Clinical, Cytological and Histological Correlation of Thyroid Nodule(S): An Observation Study

*Ali Al- Dabbagh, **Mohanad Mohammed Ibraheem

*Department of Surgery, Medical College, Hawler Medical University

**Erbil Health Directorate

Abstract:

Background: Fine-needle aspiration and cytology is the cornerstone of preoperative evaluation of thyroid nodules, but Fine-needle aspiration and cytology diagnostic performance has varied across different studies. Several published guidelines provide recommendations for selecting nodules for cytology based on US appearance and nodule size. Some US parameters have been associated with increased risk of malignancy; however no characteristic seems sufficiently reliable in isolation to diagnose malignancy. The incidental thyroid nodule is one of the most common incidental findings on imaging studies that include the neck. An incidental thyroid nodule is defined as a nodule not previously detected or suspected clinically, but identified by an imaging study (ultra-sound, CT or MRI).

Patients and Methods: A prospective study of 75 patients were collected from Jan. 2016 till march 2017 from hospital medical data included clinical, Ultrasound, Fine needle aspiration and cytology and histopathology report. For prospective FNA collection, patients were enrolled in an institutional review board-approved protocol and informed consent was obtained.

Results: Of the 75 patients (62 female, 13 male) A considerable proportion (41.3%) of patients were suspected to be malignant the cytological study showed that (30.7%) of the patients had colloid goiter, (13.3%) had follicular cells, and (10.7%) had papillary cells. Regarding histological diagnosis, (53.3%) found to have colloid goiter. FNA had a relatively high sensitivity (81.8%) and specificity (77.5%) around one third (32.3%) of those suspected to have malignancy found to really have cancer, incident cancer were found in 6 patient of those who didn't underwent fine needle aspiration and cytology.

Conclusion: By using the Thyroid Imaging –Reporting and Data System guidelines, one can see a significant reduction in the number of thyroid nodules recommended for biopsy. False positive and false-negative results continue to present a challenge in the evaluation of thyroid nodules. Molecular testing studies are needed to more accurately refine FNA diagnosis in the cytologically indeterminate group where the majority of cases prove to be benign and surgery could be avoided.

Keywords: Thyroid, Fine Needle, Nodule.

Introduction:

The accurate diagnosis of thyroid nodules continues to challenge physicians managing patients with thyroid disease. The increased use of carotid and other neck ultrasound coupled with the improved technology and higher resolution of ultrasound machines leads to the detection of steadily increasing numbers of asymptomatic thyroid nodules, the so-called incidentalomas [(1)]. Once discovered, these nodules are generally sampled via fine-needle aspiration (FNA) for diagnosis. The rate of thyroid

nodule FNA biopsies increased threefold from 1995 to 2005 [2]. Another part of the increase in thyroid nodule FNAs may also reflect growing awareness that the incidence of thyroid cancer is rising Thyroid nodules are a common clinical problem, and differentiated thyroid cancer is becoming increasingly prevalent [3]. The incidence of thyroid cancer has increased about fivefold in the last 50 years, mostly due to small papillary thyroid cancers, the most indolent form of thyroid cancer [4], and management of thyroid gland nodule(s) is still a confusing subject and the definitive diagnosis is made histological although the availability of many diagnostic tools including clinical, radiological and cytology still there is a group of patients would undergo unnecessary fine needle aspiration and cytology (FNAC) or even surgical removal of a benign thyroid lesions that is suspected to be malignant. A clinical examination and ultrasound feature of the thyroid gland may lead to a suspicion of malignancy, palpable thyroid nodules to be approximately (5%) in women and (1%) in men living in iodine-sufficient parts of the world [5, 6]. In contrast, high-resolution ultrasound (US) can detect thyroid nodules in (19%–68%) of randomly selected individuals yet still fine needle aspiration and cytology is the method of choice as the first interventional method to assess a thyroid gland nodule(s). The clinical importance of thyroid nodules rests with the need to exclude thyroid cancer, which occurs in (7%–15%) [7]. US is the imaging method of choice for evaluating thyroid nodules [8, 9]. There are multiple published guidelines that provide recommendations for the evaluation of thyroid nodules on the basis of nodule size and appearance on US [10, 11, 12, 13].

In Imaging Reporting and Data System a nodule is classified to weather to perform a biopsy or to follow the nodule based on the maximum nodule diameter. The aim of this is to reduce unnecessary thyroid biopsies and to detect thyroid malignancies [14].

Tumor size remains a strongly influential feature on pre-operative diagnosis, with greater difficulties arising for carcinomas <5 mm. Moreover, an important contributing factor for the increased incidence of such well-differentiated cancers is the increasing diagnostic rates of papillary thyroid micro carcinoma. Other factors such as iodination programmes in low iodine intake areas, detailed histopathological examination of the excised thyroid tissue, and the increase in bilateral total excision of the thyroid gland during thyroid surgery have also been attributed to the increasing rates of large (>10 mm) and micropapillary carcinoma [15, 16, 17, 18].

The objective of this study is to: (1) find the relationship of clinical, ultrasound, FNAC and histological diagnosis of thyroid nodule(s) and (2) minimize the incidence of unnecessary FNAC or surgical removal of benign thyroid lesion.

Patients and Methods:

The prospective study consisted of 75 patients who underwent clinical, US, FNAC and surgical resection between January 2016 and March 2017 at a multiple institution (Rizgary Teaching Hospital, Erbil Teaching Hospital and Welfare Private Hospital), the only exclusion criterion for the study was (1) patients who had previous thyroid surgery and (2) patients with co-morbidity (ASA

4) (patient with sever life threatening morbidity).

Patients had been seen in the outpatient clinic went through clinical examination, US of neck, thyroid function test, FNAC and surgery all specimen were histopathologically examined, data included gender, age, clinical examination and US of the neck by different operators.

Clinical examination and US were taken into account to classify thyroid nodule whether they are suspicious for malignancy or not depending on single, hard nodule or at extreme of age, US finding of the nodule which goes with malignancy (five US features used in Thyroid Imaging Reporting and Data System, including composition, echogenicity, shape, margin, and echogenic foci. The test readers assigned each nodule a malignancy risk category that matched the five risk-stratification levels).

For prospective FNAc collection, patients were enrolled in an institutional review board-approved protocol and informed consent was obtained, FNA cytology done in 51 patients, FNA taken by senior radiologist from a single nodule under US guide and were examined by the cytological department of the hospital, results classified into colloid, papillary cells, follicular, non-diagnostic (undetermined) and thyroditis, FNAc procedures were performed using 27 G or 25 G needles with 3–5 passes per each nodule under real-time ultrasound guidance as an outpatient procedure with topical anesthesia cream for patient comfort. Patient coagulation profiles were not routinely obtained prior to FNAC. However, patients on anticoagulation therapy were asked to stop taking their medication for 5 to 7 days prior to FNAC if possible. Patients on anticoagulation were optimized prior surgery accordingly.

For final diagnosis surgery done In all patients were total thyroidectomy (52 patient) or lobectomy (27 patient) specimens of the excised thyroid gland were sent to histology department of the hospital (in the same day or the day after) samples was kept in diluted formalin solution, examined by 3 or 4 pathologist (4 pathologist as a hospital regulation) with the result finished after a week to 3 weeks.

Statistical analysis:

Data were analyzed using the statistical package for social sciences (SPSS, version 22). Frequencies and percentages were calculated. McNemar test was used (in the 2X2 table) when the results of FNA were compared with the histopathology results (of the same patients); as in the following table:

		Histopathology			P (By McNemar)
		Positive	Negative		
FNA	Positive	TP	FP	TP+FP	
	Negative	FN	TN	FN+TN	
Total		TP+FN	FP+TN	Grand total	

TP=True positive; TN=True negative; FP=False positive; FN=False negative.

Sensitivity = TP / (TP+FN)*100; *Specificity* = TN / (FP+TN)*100; *Predictive value positive* (PV^+): TP / (TP+FP) * 100; *Predictive value negative* (PV^-): TN / (FN+TN) * 100; *Total agreement* = (TP + TN) / Grand total.

Kappa statistics was calculated to assess the agreement, beyond chance, between the FNA and the histopathology results. A p value of ≤ 0.05 was considered as statistically significant.

Results:

The age range of the 75 patients enrolled in the study was 17 to 68 years. More than one third (37.3%) of the patients aged fifty years or more, and the majority (82.7%) were females, table (1).

A considerable proportion (41.3%) of patients was suspected to be malignant, and (62.7%) of them had multi-nodular goiter as presented in table (2). Thyroid function test showed that around one quarter (24%) had hyperthyroidism. The cytological study showed that (30.7%) of the patients had colloid goiter, (13.3%) had follicular cells, and (10.7%) had papillary cells. Regarding histological diagnosis, (53.3%) found to have colloid goiter.

FNA had a relatively high sensitivity (81.8%) and specificity (77.5%), but the predictive value of the positive test (PV+) was low (50%). The important thing here is that the predictive value of the negative test (PV-) was high (93.9%). So in general, a negative test may exclude malignancy. No significant difference was detected between the FNA and histopathology. The total agreement was (78.4%) and the agreement beyond chance as assessed by Kappa equals to 0.48, indicating fair agreement, table (3 a and b).

Table (4) shows that the prevalence of cancer was (21.3%). It is evident in the table that the prevalence was (41.7%) among those aged less than 30, but the difference was not significant ($p = 0.169$). No significant ($p > 0.99$) difference between the prevalence among males (23.1%) and the prevalence among females (21%).

Around one third (32.3%) of those suspected to have malignancy found to really have CA according to histopathology results compared with (13.6%) of those who were not suspected to have CA ($p = 0.053$ which is close to the significance level).

The prevalence of CA was low (5.6%) among those with hyperthyroidism, compared with (26.3%) among those with normal thyroid function ($p = 0.097$), would give a clue that thyroid cancer would be more with euthyroid patients.

The majority (87.5%) of those with papillary cells by FNA found to have CA by histopathology, while none of those with thyroiditis found to have CA. The other results of FNA and histopathology are presented in table (4) ($p < 0.001$).

Table (1): Distribution of sample by age and gender.

	No.	(%)
Age (years)		
< 30	12	(16.0)
30-39	21	(28.0)
40-49	14	(18.7)
≥ 50	28	(37.3)
Gender		
Female	62	(82.7)
Male	13	(17.3)
Total	75	(100.0)

Table (2): Clinical and laboratory characteristics of thyroid disease.

	No.	(%)
Suspicion for malignancy by US		
Yes	31	(41.3)
No	44	(58.7)
Nodularity		
Single	19	(25.3)
Multi-nodular goiter	47	(62.7)
Diffuse	9	(12.0)
Thyroid function		
Normal	57	(76.0)
Hyperthyroidism	18	(24.0)
Cytological		
Colloid cells	23	(30.7)
Follicular cells	10	(13.3)
Papillary cells	8	(10.7)
Non-diagnostic	7	(9.3)
Thyroiditis(Inflamatory)	3	(4.0)
FNA not done	24	(32.0)
Histological		
Colloid cells	40	(53.3)
Follicular CA	2	(2.7)
Papillary CA	14	(18.7)
Grave's disease	7	(9.3)
Hashimotos thyroiditis	5	(6.7)
Follicular adenoma	6	(8.0)
Amyloid thyroid disease	1	(1.3)
Total	75	(100.0)

Table (3a): Accuracy of fine needle aspirate**.**

	Histopathology		Total	p
FNA	Cancer(CA)	No CA		
CA	9	9	18	0.065*
No CA	2	31	33	
Total	11**	40	51	

*By McNemar test.

**Note: FNA was not done for 5 cases of CA, so they were not included in the analysis.

Table (3b): Indicators of accuracy of FNA.

Sensitivity	Specificity	PV+	PV-	Total agreement	Kappa
81.80%	77.50%	50%	93.90%	78.40%	0.48

Table (4): Prevalence of thyroid cancer.

	Histopathology						
	CA		No CA		Total		
	No.	(%)	No.	(%)	No.	(%)	p
Age							
< 30	5	(41.7)	7	(58.3)	12	(100.0)	0.169*
30-39	2	(9.5)	19	(90.5)	21	(100.0)	
40-49	2	(14.3)	12	(85.7)	14	(100.0)	
≥ 50	7	(25.0)	21	(75.0)	28	(100.0)	
Gender							
Female	13	(21.0)	49	(79.0)	62	(100.0)	> 0.99*
Male	3	(23.1)	10	(76.9)	13	(100.0)	
Suspicion for malignancy							
Yes	10	(32.3)	21	(67.7)	31	(100.0)	0.053
No	6	(13.6)	38	(86.4)	44	(100.0)	
Thyroid function							
Normal	15	(26.3)	42	(73.7)	57	(100.0)	0.097*
Hyperthyroidism	1	(5.6)	17	(94.4)	18	(100.0)	
Cytological FNA							
Colloid cells	1	(4.3)	22	(95.7)	23	(100.0)	< 0.001*
Follicular cells	2	(20.0)	8	(80.0)	10	(100.0)	
Papillary cells	7	(87.5)	1	(12.5)	8	(100.0)	
Non-diagnostic	1	(14.3)	6	(85.7)	7	(100.0)	
Thyroiditis	0	(0.0)	3	(100.0)	3	(100.0)	
FNA not done	5	(20.8)	19	(79.2)	24	(100.0)	
Total	16	(21.3)	59	(78.7)	75	(100.0)	

*By Fisher's exact test

Discussion:

Thyroid cancer is the most common endocrine cancer with growing incidence worldwide. More recent studies indicated that the yearly incidence has nearly tripled from 4.9 per 100,000 in 1975 to 14.3 per 100,000 in 2009, corresponding to approximately 63,000 new cases of thyroid cancer which were predicted to be diagnosed in 2014 compared with 37,200 in 2009 when the last ATA guidelines were published [27]. At present, thyroid FNA cytology is still the most accurate and cost-effective method for evaluating thyroid nodules. A uniform reporting system for thyroid FNA will facilitate effective communication among health care providers, facilitate cytologic-histologic correlation for thyroid diseases, and allow easy and reliable sharing of data from different laboratories for national and international collaborative studies.

By using the TI-RADS guidelines, one can see a significant reduction in the number of thyroid nodules recommended for biopsy and an improvement in the accuracy of recommendations for nodule management. With this system, the vast majority of the malignant nodules will be recommended for biopsy or follow-up US.

The strengths of the present's analysis are the number of nodules evaluated and the fact that all the nodules included had

a histopathologic diagnosis, which is the reference method for the definite diagnosis of thyroid nodules. Moreover, the performance of US in nodules with non diagnostic cytology was also analyzed, which constitutes the most challenging group of patients for clinical decision making. Another relevant aspect was the calculation of the likelihood ratio statistics, which summarizes how many times more (or less) likely patients with the disease are to have that particular result than patients.

Without the disease, it would be important to assess the accuracy of TI-RADS in a general population to ensure that it performs well in low-risk nodules. In addition, the radiologists were reviewing the US images on a computer system and did not have the opportunity to evaluate the images in real time. This could limit the ability of the readers to appreciate some subtle US features. This is a small study of only 75 nodules that had been selected for biopsy. To ensure the accuracy of these findings, a follow-up prospective study is needed with a larger number of nodules.

Our results confirm the findings of previous isolated studies. Moon et al. [19] evaluated 831 patients with thyroid nodules and found low sensitivity values for most of the US features. Hypoechogenicity was the only finding that showed a sensitivity of (87.2%). In the same study, taller than wide shape, speculated margins, marked hypoechogenicity, and micro-and macrocalcifications demonstrated a high specificity for malignancy, ranging from (90.8%) to (96.1%). In one of the largest series comprising 672 patients and 1141 nodules, Popovicz et al. also found low sensitivity values for most US features for malignancy. However, microcalcifications and taller than wide shape features had high specificity [20]. Moreover, in another study including 550 patients with multinodular goiter, Salmaslioglu et al. found that the presence of microcalcifications had a sensitivity of (89.3%) for malignancy [21].

The present findings have important clinical implications. They reinforce that isolated US features on their own do not provide strong evidence to confirm (likelihood ratio > 10) or rule out (likelihood ratio < 0.1) a diagnosis of malignancy. The American Thyroid Association recommends the use of a combination of US features to select thyroid nodules that should be biopsied Information about the probability of each US feature to be associated with malignancy would help the clinical decision to perform FNA biopsy.

The present findings also suggest that more accurate criteria are needed to recommend surgery in patients with non diagnostic cytology. This is an important practical matter, since it would be helpful to select better which patients should be submitted to FNA and, specially, when surgery should be indicated in those nodules with non diagnostic cytology.

Out of the 24 patients who FNA not done 6 of the patient had incidental thyroid cancer (The term “incidental” denotes malignant tumors of the thyroid gland detected by postoperative biopsy of surgical specimens resected for benign disease), in which only 2 case went through completion thyroidectomy, the presence of incidental thyroid cancer is an important issue in patients with benign thyroid diseases who underwent thyroid surgery, previous studies have also

reported the prevalence of thyroid cancer to be between (7.1%) and (16.3%) [22, 23, 24, 25, 26].

Based on the present study and previous results of prevalence, we suggest that the presence of incidental cancer is not an uncommon situation. The increasing number of total thyroidectomies appears to be an important factor for the higher rate of incidental thyroid cancer in general, incidental tumor foci are relatively smaller in size than non incidental tumor foci, this finding of this study favors a more radical aggressive therapeutic management in patients with presumably benign thyroid disease, though this remains a controversial issue. The advantages of near-total or total thyroidectomy include reduction of recurrence rate, the avoidance of rare possibilities of transformation from well differentiated to undifferentiated carcinoma, avoidance of second operation.

There are several limitations of this study that need to be considered. The 75 cases that were reviewed were selected from a cohort of nodules that had already been selected for biopsy and possibly surgery. Thus, this is a select group of nodules with a high proportion of suspicious US features.

Conclusion:

By using the TI-RADS guidelines, one can see a significant reduction in the number of thyroid nodules recommended for biopsy and an improvement in the accuracy of recommendations for nodule management. With this system, the vast majority of the malignant nodules will be recommended for biopsy or follow-up US.

In spite of recent guidelines seeking to standardize FNAC and interpretation of cytology results, false positive and false-negative results continue to present a challenge in the evaluation of thyroid nodules. Molecular testing studies are needed to more accurately refine FNA diagnosis in the cytologically indeterminate group where the majority of cases prove to be benign and surgery could be avoided.

False positive results remain a concern for FNAs with indeterminate thyroid cytopathology, as the majority of these patients undergo surgery with (66%) of the cases deemed histologically benign. The risk of malignancy in both the meta-review and the current prospective study was almost identical.

References:

[1]. Mazzaferri EL. Management of a solitary thyroid nodule. New England Journal of Medicine. 1993 Feb 25;328(8):553-9.

[2]. Ross DS 2006 Editorial: predicting thyroid malignancy. J Clin Endocrinol Metab 91:4253–4255.

[3]. Vander JB, Gaston EA, Dawber TR. The significance of nontoxic thyroid nodules: final report of a 15-year study of the incidence of thyroid malignancy. Annals of internal medicine. 1968 Sep 1;69(3):537-40.

[4]. Brito JP, Morris JC, Montori VM. Thyroid cancer: zealous imaging has increased detection and treatment of low risk tumours. BMJ: British Medical Journal (Online). 2013 Aug 27;347.

[5]. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, Evans JG, Young E, Bird T, Smith PA. The spectrum of thyroid disease in a community: the Whickham survey. Clinical endocrinology. 1977 Dec 1;7(6):481-93.

[6]. Tan GH, Gharib H. Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. Annals of internal medicine. 1997 Feb 1;126(3):226-31.

[7]. Guth S, Theune U, Aberle J, Galach A, Bamberger CM. Very high prevalence of thyroid nodules detected by high frequency (13 MHz) ultrasound examination. European journal of clinical investigation. 2009 Aug 1;39(8):699-706.
[8]. Hoang JK, Middleton WD, Farjat AE, Langer JE, Reading CC, Teefey SA, Abinanti N, Boschini FJ, Bronner AJ, Dahiya N, Hertzberg BS. Reduction in Thyroid Nodule Biopsies and Improved Accuracy with American College of Radiology Thyroid Imaging Reporting and Data System. Radiology. 2018 Mar 2;287(1):185-93.
[9]. Hoang JK, Lee WK, Lee M, Johnson D, Farrell S. US Features of thyroid malignancy: pearls and pitfalls. Radiographics. 2007 May;27(3):847-60.
[10]. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016 Jan 1;26(1):1-33.
[11]. Frates MC, Benson CB, Charboneau JW, Cibas ES, Clark OH, Coleman BG, Cronan JJ, Doubilet PM, Evans DB, Goellner JR, Hay ID. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Radiology. 2005 Dec;237(3):794-800.
[12]. Shin JH, Baek JH, Chung J, Ha EJ, Kim JH, Lee YH, Lim HK, Moon WJ, Na DG, Park JS, Choi YJ. Ultrasonography diagnosis and imaging-based management of thyroid nodules: revised Korean Society of Thyroid Radiology consensus statement and recommendations. Korean journal of radiology. 2016 Jun 1;17(3):370-95.
[13]. Russ G, Bigorgne C, Royer B, Rouxel A, Bienvenu-Perrard M. The Thyroid Imaging Reporting and Data System (TIRADS) for ultrasound of the thyroid. Journal de radiologie. 2011;92(7-8):701-13.
[14]. Tessler FN, Middleton WD, Grant EG, Hoang JK, Berland LL, Teefey SA, Cronan JJ, Beland MD, Desser TS, Frates MC, Hammers LW. ACR thyroid imaging, reporting and data system (TI-RADS): white paper of the ACR TI-RADS committee. Journal of the American College of Radiology. 2017 May 1;14(5):587-95..
[15]. Neuhold N, Schultheis A, Hermann M, Krotla G, Koperek O, Birner P. Incidental papillary microcarcinoma of the thyroid—further evidence of a very low malignant potential: a retrospective clinicopathological study with up to 30 years of follow-up. Annals of surgical oncology. 2011 Nov 1;18(12):3430.
[16]. Pelizzo MR, Rubello D, Bernardi C, Gemo G, Bertazza L, Schievano E, Fedeli U. Thyroid surgical practices shaping thyroid cancer incidence in North-Eastern Italy. Biomedicine & Pharmacotherapy. 2014 Feb 1;68(1):39-43.
[17]. Malandrino P, Pellegriti G, Attard M, Violi MA, Giordano C, Sciacca L, Regalbuto C, Squatrito S, Vigneri R. Papillary thyroid microcarcinomas: a comparative study of the characteristics and risk factors at presentation in two cancer registries. The Journal of Clinical Endocrinology & Metabolism. 2013 Apr 1;98(4):1427-34.
[18]. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). Jama. 2003 Jun 18;289(23):3095-105.
[19]. Moon WJ, Jung SL, Lee JH, Na DG, Baek JH, Lee YH, Kim J, Kim HS, Byun JS, Lee DH. Benign and malignant thyroid nodules: US differentiation—multicenter retrospective study. Radiology. 2008 Jun;247(3):762-70.
[20]. Popowicz B, Klencki M, Lewiński A, Słowińska-Klencka D. The usefulness of sonographic features in selection of thyroid

nodules for biopsy in relation to the nodule's size. European journal of endocrinology. 2009 Jul 1;161(1):103-11.
[21]. Salmaslıoğlu A, Erbil Y, Dural C, İşsever H, Kapran Y, Özarmağan S, Tezelman S. Predictive value of sonographic features in preoperative evaluation of malignant thyroid nodules in a multinodular goiter. World journal of surgery. 2008 Sep 1;32(9):1948.
[22]. Vasileiadis I, Karatzas T, Vasileiadis D, Kapetanakis S, Charitoudis G, Karakostas E, Kouraklis G. Clinical and pathological characteristics of incidental and nonincidental papillary thyroid microcarcinoma in 339 patients. Head & neck. 2014 Apr 1;36(4):564-70.
[23]. Costamagna D, Pagano L, Caputo M, Leutner M, Mercalli F, Alonzo A. Incidental cancer in patients surgically treated for benign thyroid disease. Our experience at a single institution. Il Giornale di chirurgia. 2013;33(1/2):21-6.
[24]. Dunki-Jacobs E, Grannan K, McDonough S, Engel AM. Clinically unsuspected papillary microcarcinomas of the thyroid: a common finding with favorable biology?. The American Journal of Surgery. 2012 Feb 1;203(2):140-4.
[25]. Sakorafas GH, Stafyla V, Kolettis T, Tolumis G, Kassaras G, Peros G. Microscopic papillary thyroid cancer as an incidental finding in patients treated surgically for presumably benign thyroid disease. Journal of Postgraduate Medicine. 2007 Jan 1;53(1):23.
[26]. Slijepcevic N, Zivaljevic V, Marinkovic J, Sipetic S, Diklic A, Paunovic I. Retrospective evaluation of the incidental finding of 403 papillary thyroid microcarcinomas in 2466 patients undergoing thyroid surgery for presumed benign thyroid disease. BMC cancer. 2015 Dec;15(1):330.
[27]. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association (ATA) guidelines taskforce on thyroid nodules and differentiated thyroid cancer. Thyroid. 2009 Nov 1;19(11):1167-214.