Impact of solitary thyroid nodule size on probability of thyroid malignancy

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Background
Tumor size is considered an important predictor of malignancy in many types of cancer. However, there is no clear line of characterization regarding the association between thyroid nodule size and prediction of malignancy risk. Current data continue to be variable between different studies.
Aim
To determine the impact of solitary thyroid gland nodule size as an independent factor on increasing the probability of malignancy.
Patients and methods
Our study was held as a prospective study conducted on 60 patients having a solitary thyroid nodule undergoing either total thyroidectomy or lobectomy, the 60 patients were divided into three nodule-size groups: group A: 1.5–3.5 cm (20 patients), group B: 3.6–5.5 cm (20 patients), and group C: any nodule larger than 5.5 cm (20 patients).
Results
In this study, 60 patients with solitary thyroid nodule were subdivided into equal nodule-size groups: group A:1.5–3.5 cm (20 patients), group B: 3.6–5.5 cm (20 patients), and group C: any nodule larger than 5.5 cm (20 patients), nine (15.0%) patients out of a total of 60 patients turned to be malignant by final histopathology, two (10.0%) from group A, six (30%) from group B, and one (5.0%) from group C. The result is that there is no increased probability of malignancy associated with increasing thyroid size with relative increase of probability of malignancy in group B.
Conclusion
Large solitary thyroid nodules are not associated with an increased probability of malignant disease beyond that which is expected based on their cytological classification. Furthermore, our data would suggest that thyroid nodule sizes ranging between 3.5 and 5.5 cm, as opposed to larger ones, pose a relatively increased risk of malignant disease.

Keywords:
solitary thyroid nodule, thyroid cancer, thyroid malignancy

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Introduction

Solitary thyroid nodules are discrete lesions within the thyroid gland. They are radiologically distinct from the surrounding thyroid parenchyma [1].

Thyroid nodules are commonly diagnosed; upon investigation, they are found in up to 7% of the adult population. During necropsy, thyroid nodules greater than 1 cm are frequently found in 50% of the examined autopsies. They are being discovered increasingly regularly, as a result of the increased usage of imaging in today's era [2].

Despite the fact that more than 90% of identified nodules are clinically and pathologically benign lesions, 7–15% of thyroid nodules contain malignancy [3].

Recent research has indicated that thyroid nodules larger than 4 cm in diameter may increase the risk of malignancy, hence, size may be used independently to predict the risk of malignancy in thyroid nodule patients. But, some other researches disputed these data and even reported against them [4,5].

When indicated, high-resolution ultrasonography (US) and fine-needle aspiration can be used in early management of all thyroid nodules since thyroid cancer is thought to be the most common endocrine malignancy with an increasing prevalence in both sexes [6].

Aim

To determine the impact of solitary thyroid nodule size as an independent factor for increasing probability of malignancy.

Patients and methods

Type of the study

This was a prospective study conducted on patients with a solitary thyroid nodule undergoing surgery.

Sample size

The sample size is 60 patients, divided into three groups.

Study settings

This study was conducted at Endocrine Surgery Unit at Ain Shams University Hospitals from October 2020 to January 2022. The Ethical Committee's approval was obtained, as well as written informed consent from all participants.

The 60 patients are classified into three groups:

(1) Group A (20 patients): nodule size ranged from 1.5 to 3.5 cm.
(2) Group B (20 patients): nodule size ranged from 3.6 to 5.5 cm.
(3) Group C (20 patients): any nodule larger than 5.6 cm in size.

Inclusion criteria

(1) Patients with a solitary thyroid nodule from 1.5 upward.
(2) Nodule classified as thyroid-imaging reporting and data system (TIRAD) 3 or 4 based on thyroid US criteria.
(3) Patients ranging in age from 18 to 60 years.
(4) No previous history of risk factors for developing thyroid malignancy.

Exclusion criteria

(1) Candidates with ages below 18 years old or above 60 years old.
(2) Patients who had suspicious lymph nodes.
(3) Patient refusal.

All patients included in the study were candidates for

Clinical assessment:

Detailed medical, surgical, and family history.

General examination.

Neck examination.

Investigations

(1) Routine laboratory investigations.
(2) Thyroid function tests.
(3) Vocal cord assessment.
(4) Neck US.
(5) Fine-needle aspiration cytology biopsy (FNACB).

Intervention

Patients were subjected to a lobectomy or total thyroidectomy according to surgical guidelines and patient preference.

Follow-up

The results of thyroid gland histopathology were obtained and correlated with nodule size and FNACB.

The primary outcome of the study is histologically proven malignancy per nodule-size group determined following the results.

Results

The 60 patients were classified into three groups:

Group A (20 patients): nodule ranged from 1.5 to 3.5 cm in size.
Group B (20 patients): nodule ranged from 3.6 to 5.5 cm in size.
Group C (20 patients): any nodule larger than 5.6 cm in size.

Discussion

Thyroid nodules are popular, their prevalence increases with age. Although most are benign, 10–15% turn out to be malignant, and more than 2000 patients will die from this disease [7].

Patients most frequently have a big, palpable lump in their neck or an incidental nodule discovered on imaging tests done for another cause when they are first diagnosed [8]. A single nodule within a multinodular gland is less likely to be malignant than a single dominant or isolated nodule, with an incidence of malignancy ranging from 1.4 to 10% and from 2.7 to 30%, respectively [8].

Thyroid profile, neck US, and FNAC are the main methods used to evaluate solitary thyroid nodules. These methods also help determine the best course

of treatment, which is often hemithyroidectomy, complete thyroidectomy, or radioactive iodine.

The 'gold standard' for a precise and trustworthy evaluation of a thyroid nodule is US. When compared with US, palpation and radionuclide scan are inferior as a method of diagnosis, with errors of about 32 and 34%, respectively [9].

We performed a complete thyroidectomy or lobectomy on all of our research participants who had a solitary thyroid nodule detected by US according to surgical recommendations or patient request. The mean age of the 60 patients in this research, who ranged in age from 18 to 60, was 37.57±10.43 (Table 1). Group A had a mean age of 35.70±8.93, group B had a mean age of 38.75±11.61, and group C had a mean age of 38.25 ±10.85 (Table 2, Fig. 1).

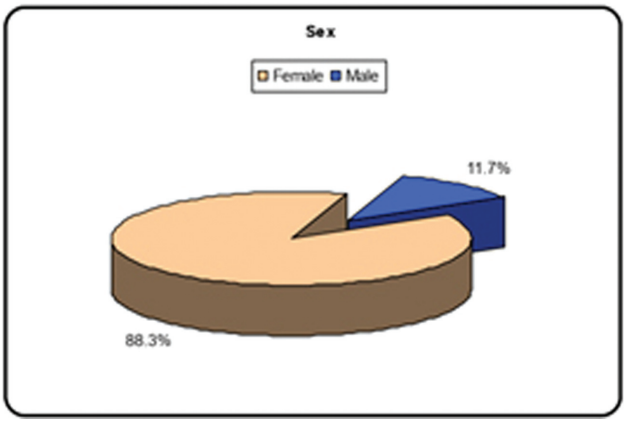
Only seven (11.7%) patients were men (Fig. 2), confirming the literature's assertion that females are more likely than males to have a solitary thyroid nodule. Solitary nodules were four times more common in women than in men, according to Tai and colleagues [10,11]. Group A included two men and 18 women, group B included three men and 17 women, and group C included two men and 18 women (Table 2, Fig. 3). In our study, thyroid cancer was more common in women than in men. Malignant nodules were found in seven of the nine females (Table 2).

Table 1 Demographic data of the all studied patients

	Total=60
Age (years)	
Mean±SD	37.57±10.43
Range	19–59
Sex [*n* (%)]	
Female	53 (88.3)
Male	7 (11.7)
Nodule size (cm)	
Mean±SD	4.12±1.58
Range	1.5–6.3

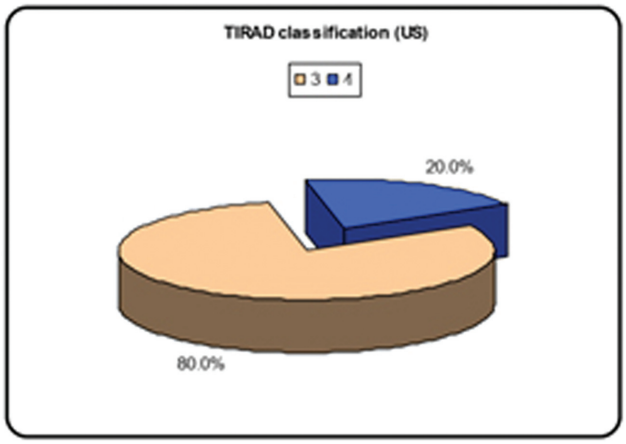
Witczak *et al.* [12] reported similar data with a high incidence of malignancy in females, on the other hand, Paul *et al.* [13] reported that the incidence of malignancy is higher in males. In another study published by Jaheen and Sakr [14], there has been no significant difference between both sexes regarding the incidence of thyroid malignancy.

Figure 1



Comparison between three groups as regards age.

Figure 2



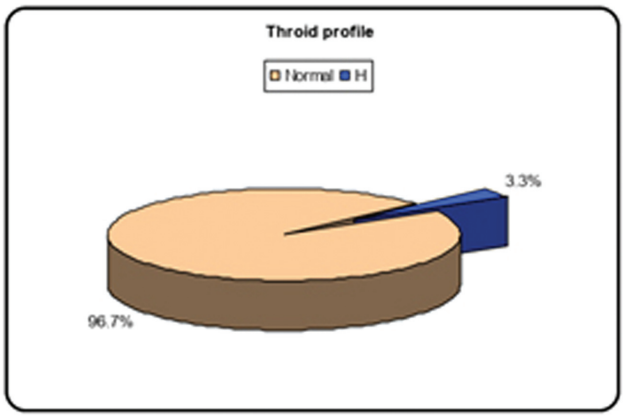
Sex.

Table 2 Demographic data of the studied group per nodule size

	Group A *N*=20	Group B *N*=20	Group C *N*=20	Test value	*P* value	Significance
Age (years)						
Mean±SD	35.70±8.93	38.75±11.61	38.25±10.85	0.483•	0.619	NS
Range	19–54	23–59	21–59			
Sex [*n* (%)]						
Female	18 (90.0)	17 (85.0)	18 (90.0)	0.323*	0.851	NS
Male	2 (10.0)	3 (15.0)	2 (10.0)			

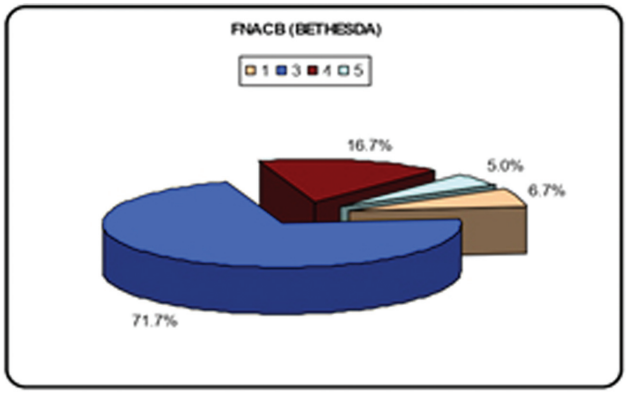
*χ^2 test. •One way analysis of variance test. *P* value more than 0.05: nonsignificant; *P* value less than 0.05: significant; *P* value less than 0.01: highly significant.

Figure 3



Comparison between three groups as regards sex.

Figure 4



Thyroid profile.

Table 3 Results of thyroid ultrasound (thyroid-imaging reporting and data system classification), fine-needle aspiration cytology biopsy (Bethesda classification), and thyroid profile per nodule-size group

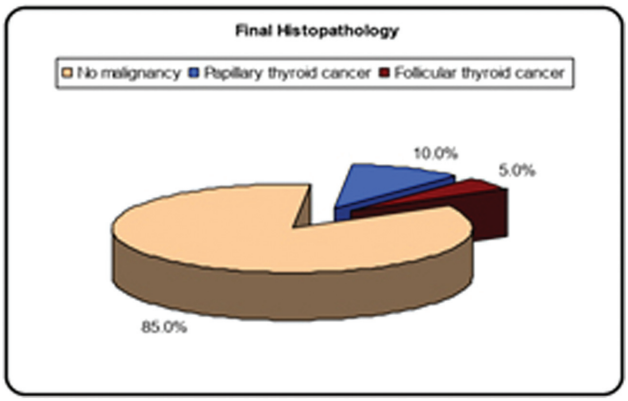
	Group A [*n* (%)] *N*=20	Group B [*n* (%)] *N*=20	Group C [*n* (%)] *N*=20	Test value	*P* value	Significance
TIRAD classification (US)						
3	16 (80.0)	15 (75.0)	17 (85.0)	0.625*	0.732	NS
4	4 (20.0)	5 (25.0)	3 (15.0)			
Thyroid profile						
Normal	18 (90.0)	20 (100.0)	20 (100.0)	4.138*	0.126	NS
H	2 (10.0)	0	0			
FNACB (Bethesda)						
1	2 (10.0)	0	2 (10.0)			
3	13 (65.0)	16 (80.0)	14 (70.0)	10.926*	0.091	NS
4	5 (25.0)	1 (5.0)	4 (20.0)			
5	0	3 (15.0)	0			

FNACB, fine-needle aspiration cytology biopsy; TIRAD, thyroid-imaging reporting and data system. *χ^2 test. *P* value more than 0.05: nonsignificant; *P* value less than 0.05: significant; *P* value less than 0.01: highly significant.

Moreover, Jang *et al.* [15] found no statistically significant difference in the incidence of thyroid malignancy between males and females. This difference between studies may be due to the geographic variations and the number of population included.

In total, 58 (96.7%) were euthyroid, while only two (3.3%) were hypothyroid, and none were hyperthyroid (Fig. 4). The two hypothyroid patients were in group A (Table 3, Fig. 5). In our study, we found that all cancer patients had normal thyroid function, which indicates that thyroid function tests are not indicators of thyroid cancer and that most people with thyroid cancer have normal thyroid function [7].

Figure 5



Comparison between three groups as regards thyroid profile.

The nodule sizes ranged from 1.5 to 6.3 cm, with a mean 4.12±1.58 cm (Table 1). In total, 48 (80.0%) showed TIRADS 3, and 12 (20.0%) showed TIRADS 4 by US (Table 4, Fig. 6). Group A contained four TIRAD 4 nodules, group B contained five nodules, and group C contained three nodules; the remaining nodules were classified as TIRAD 3 (Table 3, Fig. 7). All malignant nodules in this study came back as

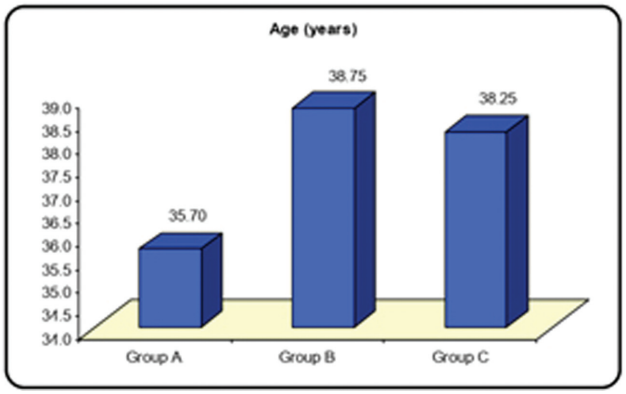
TIRAD 4 in the preoperative assessment, demonstrating the accuracy of the US in detecting suspicious lesions.

Table 4 Ultrasound, fine-needle aspiration cytology biopsy, and thyroid profile results of all studied patients

	Total=60 [*n* (%)]
TIRAD classification (US)	
3	48 (80.0)
4	12 (20.0)
Thyroid profile	
Normal	58 (96.7)
H	2 (3.3)
FNACB (Bethesda)	
1	4 (6.7)
3	43 (71.7)
4	10 (16.7)
5	3 (5.0)

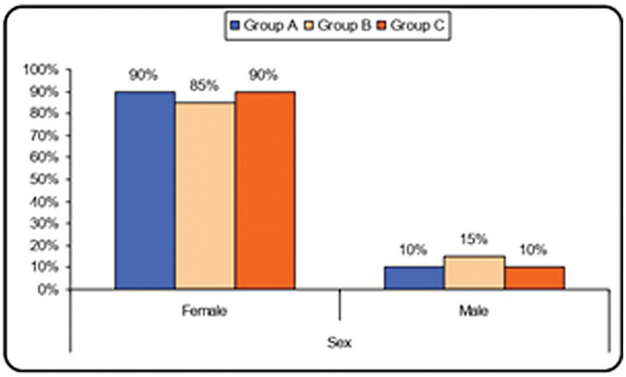
FNACB, fine-needle aspiration cytology biopsy; TIRAD, thyroid-imaging reporting and data system.

Figure 6



TIRAD classification. TIRAD, thyroid-imaging reporting and data system.

Figure 7



Comparison between three groups as regards TIRAD classification (US). TIRAD, thyroid-imaging reporting and data system; US, ultrasound.

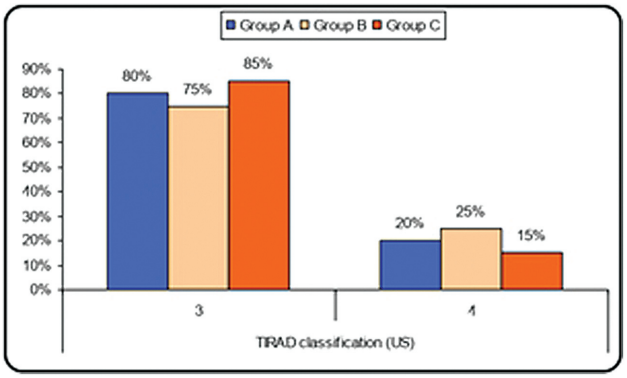
Regarding preoperative FNACB, most studied cases 43 (71.7%) came out as Bethesda 3 (follicular lesion of undetermined significance), 10 (16.7%) cases as Bethesda 4 (suspicious for follicular neoplasm), three (5.0%) cases as Bethesda 5 (suspicious for malignancy), and four (6.7%) cases as Bethesda 1 (nondiagnostic/ unsatisfactory) (Fig. 8).

They were divided into three groups, as shown in Fig. 9.

The three nodules classified as Bethesda 5 were all confirmed malignant by final histopathology; of the 10 nodules classified as Bethesda 4, only four turned out to be malignant, and of the 43 nodules classified as Bethesda 3, only two came out as malignant nodules.

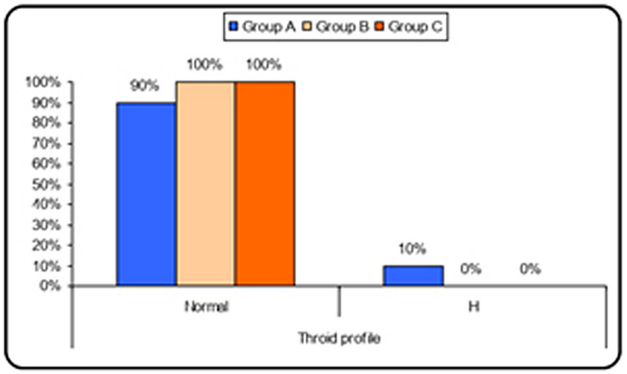
FNACB is an important diagnostic tool used to predict the nature of suspicious nodules detected by US. However, we cannot rely solely on FNACB results because many of them are incongruent with final histopathology, and every nodule should be treated

Figure 8



FNACB (Bethesda). FNACB, fine-needle aspiration cytology biopsy.

Figure 9



Comparison between three groups as regards FNACB (Bethesda). FNACB, fine-needle aspiration cytology biopsy.

with caution regardless of FNACB result, especially if there is radiological or pathological incongruence.

On the final histopathology result, 51 (85.0%) out of 60 cases were found to be benign: 22 (63.6%) colloid nodules, 20 (33.3%) hyperplastic nodules, and nine (15%) thyroiditis. In total, nine (15%) cases were confirmed to be malignant: six (10.0%) papillary thyroid carcinoma, three (5.0%) follicular cell carcinoma (Table 5, Fig. 10).

In order to determine the ideal cutoff diameter that can predict malignancy, we separated the nodules into groups.

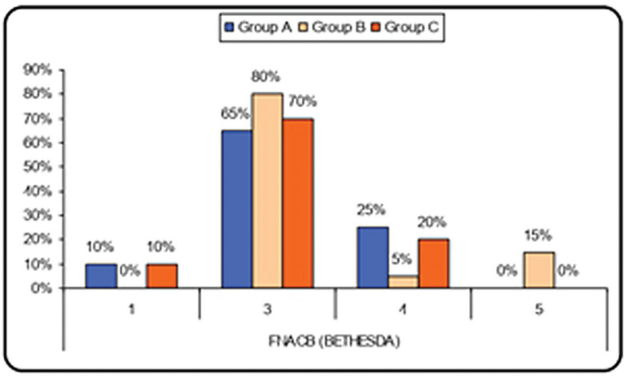
The nodules were divided into three groups (A–C) based on their sizes:

(1) Group A (20 patients): 1.5–3.5 cm.
(2) Group B (20 patients): 3.6–5.5 cm.
(3) Group C (20 patients): any nodule larger than 5.5 cm.

Table 5 Results of final histopathology for all studied patients

	Total=60 [*n* (%)]
Final histopathology after definite surgery	
No malignancy	51 (85.0)
Malignancy	9 (15.0)
Papillary thyroid cancer	6 (10.0)
Follicular thyroid cancer	3 (5.0)

Figure 10



Final histopathology.

Numerous studies have divided nodules into size categories to facilitate comparisons and pinpoint the group size that carries the most risk with nodule-size groups that differ between them.

For example, Kamran *et al.* [8] included a total of 9339 nodules more than or equal to 1 cm. The mean nodule size was 2.6 cm. The nodules were subdivided into the following groups by size: 1–1.9, 2–2.9, 3–3.9, and more than or equal to 4 cm.

Some researchers like Hammad *et al.* [16] categorized their 10 817 nodules into three groups: a control group with nodules less than 3, two other groups: 3–5.9, and greater than 6.

Also, Bestepe *et al.* [17] conducted their study on 2463 patients and grouped their nodule diameters as less than 1, 1–1.9, 2–3.9, and more than 4 cm.

Postoperative histopathological reports show that nodule sizes are the same as in the US, with a 1–3-mm difference, which did not affect our categorization of nodules based on size.

In group A, in which the nodules measured 1.5–3.5 cm by US, two (10.0%) of the nodules were found to be malignant by final histopathology, both were papillary thyroid carcinoma. In group B, in which the nodules measured 3.6–5.5 cm by US, six (30.0%) of the nodules were found to be malignant by final histopathology, four were papillary thyroid carcinoma and two were follicular thyroid carcinoma. In group C, in which the nodules were larger than 5.5 cm by US, only one (5.0%) nodule was found to be malignant by final histopathology and was papillary thyroid carcinoma (Tables 6 and 7).

Figure 11 demonstrates a comparison of three groups in terms of final histopathology.

In our study, patients in the nodule group of size 3.5–5.5 cm (group B) have a 30% higher malignancy risk compared with those less than 3.5 cm (group A) in size. On the other hand, the risk of malignancy was found to drop by 16.6% when nodule size is greater than 5.5 cm (group C).

Table 6 Result of final histopathology per nodule-size group

Final histopathology	Group A [*n* (%)] *N*=20	Group B [*n* (%)] *N*=20	Group C [*n* (%)] *N*=20	Test value	*P* value	Significance
No malignancy	18 (90.0)	14 (70.0)	19 (95.0)	5.490*	0.064	NS
Papillary thyroid cancer	2 (10.0)	4 (20.0)	0	4.444*	0.108	NS
Follicular thyroid cancer	0	2 (10.0)	1 (5.0)	2.105*	0.349	NS

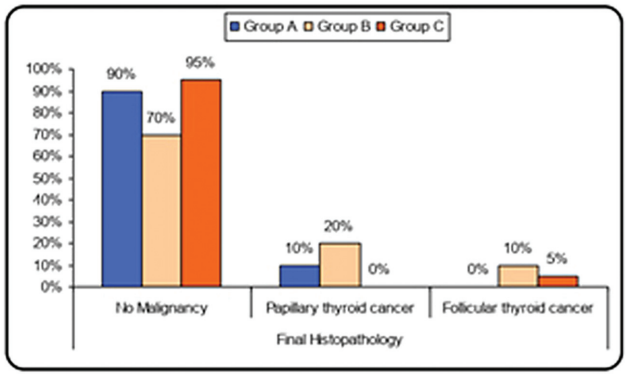
*χ^2 test. *P* value more than 0.05: nonsignificant; *P* value less than 0.05: significant; *P* value less than 0.01: highly significant.

Table 7 Result of final histopathology per nodule-size group

Final histopathology	Group A [*n* (%)] *N*=20	Group B [*n* (%)] *N*=20	Group C [*n* (%)] *N*=20	Test value	P value	Significance
No malignancy	18 (90.0)	14 (70.0)	19 (95.0)	5.490*	0.064	NS
Malignancy	2 (10.0)	6 (30.0)	1 (5.0)			

*χ^2 test. *P* value more than 0.05: nonsignificant; *P* value less than 0.05: significant; *P* value less than 0.01: highly significant.

Figure 11



Comparison between the three groups as regards final histopathology.

Postoperative histopathology reveals that papillary thyroid carcinoma is the most common type of malignant nodule.

Large solitary thyroid nodules are not associated with an increased probability of malignant disease, and thyroid nodule sizes ranging between 3.5 and 5.5 cm, as opposed to larger ones, pose a relatively increased risk of malignant disease, yet the *P* value is insignificant regarding the relation between nodule size and probability of malignancy.

In agreement with our study, Bohacek *et al.* [18] reported that there is no trend toward a higher prevalence of malignancy with larger nodule size overall, but when nodules were categorized by size in centimeters, there was a statistically significant difference in the rate of malignancy among nodules of the 2–3-cm (36.7%) category compared with the rest, as well as in the 3–4 cm.

Also, in agreement with our results, Shrestha *et al.* [19] reported no suggested difference in malignancy prevalence according to size.

Albuja-Cruz *et al.* [20] reported that a nodule size greater than or equal to 4 cm is not associated with a higher prevalence of malignancy overall.Cavallo *et al.* [21] reported that the risk of malignancy is inversely related to the nodule size. McHenry *et al.* [22] reported that the likelihood of malignancy significantly decreased nonlinearly with increasing size.

Bestepe *et al.* [17] reported that malignancy risk does not increase with increasing nodule diameter. There was no optimal cutoff value. The diameter or volume of the nodule cannot be used to predict malignancy or decide on surgical resection. According to Hammad *et al.* [16], those with nodules between 3 and 5.9 cm in diameter have a 26% higher risk than those with nodules with less than 3-cm diameter. The probability of cancer is reduced in nodules under 6 cm (16% compared with the reference group). Due to their increased risk of developing cancer, patients with nodules 3–5 cm in size should carefully consider surgical management, especially if additional clinical and/or US signs of cancer are present.

On the contrary, Kuru *et al.* [23] reported that nodule size greater than or equal to 4 cm was an independent factor associated with malignancy. Carrillo *et al.* [24] reported that nodules greater than or equal to 4 cm were significantly more likely to contain malignancy.

Kamran *et al.* [8] reported that increasing thyroid nodule size impacts cancer risk in a nonlinear manner with a threshold of 2.0 cm.

Conclusion

Our study demonstrates that large solitary thyroid nodules are not associated with an increased probability of malignant disease. Furthermore, our data would suggest that thyroid nodule sizes ranging between 3.5 and 5.5 cm, as opposed to larger ones, pose a relatively increased risk of malignant disease, and the nodule size alone cannot be used as an independent factor for increasing probability of thyroid malignancy.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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