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ORIGINAL ARTICLE

Trends in Thyroid Nodules and Malignancy: A Two-Year Retrospective Study in a Tertiary Care Centre

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Abstract Thyroid nodules are one of the most common presentations faced by ENT clinicians, and the prevalence of differentiated thyroid cancer is increasing worldwide. We found no other study showing a clear occurence of cancer in thyroid nodules in the state of West Bengal. Hence, we undertook this study to determine the occurence of thyroid cancer among people with thyroid nodules. A retrospective review was performed for 96 patients with thyroid nodules who underwent USG and Fine Needle Aspiration Cytology (FNAC) and thyroid surgery at a tertiary hospital in Kolkata over a 2-year period from January 2020 to December 2021. The occurence of thyroid cancer in patients with thyroid nodules; association with age, sex, duration of thyroid swelling and thyroid stimulating hormone (TSH) levels of the patients; the sonographic findings (nodule size and number) and Bethesda classification on FNAC were reviewed. A total of 96 cases were reviewed. The highest malignancies were seen in swellings of 3–5 years duration (50%), and in patients with increased TSH levels (60%). Patients with single vs. multinodular goitre had comparable rates (23.07 vs 22.22%). The highest risk was seen in nodules 1–2 cm in size. A TIRADS score of 2 had a negative predictive value of 86.95% and a score of 5 had a positive predictive value of 100%. BETHESDA II lesions had a 3.44% rate of malignancy, while BETHESDA V and VI had rates of 100% and 75% respectively. While most of the thyroid swellings were benign, 22.91% were malignant, the most common being papillary carcinomas.

Keywords Thyroid nodules · Bethesda · TIRADS · Thyroidectomy · Malignancy · Fine Needle Aspiration Cytology

Introduction

With an annual incidence of 0.5–10/100,000 cases across the world, thyroid cancers account for 1% of all cancers diagnosed in the United States and are the most common endocrine cancers worldwide [1].

The epidemiology is varied and multifactorial, including but not limited to variations in genetic influences, viral infections, environmental factors, iodine intake, geographical location and chronic TSH stimulation in existing goitre [2].

Thyroid nodules can often be associated with thyroid cancers, and there are a few prevalence studies in various countries that have shown their association based on preoperative diagnoses and post operative histopathological examination (HPE) results [3, 4].

With thyroid cancers becoming increasingly common [5], it is imperative to get as accurate a diagnosis as possible, before planning forward with the line of management. We undertook this retrospective study since we did not find many studies showing the association and occurence of thyroid nodules with thyroid cancers in West Bengal, a

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state with a population of nearly 98 million. Our aim was to determine the occurrence of thyroid cancer in patients having palpable thyroid nodules, and their co-relation with multiple factors such as age, sex, TSH level, duration of thyroid swellings, TIRADS score (with number and size of nodules), and Bethesda category.

Materials and Methods

This was a retrospective study that was undertaken in a cohort of patients presenting with palpable thyroid nodules at our institution over a period of 2 years (January 2020 to December 2021).

All patients who presented to the ENT out patient department in our tertiary referral centre with palpable thyroid nodules and were subsequently operated were included in the study. After the records of all patients who underwent surgery were collected, all patients were sorted by age into groups as: < 20 years, 20–40 years, 40–60 years, > 60 years of age. The duration of the thyroid swelling as was either seen or felt by the patient was checked and patients were sorted as: ≤ 1 year, 1–2 years, 2–3 years, 3–5 years, > 5 years. Next the thyroid profile and TSH levels of all patients on initial presentation were noted. TSH levels between 0.4–4 mIU/L was considered normal, < 0.4 was considered hyperthyroid, > 4 was considered as hypothyroid. Since all patients underwent ultrasonography (USG) to find out number of nodules, size of largest nodule, and the TIRADS scoring for the most suspicious nodule, these records were reviewed.

A standardised method for describing the sonographic characteristics of thyroid nodules (known as TIRADS) was developed by the American College of Radiology (Table 1). The American college of radiology advocated USG guided FNAC in nodules of TIRADS 3 (if size > 2.5 cm), TIRADS 4 (if size > 1.5 cm) and TIRADS 5 (if size > 1 cm). At our institution, due to irregular follow up by patients, many not being completely literate, we normally counsel all patients for a USG guided FNAC from most suspicious nodule, to decrease the inconvenience of repeated follow ups for the patient.

FNAC was scored on the basis of the BETHESDA system, which was developed in 2009 to provide uniform terminology for the same (Table 2). Patients with BETHESDA III, IV and V underwent hemithyroidectomy, while patients with BETHESDA VI on FNAC underwent total thyroidectomy (with or without neck dissection based on lymph node status on contrast imaging). Patients with Bethesda II who wanted surgery for cosmetic purposes or to decrease pressure effects of the nodule were also operated. The post operative histopathological examination (HPE) was classified as per the WHO classification of tumours of the thyroid gland.

The results were then checked for any significant association between malignancy on post operative HPE and age, gender, thyroid profile, duration of nodule, number of nodules, size of largest nodule, TIRADS score of most suspicious nodule and BETHESDA category of most suspicious nodule. Significance was calculated using SPSS software, with chi square testing, with a p value < 0.05 being statistically significant and a confidence interval of 95%.

Table 1 TIRADS score and its interpretation

TIRADS score	Interpretation
1	Benign
2	Not suspicious
3	Mildly suspicious
4	Moderately suspicious
5	Highly suspicious

Results

We had a total of 96 patients that were included in the study.

12 of the patients (12.5%) operated were either 20 years of age or below, while 58 patients (60.41%) were between 21–40 years of age. 26 patients (27.08%) were between 41–60 years of age, while none of our patients were above 61 years of age. The mean was 33.5 years. 4 of the 12 patients (33%) who were 20 or below were found to have

Table 2 BETHESDA category and its interpretation

Cytopathological category	Risk of malignancy (%)	BETHESDA category
Non-diagnostic or unsatisfactory	1–4	I
Benign	0–3	II
Atypia of undetermined significance or follicular lesion of undetermined significance	5–15	III
Follicular neoplasm or suspicious for a follicular neoplasm	15–30	IV
Suspicious for malignancy	60–75	V
Malignant	97–99	VI

Table 3 General characteristics of patients included in the study

Variable	Mean	N	%
Age	33.5 yrs		
< 20		12	12.5
21–40		58	60.41
41–60		26	27.08
> 61		0	0
Sex			
Male		6	6.25
Female		90	93.75
Thyroid profile			
Euthyroid		80	83.33
Hypothyroid		10	10.41
Hyperthyroid		6	6.25

malignant nodules, while 10 of 58 patients in the 21–40 age group (17.24%) had malignancies, and 2 patients with Non-Invasive Follicular Tumour with Papillary like nuclear changes (NIFTP) (3.44%). 8 out 26 patients in the 41–60 group (30.76%) had malignancies (Tables 3, 5).

90 of the total patients were female (93.75%), with 6 males (6.25%). Out of the males operated on, 4 of the 6 patients had papillary cancer on their final histopathology (66.6%), while 18 of the 90 females had a final diagnosis of Ca (20%), and 2 had NIFTP on HPE. With a *p* value of 0.008 there was a statistically significant higher number of men with nodules that turned out to be malignant (Tables 3, 5).

50 patients (52.08%) had a swelling in the thyroid region of 1 year duration or less, which was noticed either by them on palpation or seen by their friends/family. 24 people (25%) had swellings lasting 1–2 years in duration, 8 people (8.33%) had swellings lasting for 2–3 years duration, 12 (12.5%) had a swelling lasting 3–5 years in duration, while 2 (2.08%) had a duration of more than 5 years. The highest occurrence of malignancy (50%) was seen in patients who had a swelling between 2–3 years duration (4 out of 8 patients), followed by those with a swelling of 1–2 years (8 malignancies [33.3%] and 2 cases of NIFTP [8.3%] out of 24 patients). In the < 1 year range, 10 of the 50 patients had Ca (20%). None of the patients with nodule duration of either 3–5 years or more than 5 years had any malignancy. At a *p* value of 0.059, the duration of the nodules was not significant with the probability of malignancy (Tables 4, 5).

Most of our patients (80 out of 96) were euthyroid on initial presentation with 10 patients being hypothyroid on initial presentation. 6 patients were hyperthyroid on initial presentation. The maximum percentage of Ca cases were seen in hypothyroid cases (6 out of 10, or 60%), followed by euthyroid cases (16 out of 80, 20%) while the 2 cases of NIFTP were also euthyroid. None of the 6 cases of hyperthyroidism had malignancy (Tables 3, 5).

Table 4 Nodule characteristics, along with TIRADS SCORING AND BETHESDA classification

Variable	N	%
Duration of nodule		
< 1 year	50	52.08
1–2 years	24	25
2–3 years	8	8.33
3–5 years	12	12.5
5 years	2	2.08
Number of nodules		
Single	78	81.25
Multiple	18	18.75
Size of largest nodule		
< 1 cm	2	2.08
1–2 cm	22	22.91
2–4 cm	48	50
> 4 cm	24	25
TIRADS score		
1	0	0
2	46	47.91
3	26	27.08
4	16	16.66
5	8	8.33
BETHESDA		
I	0	0
II	58	60.41
III	14	14.58
IV	8	8.33
V	8	8.33
VI	8	8.33

78 (81.25%) of the patients in the study had a single nodule while 18 (18.75%) had more than one nodule on USG. Of the patients with a single nodule, 23.07% (18 out of 78) had a malignancy on HPE, while 2 had NIFTP. 22.22% (4 out of 18) of patients having multiple nodules showed malignancy. The difference between the two groups was not statistically significant, with a *p* value of 0.938 (Tables 4, 5).

We had 2 patients (2.08%) in whom the size of the largest nodule was less than 1 cm across the longest dimensions, 22 patients (22.91%) whose nodule size was between 1–2 cm in the largest dimensions, 48 patients (50%) whose largest nodule was 2–4 cm in size across the longest dimension and 24 patients (25%) with swellings being more than 4 cm on presentation. The highest incidence of malignancy was seen in patients with nodules 1–2 cm in size (6 out of 22, 27.27%), followed by those in the size range of > 4 cm (6 out of 24, 25%) followed by those in the range of 2–4 cm (10 out of 48 [20.83%] malignant and 2 out of 48 [4.16%] NIFTP). Neither patient of size < 1 cm had a malignancy. Although 1–2 cm size nodules showed the highest risk of malignancy,

Table 5 Cancer prevalence according to the different parameters assessed in the study, based on final HPE reports

Variable	Total N (% of 96)	Cancer N (% of total N)	Non-Cancer N (%of total N)	Chi square value, df value, *p* value
Age				2.702, 2, 0.259 (not significant)
< 20 years	12 (12.5)	4 (33.3)	8 (66.6)	
21–40	58 (60.41)	10 (17.24)	48 (82.75)	
41–60	26 (27.08)	8 (30.76)	18 (69.23)	
> 61	0 (0)	NA	NA	
Sex				6.935, 1, 0.008 (significant)
Male	6 (6.25)	4 (66.6)	2 (33.3)	
Female	90 (93.75)	18 (20)	72 (80)	
Duration of nodule				9.199, 4, 0.059 (not significant)
< 1 years	50 (52.08)	10 (20)	40 (80)	
1–2	24 (25)	8 (33.3)	16 (66.6)	
2–3	8 (8.33)	4 (50)	4 (50)	
3–5	12 (12.5)	0 (0)	12 (100)	
> 5	2 (2.08)	0 (0)	2 (100)	
Thyroid profile				
Euthyroid	80 (83.33)	16 (20)	64 (80)	
Hypothyroid	10 (10.41)	6 (60)	4 (40)	
Hyperthyroid	6 (6.25)	0 (0)	6 (100)	
Number of nodules				0.006, 1, 0.938 (not significant)
Single	78 (81.25)	18 (23.07)	60 (76.92)	
Multiple	18 (18.75)	4 (22.2)	14 (77.7)	
Size of largest nodule				1.008, 3, 0.799 (not significant)
< 1 cm	2 (2.08)	0 (0)	2 (100)	
1–2	22 (22.91)	6 (27.27)	16 (72.72)	
2–4	48 (50)	10 (20.83)	38 (79.16)	
> 4	24 (25)	6 (25)	18 (75)	
TIRADS score				31.4496, 1, 0.000000001 (significant)
1	0 (0)	NA	NA	
2	46 (47.91)	6 (13.04)	40 (86.95)	
3	26 (27.08)	0 (0)	26 (100)	
4	16 (16.66)	8 (50)	8 (50)	
5	8 (8.33)	8 (100)	0 (0)	
BETHESDA				66.595, 2, 0.000000001 (significant)
I	0 (0)	NA	NA	
II	58 (60.41)	2 (3.44)	56 (96.55)	
II	14 (14.58)	0 (0)	14 (100)	
IV	8 (8.33)	6 (75)	2 (25)	
V	8 (8.33)	8 (100)	0 (0)	
VI	8 (8.33)	6 (75)	2 (25)	

For the sake of convenience, the following rows have been clubbed together during statistical analysis to prevent the pitfalls of zero value cells: TIRADS 2 with TIRADS 3, TIRADS 4 with TIRADS 5, BETHESDA II with BETHESDA III, BETHESDA V with BETHESDA VI

the association was not significant with *p*value being 0.799 (Tables 4, 5).

46 patients had a TIRADS score of 2, while 26 had a score of 3, 16 patients had a score of 4 and 8 had a score of 5. Of the patients with a TIRADS score of 2, 40 out of 46 (86.95%) were benign and 6 (13.04%) had a malignancy on final HPE, while in patients with a score of 3, 100% were benign (26 patients). Of the 16 patients with a score of 4, 8 (50%) were malignant, 2 (12.5%) had NIFTP, and 6 (37.5%) were benign. All (100%) of the 8 patients with a TIRADS score of 5 had malignancy in their nodules. The score had a significant association (*p*-0.000000001) with the risk of

malignancy and those who had TIRADS score 4 and 5 had 22 times more chance of having a malignancy than who had TIRADS score 2 and 3 (Tables 4, 5).

USG guided FNAC was taken from the nodule with the highest TIRADS score in case of multiple nodules. 58 patients had a BETHESDA category II swellings, 14 had category III and 8 patients each had a BETHESDA category of IV, V and VI. 2 of the 58 patients (3.44%) with category II had a malignancy in their final HPE. None of the patients with BETHESDA III had a malignancy, 6 of the 8 patients of category IV had malignancy (75%), while 2 had NIFTP, all of the 8 patients of category V had a malignancy, and 6 patients out of 8 (75%) with BETHESDA VI had a malignant nodule on HPE. The association between BETHESDA score and HPE showed a significant association with p value being 0.000000001 (Tables 4, 5).

66 patients had a histopathological report compatible with colloid goitre (a few with cystic changes seen). 20 patients had papillary carcinomas as their final histopathological diagnosis, 2 had anaplastic carcinomas, 2 had follicular hyperplasia with cystic changes, 2 had NIFTP, 2 patients had lymphocytic thyroiditis, while 2 had thymic epithelial cysts.

Discussion

Palpable thyroid nodules are prevalent in about 5% women and 1% men in non-iodine deficient parts of the world, while USG detectable nodules are found in 19–68% of the population. Keeping factors such as age, sex, race etc. in mind, 7–15% of these nodules maybe carcinomas, the majority being differentiated carcinomas [5].

The highest number of malignancies in our study was seen in the < 20 age group, where 4 of the 12 patients (33%) were found to have malignant nodules. This was followed by the 41–60 age group (30.76% malignancy). In general, higher rates of follicular cancer are noted in the older age groups for both men and women [6], with follicular cancer being shown to have a maximum incidence in the 41–50 age group [3]. On the other hand, Alseddeeqi et al. [4] saw that though the highest proportions of thyroid nodules occurred among patients aged 40–49 years, the prevalence of thyroid malignancy was highest in thyroid nodules in women aged 18–29 years and in men aged 30–39 years.

Although the gender disparity in thyroid cancer is well established (about 2.7 times more prevalent in women than men), the reasons for this are not well understood, with most studies concluding that genomic and proteomic approaches are required to identify the causes for this gender gap [7]. Also, previous research has demonstrated a female/male incidence rate ratio (IRR) of about 3 for papillary thyroid cancer and about 2 for follicular cancer [6]. Out of the males operated on in our study, 4 of the 6 patients had papillary cancer on their final histopathology (66.6%), while 18 of the 90 females had a final diagnosis of Ca (20%) on HPE. Hence although the number of women who had a Ca in their final HPE reports was higher, among the men who presented with thyroid swelling, the percentage who had Ca in their HPE was higher. This has also been seen in other studies by Al-Sharafi et al. [3] and Lin et al. [8] wherein although total number of women presenting with Ca may be higher, but males have a higher chance of having a malignancy on presentation with a thyroid nodule [3, 8].

Nodules rapidly increasing in size over a short duration of time have often been considered to have a higher malignant potential by conventional teachings. Huan et al. [9] divided their patients into 3 cohorts depending on disease duration (< 1 month, 1 month-1 year, > 1 year), with the highest incidence of malignant nodules being found in patients who had a history of less than a month, and the malignant potential decreasing as the disease history lengthened. We found the highest occurrence of malignancy (50%) in patients who had a swelling between 2–3 years duration, followed by those with a swelling of 1–2 years of duration (33.3%).

A high TSH value has often seen to be significantly associated with increased chances of thyroid malignancy and a high preoperative mean TSH may be used as a predictor for thyroid malignancy [10]. In fact, as seen by Boelaert et al. [11], thyroid malignancy rates have been shown to correlate even with a rise in TSH levels even within the normal range. We also saw that the maximum rates of Ca were seen in our hypothyroid cases (6 out of 10, or 60%), followed by euthyroid cases (16 out of 80, 20%). This again was in line with previous studies showing that hypothyroidism with increased TSH was a risk factor for malignancy.

Out of the patients in our study with a single nodule, 23.07% (18 out of 78) had a malignancy on HPE, while 2 had NIFTP. 22.22% (4 out of 18) of patients having multiple nodules showed malignancy. While both the results were similar, Brito et al. [12] found (via a meta-analysis) that there was low quality evidence to suggest that thyroid cancer was less frequent in multinodular goitre when compared to single nodules, particularly in areas outside the United States. Al-Sharafi saw in a 3-year retrospective analysis of thyroid nodules that the rates of cancer in thyroid nodules was completely independent of the size of nodules, and this was also seen by Frates et al. in a retrospective study from 1995 to 2003 [3, 13]. The 2015 American Thyroid Association guidelines also state that patients with multiple thyroid nodules carry the same risk of malignancy as those with single nodules, and the risk of malignancy per patient is independent of the number of nodules [5].

We found the highest occurrence of malignancy in patients with nodules 1–2 cm in size (6 out of 22, 27.27%), followed by those in the size range of > 4 cm (6 out of 24, 25%) followed by those in the range of 2–4 cm (10 out of 48

[20.83%] malignant and 2 out of 48 [4.16%] NIFTP). Our findings are similar to other findings by Kamran et al., who saw that although greater nodule size influences cancer risk, a threshold effect is detected at approximately 2.0 cm in nodule diameter. Thereafter, larger nodule size imparts no further malignant risk, even if 4.0 cm or larger. Similarly, Cavallo et al. found that thyroid nodule size is inversely related to malignancy risk, as larger nodules have lower malignancy rates and all nodules, regardless of FNA status demonstrate a risk trough at ≥ 2 cm [14, 15].

USG is superior to other available imaging modalities in characterizing thyroid nodules, because of which a standardised method for describing the sonographic characteristics of thyroid nodules (known as TIRADS) was developed by the American College of Radiology [16]. The American college of radiology advocated USG guided FNAC in nodules of TIRADS 3 (if size > 2.5 cm), TIRADS 4 (if size > 1.5 cm) and TIRADS 5 (if size > 1 cm). Due to irregular follow up by patients, many not being completely literate, we counselled patients for a USG guided FNAC from most suspicious nodule in all patients, to decrease the inconvenience of repeated follow ups for the patients. Of the patients with a TIRADS score of 2, 40 out of 46 (86.95%) were benign and 6 (13.04%) had a malignancy on final HPE, while in patients with a score of 3, 100% were benign (26 patients). Of the 16 patients with a score of 4, 8 (50%) were malignant, 2 (12.5%) had NIFTP, and 6 (37.5%) were benign. All (100%) of the 8 patients with a TIRADS score of 5 had malignancy in their nodules. A TIRADS score of 2, which is classified as 'not suspicious' had a negative predictive value of 86.95% where in predicting nodules as being not malignant. A score of 5, which is 'highly suspicious' had a positive predictive value of 100% in detecting malignancies on USG. Gao et al. had published a paper in 2019 about the diagnostic efficiency of TIRADS in thyroid nodules, where they had seen that the malignancy percentage of TIRADS category 1, 2, 3, 4, and 5 were 0%, 1.3%, 9.1%, 52.5%, and 88.8%, respectively [17].

A working pre-operative diagnosis in most euthyroid patients is arrived at on FNAC, reducing the risk of unnecessary surgery and the BETHESDA system developed in 2009 provides uniform terminology for the same [18]. 58 of our patients had a BETHESDA category II, 14 had category III, 8 had category IV, 8 had category V and 8 had a BETHESDA category of VI. 2 of the 58 patients (3.44%) with category II had a malignancy in their final HPE which is slightly higher than the prediction standards offered by the BETHESDA classification (0–3% malignancy). None of the patients with BETHESDA III had a malignancy (category III has a 5–15% risk of malignancy), 6 of the 8 patients of category IV had malignancy (75%), while 2 had NIFTP (15–30% risk of malignancy as per BETHESDA guidelines), all of the 8 patients of category V had a malignancy (60–75% risk), and 6 patients out of 8 (75%) with BETHESDA VI had a malignant nodule on HPE (97–99% risk). This was similar to another study by Mondal et al. [19] who validated the BETHESDA scores with HPE and found that rates of malignancy reported on follow-up HPE were non-diagnostic 0% for BETHESDA I, 4.5% for BETHESDA II, 20% for BETHESDA III, 30.6% for BETHESDA IV, 75% for BETHESDA V, and 97.8% for BETHESDA VI.

20 patients in our study had papillary carcinomas as their final histopathological diagnosis, 2 had anaplastic carcinomas, 2 had follicular hyperplasia with cystic changes and 2 had NIFTP. The most common carcinoma reported in our study was papillary carcinoma (90.9%), which is similar to other studies [3], and while we found no cases of follicular carcinoma or medullary carcinomas, anaplastic carcinomas comprised the next most common variety as seen by us (9.09%). The overall crude occurence of cancer in thyroid nodules seen was 22.91%.

Conclusion

In the patients having thyroid nodules; age, sex, duration of thyroid swelling, TSH levels, the sonographic findings (nodule size and number) and BETHESDA classification on FNAC provide a basic framework for screening patients, and to see which factors have a higher chance of developing thyroid cancer.

The highest occurence of malignancy was seen in the young age group (< 20 yrs), in patients with nodules 1–2 cm in size (27.27%), with a duration of swelling between 2–3 years (50%) and in patients with hypothyroidism (60%). Although the occurrence of a thyroid swelling is more common in females than males (93.75% vs 6.25%), the final HPE reports of Ca was found to be more among males than females (66.6% vs 20%). Patients with multiple thyroid nodules carry the same risk of malignancy as those with single nodules, and the risk of malignancy per patient is independent of the number of nodules.

A TIRADS score of 2 had a negative predictive value of 86.95% predicting nodules as being not malignant. A score of 5 had a positive predictive value of 100% in detecting malignancies. BETHESDA scoring can be considered as an indicating tool for directing the management of the nodules, but cannot be stamped as conclusive evidence.

Our study will provide a data set that could be used in studies in the future and to provide a reasonably verifiable database for meta-analysis, in the form of a tertiary centre based high power study. While being done over a 2-year period, our study has the limitation of being over a short duration and a comparatively smaller pool of patients.

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Declarations

Conflicts of Interest All the authors declare they have no conflicts of interest.

Ethical Approval All procedures performed in the study were in accordance with the ethical standards of the institute.

Informed Consent Written informed consent was obtained from all the individual participants in the study.

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