Assessment of the relationship between clinical and histopathological features in cases of thyroidectomy

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AIM: *The aim of this study is to evaluate the relationship between clinical parameters and ultimate histopathologic features of patients underwent thyroid surgery.*
METHOD: *Demographic and clinicopathologic parameters of patients who underwent thyroid surgery for benign or malignant disease in our clinic between June 2006 and March 2014 were retrospectively reviewed. Pearson's Chi-Square, Independent Sample T test, ROC Curve and Youden J Index were used to investigate whether there was any relationship between the clinical parameters and permanent histopathologic features of patients.*
RESULTS: A *total of 3059 patients (Benign: 2727; Malign: 332) aged between 15 and 90 years were reviewed. The patients age was higher in malign group (mean ± SD: 46.8 ± 4.2) than benign group (mean ± SD: 43.7 ± 12.9 yr) and this difference was statistically significant (p <0.001). The nodule diameter (mean ± SD: 30.8 ± 13.5 mm) was greater in malign group than the benign group (mean ± SD: 28.3 ± 13.4 mm) and this difference was statistically significant (p = 0.002). The sensitivity and specificity rates of the most appropriate cut-off point (> 26 mm) for the nodule size were 60% and 49.05%, respectively. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of FNAB were calculated as 4.17 %, 100 %, 100 %, 89.96% and 90 %, respectively.*
CONCLUSION: *This study showed that higher age and greater nodule diameter (> 26 mm) are associated with malignancy.*

KEY WORDS: Age, Large Nodule Diameter, Risk factors, Thyroid disease,Thyroid Cancer

Introduction

Although there are differences regionally, thyroid diseases are among the most common endocrine diseases. In parallel with the widespread use of radiological instruments, the incidence of thyroid nodules is significantly increased. This explains why the incidence of thyroid cancer is increasing nowadays [1]. In studies performed in an adult patient population, rates of thyroid nodule detection by palpation and thyroid ultrasonography were found to be 4-7% and 19-67%, respectively. Most thyroid diseases, especially thyroid nodular diseases, are more common in women and in older people [2].

An epidemiological study showed that the incidence of thyroid nodules increased from 10.2% in 2006 to 18.6% in 2010, in China [2]. Turkey is one of the countries where thyroid iodine deficiency and consequent nodular goiter are endemic. Therefore, total, near total and subtotal thyroidectomy due to nodular goiter are among the most frequently performed surgical procedures in Surgery Clinics in Turkey.

In regions where iodine deficiency is endemic, multinodular goiter is the most common endocrine disease. The surgical indications for these patients include compression of symptoms caused by large goiter such as dysphagia and breath shortness, radiological or FNAC results

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in favor of cancer, retrosternal placement, medical treatment resistant hyperthyroidism and cosmetic reasons. European and American guidelines for endocrine surgery associations suggest total thyroidectomy in benign multinodular goiter treatment to avoid complications of reoperation in cases of recurrent or incidentally proved thyroid cancer [3].

The incidence of differentiated thyroid microcarsinoma (tumor ≤1 cm) is rapidly increasing, especially in thyroid cancers. Although differentiated thyroid microcarcinomas show more benign behavior than large sized thyroid cancers, subgroups may be aggressive and require treatment as large-sized cancers. TSH does not only stimulate normal tissue in the thyroid tissue, it also stimulates malignant thyroid tissue. There are some studies that show the effect of TSH on the development of thyroid cancer [2]. The aim of this study is to evaluate the relationship between clinical parameters and permanent histopathological findings of patients undergoing thyroid surgery especially relationship between thyroid cancer and clinic parameters.

Material and Methods

Between March 2006 and March 2014, a total of 4356 patients who had undergone thyroid surgery with a diagnosis of multinodular goiters, diffuse goiter, hyperthyroidism, graves disease or preliminary diagnosis of thyroid cancer in the Department of Surgery, Diyarbakir Education and Research Hospital, Turkey were retrospectively reviewed. Patients' age (years), gender (female, male), nodule diameter (mm), number of nodules, nodule localization (right lobe, left lobe, bilateral), thyroid function tests (hyperthyroidism, hypothyroidism, euthyroidism) , surgical note and pathology reports were examined by two investigators (SA, HS) and the obtained data were recorded in excel file. As a result of this screening, both blood tests and pathology reports of a total of 3059 patients were reached, while either demographic data or thyroid function tests of the remaining 1297 patients couldn't be reached. Because of this, these patients were excluden from the study. While total or near total thyroidectomy was performed in 2566 patients included in this study, 493 patients underwent either bilateral subtotal thyroidectomy or unilateral total plus contralateral subtotal surgery. Thyroid function tests and thyroid ultrasonography were performed after routine physical examination in patients who were admitted to our clinic from external centers with the suspicion of benign thyroid diseases or thyroid cancer. Thyroid scintigraphy was performed in cases in which signs and symptoms of hyperthyroidism or suspicion of cancer were identified. Only 391 of the 3059 patients included in this study performed FNAC in the guidance of palpation or ultrasound. Unfortunately, our experience with FNAC was limited before 2010. The primary purpose of this study is to assess if there is a relationship between the histopathological findings of the thyroidectomy specimen and the demographic and clinical parameters of the patients. IBM SPSS Statistics v23.0 and Medcalc 9.0 package programs were used for statistical analysis of this study. Quantitative data were given in the form of mean ± SD and qualitative data were given as number and percentage (%). The relationship between permanent histopathological findings and FNAC findings was calculated by cross-tabulation. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value for FNAC were given as percentage (%). Pearson's Chi-Square test based on the Exact approach was used to determine the relationship between the permanent histopathological findings, gender and thyroid function tests. Independent Sample T test based on Exact approach was used to determine the relationship between permanent histopathological findings, age, and largest nodule diameter. Receiver Operating Characteristic (ROC) curves were used to determine the optimal cut point for the nodule size variable. The Youden Index J value was used to calculate the most appropriate cutting point. 1000 repeat Bootstrap method and random number seed approach were used to calculate confidence interval. A P value of 0.05 was considered significant for all statistical analyzes.

Results

A total of 3059 patients aged between15 and 90 were included in this study, 2712 (88.7%) of whom were female and 347 (11.3%) were male. The ages of the male patients ranged from 16 to 85 (Mean ± SD: 46.8 ± 16.1 yr), while the ages of the female patients ranged from 15 to 90 (mean ± SD: 43.7 ± 13.0 yr). In 2727 (89.1%) of the patients included in the study, permanent pathology was reported as benign thyroid diseases, 332 (10.9%) were reported pathological as malignant thyroid diseases. The frequency of benign diseases is as follows: nodular hyperplasia (n = 2063), Follicular adenoma (n = 219), Adenomatous hyperplasia (n = 113), Focal Lymphocytic thyroiditis (n = 106), Lymphocytic thyroiditis (n = 98), Hashimoto thyroiditis (n = 49), Hurthle cell adenoma (n = 32), Graves' disease (n = 17) Adenomatous nodule (n = 11), Subacute granulomatous thyroiditis (n = 7), Tuberculous thyroiditis (n = 7), Riedel thyroiditis (n = 3) and hydatid cyst (n = 2). The most common malignant diseases are Papillary carcinoma (n = 171), Papillary microcarsinoma (n = 88), Follicular carcinoma (n = 39), Hurthle cell carcinoma (n = 19), Medullary thyroid carcinoma (N = 2), Lenfoma (n = 2) Aanaplastic cancer (n = 2), Hemangioendotelioma (n = 1) and Squamous cancer (n = 1).

Benign thyroid disease was detected histopathologically in 304 (87.6%) of males while malignant thyroid disease was detected in the remaining 43 (12.4%) male

TABLE I - *Relationship between gender and histopathologic findings*

			Pathology		
			Benign	**Malign**	**Total**
Sex	Male	Count	304	43	347
		% within Sex	87.6	12.4	100
		% within Pathology	11.1	13.0	11.3
		% of Total	9.9	1.4	11.3
	Female	Count	2423	289	2712
		% within Sex	89.3	10.7	100
		% within Pathology	88.9	87.0	88.7
		% of Total	79.2	9,4	88.7
Total		Count	2727	332	3059
		% within Sex	89.1	10.9	100
		% within Pathology	100	100	100
		% of Total	89.1	10.9	100

TABLE II - *Relationship between histopathologic details and thyroid function tests*

			Pathology		
			Benign	**Malign**	**Total**
TFT	Hyperthyroidism	Count	620	63	683
		% within TFT	90.8	9.2	100
		% within Pathology	22.7	19.0	22.3
		% of Total	20,3	2.1	22.3
	Euthyroidism	Count	2028	263	2291
		% within TFT	88.5	11.5	100
		% within Pathology	74.4	79.2	74.9
		% of Total	66.3	8.6	74.9
	Hypothyroidism	Count	79	6	85
		% within TFT	92.9	7.1	100
		% within Pathology	2.9	1.8	2,8
		% of Total	2.6	0.2	2,8
Total	Count	2727	332	3059	
		% within TFT	89.1	10.9	100
		% within Pathology	100	100	100
		% of Total	89.1	10.9	100

TABLE III - *Cross tabulation of thyroid FNAB findings with the permenant histopathologic findings*

			Permenant Pathology		
			Benign	**Malign**	**Total**
FNAB	Benign	Count	206	23	229
		% within FNAB	90.0	10.0	100
		% within pathology	61.1	42.6	58.6
		% of total	52.7	5.9	58.6
	Suspicious	Count	62	24	86
		% within FNAB	72.1	27.9	100
		% within pathology	18.4	44.4	22.0
		% of total	15.9	6.1	22.0
	Malign	Count	0	1	1
		% within FNAB	0.0	100	100
		% within pathology	0.0	2.0	0.2
		% of total	0.0	0.2	0.2
	Non diagnostic	Count	69	6	75
		% within FNAB	92	8.0	100
		% within pathology	20.4	11.1	19.2
		% of total	17.6	1.5	19.2
Total		Count	337	54	391
		% within FNAB	86.2	13.8	100
		% within pathology	100	100	100
		% of total	86.2	13.8	100

patients. Two thousand four hundred twenty three (89.3%) of the female patients were diagnosed with benign thyroid disease while in the remaining 289 (10.7%) female patients had malignant thyroid diseases. As a result of analysis to show whether there is a relationship between gender and permanent thyroid pathology no statistically significant relationship was found between thyroid malignancy and sex (p = 0.36) (Table I). Two thousand two hundred and ninety one (74.9%) of the patients included in the study did not receive any thyroid hormone replacement or antithyroid drug therapy in the preoperative period (Euthyroidism). In contrast, 683 patients (22.3%) received antithyroid drug therapy (Hyperthyroidism) and 85 patients (2.8%) received thyroid hormone replacement therapy (Hypothyroidism). In 620 (90.8%) patients with hyperthyroidism, benign thyroid pathology was detected and 63 (9.2%) patients had malignant thyroid disease. When benign thyroid pathology was detected in 2028 (88.5%) of the patients who were diagnosed with euthyroidism, 263 (11.5%) patients had malignant thyroid disease. While 79 (92.9%) patients with hypothyroidism were diagnosed with benign thyroid pathology, 6 (7.12%) patients had malignant thyroid disease. There was no statistically significant relationship between thyroid malignancy and thyroid function tests (p = 0.12) (Table II), as a result of the analysis to show whether there was a relation between preoperative thyroid function tests and permanent thyroid pathology.

The mean age of 2727 patients with benign thyroid disease was mean ± SD: 43.7 ± 12.9 (SE: 0.247) years, while the mean age of 332 patients with malignant thyroid disease was found to be ± SD: 46.8 ± 4.2 (SE: 0.779) years (p <0.001). There was a statistically significant relationship between age and permanent thyroid pathology. Similarly, in patients with benign thyroid pathology, the largest nodule diameter was calculated as mean ± SD: 28.3 ± 13.5 (SE: 0.260) mm, while in patients with malignant thyroid pathology the largest nodule diameter was calculated as mean ± SD: 30.8 ± 13.6 (SE: 0.748) mm. There was a statistically significant relationship between nodule size and permanent thyroid pathology (p = 0.002). ROC Curve and Youden Index J tests were used to determine the most appropriate cut point in terms of the relationship between nodule size and malignancy. The sensitivity was 60% and the specificity was 49.05% when the nodule size

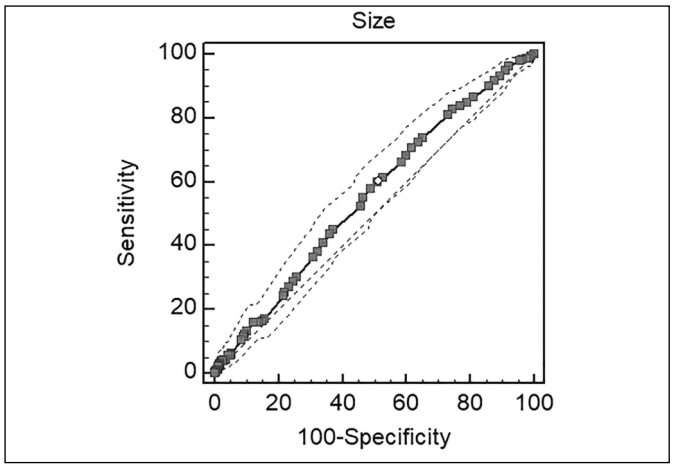

Fig. 1: Sensitivity (60%) and specificity (49.05%) for nodule size (cut-off point >26 mm)

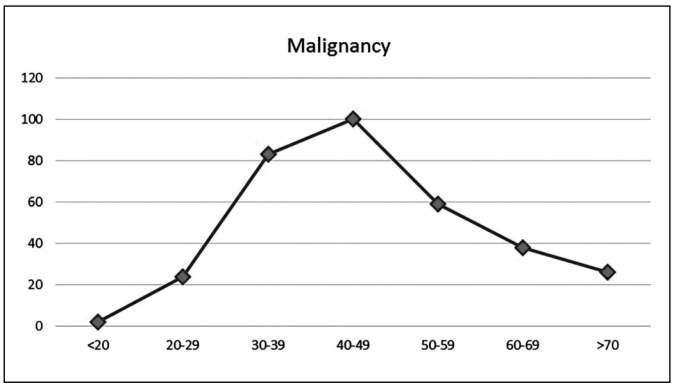

Fig. 2: Distribution of malignancy according to patient age groups.

was> 26 mm. The Weiden Index J value was calculated as 0.0905 at this point (26 mm) (Fig. 1).
Totally 391 (12.8%) patients underwent preoperative fine needle aspiration biopsy (FNAB). Cytological examination results were reported as benign in 229 patients, suspicious in 86 patients, non-diagnostic in 75 patients, and malignant in one remaining patient. The permanent pathological results of thyroidectomy specimen obtained from the same patient group were reported as benign in 337 patients and malignant in 54 patients (Table III). A cross table was used to show the relationship between the FNAB results and the permanent pathology results. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of FNAB were calculated as 4.17%, 100%, 100%, 89.96% and 90%, respectively.

Discussion

Thyroid cancers account for about 90% of all endocrine cancers and the worldwide incidence has increased by 48.0% in males and 66.7% in females over the last 30 years. Thyroid cancer accounts for 1.0-1.5% of new cancer cases diagnosed every year in the USA and has risen to 5th among the most common cancers in women [4,5]. The most common thyroid pathology is palpable or non-palpable nodular lesions and most of these nodules are benign. The incidence of nodules is higher in elders, women, iodine deficiency and radiation exposed patients than in the normal population. Most studies have found nodule prevalence rates 2-7% in palpation, 19-67% in ultrasonography and 8-65% in autopsy series [2,6].

Patient's Age and Thyroid Cancer

Many studies have shown a significant association between the patient's age and thyroid cancer [7,8]. In other words, age has been shown to be a risk factor for thyroid cancer. In western societies, age below 20 and over 70 have been considered as risk factors for thyroid cancer [9]. He *et al.* [2] showed that patients with malignant thyroid disease in a study performed on 1400 patients were younger than patients with benign thyroid disease (p <0.001). The authors also statistically showed that the prevalence of thyroid cancer below the age of 40 and over 70 years is higher than other age groups. Do *et al* [10] received a cutoff of 45 years of age in 1022 patients who underwent thyroid surgery and reported that there were no differences between the two groups (<45 vs ≥45 yr) in terms of factors such as thyroid cancer and lymph node metastasis (p = 0.111). In the same study, the authors performed a cutoff of 50 years and found that differentiated thyroid cancer (P = 0.031) and lymph node metastasis (p = 0.0496) are higher in age below 50 years old and Micropapillary carcinoma (p = 0.0035) were seen higher in patients older than 50 years. Luo *et al.* [11] demonstrated in a multivariate study that young age was an effective risk factor for malignancy development in a study (p <0.001). In contrast to most studies in the literature, the mean age of patients with malignant thyroid pathology analyzed in this study was higher than the benign patient group and this difference was statistically significant (Mean ± SD: 46.8 ± 4.2 vs 43.7 ± 12.9 p<0.001). In Graphic 2 we showed that a significant portion of malignant patients analyzed in our study were between 30 and 49 years of age. In this graph, we have also shown that the incidence of cancer is decreasing in parallel with aging.

Gender and Thyroid Cancer

The fact of whether male sex is a risk factor for thyroid cancer is questionable [2]. There are publications that support the high incidence of thyroid cancer in males (7-9) as well as in publications that suggest that gender

has no direct contribution to tumor development [2,12-14]. Luo *et al.* [11] published a study analyzing the risk factors affecting malignancy and showed multivariate analysis of male gender as an independent risk factor for malignancy (p <0.001). In our study, although the incidence of malignancy was higher in males (12.4%) than females (10.6%), we could not find a statistically significant relationship between thyroid cancer and gender (p = 0.36).

Thyroid Function Tests and Thyroid Cancer

The debate about the relationship between thyroid function tests and thyroid cancer has not yet gotten any clearer. Several opinions have been put forward in this fact. Yeh *et al.* [15] have shown that there is a clear correlation between hyperthyroidism itself and the duration of hyperthyroidism and thyroid cancer as a result of community-based studies involving a large patient population. On the other hand, there were no statistically significant differences in risk of cancer between goiter and hyperthyroidism patients and non-hyperthyroidism patients in two studies conducted for about ten years following of patients [16,17]. In general, the prevalence of thyroid cancer in patients with hyperthyroidism ranges from 1.6 to 21.1% [18]. These rates vary according to whether the patient is graves (0.15-15.0%), toxic multinodular goiter (1.6-8.8%) or toxic adenoma (2.5-12.0%) [2]. According to extensive literature analysis by Pazaitou-Panayiotou *et al.* [18], the incidence of thyroid cancer in graves disease is higher than toxic multinodular goiter and toxic solitary adenomas. The authors also showed that cancer foci in graves disease are larger, multifocal, and aggressive. There is no clear debate in the literature regarding the relationship between hypothyroidism and cancer, but the relationship between hashimoto thyroiditis, mostly with hypothyroidism, and papillary thyroid cancer has been shown in many publications [19]. Luo et al. [11] in a study showed that preoperative TSH and free T4 levels are not effective risk factors for thyroid malignancy (P <0.30). The incidence of cancer in the euthyroid, hyperthyroidic and hypothyroid cases we presented in this study were calculated as 9.2%, 11.5% and 7.1%, respectively. These results indicate that there is no relationship between cancer development and thyroid functions (p = 0.12).

Nodule Size, Nodule Number and Thyroid Cancer

It is generally accepted that the incidence of thyroid cancer is higher in patients with solitary nodule than multinodular disease. However, in some studies, there was no difference in the incidence of thyroid cancer between the two[1]. McHenry *et al.* [20] performed thyroidectomy on 676 of 1023 patients with nodular thyroid disease and reported that the diameter of malign nodules (33 ± 22 mm) was smaller than the benign nodule diameter (44 ± 24 mm) and that these results were statistically significant (P <0.05). The authors as a result of this study noted that the increase in nodule size cannot be considered as a predictive value for thyroid cancer. However, He *et al.* [2] stated that the malign nodule diameter (23.3 ± 1.2 mm) was higher than the benign nodule diameter, but this result was not statistically significant (p = 0.235). Kamran *et al.* [21] evaluated 7348 nodules of 4955 patients to demonstrate nodule diameter and its relation with cancer. Cancer was detected in 13% of these nodules. The incidence of cancer was 10.5% when the nodule diameter was 10-19 mm and the rate of cancer was 15% when the nodule diameter was > 20 mm. This difference was statistically significant (p <0.01). However, no statistically significant difference was found in the risk of cancer in patients with nodule diameter 20-29 mm, 30-39 mm and> 40 mm (p = 0.14). In other words, there is no gradual increase in risk of cancer beyond 20 mm threshold. Luo *et al.* [11] found that the number of nodules <5 in multinodular goiter patients, male gender, young age, small thyroid gland and small nodule diameter are independent risk factors by multivariate logistic regression model. In the same study, the authors noted that more effective predictive methods are needed in patients with multinodular goiter due to the low predictive value of FNAB. Statistically, we showed that the diameter of the nodule was larger in the malignant group of patients included in our study, compared to the studies we summarized above (p = 0.002).

Ultrasonographical Evaluation and Thyroid Nodules/ Cancer

In general adult population, 2-7% of cases can be diagnosed with palpation thyroid nodule without using any radiological instrument. However, when ultrasonography is used, this rate can be increased to 19-67%. Approximately cancers are found in 5% of permanent pathologies of nodules palpated on physical examination. Ultrasonography performed on experienced hands can give us good results about the both nodule properties and the structure of non-nodular thyroid tissue but it is not that much helpful as general thought about malignant-benign distinction [22]. Since the cancer rate varies between 5% and 15% at any nodule diameter, the current thyroid guide suggests that all patients with suspected thyroid nodules should be evaluated with ultrasound. According to the guidelines, fine needle aspiration biopsy should be performed to a suspicious nodule [23]. Internal calcifications, hypoechogenicity, increased central blood flow, presence of tall nodules, solid and large diameters are the predictors of malignancy in ultrasonography. However, echogenic, increased peripheral blood flow,

spongiform or cystic nodules are predictive for benign nodular disease [23]. In this presented study we could reach to the results of thyroid ultrasonography of 113 (34.0%) of the cancer cases and 88.5% of them could indicate malignancy as microcalcification, increased blood flow, border irregularity and hypoechogenic findings were reported. One of the most important factors limiting us in this study was the difficulty of accessing patients' ultrasonography reports. Because most of the patients referred to us with ultrasonography report made at another center. So we did not have access to these reports during the preparation of this study.

Fine Needle Aspiration Biopsy (FNAB) and Thyroid Cancer

Many algorithms and classification have been defined in textbooks about FNAB and diagnosis of thyroid cancer. In the majority of these classifications, FNAB showed no clear results in a third of the patients. There is general consensus that FNAB is not reliable, especially in multinodular goiter and nodules less than 10 mm in diameter. Thus, FNAB has been shown to have low predictive values [11]. Because the dominant nodule in multinodular goiter may not be cancerous in which biopsy is taken, but in a smaller nodule, a new cancer center may have been ignored [1,24,25]. Non-palpable nodules have the potential to develop thyroid cancer as well as other palpable nodules of the same size. Further, incidentally revealed nodules below 10 mm have a same risk of developing thyroid cancer as clinically significant nodules above 10 mm [1,26,27]. Three hundred and ninety one of the patients included in this study had preoperative FNAB and the Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of FNAB were calculated as 4.17 %, 100 %, 100 %, 89.96% and 90 %, respectively. Although FNAB in our study has a high predictive value, we believe that this issue is in need of supporting literature.

Highlight Topic

While some of the results we give in this study are in accordance with the literature, some of them show differences according to the literature.
Prospective and multicenter studies should be performed on parameters such as age, gender, nodule diameter, number of nodules, thyroid function tests, FNAB, ultrasonographic findings supporting malignancy, presence of cervical lymph nodes, and thyroid cancers.
The most important factors limiting us in this study are the retrospective nature of the study and the inability to reach the majority of clinical findings, i.e. our records are inadequate.

Riassunto

Scopo di questo studio è la valutazione della relazione tra I parametrici clinici e l'accertamento istologico definitive di pazienti sottoposti a chirurgia tiroidea. Si tratta di un studio retrospettivo dei parametri demografici e clinico-patologici di pazienti sottoposti nella nostra clinica a chirurgia tiroidea per patologia benigne e maligna tra Giugno 2006 e Marzo 2014.
L'analisi statistica si è avvala del Chi-quadro di Pearson, del Test di campionatura indipendente, della curva ROC e dell'Indice di Youden J per accertare una eventuale relazione tra i parametri clinici e la diagnosi istologica definitiva dei pazienti.
La casistica riguarda un totale di 2059 pazienti, di cui 2727 con patologia benigna e 332 con patologia maligna, con età compresa tra 15 e 90 anni. L'età è risultata più elevata nel gruppo dei maligni (media ± SD: 46.8 ± 4.2 anni) che non in quello dei benigni (media ± SD: 43.7 ± 12.9 anni) e dunque con differenze statisticamente significative ($p < 0.001$).
Il diametro del nodulo (media ± SD: 30.8 ± 13.5 mm) di dimensioni maggiori nel gruppo dei maligni che non in quello dei benigni (media ± SD: 28.3 ± 13.4 mm) con differenza statisticamente significativa ($p = 0.002$). Il tasso di sensibilità e di specificità del punto più appropriato di differenza delle dimensioni del nodulo (>26 mm) è risultato rispettivamente del 60% e del 49,05%, Sono state calcolate sensibilità, specificità, valore predittivo positivo, valore predittivo negativo e accuratezza della FNAB, rispettivamente come 4.17 %, 100 %, 100 %, 89.96% e 90 %.
Questo nostro studio indica che l'età più avanzata e le maggiori dimensioni del nodulo sono associate con la natuta maligna.

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