ORIGINAL ARTICLE

The role of ^{99m}Tc-sestamibi scintigraphy in the differential diagnosis of thyroid cold nodule

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ABSTRACT

Background: The evaluation of a thyroid nodule involves fine-needle aspiration cytology, ultrasound scans and nuclear scintigraphy and the main objective being excluding thyroid malignancy. The prevalence of malignancy is high in non-functioning thyroid nodules.

Objective: The objective of our study was to find utility of ^{99m}Tc-sestamibi (MIBI) scans in the evaluation of cold thyroid nodules.

Patient and Method: We studied 30 euthyroid patients with cold nodule as evidenced in ^{99m}Tc-Pertechnetate radionuclide scans.

Results: The mean age of our study patients were 41.9±10.8. Adenoma was seen in 7 patients, carcinoma in 6 patients and colloid nodule in 17 patients. In MIBI scanning, 33% of the nodules were cold and 67% of the nodules were warm/hot. 100% of our benign and malignant nodules were warm/hot in MIBI images compared to 41% of our colloid nodule ($P < 0.05$). Significant retention of MIBI in late images was seen in 67% of our malignant nodule, 57% of our benign neoplastic nodule and only in 18% of colloid nodules. Retention of MIBI in delayed images was useful in the differentiation of colloid nodule from the neoplastic nodule (Both malignant and benign) ($P < 0.05$), but could not significantly differentiate malignant and benign neoplasia.

Conclusion: Our study has shown that a noninvasive investigation like MIBI scanning is a useful method in the differential diagnosis of cold thyroid nodules. Nodules, which are cold on both 99mTc-Pertechnetate and MIBI scan, can indicate the possible presence of a colloid nodule rather than neoplasia and this could avoid unnecessary thyroidectomy. [IJEM 2007;11(1&2):23-26]

Key words: Thyroid nodule, fine needle aspiration cytology, MIBI scintigraphy, thyroid malignancy

INTRODUCTION

The prevalence of thyroid nodules varies between 4% by palpation(1) and between 19% to 35%(2,3) by ultrasonography. In autopsy series, up to 50% of clinically normal thyroid glands contain nodules(4). The main objective in evaluation of a euthyroid thyroid nodule is to exclude malignancy. Fine-needle aspiration cytology (FNAC), ultrasound scan and nuclear scintigraphy have been used in the evaluation of thyroid nodules: however, deciding between surgery or conservative treatment is difficult in certain situations. FNAB has become the primary diagnostic tool and the success of a biopsy depends on the adequacy of the specimen together with the skill of the cytopathologist. Two particular cytologic readings that frustrate both cytopathologists and surgeons are follicular neoplasm and cells that show atypia. Sahin *et al* showed that the prevalence of malignancy in patients with cytology showing follicular neoplasm and atypical cells was 15% and 51.7% respectively(6). Apart from this, 15% of FNAC yield a non diagnostic report. Some nodules, particularly those that are cystic, continue to yield no diagnostic cytology results despite repeated biopsies, and may be malignant at the time of surgery(7, 8). Ultrasound scan and nuclear scintigraphy studies could be helpful in deciding the malignant potential in such situation.

Radionuclide scanning is usually reserved for those

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patients with indeterminate cytology or thyrotoxicosis. The thyroid scan can be performed with Iodine-123, Iodine-131, or 99mTc-Pertechnetate. A similar uptake in both lobes of the thyroid gland is considered normal scan(9). About 5 to 15 percent of thyroid cold nodules are malignant(10). Radionuclide scans that use 99mTc-Pertechnetate or I-123 currently lack the specificity to assess the malignant potential of nodular lesions of the thyroid gland. However, seeing a cold nodule in 99mTc-Pertechnetate scan and indeterminate cytology would usually necessitate surgical excision of the nodule. These nodules need not always be malignant and they could be colloid nodule or even, benign neoplasm. We need to find out other modalities, which would help us, further in deciding the need for surgical excision in such situations.

During the last decade, 99mTc-sestamibi (MIBI), a lipophilic cationic molecule, was introduced as a myocardial perfusion and viability-imaging agent. MIBI has been reported to accumulate in benign and malignant lesions, such as lung, brain, parathyroid tumors and bone lesions. Recently, a positive MIBI scan has been reported in different thyroid tumors. Although exact mechanism of increased technetium MIBI uptake in tumor cells is not understood, it has been suggested that it may be related to factors such as passive diffusion, plasma membrane electrical potential, mitochondrial index and its lipophilicity(11). Since malignant thyroid cells have increased mitochondrial activity, MIBI uptake and retention could be used to determine the neoplastic potential. We hypothesize that MIBI gets concentrated in tissues with neoplastic potential and retention of MIBI is seen in malignant nodules. Thus uptake of MIBI in cold nodule can be used to differentiate neoplastic nodules from colloid nodules and retention of MIBI in delayed images could further be helpful in differentiation of benign from malignant neoplasia. The objective of our study was to find utility of MIBI scans in the evaluation of cold thyroid nodules.

METHODS

The study was a prospective study. A total of 30 patients were enrolled in the study. Patients were included in the study if they clinically had either solitary or multiple thyroid nodules and had single cold nodule as evidenced in 99mTc-Pertechnetate radionuclide scans. They were excluded from the study it they had hypo or hyperthyroidism, pregnancy, and if they had multiple cold nodules in 99mTc-Pertechnetate radionuclide scans. All patients gave informed consent to participate in the study.

Study patients underwent a detailed clinical examination and thyroid nodule was confirmed by ultrasound scan if required. Free T4 and TSH were done in every patient to assess the thyroid function. These patients were subjected to 99mTc-Pertechnetate scan and if a cold nodule was detected, they were enrolled in the study. They were further subjected to MIBI scanning and FNAB of thyroid cold nodule (Fig. 1). A wash out period of 48 hours was given in between 99mTc-Pertechnetate and MIBI scanning.

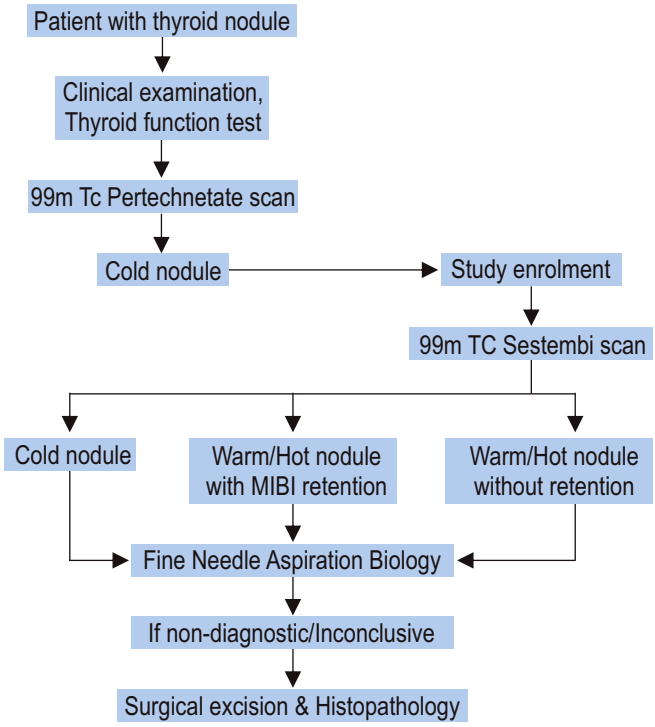

Fig. 1: Flow chart of our study protocol

99mTc-Pertechnetate radionuclide scan was performed with 4 mCi of $99mTc0_4$ (Technetium Pertechnetate) which was injected intravenously and dynamic and static anterior images of thyroid were obtained using a high resolution collimator on a variable angle, dual head Gamma Camera. Thyroid MIBI scan was performed after injecting 5 mCi 99mTc-sestamibi intravenously and initial and delayed images of neck were acquired using dual head Gamma Camera. Based on MIBI uptakes in early image and retention in late images the nodule was further characterized in to cold nodule (Fig. 2), warm/hot nodule with complete washout or significant retention of the tracer (Fig. 3).

FNAB was done in all cold nodules as defined by 99mTc-Pertechnetate after MIBI scan to define the cytopathology of the nodule. FNAB was done after the

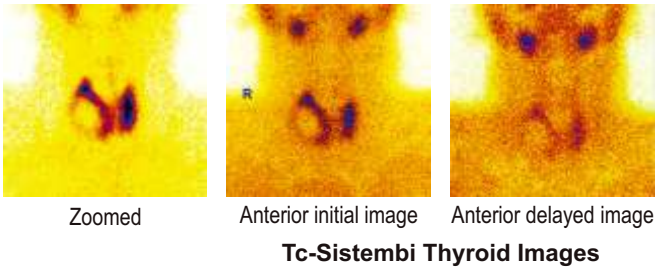

Fig. 2: Cold nodule in ^{99m}Tc-pertechnetate Scan, which shows no uptake in early MIBI images and no retention in delayed images.

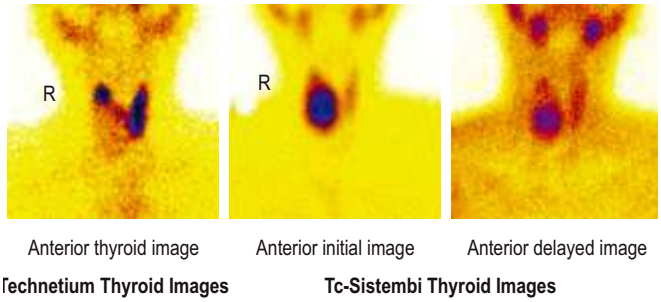

Fig. 3: Cold nodule in ^{99m}Tc-pertechnetate Scan, which shows significant uptake in early MIBI images with retention in delayed images.

nuclear scans in order to avoid artifacts or false reports due to needle track injury. If FNAB was suggestive of malignancy or was inconclusive, surgical excision of the thyroid nodule was done for further confirmation and histopathology report was taken for the pathological diagnosis of the nodule. Pathological reports were categorized in to neoplastic nodule and colloid nodule. Neoplastic nodules were further classified in to benign (Adenoma) and malignant (carcinoma) neoplasm.

Statistical Package Software System 11.0 for Windows (SPSS) was used for statistical analysis. Numerical variables were reported in terms of mean and standard deviation. Categorical variables were reported in terms of number and percentage. Differences were considered statistically significant if p value is less than 0.05 ($p < 0.05$).

RESULTS

A total of 30 patients were recruited in the study. The mean age of our study patients were 41.9±10.8 and there was 9 males and 21 females. Pathological diagnoses in our patients were adenoma in 7 patients (23%), carcinoma [Both follicular and papillary thyroid carcinoma (PTC)] in 6 patients (20%) and colloid nodule in 17 patients (57%). PTC comprised 83% of our malignant tumor. There was no correlation between the size and duration of the nodule with the malignant potential of the tumor in our series.

All patients had cold nodule in static images on pertechnetate scan. As per the dynamic images on pertechnetate scan, vascularity was increased only in 29% of colloid nodules compared to 83% in malignant nodules and 71% in benign neoplastic nodules ($p < 0.05$). There was no statistical difference in the proportion of increased vascularity, when compared between the malignant and benign nodules. The sensitivity, specificity and positive predictive value (PPV) of increase in vascularity in determining the neoplastic potential of a nodule (Both malignant and benign) being 0.77, 0.71 and 0.67 respectively.

The MIBI characteristics of our patient are shown in Table-1. In MIBI scanning, 33% of the nodules were cold, 30% of the nodules were warm/hot with significant washout in late images and 37% of the nodules were warm/hot with significant retention in late images (Figure - 4). 100% of our benign and malignant nodules were warm/hot in MIBI images compared to 41% of our colloid nodule ($p < 0.05$). The sensitivity, specificity and PPV of warm/hot nodule in MIBI scan in differentiating neoplastic nodule (Both benign and malignant) from colloid nodule were 1.0, 0.59 and 0.65 respectively.

Table 1: MIBI characteristics of our patients

	Malignant Nodule (n=6)	Benign nodule (n=7)	Colloid nodule (n=17)
Cold Nodule	0	0	10
Warm/Hot nodule	6	7	7
Retention (Delayed images)	4	4	3
No retention (Delayed images)	2	3	4

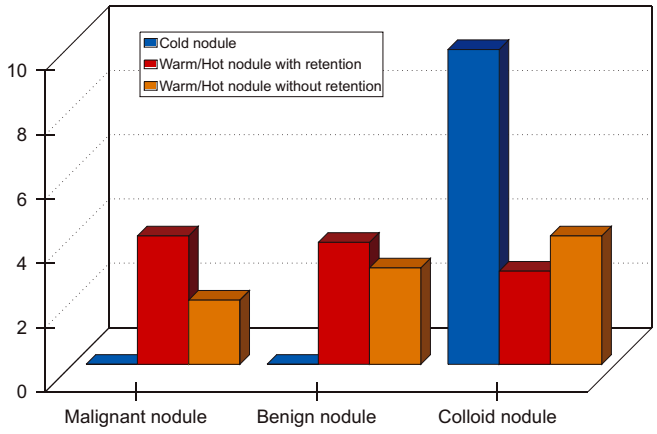

Fig. 4: Bar diagram showing uptake of MIBI in various nodule types

Retention of MIBI in delayed images was seen in 37% of our study population (i.e., 55% of those warm/hot nodules showed retention of MIBI in delayed images). Significant retention of MIBI in late images was seen in 67% of our malignant nodule, 57% of our benign neoplastic nodule and only in 18% of colloid nodules ($p < 0.05$). When retention of the MIBI in delayed images was considered the specificity in differentiating the neoplastic nodule from colloid nodule increased to 0.77. Thus retention of MIBI in delayed images could differentiate colloid nodule from the neoplastic nodule (Both malignant and benign) but could not differentiate malignant and benign neoplasia. The sensitivity and specificity of MIBI uptake in differentiation of carcinoma from benign neoplasm was 0.67 and 0.43 respectively.

DISCUSSION

FNAB has become the cornerstone in the diagnostic evaluation of solitary thyroid nodules, cysts, and dominant

nodules within multinodular goiters, since in most cases it allows one to define the precise histology in a simple and non-invasive fashion with accuracy ranging between 69% and 93%. 99mTc-Pertechnetate has been less frequently used in the initial routine evaluation but can be useful in nondiagnostic biopsies as malignant nodules show reduced concentrations of radioisotope, whereas hyperfunctional nodules are rarely malignant. 99mTc-Pertechnetate scan lacks specificity and intense MIBI uptake increases the probability of thyroid cancer, whereas reduced uptake drastically decreases the probability of malignancy(12). After a cold nodule had been detected using 99mTc-Pertechnetate, a second scan with high MIBI uptake increases the probability of the nodule to be a differentiated cancer by 7.8 times(13). Our study showed that MIBI scan, with warm/hot nodule and retention in delayed images was 100% sensitive and 77% specific in differentiating neoplastic nodule from colloid nodule, but it was only 43% specific in differentiation of carcinoma from benign neoplasia.

Alonso *et al* showed that MIBI scanning of the thyroid gland was helpful in evaluating the malignant probability of cold solitary thyroid nodules, preoperatively(14). A study by Sundaram FX and Mack P(15) showed that the overall sensitivity and specificity of the warm nodule on MIBI scan was 79% and the 80%, with a positive predictive value of 55%. Positive retention apart from increased uptake in the early and delayed MIBI images had a sensitivity, specificity and accuracy of 67%, 91% and 86% in differentiation of malignant from benign thyroid nodules(16). MIBI scan has also been studied in hurthle cell tumors and Bio *et al* showed that although an MIBI-negative scan strongly supported the absence of true hurthle cell tumor, this scan was not sufficiently specific to differentiate true hurthle cells neoplasias from other thyroid lesions showing hurthle cells at FNAB(17).

The limitation of our study is the small sample size and only FNAB was done in assessing the pathology of the nodules, except for a few cases. We considered it would be unethical subjecting every patient to thyroidectomy / surgical excision of the nodule and hence surgical excision was done only when FNAB was inconclusive or was suggestive of malignancy.

A systematic approach to the evaluation thyroid nodules is important to avoid unnecessary surgery, because only malignant or large symptomatic nodules require surgery. Our study has shown that a noninvasive investigation like MIBI scanning is a useful method in the differential diagnosis of cold thyroid nodules. High MIBI uptake with significant retention increases the probability of thyroid neoplasia even though it could not adequately differentiate benign from malignant nodule. Nodules, which are cold on both 99mTc-Pertechnetate and MIBI scan, can indicate the possible presence of a colloid nodule. Thus MIBI scanning should be strongly considered in certain special situations where an individual has either cold thyroid nodule or inconclusive FNAB and this would avoid unnecessary thyroid surgeries.

CONCLUSION

The results of our study suggest that, in situations where a thyroid nodule has an indeterminate cytology and a cold nodule on pertechnetate scanning, a MIBI scan may help in the differentiation of a neoplastic nodule from a colloid nodule, and in the case of latter situation, unnecessary thyroidectomy may not be warranted. However, the results of the study need confirmation by larger studies.

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