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Original Article

Diagnostic Value of sestamibi scan in the preoperative localization of parathyroid lesions in patients with primary hyperparathyroidism

Babak Mahmoudian[1], Mitra Tootoonchian[2*], Amir Bahrami[2], Zhila Khamnian[3]

[1]Department of Radiology, Radiation Oncology and Nuclear Medicine, Radiation Sciences Research Team, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Endocrine Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Department of Community Medicine,Faculty of medicine, Tabriz University of Medical Sciences, Tabriz, Iran

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Abstract

Introduction: Preoperative localization modalities for patients with primary hyperparathyroidism today play an important role in clinical decision making, surgical procedure, and the prognosis of patients. One of the most common preoperative imaging modalities is the sestamibi scan labeled with technetium-99m, which is capable of localizing parathyroid lesions in primary hyperparathyroidism patients with a high sensitivity.

Methods: In this cross-sectional study, 25 patients with primary hyperparathyroidism referred to endocrine clinic of Tabriz University of Medical Sciences during 2016-2018 were enrolled. All patients underwent a preoperative sestamibi scan. Comparing the results of the scan with the surgical findings as a standard gold method for diagnosis, the diagnostic value of the scan was evaluated for the localization of parathyroid lesions.

Results: According to the items observed in surgery and pathologic findings, the sensitivity of sestamibi scan for the localization of parathyroid lesions was 84.6%. Specificity, positive predictive value, and negative predictive value were 95.6%, 89.6%, and 94.8%, respectively. A significant relationship was observed between the type of lesion and the sensitivity of sestamibi scan ($P=0.002$).

Conclusion: Sestamibi scan has a high sensitivity, and diagnostic and therapeutic value for patients with primary hyperparathyroidism. However, the existence of other pre- and intraoperative localization modalities, at the request of surgeons, is useful and warranted to reduce the rate of recurrent surgery as well as to minimize false negatives.

Introduction

Primary hyperparathyroidism is the most common cause of hypercalcemia in patients referring to clinics. Approximately, one in every 1000 people has primary hyperparathyroidism. Surgery is the basic treatment in primary hyperparathyroidism patients. The use of localization studies after definitive diagnosis of hyperparathyroidism by biochemical methods and before surgery is very controversial.[1,2] From the early 1990s, with the advent of more sophisticated ultrasound devices and probes and the emergence of sestamibi scan, there was a great hope that the preoperative diagnosis and localization of invasive glands would be possible with high reliability coefficient.[2-5]

Because of the necessity of surgery in most cases of primary hyperparathyroidism, surgeons have to decide on the choice of preoperative localization procedure by considering the equipment available at their treatment center and consult the referring physicians of the patients.[6]

For patients with primary hyperparathyroidism, the surgeon should identify the involved gland during the surgery, but finding the parathyroid glands in the neck is not an easy task, especially since the location of these glands is changeable and the lower glands have more displacement. In addition, vital elements such as recurrent laryngeal nerve and neck vessels are adjacent to these glands. Extensive neck exploration combined with manipulation and displacement of vital elements always carry the risk of their damage. This risk increases with the rise in the frequency of neck surgery. Therefore, it is necessary to adopt a procedure to determine the definitive cause of hyperparathyroidism and to provide complete treatment with the least damage of neck elements and even in the first surgery.[7,8]

With using parathyroid scan Tc-99m MIBI (sestamibi scans), parathyroid adenomas are precisely located for 85% of patients. Correct localization of parathyroid adenomas will allow parathyroidectomy to be performed with the least amount of invasion and using minimally invasive open parathyroid surgery. This will reduce the length

***Corresponding Author:** Mitra Tootoonchian, Email: mitra_tootoonchian@yahoo.com

of stay in hospital and improve the satisfaction of the patients.[5,6] Also, a number of studies have found that the negative results of a sestamibi scan can change the plan of treatment in patients with primary hyperparathyroidism; therefore, endocrinologists will refer the patients less frequently to the surgeons. Surgeons are also less likely to do parathyroidectomy with a negative sestamibi scan report. Localization prior to abnormal parathyroid glands surgery allows for the unilateral cervical search; thereby, reducing surgical complications and the length of stay in hospital and minimizing surgical incision.[9-13]

Due to the necessity of localization before the surgery of parathyroid lesions, the aim of this study was to evaluate the diagnostic value of sestamibi scan in the localization of parathyroid lesions in patients with primary hyperparathyroidism, referred to Imam Reza Medical Center of Tabriz University of Medical Sciences, Tabriz, Iran.

Methods

Patients

Twenty-five patients (100 parathyroid glands) were enrolled in this cross-sectional descriptive-analytical study. The statistical population was a group of patients with primary hyperparathyroidism, referred to endocrine clinics of Tabriz University of Medical Sciences, undergoing preoperative Tc-99m sestamibi scan, and then having a surgery. Based on Cochran's formula for the calculation of sample size in diagnostic studies and based on its parameters of a 95% confidence level (1-α) and an 80% power (1-β) and considering the prevalence, sensitivity, and specificity of the test in previous studies, the sample size was estimated as 25 and accordingly 100 glands were evaluated [N=(1.96)2(0.975(1-0.975))/((0.06)2×0.3)=86.7].[14] Myocardial perfusion (MIBI) is very sensitive and highly accurate for per-operative localization of parathyroid lesion in patients with primary hyperparathyroidism.[15]

Given the nature of the study that examines the diagnostic accuracy of sestamibi scan, considering the fact that each person has four parathyroid glands in the neck and that at the time of scan and surgery, all four glands are evaluated, the number obtained from Cochran's formula is considered as the number of the examined glands. The sample size was calculated to minimize the bias caused by possible variations.

Inclusion criteria included consent to participate in the study, and the diagnosis of primary hyperparathyroidism (based on the definitive laboratory tests and biochemically confirmed). Exclusion criteria were renal failure, the diagnosis of secondary or tertiary hyperparathyroidism, pregnancy, and reluctance to continue the study at any diagnostic and therapeutic stage.

Data on each patient, including demographic characteristics, results of TC 99m sestamibi scan, laboratory analysis, and findings from surgery on the type and number of pathologic lesions, the location and the involved side were collected through the forms provided for this purpose. After radiotracer (Tc-99m) injection, a number of parathyroid scans were taken at 15, 60, 120, (and even 180 minutes for needed delayed images) intervals using E-cam siemens (Erlangen/Germany dual-head gamma camera) equipped with LEHR collimators. Then, each patient's findings obtained by scintigraphy procedures were compared with those of surgery and pathology.

The measurement of preoperative serum parathyroid hormone (PTH) level, which is approximately the first step in the study and follow-up of the patients, was performed before and after surgery in all patients.

Statistical analysis

SPSS 23.0 was used for data analysis. The normal distribution of the mean of data was first analyzed using Shapiro-Wilks test, and then descriptive statistics (mean ± SD) were used. Chi-square test was used to compare the two groups in terms of quantitative and qualitative variables. Paired sample t-test was used for statistical analysis of serum PTH levels before and after the surgery. Sensitivity and specificity, positive and negative predictive values. Likelihood ratio (LR)+= sensitivity/(1-specificity), LR-= (1-sensitivity)/specificity and Accuracy (ACC)= [true positive (TP) + true negative (TN)]/[TP+TN + false positive (FP) + false negative (FN)] were also calculated according to mentioned formula. The diagnostic power of sestamibi scan in preoperative localization of parathyroid lesions for patients with primary hyperparathyroidism were also determined. $P < 0.05$ was considered statistically significant.

Results

In the present study, 16 (64%) and 9 (36%) of the patients were male and female, respectively. The mean age of the patients was 55.8 ± 15.8 years.

There was no significant relationship between the final and pathologic diagnosis of the type of parathyroid mass and the gender of patients ($P = 0.238$).

The age and pathology of the involved gland were also not significantly correlated ($P = 0.318$). No significant relationship was found between the age and gender of patients with the sensitivity of sestamibi scan with a P value of 1.23 and 0.65, respectively. The definition of these correlations is summarized in Table 1.

Regarding the location of the involved gland, the most frequent involvements were related to the right lower parathyroid (RLP) and left lower parathyroid (LLP) with a frequency of 38.46%, followed by the left upper parathyroid (LUP) with 15.38% and the right upper parathyroid (RUP) with 7.69% (Figure 1). It should be noted that in one patient, multiglandular involvement and concurrent involvements in LLP and LUP were reported. There was no significant relationship between

the anatomical position of the involved gland and the age and gender of patients with a *P* value of 0.504 and 0.366, respectively (Table 2).

Preoperative PTH

The mean preoperative serum PTH level was estimated as 357.56±367.22 ng/L which was reduced to 54.8±47.91 ng/L after surgery ($P<0.001$). This indicated a correct resection of the involved gland and a response to the treatment.

Tc-99m sestamibi scan results

The sensitivity, specificity, positive predictive value, and negative predictive value of sestamibi scan was 84.6%, 95.9%, 89.6%, and 94.8% compared to the total cases, respectively. The statistical analysis showed a significant relationship between the response to scan and the response to surgical treatment, as well as the success of the treatment ($P<0.001$). Based on the above values, LR+, LR- and ACC of the test were calculated, as 19.22, 0.16, and 0.93, respectively.

Logistic regression was performed to evaluate the predictive power as well as the influence of the anatomical location of the involved gland on the predictive power of the scan in determining the correct location of the lesion in parathyroid lesions. The implemented model was statistically significant ($P<0.001$, χ^2 (2, N=100) = 76.21).

The data supported the fact that the model can distinguish between the pathologic and normal glands. The results showed that the scan correctly detected 93% of the pathologic lesions (Cox & Snell R square = 0.53; Nagelkerke R square = 0.78). No statistically significant relationship was found to show that the anatomical location of the involved gland will affect the predictive power of the scan ($P>0.05$).

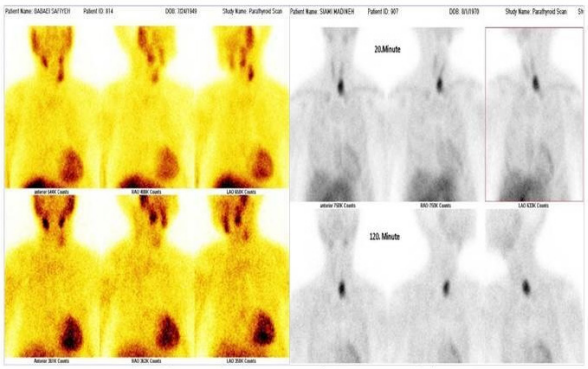

Figure 1. Planar dual phase parathyroid scan which were done 20 (upper raw) and 120 minutes (lower raw) after intravenous injection of 20 mCi Tc-99m sestamibi from Anterior, right anterior oblique and left anterior oblique projections. A) Ectopic focal uptake was noted in left lateral aspect of middlle neck in a 68 years old male patient with history of elevated serum calcium and parathyroid hormone and history of thyridectomy, which was consistent with ectopic parathyroid adenoma (left half with thermal scale). B) Exophytic focal uptake was noted in lower pole of left lobe of thyroid in a ?? years old male patient with history of elevated serum calcium and parathyroid hormone, which was consistent with exophytic parathyroid adenoma and showed more retained activity in delayed 120th minutes images (right half with gray scale).

Table 1. Correlation of pathology and sestamibi scan by age and gender parameters

Correlation of parameters		*P* value
Type of parathyroid mass	Gender	0.238
	Age	0.318
Sestamibi scan	Gender	0.23
	Age	0.65

$P<0.05$ was considered as statistically significant.

Table 2. Correlation of anatomical position of involved gland and the age and gender of patients

Correlation of parameters		*P* value
anatomical position of involved gland	Gender	0.36
	Age	0.504

$P<0.05$ was considered as statistically significant.

A hundred parathyroid glands were also surgically dissected and evaluated for the presence of any abnormal lesions. As depicted in Table 3, a total of 26 pathologic lesions were found and resected during the surgeries. Out of these lesions, 22 had been accurately localized by the MIBI scan. Meanwhile, the false-positive and false-negative values for MIBI scan compared to the surgical gold standard were 3 and 4, respectively.

The type of pathological lesions

The results of the pathology showed that about 88% of cases were reported to have parathyroid adenomas. There is a 95% overlap in the results of the scan and pathology reported for parathyroid adenoma. Thus, a significant correlation was observed between the type of the obtained gland and the sensitivity of sestamibi scan ($P=0.002$).

The number of pathological lesions

No significant relationship was found between the number of pathological lesions in each patient and the sensitivity of sestamibi scan ($P=0.33$). That is why no relationship was noticed between the volume and number of masses and the ability of sestamibi scan to detect them in the present study.

Discussion

The results of this study confirm the findings of previous researches on sestamibi scan and its value and ability to diagnose and evaluate parathyroid lesions in patients with primary hyperparathyroidism.

In a study by Greilsamer et al on the need for sestamibi scan and the value of its results in identifying cases with parathyroid cancer, it was shown that this modality had a significant impact on clinical decision making. It also revealed a high percentage of parathyroid lesions. Furthermore, it was successful in the management of

Table 3. Positive and negative scans compared to diagnosis during the surgery

		Surgery	
		Positive	**Negative**
Sestamibi Scan	Positive	22	3
	Negative	4	71

Data are presented as number.

surgical procedures and rates of parathyroidectomy in patients with primary hyperparathyroidism.[16]

In another study, Arici et al evaluated the sensitivity of sestamibi scan accompanied by ultrasound in the localization of parathyroid lesions which was reported to be 96%.[10] These results were validated in the present study. The key role of sestamibi scan was revealed given the high prevalence of its use in our hyperparathyroidism patients.

In a study by Ebner et al on the success rate of surgery in patients undergoing preoperative localization using ultrasound and sestamibi scan or both, localization was directly correlated with the success rate of the surgery.[17] In our study, this relationship was confirmed, although more robustly, and with greater percentage, but only for sestamibi scan.

In the study by Chow et al[14] on intra-operative parathyroid hormone monitoring and the study by Scerrino et al.[18] on the Mini-Gamma camera, complementary and intra-operative localization approaches, the overall result was that complementary techniques should be used during the surgery for all patients with primary hyperparathyroidism, regardless of the results of the sestamibi scan, to prevent recurrence and re-exploration of a sensitive area such as the neck and mediastinum. In the present study, we also noticed false negatives, which present serious challenges for future clinical and surgical decisions. Overall, the negative results of sestamibi scan in the presence of the clinical suspicion of hyperparathyroidism as well as the design of a correct surgical procedure and the assurance that all parathyroid lesions are diagnosed and excluded, require the use of other modalities.

In a study by Solorzano et al[4] with a comprehensive review of pre- and postoperative surgical procedures for the localization of primary parathyroid lesions, it was finally emphasized that ultrasound should be considered as a diagnostic modality for all of the patients at the first step; not only for the identification of lesions, but also for the detection of common diseases associated with primary hyperthyroidism. On the other hand, it is good to have the surgeon to choose the modality for each patient and situation. Consequently, the efficacy and success of treatment would be higher and unnecessary costs and damages could be avoided.

In a study by Ryan et al, of 94 patients with single adenomas, 66% with ultrasonography, 83% with thallium-technetium scintigraphy, and 87% with both tests were identified. Correct diagnosis by ultrasonography, thallium-technetium scintigraphy, and combination of these two methods was estimated to be 59%, 75%, and 73%, respectively. The study stated that unilateral surgical exploration with the help of the abovementioned modalities reduced surgical time and had diagnostic results similar to bilateral exploration. [11] Also, in another study by Arici et al, researchers reported the diagnostic value of sestamibi scan in the localization of the involved gland for patients with primary hyperparathyroidism to be 94%. [19] In another study, Peeler et al compared the diagnostic value of sestamibi scan with that of other diagnostic modalities including ultrasonography, CT scan, MRI, and thallium scan in the localization of parathyroid lesions, which according to the results of their study, Tc-99m sestamibi scan had the highest diagnostic value among the evaluated modalities.[20]

Given the results of the present study on the comparison of sestamibi scan results with surgical exploration and its high response rates to treatment with localization, the issue that localizing modalities by restricting surgical area and thyroidectomy makes the invasive surgical procedure more compact and less risky and reduces the length of care and the need for treatment, is right and has nowhere to leave.

In a 2017 study by Bradley and Knodle[21] patients who were likely to have primary hyperparathyroidism based on clinical and lab test results, and had a negative sestamibi scan were selected and underwent cervical exploration with ultrasound guides. The results of this study showed that sestamibi scan with a positive answer is very effective. But the false negative was about 35%, which indicates the need for follow-up investigations if the scan is negative. This high percentage of false negatives require special attention and reassessment so that patients can be on the right track by adjusting guidelines based on the results of the surgeons' studies and experiences to avoid relapse of the symptoms and higher severity of the illness.

On the other hand, considering positive and negative likelihood ratios with LR+ greater than 10, it can be concluded that the use of sestamibi scan as a diagnostic modality to rule out parathyroid lesions for patients with primary hyperparathyroidism is appropriate. However, given the LR- greater than 0.1, this test is not good in negative reporting cases, and is not suitable to rule out parathyroid lesions for patients with primary hyperparathyroidism. Therefore, as previously mentioned, in cases in which clinical and laboratory suspicion is high for primary hyperparathyroidism, if sestamibi scans are negative, other modalities should be used to diagnose and localize lesions, preoperatively.

In the present study, we focused on the diagnostic value of sestamibi scan, but given the limited results of recurrence as well as the few, but false-negative cases, and regarding the crucial role of surgeons in intraoperative and postoperative decision making, surgeons should be involved in the modality selection process and their experience should be used to improve the diagnosis

Study Highlights

What is current knowledge?

- According to current knowledge, parathyroidectomy needs exploration of all parathyroid glands for accurate localization of prathyroid adenoma

What is new here?

- This study showed that, limited neck incision is needed for selected and accurate parathyroidectomy after localization of parathroid adenoma with Tc-99m sestamibi scan.

and selection of complementary modalities. Although a number of studies have reported better results in simultaneous examination of SPECT images compared to planar images, this study was performed with planar sestamibi scan due to limitations in the gamma camera for SPECT images, and therefore, investigating planar images to evaluate all study subjects.

Conclusion

The results of the present study indicate that sestamibi scan is highly sensitive to the diagnosis and localization of parathyroid lesions, and can be used as a method to limit the extent of invasive interventions and avoid extensive neck exploration. On the other hand, this scan can be helpful in differentiating between hyperplastic lesions and adenomas. The issue needs a great deal of work due to few studies and may be the subject of future studies.

Conflict of Interest

The authors declare no conflict of interest.

Ethical Approval

Written informed consent was obtained from all participants prior to any action and the study was approved by the ethics committee of Tabriz University of Medical Sciences (Code: IR.TBZMED.REC.1395.476). All authors declare no conflict of interests.

Authors' Contribution

In this work, BM performed the sestamibi scans. MT supervised all study processes. AB selected the patients and ZK analyzed the data.

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