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Original Article,

Incidence of Thyroid Carcinoma in Large (≥4cm) Benign Thyroid Nodules: A Retrospective Single Center Study

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Abstract:

Objective: The purpose of our study is to see the incidence of thyroid carcinoma in large (≥4cm) Fine Needle Aspiration Cytology (FNAC) proven benign thyroid nodules.
Study Design: Retrospective cross-sectional study
Place & duration of Study: Department of General Surgery, Recep Tayyip Erdogan Hospital, Muzaffargarh from August 2014 to May 2021
Methodology: 238 patients with large benign thyroid nodules who underwent thyroid surgery were included in the study. The type of thyroid nodules (solitary or dominant), size of thyroid nodule (mm) and histopathology of the thyroid nodules after surgery were collected. The data was analyzed by IBM Statistical Package for Social Sciences (IBM SPSS Statistics for Windows version 20.0. Armonk, New York). Tables were constructed using Microsoft Excel 2018.
Results: A total of 238 patients with large benign thyroid nodules were included in the study. 156 patients (65.9%) had thyroid nodule size in the range of 40mm to 50mm rest of the patients had nodule size above 50mm. The incidence of thyroid carcinoma was 14.3% (34/238). There was no significant effect of age, gender & type of thyroid nodule on risk of thyroid carcinoma.
Conclusion: The risk of thyroid carcinoma in large (≥4cm) benign thyroid nodules is significant and there is a need to change our approach in their management to diagnose and manage them timely. Therefore, large (≥4cm) thyroid nodules may be considered for surgery even if preoperative FNAC is benign.

Keywords: Thyroid carcinoma, large thyroid nodules, benign nodules.

Introduction:

In terms of endocrine malignancies, thyroid cancer is the most prevalent in Pakistan and the incidence has been rising(1). This is consistent with the incidence all over the world, that has seen an upward trend of thyroid malignancies(2). Ultrasound scan (USG) of thyroid gland and evaluating it with Thyroid Imaging Reporting and Data Systems (TIRADS) score has emerged as the mandatory initial investigation of choice for assessment of a thyroid swelling owing to being cheap and readily available(3). USG scan aids in gauging the swelling as probably benign, suspicious or malignant prompting further FNAC or surgery(4). Presence of suspicious or malignant sonographic features urge the clinician to rush for FNAC, that has been materialized as one of the most important diagnostic modalities with an excellent negative predictive value of 97%(5). FNAC is very dependable in the hands of an expert with its sensitivity and specificity exceeding 90% (6). Usefulness of FNAC is widely accepted for smaller nodules but there has been some debate about its utility in lesions measuring more than 4cm. The deep seated fear of a false negative in a large thyroid nodule and the presence of undetected malignancy has been the root cause of this debate(7). Thyroidectomies have been recommended for nodules more than 4cm in size. A few surgeons use aggressive approach and

perform surgery even when the nodule just exceeds 3cm in size(7, 8).

At our hospital, we offer total thyroidectomy to patients who have a suspicious or malignant cytology, compressive symptoms or wish to get operated due to cosmetic reasons. The aim of our study is to ascertain the false negative rate of FNAC for thyroid nodules ≥4 cm in our patient population, and to analyze if thyroid nodule size is associated with risk of malignancy if ≥4 cm.

Materials and methods:

The Study was started after approval from ethical review committee of Recep Tayyip Erdogan Hospital, Muzaffargarh. The sample size was calculated to be 238. These were the patients who presented with thyroid swellings and were admitted in the surgery department from August 2014 to May 2021. They were enrolled by non-probability consecutive technique. The **inclusion criteria** involved all patients who had a large (≥4 cm) FNAC diagnosed benign thyroid nodule, were biochemically euthyroid, belonged to any gender with an age ≥15 years. Patients with history of external radiation exposure, family history of thyroid malignancy, multinodular goiter or recurrent goiter were **excluded** from this study. Demographic data like age (in years) and gender (male/female) were noted. All investigations were done from Recep Tayyip Erdogan Hospital, Muzaffargarh laboratory which includes thyroid stimulating hormone (TSH), Free triiodothyronine (T3), Free tetraiodothyronine (T4), USG thyroid, FNAC and biopsy of excised thyroid gland. All collected data was entered into SPSS version 20 and analyzed. Quantitative data like age (in years) and size of thyroid nodule was presented as means and standard deviations. Qualitative data like gender, type of discrete swelling and malignancy on final histopathology report (yes/no) was presented as frequency and percentages. Confounders were controlled by stratification of data with regard to age, gender, type of discrete swelling and thyroid nodule size. Post stratification chi-square test was applied. P-value ≤ 0.05 was considered significant.

Results:

The age of patients ranged from 15-60 years, mean 38±10.65 years. Out of 238 patients participating in the study 204 (85.7%) were females and 34 (14.3%) were males, majority of the patients 183 (76.9%) were below the age of 45 years. The size of thyroid nodules ranged from 40-70mm, mean 49.7±9.1 and 156 (65.9%) patients had nodule size from 40-50mm. Most of the thyroid nodules 208 (87.4%) were solitary and 30 (12.6%) were dominant nodules, each patient having only one thyroid nodule ≥4cm.

Final histopathology showed 34 (14.3%) malignant nodules. On further stratification of data with regard to age, gender, type of thyroid nodule & size we concluded that 28 (82%) patients having malignant lesions were in age group of 15-45 years, p-value 0.797 (non-significant). Out of 34 patients having malignant thyroid nodule on histopathology 28 (82%) were female and 6 (18.7%) were male, p-value 0.545. 23 (67.6%) malignant thyroid nodules were 40-50mm in size, (p-value 0.750). 30(88.2%) malignant nodules were solitary and 4 (11.8%) were dominant, p-value 0.873.

Table 1 (Profile of patients with large (≥ 4cm) benign thyroid nodules and final histopathology)

Variables	No. of patients	Percentage
Age (in years)		
15-25	26	10.9
26-35	79	33.2
36-45	78	33.8
46-55	36	15.1
56-65	19	8
Mean±SD	38±10.6	
Range	15-60 yrs	
Gender	**No. of patients**	**Percentage**
Female	204	85.7
Male	34	14.3
Nodule size (mm)	**No. of patients**	**Percentage**
40-45	111	46.6
46-50	46	19.3
51-55	14	5.9

56-60	33	13.9
61-65	21	8.8
66-70	13	5.5
Mean±SD	49.7±9.1	
Range	40-70	
Type of nodule	**No. of patients**	**Percentage**
Solitary	208	87.4
Dominant	30	12.6
Histopathology	**No. of patients**	**Percentage**
Benign	204	85.7
Malignant	34	14.3

Table 2 (Stratification of different variables with histopathology (p-value≤0.05 is significant)

Variables	**Histopathology**		**p-value**
Age (in years)	**Benign**	**Malignant**	
15-25	22	4	**0.797**
26-35	68	11	
36-45	65	13	
46-55	31	5	
56-65	18	1	
Gender	**Benign**	**Malignant**	**p-value**
Female	176	28	**0.545**
Male	28	6	
Nodule size (mm)	**Benign**	**Malignant**	**p-value**
40-45	94	17	**0.750**
46-50	40	6	
51-55	13	1	
56-60	30	3	
61-65	17	4	
66-70	10	3	
Type of nodule	**Benign**	**Malignant**	**p-value**
Solitary	178	30	**0.873**
Dominant	26	4	

Discussion:

The results showed that there is no significant correlation of the size of nodule with the presence of malignancy (p value of 0.75). These results also consolidated our established reasons for trusting FNAC as a diagnostic modality of choice in clinic. The inference that the results of FNAC are unaffected by the size of the swelling has been settled by other studies as well(9). In fact, there are a number of studies that have pointed out that malignancy and size of the nodule are inversely related. Cavallo A et al showed that larger the size of the nodule, smaller the chances of malignancy(10). These findings were in accordance with another research carried out in Saudi Arabia that showed nodules with size between 1-1.9 were more probable to be malignant(11).

A number of researches matched our findings that FNAC has a very low false negative rate. Abi-Raad R et al took it upon himself to compare the false negatives in follicular and papillary carcinomas. A total of 802 FNACs were taken and it showed follicular neoplasm was far more likely to produce a false negative than papillary carcinoma or lymphocytic thyroiditis(12).A research carried out by Mehanna et al. showed comparable results as well(13). It is for this reason that FNAC is not considered ideal if the suspected diagnosis is a follicular neoplasm. A number of studies have exhibited clear cut results showing core biopsy to have an upper hand over FNAC in case of a follicular neoplasm. A research carried by Yoon RG et al showed that the Core needle biopsy group showed a significantly higher malignancy rate than FNA (57.9% versus 28%, $p<0.001$)(14). Core needle biopsy also has

shown low rates of Bethesda 1 category and inconclusive results and a higher diagnostic accuracy(15). This has led to a widespread use of core needle biopsy to minimize the risk of false negative in case of follicular neoplasm.

There is an increasing amount of contradictory literature available regarding the malignancy and the size of the nodule. Giles WH et al has shown that he false-negative rate was 11.7 % for all nodules ≥3 cm and 4.8 % for nodules <3 cm (p = 0.03)(16). He deduced that larger the thyroid, greater the incidence of false negatives. These contrary views have put the clinicians in peril. Shin et al. carried out a systematic review of 15 studies and concluded that probability of malignancy in previously cytologically benign nodules in increased when the size exceeds 3cm(17). A meta-analysis carried out in 2016 yielded the same results(18). The newer literature, however, has established a different protocol. A cross sectional study carried out in 2020 has shown 1.2cm as the cutoff point for detecting malignancy(19).

In our research, we noticed that the size is not a factor in deciding if the nodule is malignant or not. The various discrepancies that are present in the literature can be due to the variability of sampling techniques, and to a lesser extent, cytological findings. Similarly, the post-test chance of malignancy can be variable depending upon the prevalence of malignancy in that specific area. A number of meta-analyses carried out recently reached the same conclusion that the size of the nodule is not the single most important factor in suspecting malignancy(20, 21).

The reason for limiting our study to thyroid nodules measuring the 4cm or more was due to the fact that it is common practice in various institutions to offer surgery to these patients regardless of cytology. The retrospective nature is primarily the limiting factor of our research. Not to mention that our research covers a single institute. The results may be variable elsewhere.

Conclusion:

The size of the nodule does not significantly contribute to the risk of malignancy. USG scan is considered the best initial investigation, followed by FNAC for suspicious nodules. In case of a follicular neoplasm, core biopsy has lesser incidence of false negative results, making it ideal for this type of lesions.

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