, along with its 95% confidence intervals and the corresponding statistical significance.

STATISTICAL METHODS

The database used for statistical analysis encompasses all cancers included in the case definition diagnosed in the Girona regions from 1994 to 2020, for incidence, mortality, and trends.

Incidence, defined as the occurrence of new cases during a specific timeframe within a distinct population, and mortality, denoting the number of deaths attributed to a particular disease within the same specified timeframe and population, from the core metrics of investigation.

Rates, as a general concept, is defined as the number of new cases (diagnosed or deaths) that occur in a population in a specific period expressed per 100,000 person-years.

The incidence and mortality parameters calculated that we use for this study would be (35):

a) Number of incident cases or deaths per year (N/year or N Annual): The number of incident cases or deaths during a specified period divided by the number of years in that period.

b) Crude Rate (CR): The number of incident cancer cases or deaths during the study period divided by the studied population. It is expressed per 100,000 men, women or persons and years

c) Age-specific rate: The number of incident cancer cases or deaths in an age group per population in the same age group. It is based on age intervals (into 4 age intervals groups: < 25, 25-49, 50-69 and > 69 years).

d) Age-adjusted rate to the European standard population: Adjusted rates should be understood as the rates that would occur in another population with an age structure identical to the one used as a standard. They are expressed per 100,000 men, women or persons and years and are used to compare incidence or mortality rates of populations with different age structures (different populations or the same population at different time periods). They have been calculated using the direct methods, using the 2013 European standard reference population. The reference populations used can be seen in Table 4.

The parameter most commonly used to assess **incidence trends** is the **Annual Percentage Change** (**APC**) of age-adjusted rates, which indicates the average annual variation expressed as a percentage increase or decrease. Joinpoint statistical software was used to quantify the evolution of incidence, as the APC, and to evaluate changes in trends over time. The APC for a period is calculated using a Generalized Linear Model (GLM) considering a Gaussian distribution for the logarithm of the age-adjusted rate. The 95% confidence interval (CI95%) of the APC is also calculated, allowing us to determine if the trend is statistically significant. If the confidence interval contains 0, the trend is not considered statistically significant, and therefore, it is deemed constant over time. If the interval does not contain 0, then the trend is interpreted as increasing (if APC > 0) or decreasing (if APC < 0). The same for the p value, if it is $p < 0.05$ the differences has statistical significance. In the study of trends over long periods, the APC may exhibit different behaviors over time, but it's not our case with TC, where the significantly increasing over last years.

Grup d'edat	Població mundial	Població europea
0-4	12000	5000
5-9	10000	5500
10-14	9000	5500
15-19	9000	5500
20-24	8000	6000
25-29	8000	6000
30-34	6000	6500
35-39	6000	7000
40-44	6000	7000
45-49	6000	7000
50-54	5000	7000
55-59	4000	6500
60-64	4000	6000
65-69	3000	5500
70-74	2000	5000
75-79	1000	4000
80-84	500	2500
≥85	500	2500
Total	100000	100000

Table 4. European and world standard population used for ASR

CanGir presents separate analyses for men and women and for the diagnostic period and histological types.

QUALITY INDICATORS

In the context of cancer registry data, several key indicators are employed to assess the quality of the collected information. These metrics play a crucial role in ensuring the reliability and accuracy of the registry's data. The primary quality indices include:

a) Death Certificate Only (% DCO): it is the percentage of cases included in the registry through the review of the death certificate, where, after exhaustive research by registry staff, it has not been possible to obtain more information than that provided by the death certificate. In DCO cases, the date of incidence is considered the date of death. Recommended values would be < 5 – 10% of the total. ''DCI'' cases are those initially reported through the death certificate before the research, i.e., those identified through the certificate but later confirmed with other sources of information.

b**) Histological Verification** (%VH): it is the percentage of registered cases with histological verification of the diagnosis. A low proportion suggests incomplete coverage of cases. A very high proportion may be caused by information collection based solely on pathology laboratories, and cases diagnosed by other means may not have been recorded.

c) Mortality / Incidence Ratio (M/I): The M/I ratio is calculated as the ratio between the number of deaths attributable to a specific cancer and the number of new cases of the same tumor within the same period and population. When considered alongside survival data, this ratio serves as an indicator of the registry's coverage.

d) Completeness. Completeness measures the extent to which all cancer cases within the covered territory are accurately captured in the registry database. It is, therefore, a very important variable, as only with good completeness in case detection, incidence rates will be close to reality. There are different calculation methods, and CanGir uses the Akaike quantitative method, which considers cases identified by the death certificate and the Mortality / Incidence ratio. The completeness for all locations combined, estimated for the recollecting data period in Girona, has been 95%.

9. RESULTS

DESCRIPTIVE ANALYSIS

A total of 1,149 thyroid cancer cases were recorded; the median age was 47 years [IQR: 37 - 60] and 76.8% were female, while 23.2% were male. At the end of the study period, from 1994 to 2020 we registered 193 deaths (16.8%) and 956 (83.2%) are still alive. This mortality rate is not strictly attribute to TC mortality, because we didn't revise for the death cause, so it could be for other neoplasms or health conditions.

N	*mean*	*standard deviation*	*min*	*Q1*	*Q2*	*Q3*	*max*	*missings*
1,149	48.72	15.91	6	37	47	60	93	0

Table 5. General age descriptive analysis of thyroid cancer in Girona population during period 1994 – 2020

	N	%
Sex		
Female	883	76.85
Male	266	23.15
Age		
0 – 14	8	0.7
15 – 24	44	3.83
25 – 49	585	50.91
50 – 69	374	32.55
70 and more	138	12.01
TOTAL	1149	100

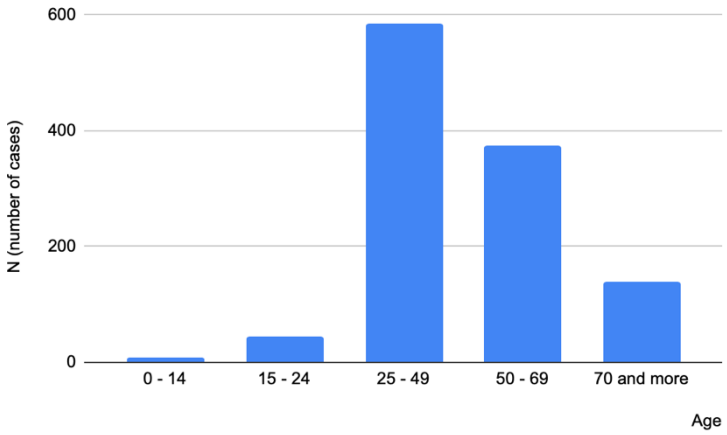


Table 6. Descriptive analysis of thyroid cancer, number of cases and percentage by sex and age group.

Figure 5. Bar chart for 5 groups age rang (0-14, 15-24, 25-49, 50-69 and 70+) of patients diagnosed with TC. We can observe that the peak is in the age between 25 – 49 years old.

Among the total cases in our study (N = 1,149 patients with TC), 91.47% (N = 1051) have a confirmed histological diagnosis. In 6.7% of cases, cytology is the sole diagnostic information, typically involving patients who either did not undergo surgery or did so outside any regional hospital in Girona. The

diagnosis of TC was stablished in 1.13% (N = 13) of cases through histology indicating metastasis. Additionally, 0.44% (N = 5) were identified through other clinical examinations, representing incidental findings. A minimal proportion, 0.17% (N = 2) is based solely on death certificates with a diagnosis of TC and only 0.09% (N = 1) the diagnostic method is unknown.

	cases (N)	***%***
Cytology	77	6.7
DCO (death certificate only)	2	0.17
Unknown	1	0.09
Histology of a primary tumor	1051	91.47
Histology of metastasis	13	1.13
For other clinical exploration (by chance) / Incidental	5	0.44
TOTAL	1149	100

Table 7. Diagnostic method of total cases of TC for our study

In the examination of histological types of TC, our analysis reveals that the papillary type emerges as the most prevalent, constituting 80.4% of cases (N = 924). Following in frequency is the follicular type, representing 8.0% (N = 92); the medullary type constitutes 5.0% of cases (N = 58); and oncocytic 2.1% (N = 24); while the anaplastic and poorly differentiated type accounts for 2.1% (N = 24). Other types collectively contribute 0.35% (N = 4). Additionally, cases categorized as ‘‘Not Otherwise Specified’’ stand at 2% (N = 23). As the new WHO 2022 histological classifications is published, now oncocytic cancers (known as Hürthle cells tumor previously) are considered a separate group outside the follicular category.

Histological type	***%***	***N***
Papillary	80.42	924
Follicular	8.01	92
Medullary	5.05	58
Oncocytic	2.09	24
Anaplastic and poorly differentiated	2.09	24
Other types	0.35	4
Not otherwise specified	2	23
TOTAL	100	1149

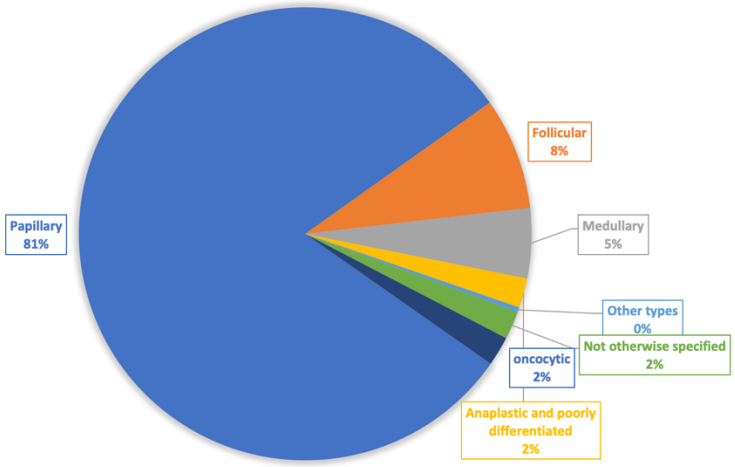


Table 8. Global descriptive analysis of histological types of TC

Figure 6. Pie chart of different histological types of TC

ICD-O-3 code	***Histological tumor subtypes***	***Cases (N)***	***%***
	Papillary	924	80.42
8340	follicular variant papillary carcinoma (c73.9)	99	8.62
8260	papillary adenocarcinoma, SAI [1]	575	50.04
8343	encapsulated papillary carcinoma (c73.9)	61	5.31
8342	oncocytic variant papillary carcinoma (c73.9)	1	0.09
8344	papillary carcinoma with columnar cells (c73.9)	9	0.78
8341	papillary microcarcinoma (c73.9)	169	14.71
8350	non-encapsulated sclerosing tumor (c73.9)	10	0.87
	Follicular	116	10.1
8339	encapsulated angioinvasive follicular carcinoma	1	0.09
8335	minimally invasive follicular carcinoma	50	4.35
8330	follicular carcinoma, SAI (c73.9)	41	3.57
	Medullary	55	4.79
8345	medullary thyroid carcinoma (c73.9)	35	3.05
8510	medullary carcinoma, SAI	20	1.74
8290	Oncocytic carcinoma	24	2.09
8020, 8021	Anaplastic / Undifferentiated	24	2.09
8337	Poorly differentiated thyroid carcinoma (c73.9)	1	0.09
8347	Mixed medullary-papillary carcinoma (c73.9)	3	0.26
8430	Mucoepidermoid carcinoma	1	0.09
9081	Teratocarcinoma	1	0.09
8000, 8010	Neoplasms or carcinoma, SAI	23	2
8200	Others	7	0.61
	TOTAL	1149	100

[1] SAI stand for *Sine Alter Indicatio* (without other indication). The expression ''SAI'' is included after topographic and morphological terms *(36)*. The code of a term followed by ''SAI'' should be used when: (1) A topographic or morphological term appears without any other modification; (2) it has an adjective that does not appear elsewhere in the classification; (3) a term is used in a general sense.

Table 9. Histological TC subtypes with its own morphological code and number of cases (N), %.

Most of thyroid cancers were diagnosed in stage I, they represents the 70% of total TC diagnosed. In second place we have stage IV, which is the 10%. And stage II and III corresponds to 7% and 8% respectively. The rest 5% we didn't have this information, it could be because they decided to not go into surgery or the treatment weren't done in our study region so we don't have it.

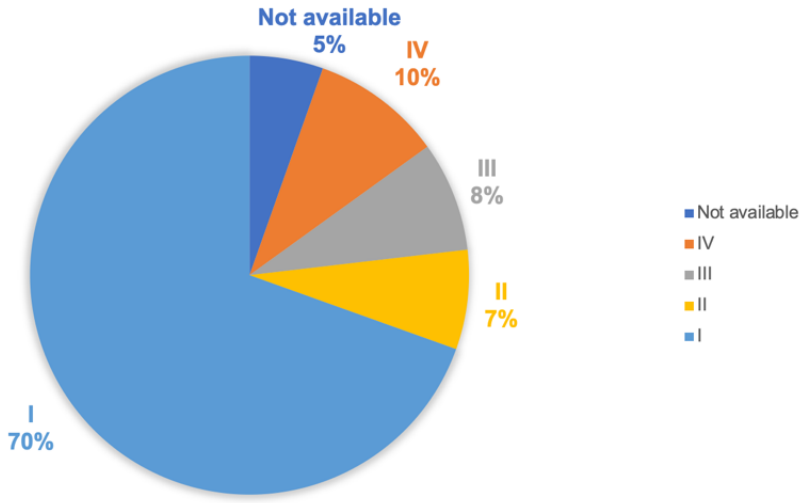


Figure 7. Pie Chart of TC stage at time of diagnosis, based in the stage classification of the year of diagnosis.

BIVARIATE ANALYSIS

Thyroid cancer incidence is higher in women than in men, with 883 and 266 cases, respectively. Men's mean age of diagnosis is 51.3 ±15.9 years old, while for women is 47.9 ± 15.8, a little bit younger and this slightly difference between sex is statistically significative (p value = 0.003). The distribution in percentage of histological TC type by sex are quite different (p value < 0.001) but they follow the same order, we have the papillary type (♂ 73.3%; ♀ 82.6%) in first place and followed by follicular (♂ 8.6%; ♀ 10.5%), medullary (♂ 8.6%; ♀ 4.0%) and anaplastic types (♂ 4.5%; ♀ 1.4%).

Most patients, regardless of sex, are diagnosed at stage I, with 77.7% in women and 62.2% in men. In men other 18.2% are diagnosed at stage IV, 10.5% at stage III and 9.1% at stage II. Conversely, in women, the percentages aren't that heterogeneous (but still statistically different, p value < 0.001) concerning the diagnostic stages II, III and IV, corresponding to 7.4%, 7.8% and 7.1%, respectively.

These differences are statistically significative, so we see that women tends to have a more early diagnosis than men. Even there are less number of cases in men the percentage of men diagnosed in later stages are higher than in women, which is statistically significative.

	MEN **N = 266** **n (%)**	**WOMEN** **N = 883** **n (%)**	**P value**	**TOTAL**
Age, mean ± SD	51.3 ±15.9	47.9 ± 15.8	0.003 *	1149
Age, median (IQR)	51 (40 – 63)	46 (36 – 59)	< 0.001 **	
Histology type				
Follicular	23 (8.6)	93 (10.5)		116
Medullary	23 (8.6)	35 (4.0)		55
Papillary	195 (73.3)	729 (82.6)	< 0.001	924
Anaplastic	12 (4.5)	12 (1.4)		24
Others	2 (0.7)	2 (0.2)		4
Neoplasm SAI	11 (4.1)	12 (1.4)		23
Stage of diagnosis				
I	130 (62.2)	580 (77.7)		710
II	19 (9.1)	55 (7.4)	< 0.001	146
III	22 (10.5)	58 (7.8)		80
IV [1]	38 (18.2)	53 (7.1)		91
[1] IV = 19 (1.98%); IVA = 48 (5%); IVB = 4 (0.42%); IVC = 20 (2.08%)				
Missings = 189 (16.45%); No reported = 5 (0.52%)				
***** t Student; ****** Wilcoxon; for the rest Xi square				

Table 10. Bivariate analysis of two variables (men and women) to compare the characteristics between them according to the median age at diagnosis, histology type and stage of diagnosis.

We compare the number of cases for 4 age range groups (< 25, 25-49, 50-69 and > 69 years old) observing that they are statistically differences by sex, histological type and stage at diagnosis. The peak of thyroid cancer diagnosis is found between 25 and 49 years old, both for men and women. And papillary in stage I is the most common TC type diagnosed in any age rang. In elderly patients, TCs are diagnosed at more advanced stages, 27.7% of > 69 years old patients are diagnosed in stage IV in comparison to 3.2% of patients between 25 – 49 years old. In this age range, there is no stage IV for PTC; it would only include medullary carcinoma.

	< 25 years **N = 52** **n (%)**	**25 - 49 years** **N = 585** **n (%)**	**50 - 69 years** **N = 374** **n (%)**	**> 69 years** **N = 138** **n (%)**	**P valor** [1] [1] Xi square
Sex					
Male	12 (23.1)	113 (19.3)	102 (27.3)	39 (28.3)	0.015
Female	40 (76.9)	472 (80.7)	272 (72.7)	99 (71.7)	
Histology type					
Follicular carcinoma	8 (15.4)	50 (8.5)	43 (11.5)	15 (10.9)	
Medullary carcinoma	4 (7.7)	18 (3.1)	26 (6.9)	10 (7.2)	
Papillary carcinoma	39 (75.0)	511 (87.3)	286 (76.5)	88 (63.8)	<0.001
Anaplastic /	0 (0)	1 (0.2)	10 (2.7)	13 (9.4)	
undifferentiated	0 (0)	2 (0.34)	1 (0.3)	1 (0.7)	
Other types	1 (1.9)	3 (0.5)	8 (2.1)	11 (8.0)	
Neoplasm SAI					
Stage at diagnoses					
I	41 (93.2)	453 (89.5)	181 (58.2)	35 (37.2)	
II	1 (2.3)	13 (2.6)	45 (14.5)	15 (16.0)	<0.001
III	0 (0)	24 (4.7)	38 (12.2)	18 (19.1)	
IV	2 (4.5)	16 (3.2)	47 (15.1)	26 (27.7)	

Table 11. Sex, histology type and stage of diagnosis according to 4 age range groups.

CRUDE INCIDENCE RATE

We calculate the crude incidence rate with the number or new cases every year during this period 1994 – 2020 divided for the Girona population, according to IDESCAT (37) registry of Catalonia's inhabitants and multiplied per 100,000 person-year. We can observe that in 1994 the number of new cases diagnosed in Girona were 21, while in 2020 there were 58 new cases of TC in our population. And considering the changes and growth of Girona population during these lasts decades, the crude incidence rate went from 4.0 in 1994 to 7.5 in 2020. So clearly, we see that incidence has increased close to the double in recent years.

	N	*%*	*Girona population*	*Crude incidence rate*
1994	21	1.83	521,304	4.028359652
1995	27	2.35	524,871	5.144121127
1996	18	1.57	528,716	3.404474236
1997	26	2.26	530,505	4.900990566
1998	22	1.91	535,077	4.111557776
1999	28	2.44	540,468	5.180695249
2000	42	3.66	546,755	7.681685581
2001	37	3.22	556,891	6.644029083
2002	30	2.61	574,342	5.223368655
2003	37	3.22	594,461	6.224125721
2004	33	2.87	616,994	5.348512303
2005	41	3.57	643,599	6.370426306
2006	38	3.31	667,724	5.690974115
2007	38	3.31	695,361	5.464787355
2008	51	4.44	720,204	7.081326957
2009	36	3.13	737,621	4.880555190
2010	44	3.83	744,485	5.910125792
2011	45	3.92	749,509	6.003930573
2012	63	5.48	751,279	8.385699587
2013	57	4.96	749,954	7.600466162
2014	53	4.61	746,451	7.100265121
2015	63	5.48	743,562	8.472729914
2016	63	5.48	745,642	8.449094874
2017	61	5.31	750,206	8.131099991
2018	51	4.44	756,137	6.744809472
2019	66	5.74	765,775	8.618719598
2020	58	05.05	777,339	7.461352126
Total	1149	100		

Table 12. Crude incidence rate for every year's population according to IdesCat provincial inhabitants registry between the period 1994 – 2020.

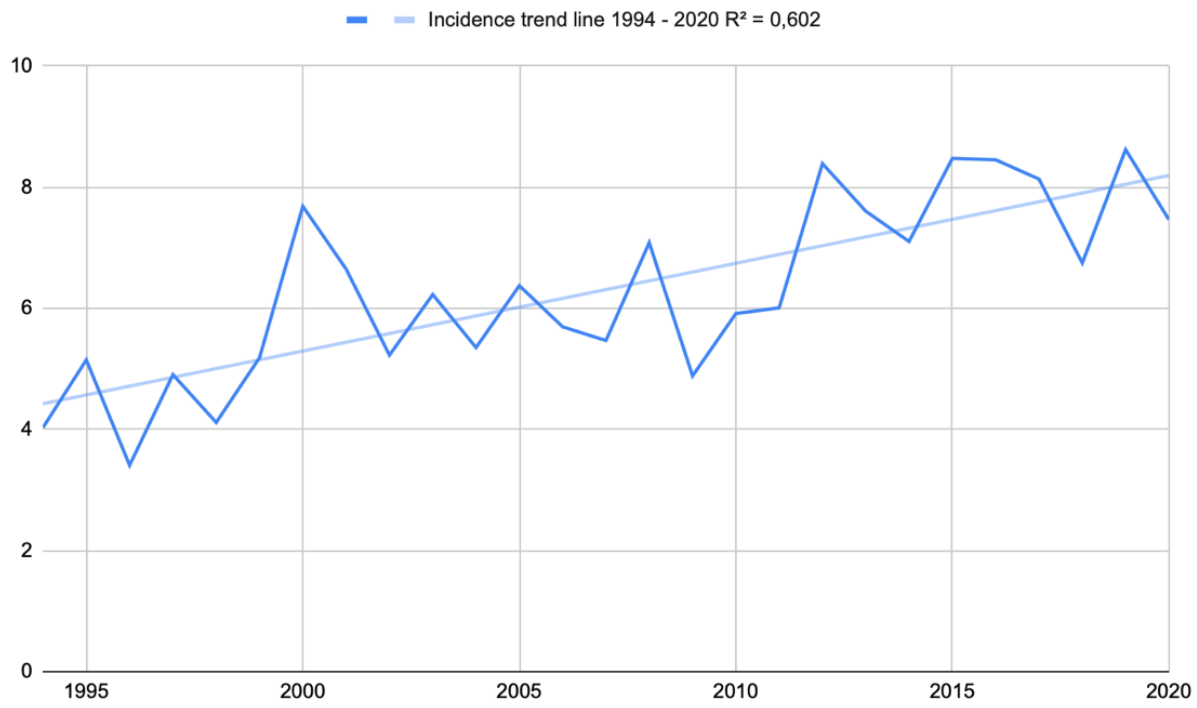


Figure 8. Linear chart for the crude incidence rate in Girona province during the period 1994 – 2020. Regression line for the crude incidence rate, where the trend is upward sloping, meaning that incidence has increased in Girona population during these 26 years

AGE-SPECIFIC INCIDENCE RATE

The age-specific incidence rate is a measure used in epidemiology to quantify the rate at which new cases of TC occur within specific age groups of a population. It is expressed as the number of new cases of the disease (thyroid cancer) in a specific group per unit of person-time at risk within that age group. Mathematically, the age-specific incidence rate is calculated as follows:

$$INCIDENCE\ RATE = \frac{number\ of\ new\ cases\ in\ a\ specific\ age\ group}{total\ person-time\ at\ risk\ in\ that\ age\ group}\ \ x\ 100{,}000\ person-year$$

This measure helps to understand how the incidence of TC varies across different age groups. We found that the highest incidence rate per 100,000 men is at the age of 55 – 59 years old,

corresponding to 5.6 with 95% CI of [3.76; 8.06], followed by 60 – 64 and 70 – 74 years old with an incidence rate of 5.5, all of them statistically significative. However, women's highest incidence rate is 16.4 [95%CI 13.53; 19.64] is around 35 – 39 years old. With these results, we can say that TC in women population are diagnosed much earlier than in men.

	MEN			WOMEN		
Age	**Incidence rate**	**Lower CI**	**Upper CI**	**Incidence rate**	**Lower CI**	**Upper CI**
0-4	0	0	0,76	0	0	0,8
5-9	0,6	0,13	1,81	0	0	0,81
10-14	0,4	0,05	1,51	0,66	0,14	1,95
15-19	0,4	0,05	1,42	2,55	1,31	4,45
20-24	0,8	0,28	2,03	4,61	2,99	6,81
25-29	0,6	0,17	1,56	9,30	7,06	12,01
30-34	2,9	1,79	4,43	12,90	10,33	15,87
35-39	3,1	2,03	4,71	16,40	13,53	19,64
40-44	4,1	2,75	5,81	15,80	12,93	19,04
45-49	5	3,5	7,06	16,10	13,15	19,58
50-54	4,8	3,25	6,97	13,50	10,63	16,83
55-59	5,6	3,76	8,06	15,20	11,97	18,96
60-64	5,5	3,53	8,07	14,00	10,8	17,84
65-69	4,7	2,82	7,32	12,35	9,25	16,16
70-74	5,5	3,31	8,59	11,80	8,64	15,75
75-79	4,9	2,6	8,37	8,00	5,28	11,66
80-84	1,6	0,34	4,82	5,90	3,35	9,53
85+	1,6	0,44	4,14	2,00	0,97	3,74

Table 13. Age-specific incidence rate by sex for 18 groups of age range (every 5 years age gap) with its 95% confidence interval.

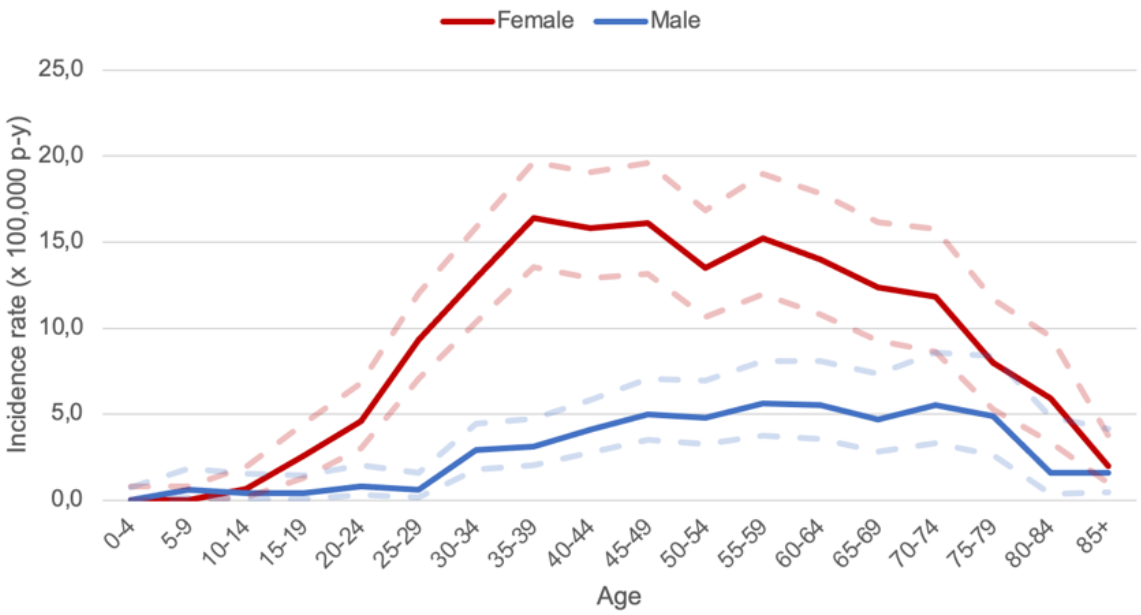


Figure 9. Line graph of age-specific incidence rate per 100,000 person-year by sex with its rang of 95% CI. A significant and evidence peak in women 35 – 50 years old.

AGE-STANDARDIZED RATE (ASR) AND ANNUAL PERCENTAGE CHANGE (APC)

ASR was calculated using the European standard population as a reference, it provides a more accurate comparison of TC burden between different populations, as it eliminates the confounding effect of differences in age structures. Global ASR is 6.42, that represents 3.06 per 100 000 men and 9.78 per 100 000 women. The most common histological type of thyroid cancer, which is the papillary has a ASR of 5.12, and stage I of diagnosis corresponds to ASR of 4.61, all these values are statistically significative.

APC used to quantify the average rate of change in a particular variable over a specified time period, typically expressed as a percentage. We couldn't calculate the APC for each variable because we didn't have enough n (cases), not strong statistical power. Global APC is +2.23% [95% CI: 1.67; 2.78], for women is APC: +2.41% [95% CI: 1.52; 3.3], papillary type has an APC of +2.31% [95% CI: 1.71; 2.91] and for stage I of diagnosis APC is +2.44% [95% CI: 1.33; 3.57]. Our APC value for men (2.23%), follicular type (2.83%) and stage IV (0.33%) are not statistically significative.

	ASR	95% CI	APC	95% CI	p value
GLOBAL	6.42	(6.05; 6.81)	2.23	(1.67; 2.78)	< 0.01
Sex					
Men	3.06	(2.70; 3.45)	2.23	(- 0.02; 3.22)	0.05
Women	9.78	(9.14; 10.46)	2.41	(1.52; 3.3)	< 0.01
Histology type					
Papillary	5.12	(4.79; 5.46)	2.31	(1.71; 2.91)	< 0.01
Follicular	0.66	(0.54; 0.79)	2.83 [3]	(- 0.5; 6.16)	0.1
Medullary	0.32	(0.24; 0.42)	-	-	
Anaplastic	0.15	(0.09; 0.22)	-	-	
Neoplasm SAI	0.13	(0.08; 0.20)	-	-	
Others	0.04	(0.02; 0.08)	-	-	
Stage [1]					
I	4.61	(4.26; 4.98)	2.44	(1.31; 3.57)	< 0.01
II	0.55	(0.43; 0.70)	- [2]	-	
III	0.57	(0.45; 0.72)	-	-	
IV	0.71	(0.56; 0.87)	0.33	(- 2.89; 3.54)	0.84
Not enough information	0.04	(0.01; 0.10)	-	-	

[1] The ASR for stage diagnosis used the Girona cancer registry data between the years 2002 and 2020 due to not having enough n (cases).

[2] There's no enough statistical power to calculate all the APC for each histological type and all 4 stages of diagnosis.

[3] APC for follicular TC type was calculated for the period between 1994 and 2020.

Table 14. Trends in Thyroid cancer incidence by sex, histology type and stage. Girona, 1994 - 2020. Age-standardized rates (ASR), Annual Percentage Change (APC) and confidence interval (CI).

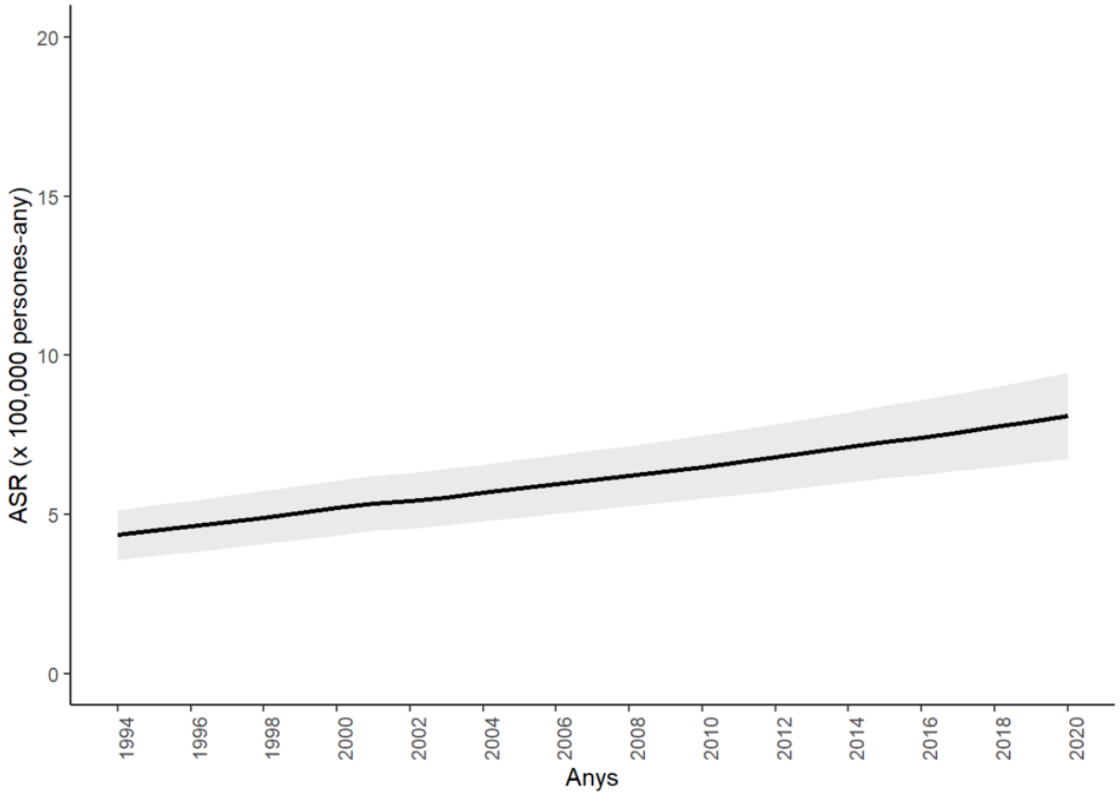


Figure 10. Age standardized rate (ASR) in thyroid cancer incidence. Girona, 1994 – 2020.

10. DISCUSSION

We provide here the first global assessment and comparison of thyroid cancer incidence trends and its major histological subtypes using data from high-quality Girona population-based cancer registry (GCR). In the study period 1994 – 2020, rapid increases were observed in general for TC, mainly due to papillary histologic type whereas no consistently clear changes were noted for other histological subtypes.

Our analyses show that in both sexes the most common histological types among the period 1994 – 2020 were papillary (80.4%) and follicular (10.1%). The incidence has increased during the study period mainly due to papillary carcinoma, which raised annually around 2.31% in both men and women, being statistically significant.

Our analysis uses stage at disease diagnosis to quantify the increase proportion of PTC incidence in Girona by age and sex. After revising a total of 1,149 cases of TC, the mean age was 48.72 years ± 15.91. Among the cases, 76.8% were female (mean age 47.9 years ± 15.8), and 23.2% were male (mean age 51.3 years ±15.9).

Our global Age Standardized Incidence Rate (ASR) is 6.42 per 100 000 person-year, comprising 3.06 per 100 000 men-year and 9.78 per 100 000 women-year. Furthermore, we observed that trends in incidence significantly increased over the period 1994 – 2020 in Girona with a global APC: +2.23%, specially in women APC: +2.41% [95% CI: 1.52; 3.3], for PTC APC: +2.31% [95% CI: 1.71; 2.91] and 77.7% diagnosed in stage I APC: +2.44% [95% CI: 1.33; 3.57].

Now, having a global look and comparing to other countries, from 1990 to 2013, the global age-standardized incidence rate of thyroid cancer increased by 20% (38). High-income countries have the highest rates of TC overall, they are defined by the World Bank, and they include most of the countries of Western Europe, Australia, South Korea, Japan, Chile, the USA and Canada.

Data from North America. In the United States, this cancer has nearly tripled since 1975, while its mortality has remained stable (39,40). An USA review showed a significantly increase APC +6.26% of PTC, followed by follicular and medullary thyroid cancer APC of 1.57% and 1.87%, respectively, between 1993 and 2012 (41). In California, USA, women have seen the highest increase in incidence, with 22.2 new cases per 100 000 people diagnosed in USA in 2014. Another study from USA using

data form the Surveillance, Epidemiology, and End Results-9 (SEER-9) cancer registry program with TC diagnosed from 1974 – 2013, among 77,276 patients (mean age at diagnosis, 48 ± 16 years). TC incidence increased, on average, 3.6% per year (95%CI 3.2 – 3.9%), primarily driven by increases in PTC with APC: +4.4% (95%CI 4.0 – 4.7%) (42).

In Canada, the incidence of TC in women ranged from 4.3 cases per 100 000 women in Yukon (a rural area) to 39.2 cases per 100 000 women in Ontario (an urban area).

Data from Europe. A study of 8 French cancer registries found a tend fold increase in TC with age-standardized incidence ranged from 0.33 to 1.01. Moreover, the French region of Tarn experienced the highest incidence of PTC, with an ASR ratio of 1.42 (38). In an analysis of Danish Cancer Registry, the ASR of TC increased from 0.41 to 1.57 cases per 100 000 men and from 0.90 to 4.11 cases per 100 000 women between 1943 and 2008. Over the period of the study, women were diagnosed with TC 2.4 times more than men, and was driven mostly by PTC.

A cancer registry from Venezia, Italy during 2002 – 2013, 1701 TC cases were reported, with papillary TC (78.2%) as the most frequent histologic type. ASR increased from 12.4 to 16.5 in women and from 4.3 to 6.2 in men (+33.1% and +44.2%, respectively) (43).

A similar study in South Spain, **Granada** during 1985 – 2013 period, there were 1265 diagnosed cases of TC (72.6% in women). Incidence trends significantly increased in both men (APC: +5.4%) and women (APC: +4.7%). The most common histological types in both sexes were papillary (74.8%) and follicular (16.8%). PTC during the study period had increased annually around 6% in both sexes (28).

Another Spanish study done in North Spain, **Navarre** the global incidence of TC has increased over these 25 years, with a rise in the adjusted rate in males from 2.24 (1986 – 1990) to 5.85 (2006 – 2010) per 100,000 inhabitants per year ($p < 0.001$), and in female from 9.05 to 14.04, respectively ($p < 0.001$) (44).

In April 1986, the Chernobyl nuclear reactor explosion released radioactive materials into the atmosphere, which spread into Belarus, Ukraine and the western parts of Russia and Poland. A study of Belarusian national cancer registry between 1970 and 2001 found the ASR incidence increased from 0.4 to 3.5 cases per 100,000 men and 0.8 to 16.2 cases per 100 000 women. Moreover, the highest incidence in TC was observed among those who were aged 0 – 14 years and living in areas of higher exposure to radiation from the 1986 Chernobyl disaster (38).

Data from Australia. In Australia, between 1982 and 1997, the yearly overall incidence of TC rose by 6.7% for women and 4.4% for men, this trend was primarily driven by PTC. Moreover, Tasmania, an area with a history of iodine deficiency and radioactive iodine exposure due to nuclear weapon testing in the 1950s, experienced a higher incidence of PTC than any other Australian state.

Data from Asia. Korea analyses between 1999 and 2010 demonstrated an annual increase of 3.3% for all cancers and 24.4% for TC alone. In 2010, the ASR in South Korea was 52.7 cases per 100,000 men and 87.4 cases per 100,000 women due to the implementation of a national screening program in 1999. This has resulted in a 15-fold increase in TC incidence in an 8-year period with no change in mortality (45).

In Japan, cancer registries estimated the cancer incidence in 2009, the age-standardized overall TC incidence rate was 4.2 cases per 100,000 men and 11.2 cases per 100,000 women (46). In 2011, after the great east Japan earthquake and tsunami, radioactive elements were released by the meltdown of three reactors at the Fukushima Daiichi nuclear power plant. In response to this incident, they initiated multiple rounds of TC screening by US. Compared with the national mean annual incidence rate, a 30-fold higher TC incidence rate was found among populations exposed to radiation by the Fukushima plant.

Data from upper middle-income countries. In Shanghai, China, thyroid cancer incidence tripled between 1983 and 2007. Furthermore, among Shanghai women, TC incidence increased from 2.6 to 11.6 per 100,000 women between 1983 and 2007.

Data from lower middle-income countries. In Morocco, a regional cancer registry based in Rabat identified between 2006 and 2008 2,473 new cancer cases. Among women, TC constituted 3.4% of all malignances, with an ASR of 3.9 cases per 100,000 women. However in men was only 0.8% of all malignances, with an ASR of 0.9 cases per 100,000 men.

In South India from 2012 to 2014 included 15,649 incident cases of all cancers. But in India we observed large differences even within the same country, from 1.3 cases per 100 000 women in Pune and Tripura (both rural areas) to 15.6 cases per 100,000 in Thiruvananthapuram (an urban area).

In Nigeria, a retrospective study from 2000 to 2014 identified 61 cases of TC. Most cases (83.6%) were in women, the mean patient age was 45.9 years and PTC was the most common histologic type.

In Pakistan, a 5-year retrospective study between 2000 to 2005 identified 153 cases of TC in the general population, again affecting mostly women (82.4%) with papillary histology being the most common (90.2%).

	Spain			Europe				North America		Oceania	Asia			
	Girona	Granada	Navarre	France	Denmark	Venezia	Belarus	USA	Canada	Australia	S Korea	Japan	China	India
APC (%)	2.23	5.4 ♂						4.4		4.4 ♂				
	2.41 ♀	4.7 ♀								6.7 ♀				
ASR	3.06 ♂		5.85 ♂	1.01	1.57 ♂	6.2 ♂	3.5 ♂		4.3 ♀ (rural)		52.7 ♂	4.2 ♂		1.3 ♀ (rural)
(10^5-y)	9.78 ♀		14.04 ♀		4.11 ♀	16.5 ♀	16.2 ♀		39.2 ♀ (urban)		87.4 ♀	11.2 ♀	11.6 ♀	15.6 ♀ (urban)

Table 15. APC and ASR from different countries

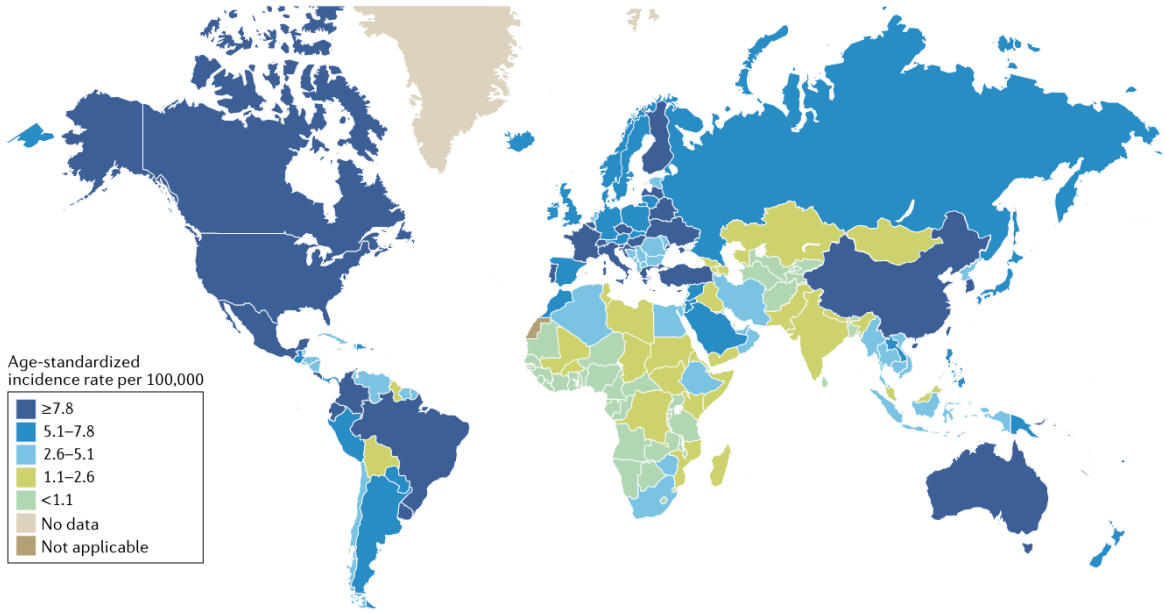


Figure 11. Global estimated age-standardized incidence rates of thyroid cancer in 2018. TC incidence is higher in high-income countries compared with low-income and middle-income countries. Global variability in the incidence of thyroid cancer has been attributed to multiple causes such as differences in diagnostic practices, health-care systems, environmental exposures and individual risk factors (38).

Overdiagnosis, clinically speaking, refers to the diagnosis of a condition that otherwise would not have caused symptoms or death. It is an inevitable consequence of screening and diagnostic testing, and can result from increased sensitivity of diagnostic tests or excessively widened disease definitions (47). Harms from overdiagnosis occur because of unnecessary diagnostic tests, follow-up from which the patient does not receive any benefit and it leads to overtreatment.

An ideal cancer screening test not only identifies early-stage preclinical diseases but also reduces the occurrence of advanced and metastatic cancers, leading to a decline in cancer-related deaths. If a screening test merely detects non-progressing or slowly progressing lesions that would not cause symptoms during a person's natural lifespan, it may result in ''overdiagnosis'', uncovering conditions that may not have a significant impact on health (48).

The increased incidence observed for thyroid cancer over the past three decades is likely due to both the overdiagnosis of incidental carcinomas and maybe some real etiologic factors. This analysis suggests considerable overdiagnosis of papillary thyroid cancer among population in our region.

On the basis of the assumption that none of the increase in TC incidence is ''real'' (solely attributed to early detection rather than actual environmental risk factors), should theoretically lead to a reduction in thyroid cancer-related mortality. However, our study, covering 193 deaths from 1994 to 2020 in Girona, couldn't analyze the specific causes of mortality. Consequently, we are unable to ascertain the true mortality attributed to TC, hindering the assessment of whether increasing incidence trend is primarily explained by overdiagnosis.

Thyroid cancers were histologically found by palpation, frequently in patients already presenting with compression symptoms or visible neck masses. Since the 1980's, the advent of the neck ultrasonography and of US-FNB, together with portable ultrasound machines, and along with increased use of diagnostic imaging modalities, such as CT, MRI and PET, enabled the diagnosis of previously undetectable millimetric nodules (27). These techniques have led to the detection of a number of indolent thyroid lesions, even as thyroid-cancer-related mortality rates have not changed substantially.

The enormous increase in thyroid cancer incidence in South Korea (1993 – 2011) subsequent to opportunistic ultrasonography-based screening sends a strong warning about data interpretation in the context of large-scale screening of the thyroid gland (49).

Intensified surveillance and scrutiny of the thyroid gland has led to an increased detection of small, early stage tumors that wouldn't cause any difference in the patient's life (39). Even though, we can't exclude the possibility that this findings might be the result of a true increase of the disease due to the enhanced exposure to selected risk factors, such as: iodine deficiency, ionizing radiation exposure for medical reasons, that has increased in areas with a broad access to health care, due to the increase of medical imaging procedures (50). Radiation exposure, particularly during childhood, because it's when the thyroid gland is more sensitive to develop mutations that leads to thyroid cancer after 20 years of latency time. And the existence of more survivals from pediatric cancers that have gone through intense radiotherapy in early ages. The exposure to certain endocrine-disrupting chemicals, including some pesticides, flame retardants and food packaging materials, was associated to thyroid hormone axis disorders. Lifestyle and nutritional transition (from a traditional diet to a Western-style nutrition rich in saturated fats and added sugars) could have also partly contributed to comparatively high incidence (51). However, it seems difficult to conceive any modern lifestyle or environmental risk factor that may have abruptly affected TC incidence (52). Detection biases might have partly influenced this association, as a more intense diagnostic scrutiny could occur among patients with underlying obesity-related chronic conditions or diabetes. Hormone-related events in women's lifetime (eg, contraception and pregnancy) seem to have a weak to negligible role in thyroid carcinogenesis, while they contribute to expose women to more intensive medical surveillance (27). Our observations also reveal that overdiagnosis of papillary thyroid cancer is occurring primarily in women (3 times greater than in men), one possible explanation could be that women are diagnosed with more thyroid nodules, possible due to some association with their hormones (53).

Although the role of many of the above mentioned risk factors has not been clearly established, their exposure might be associated with this increased incidence. Besides, a higher level of health care access, both sociodemographic and age related factors, correlate with increased incidence rates of PTC. Population with broader healthcare accessibility and more private medicine tend to exhibit higher diagnosis of PTC. Interestingly, the association between healthcare access and overdiagnosis has been observed in other cancers, including prostate and breast cancer (28). It seems that the organization of the health systems and the penetration of new diagnostic and screening practices are key elements that nowadays differ substantially even across the most developed countries (52).

One of the best established risk factors for thyroid carcinoma is exposure to ionizing radiation, especially in childhood for PTC (28,54). There is strong evidence that thyroid cancer increased in children because of Chernobyl accident (55). Regarding this, there is some evidence that ionizing radiation exposure has increased in the last decades, making the exposure of more population to this risk factor more plausible (56,57).

So, the fact that the rising incidence is almost exclusively due to an increased detection of early stage papillary thyroid cancer; the known existence of a large reservoir of subclinical tumors in the thyroid gland, as described in autopsy studies (58,59); and the gradual change of the age-specific curves of incidence, which now peaks at around the age of 40 or 50 years, instead of increasing with age, similar to the period before the introduction of modern diagnostic techniques and intense surveillance. All these epidemiological characteristics are strongly suggestive of a large effect of overdiagnosis. Therefore, these evidence have led to consider that screening should be discouraged in asymptomatic individuals (33).

Currently the standard treatment for thyroid cancer is complete surgical removal of the thyroid gland. It's important to bear in mind that the vast majority of patients who received a high diagnosis of thyroid cancer in the countries we studied underwent total thyroidectomy, and ahigh proportion also received other harmful treatments (neck lymph-node dissection) – practices recently discouraged in the guidelines of the ATA. Furthermore, studies from Japan have shown that immediate surgery and watchful waiting are equally effective in averting deaths from thyroid cancers < 1 cm (30,60). Overdiagnosis of cancer ultimately leads to over-treatment in patients, which is costly and potentially harmful. While thyroidectomy is generally considered a relatively safe procedure it is not without its own risks and requires compulsory lifetime thyroid hormone replacement therapy (34).

Further studies into the prevention, risk stratification and optimal treatment of papillary thyroid cancer are warranted in response to these trends. Thus, it seems advisable to find less harmful alternatives to thyroidectomy, which requires lifelong medication, for treating and preventing low risk thyroid cancer (61).

The issue of thyroid cancer overdiagnosis *versus* true etiological factors leading to increases in thyroid cancer incidence is a complex issue an the exact contributions of these factors cannot be

easily disentangled. Accurately estimating the magnitude of overdiagnosis in thyroid cancer or any cancer, requires data form large randomized screening trials.

Given the significant proportion of thyroid cancer potentially attributable to overdiagnosis, it is crucial for clinicians to contemplate an alternative paradigm to the one size fits all treatment of thyroidectomy.

No professional medical society recommends population based screening for thyroid cancer. South Korea appears to be the only country that regularly practices screening for asymptomatic TC using US, suggesting overdetection (26,29,58).

But what are the benefits of treating all overdiagnosed cases? Does treatment of screen-detected TC reduce thyroid-specific mortality or morbidity, reduce all-cause mortality, and/or improve quality of life? It is uncertain if earlier or immediate treatment vs delayed or no surgical treatment improves patient outcomes for papillary carcinoma. One Japanese trial observational study showed that after 4 years of follow-up, no patients in either group developed distant metastases or died from TC (62). In other published studies, there are potential confounders between treated patients and patients receiving delayed treatment, which limits the ability to compare the effect of treatment on patient outcomes.

Therefore, we should put in a balance whether it is worth to treat all cases of thyroid cancers, considering the downside of the surgery, in preventing the low percentage of mortality associated with this disease, or allowing the scape of those few patients who could have been saved by earlier detection because their tumors are inherently more aggressive (such as medullary, anaplastic, or poorly differentiated carcinoma). From a cost-benefit perspective, it is clear that it is not sustainable at the public system level. However, even if it pertains to a small percentage of these high-risk patients, they would benefit, and there would be no deaths from TC. Indeed, perhaps a better definition and more evidence are needed when classifying patients to better tailor their management and avoid long-term harm.

CHANGES IN CLINICAL RECOMMENDATIONS

The last ATA practice guidelines from 2015 (63) differ significantly from the previous version in 2009, seeming now to acknowledge the problem of overdiagnosis and overtreatment of a disease that is typically indolent, where treatment-related morbidity might not be justified by a survival benefit. For the first time, the guidelines discuss active surveillance management as a safe and effective alternative to immediate surgical resection in properly selected patients with small PTC < 1cm. In patients for whom surgery is indicated, the guidelines support consideration of ipsilateral thyroid lobectomy as an alternative to total thyroidectomy for low-risk DTCs. Certainly, this only pertains to the theoretical aspect, but in actual clinical practice, it is possible to consider as an option for very specific patient cases. Regarding radioactive iodine ablation, the guidelines advocate less frequent use and, if indicate, use of lower doses. Molecular testing was discussed as an adjunct to US-FNAB to potentially better triage the risk of malignancy in the setting of cytologically indeterminate thyroid nodules. The ATA clinical practice guidelines also address future research needs to further improve risk stratification for treatment decisions and clinical management (41). For instance, current AJCC/UICC TNM staging classifies young patients with PTC (that is, those aged < 55 years) with cervical lymph node metastases as having stage I PTC, with no recognition that nodal metastases seem to be associated with reduced survival. In our study, we exclusively analyzed patients based on their stage (risk group according to ATA at the year of diagnosis) and not by the TNM classification of the tumor. Thus, within stage I, all individuals < 55 years old are included (as per ATA 2015 guidelines, while in previous version, the age cutoff was 45 years), constituting a wide group encompassing all TN M0 stage and histological types..

The new version of the ATA guideline is expected to be released very soon, reflecting all the innovations related to the increase in incidence trend observed worldwide in recent years.

11. CONCLUSIONS

In summary, our study offers an extensive and up-to-date analysis of incidence data of thyroid cancer in Girona (Spain) obtained from a high-quality cancer registration system from 1994 to 2020.

This study examined incidence patterns and trends of major thyroid cancer histological types, revealing distinct epidemiological patterns for papillary, follicular, anaplastic, medullary thyroid cancer and other subtypes. Although the increases in the incidence of papillary thyroid cancer (APC: +2.31% [95%CI: 1.71-2.91]), the subtype most likely to be found in a subclinical form (stage I) and therefore detected by intense scrutiny of the thyroid gland, are consistent in all other's countries literature and international reviews.

Additionally, the disproportionate impact is evident in women, with an absolute increase almost 3 times greater than in men (76.8% in female and 23.2% in male).

In the vast majority of TC patients total thyroidectomy is performed and even it's a safe surgery in most cases, it's also associated with postoperative complications, such as permanent hypoparathyroidism and vocal cord paralysis, and implies lifelong thyroid replacement therapy and monitoring (52). Different ways to address the problem of overdiagnosis and overtreatment of low-risk TC can be conceived of as a possibility. They include: (1) avoidance of TC screening activities; (2) establishment of randomized clinical trials or observational cohorts of watchful-waiting approaches.

Thyroid cancer poses a growing global health concern due to heightened diagnostic practices, such as imaging and biopsies, leading to increased detection of latent, predominantly small tumors. Girona's data reveals a rise in stage I PTCs, especially significant in women. A comprehensive clinical and public health approach is crucial to mitigate thyroid cancer incidence and minimize patient risks. Recent ATA guidelines advocate a more conservative evaluation of thyroid nodules and judicious use of treatment. Monitoring population-level trends is vital to assess the impact of these guidelines. Emphasizing large-scale epidemiological and laboratory studies is key to identifying modifiable risk factors and targets for thyroid cancer prevention. Factors with the highest attributable risks would make the best candidates to target in future TC prevention efforts (41).

12. ETHICAL AND LEGAL CONSIDERATIONS

PRIVACY AND CONFIDENTIALITY

Patient confidentiality and privacy are guaranteed in accordance with *Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los. Derechos Digitales* (64) and *Regulation (EU) 2016/679 of the European Parliament and of the Council of 27April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data* (65). Any personal and clinical information pertaining to patients gathered in this study will remain anonymous and confidential, as they will be identified through a randomized code in the database. Furthermore, the collected data will be accessible exclusively to the research team and will be used only for the purpose of the research.

ETHICS STATEMENTS

This project does not contain any studies with human participants or animals performed by any of the authors. This study is based on secondary administrative data.

The participating cancer registry adheres to data management policies designed to safeguard patient confidentiality, with ethical approval obtained from local regulatory bodies. The study was conducted in accordance with the guidelines of the Declaration of Helsinki (66) and underwent review by the institutional review board at Hospital Universitari Dr. Josep Trueta de Girona. It did not require informed consent in alignment with the legal framework, laws 14/1986 and 33/2011 pertaining to Spanish general and public health, as well as law 8/2011 of June 14, regarding the 2001 – 2004 Statistical Plan for Catalonia, which recognizes the GCR as a statistical database.

This study respects obeys the **Principles of Biomedical Ethics from Beauchamp and Childress**, more commonly known as the four fundamental ethical principles:

- **Autonomy**: patient will be properly informed and the decision whether or not to participate in the study will be respected as it indicates *Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica* (67).

- **Beneficence**: epidemiological studies aim to investigate the distribution and determinants of health-related states or events in specific population in order to maximize benefits and minimize harm to individuals and communities.
- **Non-maleficence**: researchers will prioritize the safety and well-being of participants, they will be all anonymized to preserve their privacy.
- **Justice**: all the patients living in Girona province will have equal opportunity to participate in the study and equal accessibility.

COMITÈ D'ÈTICA D'INVESTIGACIÓ CLÍNICA (CEIC)

The present Project was submitted to the CEIC from HUJT and all the other centers involved, and posteriorly to the CEICs approval before starting it. The monitoring system to be carried out during the course of the research will be in accordance with the **Biomedical Research act 14/2007, dated July 3rd** (68). We obtained the CEIC approval on August 2022 (Annex V).

TRANSPARENCY

The investigators of this study declare that there are no conflicts of interest, and they commit to publish all data and results with complete transparency, including unfavorable data or events. The main goal of this research is to contribute to national thyroid cancer epidemiology data in order to improve human health and quality of life. Investigators agree to publish all data and results with total transparency including different statistical data that diverges from the findings in the literature already published.

13. LIMITATIONS AND STRENGTHS

LIMITATIONS

This study is subject to certain limitations, such as its retrospective design and reliance on regional data. Access to early data could not always be granted, slightly raveling the reliability of early data.

Changes in histological classification guidelines, together with difficulties in disease ascertaining and in certifying the causes of death, might have affected the accuracy of incidence and mortality. We can't assure that our mortality rate in our analyses (N = 193) are due to TC. Reporting might have biased the incidence and mortality estimates, possibly resulting in an underestimation of incidence rates in the times when patient's clinical history is not computerized yet, and in that times medical records could be delayed, incomplete or inaccurate.

A limitation of this study was the absence of data by tumor size and the degree of surveillance after treatment of thyroid cancer, as these data are not collected routinely in cancer registries. The availability of this information would have improved the understanding of the effect of overdiagnosis and whether other factors might have partly contributed to the increase of thyroid cancer incidence trends.
Other limitations of this study include the fact that we were not able to present data for the rarest variants of thyroid cancer (eg, mixt medullary-papillary cancer) according to sex and age.

In addition, this is a Girona cancer registry, from the northeast region of Spain, that might not be completely representative of the entire country. Although variations in registry practices in collecting information on cases depending on the professional criteria and on the year of diagnosis might create bias in international comparisons, all registries included have been assessed to ensure the registry meets the high standards.

Stages are classified according to the edition in the year the patient was diagnoses of thyroid cancer, and over the years, different editions have undergone changes. It is important to consider that this could introduce a bias in the classification and limit the comparability between patient groups. Additionally, our study does not take into account the TNM classification of diagnosed TC cases; instead, we only considered the risk stages, which include a broad group of patients without

considering the tumor size (an important prognostic factor). Essentially, in stage I, there are included all young individuals (cut-off age of 55 years old in the latest edition) with TN M0, regardless of the tumor size and the presence of lymph nodes, without distant metastasis. This could result in underestimating a little the survival of PTC, as there are histologies inherently associated with worse prognosis, such as medullary, anaplastic, and poorly differentiated carcinomas, even they are diagnosed in early stages. Another recent update is the new WHO 2022 TC classification where a subgroup that was previously categorized within differentiated carcinomas is now considered an independent group: differentiated high-grade thyroid carcinoma (DHGTC), which, due to their histological characteristics, are deemed to have a worse prognosis. Unfortunately, in our results, we couldn't reevaluate all cases to reclassify and include them in the database as a separate group.

STRENGTHS

This study is designed including multiple centers throughout the autonomous community of Catalonia. We include all Girona population, we could even have access to private medical clinics and consequently, all cases of TC are included and evaluated in the study. This fact implies that if the study results are significant, they could be more easily generalized.

The most notable aspect is that this is a population-based study, a sample was not used. Therefore, there is no possibility of introducing population bias or selection bias. The use of real data from clinical medical record, the big sample size (N = 1149) and the long follow-up period provided further reliability to the results.

As a long term prospective study design, we have the possibility of extending the patient recruitment period and update Girona's epidemiological data.

By recruiting patients in centers of the same autonomous community, and Hospital Josep Trueta is the provincial reference hospital (where most the patients come from) in the public healthcare system for treating this disease; the treatment regimens are standardized, thus, it is easier to compare the cases within the study, eliminating confounding factors in between.

14. CLINICAL AND HEALTHCARE IMPACT

Studying the increasing incidence trend in thyroid cancer has the potential to improve early detection, treatment approaches, resource allocation, public health interventions, and overall patient outcomes. It also provides valuable insights for researchers, healthcare professionals, and policymakers to address the challenges associated with the rising prevalence of TC. Healthcare systems can allocate resources more efficiently by anticipating the rise in TC cases and a better alternative treatment than surgery, individualizing better the management for every patient. Studying the incidence trend can guide public health initiatives to address risk factors or causes associated with the increase and raise awareness about preventive measures and early detection, like avoid unnecessary radiations, and if it is necessary protect the thyroid gland, have a closer surveillance to pediatric cancer survivors… Addressing long-term consequences and quality-of-life issues in managing the increasing number of patients diagnosed of TC.

To systematically review the benefits and harms associated with thyroid cancer screening and treatment of early TC in asymptomatic adults to inform the Spain Preventive Services Task Force.

15. WORK PLAN AND CHRONOGRAM

The sequence of activities at individual level or for the entire research team is described below following the scheme: Activity – Description – Date.

Pathologists and clinical physicians such as endocrinologists, oncologists, radiologists, general surgeons subspecialized in thyroidectomies, hired by the National Health System and the Institut Català de Salut (ICS), will compound the medical team in this study. And our team of statistics played an important role to analyze the database GCR.

Preparation (PHASE 0)

Activity 1. Meetings with the Final Degree Project (FDP) mentor Dr. Josefina Biarnés Costa to decide about the topic of the FDP (June – September 2023)

Activity 2. CEIC approbation (Annex III). The protocol was delivered to CEIC ethical committee and sent to the director and head services of each hospitals in order to have their approval (finally approved on August 2022)

Activity 3. Meeting with the director of Girona Cancer Registry (GCR) Rafael Marcos Gragera to design the study (October -November 2023)

Activity 4. Formation about biostatistics concepts (December 2023)

Data collect (PHASE 1)

Activity 5. Identification and anonymization of cases. In the database of GCR for our study analyses (August 2022 – June 2023).

Activity 6. Debugging of the database to allow us to calculate the incidence and demographic characteristics of the study population (June – July 2023).

Analyses and final evolution (PHASE 2)

Activity 7. Incidence analyses (April – October 2023)

Activity 8. Demographic characteristics of incidence TC by age, sex and histological type (December 2023)

Activity 9. Age-standardized rate (ASR) and Annual Percentage Change (APC) (January 2024)

Activity 10. FDP writing (September 2023 – February 2024)

Activity 11. Results, discussion and conclusions (February 2024).

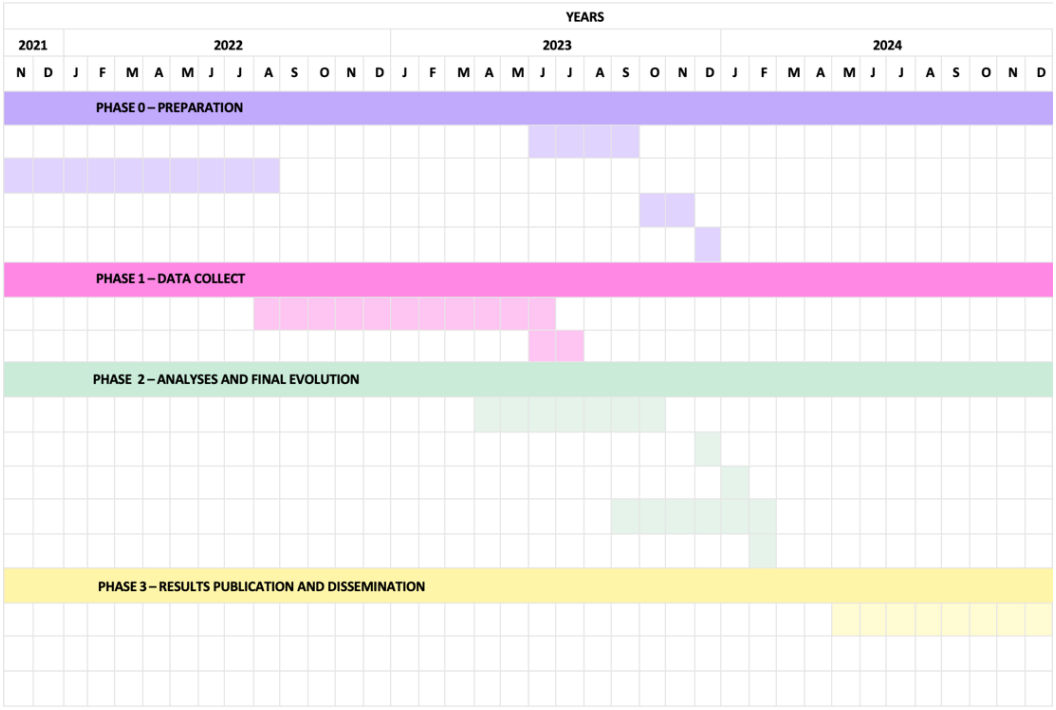
Results publication and dissemination

Activity 12. Article writing (from May 2024)

Activity 13. Revision and publication of medical paper

Activity 14. Dissemination

ACTIVITY	Plan duration	PROGRESS
Preparation (PHASE 0)		
Meetings to define FDP	June - Sept 2023	100%
CEIC approbation	10 months	100%
Meetings at GCR	Oct - Nov 2023	100%
Statistiscs formation	December 2023	100%
Data collect (PHASE 1)		
Data collection	Aug 22 - June 2023	100%
Debugging database	June - July 2023	100%
Analyses and final evolution (PHASE 2)		
Statistical analysis	Apr - Oct 2023	100%
Incidence trend	December 2023	100%
ASR and APC	January 2024	100%
FDP writing	Sept 23 - Feb 2024	100%
Results & Discussion	February 2024	100%
Results publication and dissemination (PHASE 3)		
Article writing	from May 2024	25%
Revision & publication		0%
Dissemination		0%



RESOURCES

All the interventions that this study analyzes are already included in the normal clinical practice of a TC diagnosis, follow-up and treatment, so no extra material or health professionals will be required. The salaries of these professionals are already provided by the National Health System, except for the statistician's and the research manager's salaries.

16. BUDGET

The budget of our final degree project has been **0** €.

This is because the database we used for the study was already done and it had all the essential analyses results. Computers and programmes used to realize the present study are used in daily practice.

The following budget is part of an alternative project if we build all the database and registering all the exposure to different risk factors at each patient by reviewing patient's health record.

BUDGET	
	COSTS
Staff	
- Research team	0€ included in National Healthcare System
- Statistician	40€/h x 200 h = 8000€
- Researcher manager	50€/h x 60h x 15 months = 45000€
- Meetings and formation: 500€ x 3 members	1500€
- Prints	20€
	Subtotal:1520€
Data collection and statistical analysis	
- Reviewing patients' medical record: 1149 patients	1149 x 20€/each patient's health record = 22,980€
- Statistical team: 20€/h	20€/h x 10h for this FDP = 200€
	Subtotal: 23,180€
Travel and subsistence costs	
- National congress	1500€
- International congress	3000€
	Subtotal: 4500€
Publication	
- Paper revision, english edition	500€
- Paper publication (*Cancer epidemiology*)	3000€
	Subtotal: 3500€
TOTAL: **32,700**€	

Table 16. Budget for our FDP

The medical research team, comprised of National Health System staff, incurs no additional salary expenses. Despite being a multicenter study, all hospital coordinators and research teams operate

within the National Health System, aligning with national budget allocations. The research team, responsible for bibliographic research, data collection and publication activities, ensures that these tasks do not result in any supplementary personnel costs.

The initial personnel-related expenditure arises from the engagement of a statistician for the statistical analysis. With an anticipated cost of €40 per hour and an estimated 200 hours of statistical work, an expenditure of approximately €8,000 is anticipated.

The subsequent personnel cost pertains to an external researcher manager assigned during the recruitment phase. This manager will oversee information and procedural reviews biweekly across all participating hospitals throughout the 15-month recruitment period. Additionally, the external manager will deliver two training sessions, as detailed in the following paragraph. With an estimated commitment of 60 hours per month at a rate of €50 per hour, the 15-month duration requires a budget of approximately €45,000.

MATERIALS AND FORMATION

As it is an observational study, the materials, procedures, and reports are aligned with routine clinical practices, do not require any extra procedure. Therefore, these services are covered by the respective budgets of the hospital centers.

To ensure uniformity in the execution of data collection, each participating center will undergo two training sessions. The initial session, applicable to both Endocrinology and Oncology services, will delineate criteria for patient enrollment into the study and the requisite documentation procedures. The subsequent session will elucidate and standardize information gathering processes, conducted within the relevant centers and services.

REVISION AND PUBLICATION

The writing of the study and its publication sheet will be subjected to a grammatical revision in English by an external service. It is estimated that this process has a final cost of €500. The study publication fee is estimated to be around €3000.

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ANNEX I. TI-RADS

European (EU)-TI-RADS is a classification system that uses ultrasound imaging for classification of thyroid nodule malignancy risk stratification. It consists of five categories, each which is scored in correspondence to features from the US examination:

EU-TI-RADS 1 refers to a US examination where no thyroid nodule is found, while the other 4 categories—nodules benign and with low, intermediate, and high risk—correspond in an increasing risk of malignancy (69).

EU-TI-RADS 2, with a risk of malignancy close to 0%, includes two patterns: pure/anechoic cysts and entirely spongiform nodules; these nodules should be considered as benign and FNA is not indicated.

EU-TI-RADS 3, with a risk of malignancy around 2–4%, consists of nodules with oval shape, smooth margins, isoechoic or hyperechoic features, and a lack of any high-risk features; these nodules should be submitted to FNA only if >20 mm.

EU TI-RADS 3, with a risk of malignancy around 6–17%, consists of nodules with oval shape, smooth margins, mildly hypoechoic features, and a lack of any high-risk features; the evidence of a thin halo, cystic components, comet-tail artefacts, peripheral vascularization, and low stiffness, lower the malignancy risk in this group, while the presence of discontinuous peripheral or rim macrocalcifications, a thick halo, predominantly central vascularization, and high stiffness, increase the risk of malignancy; the threshold for FNA is 15 mm.

EU TI-RADS 4 include thyroid nodules with features that raise concerns about the possibility of malignancy (suspicion moderate to high). FNA biopsy is recommended to determine whether they are benign or malign.

EU-TI-RADS 5 involves nodules presenting at least 1 of the following high-risk signs: non-oval shape, irregular margins, microcalcifications, marked hypoechogenicity; the malignancy rate is 26–87% and nodules must be submitted to FNA when >1 cm.

In addition, the authors of EU-TI-RADS noted that extrathyroidal extension with disruption of the capsular margin increases the malignancy risk of a nodule and should be described in the report. On the other hand, hyperechoic spots associated with comet-tail artefacts, along with thin halo, are suggestive of benignity and reduce the suspicion of malignancy.

ANNEX II. ATA GUIDELINE RECOMMENDATIONS OF THYROID NODULE MANAGEMENT

Sonographic pattern	*US features*	*Estimated risk of malignancy, %*	*FNA size cutoff (largest dimension)*
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule ***with*** one or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of ETE	>70–90[a]	Recommend FNA at ≥1 cm
Intermediate suspicion	Hypoechoic solid nodule with smooth margins ***without*** microcalcifications, ETE, or taller than wide shape	10–20	Recommend FNA at ≥1 cm
Low suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, ***without*** microcalcification, irregular margin or ETE, or taller than wide shape.	5–10	Recommend FNA at ≥1.5 cm
Very low suspicion	Spongiform or partially cystic nodules ***without*** any of the sonographic features described in low, intermediate, or high suspicion patterns	<3	Consider FNA at ≥2 cm Observation without FNA is also a reasonable option
Benign	Purely cystic nodules (no solid component)	<1	No biopsy[b]

Table 17. Description of the US-FNB indications according to the ultrasound characteristics of the thyroid nodule. From ATA (American Thyroid Association).

The main ultrasonographic criteria suggesting malignancy include a solid hypoechoic nodule, multiple hyperechoic foci without posterior shadow (psammoma bodies) for microcalcifications, non-round nodules that are taller than wide (with the anteroposterior diameter exceeding the transverse), and irregular margins (infiltrative or microlobulated). The presence of a hypoechoic halo indicates regular margins and well-delimited nodules. Additionally, centipede vascularization, where tumors exhibit increased vascularity in the middle of the nodule detected by ECO Doppler, distinguishes them from benign nodules, which either lack vascularization or show it only in the periphery. Other indicators of malignancy include the appearance of associated adenopathies and extra-thyroidal extension. The higher the number of these risk factors, the greater the probability of malignancy.

ANNEX III. NEW BETHESDA CLASSIFICATION 2023

The Bethesda System for Reporting Thyroid Cytopatology (TBSRTC) has publish its third edition this 2023. The atlas is updated and has expanded stablishing a simplified, 6 category-based reporting system for thyroid fine needle aspiration (FNA). Using TBSRTC can efficiently communicate thyroid FNA interpretations and avoid confusions or ambiguities. TBSRTC 2023 consider 6 categories and recommend that the names of the categories (and not just their numerical designations) should be used for reporting results, *for example: follicular neoplasm (Bethesda IV) or suspicious for malignancy (Bethesda V) - suspicious for papillary thyroid carcinoma*. Each of the categories has an implied risk of malignancy (ROM), which has been updated too (70).

I. Nondiagnostic
- Cyst fluid only
- Virtually acellular specimen
- Other (obscuring blood, clotting artifact, drying artifact, etc.)

II. Benign
- Consistent with follicular nodular disease (includes adenomatoid nodule, colloid nodule, etc.)
- Consistent with chronic lymphocytic (Hashimoto) thyroiditis in the proper clinical context
- Consistent with granulomatous (subacute) thyroiditis
- Other

III. Atypia of undetermined significance
- Specify if AUS-nuclear atypia or AUS-other

IV. Follicular neoplasm
- Specify if oncocytic (formerly Hürthle cell) type

V. Suspicious for malignancy
- Suspicious for papillary thyroid carcinoma
- Suspicious for medullary thyroid carcinoma
- Suspicious for metastatic carcinoma
- Suspicious for lymphoma
- Other

VI. Malignant
- Papillary thyroid carcinoma
- High-grade follicular-derived carcinoma
- Medullary thyroid carcinoma
- Undifferentiated (anaplastic) carcinoma
- Squamous cell carcinoma
- Carcinoma with mixed features (specify)
- Metastatic malignancy
- Non-Hodgkin lymphoma
- Other

Adapted, with permission, from Ali and VanderLaan.[7]
AUS, atypia of undetermined significance.

Table 18. The 2023 Bethesda System for reporting thyroid cytopathology: diagnostic categories

Diagnostic category	*ROM*[a] *Mean % (range)*	*Usual management*[b]
Nondiagnostic	**13** (5–20)[c]	Repeat FNA[d] with ultrasound guidance
Benign	**4** (2–7)[e]	Clinical and ultrasound follow-up
Atypia of undetermined significance[f]	**22** (13–30)	Repeat FNA,[d] molecular testing, diagnostic lobectomy, or surveillance
Follicular neoplasm[g]	**30** (23–34)	Molecular testing,[h] diagnostic lobectomy
Suspicious for malignancy	**74** (67–83)	Molecular testing,[h] lobectomy or near-total thyroidectomy[i]
Malignant	**97** (97–100)	Lobectomy or near-total thyroidectomy[i]

Table 19. Each diagnostic category with its risk or malignancy percentage (% ROM) and recommended management

I. Nondiagnostic. Every thyroid FNA should be evaluated for sample adequacy (quantity and quality of the cellular and colloid components). For an adequate sample in term of quantity TBSRTC 2023 recommend a ≥ 6 groups of well-preserved, well-visualized follicular cells, with each group comprising ≥ 10 cells. If there's any limiting factors such as abundant obscuring blood or extensive air-drying artifacts could be included into the term of ''unsatisfactory'' specimen (contains no diagnostic information).

The ROM for nondiagnostic FNA is around 13%, but this number is difficult to calculate because most such noodles are not surgically resected, so it exists the selection bias. Recommended management is a repeat aspiration with ultrasound guidance, which helps to yield diagnostic results in 70% of cases.

II. Benign. Improve the reliability in identifying benign thyroid nodules can avoid unnecessary surgical resection for most patients with nodular thyroid disease. In light of the 2022 WHO classification of thyroid tumors, is preferred to refer into the spectrum of ''follicular nodular disease'' (colloid nodule, hyperplastic nodule, adenomatous nodule or benign follicular nodule). It's associated with a very low ROM when these nodules undergo surgical resection around 4%. But as they are benign, the best overall ROM estimate is based on long-term follow-up studies which shows that is approximately 1 - 2%.

III. Atypia of undetermined significance (AUS). The cytopathologic interpretation of AUS convey a diagnosis that is not definitively benign or malignant. Is used for cases with atypia that is insufficient for ''follicular neoplasm '' nor ''suspicious for malignancy''.

Based on surgical resection data (which likely overestimate) the ROM average is 22%. TBSRTC 2023 has introduced 2 subcategories for AUS: ''nuclear'' (previously ''cytologic'') and ''other''

(includes architectural atypia, oncocytic atypia and lymphocytic atypia…). Due to its difference in their ROM, the subclassification oof AUS puts emphasis on the importance of distinguishing nuclear atypia from all other AUS morphologic patterns, which conveys a relatively lower risk.

IV. Follicular neoplasm. the 3rd edition provides more detailed description of the diagnostic clues for cytologic recognition of previously called NIFTP (noninvasive follicular thyroid neoplasm with papillary-like nuclear features). For its diagnosis is that follicular-patterned aspirates with only mild nuclear changes (like mild degree of enlargement, contour irregularity and/or chromatin clearing) and make sure that true papillae, intranuclear pseudoinclusions are absent. TBSRTC 2023 reiterates its correct diagnosis to avoid over diagnosing them as ‘‘malignant or suspicious for papillary thyroid carcinoma’’ that could unnecessarily result in aggressive management, when the recommended treatment for NIFTP is conservative surgery (lobectomy). The recommended management of follicular neoplasm is surgical excision of the nodule, most often hemithyroidectomy or lobectomy.

Differential diagnosis for this entity: benign nodules with focal oncocytic hyperplasia and other neoplasms with oncocytic features (medullary thyroid carcinoma and subtypes of papillary thyroid carcinoma).

V. Suspicious for malignancy (SFM) is used when the cytomorphologic features of a thyroid FNA are alarming for papillary thyroid carcinoma, medullary thyroid carcinoma, lymphoma or another malignant neoplasm but are quantitatively and/or qualitatively insufficient for a definitive malignant diagnosis. In such cases, deescalating the surgical management with lobectomy rather than total thyroidectomy could be a good approach.

VI. Malignant. ‘‘Malignant (Bethesda VI)’’ is used whenever it meets conclusively the diagnostic morphologic criteria of thyroid malignancies. A few updates about the 2023 OMS classification explained above:

1. The term ‘‘variants’’ of papillary thyroid carcinoma has been removed, now changed to ‘‘papillary thyroid carcinoma subtypes’’ to avoid confusion with the term ‘‘genetic variant(s)’’, which is based on the molecular classification.

2. ‘‘Cribriform morular variant’’ now is designated as a separate tumor entity.

3. ‘‘High-grade follicular-derived thyroid carcinoma’’ is introduced to replace the ‘‘poorly differentiated thyroid carcinoma’’

ANNEX IV. AJCC TNM STAGING 7TH VS 8TH EDITION OF TC

The AJCC TNM staging 7th and 8th editions of thyroid cancer.

Category	7th edition	8th edition
Primary tumor (T)		
TX	Primary tumor cannot be assessed	Primary tumor cannot be assessed
T0	No evidence of primary tumor	No evidence of primary tumor
T1	Tumor size ≤ 2 cm AND intrathyroidal	Tumor size ≤ 2 cm AND intrathyroidal
T1a	Tumor size ≤ 1 cm	Tumor size ≤ 1 cm
T1b	1 cm < tumor size ≤ 2 cm	1 cm < tumor size ≤ 2 cm
T2	2 cm < tumor size ≤ 4 cm AND intrathyroidal	2 cm < tumor size ≤ 4 cm AND intrathyroidal
T3	Tumor size > 4 cm OR minimal extrathyroidal extension (sternothyroid muscle, perithyroid soft tissues)	T3a – Tumor size > 4 cm AND intrathyroidal T3b – gross extrathyroidal extension (sternohyoid, sternothyroid, thyrohyoid, omohyoid muscles)
T4	Gross extrathyroidal extension from tumor at any size	Gross extrathyroidal extension from tumor at any size
T4a	Extension beyond thyroid capsule (subcutaneous soft tissue, larynx, trachea, esophagus, recurrent laryngeal nerve)	Extension beyond thyroid capsule (subcutaneous soft tissue, larynx, trachea, esophagus, recurrent laryngeal nerve)
T4b	Invasion to prevertebral fascia OR encasing the carotid artery, mediastinal vessels	Invasion to prevertebral fascia OR encasing the carotid artery, mediastinal vessels
Regional lymph nodes (N)		
NX	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	Regional lymph node metastasis	Regional lymph node metastasis
N1a	Metastasis to level VI	Metastasis to level VI, VII
N1b	Metastasis to level I, II, III, IV, V, VII, retropharyngeal lymph nodes	Metastasis to level I, II, III, IV, V, retropharyngeal lymph modes
Distant metastasis (M)		
M0	No distant metastasis	No distant metastasis
M1	Distant metastasis	Distant metastasis
Stage grouping		
	Age < 45 years old	Age < 55 years old
Stage I	Any TAny NM0	Any TAny NM0
Stage II	Any TAny NM1	Any TAny NM1
	Age ≥ 45 years old	Age ≥ 55 years old
Stage I	T1N0M0	T1–T2N0M0
Stage II	T2N0M0	T1–T2N1M0 T3Any NM0
Stage III	T1–T2N1aN0 T3N0M0	T4aAny NM0
Stage IVA	T4aAny NM0 Any TN1bM0	T4bAny NM0
Stage IVB	T4bAny NM0	Any TAny NM1
Stage IVC	Any TAny NM1	

Table 20. AJCC TNM staging 7th and 8th editions of thyroid cancer (10)

ANNEX V. CEIC APPROVAL

Hospital Universitari de Girona Doctor Josep Trueta

IAS Institut d'Assistència Sanitària

INFORME DEL COMITÈ D'ÈTICA D'INVESTIGACIÓ AMB MEDICAMENTS CEIM GIRONA

El Comitè d'Ètica d'Investigació amb Medicaments CEIM GIRONA en la reunió del 01/08/2022 (Acta nº 12/2021) després de l'avaluació de l'estudi:

Títol: Análisi en base poblacional de la tendencia y supervivencia del cáncer de tiroides en Girona y Tarragona durante el período 1994-2017
Codi Protocol: GEDGPC-TIR-2022-01
Protocol v22/07/2022
Investigador principal: JORDI RUBIÓ CASADEVALL INSTITUT CATALÀ D'ONCOLOGIA servei Oncologia Mèdica
Promotor: INSTITUT D'INVESTIGACIÓ BIOMÈDICA DE GIRONA DR. JOSEP TRUETA
Codi. CEIM: 2022.141

considera que:

1. L'estudi avaluat compleix els requisits metodològics i tècnics.
2. La competència dels investigadors i els mitjans disponibles són apropiats per dur a terme l'estudi.
3. Els riscos i molèsties previsibles de la investigació són acceptables en relació amb els beneficis esperats.
4. El procés de selecció dels participants és apropiat.
5. S'accepta l'exempció de consentiment proposat per aquest estudi.
6. Les compensacions econòmiques previstes són adequades i no interfereixen amb la resta de postulats ètics.
7. El CEIM GIRONA , tant en la seva composició como en els seus PNT's, compleix amb les normes de BPC (CPMP/ICH/135/95).

I EMET INFORME FAVORABLE per la realització de l'estudi

MARTA RIERA JUNCÀ - DNI 40325373W
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Sra. Marta Riera Juncà
Secretaria Tècnica CEIM Girona
Girona, 13/10/2022