

Correlation of Single Image Tc-99m MIBI Scan and Ultrasonography with Fine Needle Aspiration Cytology (FNAC) to assess Neoplasia in Solitary “Cold” Thyroid Nodules

Sohaib M¹, Saeed S¹, Naseeb HK¹, Hyder SW²

¹ Department of Medical Sciences, Pakistan Institute of Engineering and Applied Sciences, Islamabad Pakistan

² Centre for Nuclear Medicine, Mayo Hospital, Lahore

Abstract

Various investigative approaches for the management of solitary thyroid nodules have been adopted, which involve Tc-99m pertechnetate scan, ultrasonography and fine needle aspiration cytology (FNAC). Incidence of neoplasm in a solitary thyroid nodule showing cold lesion on Tc-99m pertechnetate scan vary from 9 to 26%. In the current study we evaluated the utility of Tc-99m labeled Hexakis2-methoxyisobutyl isonitrile (Tc-99m MIBI) in differentiating neoplastic from non-neoplastic lesions among nodules which are cold on Tc-99m pertechnetate scan and solid or mixed on ultrasonography. Forty-nine patients, all having solitary cold nodules on Tc-99m Pertechnetate scans were included in the study. All underwent ultrasonography, Tc-99m MIBI scan and FNAC. Ultrasound findings were categorized as solid, mixed and cystic. Anterior images of thyroid were acquired 15 minutes after intravenous injection of Tc-99m MIBI. The thyroid nodules were classified into 5 categories depending on the degree of MIBI uptake. They were; Category-1 showing intense uptake, Category-2 showing slightly higher uptake than the surrounding normal thyroid tissue, Category - 3 with uptake equal to the normal thyroid, Category -4 showing less uptake than the surrounding normal tissue and Category -5 showing no or negligible uptake of Tc-99m MIBI. Receiver Operating Characteristic (ROC) curve was

generated using Tc-99m MIBI results. FNAC revealed 10 nodules with neoplastic lesions (8 follicular and two pleomorphic), 29 with colloid goiter and 5 with benign cystic lesions. Tc-99m MIBI images revealed Categories-1,2,3,4 and 5 scintigraphic patterns in 2,12, 11, 10 and 14 patients respectively. One patient in Category 1 and 9 in Category 2 proved to be neoplastic in nature, while none of the patients in category 3 to 5 had evidence of neoplasm on FNAC. The ROC curve revealed excellent performance of Tc-99m MIBI scan in diagnosing neoplastic lesions in the solitary cold thyroid nodules. Considering Category-1 and 2 as true positive results sensitivity, specificity, positive predictive and negative predictive values of Tc-99m MIBI scanning were found to be 100, 90, 71 and 100% respectively. Ultrasonography also had a sensitivity of 100% considering solid and cystic lesions as test positive. But specificity of US was found to be only 13%. The sensitivity and specificity of the combined results of Tc-99m MIBI scintigraphy and ultrasonography were also not found to be significantly different from those of Tc-99m MIBI scan alone (100% and 91% respectively). Hence in patients with solitary cold thyroid nodules on Tc-99m Pertechnetate study, a single Tc-99m MIBI scan can be used reliably to assess neoplastic nature of the nodule with high degree of sensitivity and specificity.

Keywords: Solitary Thyroid Nodules, Tc-99m MIBI, FNAC, Thyroid Neoplasm

World J Nucl Med 2007;6:87-91

Introduction

A Tc-99m pertechnetate scan showing iso-functioning (warm) or hyper-functioning (hot) nodule reliably excludes the possibility of malignancy (1). In a solitary nodule showing hypo-functioning (cold) lesion on a pertechnetate scan after excluding hyper and hypothyroidism, the fine needle aspiration cytology (FNAC) is the first and most important diagnostic procedure (2,3). It is now considered as the gold standard for evaluation of such nodules (4,5). The diagnostic accuracy of the test is about 95% (6). Conventional imaging methods have less value in

Correspondence:

Dr. Muhammad Sohaib

Associate Professor

Department of Medical Sciences,

Pakistan Institute of Engineering and Applied Sciences (PIEAS)

P.O. Nilore, Islamabad-45650

PAKISTAN

Email: drsohaib@yahoo.com

Fine Needle Aspiration Cytology (FNAC)		Results of Tc-99m MIBI scintigraphy					Results of Ultrasonography		
		C-1	C-2	C-3	C-4	C-5	Solid	Cystic	Mixed
Neoplastic (n=10)	Follicular (n=8)	1	7	-	-	-	6	-	2
	Pleomorphic (n=2)	-	2	-	-	-	2	-	-
Non-neoplastic (n=39)	Colloid goitre (n= 29)	1	3	10	8	7	27	-	2
	Cyst + haemorrhage (n=10)	-	-	1	2	7	4	5	1
		2	12	11	10	14	39	5	5

C= category, n = number

Table-1: Correlation of FNAC with the results of Tc-99m MIBI scintigraphy and Ultrasonography in patients of solitary “cold” thyroid nodule on Tc-99m Per technetate study (n=49)

differentiating benign from malignant thyroid nodules. Ultrasonography (US) is one of the frequently performed imaging procedures in such cases. The echo structure types that can be seen on an ultrasound image are solid, cystic and mixed. Simple cystic lesions which are 10-20% of all nodules are less likely to be cancerous (7). Most of the neoplastic lesions are solid in nature. But such ultrasound findings are less reliable (8,9).

Tc-99m labeled hexakis(2-methoxyisobutyl isonitrile) (Tc-99m MIBI), a myocardial perfusion-imaging agent, has been in use for tumour imaging. It has also been employed in evaluating thyroid nodules. However there appears to be some controversies and disagreements among various authors as to the actual role of MIBI scan in the evaluation of thyroid nodules (10,11).

The aim of the current study was to assess the value of Tc-99m MIBI scintigraphy in differentiating neoplastic from non-neoplastic lesions in solitary thyroid nodules showing 'cold' lesions on Tc-99m per technetate scan.

Materials & Methods

Before the start of the study appropriate Ethics committee approval was obtained from the institutional ethics committee of the PIEAS. Informed consents were obtained from all patients before including them in the study.

The study was conducted on forty-nine euthyroid patients with hypo-functioning (“cold”) solitary lesion on Tc-99m per technetate scans. All patients were subjected to FNAC, US and Tc-99m MIBI scintigraphy. Pregnant women, breast-feeding mothers and patients who did not sign the consent were not included in the study. Mean \pm SD of age of patients was 33 ± 1 years with male to female ratio of 1:5. Twenty-five patients had nodules in the right lobe, 22 in the left lobe while two in the isthmus.

FNAC tests were performed in the Pathology Department of King Edward Medical College. A disposable 23-gauge needle attached to a 10-ml plastic syringe was used. Where FNAC results were non-diagnostic due to insufficient number of thyroid cells, the tests were repeated until

satisfactory results were obtained (12). Ultrasonography was performed using a Toshiba 38-B US equipment with a linear probe of 7.5 MHz. The results of US examinations were categorized into three groups; namely solid, cystic and mixed lesions. The Tc-99m MIBI images of anterior neck were acquired using a Siemens E-CAM gamma camera attached with a low energy parallel-hole collimator following an intravenous injection of 5-10 mCi of Tc-99m MIBI. MIBI kits were obtained from PINSTECH (Pakistan Institute of Nuclear Science & Technology, Islamabad) and labeled with freshly eluted Tc-99m per technetate as per procedure described by the manufacturer. Quality control procedures were performed before injecting the radiolabeled pharmaceutical into the patient. The scintigraphic findings were classified into the following Categories: Category-1 showing intense uptake of Tc-99m MIBI in the nodule; Category-2 showing slightly higher uptake in the nodule than the surrounding normal thyroid tissue; Category - 3 with nodular uptake equal to the surrounding normal thyroid; Category -4 showing less uptake in the nodule compared to the surrounding normal tissue and Category -5 showing no or negligible uptake of Tc-99m MIBI in the nodule.

Receiver operating characteristic (ROC) curve was generated to assess the performance of Tc-99m MIBI scan in differentiating neoplastic and non-neoplastic lesions. Sensitivities, specificities, positive predictive values (PPV) and negative predictive values (NPV) of Tc-99m MIBI scan and US were determined.

Results

The results of FNAC of solitary “cold” thyroid nodules in 10 out of 49 (20.4%) patients revealed to have neoplastic lesions (Table-1). Figure 1 shows examples of various scintigraphic patterns seen on Tc-99m MIBI studies.

ROC curve (Figure 2) was generated to assess the performance of Tc-99m MIBI scanning after taking following into consideration:

- Category 1 as test positive (1 true positive and 1 false

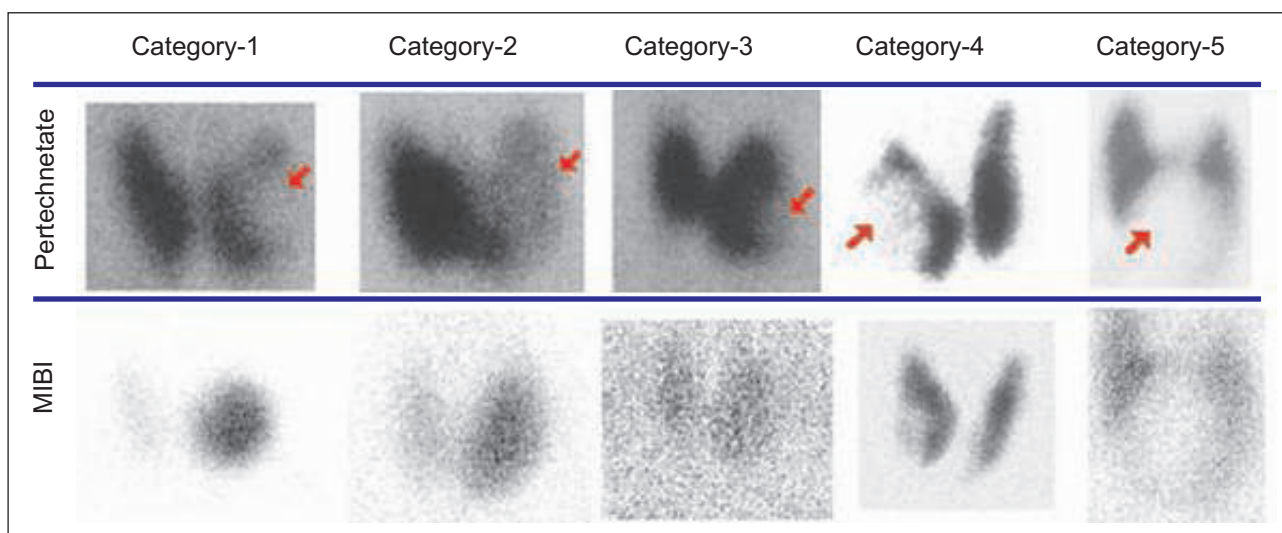


Figure 1. Pattern of Tc-99m MIBI uptake in the solitary cold thyroid nodules (Lower row). Corresponding Tc-99m Per technetate scans are seen above each MIBI scan (Upper row). Based on the pattern of MIBI uptake the scans are categorized into five categories, Category-1,2,3,4 and 5 from left to right (Bottom row).

- positive)
- Categories 1 and 2 as test positive (10 true positive and 4 false positive)
- Categories 1, 2 and 3 as test positive (10 true positive and 15 false positive)
- Categories 1, 2, 3 and 4 as test positive (10 true positive and 25 false positive)
- All Categories as test positive (10 true positive and 39 false positive)

The sensitivity of the test reached 100% when patients in group-1 and 2 were considered as test positive (i.e. all 10 disease positive cases were in these groups) with specificity of 90%. The positive and negative predictive values were estimated to be 71% and 100% respectively.

On the other hand the results of ultrasound examination revealed solid lesions in 39 (80%), cystic lesions in 5 (10%) and mixed solid/cystic lesions in 5 (10%) patients. All the disease positive (neoplastic) cases were either solid (80%) or mixed in echogenicity (20%). The sensitivity of US was 100% while the specificity was only 13% when solid and mixed lesions were considered as test positive. The positive and negative predictive values of US were 23% and 100% respectively.

Discussion

Nearly all thyroid neoplasms present as cold lesions on Tc-99m per technetate scans. But it may be noted that all cold nodules are not always malignant. Several benign conditions like colloid goiter and cysts, etc may also present as cold nodules on Tc-99m per technetate thyroid scans. There are controversies with regard to the most appropriate approach towards investigating such cold nodules in order to arrive at a final diagnosis and subsequent management. One of the most common approaches is to perform a thyroid

ultrasound examination and further characterize these nodules, into solid, cystic or mixed types(13,14). Simple cystic patterns on US would virtually exclude malignancy. Regardless of presentation, thyroid cancer is seen only in about 10% of cases, which are cold on Tc-99m Per technetate scan and showing solid or mixed pattern on ultrasound. This shows that a large number of patients with non-neoplastic lesions are unnecessarily subjected to FNAC. In this regard Tc-99m MIBI scan could be of value in further screening of patients before subjecting them to FNAC.

Tc-99m MIBI is primarily a myocardial-imaging agent. The mechanism of its uptake by a neoplastic lesion has not been well understood. However it is believed that its cellular uptake is due to its lipophilic nature and charge on its molecule. Within the cell its positively charged molecule is attracted towards the negatively charged mitochondria (15). Its utility in carcinoma breast has been well established and a few other studies have demonstrated its role in brain, bone, soft tissue and thyroid cancers. In the current study we have assessed its usefulness in evaluating thyroid nodules and detecting thyroid cancers.

Many previous studies have used complex methodologies like radionuclide thyroid angiography (RTA) and retention index (RI), using early and delayed images while performing and interpreting Tc-99m MIBI scans in patients with solitary cold nodules on Tc-99m Per technetate scans. Demirel et al (10) have reported sensitivity, specificity and accuracy of 89, 100 and 97% for RTA in the diagnosis of neoplasm in thyroid nodules. Erdil et al (11) have reported sensitivity, specificity and accuracy of 95, 89 and 92.5% for RI in the diagnosis of malignancy.

In the current study the findings of a single 15 minute image of Tc-99m MIBI scan were categorized on the scale of 1 to 5 according to its decreasing intensity of uptake in the

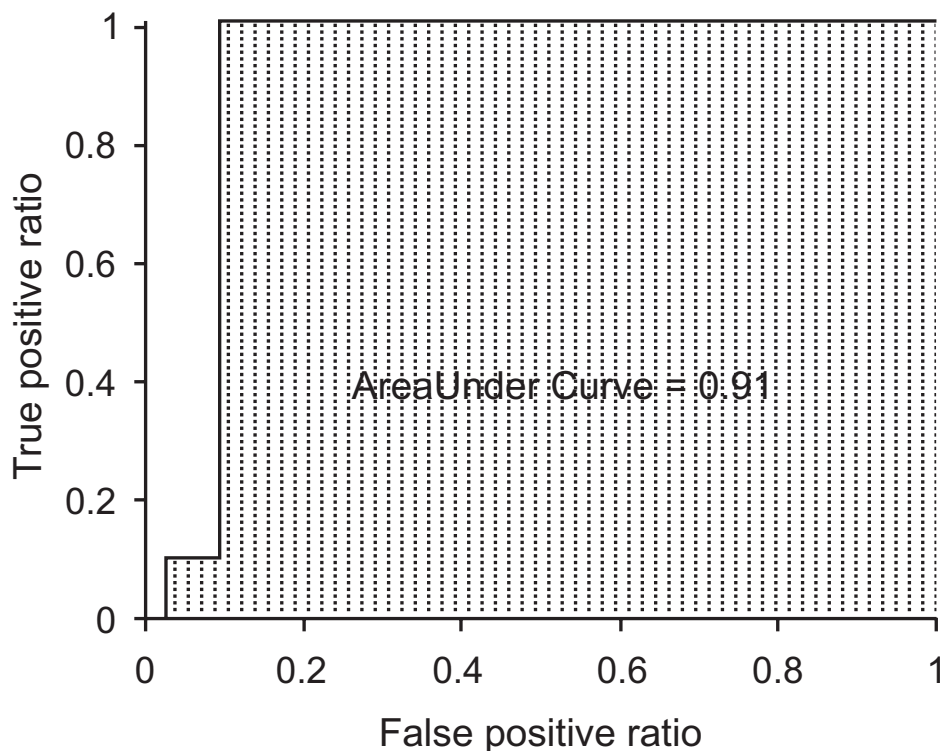


Figure 2: Receiver Operating Characteristic (ROC) Curve of Tc-99m MIBI scan for solitary cold thyroid nodules. True positive ratio = sensitivity, false positive ratio = 1-specificity

nodules previously found to be hypo-functioning (“cold”) on Tc-99m pertechnetate study. Table 1 shows that all the nodules, which showed neoplastic lesions on FNAC, belonged to Categories 1 and 2 (100% sensitivity). This has also been demonstrated by ROC curve (Figure 2). None of the FNAC proven neoplastic lesion revealed less uptake in the nodule than the surrounding normal thyroid tissue. This suggests that the negative predictive value of this test is 100%. However four of the non-neoplastic lesions showed false positive results. Therefore if MIBI scans were done before FNAC and Category 1 and Category 2 considered as MIBI positive, 71% of the patients could have been excluded from FNAC list without any false negative case. Demirel et al also evaluated similar single image method and reported sensitivity, specificity, PPV and NPV of 89%, 76%, 50% and 96% respectively for Tc-99m MIBI imaging of solitary thyroid nodule.

On the other hand ultrasound criteria of solid or mixed lesion undergoing FNAC could have excluded only 5 (10%) cases, which were cystic in consistency. None of these 5 cases showed MIBI uptake higher than the surrounding tissue.

Keeping in view the above results, the investigative algorithm in a case of solitary thyroid nodule may be modified as shown in figure 3. The patients presenting with solitary nodules palpable clinically should first undergo a Tc-99m pertechnetate scan, which would functionally characterize the nodule as hypo-, hyper- or iso-functioning. It would also exhibit underlying multi-nodular disease. An ultrasound examination of the cold nodules would further characterize the nodule as solid or cystic. The cystic

nodules are less likely to be malignant (8). The solid nodules appearing as “hot” on the TC-99m MIBI scan are most likely to be malignant. These should then be subjected to FNAC and/or biopsy. A decision as to subjecting the patients with thyroid nodular uptake of MIBI equal or less than the normal surrounding tissue should be based on clinical data and ultrasonographic results.

Conclusion

Scintigraphy with Tc-99m MIBI is a reliable and accurate method to evaluate solitary cold thyroid nodule for its neoplastic nature. It has 100% sensitivity and 90% specificity and can be easily incorporated into the investigative algorithm of clinically palpable solitary thyroid nodules. Ultrasound is non-specific; it does not offer any significant and/or specific advantage over the radionuclide procedures.

Acknowledgement

We would like to thank Dr. I.A. Naveed, Head of Pathology Department of King Edward Medical College for his valuable technical support. This work was also supported by Dr. Mansoor of Centre for Nuclear Medicine, Mayo Hospital Lahore and Dr. Tariq Majeed of Pakistan Institute of Engineering and Applied Sciences, Islamabad.

References

1. Falk SA. Thyroid disease. 2nd ed. Philadelphia, PA;

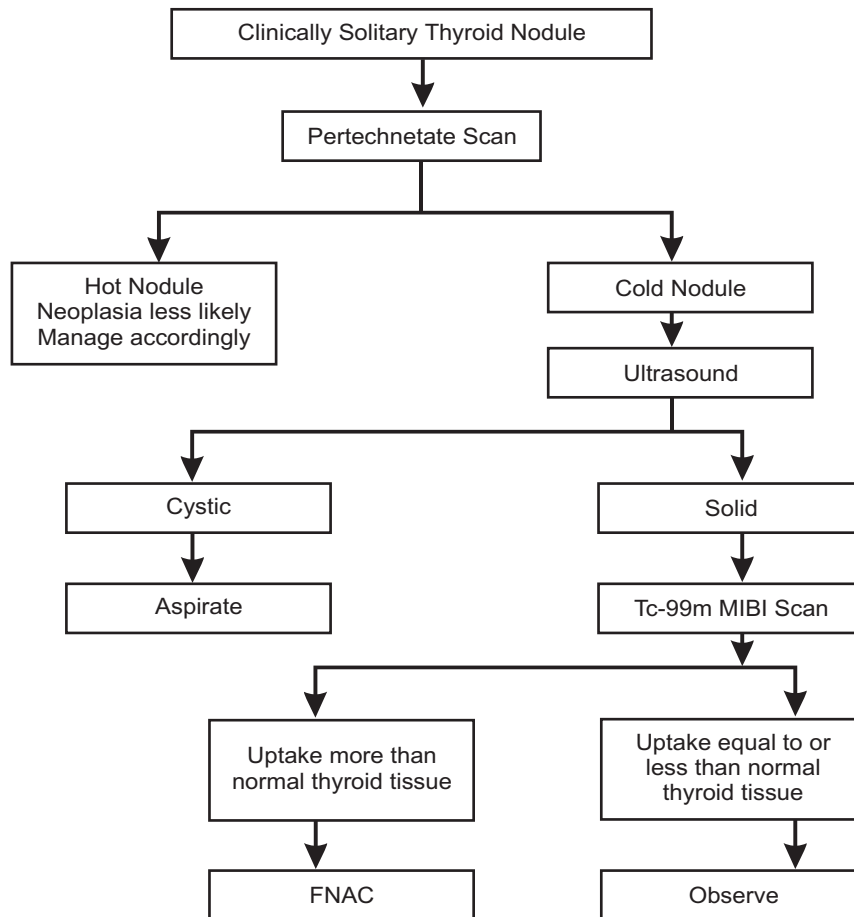


Figure 3: Suggested diagnostic algorithm for the management of solitary thyroid nodule

- Lippincott-Raven; 1997.
- Belfiore A, Rosa GL. Fine-needle aspiration biopsy of the thyroid. *Endocrin Metab Clin* 2001; 30:361-398.
 - Gharib H. Fine-needle aspiration biopsy of thyroid nodules: advantages, limitations, and effect. *Mayo Clin Proc* 1994; 69:44-49.
 - Kim N, Lavertu P. Evaluation of a thyroid nodule. *Otolaryng Clin N Am* 2003; 36(1):17-33.
 - Cases JA, Surks MI. The changing role of scintigraphy in the evaluation of thyroid nodules. *Semin Nucl Med* 2000; 30:81-87.
 - Castro MR, Gharib H. Thyroid fine-needle aspiration biopsy: progress, practice, and pitfalls. *Endocr Pract* 2003; 9:128-136.
 - Kurtz AB, Middleton WT. *Ultrasound: the requisites*. Missouri, Mosby, 1995.
 - Iannuccilli Jason D, Cronan JJ, Monchik JM. Risk for malignancy of thyroid nodules as assessed by sonographic criteria: the need for biopsy. *J Ultrasound Med* 2004; 23:1455-1464.
 - Wienke JR, Chong WK, Fielding JR, Zou KH, Mittelstaedt CA. Sonographic features of benign thyroid nodules: inter-observer reliability and overlap with malignancy. *J Ultrasound Med* 2003; 22:1027-1031.
 - Demirel K, Kapucu Ö, Yücel C, Özdemir H, Ayvaz G, Taneri F. A comparison of radionuclide thyroid angiography, Tc-99m MIBI scintigraphy and Power Doppler ultrasonography in the differential diagnosis of solitary cold thyroid nodules. *Eur J Nucl Med & Mol Imaging* 2003;30:642-649.
 - Erdil TY, Özker K, Kabasakal L, et al. Correlation of Technetium-99m MIBI and Thallium-201 retention in solitary cold thyroid nodules with postoperative histopathology. *Eur J Nucl Med* 2000;27:713-720
 - Alexander EK, Heering JP, Benson CB, Frates MC, Doubilet PM, Cibas ES et al. Assessment of nondiagnostic ultrasound-guided fine needle aspirations of thyroid nodules. *J Clin Endocr Metab*: 2002;87:4924-4927.
 - Pacini F, Burrioni L, Ciulli C, Cairano GD, Guarino E. Management of thyroid nodules: a clinicopathological, evidence based approach. *Eur J Nucl Med & Mol Imag* 2004;31:1443-1449.
 - Maisey MN. Thyroid. In: Maisey MN, Britton KE, Collier BD, Siraj QH, eds. *Clinical Nuclear Medicine*. London, UK: Chapman & Hall; 1998:331-356.
 - Ziessman HA, O'Malley JP, Thrall JH. *Nuclear Medicine: The Requisites*. 3rd ed. Philadelphia, PA: Mosby, 2006.