Relationship of Nodule Type and Size with Thyroid Malignancy

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ABSTRACT
Thyroid carcinoma was the common head-neck malignancy. Clinical examination was essential at the initial suspicion of thyroid malignancy. Thyroid size and nodularity were the first things in a physical examination of the thyroid. This study aimed to determine the relationship between the type and size of thyroid nodules and their malignancy. This research was a case-control study. The case group was malignant thyroid nodules, while the control group was benign thyroid nodules. The study subjects were patients with thyroid nodules who underwent thyroidectomy surgery at RSUP. Dr. Sardjito Yogyakarta, between 2016-2018. The type of nodules was determined by computerized tomography (CT) scan. The size of the nodules was determined by a CT scan. The difference of nodularity was analyzed within each group and between study groups. The subject consisted of 50 patients who underwent thyroidectomy, each group consisted of 25 patients. There was no significant difference in nodule type (multinodular and unimodular) between benign and malignant thyroid nodul with p value 0.079 ($p< 0.05$, 95% CI). There was no significant difference in nodule size between benign and malignant thyroid nodul with p value = 0.148 ($p> 0.05$, 95% CI) and Odds Ratio (OR)= 0.67 (95% CI 0.19 -2.32). Multivariate analysis was performed. The dependent variable was nodule malignancy. The independent variables were age, sex, TSH level, free-T4 level, nodule type and nodule size. The results of the logistic regression analysis showed statistically significant results only at TSH levels with p value = 0.005. The conclusion of this study was that the type of nodule (multinodular and uninodular), and nodule size were not related to the thyroid malignancy statistically.

Keywords: *thyroid nodule, multinodular, uninodular, thyroid nodule size, thyroid malignance.*

1. INTRODUCTION

Thyroid cancer represented about 1% of new cancer diagnoses in the United States each year. Thyroid malignancies were divided into papillary carcinoma (80%), follicular carcinoma (10%), medullary thyroid carcinoma (5-10%), anaplastic carcinoma (1-2%). Approximately 23,500 cases of thyroid carcinoma were diagnosed each year in the United States. The incidence of disease was higher in women than men. A study conducted by Weir *et al*. from the Centers for Disease Control and Prevention (CDC), estimated that in 2020 the highest increase in the incidence of cancer in women was thyroid carcinoma [1].

Whether the prevalence of thyroid cancer was different in thyroid glands with a solitary nodule (SN)/ uninodular versus multinodular goiter (MNG)/ remains uncertain. Thyroid carcinoma was the common head-neck malignancy. Clinical examination was essential at the initial suspicion of thyroid malignancy. Thyroid size and nodularity were the first things in a physical examination of the thyroid. This study aimed to determine the relationship between the type and size of thyroid nodules and their malignancy [2].

Physical examination was essential at the initial suspicion of a thyroid lesion. In primary health care facilities, the role of knowledge of thyroid physical examination was important to guide the diagnosis of malignancy in the thyroid gland. These differences in thyroid cancer risk might impact recommendations and practice. Therefore, this study aimsed to give available comparative prevalence of adults thyroid malignancy with single or multiple thyroid nodules undergoing evaluation after surgery [2]. Although other ultrasound characteristics were important in predicting thyroid malignancy, physical examination was the initial examination performed on a patient [3].

The main indication for fine needle aspiration (FNA) of the thyroid has been the presence of a solitary nodule. Patients with intraglandular dissemination, and without nodular goiter or Hashimoto's thyroiditis more often had regional lymph node metastases. Lower rates of regional lymph node metastases in patients with and Hashimoto's thyroiditis are probably due to smaller papillary carcinoma nodule sizes found during routine follow-up of these benign diseases[4].

2. OBJECTIVES

This study aimed to determine relationship between multinodular goiter (MNG) versus uninodular tiroid nodule and other variables with thyroid malignancy.

3. METHOD

This research was a case control study. The case group was malignant thyroid nodules, while the control group was benign thyroid nodules. The subjects of the study were patients with thyroid nodules who underwent thyroidectomy surgery at RSUP. Dr. Sardjito Yogyakarta, between 2016-2018. Type of nodules was determined by a CT scan. Size of nodules was determined by CT scan. The difference of nodularity was analyzed within each groups and between study groups. The subject consisted of 50 patients who underwent thyroidectomy, each group consisted of 25 patients. There was no significant difference in nodule type (multinodular and unimodular) between benign and malignant thyroid nodul with p value = 0.148 (p> 0.05, 95% CI) and Odds Ratio (OR)= 0.67 (95% CI 0.19). - 2.32). Multivariate analysis was performed. The dependent variable was nodule malignancy. The independent variables were age, sex, TSH level, free T4 level, nodule type and nodule size. The results of the logistic regression analysis showed statistically significant results only at TSH levels with p value = 0.005.

This research was an analytic observational study with the research design used was a case-control study. The case group was malignant thyroid nodules and benign thyroid nodules as the control group. The research sample data were taken from medical records from 2015-2017, namely patients who had undergone thyroidectomy surgery at RSUP. Dr. Sardjito Yogyakarta. Type of nodules was determined by a CT scan. size of nodules was determined by CT scan.

4. RESULTS AND DISCUSSION

Researchers found 50 patients who met the inclusion and exclusion criteria, 25 patients diagnosed as malignant thyroid nodules and 25 patients diagnosed as benign thyroid nodule.

In Table 1, there was no statistically significant.

Table 1. Characteristics of research subjects

characteristics	Histopatology		Σ n(%)	P value
	Malignant n(%)	Benign n(%)		
Sex				
Male	5 (20.0%)	5 (20.0%)	10 (20.0%)	1.000
Female	20 (80.0%)	20 (80.0%)	40 (80.0%)	
Age				
< 45 year	9 (36.0%)	11 (44.0%)	20 (40.0%)	0.773
>/= 45 year	16 (64.0%)	14 (56.0%)	30 (60.0%)	
Age Category				
10-19 year	1 (4.0%)	1 (4.0%)	2 (4.0%)	0.966
20-29 year	4 (16.0%)	3 (12.0%)	7 (14.0%)	
30-39 year	2 (8.0%)	3 (12.0%)	5 (10.0%)	
40-49 year	9 (36.0%)	10 (40%)	19 (38.0%)	
50-59 year	5 (20.0%)	5 (20.0%)	10 (20.0%)	
60-69 year	3 (12.0%)	3 (12.0%)	6 (12.0%)	
70-79 year	1 (4.0%)	0 (0.0%)	1 (2.0%)	

*p value is significant if<0.05

Difference between the sexes and gender variables in case group and control group. Most of the research subjects were women. Thyroid nodules were common in women.

Soleimanisardo *et al*., 2021, a total number of 77 patients, 65 out of which were female with differentiated thyroid carcinoma, while Golbert *et al*., 2017, total of 615 patients participated in the study, 544 (88.5%) were female[5,6].

Table 2. Age categories

Age	n	%
10-19 th	2	4.0
20-29 th	7	14.0

Age	n	%
30-39 th	5	10.0
40-49 th	19	38.0
50-59 th	10	20.0
60-69 th	6	12.0
70-79 th	1	2.0
Σ	50	100.0

The youngest subject of this study was 17 years old and the oldest was 71 years old with an average patient age was 44.5 years. Age range 40-49 years was the most dominant as 19 (38%) subjects. This result was the same as the research conducted by Soleimanisardo *et al*., 2021, the age distribution of the subject group shows that 2 (2.5%) patients were under 20 years old, 37 (48.1%) patients were 20–40 years old, 34 (44.2%) patients were 41–60 years old, and 4 (5.2%) patients were over 60 years old [5].

Uninodular was the most common thyroid enlargement in the subjects of this study (Table 3), as many as 31 patients. There was a significant difference between the type of nodule and sex. Thiswas consistent with the characteristics of thyroid nodules which were more common in women. There was no significant difference between age variables.

To determine the mean difference TSH and free T4 each group using the independent sample t-test. In table 4, there was a significant mean difference of TSH levels between the multinodular and uninodular groups, with a value of p =0.007. Therewas no significant difference in the free T4 variable.

Table 3. Proportion differences of nodule types in each variable

	Nodul Type					
	Multinodular n(%)	Uninodular n(%)	Σ n(%)	p value	OR	CI 95 %
Sex						
Male	1(5.3%)	9(29.0%)	10(20.0%)	0.041**	0.136	0.01-1.17
Female	18(94.7%)	22(71.0%)	40(80.0%)			
Age						
< 45 yr	8(42.1%)	12(38.7%)	20(40.0%)	0.812*	1.15	0.36-3.68
>/= 45 yr	11(57.9%)	19(61.3%)	30(60.0%)			
Age Category						
10-19 th	0(0.0%)	2(6.5%)	2(4.0%)	0.501**	*	*
20-29 th	1(5.3%)	6(19.4%)	7(14.0%)			
30-39 th	3(15.8%)	2(6.5%)	5(10.0%)			
40-49 th	8(42.1%)	11(35.5%)	19(38.0%)			
50-59 th	5(26.3%)	5(16.1%)	10(20.0%)			
60-69 th	2(10.5%)	4(12.9%)	6(12.0%)			
70-79 th	0(0.0%)	1(3.2%)	1(2.0%)			

*Chi square test , ** Fisher exact test

A study by Rinaldi *et al*., 2014, found a significantly increased risk of papillary thyroid carcinoma associated with TSH levels below the normal range among women and with TSH levels above the normal range among men. Fighera et al., 2015, suggested that in patients with nodular thyroid disease the carcinoma risk rose in parallel with serum TSH concentration, with significant increases evident in patients with serum TSH greater than 1.64 mU/L. This study did not directly determine the relationship between TSH levels and nodule type. In this study, it was concluded that TSH levels were an independent risk factor for thyroid malignancy separate from the type of nodule [7,8].

The main outcome in this study was to examine the relationship between the types of thyroid nodules (uninodular and multinodular) TSH and thyroid malignancy.

To determine differences of thyroid malignancy in multinodular and uninodular types, a hypothesis test was performed using the x^2 test. In Table 5, it appears that the p value = 0.079. The malignant nodule was uninodular dominant, but it wasn't statistically significant. In the table 6, there was no significant difference in nodule size in malignant and benign thyroid nodules. In this study, the size of the thyroi nodule was not related to thyroid malignancy.

Table 4. Mean differences of TSH dan free T4 in each variables

Variables	Mean (SD)	p value	Mean Difference CI 95 %
TSH level			
Multinodular	0.6 (0.42)	0.007*	0.51 (0.14-0.88)
Uninodular	1.1 (0.72)		
Free T4 level			
Multinodular	0.9 (0.12)	0.534	0.02 (-0.8-0.15)
Uninodular	1.0 (0.22)		

*p value < 0.05

Table 5. Relationship between Nodule Type and Tyroid Malignancy

Characteristics	Histopatology		Σ n(%)	P value
	Malignant n(%)	Benign n(%)		
Nodul Type				
Multinodular	6 (24%)	13 (52,0%)	19 (38,0%)	0,079
Uninodular	19 (76,0%)	12 (48,0%)	31(62,0%)	

We did a multivariate test, which was a logistic regression test to assess the relationship between variables and the dependent variable using dichotomous categorical data. We assessed gender, age, TSH, free T4, nodule type and nodule size for thyroid malignancy.

In the logistic regression test for variables, only the TSH was significant. With the prerequisite Omnibus test, the significance value was p <0.001, (p <0.05) and the Hosmer and Lemeshow Goodness of Fit Test with a significance result of 0.650 (p> 0.05). The results of Nagelkerke R Square are 0.48 (48%), meaning that the independent variable significantly affects the clinical stage by 48%, the remaining 56% was influenced by other variables outside of our study.

Table 6. Mean difference of Nodule Size of Thyroid Malignancy

		n	Mean (SD)	P value	Mean difference CI 959
Nodule size					
	Malignant	25	3.9 (2.42)	0.148	-1.39 (-3.29-0.51)
	Benign	25	5.3 (4.05)		

Logistic regression analysis was carried out, it was found that only significant results were obtained on the TSH variable with a p value = 0.005. Uninodular, multinodular nodule type, and nodule size statistically had no effect on thyroid malignancy.

Table 7. Logistic Regression Test

Variables	B	Sig.	Exp (B)	95% C.I.for EXP(B)	
				Lower	Upper
Age	0.01	0.972	1.01	0..94	1.07
Sex	0.89	0.330	2.44	0.41	14.72
TSH	.-3.01	0.005*	0.05*	0.01*	0.38*
FreeT4	.-0.15	0.654	0.86	0.44	1.67
Nodul Type	0.13	0.878	1.14	0.21	6.22
Nodule Size	0.03	0.827	1.02	0.80	1.32

Multinodularity did not increase the risk of thyroid malignancy. However, patients with multinodular who develop papillary carcinoma were at an increased risk of cancer multifocality [9]. Another study by Shresta *et al*.,2015 stated the risk of malignancy in multinodular goi-ter should not be underestimated as significant number of patients with thyroid malignancies present with multinodular goiter [10].

Bhuiyan *et al*., 2015, in their study stated adenoma and multinodular goiter were the predominant non-malignant conditions (85.6%). The prevalence of thyroid cancer in their study was 11.1%, and of all 90 patients, 7.8% had follicular carcinoma. The risk of malignancy in multinodular goiter was 8.9%. Age was important risk factor in thyroid nodule malignancy. With advancing age, the prevalence of clinically relevant thyroid nodules increases, whereas the risk that such nodules are malignant decreases [11,12].

Brito *et al*. 2013, conducted a study about tiroid nodularity. MNGs were associated with a lower risk of thyroid cancer than solitary nodule (pooled odds ratio 0.8 (95% confidence interval 0.67–0.96). Subgroup analysis suggested that this difference depends on the inclusion of studies conducted outside the United States. Thyroid cancer might be less frequent in multinodular goiter compared to solitary nodule, particularly outside the United States and perhaps in iodine- deficient areas [2].

Patients with papillary carcinoma and nodular goiter or Hashimoto's thyroiditis less often had regional lymph node metastases, due to smaller nodule size found during routine follow-up. Papilary carcinoma was more commonly confirmed in the dominant nodule [4].

Risk of malignancy was defined by FNAB for thyroid nodules but sometimes, it was difficult. The initial workup for thyroid nodules comprised a thorough history and physical examination, thyroid function tests, a dedicated thyroid ultrasound, and fine-needle aspiration of any suspicious lesions. Management range from observation and reassurance to surgical resection and depended on the cytologic diagnosis. In cases of cytologically indeterminate or discordant nodules, surgical excision offers a definitive diagnosis [4,13–15].

Limitations of this study were that thyroid size and nodularity were not the only influential variables to help predict thyroid malignancy. There were still other variables that also influence the thyroid malignancy that could not be explored through this research, so it was necessary to carry out further research with more variable coverage.

5. CONCLUSION

The conclusion of this study was that the type of nodule (multinodular and uninodular), and nodule size were not related to the thyroid malignancy statistically.

ETHICAL APPROVAL

The study is in compliance with the Declaration of Helsinki.

CONSENT

The authors have confirmed during submission that patient consent has been signed and collected in accordance with the journal's patient consent policy.

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