

# Incidental Thyroid Carcinoma in Patients Treated Surgically for **Thyroid Disease**

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Tharwat I Sulaiman ***	FRCSI, FRCS ENG., CABS
Labeed S Hamid*	FIBMS
Mohamad Q AbdulJabbar **	CABS

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#### Abstract:

Background: The occurrence of incidental thyroid cancer (ITC) has increased by three times during the last decades and this rise could be attributed to many factors. To limit the prevalence of ITC with goiter especially nodular goiter, total thyroidectomy can become a procedure of choice.

Objective: To determine the extent of incidental thyroid carcinoma (ITC) and to plan a proper preoperative diagnostic work up and a convenient operative procedure for patients with different thyroid diseases.

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Material and Methods: A prospective study was conducted during the period from October 2013 to October 2016 at Baghdad teaching hospital (main tertiary hospital in Iraq), first surgical unit by a single surgeon and his trainees. The study included 473 patients who were referred for surgical treatment of different thyroid diseases. About 71 patients were excluded from the study due to the diagnosis of malignancy (MNG) by FNAC or history of surgery. The remaining 402 patients were evaluated for the presence of the cancer by post-operative pathological examination.

Results: ITC was found in 77 patients (19.15%). While, 63 patients with non-toxic MNG (15.6%), 12 patients with non-toxic solitary thyroid nodule (3%) and two patients (0.5%) with toxic MNG were observed in the study. Out of 77 patients with ITC, 56(72.7%) were <45 years and the remaining 21  $(27.3\%) \ge 45$  years. The 15 patients were males and 62 patients were females in these groups.

Conclusions: Although ITC in this study is relatively high especially in MNG; a more radical surgical treatment seems needed in the management of patients with presumably benign thyroid disease. The authors identify a potential benefit in performing total thyroidectomy instead of near or subtotal when considering management of MNG.

Keywords: Incidental thyroid cancer, malignancy.

#### Introduction:

Incidental thyroid cancer (ITC) is defined as any malignancy (MNG) of thyroid origin not detected by clinical examination or in preoperative imaging tests, which is diagnosed by the pathological study of a surgical specimen excised for an initially benign condition (goiter or hyperthyroidism)1,2 or outside the index nodule for which surgery was indicated3. By 2019, it is expected that ITC will become the third most common cancer in women in the United States after lung and breast cancer4-7. They are more frequent in females, and although the main age of onset is between 40 and 60 years, they can also arise in childhood and youth8, 9. Among patients operated for benign thyroid disease, the occurrence of ITC is not frequent. The incidence ranges is between 3% and 16% according to case selection1, 2 with some series

\*Numan's Teaching Hospital, Baghdad, Iraq. Email: <u>drlabeed@gmail.com</u>.

\*\*Specialty Doctor in General Surgery, Baghdad Teaching Hospital, Email: mohammedmk5@gmail.com.

\*\*\* Department of Surgery, College of Medicine, University of Baghdad. Email: tharwatsulaiman@yahoo.com.

reporting incidence rates of 25-26%2, 9. ITC can also occur in patients with a history of hyperthyroidism, who have long been believed to be protected against cancer by suppression of thyroid stimulating hormone (TSH) 1,2,10. Further, the detection rate of ITC on autopsy examination has been reported to be steadily rising, with an estimated increase from 6% in 2003 to 20% in 20122, 9. The majority of lesions are microcarcinomas (papillary tumors less than 1 cm in size) 1, 2, 7. Thyroid cancer, particularly papillary thyroid cancer, has been reported to complicate Graves' disease in the range of 1 to 9% of cases6 and even higher in some studies (18.3%) 10-12. Also, there is increasing evidence linking lymphocytic or Hashimoto's thyroiditis to thyroid cancer3, 12. Hypocalcemia was defined as serum calcium levels less than 2.0mmol/L on two separate occasions and/or presence of symptoms (perioral paresthesia) or signs Chvostek's (positive or Trousseau's) of hypocalcaemia clinically irrespective of the serum calcium levels. Permanent hypoparathyroidism was defined as that persisting longer than six months although some patients returned to normal after one year. Permanent palsy was defined as that persisting more than one year after surgery. The optimal surgical procedure for MNG patients remains a

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subject of debate, due to not only the increasing prevalence of ITC among these patients but also the incidence of TC in recurrent goiter9, 13. The use of Total Thyroidectomy (TT) remains for long time controversial for treating benign disease (MNG) 13, 14. Although the complication rates of permanent recurrent laryngeal nerve palsy (0-1.3%) and permanent hypoparathyroidism (1%) following subtotal thyroidectomy were found to be similar to those after TT, but a further advantage of TT is the definitive removal of ITC13. The fact that completion thyroidectomy is a very difficult surgery that every surgeon wishes to avoid14. With this background, we aim to determine the extent of incidental thyroid carcinoma and to plan a proper preoperative diagnostic work up and a convenient operative procedure for patients with thyroid diseases.

#### Material and Methods:

Patient enrollment: This prospective study was conducted during the period from October 2013 to October 2016 at Baghdad teaching hospital, first surgical unit Al-Mustansyria private hospital by a single surgeon and his trainees. During this period, 473 patients were referred for surgical treatment of different thyroid disease. Seventy one patients were excluded from the study due to cytological evidence of malignancy (MNG) by FNAC and ultrasonic findings or histopathological findings of surgery history (those were subjected for completion thyroidectomy and excluded from the study). Remaining 402 patients were included in the present study.

Methodology: All enrolled patients (n=402) had been preoperatively sent for ultrasound (U/S) examination to assess thyroid gland size, any abnormal nodule(s) with their number, size and site, presence of calcification and vascularity of the nodules and any lymph node (LN) enlargement. Neck and chest CT scans were also used for some patients with retrosternal extension. The patients had undergone FNAC on dominant nodules revealing benign disease in all cases. The patients had thyroid function tests; there were 257 euthyroid patients (64%), 77 thyrotoxic patients (19.1%) and 68 Hypothyroidism patients (16.9%). Toxic nodular goiter (solitary or multinodular) was diagnosed in patients presented with nodular thyroid and suppressed thyroid stimulating hormone (TSH) with or without overt elevation of T3 and/or T4. All thyrotoxic patients were received medical treatment, which was continued until the day of the surgery to prevent perioperative thyroid crisis. Hypothyroid received thyroxine replacement. patients Preoperative laryngoscopy was done in all patients to evaluate the mobility of the vocal cords. Decision of operation was decided preoperatively according to each surgeon's training and routine operation. Surgical operations performed were total lobectomy with isthmusectomy (Hemithyroidectomy), sub-total thyroidectomy, near-total and total thyroidectomy. Sternotomy was needed in two patients only with

large retrosternal extension. Identification of the recurrent laryngeal nerves and the parathyroid gland was routinely carried out. The postoperative complications were recorded, including change of voice, hypocalcemia, bleeding and wound infection. Unilateral or bilateral recurrent nerve injury was assessed clinically and by using laryngoscopy. Bleeding was assessed and two patients required reexploration in the theatre. Tracheostomy was prophylactically performed in two patients with huge goiter, no emergency tracheostomies were required. The specimens were sent for histopathological examination at teaching laboratories in medical city complex and in Al-Sharjah private laboratory.

#### Statistical analysis:

Statistical analysis performed by using the statistical package for social sciences (SPSS) software for windows version 20. Age of the patients was categorized into two groups (<45 and  $\geq 45$ ) years according to the latest TNM classification. Other variables were presented as frequencies (number of patients) and percentages. Cross-tabulation of age group, sex, diagnosis and thyroid profile against the final diagnosis (ITC or benign) was performed, Chi square test was used to assess the significance (p value) of the differences between these variables.

#### **Results:**

In the present study, 402 patients underwent surgical treatment of presumed benign thyroid disease; 78 (19.4%) were males and 324 (80.6%) were females with a mean age of 44 years (range 16-72 years). Patients were divided into two groups according to their age, below 45 years (n=287) and above 45 years. About 287 (71.4%) patients were included in the below 45 years groups while 115 (28.6%) patients were above 45 years. The thyroids functions were categorized in to toxic and non-toxic. About 77 patients (19%) were found to be toxic and 325 patients (81%) were nontoxic.







The sample diagnosis of thyroid gland status prior to surgery was: Nontoxic MNG (n=254; 63.2%), nontoxic solitary thyroid nodule (n=71; 17.7%), toxic

MNG (n= 45; 11.1%), toxic nodule (n=20; 5%) and diffuse toxic goiter (n=12; 3%) (Figure 2).



Figure 2: Frequency distribution according to pre-operative diagnosis (n=402).

The post-operative pathological examination of the surgical specimens showed the presence of incidental thyroid carcinoma in 77 cases (19%) of total number of patients, 15 of them were males (19.4%) and 62 were females (80.6%) with a mean age of 39 years (range from 16-62 years).



Figure 3: Frequency distribution of the sample according to the result of Histopathology (n=402).

The incidentally detected carcinomas were of micropapillary histotype in 35 cases (45.5%), classic papillary histotype in 20 cases (26%), Papillary carcinoma with follicular variant in 11 cases (14.3%), Follicular carcinoma in 7 cases (9%), Medullary carcinoma 1 case (1.3%), Anaplastic carcinoma 2 cases (2.5%) and one case was Lymphoma (1.3%). As it is shown in (Table 1), out of the 77 patients with ITC, 56 (19.5%) aged <45 years and the other 21

(18.3%) aged  $\geq$ 45 years, on the other hand 15 males had ITC (19.2%) and the remaining 62 (19.1%) were females, however there was no statistically significant differences in age and gender in between those with ITC and benign lesions, in both comparison, P>0.05. In relation to the thyroid function, 75 patients were in the nontoxic category (97.4%) and two patients with toxic MNG (2.6%) and there is a significant correlation between the functional status of the gland and the development of malignancy (P value= 0).

Table	1:	Relationship	between	ITC	with
catego	rical	variables (n=40	2).		

		~ ().		
Variable		ITC	Benign	P Value
Age	< 45	56 (19.5%)	231 (80.5%)	0.773 <sup>(NS)</sup>
(Years)	$\geq$ 45	21 (18.3%)	94 (81.7%)	
Gender	Male	15 (19.2%)	63 (80.8%)	0.985 <sup>(NS)</sup>
	Female	62 (19.1%)	262 (80.9%)	_
Thyroid	Toxic	2 (2.6%)	75 (97.4%)	$0.000^{(*)}$
function	Nontoxic	75 (23.1%)	250 (76.9%)	

NS is not significant. \* is statistically significant at alpha level of < 0.05.

The distribution of incidentally detected thyroid carcinomas according to the pre-operative diagnosis and thyroid profile is summarized in Table 2.

 Table 2: Incidental thyroid carcinoma incidence

 and correlation related to preoperative diagnosis.

Preoperative diagnosis		Number of	ITC No. (%)
		cases (%)	
Nontoxic MNO	£	254 (63.2%)	63 (81.8%)
Nontoxic thyroid nodule	Solitary	71 (17.7%)	12 (15.6%)

Toxic MNG	45 (11.2%)	2 (2.6%)
Toxic nodule	20 (4.9%)	0 (0.0)
Diffuse goiter	12 (3%)	0 (0.0)
Total number	402 (100%)	77 (100%)
ITC % of the whole		
series 19.1%		

Nontoxic solitary nodule	12 (16.9)	59 (83.1)
Toxic MNG	2 (4.4)	43 (95.6)
Toxic nodule	0 (0)	20 (100)
Diffuse toxic goiter	0 (0)	12 (100)

Chi square test has been done to measure the association. \*P< 0.05.

The relationship between ITC and Pre-operative thyroid diagnosis is described in Table 3. There was a significant (P=0.001) relationship between type of thyroid disease and risk of malignancy with nontoxic MNG.

# Table 3: Relationship between ITC with pre-<br/>operative diagnosis (n=402)

	No. of ITC	No. of	P Value
	cases (%)	Benign	
		cases (%)	
Nontoxic MNG	63 (24.8)	191 (72.2)	0.001(*)

Total Thyroidectomy was the most commonly performed surgical procedure followed by near total thyroidectomy. Out of 402 patients 284 patients underwent total thyroidectomy (70.6%) and 98 patients near total thyroidectomy (24.4%) while the remaining 20 cases were operated as hemithyroidectomy (10 cases) and subtotal thyroidectomy (10 cases) which represent 2.5% each.



Figure 5: Frequency distribution according to the type of operation (n=402)

Table 4: Distribution of the operative type within the preoperative diagnosis					
	Total thyroidctomy	Near total	Subtotal	Hemi-thyroidectomy	Total
MNG	192 (75.6%)	52 (20.5%)	10 (3.9%)	0 (0.0%)	254 (100%)
Solitary	33 (46.5%)	28 (39.4%)	0 (0.0%)	10 (14.1%)	71 (100.0%)
Nodule					
Toxic	34 (75.6%)	11 (24.4%)	0 (0.0%)	0 (0.0%)	45 (100.0%)
MNG					
Toxic	13 (65.0%)	7 (35.0%)	0 (0.0%)	0 (0.0%)	20 (100.0%)
Nodule					
Diffuse	12 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (100.0%)
goiter					

#### Table 4: Distribution of the operative type within the preoperative diagnosis



Figure 6: Complications related to all surgical procedures (n=402)

The postoperative complications (recurrent laryngeal nerve palsy and hypocalcaemia, hematoma, tracheostomy and wound infection) were reported in 116 patients (28.8%) included:

• Temporary change in voice in 25 patients (6.2%)

• Permanent unilateral recurrent nerve palsy in four patients (1%)

• Transient symptomatic hypocalcemia in 80 patients (19.9%)

- Permanent hypocalcemia in four patients (1%)
- Hematoma and bleeding in five cases (1.2%) Three of them needed re-exploration

• Tracheostomy was prophylactically performed in two patients (0.5%) followed by successful weaning and closure

• Wound infection was recorded in three patients (0.7%) responded to antibiotics treatment

• Permanent bilateral recurrent nerve palsy didn't occur in any patient

# **Discussion:**

The management of thyroid diseases especially the differentiation between benign and malignant nodules is becoming a challenging issue in spite of the use of clinical, radiological and laboratory parameters13. Thyroid carcinoma is the most common endocrine tumors, as it represents almost 90% of all endocrine malignancies13. Papillary carcinoma which is the most common histotype of thyroid cancer, accounts for about 85% of malignant thyroid carcinoma. Its prognosis is good with a mortality rate below 5% at 10 years after diagnosis15, 16. Papillary thyroid microcarcinoma which is a distinct type of papillary carcinoma is characterized by a diameter less than 1 cm, less aggressive behavior and a very low tendency for distant metastases, in fact the papillary thyroid microcarcinoma is the most common malignant thyroid tumors detected incidentally2, 15 and it carries a very good prognosis. Many studies mentioned that mortality and relapses were markedly higher in non-incidental cancers as compared to incidental cancers (4.4% vs 0% and 13.2% vs 4.8%) respectively2. Lin et al (2016) found in their study the incidental thyroid carcinoma in

MNG and SNG to be 15.6% and 10.1% respectively17. Miccoli et al (2006) found in their study 10.4% of incidental thyroid carcinoma1, while Smith et al (2012) found in their study 18.3% of incidental thyroid carcinoma11.

In our study incidental thyroid carcinoma was detected in 19.1% of patients which in fact could be attributed to performing FNAC blindly (not under ultrasound guidance) hence only the dominant or palpable nodule was aspirated, furthermore the majority of patients in our study had multinodular goiter, and as it is known that multinodularity decreases the diagnostic accuracy of FNAC9, 15, 18, 19, taking both into account, these might explain the causes for the high incidence. Ultrasound guided FNAC should improve the pre-operative detection of thyroid carcinoma, nodules should be selected not just upon their size, but a lesion that has grown progressively, has become dominant or has changed in consistency over a period of follow up should be biopsied9, or aspirate the nodule with suspicious sonographic features (i.e., solid nodules, hypoechoic lesion, ill-defined margins, microcalcifications in the nodule, or increased vascularity)17,20, sometimes multiple punctures are required to cover the availabilitv suspicious nodules2,15. The of ultrasound guided FNAC, the limitation of cytology to distinguish follicular and Hurthle cell carcinomas from the respective benign adenomas13 and the cytologist's experience are factors that probably explain the worldwide difference in the incidence21, 22. In our study, ITC had been detected mainly in females (80.5%). In regard to age, ITC was noticed in the age category of below 45 years; however no significant statistical association was noted in ITC with gender and age. Similar observations have been reported in other studies2, 15, and 23. The incidence of carcinoma in MNG in this series was significantly higher (p=0.001) from carcinoma in solitary thyroid nodule. So, multinodularity does not represent a certain indicator of benign thyroid disease. Same results were reported in other studies9, 15,16,21,23. In contrast, other studies showed that incidence of cancer is higher in patients with solitary thyroid nodule than MNG, however no significant statistical difference was found20, 23. The analysis of the size of the tumor showed that the majority of incidental thyroid carcinoma (45.5%) were papillary microcarcinoma (tumor size less than 1 cm), and (40.3%) were papillary macro-carcinoma exceed one cm in diameter. This relative high incidence of the incidental papillary thyroid carcinoma greater than one cm in size could be explained by the fact that needle aspiration cytology is not always adequate in detecting cancers especially in multinodular goiter. Thus, it would be more appropriate to take multiple samples from multiple nodules by performing a greater number of needle aspirations1,15. Although there was a significant difference in the incidence of cancer between nontoxic and toxic goiter in our series; (p<0.001), and this finding was matched with other studies1,2,13,23, however hyperthyroidism per se is no longer to be considered protective against developing thyroid carcinoma1,9,24. In fact some reports structured that higher rate of aggressive variants of papillary cancer in patients undergoing surgery for hyperthyroidism should be noted2. Regarding the major post-operative complications, namely RLN injury and hypoparathyroidism, in early post-operative period; although the change of voice and hypocalcemia were considered high (6.2% and 19.9% respectively), they were comparable with other studies2,14,17,18. It is worth mentioning that permanent complications were similar to those with less radical procedures9,19. The findings of this study suggest that incidental thyroid cancer should be considered a common finding in terms of frequency in patients treated surgically for a presumed benign disease; it is found more frequently in cases of multinodular disease and favors a more radical aggressive therapeutic management. To be considered, usually there is no normal thyroid tissue in patients with multinodular disease, therefore leaving abnormal tissue in a patient with bilateral nodular disease might subsequently require reoperation18. We agree with most authors that total and near-total thyroidectomy procedures are the preferred types of operations in the management of thyroid nodular disease upon the advantages of this approach which include the elimination of the papillary thyroid multifocal and bilateral microcarcinoma, thereby reducing recurrence rates, avoids the risk of reoperation which is associated with an increased morbidity, obviously the avoidance of a second operation is preferred by both the patient and the surgeon18,25, the avoidance of the rare possibility of transformation from well differentiated to carcinoma23,25. undifferentiated Additional advantage of total/near-total thyroidectomy is the better monitoring of treated patient by thyroglobulin measurements to detect residual or recurrent disease and optimize the effect of postoperative radioactive iodine therapy16,18,25. Interestingly, non-total bilateral thyroidectomy does not ensure the preservation of thyroid hormone function. Hormone replacement therapy will be required in most patients (about 50%) following more limited thyroid resection

(i.e., lobectomy or subtotal thyroidectomy) thereby eliminating the theoretical advantage of less radical thyroid surgery 17,16,22,25.

#### **Conclusions:**

Multinodular thyroid disease is a risk for undetected malignancy due to the presence of multiple nodules which lower the accuracy of FNAC; however, multinodularity by itself is not a direct risk for malignancy. FNAC need to be done under ultrasound guidance, taking into consideration that multiple aspirations may be required to cover the suspicious nodules. Hyperthyroidism is no longer to be considered protective against malignancy, although we found that nontoxic patients were the majority harboring ITC. Total thyroidectomy eliminates the risk to miss undiagnosed malignancy and allows for better post-operative monitoring of recurrence.

# Ethical approval

The study protocol was approved by the local committee of the scientific council of surgery. Written consent was obtained from all patients prior to participation in the study and prior to perform the operation.

#### **Authors' Contributions:**

Study conception: dr tharwat I sulaiman

Study design: dr tharwat sulaiman

Acquisition of data: dr Mohamed kasim, dr labeed salman

Analysis and interpretations of data: dr Mohamed kasim, dr labeed salman, dr nawfel al shadood Drafting of manuscript: dr labeed salman dr

Mohamed kasim, dr nawfel alshadood

Critical revision: dr tharwat Idrees sulaiman

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25. Sakorafas G.H., Stafyla V, Kolettis T et al,. Microscopic papillary thyroid cancer as an incidental finding in patients treated surgically for presumably benign thyroid disease, J. postgraduate medicine, 2007; 53(1):23-26. سرطان الغدة الدرقية العرضي في المرضى المعالجين جراحيا لأمراض الغدة الدرقية خلال ثلاث سنوات

أ.د. ثروت إدريس سليمان \*\*\* فرع الجراحة, كلية الطب, جامعة بغداد. د. لبيد سلمان حامد \* مستشفى النعمان التعليمي د. محمد قاسم عبد الجبار \*\* مستشفى بغداد التعليمي

# الخلاصة:

**الخلفية :** تعد عقيدات الغدة الدرقية من المشاكل الصحية الشائعة تبرز أهميتها بإستبعاد الاور ام السرطانية من هذه العقد والتي تحصل بنسبة 7% -15% من الحالات ومن الجدير بالذكر أنه ونتيجة لعوامل متعددة أصبح المعدل السنوي للإصابة بسرطان الغدة الدرقية ثلاثة أضعاف ماكان عليه في السابق . إن سرطان الغدة الدرقية العرضي هو أي سرطان تابع للغدة الدرقية والذي لم يستدل عليه عن طريق التحقيقات والفحوصات السابقة للعمليات الجر احية وتم تشخيصه عن طريق الدراسة النسيجية لعينه جر احية مستأصلة لحلاة يفترض أنها حميدة في البداية .

إن هذه النوع من الاورام هو الاكثر شيوعاً في الاناث ولايوجد عمر محدد للإصابة بها حيث ممكن أن تحدث في أي عمر كما أن معضم هذه الاورام هي صغيرة دقيقة تحمل تنبؤ جيد عند علاجها , أيضاً إن هذا النوع من الاورام يحدث في المرضى المصابين بفرط نشاط الغدة الدرقية والذي كان يعتبر سايقاً عامل حماية للإصابة بسرطان الغدة الدرقية.

**هدفُّ الدراسة:** تحديد مدى وحجمُ وجوُد سرطانُ الغدَّة الدرقية العرضي وإمكانية إيجاد خطة تشخيصية ملائمة مع أفضل إجراء جراحي للمرضى ا المصابين بأمراض الغدة الدرقية .

**المرضى وطرق العمل:** دراسة مستقبلية أجريت خلال مدة ثلاث سنوات من قبل جراح واحد وفريقه من المتدربين , أجريت العلميات في مستشفى بغداد التعليمي ومستشفى المستنصيرية الاهلي تم خلال هذه الفترة إستقبال 473 مريض يعانون من مختلف أمراض الغدة الدرقية, تم إستثناء 71 مريض منهم كونهم مشخصين مسبقاً بسرطان الغدة الدرقية , تم تقييم المرضى الباقين والبالغ عددهم 402 مريض بواسطة الزرع النسيجي للغدة المستأصلة جراحياً حول وجود إصابات بسرطان الغدة الدرقية وتعددت أنواع العمليات الجراحية المراحية المراض المندي أ

**النتائج:** وجد سرطان الغدة الدرقية في 77 مريض (19و15%) , 62 منهم من الاناث (80.5%) و 15 من الذكور . 63 حالة (15.6%) منهم ضمن مرض تضخم الغدة الدرقية المفصص (متعدد العقيدات), 12 (3%) مريض بمرض عقدة الغدة الدرقية الاحادي والمجموعتين لم يكونوا ضمن فرط نشاط الغدة الدرقية بالاضافة الى مريضين (0.5%) كانوا يعانون من فرط نشاط الغدة الدرقية متعدد العقيدات. وبتقسيم المرضى حسب المرحلة العمرية وجد 56 مريض (72.7%) ضمن الاعمار الاقل من 45 سنة و 21 مرض (27.3%) ضمن المرحلة الاكثر.