The frequency of thyroid carcinoma in patients with solitary and multiple nodules utilizing ultrasound guided fine needle aspiration cytology (FNAC): A prospective study (Thyroid carcinoma and U/S guided FNA)

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Summary:

Background: Population studies suggest that 3–8% of asymptomatic adults have thyroid nodules. Nodules have a 5–15% prevalence of malignancy. Fine-needle aspiration cytology is the primary and frequently initial tool for assessing the risk of malignancy in thyroid nodules and selecting patients for thyroid surgery.

Patients and Methods: This prospective study was done during the period from June 2007 to November 2008. The study includes 141 patients with palpable solitary or multiple thyroid nodules. Only patients with normal or low TSH values were referred for ultrasound examination and ultrasound guided FNAC, which were done using fine needles (G 20).

Results: eleven patients (7.8%) have insufficient or non-diagnostic aspirates and were excluded from the study. Of the remaining 130 patients that were included in our study, only 20 patients had thyroid carcinoma (15.3%). Seventy-nine patients (60.7%) had solitary nodule larger than 10 mm in largest dimension and 51 patients (39.3%) had two or more such nodules. The rate of cancer in males with thyroid nodules was higher than in females. The prevalence of thyroid cancer did not differ between patients with a solitary thyroid nodule (12 of 79 patients, 15.1%) and patients with multiple nodules (8 of 51 patients, 15.7%), the deference is statistically insignificant (P = 0.95). A nodule that is one of several nodules had a lower likelihood of being malignant than did a solitary nodule: (8.9% versus 15.1%) (P < 0.001).

Conclusion: Ultrasound guided FNAC is the primary and frequently initial tool for assessing the risk of malignancy in thyroid nodules. The prevalence of thyroid cancer did not differ between patients with a solitary thyroid nodule and those with multiple thyroid nodules. FNAC have limited role in cytological diagnosis of follicular carcinomas, unless it is confirmed by histopathological diagnosis.

Keywords: thyroid nodules, thyroid carcinoma, Ultrasound guided FNAC.

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Introduction:

Thyroid nodule is a localized swelling in a thyroid gland with an otherwise normal appearance. Thyroid nodules are common and may be caused by a variety of thyroid disorders (1). Thyroid nodules are a common medical problem (2). Although they are traditionally found as palpable masses at neck examination in patients with or without suspected thyroid disease, the apparent prevalence of non-palpable nodules (i.e.<1 cm in diameter) in the general population has recently increased, probably as a consequence of the increasing application of ultrasound (3-5). Population studies suggest that 3–8% of adults have asymptomatic thyroid nodules (6, 7). The prevalence of such nodules increases with age. Thyroid nodules are four times more common in women than in men (5). Most nodules are benign. Thyroid cancers are rare, accounting for only 1% of all cancers in most populations and 0.5% of all cancer deaths (4). Nodules have a 5–15% prevalence of malignancy (3, 5, and 8), the carcinomas in these nodules are: papillary (81%), follicular & hurthle cell (14%), medullary 3%, and anaplastic 2% (9). The evaluation of patients with thyroid nodules 1cm or more in diameter typically includes measurement of serum TSH and fine needle aspiration cytology (FNAC). This approach has been proven to be effective for the detection of thyroid cancer (8). Fine-needle aspiration cytology is the primary and frequently the initial tool for assessing the risk of malignancy in thyroid nodules and in selecting patients for thyroid surgery (10). FNAC is recommended for palpable nodules, but the indication for this procedure in non-palpable nodules is a matter of controversy. Some clinicians recommend ultrasonography-guided FNAC (US-FNAC) (11), whereas others consider that a clinical

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follow-up (neck palpation) is sufficient in the absence of family history of thyroid cancer or head/neck irradiation [12]. Although the majority of aspirates are adequate for cytological diagnosis, 5–20% will be insufficient or non-diagnostic (8, 13).
AIMS: Our goal was to compare the risk of thyroid cancer in patients with solitary nodules to those with multiple nodules by using ultrasound guided FNAC.

Patients and Methods:
Between June 2007 and November 2008 at Al-Kadhimyia teaching hospital, Baghdad, Iraq, this prospective study included 141 patients with either solitary or multiple thyroid nodules. All patients underwent US Guided FNAC before thyroidectomy. Eleven patients have insufficient or non-diagnostic aspirates and thus were excluded from the study. The remaining (130 patients) with 202 thyroid nodules larger than 10 mm in diameter were included in the study: they comprised 111 females and 19 males. All the patients were examined by a surgeon; they had visible evidence of thyroid enlargement, or palpable thyroid nodule on clinical examination. T3, T4 & TSH estimations were done for all the patients. Only those patients with normal or low TSH values were referred for ultrasound examination and ultrasound guided FNAC, none of the patients included in the study have high TSH value. The patients were examined by U/S using a high-resolution sonography system (Sonoline Versa pro, Siemens Medical System) using a 7-10 MHz linear array transducer. US characteristics that were evaluated included: size of nodule, number of nodules, margin (well defined or ill defined), shape (regular or irregular), consistency (whether solid of cystic), presence of calcification, halo sign (present or absent). The nodules were considered as solitary when one nodule larger 10mm is present and as multiple when more than one nodule larger 10mm were present. All the nodules (solitary and multiple) undergo U/S guided FNAC by the histopathologist using fine needle (G 20). The aspirated material was spread on 2 slides and fixed in 90% alcohol, stained by Hematoxylin and Eosin (H and E) and examined under light microscope. A sufficient sample was generally defined as when there was at least single slide that had six or more groups of >10 follicular epithelial cells [14-16]. Those aspirates that had yielded insufficient or inadequate materials for diagnosis were excluded from the study (11 patients). The final diagnosis of those patients with thyroid cancer (20 patients) were confirmed by subsequent histopathological examination of the excised specimen after thyroidectomy except in 2 patients with papillary carcinoma were the diagnosis was solely cytological because the patients were unfit for surgery. All the aspirated and biopsy materials which were taken in Al-Kadhimyia teaching hospital were examined in the laboratories of AL- Yarmook teaching hospital and some Private laboratories, Baghdad, Iraq. Statistical analyses were done by using the program SPSS (version 13 for Microsoft Windows). Statistical significance was indicated by a p value of less than 0.05.

Results:
Of the 130 patients 19 were males (14.6%), and 111 were females (85.4%). Among the 130 patients included in this study, only 20 patients had thyroid carcinoma (15.3%) The mean age of patients with thyroid cancer was 48.5 ± 0.8 yr (mean ± SD) compared with 42.4 ± 0.2 yr in those without cancer ($P < 0.01$) Seventy nine patients (60.7%) had solitary nodule more than 10 mm in largest dimension and 51 patients (39.3%) had two or more such nodules. The rate of cancer in males with thyroid nodules (4 patients out of 19 (21.0%)) was higher than in females with thyroid nodules (16 patients out of 111 (14.4%)) ($P < 0.03$) as shown in figure 1. The prevalence of thyroid cancer did not differ between patients with a solitary thyroid nodule (12 of 79 patients or 15.1%) and patients with multiple nodules (8 of 51 patients or 15.7%) the differences however are not statistically significant ($P = 0.95$). The types of thyroid cancer were also roughly similar in the two groups: among the 12 cancerous solitary nodules: 9 (76%) were papillary (figure 4), 1 (8%) was follicular, and two (16%) were undifferentiated carcinoma, whereas the corresponding numbers for the 8 cancers in glands with multiple nodules were 6 (75%) papillary, 1(12.5%) follicular, and one (12.5%) undifferentiated carcinoma as shown in figure 2. A nodule that is one of several nodules had a lower likelihood of being malignant than did a solitary nodule: 12 of 79 solitary nodules (15.1%) were malignant, as opposed to 11 of 123 non-solitary nodules (8.9%) ($P < 0.001$). The per-nodule likelihood of cancer decreased progressively as the number of nodules larger than 10 mm increased (table 1). Figure (3) show ultrasound picture of 2 malignant thyroid nodules, while figure 4 show cytological features of papillary carcinomas of thyroid from aspirated material by ultrasound guided FNA.

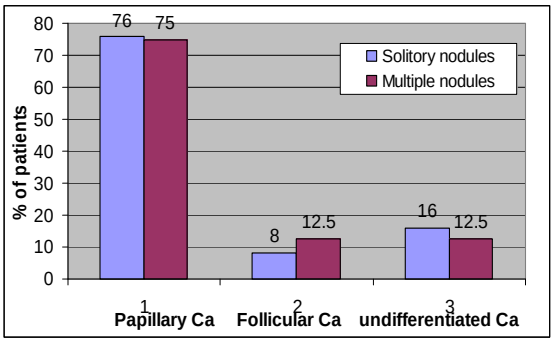

Figure 1: Percentage incidence of thyroid carcinoma according to the sex of patients.

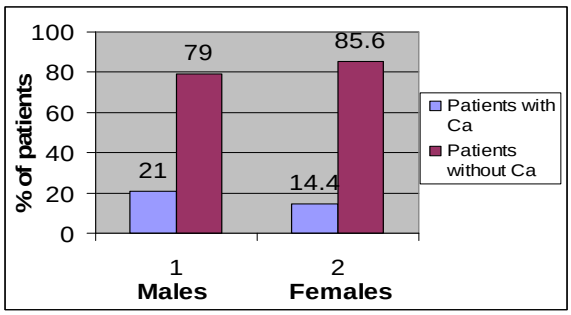

Figure 2: Percentage of the histological types of thyroid cancer in patients with solitary nodules and those with multiple nodules.

Table 1: Prevalence of thyroid cancer per patient and per nodule according to the number of nodules larger than 10 mm in maximum diameter

Solitary thyroid nodule						
	No. of patients	Patients with thyroid cancer		No. of Thyroid nodules	Malignant nodules	
	No.	No.	%	No.	No.	%
	79	12	15.1	79	12	15.1
Multiple thyroid nodules						
	No. of patients	Patients with thyroid cancer		No. of Thyroid nodule	Malignant nodules	
	No.	No.	%	No.	No.	%
2nodules	25	5	20.0	46	5	10.8
3nodules	14	2	14.2	35	3	8.5
4nodules	12	1	8.3	42	3	7.1
Total	51	8	15.7	123	11	8.9

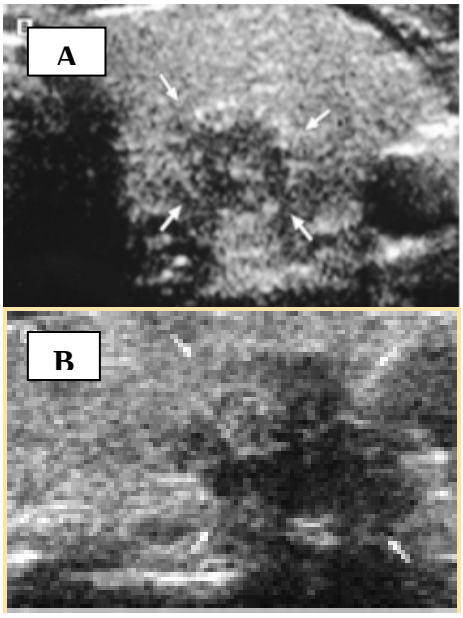

Figure 3: Ultrasound image of 2 malignant thyroid nodules. A:Regular and well-defined solid nodule with hypoechogenicity. B:Regular and well-defined solid nodule with hypoisoechogenicity and fine calcification (arrows).

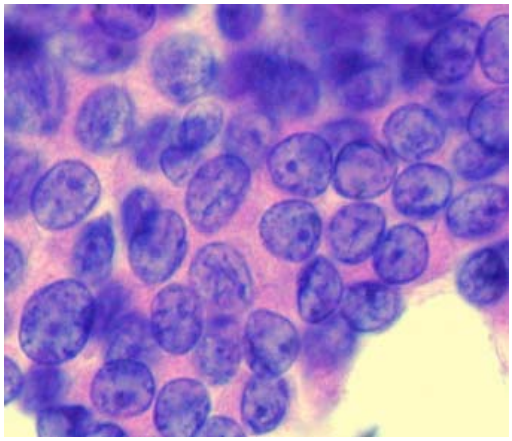

Figure 4: Cytological features of papillary carcinomas of thyroid from aspirated material by ultrasound guided FNA

Discussion:

Thyroid nodules are common, and have a 5–15% prevalence of malignancy (3, 5, and 8); thus, it is important to differentiate malignant nodules from benign nodules to avoid unnecessary thyroidectomy. FNAC is the initial and frequently the only tool for assessing the risk of malignancy in thyroid nodules and selecting patients for thyroid surgery (10). In experienced hands, the false negative rate is less than 5%, and the false positive rate less than 1%. A diagnostic sample is generally defined as when there are at least single slide that have six or more groups of >10 well-preserved follicular epithelial cells (14-16). Non-diagnostic FNAs of thyroid nodules remain a significant clinical dilemma. Despite improved aspiration techniques and ultrasound guidance, a 5–15% of initial aspirations may be non-diagnostic (17). In our study, 11 patients (7.8%) have insufficient or non-diagnostic aspirates and were excluded from the study. Non-diagnostic smears occur when there are insufficient follicular cells to make a cytological diagnosis [(15)]. Aspirates of cystic nodules are a source of unsatisfactory specimens and are thought to be a result of sampling error (16, 18). Other factors have been reported to influence the success of FNA, including small nodule size, position of the nodule within the thyroid, and patient age and body built whether the patient is fatty with short neck on not (13). The rest (130 patients) with sufficient and diagnostic aspirates were included in our study. Thyroid nodules are four times more common in women than in men (5). In our patients: 19 were males (14.6%) and 111 were females (85.4%), F/M ratio is about 6:1. Risk factors for malignancy included male sex and age less than 30 years or greater than 60 years (19). In our study the mean age of patients with thyroid cancer was 48.5 ± 0.8 yr (mean ± SD) compared with 42.4 ± 0.2 yr in those without cancer ($P < 0.01$). The rate of cancer in males with thyroid nodules (4 patients out of 19 (21.0%)) was higher than in females with thyroid nodules (16 patients out of 111 (14.4%)) ($P < 0.03$), these results are comparable with those

reported in previous studies (3, 8, 9). Seventy-nine 79 (60.7%) of our patients had solitary nodule larger than 10 mm in largest dimension and 51 (39.3%) had two or more such nodules. Only 20 patients (15.3%) out of 130 had thyroid carcinoma. These results are comparable with those reported in previous studies (3, 5, 8, 9), but others give a lower percentage of malignancy (20). The higher malignancy rate in our study is probably due to the biased selection of the lesions submitted to FNA. Moreover, the systematic use of US-FNA evaluation of thyroid nodules could have detected a few microcarcinomas in small nodules devoid of aggressive ultrasound behavior and destined not to grow into palpable lesions. Also in the previous studies not all the nodules suspicious or malignant at cytological evaluation had been submitted to surgery The prevalence of thyroid cancer did not differ between patients with a solitary thyroid nodule (12 of 79 patients or 15.1%) and patients with multiple nodules (8 of 51 patients or 15.7%) the deference is statistically insignificant (P = 0.95). These results are comparable statistically with those reported in previous study (9). On the other hand another study showed that solitary nodules presented a higher but not significantly increased risk of cancer as opposed to multinodular goiters (19). The types of thyroid cancer were roughly similar in the two groups: among the 12 solitary nodules that were cancers: 9 (76%) were papillary, 1(8%) was follicular, and two (16%) were undifferentiated carcinoma, whereas the corresponding numbers for the 8 cancers in glands with multiple nodules were: 6 (75%) were papillary, 1(12.5%) was follicular, and one (12.5%) was undifferentiated carcinoma. These results are comparable statistically with those reported in one study regarding papillary and undifferentiated carcinoma (9), but the low percent of follicular carcinoma in our study could be due to the fact, that FNAC have no role in diagnosis of follicular carcinomas (9, 14). A nodule that is one of several nodules had a lower likelihood of being malignant than did a solitary nodule: 12 of 79 solitary nodules (15.1%) were malignant, as opposed to 11 of 123 non-solitary nodules (8.9%) (P < 0.001). The per-nodule likelihood of cancer decreased progressively as the number of nodules larger than 10 mm increased (table 1). FNA of more than one nodule is uncomfortable, time consuming, costly, and carries a small but definite risk of malignancy (9). It would be desirable to be able to identify nodules with either a very high or a very low risk of malignancy to permit prioritization for FNA. The sonographic feature most closely associated with malignancy is nodule composition: the more cystic a nodule, the less likely it is to be malignant, and completely cystic nodules were never malignant in our study population. Other sonographic characteristics that correlate with malignancy include the presence and nature of calcifications, and (in nodules that are >50% solid) the nodule's echogenicity. In contrast, nodule size, margin definition, and presence and extent of a halo around the nodule are all unrelated to its risk of malignancy, at least among nodules with maximum diameter larger than 10 mm. Among non sonographic features, patient age does not correlate with the likelihood of malignancy, but gender does. A nodule in a man is significantly more likely to be malignant than is a similar nodule in a woman (9). In a patient with one or more thyroid nodules larger than 10 mm in maximum diameter, the likelihood of thyroid cancer is independent of the number of thyroid nodules. In patients with a thyroid cancer and multiple thyroid nodules, the cancer is often unifocal but not necessarily present in the largest nodule. Thus, for confident exclusion of thyroid cancer in a gland with multiple nodules larger than 10 mm, up to four nodules larger than 10 mm should be considered for aspiration when present (9).

Conclusions:

Thyroid cancer is more common in males. Ultrasound guided FNAC is the primary and frequently initial tool for assessing the risk of malignancy in thyroid nodules and selecting patients for thyroid surgery. The prevalence of thyroid cancer did not differ between patients with a solitary thyroid nodule and those with multiple thyroid nodules. FNAC have limited role in cytological diagnosis of follicular carcinomas, unless it is confirmed by histopathological diagnosis. A nodule that is one of several nodules had a lower likelihood of being malignant than did a solitary nodule. In cases of multiple nodules FNAC should be limited only to nodules with a very high risk of malignancy as determined by ultrasound examination.

References:

1. Castro MR, Gharib H. Thyroid nodules and cancer. When to wait and watch when to refer. Postgrad Med 2000; 107:113-6, 119-20, 123-4.

2. Mandel SJ. A 64-year-old woman with a thyroid nodule. JAMA 2004; 292: 2632–42.

3. Hegedus L. Clinical practice. The thyroid nodule. N Engl J Med 2004; 351:1764–1771.

4. Castro MR and Gharib H. Continuing controversies in the management of thyroid nodules. Ann Intern Med. 2005; 142: 926–31.

5. Mazzaferri EL. Management of a solitary thyroid nodule. N Engl J Med. 1993; 328:553–559.

6. Wiest PW, Hartshorne MF, Inskip PD, Crooks LA, Vela BS, Telepak RJ, et al. Thyroid palpation versus high-resolution thyroid ultrasonography in the detection of nodules. J Ultrasound Med. 1998; 17:487–496.

7. Burguera B, Gharib H. Thyroid incidentalomas. Prevalence, diagnosis, significance, and management. Endocrinol Metab Clin North Am 2000;29:187–203.

8. Gharib H, Goellner JR. Fine-needle aspiration biopsy of the thyroid: an appraisal. Ann Intern Med. 1993; 118:282–289.

9. Mary C. Frates, Carol B. Benson, Peter M. Doubilet, Elizabeth Kunreuther, Maricela Contreras, Edmund S. Cibas, et al. Prevalence and distribution of carcinoma in patients with solitary and multiple thyroid nodules on sonography. J Clin Endocrinol Metab. 2006; 91(9):3411-17

10. Ross DS. Diagnostic approach to and treatment of thyroid nodules. 2006; 14:2.

11. Papini E, Guglielmi R, Bianchini A, Crescenzi A, Taccogna S, Nardi F, et al. Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-doppler features. J Clin Endocrinol Metab. 2002; 87: 1941–6.

12. Tan GH and Gharib H. Thyroid incidentalomas: management approaches to non-palpable nodules discovered incidentally on thyroid imaging. Ann Intern Med. 1997; 126: 226–31.

13. Danese D, Sciacchitano S, Farsetti A, Andreoli M, Pontecorvi A. Diagnostic accuracy of conventional versus sonography-guided fine-needle aspiration biopsy of thyroid nodules. Thyroid: 1998; 8:15–21

14. Emily J Mackenzie and Robin H Mortimer. Thyroid nodules and thyroid cancer. MJA 2004; 180 (5): 242-247.

15. Gharib H, Papini E. Thyroid nodules: Clinical importance, assessment, and treatment. Endocrinol Metab Clin North Am 2007;36:707–735.

16. Ogilvie JB, Piatigorsky EJ, Clark OH. Current status of fine needle aspiration for thyroid nodules. Adv Surg 2006;40:223–238.

17. Erik K. Alexander, Jenny P. Heering, Carol B. Benson, Mary C. Frates, Peter M. Doubilet, Edmund S. Cibas. Assessment of Nondiagnostic Ultrasound-Guided Fine Needle Aspirations of Thyroid Nodules, The Journal of Clinical Endocrinology & Metabolism 2002: 87 (11): 4924-4927.

18. McHenry CR, Slusarczyk SJ, Khiyami A. Recommendations for management of cystic thyroid disease. Surgery. 1999; 126:1167–1172.

19. Belfiore A, La Rosa GL, La Porta GA. Cancer risk in patients with cold thyroid nodules: relevance of iodine intake, sex, age, and multinodularity. Am J Med 1992; 93: 363-369.

20. C. Cappelli, M. Castellano, I. Pirola, D. Cumetti, B. Agosti, E. Gandossi, et al . The predictive value of ultrasound findings in the management of thyroid nodules. QJM 2007 100(1):29-35.