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Highlights in the Diagnostic Dilemma of Solitary Thyroid Nodule; Fine Needle Aspiration Cytology in Comparison of Isotope Thyroid Scan

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Abstract: ***Thyroid nodules are common, with up to 8% of the adult population having palpable nodules. With the use of ultrasound, up to 10 times more nodules are likely to be detected. The majority of thyroid nodules are benign and asymptomatic. The primary aim in investigating a thyroid nodule is to exclude the possibility of malignancy, which occurs in about 5% of nodules. Objective: This was a comparative study between fine needle aspiration cytology and thyroid scan used to diagnose the solitary thyroid nodule and histopathology was used as gold standard to compare the results of both modalities. Materials and Methods: This study comprised of 40 patients with solitary thyroid nodules presented to endocrinology clinic in outpatient department. After clinical examination and ultrasound documentation; these patients were referred to nuclear medicine unit, for isotope thyroid scan .These patients underwent fine needle aspiration cytology in the department of Pathology. The cases were operated and evaluated for histopathological changes. Results. On thyroid scan, 30 patients (75%) having cold nodule were labeled as suspicious 10 patients (25%) had hot nodule. On FNAC 23 patients (57.5%) had benign lesion, 13 patients (32.5%) had indeterminate lesion and 4 patients (10%) had malignant lesions. On histopathology, 36 patients (90%) were confirmed to have benign lesions and 4 patients (10%), malignant lesions. After comparison of results of thyroid scan and fine needle aspiration cytology with histopathology, the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of thyroid scan were 75%, 25%, 10%, 90% and 30%, respectively whereas those of fine needle aspiration cytology were 75%, 97.2%, 75%, 97.2% and 95%, respectively. Conclusion: Fine needle aspiration was a significantly better predictor of malignancy than thyroid scan and resulted in a smaller proportion of excisions for benign nodules.***

Keywords: thyroid nodule, fine needle, thyroid scan, nodule, comparison

1. Introduction

Evaluation of solitary thyroid nodules (STN) requires the collaboration of the primary care physician, endocrinologist, pathologist, radiologist, and head and neck surgeon to provide comprehensive and appropriate management of this clinical entity. The prevalence of thyroid nodules within a given population depends on a variety of factors that include age, sex, diet, iodine deficiency, and therapeutic and environmental radiation exposure. These are more common in women and in areas of iodine deficiency. Exposure to ionizing radiation in childhood and adolescence increases the risk of solitary thyroid nodule and thyroid carcinoma [1].A solitary thyroid nodule is a palpable swelling in thyroid gland that has otherwise a normal appearance [2]. The majority of thyroid nodules are benign and asymptomatic. The primary aim in investigating a thyroid nodule is to exclude the possibility of malignancy, which occurs in about 5% of nodules. This begins with a thorough history, including previous exposure to radiation, diet habits and any family history of thyroid cancer or other endocrine diseases. Clinical examination of the neck should focus on the thyroid nodule and the gland itself, but also the presence of any cervical lymphadenopathy. Biochemical assessment of the thyroid needs to be followed by thyroid ultrasound, which may demonstrate features that are associated with a higher chance of the nodule being malignant [2]. A variety of tests have been employed to separate benign from malignant thyroid nodules These tests include isotope thyroid scanning and fine needle aspiration cytology (FNAC) [3]. Isotope scanning was generally used to classify nodules into nonfunctioning (cold) or functioning (warm or hot) nodules. The scans used either Iodine123 or technetiumTc99m pertechnetate. Only 5 to 15% of the cold nodules are malignant [4, 5].Fine needle aspiration cytology of thyroid nodules is the single most sensitive, specific, and cost-effective method of investigation of thyroid nodules. Now it is safely and widely recommended for the preoperative selection of patients. The challenge remains in the management of nodules that fall under the "indeterminate" category. These may be subject to more surgical intervention than is required because histological examination is the only way in which a malignancy can be excluded [6]. Another major pitfall of this procedure is that fine needle aspiration cytology cannot differentiate between follicular adenoma and follicular carcinoma [7, 8]. In this study we compared the individual efficacy of FNAC and thyroid scan in the management of solitary thyroid nodules and histopathology was used as gold standard to assess the results of both modalities.

2. Material and Methods

This was a comparative cross-sectional study and carried out at the Departments of Medicine, Surgery, Nuclear Medicine, and Pathology, Zagazig University hospitals in Egypt. It was conducted on 40 patients of solitary thyroid nodule in the period from December 2011 up to October 2012. *Inclusion Criteria include :*(1) Age 20 to 70 Years.

(2) Both genders.(3) Patient presenting with solitary swelling arising from any lobe of thyroid selected by clinical palpation. *Exclusion Criteria include:*(1) Patients with diffuse thyroid swelling.(2) All toxic and colloid goiters confirmed by clinical evaluation.(3) Patients with history of any type of thyroid surgery (lobectomy or total thyroidectomy).All

patients presenting with solitary thyroid nodules in endocrinology clinics documented by clinical palpation and thyroid ultrasound and fulfilling the inclusion criteria were included in this study. Informed consent from all the patients was taken. All the patients were recorded for their demographic features, that is, age, sex, and address (for follow up). Thorough initial clinical evaluation includes history of the thyroid mass, past medical history, previous exposure to radiation, diet habits, and stressing on symptoms such as neck pain, stridor, dysphonia, and dysphagia because it increase clinical suspicion of a thyroid malignancy. Family history of pheochromocytoma, hyperparathyroidism, chronic constipation and diarrhea, hypertension, and episodes of nervousness or excitability also taken in consideration because it might point to the possibility of familial MEN 2a or 2b syndrome .Complete head and neck clinical examination was performed focusing on the thyroid nodule, gland itself and the presence of any cervical lymphadenopathy. Physical characteristics of a thyroid nodule even are poor predictors of malignancy because both malignant and benign solitary thyroid nodules could be soft or firm, smooth or irregular upon examination. However; size of a thyroid nodule, fixation to or invasion of surrounding structures and the presence of palpable lymph nodes in the neck were taken in consideration. All routine investigations and serum FT3, FT4, and TSHL evelswere performed by Radioimmunoassay (RIA), (normalrange of T3, 2.5–5.8 pmol/L, T4, 11.5–23.0 pmol/L, and TSH, 0.2–4.0mIU/L). Patients with solitary thyroid swelling underwent thyroid scan then FNAC was performed. Cytological diagnosis was categorized into three groups: negative for malignancy, indeterminate (suspicious) formalignancy and positive for malignancy. The cases were operated and evaluated for histopathological changes. The results of thyroid scan, fine needle aspirationcytology, and histopathology were compared. Histopathology was taken as gold standard.

3. Statistical Analysis

All the data was analyzed with SPSS version 11. The variables included were demographic information, routine investigations, thyroid scan, and thyroid function tests. For quantitative data, that is, thyroid function tests, duration and size of thyroid nodule, mean, and standard deviation were calculated. For qualitative data, that is, a result of thyroid scan, fine needle aspiration cytology, and histopathology, percentages was calculated. A 2×2 table was used to calculate sensitivity, specificity, positive predictive value, negative predictive value, and accuracy.

4. Results

The age of patients ranged from 21 to 70 years with mean age34.75± 16.29 years. 34 patients (85%) were females, and 6 (15%) were males (male to female ratio 1 : 5.66).

Regarding thyroid function tests, 37 patients (92.5%) were euthyroid, 3 patients (7.5%) were hypothyroid, and no patient was hyperthyroid. The mean for serum T3, serum T4, and serum TSH were 3.1 ± 1.1, 13.4 ± 3.5, and 2.1 ± 1.2, mg/dl respectively, . There were30 patients (75%) who had cold nodule on thyroid scan of which 5 patients (12.5%) were males and 25 patients (62.5%)were females**.** There were10 patients (25%) who had hot nodule on thyroid scan of which one patient (2.5%) was male and 9 patients (22.5%)were females. table (1)

Table 1: distribution of patients according to isotope thyroid scanning

	Hot nodule	Cold nodule
Female	9 (22.5%)	25(62.5%)
Male	1 (2.5 %)	5 (12.5%)

The mean for size of thyroid nodule was 2.9± 1.63 cm.30 patients (75%) had 1–3 cm sized thyroid nodules, and 10 patients (25%) had 3–6 cm thyroid nodules. No patient had thyroid nodule greater than 6 cm in size.

On FNAC, 23 patients (57.5%) had benign lesion, 13 patients (32.5%) had indeterminate lesion and 4 patients (10%) had malignant lesions. Among patients with the benign lesions 23 (57.5%); 7 (17.5%) colloid cyst two of them were males (5%) and 5 were females (12.5%), 2(5%) colloid goiter both of them were females, 12 (30%)colloid nodule all were females, and 2(5%) chronic lymphocytic thyroiditis one was male (2.5%) and the other was female(2.5%)). Out of the 13 (32.5%) patients with in determinant FNAC, 2 patients (5%) had follicular lesion, both of them were females, and 11 patients (27.5%) had follicular neoplasm, 2 (5%) were males and 9 (22.5%) were females. Out of the 4 patients with malignant FNAC (10%), 3 patients (7.5%) had papillary carcinoma, 1 (2.5%) male and 2 (5%) females; 1 patient (2.5%) had medullary carcinoma who was female table (2).

Table 2: Distribution of patients according to the results of FNAC

	benign lesions 23 (57.5%)				**indeterminate lesion 13 (32.5%)**		**malignant lesions 4 (10%)**	
Type	Colloid cyst 7(17.5%)	Colloid goiter 2(5%)	Colloid nodule 12(30%)	Chronic lymphocytic thyroiditis 2(5%)	Follicular Lesion 2(5%)	Follicular neoplasm 11(27.5%)	papillary carcinoma 3(7.5%)	medullary carcinoma 1(2.5%)
Female	**5 (12.5%)**	2(5%)	12(30%)	1(2.5%)	2(5%)	9(22.5%)	2(5%)	1(2.5%)
Male	2(5%)	-	-	1(2.5%)	-	2(5%)	1(2.5%)	-

On histopathology, 36 patients (90%) were confirmed to have benign lesions and 4 patients (10%) malignant lesions. Out of 36 patients with benign lesions on histopathology, 7 patients (17.5%) had colloid cyst, 2 (5%) males and5 (12.5%) females; 2 patients (5%) had colloid goiter, both of them were females; 12patients (30%) had colloid nodule, all of them were females; 2patients (5%) had chronic lymphocytic thyroiditis, 1(2.5%)male and 1(2.5%) females; 10patients (25%) had follicular adenoma, 2 (5%)males and 8 (20%) female; 1 patient (2.5%) had diffuse hyperplasia which

was female, and 2 patients (5%) hadhyperplastic nodule, all of whom were females. Out of 4 (10%) patients with malignant lesions on histopathology, 2 patients (5%) had pure papillary carcinoma, 1 (2.5%) male and 1(2.5%) female; 1 patient (2.5%) had medullary carcinoma who was female and 1 patient (2.5%) had angioinvasivefollicular carcinoma table (3).

Table 3: Distribution of patients according to the results of histopathology

	Benign lesions 36 (90%)							**Malignant lesions**		**4 (10%)**
	Colloid cyst 7(17.5%)	Colloid goiter 2(5%)	Colloid nodule 12(30%)	Chronic lymphocytic thyroiditis 2(5%)	Follicular adenoma 10(25%)	Diffuse hyperplasia 1(2.5%)	Hyperplastic nodule 2(5%)	Papillary	Medullary	Angio-invasive follicular
Female	5(12.5%)	2(5%)	12(30%)	1(2.5%)	8(20%)	1(2.5%)	2(5%)	1(2.5%)	1(2.5%)	1(2.5%)
Male	2(5%)	-	-	1(2.5%)	2(5%)	-	-	1(2.5%)		

On comparison of results of thyroid scan with histopathology taken as gold standard, out of 40 patients, 3 patients were true positive, 9 patients were true negative, 27 patients were false positive, and one patient was false negative. The sensitivity of thyroid scan was found to be 75%, specificity25%, diagnostic accuracy 30 % positive predictive value 10%, and negative predictive value 90% Table (4).On comparison of results of FNAC with histopathology taken as gold standard, out of 40 patients, 3 patients were true positive, 35 patients were true negative, one patient was false positive, and one patient was false negative. The sensitivity of FNAC was 75 %, specificity 97.2%, diagnostic accuracy 95%, positive predictive value 75%, and negative predictive value97.2 %Table(4).

Table 4: Sensitivity, Specificity, Diagnostic accuracy, Positive predictive value and Negative predictive value of isotope thyroid scanning and FNAC in detecting malignancy in patients with solitary thyroid nodules

	Sensitivity	*Specificity*	*Diagnostic accuracy*	*Positive predictive value*	*Negative predictive value*
Isotope scanning	75%	25%	30%	10%	90%
FNAC	75%	97.2%	95%	75%	97.2%

Morphological comparison of different lesions on FNAC and Histopathology is shown in Figures 1-7.

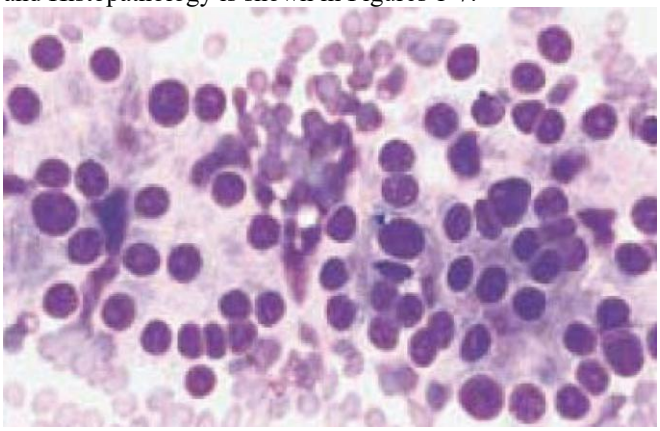

Figure 1: Photomicrograph of FNAC.(H&E) follicular neoplasms, showing marked cellularity, discohesion, single cells, predominantly microfollicles and/or trabeculae, uniformly enlarged cells, crowding, scant colloid, marked nuclear atypia, mitosis and necrosis is uncommon(H&E 20x).

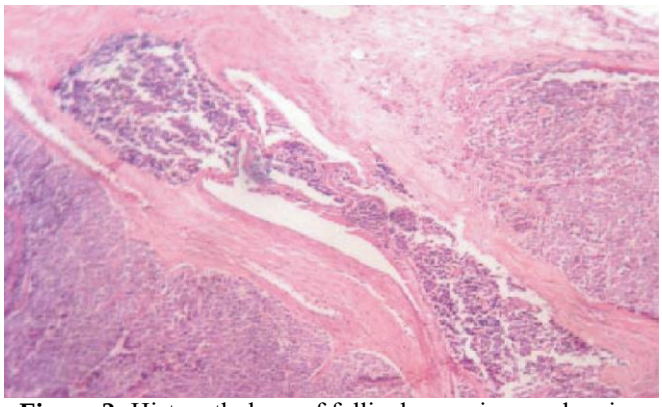

Figure 2: Histopathology of follicular carcinoma showing capsular and vascular invasion (H&E 10x).

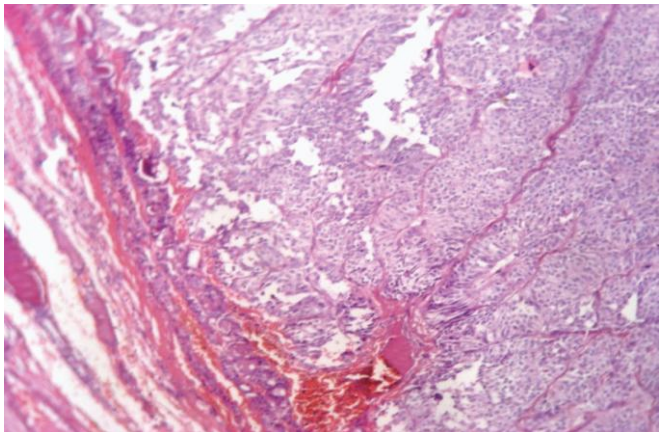

Figure 3: Follicular adenoma, where no capsular invasion is seen, while histologic evidence of invasion is the gold standard of malignancy for the follicular lesions (H&E 10x).

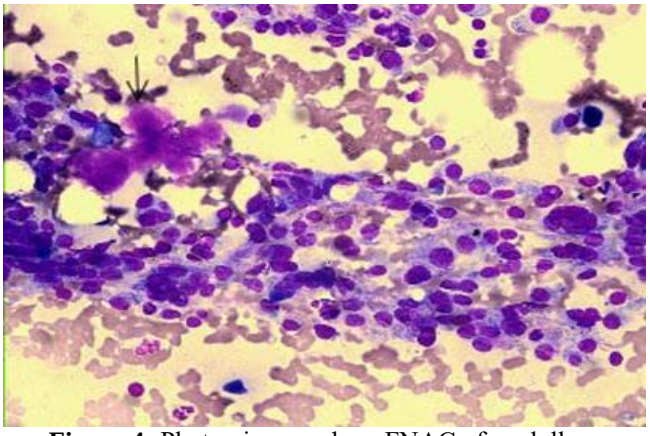

Figure 4: Photomicrograph on FNAC of medullary carcinoma with isolated, loosely cohesive, syncytial fragments, round, oval, cuboidal, plasmacytoid, spindle, round cells, and extracellular amyloid (arrow , Giemsa stain)(H&E20x).

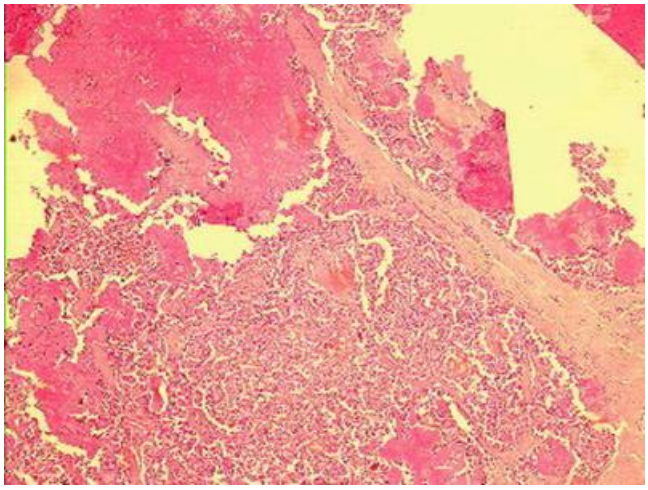

Figure 5: Histopathology of same case(medullary carcinoma)showing densely packed sheets of polygonal cells with oval nuclei with some delicate fibrovascular septa and prescence of large irregular deposite of amyloid (upper left corner) (H&E 20X).

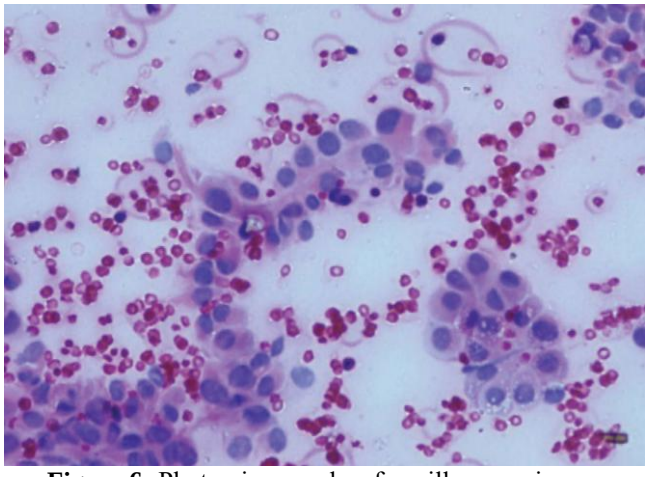

Figure 6: Photomicrographs of papillary carcinoma showing hypochromasia/pallor, nuclear grooves, intranuclear cytoplasmic inclusions, ovoid nucleus, and micronucleolus.

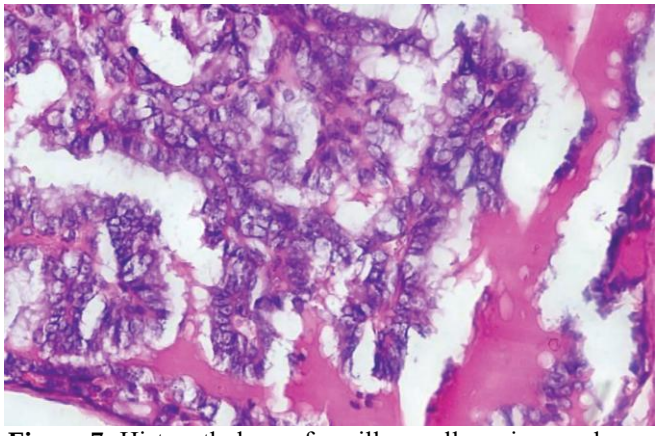

Figure 7: Histopathology of papillary cell carcinoma shows complex branching papillae with fibrovascular core and enlarged, overlapping clear nuclei (H&E20X).

5. Discussion

Thyroid nodules are frequently-encountered entities in clinical practice, occurring with a prevalence of 4% by palpation, 33% to 68% by ultrasound examination, and 50% on autopsy series [9]. While approximately 95% of thyroid nodules are benign, certain historical, laboratory, and sonographic features raise the suspicion for malignancy [10].The primary aim in investigating a thyroid nodule is to exclude the possibility of malignancy. A variety of tests have been employed to separate benign from malignant thyroid nodules These tests include isotope thyroid scanning and fine needle aspiration cytology (FNAC) [1].

Many investigators have shown that fine needle aspiration cytology is the single most sensitive, specific, and cost-effective method in the investigation of solitary thyroid nodules [11, 12]. Despite studies supporting the cost-effectiveness of fine needle aspiration cytology as the diagnostic test of choice, I-131 scintigraphy continues to be used by frontline providers as primary diagnostic tools in the management of patients with nodular thyroid diseases. Justifications for the continued use of this alternative diagnostic strategy usually range from historical practice patterns within institutions to faster turnaround time for results when compared with waiting for FNAC pathology reports[13].In our study, the age of patients ranged from 21 to 70 years with mean age34.75± 16.29 years. The highest number of patients was aged between 21–30 years, that is, 17 (42.5%).In a study from Saudi Arabia, the mean age was 36.17 ± 12.3years (range 15–67 years) which is very close to our study[14]. In our study, 34 patients (85%) were females, and 6 (15%) were males (male to female ratio 1 : 5.66).These results are close to Hussain and Anwar, who found female to male ratio as 6.9 : 1 [4]. In our study, 30 patients (75%) had cold nodule on thyroid scan. 10 patients (25%) had hot nodule on thyroid scan. In a study from India, 77.77%patients had cold nodule on thyroid scan while 22.22%patients had hot nodule on thyroid scan, which is close to our study [15].In the literature, it is clearly indicated that the nodule size is only a weak predictor of histological malignancy [10].In our study, the mean size of thyroid nodule was 2.9± 1.63 cm.30 patients (75%) had 1–3 cm sized thyroid nodules, and 10 patients (25%) had 3–6 cm thyroid nodules .The rate of malignancy was almost the same in our data, and the chances of

malignancy were independent of its size. Our findings are consistent with other studies [16].After comparison of our results of thyroid scan with histopathology, Overall sensitivity of thyroid scan was found to be 75%, specificity 25%, positive predictive value 10%, and negative predictive value 90%. The overall accuracy was 30%. In one study of thyroid scan, it was reported to have sensitivity 100% and specificity 24% which is close to our study [15]. This shows that thyroid scan is more sensitive than specific in detecting thyroid malignancy. In our study showed according to results ofFNAC23 patients (57.5%) had benign lesion, 13 patients (32.5%) had indeterminate lesion and 4 patients (10%) had malignant lesions. In a study from Pakistan, 39.47% of patients were of benign FNAC, 43.42% were of in determinant FNAC, and 11.84% were of malignant FNAC, which is also close to our study [17].Among patients with the benign lesions 23 (57.5%); 7 (17.5%) colloid cyst, 2(5%) colloid goiter, 12 (30%) colloid nodule, and 2(5%) chronic lymphocytic thyroiditis. All the patients with benign FNAC were confirmed to have the same results on histopathology. Out of the 13 (32.5%) patients with indeterminant FNAC, 2 patients (5%) had follicular lesion and 11 patients (27.5%) had follicular neoplasm. On histopathology, patients with follicular lesions were confirmed to have hyper plastic nodule, and out of the 11 patients with follicular neoplasm, 10 patients (40%) were confirmed to have follicular adenoma whereas 1 patient (2.5 %) had follicular carcinoma. The intermediate findings were the main pitfalls of FNAC thyroid. This could be due to over-diagnosis on cytological reporting [17]. Our findings are consistent with Flanagan et al. [18].In our study out of the 4 patients with malignant FNAC (10%), 3 patients(7.5%) had papillary carcinoma, 1 patient (2.5%) had medullary carcinoma .On histopathology, out of3 patients with papillary carcinoma, 2 patients (5%), were confirmed to have papillary carcinoma whereas 1 patient (2.5%) had diffuse hyperplasia. Patient with medullary carcinomaon FNAC were found to have the same on histopathology. Therefore, in this study the concordance between the malignant FNAC diagnosis and histologic follow up was 75%. This is comparable to other studies in the literature [17–19].After comparison of our results of FNAC with histopathology; overall sensitivity of FNAC was 75%, specificity 97.2%, positive predictive value 75%, and negative predictive value 97.2%.

The overall accuracy was 96%. Our results are consistent with results of other studies. In a review on FNAC of the thyroid nodule, it was reported to have sensitivity of 65–98% and a specificity of 72–100% [20]. This shows that FNAC is more specific than sensitive in detecting thyroid malignancy, and therefore, it is used as a reliable diagnostic test [1].

The overall accuracy for FNAC was 95%, which exactly the same with other studies of 95% [21]. In our study, sensitivity of FNAC was 75%, which was equivalent to the sensitivity of thyroid scan. However, specificity of FNAC was 97.2%compared to only 25% for thyroid scan. The very low specificity of thyroid scan might make it appear as a superfluous investigation compared to FNAC. The overall accuracy of FNAC was 95% while that of thyroid scan was only 30%.These findings are consistent with the data found worldwide [7, 12, 19].

6. Conclusion

Fine needle aspiration cytology is more specific than sensitive whereas thyroid scan is more sensitive than specific in detecting thyroid malignancy. Fine needle aspiration cytology is highly accurate and better than thyroid scan in the evaluation of solitary thyroid nodule. Therefore, FNAC should be adapted as an initial investigation of thyroid diseases in all tertiary hospitals. The use of FNAC has reduced the number of patients with solitary thyroid nodules undergoing unnecessary surgery and has led to proper planning of surgery in malignant cases however, the challenge remains in the management of nodules that fall under the "indeterminate" category because histopathological examination is the only way in which a malignancy can be excluded. Another major pitfall of this procedure is that fine needle aspiration cytology cannot differentiate between follicular adenoma and follicular carcinoma.

References

[1] R. Basharat, M. Bukhari, S.Saeed and T. Hamid, “Comparison of Fine Needle Aspiration Cytology and Thyroid Scan in Solitary Thyroid Nodule” Pathology Research International Volume 2011, Article ID 754041
[2] M. J. Welker and D. Orlov, “Thyroid nodules, ” *American Family Physician*, vol. 67, no. 3, pp. 559–573, 2003.
[3] H. Nggada, A.Musa, B. Gali, and M. Khalil, “Fine needle aspirationcytology of thyroid nodule (S): a Nigerian tertiary hospital experience, ” *Internet Journal of Pathology*, vol. 5, no.1, 2006.
[4] N. Hussain and M. Anwar, “Pattern of surgically treated thyroid diseases in Karachi, ” *Biomedica*, vol. 21, no.1, pp. 18–20, 2005.
[5] W. Lawrence Jr. and B. J. Kaplan, “Diagnosis and management of patients with thyroid nodules, ” *Journal of Surgical Oncology*, vol. 80, no. 3, pp. 157–170, 2002.
[6] F. Lumachi, L. Varotto, S. Borsato et al., “Usefulness of 99mTcpertechnetatescintigraphy and fine-needle spiration cytologyin patients with solitary thyroid nodules and thyroid cancer, ” *Anticancer Research*, vol.4, no. 4, pp. 2531–2534, 2004.
[7] A. N. Khalid, C. S. Hollenbeak, S.A.Quraishi, C. Y. Fan, and B.C. Stack Jr., “The cost-effectiveness of iodine 131 scintigraphy, ultrasonography, and fine-needle aspiration biopsy in theinitial diagnosis of solitary thyroid nodules, ” *Archives of* Pathology Research International 9*Otolaryngology—Head and Neck Surgery*, vol. 132, no. 3, pp.244–250, 2006.
[8] A. Magdy, Y.Sheta, and M, Mursy “Accuracy of HBME-1 as an immunohisto chemical Marker Differentiating Benign from Malignant Follicular Thyroid Nodules, ”British Journal of Science September 2012, Vol. 6 (2)
[9] S. Guth, U. Theune, J. Aberle and A. Galach “Very high prevalence of thyroid nodules detected by high frequency (13 MHz) ultrasound examination, ” Eur J Clin Invest 2009, 39:699-706.
[10] L. Hegedus“ Clinical practice. The thyroid nodule, ”N Engl J Med 2004, 351:1764-1771

[11] C. Cappelli, I. Pirola, E. Gandossi, E. de Martino, B. Agosti, and M. Castellano, "Fine-needle aspiration cytology of thyroidnodule: does the needle matter?" *Southern Medical Journal*, vol. 102, no. 5, pp. 498–01, 2009.
[12] S. Moslavac, N. Matesa, and Z. Kusi´c, "Thyroid fine needle aspiration cytology in children and dolescents, " *Collegium Antropologicum*, vol. 34, no. 1, pp. 197–200, 2010.
[13] U. Kini, A. Buch, and G. Bantwal, "Role of FNA in the medical management of minimally enlarged thyroid, " *diagnostic Cytopathology*, vol. 34, no. 3, pp. 196–200, 2006.
[14] F. A. Qari, "Pattern of thyroid malignancy at a University Hospital in Western Saudi Arabia, " *Saudi Medical Journal*, vol.25, no. 7, pp. 866–870, 2004.
[15] R. D. Bapat, P. Pai, S. Shah, and S. D. Bhandarkar, "Surgeryfor thyroid goiter in western India. A prospective analysis of334 cases, " *Journal of Postgraduate Medicine*, vol. 39, no. 4, pp.202–204, 1993.
[16] D. V. Mihailescu and A. B. Schneider, "Size, number, and distribution of thyroid nodules and the risk of malignancy in radiation-exposed patients who underwent surgery, " *Journal of Clinical Endocrinology and Metabolism*, vol. 93, no. 6, pp.2188–2193, 2008.
[17] M. H. Bukhari, S. Niazi, G. Hanif et al., "An updated audit of fine needle aspiration cytology procedure of solitary thyroidnodule, " *Diagnostic Cytopathology*, vol. 36, no. 2, pp. 104–112, 2008.
[18] M. B. Flanagan, N. P. Ohori, S. E. Carty, and J. L. Hunt, "Repeat thyroid nodule fine-needle aspiration in patients with initial benign cytologic results, " *American Journal of Clinical Pathology*, vol. 125, no. 5, pp. 698–702, 2006.
[19] J. Y. Kwak, H. Koo, J. H. Youk et al., "Value of US correlation of a thyroid nodule with initially benign cytologic results, "*Radiology*, vol. 254, no. 1, pp. 292–300, 2010.
[20] J. I. Hamburger, "Extensive personal experience: diagnosis of thyroid nodules by fine needle biopsy: use and abuse, " *Journal of Clinical Endocrinology and Metabolism*, vol. 79, no. 2, pp.335–339, 1994.
[21] K. C. Suen, F. W. Abdul-Karim, D. B. Kaminsky et al., "Guidelines of the Papanicolaou Society of Cytopathology for the examination of fine-needle aspiration specimens from thyroid nodules. The apanicolaou Society of Cytopathology Task Force on Standards of Practice, "*Modern Pathology*, vol. 9, no. 6, pp. 710–715, 1996.