

Clinicopathological study of malignancy in solitary thyroid nodule

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ABSTRACT



Objectives. To study proportion of malignancy in patients with solitary thyroid nodule who had underwent hemi/total thyroidectomy. **Methodology.** Study design: Cross sectional study. Study setting: Patients in the Out-patient and In-patient Department of General Surgery, Government Medical College, Thiruvananthapuram. Sample size: 150 patients Study Procedure: Data was collected using a structured proforma. An informed consent written in the local language was read out to the study subjects and signature was obtained. All the questions in the proforma were read to the study subjects and responses recorded. Investigation reports and previous medical reports were used for filling relevant parts of the proforma. **Analysis:** Data collected was entered in excel sheets and analyzed using SPSS software. **Results.** 150 patients were operated for clinically detected STN. 16 (10.67%) were malignant. Papillary thyroid cancer was the most common type (93.75%). Mean age of patients with malignancy (n = 58) was 39.94 ± 14.83 years. Out of them 12 were females and 4 were male patients (F: M = 3: 1). 134 STNs were benign (23 males and 111 females). Malignant STN was reported in 14.81% males and 9.76% females. No significant correlation between tumour size and the risk of malignancy (P = 0.338). Altered thyroid function status is not a predictive factor for malignancy (P=0.801). FNAC (P=0.002) and USG (P=<0.001) were predictive of malignancy. Complications were more associated with total thyroidectomy (53.57%). Most frequent complication was transient hypocalcemia (15.4%). Hospital stay were more in patients who had underwent total thyroidectomy (P=<0.001). **Conclusions.** STN has high malignant potential compared to MNG. Preoperative evaluation with thorough history, physical examination, USG and FNAC could diagnose STN as benign or malignant. Strong predictors of malignancy include male gender, micro calcification and cervical lymphadenopathy. Complications are more associated with Total thyroidectomy. Hypocalcemia was the most common complication following thyroid surgery.

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Introduction

Thyroid nodules are very common entity, with an estimated prevalence based on palpation of 3–7%, and based on ultrasound examination of 20–76%, respectively [1–6]. Patients with a palpable thyroid nodule have a 20–57% chance of additional thyroid nodules being discovered in the ultrasonographic examination [7]. The prevalence of palpable thyroid nodule in South India is about 12.2% [8]. However, reported general incidence of thyroid carcinoma is only approximately 5% in the population, regardless of their size [5,6,9–11]. The recent data suggest that the incidence of thyroid malignancy is increasing over the past years [9,12]. The incidence of malignancy is more in solitary thyroid nodules (STN) compared to that in a case of multinodular goiter (MNG). [12–14]. Apart from malignancy there are many other differential diagnoses for a thyroid nodule which we must keep in mind while

evaluation. The preoperative evaluation of thyroid nodules to distinguish between benign and malignant nodules is of much importance. It is not possible to use all tests to evaluate the nature of the nodule in a patient with STN. So, it is necessary to identify the predictors of malignancy so as to select appropriate treatment strategies that can avoid unnecessary extensive surgical procedures and diagnostic thyroidectomy which may bring potential adverse effects, such as hypothyroidism, hypocalcemia, and recurrent laryngeal nerve injury [12–14].

The main purpose of our study is to determine the incidence of malignancy in STN, and thus to know the predictors of malignancy so that thorough preoperative evaluation can be done in a systematic way for patients with STN and give adequate treatment for them. More extensive surgery in the form of total thyroidectomy may be reserved for patients with high probability of malignancy and for those with less chance of malignancy a

conservative type of surgery in the form of hemithyroidectomy may be done. The primary objective is to study proportion of malignancy in patients with Solitary Thyroid Nodule who had underwent hemi/total thyroidectomy. Secondary objectives: to study regarding determinants of malignancy in solitary thyroid nodule, and to study histological variants in solitary thyroid nodule.

Materials and Methods

The present study was based on patients who were operated for clinically detected STN. The study was done in a tertiary care center of Kerala, South India. It included patients with clinically detected STN who had undergone any thyroidectomy between February 2019 and January 2020. The patients and their relatives gave consent to use the information for study purpose. Institutional Ethics Committee approved the study.

For all patients the following data were collected: age, gender, history of radiation exposure, family history of thyroid disease, family history of any malignancy, drug intake history and the thyroid hormone profile. The operative procedure was based on the different parameters like age of the patient, clinical examination, fine needle aspiration cytology (FNAC) findings and USG interpretation. The decision for surgery was solely based on individual patient's examination and relevant investigation findings.

In almost all of the patients the plan of surgery was decided beforehand. For SNT, diagnosed clinically as well as ultrasonographically, hemi-thyroidectomy of the involved side was the surgery done and the specimen was sent for routine histopathological examination (HPE).

During surgery hemostasis, safeguarding of the recurrent laryngeal nerve, parathyroid, and other vital structures was taken care of. Adequate measures were taken to correct postoperative hypocalcemia and hoarseness of voice. Further treatment plan was based on the histopathology report. If the report was benign, the patient was kept in follow up by regular monitoring of hormone levels, with or without thyroid hormone supplementation.

Hypocalcemic features were managed by supplementing of oral or intravenous calcium preparations. If the final histopathology report came malignant, the patients were advised to undergo I-131 whole body scan within 4–6 weeks after surgery and radioactive iodine ablation was advised for residual lesion or tissue in the thyroid bed. All the patients were kept under regular follow-up.

Statistical analysis was done with the help of Statistical Packages for Social Sciences (SPSS). Comparison of proportions between groups was done by the χ^2 test, taking $P < 0.05$ as significant.

Results

150 patients were operated for clinically detected STN. Majority of the patients with STN were females ($n = 123$, 82%). Mean age was 39.3 ± 12.5 years, with a wide range (min– max: 16-71 years).

Table 1. Distribution of patients by age groups

Age in years	Frequency	Percent
≤ 20	10	6.7
21 - 30	28	18.7
31 - 40	50	33.3
41 - 50	34	22.7
51 - 60	18	12
>60	10	6.7
Total	150	100

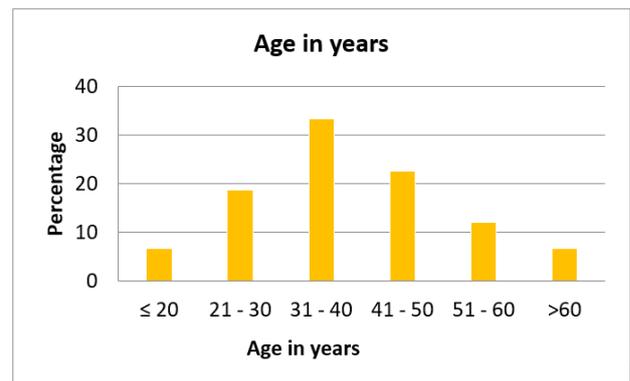


Figure 1. Age group distribution

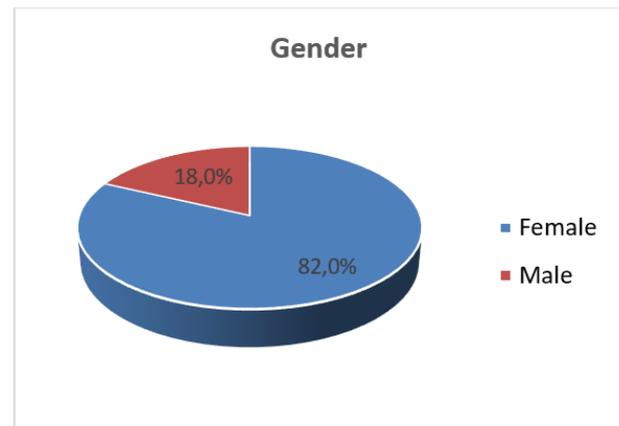


Figure 2. Gender frequency distribution

The most common presentation of STN was as a swelling over the anterior aspect of the neck. The swelling was noticed by patient or their relatives in most cases. Other fewer common symptoms were associated pain, hoarseness and dysphagia.

Ultrasonography. Ultrasonographic examination findings were available in 146 patients. Out of them 123 had SNT, 22 had MNG and 1 showed normal thyroid gland. TIRADS categorization is depicted in Table 2.

Table 2. TIRADS frequency distribution

USG	Frequency	Percent
TIRADS 1	2	1.4
TIRADS 2	116	79.5
TIRADS 3	24	16.4
TIRADS 4	2	1.4
TIRADS 5	2	1.4
Total	146	100.0

On postoperative histopathology, 16 (10.7%) were reported as malignant. Mean age of patients with malignancy (n = 16) was 39.94 ± 14.83 years. Out of them 12 were females and 4 were male patients (M: F ratio of 1:3). Rest 134 STNs were reported as benign (23 males and 111 females). Malignant STN was reported in 4 out of 27 (14.81%) males and 12 out of 123 (9.76%) females.

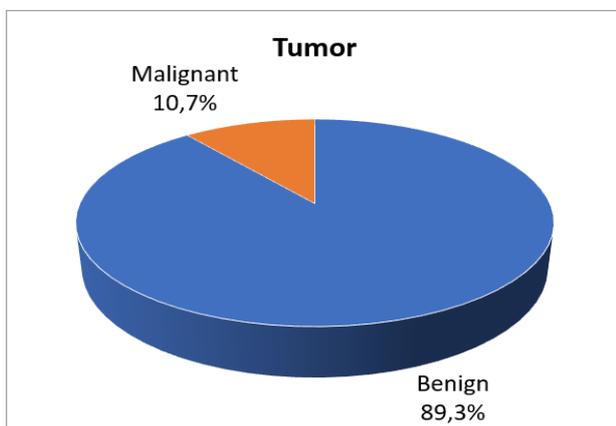


Figure 3. Distribution of the final diagnosis

Majority of the nodules (n=72, 48%) were <2 cm in size. However, there was no significant correlation between tumour size and the risk of malignancy (P = 0.338).

Thyroid function test and fine needle aspiration cytology

Thyroid function test was available for all patients. 128 (85.3%) patients were euthyroid, 21 (14%) hypothyroid and 1 (0.7%) patient was hyperthyroid. Before surgery, these patients were made euthyroid by supplementing thyroxin or by treatment with anti-thyroid drugs.

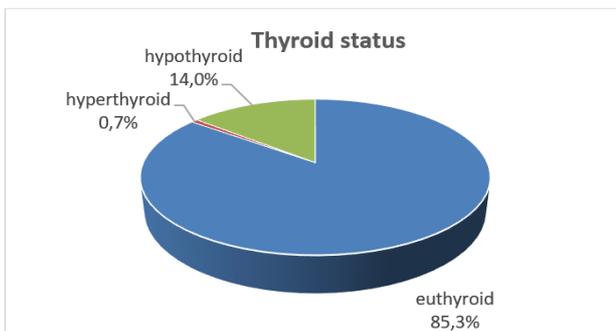


Figure 4. Distribution of patients' thyroid status

Fine needle aspiration cytology was available for 146 patients and was reported based on TBSRTC.

Table 3. TBSRTC frequency distribution

FNAC	Frequency	Percent
BETHESDA1	8	5.5
BETHESDA2	121	82.9
BETHESDA3	4	2.7
BETHESDA4	12	8.2
BETHESDA 5	1	0.7
Total	146	100

Type of Surgery and operative findings

Hemithyroidectomy was done in 122 (81.3%) patients. Total thyroidectomy was performed in 28 (18.7%) patients. Among the patients with final HPR as benign, total thyroidectomy was performed in 23 patients (17.16%). Postoperative hospital stay ranged from one to 6 days, mean hospital stay being 2.8±1.0 days. Postoperative hypocalcemia was seen in 23 (15.4%) patients. It was transient in all patients and most of the patients were asymptomatic. The complications of surgery also included hematoma in 2 (1.4%) patients and recurrent laryngeal nerve injury in 6 patients (4%) in form of neuropraxia and improved afterward.

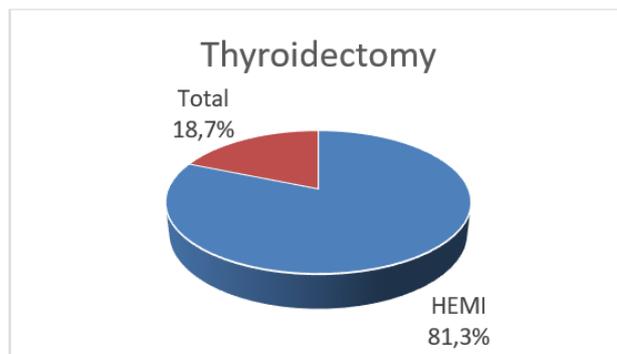


Figure 5. Distribution of the type of thyroidectomy

Table 4. Post operative complications frequency

Complication	Frequency	Percent
Hematoma	2	1.4
Hypocalcemia	23	15.4
Neuropraxia	6	4
Nil	120	80

Histopathology findings

Histopathology was Follicular adenoma [FA] in 81 (54%), Nodular goiter [NG] in 41 (27.33%), Hashimoto's thyroiditis [HT] in 4 (2.67%), non-invasive follicular thyroid neoplasm with papillary like nuclear features [NIFTP] in 1 (0.67%), follicular carcinoma [FTC] in 1 (0.67%), papillary carcinoma [PTC] in 15 (10%),

lymphocytic thyroiditis [LT] in 7 (4.67%). Of the 15 patients with papillary carcinoma, 2 were reported as the follicular variant of papillary carcinoma [FVPTC] on histopathology thyroiditis was found among 34 patients (22.67%).

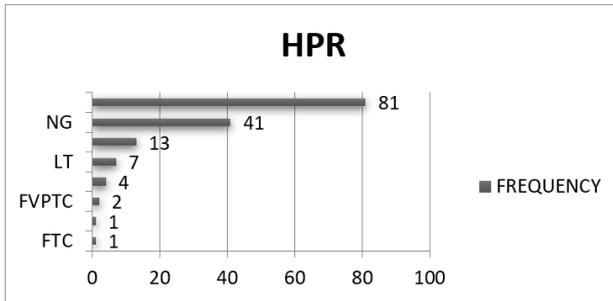


Figure 6. Final HPR – frequency distribution of histopathological results

Discussion

Thyroid nodule refers to a distinct lesion within the thyroid gland that is palpably or radiologically distinct from the surrounding thyroid parenchyma [15]. Benign causes of a thyroid nodule include the colloid nodule and the multinodular goiter. In patients with Hashimoto's thyroiditis and Graves' disease, nodularity is noticed occasionally. Malignant causes of nodules include thyroid cancer, lymphoma as well as metastasis to the thyroid gland [16]. Therefore, it is recommended that all thyroid nodules >1 cm in size should undergo evaluation. This includes both palpable and nonpalpable nodules, detected by imaging [16].

As the literature suggests, STN has a higher risk of malignancy compared to MNG [12]. Because of this reason, surgeons evaluate STN with high degree of suspicion and plan treatment in a systematic manner. Clinically, STNs are common, being present in up to 50% of the elderly population. The majority of STNs are malignant [12-14]. Preliminary investigation includes careful history taking and thorough clinical examination and thyroid function tests [17].

Out of 150 patients with clinically detected SNT, 102 (68%) were truly SNT and remaining (48pts, 32%) were MNG on post operative HPR.

Malignancy was the final diagnosis in 16 patients, of which 10 were SNT (62.5%) and 6 were MNG (37.5%). Incidence among SNT was 9.81% and among MNG was 16.67%. This increase in incidence of malignancy in MNG compared to SNT may be due to the reason that our study group didn't include SNTs with clinically or sonologically detected cervical lymphadenopathy, which is one among the strong individual predictors of malignancy as noted by Tai et al and Mohamed et al. [12,18].

In a study from Nigeria, the authors have described malignancy in 1 out of the 13 cases of STN (7.6%) and

twenty four out of 160 cases of MNG (15%) [19]. Our study results were similar to this. Hence, multinodularity does not necessarily exclude malignancy.

There were 146 cases of clinically detected STN with an available ultrasound finding in the study group. 16 (10.67%) clinically detected STNs were reported as malignant in the final HPE. This high incidence of malignancy reported in our study is similar to that of Tai et al. [12].

Further investigation should be considered if the following factors are present in addition to the thyroid nodule like male gender, extremes of age (<20 or >70 years), history of neck irradiation, nodule >4 cm in size or the presence of any pressure symptoms [16]. None of our patients in the study group had history of radiation exposure. Age of the patient was not a risk factor for malignancy.

Thyroid nodules are more common in females as noted in the present study [12,20]. But in males the incidence of malignancy is more common [12,21]. During our study period, there were 123 (82%) females with STN. Among female patients 12 (9.76%) were reported as malignant in HPE. Final HPE showed malignancy in 4 (14.81%) out of 27 male patients with STN. Hence, the predominance of thyroid nodules in females and increased incidence of malignant thyroid nodules in males noted in our study are similar to that of Tai et al. [12].

Size of the nodule has no relation with malignancy in our study ($P=0.338$) which was also reported by Tai et al. [12]. A study by Kamran et al. opined that the risk of follicular carcinomas and other rare thyroid malignancies increases as nodules enlarge [22]. However, no such association with size was seen in our study.

Ultrasonography is the most cost-effective imaging procedure, and is highly sensitive in assessing nodule size and number. There are a few USG patterns which suggest malignancy like irregular shape, ill-defined borders, hypoechogenicity, solid echotexture, heterogeneous internal echoes, micro calcification, absence of a 'halo', an anteroposterior to transverse diameter ratio (A/T) >1, infiltration into regional structures, and suspicious regional lymph nodes [16].

An article by Rago et al. noted that only atypia at cytology and spot micro calcification at ultrasound was predictive of malignancy. Male gender, normal thyroid volume, single nodularity, nodule hypo echogenicity, size and blurred margins were also associated with malignancy, but not significantly as noted in their study [23]. Papini et al in their article suggests that USG guided FNAC should be performed on all 8–15 mm hypoechoic nodules with irregular margins, intranodular vascular spots or micro calcification [24]. This study mainly highlighted the USG findings.

Fine needle aspiration cytology is recommended to be a cost-effective procedure in the initial evaluation and management of thyroid nodules [12,14]. It is recommended that every patient with a palpable thyroid nodule should undergo an FNAC. USG-guided FNAC can lower the occurrence of non-diagnostic smears. Whenever FNAC diagnosis was inconclusive due to inadequate material or difficulty in aspiration by conventional method, USG guided FNAC was performed. In our experience also we have noted, better yield of diagnostic cytological material with the help of the USG-guided aspirations compared to blind FNAC [25,26]. All our patients had FNAC done before surgery and it helped us to decide the type of surgery to be under taken. When FNAC report was malignant, total thyroidectomy was done. In all other cases, hemi thyroidectomy was done.

In a recent article, the authors have noted regarding the role of USG by suggesting that nodules with a non-diagnostic FNAC result in the setting of low-risk demographics and benign appearance at ultrasound can be followed with serial ultrasound examinations, thereby avoiding repeat FNAC [27]. These findings are in contrast to the recommended current guidelines to repeat FNAC after a non-diagnostic result [28].

The management of thyroid nodules is based on a combination of clinical evaluation followed by appropriate investigations. An individualized approach, rather than a broad algorithm is increasingly becoming relevant in the management of thyroid nodules [16]. Determining the nature of STN is very important as aggressive surgery may be regarded as an excessive mode of treatment [12]. We opted for surgery in all the patients as there is a high incidence of malignancy in STN patients as reported in literature [12]. The postoperative histopathology reports corroborated our findings as ~1 in 10 (981 in 10000) of STN were reported as malignant.

We have performed hemi thyroidectomy in FNAC reported benign nodules. Total thyroidectomy was done in those cases where FNAC was reported as malignant. In our study total thyroidectomy was done in 28 (18.7%) patients. out of them 5 (17.86%) patients had their HPR as malignancy and the remaining 23 were benign. In most of the instance patients chose for total thyroidectomy as their surgery even though hemithyroidectomy was an option. Among the 23 benign cases that had total thyroidectomy the incidence of complication was higher. Out of the 122 patients who underwent hemithyroidectomy, complications developed in 15 patients (12.29%). Out of the 28 patients who underwent total thyroidectomy, 15 (53.57%) patients had developed complications.

11 out of 16 patients, who on post operative HPE was malignant, had undergone hemi thyroidectomy. These patients were kept in follow up and few opted for completion thyroidectomy, rather than a follow up.

The result of our study shows that the incidence of malignancy in STNs is indeed high. Multinodularity does not necessarily exclude malignancy. The probability of malignancy is more in those nodules where USG shows solid echogenicity, presence of micro calcification in nodule and associated cervical lymphadenopathy. Total thyroidectomy definitely has higher risk of complication. Hence, we conclude that clinically detected solitary nodules should be treated with high degree of suspicion and patients should be evaluated further with USG and FNAC. More radical surgery in form of total thyroidectomy should be done in patients who have features suggesting of a high risk of malignancy. However, further management should be on individual basis, depending on the results.

Conclusions

Solitary thyroid nodule is a common problem encountered. It has got a high malignant potential compared to multinodular goiter. The preoperative evaluation of thyroid nodules to distinguish between benign and malignant nodules is of much importance. Incidence of thyroid disease is more common in females and the highest incidence found in the age group of 31-40 years. Among 150 samples majority of the case was found to be benign but 16 cases were found to be malignant. Most common type of malignancy was found to be papillary carcinoma. Incidence of malignancy was more in males. With thorough history, physical examination, US thyroid and FNAC, most of the solitary nodule can be diagnosed whether it's benign or malignant. Strong predictors of malignancy include male gender, micro calcification and cervical lymphadenopathy. In our study we excluded patients with clinically or US detected cervical lymphadenopathy because it had a high likely hood of malignancy and total thyroidectomy with neck dissection was the minimum surgery needed for these patients and our idea of more conservative surgery for a likely benign SNT wouldn't be adequate for them. Complications are more associated with total thyroidectomy. Hypocalcemia was the most common complication following thyroid surgery.

So, we conclude that clinically detected solitary nodules of thyroid gland should be treated with high degree of suspicion and patients should be evaluated further with USG and FNAC. More extensive surgery in form of total thyroidectomy should be done in patients who have features highly suggesting malignancy. However, management should be done on individual basis.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

References

- Hegedüs L. Clinical practice. The thyroid nodule. *N Engl J Med.* 2004 Oct 21;351(17):1764-71. doi: 10.1056/NEJMcp031436
- Vander JB, Gaston EA, Dawber TR. The significance of nontoxic thyroid nodules. Final report of a 15-year study of the incidence of thyroid malignancy. *Ann Intern Med.* 1968 Sep;69(3):537-40. doi: 10.7326/0003-4819-69-3-537
- Tan GH, Gharib H. Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. *Ann Intern Med.* 1997 Feb 1;126(3):226-31. doi: 10.7326/0003-4819-126-3-199702010-00009
- Ezzat S, Sarti DA, Cain DR, Braunstein GD. Thyroid incidentalomas. Prevalence by palpation and ultrasonography. *Arch Intern Med.* 1994 Aug 22;154(16):1838-40. doi: 10.1001/archinte.154.16.1838
- Mazzaferri EL. Thyroid cancer in thyroid nodules: finding a needle in the haystack. *Am J Med.* 1992 Oct; 93(4):359-62. doi: 10.1016/0002-9343(92)90163-6
- Gharib H, Goellner JR. Fine-needle aspiration biopsy of the thyroid: an appraisal. *Ann Intern Med.* 1993 Feb 15;118(4):282-9. doi: 10.7326/0003-4819-118-4-199302150-00007
- Brander A, Viikinkoski P, Tuuhea J, Voutilainen L, Kivisaari L. Clinical versus ultrasound examination of the thyroid gland in common clinical practice. *J Clin Ultrasound.* 1992 Jan;20(1):37-42. doi: 10.1002/jcu.1870200107
- Usha Menon V, Sundaram KR, Unnikrishnan AG, Jayakumar RV, Nair V, Kumar H. High prevalence of undetected thyroid disorders in an iodine sufficient adult south Indian population. *J Indian Med Assoc.* 2009 Feb;107(2):72-7.
- Yeung MJ, Serpell JW. Management of the solitary thyroid nodule. *Oncologist.* 2008 Feb;13(2):105-12. doi: 10.1634/theoncologist.2007-0212
- Giuffrida D, Gharib H. Controversies in the management of cold, hot, and occult thyroid nodules. *Am J Med.* 1995 Dec;99(6):642-50. doi: 10.1016/s0002-9343(99)80252-6
- Castro MR, Gharib H. Thyroid nodules and cancer. When to wait and watch, when to refer. *Postgrad Med.* 2000 Jan;107(1):113-6, 119-20, 123-4. doi: 10.3810/pgm.2000.01.808
- Tai JD, Yang JL, Wu SC, Wang BW, Chang CJ. Risk factors for malignancy in patients with solitary thyroid nodules and their impact on the management. *J Cancer Res Ther.* 2012 Jul-Sep;8(3):379-83. doi: 10.4103/0973-1482.103516
- Gupta M, Gupta S, Gupta VB. Correlation of fine needle aspiration cytology with histopathology in the diagnosis of solitary thyroid nodule. *J Thyroid Res.* 2010 Apr 18;2010:379051. doi: 10.4061/2010/379051
- Iqbal M, Mehmood Z, Rasul S, Inamullah, H Shah SS, Bokhari I. Carcinoma thyroid in multi and uninodular goiter. *J Coll Physicians Surg Pak.* 2010 May;20(5):310-2.
- Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Sherman SI, Tuttle RM; American Thyroid Association Guidelines Taskforce. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid.* 2006 Feb;16(2):109-42. doi: 10.1089/thy.2006.16.109
- Unnikrishnan AG, Kalra S, Baruah M, Nair G, Nair V, Bantwal G, Sahay RK. Endocrine Society of India management guidelines for patients with thyroid nodules: A position statement. *Indian J Endocrinol Metab.* 2011 Jan;15(1):2-8. doi: 10.4103/2230-8210.77566
- Delbridge L. Solitary thyroid nodule: current management. *ANZ J Surg.* 2006 May;76(5):381-6. doi: 10.1111/j.1445-2197.2006.03727.x
- Mohamed HE, Mohamed SE, Anwar MA, Al-Qurayshi Z, Sholl A, Thethi T, Khan A, Aslam R, Kandil E. The significance of enlarged cervical lymph nodes in diagnosing thyroid cancer. *J Cancer Res Ther.* 2016; 12(2):1006-9. doi: 10.4103/0973-1482.171360
- Edino ST, Mohammed AZ, Ochicha O, Malami SA, Yakubu AA. Thyroid cancers in nodular goiters in Kano, Nigeria. *Niger J Clin Pract.* 2010 Sep;13(3):298-300.
- Mazzaferri EL. Management of a solitary thyroid nodule. *N Engl J Med.* 1993 Feb 25;328(8):553-9. doi: 10.1056/NEJM199302253280807
- Kuru B, Gulcelik NE, Gulcelik MA, Dincer H. Predictive index for carcinoma of thyroid nodules and its integration with fine-needle aspiration cytology. *Head Neck.* 2009 Jul;31(7):856-66. doi: 10.1002/hed.21049
- Kamran SC, Marqusee E, Kim MI, Frates MC, Ritner J, Peters H, Benson CB, Doubilet PM, Cibas ES, Barletta J, Cho N, Gawande A, Ruan D, Moore FD Jr, Pou K, Larsen PR, Alexander EK. Thyroid nodule size and prediction of cancer. *J Clin Endocrinol Metab.* 2013 Feb;98(2):564-70. doi: 10.1210/jc.2012-2968
- Rago T, Di Coscio G, Basolo F, Scutari M, Elisei R, Berti P, Miccoli P, Romani R, Faviana P, Pinchera A, Vitti P. Combined clinical, thyroid ultrasound and cytological features help to predict thyroid malignancy in follicular and Hupsilonnrthle cell thyroid lesions:

- results from a series of 505 consecutive patients. *Clin Endocrinol (Oxf)*. 2007 Jan;66(1):13-20. doi: 10.1111/j.1365-2265.2006.02677.x
24. Papini E, Guglielmi R, Bianchini A, Crescenzi A, Taccogna S, Nardi F, Panunzi C, Rinaldi R, Toscano V, Pacella CM. Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-Doppler features. *J Clin Endocrinol Metab*. 2002 May; 87(5):1941-6. doi: 10.1210/jcem.87.5.8504
25. Patnayak R, Vijaylaxmi B, Durgasi S, Jena A, Chowhan A. Seeking help from shadows. *Am J Clin Pathol*. 2012;137(3):501. doi: 10.1309/AJCPNJVEXYCKT78U
26. Yalagachin G, Lakshmikantha N, Mashal SB. Prevalence of nodular goiter in patients with breast diseases. *J Clin Invest Surg*. 2020;5(2):91-95. doi: 10.25083/2559.5555/5.2/91.95
27. Anderson TJ, Atalay MK, Grand DJ, Baird GL, Cronan JJ, Beland MD. Management of nodules with initially nondiagnostic results of thyroid fine-needle aspiration: can we avoid repeat biopsy? *Radiology*. 2014 Sep; 272(3):777-84. doi: 10.1148/radiol.14132134
28. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver 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 Nov;19(11):1167-214. doi: 10.1089/thy.2009.0110