



Research Article

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Thyroid Differentiated Cancer: Characterization Over 10 Years



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Abstract

Introduction: Differentiated thyroid cancer (DTC) is the most common endocrine neoplasia. Its prognosis is good, however there are various risk factors described for a more severe involvement.

Objectives: Characterize a population of patients with DTC over 10 years, determine the frequency of risk factors for DTC development and postoperative complications and establish the agreement of different risk stratification models for DTC initial recurrence according to different guidelines.

Materials and methods: Observational, descriptive, retrospective study in the Clinic of Endocrinology and Metabolism at Hospital de Clínicas between 2011- 2021. Quantitative variables were represented by mean and median; qualitative variables were described with absolute and relative frequency. The agreement between recurrence scales was evaluated using Cohen's coefficient.

Results: 101 patients, 92% women, average age 42 years. Papillary thyroid carcinoma (PTC) accounted for 89% of cases.

Risk factors: 2% had a personal history of radiation, 39% were overweight and 34% obese, 34% smokers, and 7% had first-degree family history of DTC. 89% were diagnosed with suspicious thyroid nodule and 11% with incidentaloma. Total thyroidectomy was performed in 95%, lobectomy in 3%, and lobectomy plus isthmectomy in 2%. Postoperative complications included transient hypoparathyroidism in 48.5%, permanent hypoparathyroidism in 8.9%, and recurrent laryngeal nerve (RLN) damage in 7.9%. Pathological analysis showed 89% papillary variant and 11% follicular variant. 85% belonged to stage I of the mortality scale. The agreement between the scales was substantial.

Conclusion: DTC is more frequent in women (9:1) in the 4th-5th decade of life. The most common subtype was PTC. Risk factors included obesity, smoking, family history of DTC, and radiation. Most cases underwent total thyroidectomy, and the most frequent complication was transient hypoparathyroidism in almost half of the sample. Most cases corresponded to stage I according to AJCC. There is a high concordance between the risk stratification scales for initial recurrence according.

Keywords: Thyroid Differentiated Cancer; Recurrence Risk; Mortality

Abbreviations: TC: Thyroid Cancer; FTC: Follicular Carcinoma; RLN: Recurrent Laryngeal Nerve; AJCC: American Joint Committee on Cancer; ATA: American Thyroid Association; ETA: European Thyroid Association; LATS: Latin American Thyroid Society; CPT: Papillary Carcinoma; TT: Total Thyroidectomy; DTC: Differentiated Thyroid Carcinoma; PTC: Papillary Thyroid Carcinoma

Introduction

Thyroid cancer (TC) is the most common endocrine neoplasm and has shown an increasing incidence worldwide in recent years, which may be associated with the widespread use of imaging studies, particularly ultrasound. It represents 1-2%

of all cancers [1], and Uruguay has an incidence of 13.2 per 100,000 inhabitants [2]. It generally has a benign behavior, but in isolated cases, it can have a poor prognosis [3] that depends on various factors, including anatomopathological variants [4].

There are risk factors associated with the development of TC, such as radiation, mainly in the head and/or neck, which is the most clearly defined environmental factor. A sedentary lifestyle, associated with overweight or obesity, leads to a proinflammatory state and oxidative stress and has been linked to an increased risk of TC. Other factors, such as smoking, are postulated to cause DNA rearrangements, and a family history of TC in first-degree relatives is also a risk factor [5].

Differentiated thyroid carcinoma, derived from the follicular epithelium, is the most common type, accounting for approximately 95% of cases [1]. It affects all ages but predominates between 25-65 years and in females, with a male-to-female ratio of 1:4 [3]. It is usually asymptomatic and often presents as a thyroid nodule detected during physical examination or through various radiological methods requested for other reasons [6]. Evaluation is complemented by ultrasound, and depending on the characteristics and size, a cytological study is performed using fine-needle aspiration biopsy [7]. Regarding the pathological variants of DTC, there are several types, with papillary carcinoma (PTC) representing 80% and follicular carcinoma (FTC) being the second most common, accounting for 6-10% [4].

Thyroidectomy, radioactive iodine, and hormonal suppression therapy with levothyroxine are the pillars of treatment [8]. The main objective of surgery is to remove the macroscopic primary tumor, and this procedure requires significant skill of the surgeon to perform a comprehensive thyroidectomy and reduce postoperative complications, which have a significant impact

on prognosis [9]. The most frequent complication is transient or permanent hypoparathyroidism. In the case of transient hypoparathyroidism (lasting less than one year after surgery), its frequency ranges from 6.9% to 46% [8]. The incidence in our center until 2016 was 95%, while it decreased to 75.7% by 2019 [10]. As for permanent hypoparathyroidism, the reported incidence ranges from 0.4% to 33% [8], and in our center, it was 7.3% [10]. Another feared complication of thyroidectomies is recurrent laryngeal nerve (RLN) injury, with an incidence of 3 to 4% [11]. Once the surgical specimen and pathological results are obtained, the risk of mortality and recurrence is stratified. The risk of mortality is assessed using the TNM staging system of the American Joint Committee on Cancer (AJCC) [12].

The TNM staging system is the most widely used internationally, is based on age, size and extent of the primary tumor, and presence or absence of locoregional or distant metastatic involvement. The letter T determines the tumor size, N indicates lymph node invasion, and M indicates distant metastasis (Table 1). By combining the TNM staging results with the patient's age, the risk stages for mortality and the 10-year survival of the patient can be determined (Table 2) [12]. The risk of recurrence is determined using the scales proposed by the Thyroid Associations: American Thyroid Association (ATA), European Thyroid Association (ETA), and Latin American Thyroid Society (LATS) (Table 3) [13,14]. These stratifications help establish the need for adjuvant treatment with radioactive iodine, goals for TSH suppression, and the frequency of follow-up [13].

Table 1: TNM Staging System for Thyroid Cancer (12).

T Category	T Criterion
T0	No evidence of primary tumor
T1	Tumor ≤ 2cm in its greatest dimension, limited to the thyroid
T1a	Tumor ≤ 1cm in its greatest dimension
T1b	Tumor > 1cm but ≤ 2cm in its greatest dimension, limited to the thyroid
T2	Tumor > 2cm but ≤ 4cm in its greatest dimension, limited to the thyroid
T3	Tumor > 4cm, limited to the thyroid or with extrathyroidal extension (perithyroidal muscle involvement)
T3a	Tumor > 4cm, limited to the thyroid
T3b	Tumor of any size, without macroscopic extrathyroidal invasion, involving only perithyroidal muscles
T4	Macroscopic invasion with extension to other neck structures
T4a	Tumor of any size with macroscopic invasion of subcutaneous tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve (RLN)
T4b	Tumor of any size invading prevertebral fascia, carotid artery, or mediastinal vessels.

N Category	N Criterion
NX	Ganglia cannot be evaluated
N0	No evidence of lymph node metastasis
N0a	One or more lymph nodes confirmed as benign by histology or cytology
N0b	No clinical or radiological evidence of lymph node metastasis
N1	Metastasis to regional lymph nodes
N1a	Metastasis to level VI or VII pretracheal, paratracheal, or prelaryngeal lymph nodes. Unilateral or bilateral
N1b	Metastasis to lateral cervical lymph nodes, unilateral, bilateral, or contralateral (I, II, III, IV, or V) or retropharyngeal lymph nodes.

M Category	M Criterion
M0	No distant metastasis
M1	Distant metastasis

Table 2: AJCC Risk Stratification for Mortality (12).

Stage	Characteristics			Survival at 10 years
	Age < 55 years			
	T	N	M	
Stage I	Any T	Any N	M0	98 - 100%
Stage II	Any T	Any N	M1	85 - 95%
	Age > 55 years			
Stage I	T1a, T1b, T2	N0	M0	98 - 100%
Stage II	T3	N0	M0	85 - 95%
Stage III	T4a	Any N	M0	60 - 70 %
Stage IV A	T4b	Any N	M0	< 50 %
Stage IV B	Any T	Any N	M1	< 50 %

Table 3: Risk of Recurrence for Differentiated Thyroid Cancer (CDT) according to LATS, ETA, and ATA Guidelines (Summary) (13,14).

Risk	LATS	ETA	ATA
Very Low	Unifocal < 1cm NO MO No extrathyroidal extensión	Unifocal < 1cm NOM= No extrathyroidal extension	-
Low	Unifocal/multifocal 1-4cm, intrathyroidal NO, MO No aggressive histology No vascular invasion No extrathyroidal extension Uptake only in the thyroid bed	Multifocal 1-4 cm intrathyroidal NO, MO	Any T, intrathyroidal NO, MO No aggressive histology No vascular invasion No uptake outside the thyroid bed
Intermediate	-	-	N1 Minimal extrathyroidal invasion Vascular invasion Aggressive histology Uptake outside the thyroid bed
High	N1 Distant metastasis Residual disease Aggressive histology Extrathyroidal invasion >4cm Gross capsule invasion	>4cm extrathyroidal invasion N1, M1	Extrathyroidal invasion Incomplete tumor resection M1 Inappropriately elevated Tg (thyroglobulin)

In this study, we evaluated the clinical and epidemiological characteristics of CDT, as it is the most common endocrine neoplasm with an increasing incidence worldwide. We also assessed the prevalence of postoperative complications associated with treatment, as they are an important cause of morbidity and reduced quality of life. Additionally, we established the concordance between the different risk stratification scales for CDT recurrence, as choosing one of the three scales can be a challenge for endocrinologists.

Materials and Methods

This was an observational, descriptive, retrospective study conducted at Endocrinology and Metabolism Clinic of Hospital de Clínicas (Dr. Manuel Quintela) in Montevideo, Uruguay, between January 2011 and January 2021. Patients with CDT, aged 18 years and older, who were treated during the study period, were included. The initial sample consisted of 207 patients diagnosed with CDT, but 79 patients were excluded due to a lack of follow-up at the study site after treatment, and 27 patients did not participate due to missing data required for the study in their medical records. The final number of participants was 101. Data were collected from medical records, including demographic information, personal history (smoking, overweight, obesity, head, and neck radiation), and first-degree family history of CDT, which are considered risk factors for CDT development according to the American Cancer Society [5]. Diagnostic form (nodule, incidentaloma), extent of surgery (total thyroidectomy, lobectomy, lobectomy plus isthmectomy), pathology results (CPT and

CFT), and postoperative complications (transient or permanent hypoparathyroidism and RLN injury) were also recorded.

Hypoparathyroidism was defined as calcium levels ≤ 8.5 mg/dL and/or symptoms of hypocalcemia (cramps, paresthesia, and positive Trousseau sign). Transient hypoparathyroidism occurred within the first year after surgery, while permanent hypoparathyroidism persisted despite hypocalcemia treatment beyond that time. RLN damage was considered present when direct laryngoscopy determined paralysis of at least one vocal cord. The 10-year mortality risk was calculated using the TNM staging system of the 8th edition of AJCC [12]. The risk of recurrence was stratified using the latest ATA, LATS, and ETA scales [13,14], and the results were correlated among them.

Quantitative variables (age, age at diagnosis, weight, height, BMI) were represented using mean and median as measures of central tendency, while dispersion was represented by standard deviation and range. Qualitative variables (gender, personal history of smoking, obesity, head and neck radiation, family history of CDT) were expressed as absolute and relative frequencies. The concordance between recurrence scales was evaluated using Cohen’s Kappa coefficient (Table 4), and association was tested using Fisher’s exact test. All statistical tests were two-tailed, and p-values less than 0.05 were considered significant. Statistical analysis was performed using JASP v0.16 (JASP Team, 2023) and GraphPad Prism v8.4.3 (2020).

The study was approved by the Ethics Committee of Hospital de Clínicas with resolution number 38-22.

Table 4: Cohen’s Kappa Coefficient.

Cohen's Kappa	Interpretation
0	No agreement
0.10 - 0.20	Slight agreement
0.21 - 0.40	Fair agreement
0.41 - 0.60	Moderate agreement
0.61 - 0.80	Substantial agreement
0.81 - 0.99	Near perfect agreement
1	Perfect agreement

Results

A total of 101 patients were included, with the majority being female. The mean age at CDT diagnosis was in the fourth decade of life, and a large percentage of patients were overweight (Table 5). Regarding the risk factors considered for CDT development, 34% were smokers, 39% were overweight, 34% were obese, 2% had a personal history of head or neck radiation, and 7% had a first-degree family history of CDT. Among the CT patients, 89% were diagnosed based on a suspicious thyroid nodule, and 11%

were diagnosed incidentally. In terms of the type of surgery, 95% underwent total thyroidectomy, 3% underwent lobectomy, and 2% underwent lobectomy plus isthmectomy.

Regarding postoperative complications, nearly half of the sample experienced transient hypoparathyroidism, less than 10% of participants had persistent hypoparathyroidism after the first year of surgery, and a small percentage developed RLN damage (Figure 1). Papillary carcinoma (CPT) was observed in 89% of the pathological findings, while 11% had follicular carcinoma (CFT).

Regarding the risk stratification of mortality based on TNM, most patients belonged to stage I of the AJCC, followed by stage II (Table 6). The correlation between ATA-ETA and ATA-LATS scales was 82.2% for both correlations, with a Cohen's Kappa coefficient

(95% CI) of 0.64 (0.49 to 0.79) (Table 7 and 8). The correlation between ETA and LATS scales was 90.1% with a Cohen's Kappa coefficient (95% CI) of 0.82 (0.69 to 0.92) (Table 9).

Table 5: Description of Patients in the Sample.

	Total (N=101)
Sex	
Female	93 (92.1%)
Male	8 (7.9%)
Age	
Average (Standard Deviation)	49.3 (15.4)
Median[Min, Max]	48 [21, 84]
Age at diagnosis	
Average (Standard Deviation)	41.7 (15.4)
Median[Min, Max]	42 [13, 73]
Weight	
Average (Standard Deviation)	73.4 (17.6)
Median[Min, Max]	68.5 [42, 129]
Height	
Average (Standard Deviation)	1.6 (0.1)
Median[Min, Max]	1.6 [1.5, 1.8]
IMC	
Average (Standard Deviation)	28.4 (6.5)
Median[Min, Max]	27.1 [18.3, 47.7]

Table 6: Stratification of the Sample into Risk Stages of Mortality.

Mortality Risk (AJCC)	
I	85%
II	12,8%
III	1,9%
IV B	0.90%

Table 7: Correlation between ATA and ETA Scales.

ETA			
ATA	Very Low and Low Risk (N=50)	High Risk (N=51)	P value
Low Risk	40 (80.0%)	8 (15.7%)	<0.001
Intermediate or High risk	10 (20.0%)	43 (84.3%)	

Table 8: Correlation between ATA and LATS Scales.

LATS			
ATA	Very Low and Low Risk (N=44)	High Risk (N=57)	P value
Low Risk	37 (84.1%)	11 (19.3%)	<0.001
Intermediate or High risk	7 (15.9%)	7 (15.9%)	

Table 9: Correlation between ETA and LATS scales.

ETA	LATS		P value
	Very Low and Low Risk (N=44)	High Risk (N=57)	
Very low and Low Risk	42 (95.5%)	8 (14.0%)	<0.001
High risk	2 (4.5%)	49 (86.0%)	

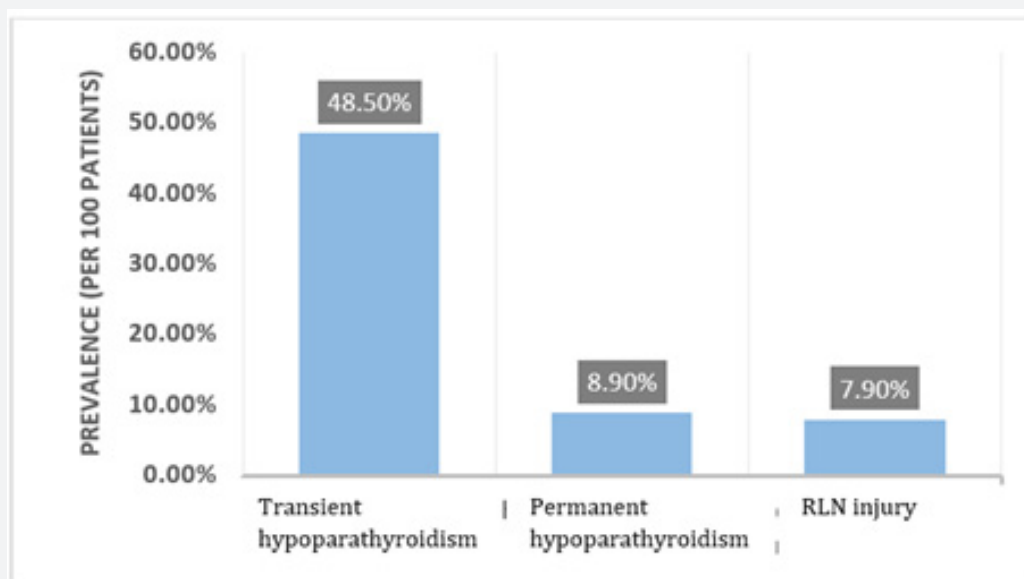


Figure 1: Postoperative Complications.

Discussion

In our study, 92.1% of the patients were women, and the average age at diagnosis was 42 years, with a median ranging from 13 to 73 years. These findings are consistent with the study by Carles Zafón et al. [15] conducted in Catalonia, which had a similar population to ours. In their study, 89% of the patients were women, with an average age at diagnosis of 44 years. It is also like the study by Nelson Arias [16] conducted in Manizales, Colombia, which analyzed 672 patients. In that study, 85% of the patients were women, with an average age at diagnosis of 51.1 years. This high prevalence in women can be attributed to several factors, such as the higher prevalence of this pathology in females as described in the literature [3], the significant healthcare demand from the female population, or sample bias. An important risk factor for the development of differentiated thyroid cancer (CDT) is a family history of the disease in first-degree relatives. In our study, 7% of the patients had this risk factor, which is consistent with the results of the study by Alma Vidaurri [17] conducted in Cancun, Mexico, where 6.8% of the patients had a family history of CDT. This finding is also like the study by Gonzalez et al. [18], where 8% of their patients had a significant family history. This can be attributed to the presence of gene mutations located on

chromosome 19 and chromosome 1, which have been associated with familial cases [4].

In our study, 89% of the patients were diagnosed based on a thyroid nodule reported by the patient or found on physical examination, while 11% had incidentalomas. These results are consistent with the study by Vidaurri [17], where 86% of CDT cases were diagnosed based on a nodule, and 11% were incidentalomas. The frequency of CDT diagnosis in this manner may be attributed to increased awareness of the disease by patients and primary care medical teams, more widespread use of ultrasound, and improvements in ultrasound equipment that allow for early detection. In 96% of the sample, total thyroidectomy (TT) was performed. Similar results were found in the study by Andrés Chala et al. [19], where 94% of the patients underwent TT. However, this differs from the study conducted by Vidaurri [17], where TT was performed in only 61% of the patients.

This can be explained by the fact that the latter study included many patients with a diagnosis of papillary microcarcinoma, where lobectomy can be used as the treatment of choice. In patients with differentiated thyroid cancer (CDT), total thyroidectomy (TT) is the preferred surgery because it offers a lower recurrence rate, better survival, and greater effectiveness

in radioiodine therapy, facilitating follow-up with biochemical markers such as thyroglobulin and anti-thyroglobulin antibodies [20]. The most common postoperative complication was transient hypoparathyroidism, with a prevalence of 48.5%. This differs from the findings of the study by Joao Goncalvez et al. [20] conducted in Sao Paulo, Brazil, with a similar follow-up period to ours, which reported transient hypoparathyroidism in 13.1% of cases, and from the study by Mintegui et al. [10] conducted at our hospital between 2011 and 2019, which included a total of 202 patients and found that 75.7% of participants experienced this complication. We attribute these differences to the fact that our center is a university teaching hospital where surgeries are performed by residents with varying degrees of academic training. However, we did observe a reduction in the prevalence of this complication compared to the previous study, and we believe this may be due to the larger sample size.

Permanent hypoparathyroidism occurred in 8.9% of patients, which is consistent with the findings of the Mintegui et al. [10] study conducted years ago, which reported an incidence of permanent hypoparathyroidism of 7.3%, and the report by Pitoia et al. [21] conducted in Argentina with a similar geographic area and population to ours, which found permanent hypoparathyroidism in 5.7% of patients. Our findings are like both studies; however, compared to the Mintegui study, we observed a higher percentage of permanent hypoparathyroidism in our sample. We believe this is because the previous study included patients with indications for total thyroidectomy due to both benign and malignant pathology, unlike our sample, which consists only of patients with CDT who require more extensive and complex surgeries, usually

involving lymph node dissection, which may increase the risk of this complication [22]. Vocal cord nerve injury occurred in 7.9% of patients. These findings are like those found in the systematic review by N. Christou et al. [22] conducted in France with a similar population, which reported vocal cord nerve injury in 5% to 11% of patients, and the study by Fretes et al. [23] conducted in Paraguay with an incidence of 4.5%.

The most common histological subtype was papillary thyroid carcinoma (CPT), present in 89% of patients, which is consistent with the various studies conducted by Nelson Arias [16] and Alma Vidaurri [17], where the predominant histology was CPT, with 82% and 76%, respectively. When comparing the frequency of categorization into mortality stages of the AJCC with other studies, it is evident that our data is like the study by Carolina Gonzalez [18] conducted in Córdoba, Argentina, with 171 patients, and to the study by Sergio Donay [24] conducted in Madrid with 150 patients. However, it differs from the study by Alma Vidaurri [17] in Mexico, which included 44 patients.

Our study showed similar Stage I figures compared to other studies and slightly higher than the study in Mexico. Unlike the latter, we did not have patients in Stage IV A. These differences can be attributed to the variation in sample size, and the Mexican study reported a higher number of patients in Stage IV than described in the literature. It is noteworthy that all these studies utilized the AJCC scale for assessing mortality. A high correlation was found between the three recurrence risk scales, with a Cohen's kappa coefficient indicating substantial agreement between ETA-ATA and ATA-LATS, and near-perfect agreement between ETA-LATS (Table 10) [25].

Table 10: Comparison of mortality stage categorization in DTC with similar studies.

AJCC Stage	Our Study	C. Gonzalez (18)	S. Donay (24)	A. Vidaurri (17)
Stage I	84%	76%	76%	61%
Stage II	13%	15%	9%	7%
Stage III	2%	6%	6%	9%
Stage IV A	-	-	8%	20%
Stage IV B	1%	3%	-	-

Table 11: Comparison of correlation between different risk recurrence scales in DTC.

	Our Study	Aldona Kowalska (25)	Fabián Pitoia (21)
Correlation ATA - ETA	82%	95%	-
Correlation ATA - LATS	82%	-	82%
		no comparable studies	
Correlation LATS - ETA	90%	-	-

When comparing these results with other studies, similar results were found, as shown in (Table 11). These findings can be attributed to the fact that these scales measure the risk of recurrence in CDT and use similar characteristics for classification,

such as size, focality, lymph node and metastatic spread, aggressive histology, and vascular invasion. The superiority of the correlation between ETA-LATS is attributed to the fact that both scales use the same stages.

Conclusion

Differentiated thyroid carcinoma (DTC) was more common in women, with an average age of diagnosis between 40 and 50 years, and most patients were overweight. The diagnosis was primarily made based on a suspicious thyroid nodule. Most patients underwent total thyroidectomy, and the most frequent postoperative complication was transient hypoparathyroidism, observed in almost half of the sample. The most common histological subtype was papillary thyroid carcinoma (PTC), and most cases were classified as stage I according to the AJCC classification, indicating low mortality risk. There was a high concordance among the initial risk stratification scales (ATA, ETA, and LATS), suggesting that any of these scales can be used to assess the risk of recurrence in DTC patients.

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