IMPACT: International Journal of Research in Applied, Natural and Social Sciences (IMPACT: IJRANSS)
ISSN (P): 2347–4580; ISSN (E): 2321–8851
Vol. 12, Issue 3, Mar 2024, 1–12

THE PREVALENCE OF DIFFERENTIATED THYROID CANCER IN MULTINODULAR GOITER VERSUS SINGLE THYROID NODULE IN KARBALA

Zaidalisaadhuseeni[1], Sabah Kareem Hamzah[2] & Ali Abdulrasool Abbood[3]

[1]Karbala Health Institute\ Surgery, Karbala, IRAQ.

[2]Karbala Health Institute\ Surgery, Karbala, IRAQ

[3]Karbala Health Institute\ Surgery, Karbala, IRAQ

Received: 07 Mar 2024 **Accepted:** 30 Mar 2024 **Published:** 31 Mar 2024

ABSTRACT

Background*: Thyroid cancer is the most common cancer affecting the endocrine system, accounting for approximately 1% of all human cancers, thyroid cancer occurs in 5–15% of cases with thyroid nodules depending on age, sex, radiation exposure history, family history, and other factors.*

Objectives*: To determine the prevalence of differentiated thyroid cancer in patients with multinodular goiter (MNG) and single thyroid nodule undergoing surgery in Karbala city.*

Methods*: A prospective study that was conducted at Imam Al-Hussain medical city and Safeer Al-Hussain hospital, Karbala, Iraq, over a period of twelve months starting from 1st of December 2021 to 1st of December 2022. During this period a total of 100 patients (88 female and 12 male) undergo thyroid surgery for different causes have been enrolled in the study.*

Results*: The overall prevalence of differentiated thyroid cancer was (19%), there is a strong relationship between nodularity and pathology types .which shows 16 (66.7) of patients with follicular adenoma, 9 patients (60%) with papillary thyroid cancer, and all patients 4(100%) with follicular thyroid cancer were single thyroid nodule, while 45 (84.9) of patients with colloid goiter and all patients with thyroiditis were multi nodular.*

Conclusions*: The prevalence of malignancy was significantly higher in single thyroid nodule than multi nodular goiter, with papillary thyroid cancer being the most common histological subtype. But, the prevalence of malignancy in multi nodular goiter was also quite high and cannot be underestimated, ultrasonography and Fine Needle Aspiration Cytology are both important tools that predicting malignancy in suspicious thyroid diseases (nodular).*

KEYWORDS: *Multi Nodular Goiter, Papillary Thyroid Cancer, Solitary Thyroid Nodule , Follicular Thyroid Cancer.*

INTRODUCTION

Thyroid cancer is the most common cancer affecting the endocrine system, accounting for approximately 1% of all human cancers. it has annual incidence of (0.5-10 /100000) people worldwide(1).Differentiated thyroid cancer (DTC) is increasing in incidence with mostly excellent prognosis. The appearance of DTC depends on age, sex, family history, radiation exposure and many other factor(2).DTC occurs in 7–15% of patients with thyroid surgery. In the year 2014, approximately 63,000 new cases of DTC were diagnosed in the US, Compared to 2009 with only 31,200 new cases. In Germany there are

about 6000 new cases of DTC per year. The growing incidence of thyroid cancer and the tumor shift to diagnosis of smaller tumors is due to the increased usage of diagnostic methods, such as ultrasound of the neck[3].

Differentiated thyroid cancer includes papillary and follicular cancer that derive from thyrocytes and express the sodium iodine symporter. DTC represents the majority (90%) of all types of thyroid cancer[4]. Papillary thyroid carcinoma (PTC) is the most common form of DTC. Histologically it is a tumor of follicular cells of the thyroid gland with characteristic nuclear signs. There are more than 10 histological variants of papillary thyroid cancer documented, can be seen in table (1) WHO classification

Table 1: WHO Classification for Differentiated Thyroid Cancer

Histology	Histological variant
Papillary	Classic (usual) Clear cell Columonar Diffuse sclerosing Tall cell Solid
Follicular	Oncocytic (hurthle cell) Clear cell Mucinous

Table 2: TNM Classification for Thyroid Cancer

T	PRIMARY TUMOR
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor is found
T1	Tumor 2 cm or less in greatest dimension limited to the thyroid
T1a	Tumor 1 cm or less, limited to the thyroid
T1b	Tumor > 1 cm but less than or equal to 2cm in greatest dimension, limited to the thyroid
T2	Tumor > 2 cm but not more than 4 cm in greatest dimension limited to the thyroid
T3	Tumor > 4 cm in greatest dimension limited to the thyroid or any tumor with minimal extrathyroid extension invading only strap muscles
T3a	Tumor size > 4 cm, limited to the thyroid
T3b	Any size tumor with gross extrathyroidal extension invading only strap muscles
T4a	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels

All anaplastic carcinomas are considered T4 tumors

N	REGIONAL LYMPH NODES
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)
N1b	Metastasis to unilateral, bilateral or contralateral cervical, or superior mediastinal lymph node(s)

M	DISTANT METASTASIS
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Follicular thyroid carcinoma (FTC) is a malignant tumor, histologically derived from follicular thyroid cells, showing transcapsular or vascular invasion and missing the typical nuclear signs of papillary carcinoma. In the traditional classification of FTC there are two groups: minimally invasive and widely invasive[5,6,7].

Thyroid nodules are a common clinical problem. Epidemiologic studies have shown the prevalence of palpable thyroid nodules to be approximately 5% in women and 1% in men living in iodine-sufficient parts of the world[8,9]. In contrast, high-resolution ultrasound (US) can detect thyroid nodules in 19–67% of randomly selected individuals with higher frequencies in women and the elderly[10].The clinical importance of thyroid nodules rests with the need to exclude thyroid cancer which occurs in 5–15% depending on age, sex, radiation exposure history, family history, and other factors[11,12].Fine needle aspiration cytology (FNAC) is the clinical procedure of choice for evaluating whether a nodule is benign or malignant[13].It is a simple, safe and most accurate method for selecting the patients who will need surgical resection or follow-up. Ultrasound-guided FNA (USgFNA) has improved diagnostic accuracy compared to FNA by palpation[14,15].Both the European Thyroid Association and the American Thyroid Association have issued clinical practice guidelines and recommendations as to how to evaluate thyroid nodules. Nodules that are usually 1.0 cm or greater in dimension and are nonfunctioning require further evaluation by FNA. If the TSH is suppressed, then radionuclide scintigraphy is indicated to rule out a functioning nodule. Nodules that are less than 1.0 cm but have suspicious ultrasound characteristics also require further investigation. These characteristics are: hypoechogenicity, microcalcifications, irregular margins, intranodular vascularity and regional lymphadenopathy[16,17].The diagnostic cornerstone of thyroid nodules remains the ultrasound examination. It should be performed in any case of known or suspected thyroid nodules or cervical lymphadenopathy to assess if further diagnostic is needed. Sonographic patterns suspicious of malignancy are microcalcifications, irregular margins, solid consistency, hypoechogenity, extrathyroidal extension (ETE) and a tall shape rather than a wide one[18]. The ultrasonographic features of thyroid cancer [19]

Table 3: Ultrasonographic Features of Thyroid Cancer

Table 38-1 Ultrasonographic Features of Thyroid Cancer

			Predictive Value (%)	
IMAGING FEATURE	SENSITIVITY (%)	SPECIFICITY (%)	POSITIVE	NEGATIVE
Microcalcifications	26-59	86-95	24-71	42-94
Hypoechogenicity	27-87	43-94	11-68	74-94
Irregular margins or no halo	17-78	39-85	9-60	39-98
Solid	69-75	53-56	16-27	88-92
Intranodular vascularity	54-74	79-81	24-42	86-97
More tall than wide	33	93	67	75

Data from Frates MC, Benson CB, Charboneau JW, et al: Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Radiology 237:794–800, 2005.

Thyroid function tests can identify patients with unsuspected hyperthyroid states and dictate the appropriate workup.If a 1-cm or larger thyroid nodule is identified, serum TSH levels should be determined. A low serum TSH level denotes overt or subclinical hyperthyroidism and a radioisotope scan is generally indicated. A low serum TSH level also correlates with a lower likelihood of malignancy in a thyroid nodule.A high serum TSH level suggests hypothyroidism, most commonly the result of Hashimoto's thyroiditis[20]. Hashimoto thyroiditis (HT) is the most common autoimmune

disease and the most frequent cause of hypothyroidism, affecting between 2% and 15% of the global population, depending on their age[21,22,23].The pathogenesis of HT involves a chronic inflammatory infiltrate in the thyroid gland as a consequence of a breakdown in immune tolerance. This leads to activation of cellular and humoral immune responses[24]. Histologically, HT is characterized by diffuse lymphocytic infiltration of the gland, with numerous lymphoid follicles and germinal centers, fibrosis, and, ultimately, parenchymal atrophy[25,26]. Genetic and environmental factors, such as dietary iodine uptake, have been shown to contribute to the development of HT[27].

Cytological analysis is performed according to the Bethesda System for Reporting Thyroid Cytopathology. The findings are graded into six categories[28]:

Table 4: Bethesda Scoring System

The Bethesda system for reporting thyroid cytopathology: characteristics, management, and risk of malignancy for each diagnostic category

Diagnostic Categories	Characteristics	Usual management	Implied risk of malignancy (%)
Non-diagnostic or unsatisfactory	Cyst fluid only Virtually acellular specimen Other (hematoma, etc)	Repeat FNA with US-guidance	1-4
Benign	No atypical or malignant cells present, specimen adequate	Clinical follow-up	1
Atypia of unknown significance/Follicular lesion of unknown significance	Atypical cells present, no malignant cells present	Repeat FNA	5-10
Suspicious for follicular neoplasm	Follicular cells present, no malignant cells present	Surgical lobectomy	20-30
Suspicious for malignancy	Cells suspicious for malignancy, specimen adequate	Near-total thyroidectomy or surgical lobectomy	50-75
Malignant	Malignant cells present	Near-total thyroidectomy	100

AIM OF THE STUDY

Into determine the prevalence of differentiated thyroid cancer in patients with multinodular goiter (MNG) and single thyroid nodule undergoing surgery in Karbala city.

PATIENTS AND METHODS

This prospective study was conducted at Imam Al-Hussain medical city and Safeer Al-Hussain hospital, Karbala, Iraq, over a period of one year starting from 1st of December 2021 to 1st of December 2022. During this period a total of 100 patients (88 female and 12 male) undergo thyroid surgery for different indications have been enrolled in the study. All the patients have accepted to participate in this study and their verbal consent has been taken.

Most patients had preoperative assessment by history and examination, with standard pre-operative assessment which include evaluation, ultrasonography (US) of the thyroid and neck, fine-needle aspiration cytology (FNAC) of the thyroid nodule, and FT3, FT4, TSH, and TSH, also thyroid antibody titer, all patients underwent checking of vocal cord

mobility, serum calcium, In addition to routine investigations before surgery such as CBC, virology, ECG, and sometimes echo study.

Patients were divided in to two groups according to nodularity whether single thyroid nodule or multinodular goiter, with the help of thyroid ultrasound.We used special questioner regarding information from the patients like radiation exposure or family history of thyroid diseases.

All patients data have been recorded in the study paper and collected.

Regarding ultrasound and FNAC most of them done in different clinic not in one clinic, some of them in private clinic and some of them in private hospital and the others in our hospital.

The ultrasound report use the TIRAD for classification of thyroid nodules.

The FNAC report used the Bethesda scoring for thyroid nodules.

All patients admitted to the hospital and were euothyroid before the operation.

Inclusion Criteria

- Age between 14-65years.
- Patients with hypothyroidism and enlarged gland.
- Patients with hyperthyroidism and goiter.
- Patients with suspected nodule.

Exclusion Criteria

- Thyroidectomy due to metastatic cancer from other organs.
- Undifferentiated thyroid cancer.

Surgery was either total or near total (leaving only 1gm of thyroid tissue in one side) or sometimes lobectomy with isthmusectomy.

All the patients are discharged either within 24 hours to 48 hours post-surgery.

The final histopathological report received either from the senior during follow up visit or sent by the patient through the phone after a period of 10 days to 3 weeks.

STATISTICAL ANALYSIS

Statistical analysis was performed using IBM® SPSS® version 23 for Windows. Chi-square test was used to analyze the association between categorical variables, Fisher's Exact test was used instead of the former when needed. Independent Samples T-test and analysis of variables (ANOVA) were used to test the statistical significance of the difference between two variable or more, respectively.

RESULTS

This study enrolled 100 patients; 12 males and 88 females, their overall mean age was 41.1± 10.6 years, while males' mean age was 43.4± 10.2 years, while females mean age was 40.8± 1.7 years. The most frequently observed pathology was colloidal goiter with 53 (53%) cases, followed by follicular adenoma with 24 (24%) cases, while there were 15 (15%) patients with papillary carcinoma, and four (4%) patients with follicular carcinoma, and four (4%) with thyroiditis, as shown in Figure-1.

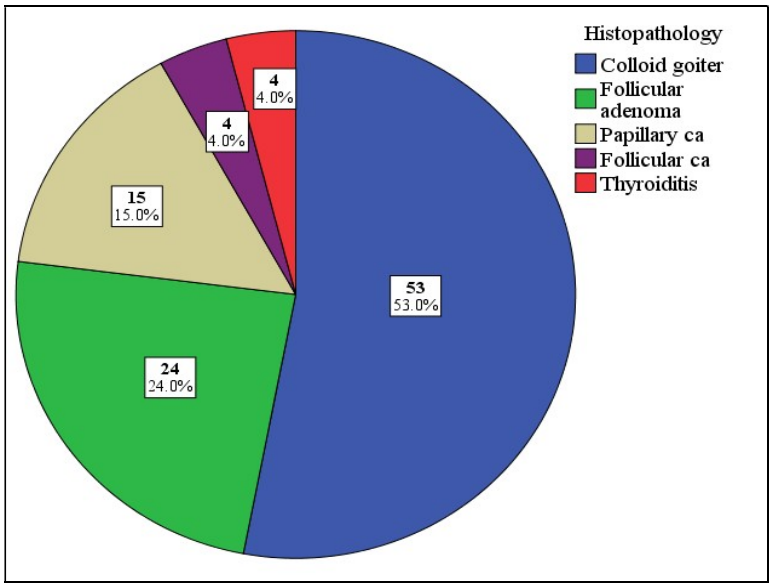

Figure 1: Distribution of the Study Sample According to Histopathology.

There was no statistically significant difference in mean age between pathology types, however it can be observed that patients with follicular adenoma and papillary ca had lower age group, with 37.5±10.6 years and 37.57±11.77 years, respectively. The gender distribution showed no significant statistical association with pathology type, probably due to low number of males in the current study. There were only five smokers; two with colloidal goiter and three with papillary carcinoma. As shown in Table 5

Table 5: Distribution of Basic Characteristics of the Study Group According to Histopathology

Variables	Colloid goiter	Follicular adenoma	Papillary ca	Follicular ca	Thyroiditis	P-value
Age (years) Mean± SD	43.53±9.7	37.5±10.6	37.57±11.77	44.5±16.68	40±3.9	0.105
Male/ Female ratio	5/48	3/21	4/11	0/4	0/4	0.444
Smokers/ nonsmokers	2/51	0/24	3/12	0/4	0/4	0.134

There were statistically significant differences between pathology types according to TIRADS and Bethesda scores, as patients with papillary and follicular ca had significantly higher scores compared to other pathologies, with mean of 4± 0.8, 3.5± 0.6 for TIRADS, and 4.5± 0.9, 4± 0.0 for Bethesda, respectively. Patients with TIRADS >3 and the histopathology showed colloid goiter were only two (3.8%), six (25%) with follicular adenoma, 10 (66.7%) with papillary ca, two (50%) with follicular ca, and nil in patients with thyroiditis. There were no patients with Bethesda scores >3 with colloid goiter, three (12.5%) with follicular adenoma, 13 (86.7%) with papillary ca, four (100%) all cases with follicular ca, and no case with thyroiditis. As shown in Table-6.

Table 6: Distribution of Histopathology Types According to Ultrasonography TIRAD and Bethesda Scoring System

Variables	TIRADS			Bethesda scoring system		
	Mean	SD	Score>3 No. (%)	Mean	SD	Score>3 No. (%)
Colloid goiter	2.5	0.6	2 (3.8%) out of 53 patients	2.2	0.4	0 (0.0%) out of 53 patients
Follicular adenoma	3.0	1.0	6 (25.0%) out of 24 patients	2.6	0.7	3 (12.5%) out of 24 patients
Papillary ca	4.0	0.8	10 (66.7%) out of 15 patients	4.5	0.9	13 (86.7%) Out of 15 patients
Follicular ca	3.5	0.6	2 (50.0%) out of 4 patients	4.0	0.0	4 (100.0) out of 4 patients
Thyroiditis	2.8	0.5	0 (0.0%) out of 4 patients	2.5	0.6	0 (0.0) Out of 4 patients
P-value	<0.001		<0.001	<0.001		<0.001

There was statistically significant association between pathology and nodularity, as 16(66.7%) cases of follicular adenoma, nine (60%) of papillary ca, and all cases of follicular ca were single nodular, while 45 (84.9%) of colloid goiter and all cases of thyroiditis were multinodular, as shown in Table-7. The percentages of papillary ca and follicular ca among patients with single nodular goiter were 24.3% and 10.8%, respectively, while the percentage of papillary ca among patients with multinodular goiter was 9.5%.

Table 7: Distribution of Histopathology Results According to Thyroid Nodularity

Histopathology	Single nodular goiter	Multi nodular goiter	P-value
	Number (%)	Number (%)	
Colloid goiter	8(15.1%)	45(84.9%)	**<0.001**
Follicular adenoma	16(66.7%)	8(33.3%)	
Papillary ca	9(60%)	6(40$)	
Follicular ca	4(100%)	0(0)	
Thyroiditis	0(0)	4(100%)	
Total	37 (37.0%)	63 (63.0%)	

Cases with single nodular goiter had higher TIRADS and Bethesda scores, and 14(70%) of TIRADS or Bethesda scores >3 had single nodular goiter, while age, gender and smoking showed no statistically significant difference according to thyroid nodularity, as shown in Table-8.

Table 8: Distribution of Study Variables According to Thyroid Nodularity

Variables		Single Nodular Goiter	Multi Nodular Goiter	P-value
		Number (%)	Number (%)	
Age (year) mean± SD		38.39±12.91	42.68±8.81	0.082
Gender	**Male**	4(33.3)	8(66.7)	1.0
	Female	33(37.5)	55(62.5)	
Smoking		1 (20.0)	4 (80.0)	0.649
TIRADS> 3		14(70)	6(30)	**<0.001**
FNA> 3		14(70)	6(30)	**<0.001**

DISCUSSION

The prevalence of thyroid cancer is increasing worldwide. This study is the first study in Karbala city regarding differentiated thyroid cancer prevalence among patients with multinodular goiter and single thyroid nodule. The overall prevalence of differentiated thyroid cancer was (19%) ,which is slightly higher in comparison in what was published in 2020 in Yemen which shows cancer prevalence was (13.8) in thyroid nodules , with mean age 37.5 [30] . but in a study in Spain published at 2011 showed that the risk of thyroid malignancy in thyroid nodules was (24.9) [31].Of these (19%) , papillary thyroid cancer was 15 (79%) with female to male (11:4) which is more predominant than follicular thyroid cancer which is only 4 (21%) and all of them were females , which may be due to small sample number.

Regarding TIRAD score , patients with PTC and FTC shows higher score than other pathologies with mean of 4± 0.8, 3.5± 0.6 for TIRADS respectively with p-value <(0.001) , which is equal to what was published in November 2022[32].Regarding Bethesda scoring patients with PTC and FTC shows higher score than other pathologies with mean score 4.5± 0.9, 4± 0.0 for Bethesda, respectively with p-value > (0.001).

Our study shows that the most common histopathology was colloid (53%), and the second most common pathology was follicular adenoma (24%), which is agreed to one study in Baghdad Medical City 2018[33].

Our study shows that patients with thyroid malignancy have higher TIRAD score and higher Bethesda score, patients with thyroid cancer and TIRAD more than 3 were 10(66%) for PTC and 2 (50%) for FTC.

Patients with PTC and Bethesda score more than 3 were 13 (86.7%) and patients with FTC and Bethesda score more than 3 were 4 (100%).From this we noticed that FNAC was more accurate than Ultrasound for diagnosis of thyroid malignancy from other thyroid diseases, which agree to what was published in 2019 in Pakistan Medical journal [34], and it could be operator dependent. Patients with papillary thyroid cancer (PTC) and patients with follicular adenoma shows lower age with regard to other pathologies with mean age 37.5±10.6 years and 37.57±11.77 years, respectively , which agreed to what was published in Journal of Korean society of surgery in 2012 [35].

Our study shows that there is a strong relationship between nodularity and pathology types .which shows 16 (66.7) of patients with follicular adenoma, 9 patients (60%) with papillary thyroid cancer, and all patients 4(100%) with follicular thyroid cancer were single thyroid nodule, while 45(84.9) of patients with colloid goiter and all patients with thyroiditis were multi nodular. The percentages of papillary ca and follicular ca among patients with single nodular goiter were 24.3% and 10.8%, respectively, while the percentage of papillary ca among patients with multi nodular goiter was 9.5%, which is agreed to what was published in USA in 2006 [36], also it agreed to meta-analysis study in USA in 2012 [37]. But some studies shows similar rate of malignancy among MNG and STN [38].

CONCLUSION

- We conclude that the prevalence of malignancy was significantly higher in STN than MNG, with PTC being the most common histological subtype. But, the prevalence of malignancy in MNG was also quite high and cannot be underestimated. It would be practically wise to keep this in mind while evaluating patients with MNG and ample effort should be made to pre-operatively identify any malignant focus, so that appropriate therapeutic protocol can be planned.

- Ultrasonography and Fine Needle Aspiration Cytology are both important tools that predicting malignancy in suspicious thyroid diseases (nodular).

RECOMMENDATIONS

- Patients with solitary thyroid nodule are more prone to thyroid malignancy than multi nodular goiter.
- Thyroid nodule in young age should be treated carefully and properly.
- Larger sample is needed to be more informative .

REFERENCES

1. *Dong, W., Zhang, H., Zhang, P., Li, X., He, L., Wang, Z., & Liu, Y. (2013). The changing incidence of thyroid carcinoma in Shenyang, China before and after universal salt iodization. Medical science monitor: international medical journal of experimental and clinical research, 19, 49.*
2. *Hegedüs, L., The thyroid nodule. New England Journal of Medicine, 2004. 351(17): p. 1764-1771.*
3. *Siegel, R., et al., Cancer statistics, 2014. CA: a cancer journal for clinicians, 2014. 64(1): p. 9-29.*
4. *Sherma, S.I., Thyroid carcinoma. The Lancet, 2003. 361(9356): p. 501-511.*
5. *BRENNAN, M. D., BERGSTRALH, E. J., van HEERDEN, J. A., & McCONAHEY, W. M. (1991, January). Follicular thyroid cancer treated at the Mayo Clinic, 1946 through 1970: initial manifestations, pathologic findings, therapy, and outcome. In Mayo Clinic Proceedings (Vol. 66, No. 1, pp. 11-22). Elsevier.*
6. *Collini, P., G. Sampietro, and S. Pilotti, Extensive vascular invasion is a marker of risk of relapse in encapsulated non-Hürthle cell follicular carcinoma of the thyroid gland: a clinicopathological study of 18 consecutive cases from a single institution with a 11-year median follow-up. Histopathology, 2004. 44(1): p. 35-39.*
7. *Lang, W., H. Choritz, and H. Hundeshagen, Risk factors in follicular thyroid carcinomas. A retrospective follow-up study covering a 14-year period with emphasis on morphological findings. The American journal of surgical pathology, 1986. 10(4): p. 246-255.*
8. *Tunbridge, W., et al., The spectrum of thyroid disease in a community: the Whickham survey. Clinical endocrinology, 1977. 7(6): p. 481-493.*
9. *Vander, J.B., E.A. Gaston, and T.R. Dawber, The significance of nontoxic thyroid nodules: final report of a 15-year study of the incidence of thyroid malignancy. Annals of internal medicine, 1968. 69(3): p. 537-540.*
10. *Tan, G.H. and H. Gharib, Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. Annals of internal medicine, 1997. 126(3): p. 226-231.*
11. *Hegedus, L., Clinical practice: the thyroid nodule [J]. N Engl Med, 2004, 351 (17): 1764–1771.*
12. *Mandel, S.J., A 64-year-old woman with a thyroid nodule. Jama, 2004. 292(21): p. 2632-2642.*
13. *Gharib H, Goellner JR: Fine-needle aspiration biopsy of the thyroid: an appraisal. Ann Intern Med 1993;118:282-289.*

14. *Marqusee E, Benson CB, Frates MC, Doubilet PM, Larsen PR, Cibas ES, Mandel SJ: Usefulness of ultrasonography in the management of nodular thyroid disease. Ann Intern Med 2000;133:696-700.*
15. *Kim DL, Song KH, Kim SK: High prevalence of carcinoma in ultrasonography-guided fine needle aspiration cytology of thyroid nodules. Endocr J 2008;55:135-142.*
16. *Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JWA, Wiersinga W: European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006;154:787-803.*
17. *Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, Mclver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM: Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-1214.*
18. *Haugen, B.R., et al., 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid, 2016. 26(1): p. 1-133.*
19. *FRATES, Mary C., et al. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Radiology, 2005, 237.3: 794-800.*
20. *BOELAERT, Kristien, et al. Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. The Journal of Clinical Endocrinology & Metabolism, 2006, 91.11: 4295-4301.*
21. *VANDERPUMP, Mark PJ. The epidemiology of thyroid disease. British medical bulletin, 2011, 99.1.*
22. *Delemer, Brigitte, et al. "An observational study of the initial management of hypothyroidism in France: the ORCHIDÉE study." European journal of endocrinology 167.6 (2012): 817-823.*
23. *McLeod, Donald SA, and David S. Cooper. "The incidence and prevalence of thyroid autoimmunity." Endocrine 42.2 (2012): 252-265.*
24. *Ajjan, Ramzi A., and Anthony P. Weetman. "The pathogenesis of Hashimoto's thyroiditis: further developments in our understanding." Hormone and Metabolic Research 47.10 (2015): 702-710.*
25. *Hiromatsu Y, Satoh H, Amino N. Hashimoto's thyroiditis: history and future outlook. Hormones (Athens). 2013;12(1):12–18.*
26. *Caturegli P, De Remigis A, Chuang K, Dembele M, Iwama A, Iwama S. Hashimoto's thyroiditis: celebrating the centennial through the lens of the Johns Hopkins hospital surgical pathology records. Thyroid. 2013;23(2):142–150.*
27. *McLeod DS, Caturegli P, Cooper DS, Matos PG, Hutfless S. Variation in rates of autoimmune thyroid disease by race/ethnicity in US military personnel. JAMA. 2014;311(15):1563–1565*

28. *Haugen, B. R., Alexander, E. K., Bible, K. C., Doherty, G. M., Mandel, S. J., Nikiforov, Y. E., ... & Wartofsky, L. (2016). 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid, 26(1), 1-133.*
29. *Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. Thyroid. 2017 Nov;27(11):1341-1346. doi: 10.1089/thy.2017.0500. PMID: 29091573.*
30. *AL-SHARAFI, Butheinah A., et al. Thyroid cancer among patients with thyroid nodules in Yemen: a three-year retrospective study in a tertiary center and a specialty clinic. Thyroid Research, 2020, 13: 1-8.*
31. *SEBASTIÁN-OCHOA, Nerea, et al. Experienciaclínica en unaconsulta de altaresolución de nódulotiroideo. Endocrinología y nutrición, 2011, 58.8: 409-415.*
32. *Bukasa-Kakamba, J., Bayauli, P., Sabbah, N., Bidingija, J., Atoot, A., Mbunga, B., & M'Buyamba-Kabangu, J. R. (2022). Ultrasound performance using the EU-TIRADS score in the diagnosis of thyroid cancer in Congolese hospitals. Scientific Reports, 12(1), 18442.*
33. *Ghadhban, Basim R. "Incidence of differentiated thyroid carcinoma in multinodular goiter patients." International Journal of Surgery Open 15 (2018): 18-24.*
34. *Alshoabi SA, Binnuhaid AA. Diagnostic accuracy of ultrasonography versus fine-needle-aspiration cytology for predicting benign thyroid lesions. Pak J Med Sci. 2019;35(3):630-635. doi: 10.12669/pjms.35.3.292. PMID: 31258566; PMCID: PMC6572947.*
35. *Cho JS, Yoon JH, Park MH, Shin SH, Jegal YJ, Lee JS, Kim HK. Age and prognosis of papillary thyroid carcinoma: retrospective stratification into three groups. J Korean Surg Soc. 2012 Nov;83(5):259-66. doi: 10.4174/jkss.2012.83.5.259. Epub 2012 Oct 29. PMID: 23166884; PMCID: PMC3491227.*
36. *Barroeta, Julieta E., et al. "Is fine-needle aspiration (FNA) of multiple thyroid nodules justified?." Endocrine pathology 17.1 (2006): 61-66.*
37. *Brito JP, Yarur AJ, Prokop LJ, McIver B, Murad MH, Montori VM. Prevalence of thyroid cancer in multinodular goiter versus single nodule: a systematic review and meta-analysis. Thyroid. 2013 Apr;23(4):449-55. doi: 10.1089/thy.2012.0156. PMID: 23067375.*
38. *Burkan, N., M. Qubati, and S. Qubati. "The Risk of Thyroid Carcinoma in Multinodular Goiter Compared to Solitary Thyroid Nodules: A Prospective Analysis of 207 Patients." Journal of Surgical Endocrinology 3 (2021): 81-88.*