

Malignancy in solitary thyroid nodule: A clinicoradiopathological evaluation

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ABSTRACT

Background: Thyroid nodules are common. They can be either benign or malignant. Solitary thyroid nodules (STN) have a high likelihood of being malignant. They should be characterized properly for optimum management. **Materials and Methods:** In this study, we have analyzed our departmental data over a period of 5 years. All the patients who presented to the outpatient department with a clinically detected STN were included in the study group. Our approach was individualized. Preoperative ultrasonography (USG) and fine-needle aspiration cytology were planned in all these patients. Hemi thyroidectomy and total thyroidectomy with and without neck dissection were performed wherever appropriate. **Results:** There were 162 cases of clinically detected STN. USG findings were available in 146 cases. Postoperative histopathology was reported as malignant in 58 cases. Malignant STN was more likely in males. Ultrasonographically detected solid STN were more prone for malignancy as compared to multinodular goiter ($P = 0.000$) Presence of micro calcification and cervical lymphadenopathy were more commonly noted in malignant thyroid swellings. **Conclusion:** Solitary thyroid nodules do have a high likelihood of harboring a malignancy. Solid echogenicity, micro calcification and cervical lymphadenopathy on USG were seen more frequently in malignant nodules.

Key words: Malignant thyroid nodule, solitary thyroid nodules, thyroid surgery

INTRODUCTION

Thyroid nodules are common. Clinically palpable nodules are encountered in about 8% of the adult population. With the use of imaging techniques, particularly ultrasound, the chance of detection of thyroid nodules has increased many folds.^[1-6] The prevalence of palpable thyroid nodule in South India is about 12.2%.^[4] However, the reported incidence of thyroid cancer in general population is low, being only about 1%. Thyroid cancers occur in approximately 5% of all thyroid nodules independent of their size.^[3] The recent data suggest that the incidence of thyroid malignancy is increasing over the years.^[1,3] The occurrence of malignancy

is more in solitary thyroid nodules (STN) compared to multinodular goiter.^[1,7,8]

The preoperative evaluation of thyroid nodules to distinguish between benign and malignant nodules is very important. It helps to avoid unnecessary extensive surgery and potential surgery related adverse effects, such as hypothyroidism, hypocalcemia, and recurrent laryngeal nerve injury.^[1]

The aim of the present study was to evaluate patients with clinically detected STN for the presence of malignancy, in relation to various factors like age, gender, and ultrasonography (USG) findings like size

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of the nodule, echogenicity, micro calcification, and presence of lymphadenopathy. We also planned to compare the prevalence of malignancy in both solitary and multiple thyroid nodules detected by USG.

MATERIALS AND METHODS

The present study was based on the review of case records of all patients who were operated for STN. The study was done in a tertiary care center of South India. It included all the patients with clinically detected STN who had undergone thyroidectomy between June 2007 and May 2012. The patients and their relatives gave consent to use the information for publication purpose. The study was approved by institutional ethics committee.

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

In most of the patients, the plan of surgery was decided beforehand. If it was a STN, diagnosed clinically as well as ultrasonographically, hemi-thyroidectomy of the involved side was done and the specimen was sent either for frozen section or for routine histopathological examination (HPE). In the event of a malignant frozen section report, completion thyroidectomy was done in the same sitting, whereas in inconclusive frozen section, we preferred to wait till the final histopathology report. The decision for other procedures like total thyroidectomy, total thyroidectomy with central neck dissection, total thyroidectomy with selective neck dissection, total thyroidectomy with modified radical neck dissection was based on the clinical, radiological, FNAC and histopathology findings.

During surgery, the site and type of incision were decided. Hemostasis, safeguarding of the recurrent laryngeal nerve, parathyroid, and other vital structures was taken care of during the dissection. Appropriate measures were taken to correct postoperative hypocalcemia and anemia and the drain was taken care of. Further treatment plan was decided based on the final histopathology report. If the report was benign, the patient was managed by regular monitoring of hormone levels, with or without thyroid hormone supplementation. Hypocalcemic features were managed with supplementation of calcium and Vitamin D.

If the final histopathology report was either follicular or papillary carcinoma, the patients were advised to undergo I-131 whole body scan, preferably within 4–6 weeks after surgery and radioactive iodine ablation was advised for residual tissue in the thyroid bed. All the patients were advised regular follow-up.

Statistical analysis was done using Statistical Packages for Social Sciences (SPSS), version 20.0 software (SPSS Inc; Chicago, IL, USA). Comparison of proportions between groups was done by the χ^2 test, taking $P < 0.05$ as significant.

RESULTS

During the study period, 350 patients were operated for various thyroid diseases. Clinically detected STN was the most common entity, accounting for 162 (46%) of the patients. The next common entity was multi nodular goiter (MNG), noted in 138 (39.6%) patients. The present study included all the patients of clinically detected STN.

Majority of the patients with STN were females ($n = 113$, 69.7%). Mean age was 36.8 ± 13.3 years, with a wide range (min– max: 8–76 years). The most common presentation of STN was as a swelling in the anterior aspect of the neck. The swelling was noticed by patient's relatives in most instances and in few cases, by patients themselves. Other less common symptoms were pain, hoarseness and dysphagia. The duration of symptoms ranged from one to 180 months.

Findings on ultrasonography and ultrasonography predictors of malignancy

Ultrasonographic examination findings were available in 146 patients out of 162 clinically detected STN. Further results pertain only to these 146 patients. Clinical diagnosis of STN was confirmed on USG in 106 (72.6%) patients, whereas in 40 (27.4%) patients, the USG revealed MNG.

On postoperative histopathology, 58 nodules were reported as malignant. Mean age of patients with malignancy ($n = 58$) was 39 ± 14.5 years. Out of them 38 were females and 20 were male patients (M: F ratio of 1:1.9). Rest 88 STNs were reported as benign (13 males and 75 females). Malignant STN was reported in 20 out of 33 (60.6%) males and 38 out of 113 (33.6%) females.

Of 106 patients of STN confirmed by USG, 49 (46.2%) turned to be malignant on postoperative histopathology, while only 9 (22.5%) of the 40 patients with MNG were malignant ($P = 0.009$). Majority of the nodules ($n=70$, 47.9%) were 2–4 cm in size. However,

there was no significant correlation between tumor size and the risk of malignancy ($P = 0.121$). Echogenicity was solid in 89 (61%) patients, cystic in 19 (13%) patients and both solid and cystic (mixed echoic) in 38 (26%) patients. However, the distribution of these echogenicity patterns was different between benign and malignant nodules ($P = 0.000$). Majority (52.3%) of the benign nodules were either cystic or of mixed echogenicity, whereas the vast majority (81%) of the malignant nodules were solid in echogenicity. In addition, USG detected micro calcification in 28 patients out of which 18 turned out to be malignant while 10 nodules with micro calcification were reported as benign. Thus, 18 out of a total 58 malignant case had micro calcification in contrast to 10 of 88 benign nodules ($P = 0.003$). Lymph nodal enlargement was detected by USG in 28 patients. Seventeen of 58 (29.3%) malignant nodules had lymph node enlargement as against only 11 of 88 (12.5%) benign nodules ($P = 0.012$) [Table 1].

Thyroid function test and fine-needle aspiration cytology

Thyroid function test was done in all 146 patients. One hundred and thirty eight (94.5%) patients were euthyroid, four (2.7%) hypothyroid and four (2.7%) patients were hyperthyroid. Before surgery, these patients were made euthyroid by supplementing thyroxin or by treatment with anti-thyroid drugs.

Fine-needle aspiration cytology was done before the surgery in all the 146 patients and was reported as nodular goiter in 62 (42.5%), follicular neoplasm in 55 (37.7%), papillary carcinoma in 25 (17.1%), Hashimoto thyroiditis in two (1.4%), toxic nodule in one (0.7%), and medullary carcinoma in one (0.7%) patient.

Type of Surgery and operative findings

Hemithyroidectomy was done in 56 (38.4%) patients. Hemithyroidectomy was followed by completion thyroidectomy in 10 (6.8%). In these ten patients frozen or paraffin section was reported as malignant. Total thyroidectomy was performed in 80 (54.8%) patients. Neck dissection was done in 33 patients, out of them 13 showed metastatic deposit in the lymph nodes.

Postoperative hospital stay ranged from one to 16 days, mean hospital stay being 5.7 days. Postoperative hypocalcaemia was seen in 13 (8.9%) patients. It was transient in nine patients and in four patients it was permanent. The complications of surgery also included recurrent laryngeal nerve injury in four patients (2.7%). Two patients had neuropraxia and improved afterward, in one patient there was unilateral accidental injury and in the other patient, the recurrent laryngeal nerve had to be sacrificed due to tumor infiltration.

Histopathology findings

Histopathology was nodular goiter in 77 (52.7%), Hashimoto's thyroiditis in 10 (6.8%), toxic goiter in one (0.7%), follicular carcinoma in nine (6.3%), papillary carcinoma in 46 (31.5%), and medullary carcinoma in three (2.1%) patients. Of the 46 patients with papillary carcinoma, 15 were reported as the follicular variant of papillary carcinoma (FVPTC) on histopathology.

Metastatic deposits in the lymph nodes were seen in 13 patients of the total 33 patients who had undergone lymph node dissection. Central node dissection was done in 22 (6 positive) patients, left side modified neck dissection (MND) in 4 (3 positive) patients, right side MND in 2 (1 positive) patients, bilateral MND in 3 patients (2 positive), left MND and central nodal dissection was performed in 2 (1 Positive) patient [Table 2].

Comparison was made between the proportion of patients in each diagnostic category as classified by preoperative FNAC versus that made after final histopathology. The 55 patients diagnosed as follicular neoplasm on FNAC turned out to be follicular adenoma in 21 patients, follicular carcinoma in five, FVPTC in 14, nodular goiter in 10 and nodular variant of Hashimoto's thyroiditis in five patients on HPE [Table 3].

All the patients reported as papillary and follicular carcinoma in HPE, were advised to undergo I-131 whole body scan. Thirty-four (61.8%) patients reported back with the scans. In five patients scan did not reveal any residual disease. Residual tissue in thyroid bed was seen in 29 patients and these patients were advised to undergo radio iodine ablation. Three patients with medullary carcinoma were kept on close follow-up.

Follow-up ranged from one to 56 months with mean follow-up of 12.1 ± 14.2 months.

DISCUSSION

Thyroid nodule refers to a distinct lesion within the thyroid gland that is palpably or radiologically distinct from the surrounding thyroid parenchyma.^[5] Benign causes of thyroid nodule include the colloid nodule and the classical multinodular goiter. Occasionally, nodularity is noticed in patients with Hashimoto's thyroiditis and graves' disease. Malignant causes of nodules include thyroid cancer, lymphoma as well as metastasis to the thyroid gland.^[5] 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.^[5]

Solitary thyroid nodules are defined clinically as a localized thyroid enlargement with an apparently normal adjacent gland. According to literature, STN has a higher risk of malignancy than multiple nodules.^[1] Because of this reason, surgeons tend to treat them 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.^[1,7,8] Preliminary investigation should include careful history and thorough clinical examination and thyroid function tests.^[9]

There were 146 cases of clinically detected STN with available ultrasound findings in the study group. Fifty-eight (39.7%) 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.*^[1]

Table 1: Comparison between nodules having a specified ultrasound characteristic between histologically proven benign nodules versus malignant nodules

Ultra sonogram characteristics	Benign (n=88) (%)	Malignant (n=58) (%)	P
Echogenicity			0.000
Solid	47.7	81	
Cystic	17	6.9	
Mixed	35.2	12.1	
Size (cm)			0.121
T1 (<2)	22.7	37.9	
T2 (2-4)	42	39.7	
T3 (>4)	35.2	22.4	
Calcification			0.003
Present	11.3	31	
Lymphadenopathy			0.012
Present	12.5	29.3	

STN: Solitary thyroid nodule, MNG: Multinodular goiter

Table 2: Type of surgery performed

Type of neck dissection	Number of patients neck dissection (n=33)	Number of patients with positive node (n=13)
Central node dissection	22	6
Left MND	4	3
Right MND	2	1
Bilateral MND	3	2
Left MND with central node dissection	2	1

MND: Modified neck dissection

Table 3: Patients with follicular neoplasm in FNAC (n=55) with final HPE

Final HPE	n=55
Follicular adenoma	21
Follicular carcinoma	5
FVPTC	14
Nodular goiter	10
Nodular variant of Hashimoto's thyroiditis	5

FNAC: Fine-needle aspiration cytology, HPE: Histopathological examination, FVPTC: Follicular variant of papillary carcinoma

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.^[5] None of our patients in the study group had history of radiation exposure.

Thyroid nodules are more common in females as noted in the present study.^[1,10] But in males the incidence of malignancy is more common.^[1,11] During our study period, there were 113 (77.4%) females with STN. Among female patients 38 (33.6%) were reported as malignant in HPE. Final HPE showed malignancy in 20 (60.6%) out of 33 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.*^[1] Size of the nodule has no relation with the malignancy in our study which was also reported by Tai *et al.*^[1] A study by Kamran *et al.* opined that the risk of follicular carcinomas and other rare thyroid malignancies increases as nodules enlarge.^[12] However, no such association with size was seen in our cases.

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 texture, 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.^[5]

In our study group, 46.2% of STNs were malignant compared to that of MNGs (22.5%). 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%).^[13] Hence, multinodularity does not necessarily exclude malignancy as seen by our study group.

Malignant cases (31%) showed micro calcification in USG whereas only 11% of the benign conditions showed micro calcification, in the present study. This finding suggests that in presence of micro calcification, the incidence of malignancy is more. Presence of solid echogenicity contributes to increased incidence of malignancy in comparison to either cystic or mixed echogenicity of the nodule.^[1] Our study showed similar results. The findings of our study also suggest that presence of cervical lymphadenopathy is high in presence of malignant thyroid nodule.

An article by Rago *et al.* suggested 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.^[14] Papini *et al.* in their article opined that USG guided FNAC should be performed on all 8–15 mm hypoechoic nodules with irregular margins, intranodular vascular spots or micro calcification.^[15] This study mainly highlighted the USG findings.

We have noted that male gender, micro calcification, solid echogenicity of the nodule, and presence of cervical lymphadenopathy was significantly associated with malignancy as noted by Tai *et al.*^[1]

Fine-needle aspiration cytology is recommended to be a cost-effective procedure in the initial assessment and management of thyroid nodules.^[16,17] It is recommended that every patient with a palpable thyroid nodule should undergo an FNAC. USG-guided FNAC can lower the occurrence of nondiagnostic smears. Whenever we had problem in preoperative diagnosis by FNAC due to inadequate material or difficulty in aspiration by conventional method we have repeated the FNAC by USG guidance. In our previous experience also we have noted, better yield of diagnostic cytological material with the help of the USG-guided aspirations compared to blind FNAC.^[16,17] All our patients underwent FNAC before surgery as it helped us to decide the type of surgery to be undertaken. When FNAC report was malignant, total thyroidectomy was done. In all other cases, hemi thyroidectomy was done and subsequent plan was decided based on conclusive frozen or paraffin section report.

In a recent article, the authors have emphasized the role of USG by suggesting that nodules with a nondiagnostic 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.^[18] These findings are in contrast to the recommended current guidelines to repeat FNAC after a nondiagnostic result.^[19]

The management of thyroid nodules requires 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.^[5] Determining the nature of STN is very important as aggressive surgery may be regarded as an excessive mode of treatment.^[1] We opted for surgery in all the patients as there is a high incidence of malignancy in STN patients as reported in literature.^[1] The postoperative histopathology reports corroborated our findings as >1/3 of STN were reported as malignant.

We have performed hemi thyroidectomy in benign nodules as reported by FNAC. In those cases where postoperative

HPE was reported as malignant either in frozen or by paraffin section, completion thyroidectomy of the remaining lobe was done. Total thyroidectomy was done in those cases where FNAC was reported as malignant.

Decision of neck dissection was taken in those cases with either palpable lymph nodes in the neck or USG finding suggestive of lymphadenopathy. In some cases decision of lymph node dissection was taken intra operatively mainly for central nodes (level VI). Central node dissection was done in all malignant cases with USG showing lymph node enlargement and also in cases with intra operative enlarged nodes.

The result of our study shows that the incidence of malignancy in STNs is indeed high. Multinodularity detected by USG does not necessarily exclude malignancy. The chance of malignancy is more in those nodules where USG shows solid echogenicity, presence of micro calcification in nodule and associated lymphadenopathy. 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. However, further management should be on individual basis, depending on the results.

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Conflict of interest

There are no conflicts of interest.

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