Risk stratification of 282 differentiated thyroid cancers found incidentally in 1369 total thyroidectomies according to the 2015 ATA guidelines; implications for management and treatment

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ABSTRACT

INTRODUCTION The purpose of this study was to evaluate the incidence of incidental differentiated thyroid carcinoma in thyroid operations for a benign preoperative diagnosis, to identify the risk factors involved and to risk stratify the cancer patients according to the 2015 American Thyroid Association (ATA) guidelines.

MATERIALS AND METHODS The study was a retrospective review of all thyroidectomy operations performed in a single institution (January 2004 to January 2009). We excluded patients with a preoperative diagnosis of thyroid malignancy.

RESULTS Incidental differentiated thyroid carcinoma was diagnosed in 282/1369 patients (21%). The incidental group had a significantly higher number of males (19% vs 14%, $P = 0.033$) and a higher number of patients with histopathological evidence of thyroiditis (35% vs 25%, $P = 0.004$). There was a higher number of lymph nodes present in the incidental group but numbers did not reach statistical significance (17% vs 13%, $P = 0.079$). There were 270 cases in the ATA low-risk group (96%) and 12 cases in the ATA intermediate-risk group (4%). Patients with an ATA intermediate risk had a statistically higher number of capsule invasion, extrathyroidal extension and angioinvasion ($P < 0.001$, $P < 0.001$ and $P < 0.001$, respectively). Overall, 22% of patients with an incidental differentiated thyroid carcinoma should be considered for radioactive iodine ¹³¹I treatment. 29 of the 191 patients in American Joint Committee on Cancer stage I should be considered for radioactive iodine treatment (15%).

CONCLUSIONS Males and patients with thyroiditis are at a higher risk for an incidental differentiated thyroid carcinoma. One of every five of patients diagnosed with cancer will need radioactive iodine treatment, even some patients with stage I disease.

KEYWORDS

Thyroidectomy – Thyroid cancer – incidental – Papillary cancer – Follicular cancer

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Introduction

Thyroid nodules are a common problem worldwide, with as many a prevalence of 1–5% in the general population living in iodine-sufficient areas.^{1,2} The vast majority of these thyroid nodules will be documented to have a benign nature and after a period of initial monitoring most patients are followed-up by their primary care physician, if at all.³ A subset of this population will undergo surgical treatment for a benign thyroid condition. Nodular goiters can cause compressive symptoms and/or cosmetic concerns for the

patients. Grave's disease can result in thyrotoxicosis and surgery is indicated when pharmacological treatment has failed and/or radioactive iodine has failed or is not indicated (pregnancy).⁴

The diagnosis of an incidental differentiated thyroid carcinoma (DTC) in the setting of a patient undergoing surgery for a benign condition is a major upset for the patient, as it changes radically the postoperative therapeutic plan. The aetiology of DTC is multifactorial; the known risk factors include a history of ionising radiation, the presence of multiple endocrine neoplasia syndrome type 2A and a familial

history of DTC.⁵ Although papillary thyroid carcinoma carries an excellent prognosis with a five-year survival of 98.1% the need for continuous monitoring for disease recurrence or metastasis imposes a significant burden both for the patient and the health-related resources (human, technological and financial) needed to achieve this task.^{5,6}

The American Thyroid Association (ATA) published their guidelines for the management of patients with DTC in 2015.⁷ Compared with the 2009 guidelines, the new edition has introduced a modified risk stratification system, categorising patients into three groups: low, intermediate and high risk, according to the histopathological findings. The new guidelines also present an algorithm for assessing the need for postoperative radioactive iodine treatment.

The purpose of this study was to evaluate the incidence of incidental DTC during thyroid operations in a single centre during a period of six years, to identify the risk factors involved and implement the new ATA guidelines to risk stratify the DTC patients.

Material and methods

This was a retrospective review of all thyroidectomy operations performed in a single institution (General Hospital of Athens Polikliniki Athinon) from 1 January 2004 to 31 December 2009. All the operations were performed by consultant general/endocrine surgeons or by their registrars under direct supervision. Inclusion criteria for the study were all thyroidectomies (total thyroidectomies or near-total thyroidectomies) performed during the above-mentioned six-year period. Patients with a concurrent diagnosis of hyperparathyroidism who underwent a thyroidectomy and parathyroidectomy at the same time were included. Exclusion criteria included: all reoperative cases, hemithyroidectomies, thyroid operations requiring sternotomy or involving neck lymph node dissections (central or lateral or both) and cases with a preoperative diagnosis of thyroid or parathyroid malignancy or a suspicion of malignancy (Thy3a, Thy3f, Thy4 or Thy5 result on preoperative fine-needle aspiration cytology, FNAC).⁸ Cases with only Thy1 cytologies (without ever having a Thy2 cytology) were also excluded from this study. The hospital ethics committee approved the study.

Operative reports and the patient's charts were reviewed to collect information regarding the demographics (sex and age at date of operation), the clinical characteristics and the operative details. Pathology reports were screened to identify the occurrence of an incidental DTC. An incidental DTC was diagnosed when there was no preoperative clinical or radiological suspicion of TC and there was no FNAC positive for DTC. The presence of DTC (type of DTC, location, focality, size of largest tumour, invasion of thyroid capsule, extrathyroidal extension and angioinvasion) and of lymph nodes (number, location, histology) was extracted from the pathology reports. For results analysis, patients were divided into two groups; patients with an incidental DTC diagnosis and patients with a benign pathology diagnosis. The American Joint Committee on Cancer (AJCC), 7th edition/Tumour Node Metastasis

Classification System for Differentiated Thyroid Carcinoma was used for the classification of DTCs in this study.⁹

The 2015 ATA guidelines for DTC were used to stratify the patients into two groups: an ATA low-risk group and an ATA intermediate-risk group (there were no cases of ATA high risk among the patients).⁷ The need for postoperative radioactive iodine treatment was assessed according to the decision-making algorithm of the 2015 ATA guidelines for DTC.⁷

Local protocol

All patients underwent a neck ultrasound and FNAC was performed whenever a nodule with suspicious feature was encountered on ultrasound and FNAC results were reported according to the guidelines from the British Thyroid Association/Royal College of Pathologists system.¹⁰ All patients were adequately prepared preoperatively to ensure normal serum levels of thyroid hormones (euthyroid status). Operated patients routinely stayed overnight and blood was tested for levels of serum calcium the next morning at 8am. Hospital discharge was on a case-by-case basis. Thyroid hormone replacement was started on day 1 after the operation. All patients were seen within two weeks after the operation in the outpatient department for a follow-up visit.

Surgical technique of thyroidectomy

Total thyroidectomy was based on the principle of capsular dissection with removal of all thyroid tissue (including pyramidal lobe where present) and with every effort made to identify and preserve all four parathyroid glands. In the case of a technically challenging thyroid gland anatomy, a minimal amount of thyroid tissue was left in proximity to the entry of the recurrent laryngeal nerve in the larynx and the operation was classified as near-total thyroidectomy.

Statistics

Statistical analysis was performed using SPSS version 20. Data collection and analysis of the results were performed with adherence to data protection principles. The study complied with local institutional review board ethics protocols. Descriptive statistics were expressed as frequencies and percentages for categorical and as means with standard deviations (SD) for continuous variables. Chi-square, Fisher exact and Mann-Whitney U tests were used for analysing the relationship between categorical and continuous variables, respectively. A value of $P \leq 0.05$ was considered as statistically significant.

Results

The total number of thyroid operations performed during the study period was 1567. Of these, 1369 operations were included in the study, while 198 operations did not meet the inclusion criteria and were excluded from further analysis. Patients were grouped into two diagnostic groups: those with a histopathological diagnosis of incidental DTC and those with a benign pathology.

The demographics, clinical and histopathologic characteristics of the patients are presented in Table 1. Incidental DTC was diagnosed in 282 patients (21%). There was a significantly higher number of males in the incidental DTC group (19% vs 14%, $P = 0.033$). There was no significant difference between groups in the mean age at the time of the operation, preoperative diagnosis, the presence of preoperative hyperthyroidism or hyperparathyroidism and mean weight of the thyroid gland ($P = 0.375$, $P = 0.712$, $P = 0.092$, $P = 0.365$ and $P = 0.953$). The incidental DTC group had a significantly higher number of cases with histopathological evidence of thyroiditis (35% vs 25%, $P = 0.004$).

Figure 1 shows a comparison of thyroid lobe (right and left) dimensions (height, width, depth) between diagnostic groups (incidental differentiated thyroid cancer versus benign pathology). There were no statistical differences detected between the groups in any of the measured lobe

dimensions. Table 2 presents the correlation between the presence of lymph nodes (on the pathology report) and the diagnostic group. There was a higher number of lymph nodes present in the incidental DTC group but this did not reach statistical significance (17% vs 13%, $P = 0.079$). There were only two patients with pathological lymph nodes identified (in the incidental DTC group). There was no statistically significant difference between groups in regard to the mean number of lymph nodes removed and the mean size (in cm) of normal lymph nodes removed ($P = 0.266$ and $P = 0.768$, respectively).

The risk stratification of patients with incidental DTC according to the 2015 Modified Initial Risk Stratification system can be seen in Table 3. There were 270 cases in the ATA low-risk group (96%) and 12 cases in the ATA intermediate-risk group (4%). Patient with an ATA intermediate risk had statistically higher numbers of capsule invasion, extrathyroidal extension and angioinvasion ($P < 0.001$, $P < 0.001$ and

Table 1 Comparison of demographics, clinical characteristics, operative procedures and pathological findings between diagnostic groups: incidental differentiated thyroid cancer (DTC) compared with benign pathology.

Factor	Incidental DTC		Benign pathology		P-value	Total	
	(n)	(%)	(n)	(%)		(n)	(%)
Sex:					0.033		
Male	55	19	155	14		210	15
Female	227	81	932	86		1159	85
Age (years) ^a (mean, SD)	51	13 (21–83)	52	13 (17–83)	0.375	52	13 (17–83)
Preoperative diagnosis:					0.712		
Nodular/multinodular goitre	271	96	1052	97		1323	97
Grave's thyroiditis	10	4	28	3		38	3
Toxic adenoma	1	0.4	7	0.6		8	0.6
Preoperative hyperthyroidism:					0.092		
Toxic	20	7	114	11		134	10
Non-toxic	262	93	973	89		1235	90
Preoperative hyperparathyroidism:					0.365		
Yes	7	3	41	4		48	4
No	275	97	1046	96		1321	96
Diagnosis of incidental DTC: ^b							
Yes						282	21
No						1087	79
Presence of thyroiditis:					0.004		
Yes	99	35	284	26		383	28
No	183	65	803	74		986	72
Thyroid gland weight (g):					0.953		
Mean (SD)	44 (43)		44 (41)			44 (42)	
Range	7–383		4–442			4–442	

^aAt date of operation.

^bOn histopathology report; $P < 0.05$ is considered significant.

$P < 0.001$ respectively). In the ATA intermediate-risk group there was one case with T1aN0Mx, eight cases of T3N0Mx and one case of T3N1aMx. Overall, 196/250 incidental DTC cases were less than one centimetre in diameter (78%). There were 1878 unifocal tumours (67%) and 94 multifocal tumours (33%) in total.

The assessment of the need for postoperative radioactive iodine treatment for the two groups is presented in Table 4. TNM and AJCC classification were available in 206 patients. No patients in the T1aN0Mx group would need radioactive iodine treatment (161/206, 78%). The remaining 45 patients (22%) should be considered for RAI treatment. Twenty-nine of the 191 patients with stage I disease would be considered for radioactive iodine treatment (15%). Picture 1 Figure 2 presents examples of the variation in size and shape observed in thyroidectomy specimens.

Discussion

There has been a surge of studies over the past 15 years reporting an increased incidence of DTC worldwide.^{11–15} According to the latest report by the Surveillance, Epidemiology, and End Results (SEER) database in the United States (1975–2012), the incidence of papillary carcinoma has almost tripled; from 4.8/100,000 to 14.9/100,000.¹⁴ The life-time risk of developing DTC at some point during their lifetime, according to the SEER database, is 1.2% (based on 2012–2014 data).¹⁵ Our study examined the incidence of incidental DTC in patients operated for a benign thyroid diagnosis and shows that 21% of patients had an unexpected histopathological diagnosis of DTC.

Previous studies have reported an incidence of incidental DTC ranging between 7% and 20%.^{6,16–26} The observed

Table 2 Comparison of lymph node-related variables, as described on pathology, between diagnostic groups: incidental differentiated thyroid cancer (DTC) compared with benign pathology.

Lymph nodes	Incidental DTC		Benign pathology		P-value	Total	
	(n)	(%)	(n)	(%)		(n)	(%)
Present:					0.079		
Yes	48	17	139	13		187	14
No	234	83	948	87		1182	86
Invaded present:					n/a		
Yes	2	4.0	0	0		2	1.1
No	48	96.0	139	139		187	98.6
Number:					0.266		
Mean (SD)	1.8		1.6	0.9		1.7	1.0
Range	1–6		1–5			1–6	
Normal size (cm):					0.768		
Mean (SD)							
Range	0.1–1.4		0.1–2.5			0.1–2.5	

Table 3 Risk stratification of patients with incidental differentiated thyroid cancer (DTC) according to the 2015 Modified Initial Risk Stratification system.^a

Tumour type	ATA risk				<i>P</i> -value
	Low		Intermediate		
	(<i>n</i>)	(%)	(<i>n</i>)	(%)	
Subtype:					< 0.001
Papillary-classical	218	81	6	50	
Papillary with follicular pattern	34	13	0		
Papillary (papillary and follicular pattern)	9	3	2	17	
Papillary with tall columnar	0		1	8	
Follicular	6	2	3	25	
Hurthle cell	3	1	0		
Localisation:					0.209
Unilateral	132	76	6	54	
Isthmus	6	3	0		
Bilateral	36	21	5	46	
Thyroid capsule invasion:					< 0.001
Yes	21	10	1	8	
No	183	90	11	92	
Extrathyroidal extension:					< 0.001
Yes	0	0	4	33	
No	204	100	8	67	
Angioinvasion:					< 0.001
Yes	0	0	6	50	
No	204	100	6	50	

Focality:					0.076
Unifocal	180	67	7	58	
Multifocal: unilateral	23	9	0		
Multifocal: bilateral	42	16	5	42	
Multifocal: unknown	24	9	0		
Size (cm):					< 0.001
< 1	193	80	3	30	
1–2	31	13	4	40	
2–4	15	6	2	20	
> 4	1	0.4	1	10	
TNM classification:					< 0.001
T1aNOMx	160	82	1	10	
T1bNOMx	18	9	0		
T2NOMx	14	7	0		
T3NOMx	3	2	8	80	
T2N1aMx	1	1	0		
T3N1aMx	0	0	1	10	
AJCC stage:					< 0.001
I	186	95	4	40	
II	9	5	0		
III	1	1	6	60	

AJCC, American Joint Committee on Cancer; ATA, American Thyroid Association.
^a Cases with missing data were excluded from each analysis' $P < 0.05$ is considered significant

Table 4 Assessment of need for postoperative radioactive iodine treatment according to the 2015 American Thyroid Association guidelines for differentiated thyroid cancer ($n = 206$).

Tumour	Need for RAI		No need for RAI	
	(n)	(%)	(n)	(%)
TNM classification:				
T1aNOMx	0	0	161	100
T1bNOMx	18	100	0	
T2NOMx	14	100	0	
T3NOMx	11	100	0	
T2N1aMx	1	100	0	
T3N1aMx	1	100	0	
American Joint Committee on Cancer stage:				
I	29	15	161	85
II	9	100	0	
III	7	100	0	

differences between reports are most likely the result of a combination of factors: small differences in inclusion criteria, different preoperative institutional policies for investigating thyroid nodules, differences in the extent of histological examination of specimens and pathology reporting and the retrospective nature of these studies.²⁷ The reported incidence in our study is one of the highest in the literature and the highest compared with two previous, much smaller, case series focusing on the Greek population.^{17,24} These differences reveal the complexity of treating patients with an apparently benign thyroid disease and the pitfalls of modern technological equipment in detecting DTC; FNAC has a false-negative rate of 1.3–11.5% and is less sensitive in detecting follicular and Hürthle-cell carcinomas.^{28,29}

The diagnosis of DTC has a significant impact on the lives of patients, especially when the preoperative diagnosis was benign. Thyroid cancer diagnosis has been associated with feelings of fear and uncertainty amongst patients and a decreased quality of life.^{30–32}

The finding of a male predominance (19%) in the incidental DTC group is in line with the findings from Ilias *et al.*, who reviewed 610 patients with DTC in Greece (males 19.5% vs females 80.5%).³³ There is continuing debate regarding the relationship between autoimmune thyroid

Figure 2 Examples of the variation in size and shape observed in thyroidectomy specimens

disease and DTC; we report a statistically significant higher number of patients with thyroiditis in the DTC group.^{34,35}

The role of hyperthyroidism in the pathogenesis of DTC is still unknown; some studies have reported that incidental DTC is associated with non-toxic thyroid disorders, while our study and others did not demonstrate a statistically significant difference in the incidence of incidental DTC between toxic and non-toxic groups.^{17,21,22,56–58} The reported incidence of 7% incidental DTC in the toxic group in our study falls within the range previously reported (0.8–8.7% DTC in thyrotoxicosis).^{58–60}

Multifocality in incidental DTC has been shown to be present between 20–41% of patients.^{22,24,41} Sakorafas *et al.* have reported that in 11 incidental DTC patients (40.7%) the tumour was multifocal and in about half of them tumour foci were found in both thyroid lobes.²⁴ In our cohort, multifocality was present in 33% of incidental DTC patients. PTC has a known propensity to be multifocal/bilateral and is an adverse prognostic factor for disease recurrence/metastasis.^{3,42,45} Patients in our cohort had a total/near-total

thyroidectomy as the initial operation and benefited by avoiding the need for a completion thyroidectomy.

The lymph node status of patients with DTC affects long-term clinical outcome, as residual metastatic lymph nodes represent the most common site of disease persistence and recurrence.^{3,44,45} The study from Gelmini *et al.* in 2010 identified nodal metastasis in the 3.6% of 739 patients.²¹ The results of our study have demonstrated that there were no significant differences between groups in regard to the presence of lymph nodes in the pathology report and the mean number and size of lymph nodes sampled. The intraoperative identification of enlarged lymph nodes does not seem to be an accurate prognostic factor for the presence of incidental DTC and in the vast majority of cases the lymph nodes are benign in nature.

Despite the rise in the incidence of DTC, the disease-specific mortality remains very low with a five-year relative survival of 96%.^{11,27} The majority of incidental DTC reported in the literature are microcarcinomas; mainly papillary thyroid carcinomas less than 1 cm in

diameter.^{14,16,21} Such papillary microcarcinomas were shown to be associated with a 1% disease-related mortality rate, a 2.5% distant metastasis rate and a 5% cervical lymph node recurrence rate, which highlights the need for a complete oncological treatment of these patients (total thyroidectomy with or without radioactive iodine), when needed.⁴⁶ Our study has shown that a significant number of patients (22%) will be diagnosed with DTC greater than 1 cm in size, while 22% of patients with an incidental DTC should be considered for postoperative radioactive iodine treatment, mainly due to the finding of an aggressive histology or vascular invasion.

Radioactive iodine treatment is not without short-term and potentially long-term adverse effects, such as infertility and a potential higher risk for leukaemia and secondary primary malignancies.⁴⁷ Furthermore, the average cost of radioactive iodine treatment for each patient has been estimated to be between US\$5,429.58 and US\$9,105.67 in a study from the United States. This is probably an underestimation, given that the authors did not include the costs associated with complications from radioactive iodine therapy and quality of life changes.⁴⁸

The study is limited by the well-known inherent biases of its retrospective nature. Every effort was made to control for some of these limitations by crosschecking the histopathology reports with operating records and patients charts. The strengths of the study include the fact that the cohort of these patients was operated in a single institution under a uniform and standardised treatment care pathway and the large sample size.

This cohort of patients represents one of the largest single-institution cohorts worldwide and the largest single-institution experience, to our knowledge, reported so far in Greece. Incidental DTC in patients undergoing thyroidectomy for benign disease was shown to occur in almost one of every five patients in our study. Males and patients with thyroiditis are at a higher risk for an incidental DTC. Physicians treating patients with benign thyroid conditions should consult them preoperatively about the risk of a histopathological diagnosis of DTC and the potential for further radioactive iodine treatment (one of five with a diagnosis of incidental DTC).

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