

Parameters predicting follicular carcinoma in thyroid nodules with indeterminate cytology



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Parameters predicting follicular carcinoma in thyroid nodules with indeterminate cytology

AIM: To determine the parameters supporting the malignancy by comparing demographic features of patients and nodule features in malign and benign nodules according to the pathology results after thyroidectomy in patients with the suspicious fine needle aspiration biopsy (FNAB) results for follicular neoplasia.

MATERIAL AND METHOD: Thyroidectomy performed 152 cases with the suspicion of follicular carcinoma owing to the FNAB results were included in the study. Age, radiation exposure history, and serum TSH levels of patients were recorded as well as the ultrasound findings of nodules as nodule count, diameter, internal structure, echogenicity, border features, presence of peripheral halo, and presence of internal micro calcifications. Scintigram findings of nodules were also recorded.

RESULTS: The mean age of the patients was 48,14 years (range: 20-71 years). Twenty five (16,5%) of the patients were male while 127 (83,5%) were female. Among patients with higher than normal TSH levels, malignancy was more common compared with the patients with normal or lower TSH levels. Presence of intranodular calcifications [Odd's Ratio: 3,1; 95 % Confidence Interval: 1,3-7,4], increase in intranodular vascularization [Odd's Ratio: 14,7; 95% Confidence Interval: 1,4-147,7], absence of halo sign [Odd's Ratio: 0,1; 95% Confidence Interval: 0,04-0,8], and ill-defined margins [Odd's Ratio: 0,1; 95% Confidence Interval: 0,49-0,3] were statistically significantly more common in malignant cases.

CONCLUSION: The ability of clinical features, and sonographic parameters to predict malignancy in indeterminate thyroid nodules should be kept in mind since ultrasound is a simple, easy and inexpensive tool in the diagnosis of thyroid nodules.

KEY WORDS: Halo sign, Ill-defined margins, Intranodular vascularization, Thyroid follicular neoplasms, Ultrasound, intranodular calcifications

Introduction

Thyroid nodules are common clinical findings with a prevalence of 4-7% of adult population ¹. Although about 5% of adult thyroid nodules are reported to be malignant, since early detection and treatment of malignant

nodules is associated with excellent outcomes, the prompt and correct diagnosis is essential in thyroid nodules ². The incidence of thyroid cancer is increasing worldwide ³. The papillary thyroid cancer is the most common type, while the follicular variant is a more aggressive form of thyroid cancer that also seems to be increasing in incidence ⁴.

Currently the treatment decisions for thyroid nodules depend heavily on the results of fine needle aspiration biopsy (FNAB), however the indeterminate cytology readings reaching 42% in some series sets significant limitations to the diagnostic accuracy of this technique ^{5,6}. The Bethesda System for reporting thyroid cytopathology

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gy is currently used in the pathology department of our hospital ⁷. In that aspect, preoperative diagnosis of follicular thyroid carcinoma (FTC) is a major clinical problem because FTC is diagnosed not by cellular atypia, but by structural atypia. The diagnosis of FTC is usually made after thyroidectomy and based on histopathological findings. In a recent study, Sugino et al reported that by FNAB 6.7% of the patients with diagnosis as benign and 28% of the patients with diagnosis as indeterminate, were diagnosed as having FTC after thyroidectomy ⁸. Thyroidectomy has a 2 to 10% rate of long-term mor⁹. Thus, surgery should ideally be reserved for required cases. In that aspect, it is important to diagnose correctly those patients with undetermined FNAB results, thereby avoiding unnecessary surgeries in patients with benign thyroid nodules.

Since technological advances in the ultrasonography (US) provide more information not only concerning the location of thyroid nodules, but also about the features that are associated with malignancy, ultrasonography plays an increasingly important role in the detection and management of thyroid nodules ¹⁰. Some characteristics discovered during sonography indicate a potential malignant thyroid tumor such as calcifications, irregular margins, hypoechogenicity, and increased blood flow revealed in power Doppler imaging¹¹.

In this study we aimed to determine the parameters supporting the malignancy by comparing demographic features of patients and nodule features in malign and benign nodules according to the pathology results after thyroidectomy in patients with the suspicious FNAB results for follicular neoplasia.

Material and Method

Total thyroidectomy performed 152 cases with the suspicion of follicular carcinoma owing to the FNAB results between years 2009 and 2012 in General Surgery department of Cukurova University Medical Faculty were included in the study. The study was approved by the local ethics committee.

Preoperative examinations included a physical examination, an ultrasound examination of the neck region as well as determination of in vitro thyroid gland parameters. Ultrasound examinations of the neck region were performed using a SonoAce 8000 SE unit with a 7.5 MHz linear probe by a physician specialized in radiology. Patients with thyroid nodules > 10mm diameter additionally underwent a thyroid scintigram with [99mTc] to exclude focal thyroid gland autonomy. The age, radiation exposure history, and serum TSH levels of patients were recorded as well as the ultrasound findings of nodules as nodule count, diameter, internal structure, echogenicity, border features, presence of peripheral halo, and presence of internal micro calcifications. Scintigram findings of nodules were also recorded.

Assessments were performed according to these criteria:

Age: Between 20-35, 36-50, 51-65 years and older than 65 years of age

Radiation exposure history: Presence of radiation exposure history on neck region in childhood

Serum TSH levels: Regarded as low, normal or high according to the reference values of our laboratory

Number of nodules: Grouped as single, 2-3, or more than 3

Nodule diameter: 0-2 cm, or larger than 2 cm

Internal structure of the nodule: Evaluated as solid, or semisolid +cystic

Nodule echogenicity: Hypoechoic, isoechoic, or hyperechoic regarding the normal thyroid parenchyma

Margins: If the distinction between normal thyroid parenchyma and the nodule borders were clear; the margins were evaluated as well defined. If the borders were not distinct or if microlobulations were present in borders; the nodule margins were evaluated as ill-defined.

Presence of peripheral hypoechoic halo around the nodule: Present or not present

Calcifications: Internal calcifications were evaluated as present or not present.

Intranodular vascularization: Increase in intranodular vascularity was assessed with color Doppler ultrasound.

Scintigram evaluation of the nodule: Hot, normal, cold

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS v16.0 for Windows (SPSS, Inc., Chicago, IL). Continuous variables are expressed as means $\pm$ standard deviation (SD), whereas categorical variables are presented as absolute values and percentages. Differences between continuous variables were analyzed by unpaired Student's t-test or ANOVA, and differences between categorical variables were analyzed using the chi square test. A p-value of <0.05 was considered statistically significant.

Results

The mean age of the patients was 48,14 years (range: 20-71 years). Twenty five (16.5%) of the patients were male while 127 (83.5%) were female. The number of malignant cases in different age groups and different TSH levels are summarized in Table I. None of the participants reported any radiation exposure history in childhood; so the effect of radiation exposure in follicular neoplasms could not be evaluated. Among patients with higher than normal TSH levels, malignancy was more common compared with the patients with normal or lower TSH levels.

The number of malignant cases according to the nodule properties are summarized in Table II.

TABLE I - The number of malignant cases in different age groups and different TSH levels

	Malign n (%)	Benign n (%)	p
Age groups (years)			
20-35	3 (10.7)	19 (15.3)	0,880
36-50	13 (46.4)	49 (39.5)	
51-65	10 (35.7)	48 (38.7)	
>65	2 (7.1)	8 (6.5)	
Sex			
Male	3(2)	22(14,5)	0,37
Female	25(16.4)	102(67.1)	
TSH Levels			
Low	1 (3.6)	12 (9.7)	0.041
Normal	23 (82.1)	108 (87.1)	
High	4 (14.3)	4 (3.2)	

TABLE II - The number of malignant cases according to the nodule properties

	Malign n (%)	Benign n (%)	p
Nodule Number			
Single	13 (46.4)	41 (33.1)	0,381
2-3	7 (25,0)	34 (27.4)	
>3	8 (28.6)	49 (39.5)	
Nodule diameter			
0-2 cm	19 (67.9)	63 (50.8)	0,076
>2 cm	9 (32.1)	61 (49.2)	
Calcification			
Present	12 (42.9)	24 (19.4)	0,008
Not present	16 (57.1)	100 (80.6)	
Nodule Structure			
Solid	20 (71.4)	72 (58.1)	0.191
Solid + Cystic	8 (28.6)	52 (41.9)	
Echogenicity			
Hypoechoic	15 (53.6)	52 (41.9)	0,295
Isoechoic	13 (46.4)	65 (52.4)	
Hyperechoic	0(0.0)	7 (5.6)	
Intranodular Vascularization			
Present	3 (10.7)	1 (0.8)	0,003
Not present	25 (89.3)	123 (99.2)	
Peripheral Halo Sign			
Present	2 (7.1)	35 (28.2)	0,012
Not present	26 (92.9)	89 (71.8)	
Nodule Margins			
Well defined	7 (25.0)	90 (72.6)	0,0001
Ill defined	21 (75.0)	34 (27.4)	
Scintigram Findings			
Cold	19 (86.4)	66 (68,0)	0,227
Normal	2 (9.1)	19 (19.6)	
Hot	1 (4.5)	12 (12.4)	

Presence of intranodular calcifications [Odd's Ratio: 3.1; 95% Confidence Interval: 1.3-7.4], increase in intranodular vascularization [Odd's Ratio: 14.7; 95% Confidence Interval: 1.4-147.7], absence of halo sign [Odd's Ratio: 0.1; 95% Confidence Interval: 0.04-0.8], and ill-defined margins [Odd's Ratio: 0.1; 95% Confidence Interval: 0.49-0.3] were statistically significantly more common in malignant cases.

Discussion

Since fine needle aspiration biopsy is safe, accurate and simple; it is the accepted standard diagnostic tool for thyroid nodules with its high sensitivity and specificity for malignancy^{12,13}. However a significant rate of non-diagnostic results ranging from 0.6% to 43.1% is the main limitation of FNAB^{14,15}. In this study we aimed to define the characteristic clinical findings of malignant thyroid nodules with the suspicious FNAB results for thyroid carcinoma before the operation and determined that nodules of patients with higher than normal TSH levels, and nodules with intranodular calcifications, increased vascularization, and ill-defined margins are more commonly malignant while halo sign was more commonly present in benign cases. These results are important in clinical practice to diagnose or at least to suspect the patients with thyroid follicular carcinoma. In FNAB results, all follicular-patterned lesions are reported as follicular lesions without a definite cytologic diagnosis of malignancy. At surgical intervention, about 20% of such specimens are determined to be malignant lesions. Clinical criteria, ultrasound features and molecular and immunohistochemical markers may improve the accuracy of cytologic diagnosis¹⁶.

There are some studies reporting the association of clinical features of patients with the malignancy. Conzo et al retrospectively evaluated 472 patients, surgically treated after a FN diagnosis and reported that age < 45 years and female gender were more frequently associated to malignancy¹⁷. We did not determine a statistically significant difference between altered age groups. In a prospective study, Boelaert et al. found that higher serum thyroid-stimulating hormone levels at presentation, even within the normal range, was an independent predictor of malignancy¹⁸. Haymart and colleagues also defined that higher serum TSH levels were associated with increased risk of differentiated thyroid carcinoma and advanced tumor stage in elderly patients¹⁹. Similarly, higher serum TSH levels were more commonly associated with malignancy in our study.

Ultrasound findings are also studied in some studies in order to determine the role of ultrasound in prediction of malignancy. Brkljacic et al demonstrated that carcinomas are more often containing nodular calcifications compared with benign nodules in 165 patients with 426 nodules (20). Recently Cordes et al compared the ultrasound characteristics of papillary thyroid carcinomas (PTCs) with FTCs and defined that FTCs are larger and more irregular than PTCs but they defined that intranodular calcification ratios are similar in both groups with about 70% ratio²¹. Popowicz et al determined that hypoechogenicity, and verification of microcalcification represent independent risk factors for the presence of thyroid cancer²². In a study comparing the sonographic features of thyroid follicular carcinoma with thyroid follicular adenoma, solid contents, hypoechoic structure,

heterogeneous echo texture, the presence of calcifications, and an absent or irregular thick halo were defined to be associated with malignancy²³. Lee et al investigated potential clinical factors for the preoperative prediction of malignancy in thyroid nodules with a cytological diagnosis of follicular neoplasm in retrospective study and determined that in comparison with the features of benign nodules, FTC presented with a large nodule size, isoechogenicity, calcifications, and peripheral halo²⁴. In a prospective study of Kuru et al on 571 euthyroid patients with thyroid nodules; size ≥ 4 cm, age ≥ 65 , cervical lymph nodes, solid structure, hypoechogenicity, microcalcification, and elevated serum thyroglobulin levels were determined to be independent predictive factors associated with thyroid malignancy and they concluded that among patients with follicular neoplasm and nondiagnostic FNAB findings, those with ≥ 2 risk factors should undergo surgery²⁵. In a recent study on 145 patients with the diagnosis of follicular neoplasm on FNAB, histological diagnosis of malignancy was obtained in 14.5% of the patients after thyroidectomy. In that study the ultrasonographic features that have been associated with malignancy were: nodule size larger than 2 cm and microcalcifications²⁶. Although nodule size was not different in our study between benign and malignant cases, microcalcifications were more common in malignant ones similar with the literature.

Vinayak et al prospectively evaluated the US characteristics of nodule margins, echogenicity, presence of microcalcifications, and vascularity on 284 patients undergoing ultrasound-guided FNAB for thyroid nodules and defined that US characterization of a thyroid nodule can accurately infer its benign nature and they have suggested the use of an US index including these 4 parameters²⁷. Carr et al defined that irregular margins and calcifications were more common in malignant nodules in their study on 140 cases with the atypia of undetermined significance/follicular lesion of undetermined significance²⁸. In a recent study, evaluating the usefulness of ultrasonography in distinguishing follicular carcinoma from adenoma, irregular shape, absence of thin halo, indistinct margin, hypoechoic appearance, punctate calcification, and absence of cystic change were more frequently associated with follicular carcinoma than with benign adenoma²⁹. In another study, the US features of isohypoechoic echogenicity, predominantly solid or mixed echotexture, and microcalcifications were reported to be more common in follicular carcinoma than in follicular adenoma³⁰. Sillery et al reported that hypoechoic appearance, absence of halo, absence of cystic change, greater patient age, size of the tumor and male sex were more frequently associated with follicular thyroid cancer than with benign adenoma³¹. However we did not determine any significant difference in echogenicity level of nodule, patient age, nodule size or nodule structure between malignant and benign cases. On the other hand, halo sign was also more common in benign cases compared with the malignant ones in our study.

There are some limitations of this study that should be

mentioned. This is a retrospective study and the results are obtained from the patient record. So, some bias may be present in the results. Secondly the number of malignant cases was low to make an exact decision.

In conclusion, some ultrasound features may play an important role in predicting malignancy among cases with the suspicious FNAB results for follicular neoplasms including intranodular calcifications, increased vascularization, and ill-defined margins. The ability of clinical features and sonographic parameters to predict malignancy in indeterminate thyroid nodules should be kept in mind since ultrasound is a simple, easy and inexpensive tool in the diagnosis of thyroid nodules. Larger, prospective studies are warranted to elucidate the exact role of ultrasound in diagnosis of follicular neoplasms.

Riassunto

La finalità dello studio è quella di cercare di determinare i parametri indicativi di malignità paragonando caratteristiche demografiche e aspetti di benignità o malignità dei loro noduli determinati sui referti anatomo-patologici dopo tiroidectomia in pazienti con citologia FNAB sospetta per neoplasia follicolare.

Lo studio è stato condotto su 152 casi di sospetto carcinoma follicolare in base ai risultati della FNAB. Sono stati presi in considerazione l'età, l'eventuale esposizione a radiazioni, livelli sierici di TSH ed i dati ecografici riguardo al numero, diametro, struttura interna, ecogenicità, caratteristiche dei margini, eventuale presenza di alone e di microcalcificazioni interne. Sono stati anche considerati i rilievi scintigrafici dei noduli.

L'età media dei pazienti era 48,14 anni (da 20 a 71); 25 (16,5%) di sesso maschile e 127 (83,5%) femminile. La natura maligna era prevalente tra i pazienti con TSH di livello superiore al normale, che non ai livelli normali o inferiori. La presenza di calcificazioni intranodulari [rapporto differenziale: 3,1; 95% di intervallo di confidenza: 1,3-7,4], aumento della vascolarizzazione intranodulare [rapporto differenziale: 14,7; 95% di intervallo di confidenza: 1,4-147,7], assenza di segni di alone [rapporto differenziale: 0,1; 95% di intervallo di confidenza: 0,04-0,8], e margini non ben definiti [rapporto differenziale: 0,1; 95% di intervallo di confidenza: 0,49-0,3] erano i dati statisticamente significativi più comuni nei casi di malignità.

Su questi dati si può concludere che su basi cliniche e su parametri ecografici è possibile fare previsioni sulla malignità di noduli tiroidei di natura indeterminata, ricordando che l'indagine ecografica è un mezzo semplice, facile e di scarso costo nella diagnostica dei noduli tiroidei.

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Commento e Commentary

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La frequente scoperta di noduli tiroidei, sia sintomatici che di scoperta ecografica, pone seri problemi diagnostici e decisionali. È di grande interesse riuscire a distinguere con ragionevole certezza quelli per cui è necessaria l'asportazione chirurgica perché neoplastici o ad alto rischio o perché significativamente sospetti, da quelli certamente benigni che necessitano solo sorveglianza e follow up. Riuscire a fare questa distinzione in fase preoperatoria è di primaria importanza per evitare interventi chirurgici pleonastici e potenzialmente dannosi e non trascurare pericoli e rischi di conservare noduli non certamente benigni. L'ecotomografia ed il color doppler possono fornire indicazioni all'esecuzione mirata della FNA, che in linea di principio potrebbe oggi rappresentare la tecnica diagnostica adeguata avvalendosi delle moderne acquisizioni di citologia, ma purtroppo presenta un angolo di ombra in cui si annidano dubbi diagnostici (15% di sospetto e 15% di incertezza), e soprattutto falsi negativi (5%), questi ultimi con percentuali variabili in relazione alla correttezza della procedura diagnostica, a fronte di falsi positivi limitati a 1%. La ragionevole certezza di benignità non supera dunque il 60% dei noduli esaminati con FNA, lasciando sospetti in caso di struttura follicolare, di scarsità di colloide, di alta cellularità e in caso di presenza di cellule di Hürthle. Lo studio presentato porta un contributo casistico, numericamente non effettivamente significativo, alla ricerca di una soluzione a questo reale dilemma, confrontando i referti anatomo-patologici dei casi operati con i rilievi citologici preoperatori con FNA, senza peraltro fare riferimento alla utile standardizzazione del Bethesda System for Reporting Thyroid Cytopathology (BSRTC), né a particolari linee guida, integrando la casistica con numerosi fattori di rischio rilevati, tra i quali però i più universalmente riconosciuti sono il sesso e le età polarizzate, e l'aspetto ecografico, peraltro di per sé variabile con l'operatore. I loro risultati danno conferma a quanto già ripetutamente affermato circa la sussistenza dei falsi negativi, senza poter dare conclusioni assolute. Queste richiederebbero una uniformazione del metodo di studio, di tipo prospettico e con la migliore ed uniforme standardizzazione possibile, su una più vasta popolazione di pazienti ed un prolungato follow up dei non operati, senza contentarsi di statistiche su numeri non veramente significativi, che non danno di fatto indicazioni assolute.

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The frequent discovery of thyroid nodules, not always symptomatic but often simply localized by means of US, poses serious problems for diagnosis and decision-making. It is of great interest to be able to distinguish among them those to be removed, at least with the entire lobe, because malignant or clearly of high-risk or merely because suspects, from those certainly benign needing only surveillance and follow-up. Being able to make preoperatively this distinction is of paramount interest to avoid unnecessary and potentially harmful surgery, and not to overlook the dangers and risks of leaving untouched nodules not certainly benign. Ultrasonography can provide guidance to the execution of targeted FNA, which in principle could now represent the appropriate diagnostic technique using modern acquisitions of cytology, but unfortunately it has an angle of shadow in which lurk diagnostic doubts (15% of suspicion and 15% of uncertainty), and especially false negative (nearly 5%), the latter whose percentages vary in relation to the accuracy of the diagnostic procedure, in front of false positives limited about 5%. It is well known that the right certainty of non malignant nature of a single nodule doesn't exceeds indeed 60% of those examined with FNA, leaving suspects in the case of follicular structure, if there is shortage of colloid, high cellularity and or presence of Hürthle cell. The study presented brings a contribution casuistic, not numerically significant indeed but deeply analysed, looking for a real solution to this dilemma, comparing the p.o. pathology reports of specimen from with those of preoperative cytologic FNA, but unfortunately without referring to the useful standardization of Bethesda System for Reporting Thyroid Cytopathology (BSRTC), or to particular guidelines, integrating instead the analysis of the casuistic with the identification of many risk factors, among which, however, the most universally recognized are sex and polarization of age, and the single sonographic appearance with the help of color Doppler, however in itself dependent from the operator's skill. Their results give confirmation to what was repeatedly said about the existence and rate of false negatives, without being able of course to give absolute conclusions. These would require a better standardization of the method of a prospective multicentric study, as uniform as possible, on a larger patient population and a longer follow-up of those non-operated, as statistics on not really significant numbers cannot give in fact reliable indications.

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