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CLINICAL STUDY

Preoperative detection of parathyroid adenomas with Tc-99m MIBI and Tc-99m pertechnetate scintigraphy: histopathological and biochemical correlation with Tc-99m MIBI uptake

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Abstract: *Aim:* The objective of this study was to compare the dual phase MIBI scinitgraphy with MIBI and Tc-99m pertechnetate (MIBI + Tc-99m) study in defining the parathyroid adenomas, and to evaluate the effect of histologic and biochemical characteristics on the imaging of parathyroid adenomas with Tc-99m methoxyisobutyl-isonitrile (MIBI) scintigraphy.
Methods: Thirty-six patients with parathyroid adenomas were studied prospectively. All patients were evaluated with both MIBI and (MIBI + Tc-99m) study. MIBI uptake of adenomas correlated with oxyphill, chief cell and tumour weight of the surgically excised glands. MIBI uptake was also compared with serum calcium (Ca), phosphorus (P) and intact parathormone (iPTH) levels.
Results: A total of 38 parathyroid adenomas were surgically excised from 36 patients. MIBI + Tc-99m identified 35 of the parathyroid lesions (92 %). Whereas, MIBI study detected 30 of the 38 parathyroid adenomas (79 % sensitivity) (p=0.0001). There were no false positives. Adenoma weight showed significiant correlation with MIBI uptake (p=0.001). Oxyphyill cell content also showed high correlation with MIBI uptake. Delayed images showed better correlation than the early views (Early MIBI p=0.033; Delayed MIBI; p=0.001).
Conclusion: MIBI + Tc-99m pertechnetate interpretation is more sensitive than only dual MIBI imaging for the detection of parathyroid adenoma. Oxyphill cell content and weight of the lesions proved to be important determinants of 99mTc-MIBI accumulation in parathyroid adenoma. We found no significant correlation between MIBI accumulation, Ca, P and iPTH serum levels *(Tab. 2, Fig. 2, Ref. 15).* Full Text (Free, PDF) *www.bmj.sk.*
Key words: Tc-99m MIBI, Tc-99m pertechnetate, parathyroid adenoma, oxyphill cell, parathyroid hormone.

Primary hyperparathyroidism (PHP) is characterized by the hypersecretion of parathyroid hormone by adenomatous or hyperplastic glands. Definitive treatment involves surgical exploration and extirpatation of the abnormal glands. In the hands of an experienced surgeon, the success rate of the first operation is 90 % to 95 % (1). Despite the high success rate of a bilateral neck dissection, most surgeons prefer to use noninvasive localization studies before the primary parathyroidectomy. Preoperative localization may reduce the duration of surgery, decrease complication rates, and reduce the incidence of persistent or recurrent PHP (2). Dual-phase Tc-99m MIBI scans are commonly used in many institutions as well as in ours for the preoperative localization of parathyroid adenomas. Hyperactive parathyroid cells have high concentrations of MIBI and accumulate more MIBI. Parathyroid adenomas usually show slower washout compared to normal thyroid glands (3). Preoperative dual-phase Tc-99m sestamibi scintigraphy detects solitary parathyroid tumors accurately, with detection rates ranging from 90 % to 100 % (4). Dual phase MIBI scintigraphy combined with thyroid substraction procedures using I-123 or Tc-99m pertechnetate scintigraphy may increase a study sensitivity (5).

The major factor influencing scintigraphic localization of parathyroid glands is their size (6). On the other hand, biochemical parameters (plasma calcium, intact parathyroid hormone levels), cellular charasteristics such as oxyphill cell content, p-glycoprotein expression have been reported to affect MIBI uptake (7).

Although it has been reported that the late retention of MIBI in dual-phase study could be related to parathytroid oxyphill cell content, some studies did not find a correlation between the MIBI uptake and the percentage of oxyphill cells (8, 9).

In this study, we compared the dual phase MIBI scintigraphy with MIBI +Tc-99m pertechnetate study. We also aimed to evaluate the role of biochemical parameters (Ca, P and iPTH plasma levels) and adenoma charecteristics (weight, oxyphill, chief cell contents) with MIBI imaging.

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Material and methods

Patients

This prospective study was performed at Gazi University Hospital between December 2003 and September 2005. The study group consisted of 36 consecutive patients with biochemical evidence of primary hyperparathyroidism who underwent the preoperative localization with MIBI parathyroid scintigraphy and subsequent parathyroid surgery. Hyperparathyroidism was preoperatively documented by the increased Ca and iPTH plasma levels and the diagnosis was confirmed by surgical resection and histopathology. The mean age of the patients was 53.20±14.77 (age range 18–87). Four of the 36 patients were male.

Scintigraphy

Parathyroid imaging was performed after the intravenous administratation of 15 mCi (555 MBq) Tc-99m MIBI. Anterior planar images of the neck were obtained 15 minutes (early) and 2 hours (delayed) after the injection using a pinhole collimator. Pinhole images were acquired on a 256 x 256 matrix for 600 seconds/view. An anterior planar image of the neck and anterior chest to the level of the diaphragma was also obtained using a high-resolution parallel-hole collimator (256 x 256, 600 seconds/ /view) attached to the same gamma camera (General Electric 2000AC gamma camera interfaced to a Starcam 4000 computer, Milwaukee, WI). Oblique images were obtained for the optimal visualization of posterior parathyroid glands. In all patients, a 15-minute Tc-99m pertechnetate (5 mCi [185 MBq]) image was also obtained.

Interpretation

All data were interpreted by the physician experienced in nuclear medicine blinded to the operative results, histopathological findings and laboratory data. Initially, early and delayed MIBI images were evaluated without Tc-99m pertechnetate scintigraphy. Two weeks later, the same MIBI images were analyzed together with Tc-99m pertechnetate scans (MIBI+Tc-99m). When only MIBI images were evaluated, foci of activity were considered positive if they were increased relative to thyroid tissue on either early or delayed images, or both. In the MIBI + Tc-99m evaluation, foci of increased activity defined on MIBI images in excess of that seen on Tc-99m pertechnetate images were considered positive for parathyroid lesion. The abnormal parathyroid glands were localized to one of four quadrants in relation to the thyroid gland. After interpreting the images, the observer was informed about the surgical and pathological results. Then the data were interpreted semi-quantitatively. A 20 pixel circular region of interest was generated over the area of the parathyroid. The parathyroid to thyroid count was determined using the average counts of the parathyroid lesions and contralateral normal thyroid glands. This analysis was made for both early and delayed images, thus early and delayed MIBI uptakes were obtained. These data were compared to the results of histopathological studies.

Surgery

All of the patients had a surgical intervention after the Tc-99m MIBI scanning and underwent a bilateral neck exploration. All patients were operated on by or under the supervision of the same surgeon. The sites of abnormal glands were localized to four quadrants in relation to the thyroid gland.

Histopathologic analysis

The surgical sample and all slides were evaluated by the experienced pathologist blinded to the results of the imaging study. All of the lesions were diagnosed as parathyroid adenoma. The image analysis was performed in hematoxyline-eosin stained sections from formalin fixed parafin embedded tissues. Cellular densities were calculated with the cell density software of the SAMBA image analyzer (Grenoble, France). The image analyzer was composed of a microscope (Olympus, Japan) attached to a PC. A 400x magnification was used and the number of oxyphill and chief cells was counted in five randomly selected areas and results expressed as the cell counts in 1 sq.mm.

Statistical analysis

Analyses were based on correlations with intraoperative findings, the site in relation to the thyroid gland, and the findings of histopathologic analysis. Statistical analysis was performed to determine if there was a correlation between the number of oxyphill, chief cells, biochemical parameters (Ca, P, iPTH serum levels) and MIBI uptake. Pearson correlation analysis was obtained. Chi-square test was used to compare the sensitivity of two imaging protocols. The results were considered statistically significant when the *P* value was below 0.05.

Tab. 1. Patient characteristics.

	Mean±SD	Range (min-max)
Age	53.19±13.68	18–87
Sex (F/M)	32/4 (n=36)	
Oxyphill cell	63.61±97.72	0–400
Chief cell	351.47±164.65	24–671
Ca (mmol/L)	2.85±0.23	2.45–3.72
P (mmol/L)	0.76±0.16	0.35–1.13
iPTH (pg/ml)	309.92±275.34	102–1239
Adenoma (gr)	**1.64±2.64**	0.18–14

Results

Thirty-six patients with primary hyperparathyroidism were evaluated in this study. Patients' characteristics are shown in the Table 1. All of the patients underwent surgery and totally 40 parathyroid adenomas were resected. In 36 patients, single parathyroid adenoma was detected and in each of the two other patients, two synchronous adenomas were observed. All patients had normal Ca, and iPTH plasma levels after surgery. The mean follow up was 3.6 years. Follow-up examinations were made at the end of the 1, 6, 12, and 24 months after surgery. After the second year, patients were contacted by phone and asked whether they had any problems.

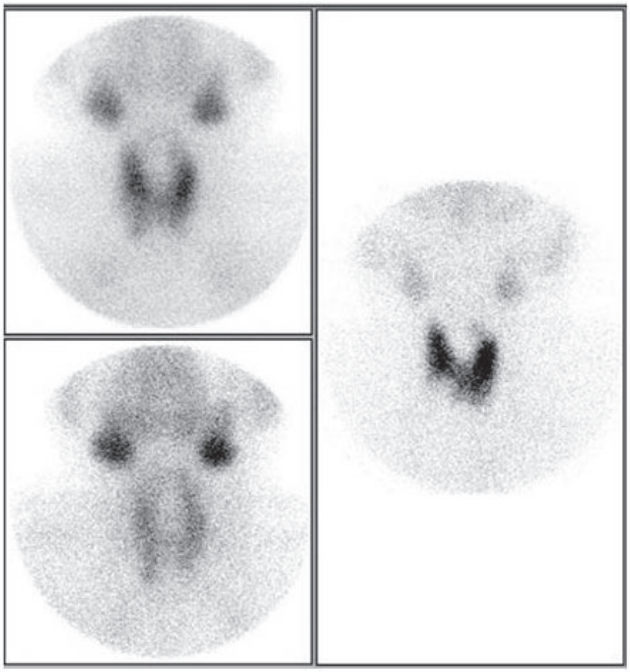

Fig. 1. Early (upper left) and delayed (lower left) MIBI images show a nonhomogenous uptake in the thyroid gland without focal activity accumulation. Tc-99m pertechnetate thyroid image (right) shows a discordant contour abnormality in the right lower pole of the thyroid, which helped the diagnosis of a right parathyroid adenoma.

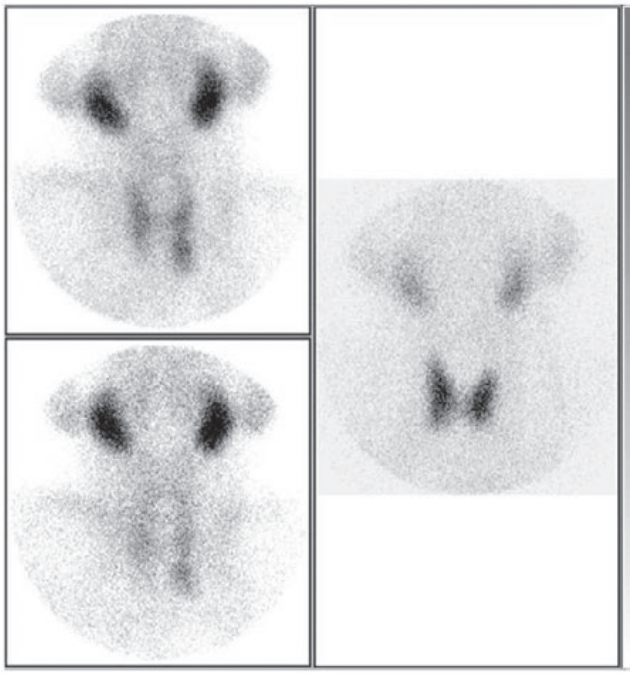

Fig. 2. Early (upper left) and delayed (lower left) MIBI images show an irregular uptake in the left lobe. Tc-99m pertechnetate (right) study shows no uptake in the region of the left lower pole of the thyroid and faciliated the diagnosis of a left parathyroid adenoma.

The sizes of 38 parathyroid lesions varied dimensionally from 0.8x0.8x1.0 cm to 3.7x2.8x2.6 cm, whereas the weight ranged from 0.18 g to 14 g (mean 1.64±2.64 g). All of the adenomas were localized to one of the four quadrants of the thyroid gland. Ectopic adenoma was not detected. In 13 (36 %) patients there was coexisting thyroid pathology. Ten out of these had thyroid adenoma, two had Hashimato thyroiditis and one had an occult papillary carcinoma. Lobectomy was performed in seven patients and total thyroidectomy was performed in the others.

Only MIBI images could detect 30 of the 38 parathyroid adenomas (79 % sensitivity)**.** On the other hand, MIBI + Tc-99m pertechnetate correctly identified 35 of the 38 parathyroid adenomas (92 % sensitivity), (p=0.0001), (Fig. 1, 2). There were no falsely positive results in neither evaluation.

In 13 patients with concomitant thyroid disease, all parathyroid adenomas were detected by a combined evaluation (MIBI + Tc-99m pertechnetate). In two of these cases it was not possible to identify parathyroid adenoma only with dual MIBI scintigraphy**.**

The average early MIBI uptake was 1.49 (range: 0.77–2.64; SD 0.42) and delayed MIBI uptake was 1.61 (range: 0.82–3.98; SD 0.56).

Table 2 presents the correlation results between MIBI uptake and laboratory/ histopathologic features. The adenoma weight showed a significiant correlation with the semi-quantitative MIBI uptake. Delayed images showed a better correlation than early images (Early MIBI: r= 0.541, p= 0.004; Delayed MIBI: r= 0.782; p=0.001). There was an obvious correlation between a high oxyphill content and a semi-quantitative MIBI uptake. Delayed images showed better correlation than early images (Early MIBI: r=0.366; p=0.033; Delayed MIBI: r=0.666; p=0.001).

Discussion

In the present study, the ability of MIBI dual phase scintigraphy and MIBI + Tc-99m pertechnetate imaging to localize parathyroid adenoma was compared. The addition of correlative thyroid imaging (visual substraction) significantly improved the sensitivity (92 % versus 79 %, p=0.0001). The dual phase MIBI technique is based on the different washout characteristics of the MIBI

Tab. 2. Correlations between the MIBI uptake and clinical/histopathologic parameters.

	Rho	2-tailed p
Early MIBI and Adenoma (g)	0.541	**0.004**
Early MIBI and chief cell	-0.022	0.900
Early MIBI and oxyphil cell	0.366	**0.033**
Early MIBI and plasma Ca	0.142	0.422
Early MIBI and plasma P	-0.248	0.172
Early MIBI and plasma PTH	-0.046	0.794
Delayed MIBI and Adenoma (g)	0.782	**0.001**
Delayed MIBI and chief cell	-0.235	0.182
Delayed MIBI and oxyphil cell	0.666	**0.001**
Delayed MIBI and plasma Ca	0.225	0.201
Delayed MIBI and plasma P	-0.197	0.281
Delayed MIBI and plasma PTH	0.075	0.675

from the thyroid and parathyroid tissue. In some patients, MIBI may show similar washout from both thyroid and parathyroid, which can result in a failure to identify parathyroid tissue (10). Thus, an addition of Tc-99m pertechnetate image clearly outlines thyroid borders and compared to the early MIBI scan may detect some adenomas showing a subtle MIBI activity. Some authours prefer to make a decision from computer substracted MIBI/Tc-99m pertechnetate or MIBI/I-123 images. On the other hand, some of the authours using the computer substraction reported a marginal improvement compared to the visual assessment (11–13). Moreover, artifacts due to prolonged immobilization caused by patient motion could not be completely avoided in substraction methods.

Hyperparathyroidism is often associated with nodular thyroid disease. Some authours reported a negative effect of thyroid abnormalities on the sensitivity of MIBI scan (14). In the present study, thyroid abnormalities did not affect the combined MIBI imaging sensitivity. This may be related to different thyroid lesion characteristics of the patient groups. We found a statistically significant association between the weight of the lesions and MIBI uptake. Oxyphill cell content has been considered as one of the factors influencing detection of parathyroid adenomas by MIBI scintigraphy. Controversial results have been reported in literature (15). In the present study, all parathyroid lesions were adenoma and we found a significant correlation between the oxyphill cell count and the MIBI uptake. Delayed MIBI images showed a higher correlation than the early ones (Early MIBI: r=0.366; p=0.033; delayed MIBI: r=0.666; p=0.001). These findings support the fact that mitochondria-rich oxyphil cells play an important role in MIBI accumulation and retention. Previous reports including patients with parathyroid hyperplasia besides adenoma did not found any correlation between the oxyphill cell content and the MIBI uptake (10, 13). It is not possible to explain the MIBI uptake only with adenoma size and oxyphill cell count. One of the two parathyroid adenomas without MIBI uptake was rather large, 470 mg. On the other hand, MIBI detected the smallest adenoma, measuring 180 mg. We also observed MIBI accumulation in 12 adenomas lacking oxiphylic cells.

Other unknown mechanisms seem to be responsible for preferential MIBI uptake in parathyroid glands. In a previous study, Torregrosa reported a positive association between the intensity of focal MIBI uptake in the parathyroid glands and the cell cycle phases. They observed a correlation with growth phases of the cell cycle. Higher uptake was observed with G2+S phases (14). In the present study we could not find an association between the 99mTc-MIBI uptake, Ca, P and iPTH plasma levels. Discordant results have been reported on this subject. Some authors found a positive association between the MIBI uptake and iPTH plasma levels. Others reported a correlation between the MIBI uptake and plasma calcium levels (8, 11, 13). Recently, Melloul reported an association between the 99mTc-MIBI uptake and plasma Ca and iPTH levels (15).

Conclusion

MIBI + Tc-99m pertechnetate interpretation was more sensitive than dual MIBI imaging only for the detection of parathyroid adenoma. Oxyphill cell content and the weight of the lesions proved to be important determinants of 99mTc-MIBI uptake in parathyroid adenoma, though they could not explain the whole uptake mechanism. We found no significant correlation between the MIBI uptake and plasma Ca, P, iPTH levels.

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