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Cure Rates of Parathyroidectomy for Primary Hyperparathyroidism with Negative Localization Studies

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Abstract

Purpose: This paper evaluates the outcomes of parathyroidectomy for primary hyperparathyroidism with negative localization studies.

Methods: All patients with primary hyperparathyroidism with negative preoperative ultrasound and MIBI scan who underwent parathyroidectomy were retrospectively included. Three groups were defined. Group 1 included the patients with negative ultrasound and MIBI. Group 2 included the patients with negative ultrasound and positive MIBI. Group 3 included the patients with positive ultrasound and negative MIBI.

Results: In Group 1, 51% and 86% of patients had one adenoma and atypical localizations respectively. Unique adenoma and atypical localizations were showed in 87% and 93% of patients in Group 2 respectively. In Group 3, 83% and 17% of patients had one adenoma and atypical localizations respectively. No cervical hematoma was noted. Transient recurrent laryngeal nerve palsy occurred in 2 patients. Seven patients required postoperative calcium supplementation for 2 months to 5 months, and one had recurrent hypercalcemia at follow-up. Cure rate was 98, 3%.

Conclusion: When US and MIBI were negative, multiple lesions and atypical localizations were frequent. The success rate and postoperative complications were not affected with this event.

Keywords: Primary hyperparathyroidism; MIBI scan; Ultrasound; Adenoma; Multiple lesions

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Introduction

Primary Hyperparathyroidism (PHPT) is a common disorder. Bilateral Neck Exploration (BNE) was the treatment of choice for PHPT with a success rate of more than 95% [1-5]. The introduction of the preoperative localization studies has led to the development of Minimally Invasive Parathyroidectomy (MIP) where only the affected gland is identified and excised [6-8]. MIP has clear benefit in terms of operative duration, shorter hospital stays, overall cost, higher patient satisfaction, less postoperative pain, smaller incisions, better cosmetic outcomes, less associated morbidity, and becoming the gold standard treatment [9-16]. The ability to perform MIP relies upon successful localization of the diseased gland(s) preoperatively by many techniques [17-19]. These techniques include neck Ultrasound (US), dual phase planar Technetium-99m (^{99m}Tc) sestamibi scans (MIBI), MRI, Single Photon Emission Computed Tomography (SPECT), combined SPECT/CT, and Four Dimensional CT scans (4D CT) [20-25]. A combination of imaging modalities is often used as no single imaging modality is 100% sensitive or specific [17,18,26,27]. Despite advancements in imaging technique, a subset of patients with non-localizing abnormal gland(s) will require the traditional method of BNE [18,19,28-35]. Decreased intraoperative success and overall cure rates, and increased in the rates of common postoperative complications have been described in non-localizing imaging for PHPT [30-32].

The aim of this study was to determine our institution's cure and complications rates of parathyroidectomy in PHPT with negative MIBI and US.

Materials and Methods

Patients selection

Between January 2000 and December 2018, all consecutive unselected patients who were admitted for parathyroidectomy for PHPT with negative preoperative MIBI and/or US were retrospectively considered for the study. The study was approved by an institutional review board. The diagnosis of primary hyperparathyroidism was based on three elevated serum calcium levels in combination with inappropriate elevation of a serum PTH level. Exclusion criteria were: patients with secondary causes of hyperparathyroidism, familial hyperparathyroidism, any of the multiple endocrine neoplasia syndromes, recurrent or persistent hyperparathyroidism after previous parathyroid operation, and if US and MIBI lead to identify the same one adenoma. The following data were collected: age at time of operation, gender, preoperative calcium and Parathyroid Hormone (PTH) levels, type of operation, surgical findings, histopathologic results, and postoperative calcium and PTH levels.

High resolution real-time US and color-Doppler sonography were the first diagnostic procedure performed by the radiologist. For US, the patient was scanned in supine position with the neck extended. Scanning was performed from high in the neck at the carotid bifurcation to as low as feasible in the base of the neck. High frequency transducers of 10 MHz were used, in combination, in some cases, with lower frequency transducer (7.5 MHz). A routine real-time sonography combined with color-Doppler imaging was used. Transverse and longitudinal views were recorded. Routine search of parathyroid glands is usually directed along the posteromedial aspect of the thyroid close to tracheoesophageal groove, and includes the entire thyroid gland and the anterior neck from the thyroid cartilage to the sternal notch and from the midline to the jugular veins. Parathyroid adenomas are typically hypoechogenic compared with the thyroid gland and are solid in sonographic appearance. Adenomas tend to be oval, bean-shaped, or oblong. Classically, an echogenic plane between the parathyroid lesion and the thyroid gland is helpful in distinguishing the lesion from a thyroid nodule. Doppler study reveals hypervascularity.

Technetium (Tc) 99m Sestamibi scan was performed in some cases especially where no definite results could be obtained by US. For MIBI scan, a dual-head gamma camera system (ADAC Vertex Plus; ADAC Laboratories, Milpitas, CA) was used for parathyroid imaging with a low-energy, high-resolution parallel hole collimator. For the dual-phase MIBI study, 20 mCi ^{99m}Tc-MIBI was administered intravenously. Fifteen minutes after injection, the first image of the neck was acquired for 10 min. A second image, targeting the mediastinum, was obtained for 10 min. These 2 images were repeated at 1 and again at 2 and at 3 h after administration of ^{99m}Tc-MIBI.

All operations were performed by one surgeon (BA) via a transverse cervicotomy. Patients in whom preoperative US or MIBI localized one abnormal parathyroid gland underwent unilateral surgical exploration of the neck under local anesthesia with intraoperative dosage of 1 to 84 PTH. BNE under general anesthesia was made when the preoperative examination failed to localize the lesion, and when justified by the surgical findings.

Reported categorical outcomes include detection of abnormal parathyroid(s), anatomic localization of the gland(s), preoperative and postoperative calcium and PTH levels (postoperative, at 6 months, and at follow up), presence of polyglandular disease and pathologic findings. Following the results of both imaging tests, three groups were established in order to further assess the discrepancy between imaging techniques: Group 1 included all patients with negative US and MIBI, Group 2 regrouped patients having negative US and positive MIBI and Group 3 included patients with positive US and negative MIBI.

Surgical anatomic localizations were subdivided in 2 groups: Typical or normal Localizations (TL) and Atypical Localizations (AL).

Parathyroid disorders characteristics were classified as adenoma, hyperplasia, or carcinoma. Final pathology results were reported in two different groups: one adenomatous lesion (A) and polyglandular disease (P) comprising hyperplastic lesion and at least 2 adenomatous lesions.

Statistical analysis

Discrepancy was evaluated by comparing outcomes between the groups using 2 × 2 Fisher's exact test; statistical significance for comparison between nominal variables was set at $p<0.05$.

Results

From January 2000 to December 2018, 74 patients with primary hyperparathyroidism and negative US or MIBI underwent parathyroidectomy. There were 51 women (69%) and 23 men, with a mean age of 57 years (range: 24 years to 83 years). Both sex groups were comparable regarding median age (56 years for women, 58 years for men, $p=0.629$).

The average preoperative PTH and serum calcium levels were 137 pg/ml and 2.67 mmol/l respectively. High resolution real-time US and color-Doppler sonography were performed preoperatively in 72 patients. Technetium (Tc) 99m Sestamibi scan was performed in 60 patients, mainly when no definite result was obtained by US.

Average size of the adenomas on US examination was 18 mm (range, 7 mm to 67 mm). Patients with correct ultrasonography localization had an adenoma in the anterior part of the neck (typical) compared to the adenoma in mediastinum or in the posterior part or in the retroesophageal groove (atypical) with negative or incorrect localization. Other factors including patient age, sex, side (right versus left) of adenoma, position (upper *vs.* lower) of the adenoma, size of adenoma, preoperative highest serum calcium, PTH, urinary calcium, serum alkaline phosphatase levels had no significant association with the accuracy of US.

Surgical anatomy

In all the patients, the preservation of the recurrent nerves was the rule. When found, adenomas were excised, hyperplasia of parathyroid glands were removed (three-and-the half parathyroidectomy associated to thymectomy) and frozen sections for parathyroid tissue were obtained. Biopsy specimens of normal macroscopic glands were not obtained in patients with excision of an obvious adenoma, whereas other visualized glands were only marked with a clip or long silk suture. When vascularization of a parathyroid gland seemed compromised, it was selectively resected and auto transplanted in the homolateral sternocleidomastoid muscle. Definitive pathology study was obtained for all resected tissues (weight and size of the lesion were measured).

Table 1: Relation between negative US, negative MIBI, surgical localizations and final pathology.

	Negative Ultrasound (n=52)	Negative MIBI (n=43)
Female	32 (62%)	31 (72%)
Atypical locations	46 (88%)	33 (77%)
Typical locations	6 (12%)	10 (23%)
Adenoma	32 (62%)	24 (56%)
Multiple lesions	20 (38%)	19 (44%)

Table 2: Relation between negative preoperative studies and surgical localizations.

	Group 1 (n= 37) Double Negative	Group 2 (n=15) US(-) and MIBI(+)	Group 3 (n=6) US(+) and MIBI(-)
Female	25 (68%)	7 (47%)	6 (100%)
Atypical locations	32 (86%)	14 (93%)	1 (17%)
Typical locations	5 (14%)	1 (7%)	5 (83%)
Total	37 (100%)	15 (100%)	6 (100%)

Table 3: Relation between negative preoperative studies and final pathology.

	Group 1 (n= 37) Double Negative	Group 2 (n=15) US(-) and MIBI(+)	Group 3(n=6) US(+) and MIBI(-)
Female	25 (68%)	7 (47%)	6 (100%)
Adenoma	19 (51%)	13 (87%)	5 (83%)
Multiple lesions	18 (49%)	2 (13%)	1 (17%)
Total	37 (100%)	15 (100%)	6 (100%)

In patients with a missing superior parathyroid gland, a careful exploration of the retro-pharyngeal area, tracheo-oesophageal groove, and posterior superior mediastinum was performed. With a missing inferior parathyroid gland, the root of the neck, thymus (thymectomy), and anterior superior mediastinum were carefully explored. The next step in patients with a missing superior or inferior parathyroid gland was opening of the carotid sheath. The final procedure in all patients with a missing and presumably diseased parathyroid gland was ipsilateral partial or total thyroid lobectomy with trunk ligation of inferior thyroid artery.

The four parathyroid glands were identified in each patient who underwent BNE. Morphologic features of abnormal parathyroid glands included: enlarged size (>50 mg), irregular shape, dark color or hypervascularization, firm consistency with lack of compressibility, and absence of surrounding fatty tissue typical of a suppressed parathyroid gland. Specimens were considered by the pathologist to be abnormal based on gross and histological criteria including: weight, cellularity, fat depletion, and morphology.

Surgery assessments of PHPT revealed 51 atypical localization of abnormal parathyroid(s) (51/74=69%) and 23 typical localizations (23/74=31%). Following appropriate surgical treatment and pathologic assessment, there were 53 parathyroid adenomas (72%) and 21 polyglandular lesions (28%). Among polyglandular lesions, 13 lesions were identified as parathyroid hyperplasia (17%) and 8 resected specimens presenting at least two adenomatous lesions each (11%). The weights of the adenomas ranged from 53 mg to 4312 mg, and mean size in greatest diameter was 18 mm.

Table 1 summarize the relation between negative US, negative MIBI, surgical localizations, and final pathology.

No patient was lost to follow-up. Within days following surgery, all patients had calcium levels in the normal range, 63 patients normalized their previously elevated PTH levels. Nine patients required postoperative calcium supplementation for 2 to 5 months, and all were normocalcemic at the time of the last clinic visit with median follow-up of 48 months (range 12 to 216). One patient had recurrent hypercalcemia 2 years after surgery. Cure rate was 98%, 6%. Two patients had transient recurrent laryngeal nerve palsy. No cervical hematoma neither permanent palsies of the recurrent laryngeal nerve were noted.

Sixteen patients: Two without US and 14 without MIBI were therefore excluded from further analysis. Among the remaining 58 patients (who had US and MIBI), 52 and 43 had a negative US and MIBI respectively. The median preoperative total calcium and PTH levels were 2.67 mmol/L and 132 mIU/mL respectively for the abnormal multiple glands patients and were 2.71 mmol/L and 136 mIU/mL respectively for the remaining patients. These differences are not statistically significant (p=0.601 and p=0.665 for calcium and PTH respectively).

As per intraoperative findings, the hyperparathyroidism was due to a solitary adenoma in 37 patients (64%), and polyglandular diseases in 21 patients (36%). Atypical localizations showed in 47 patients (81%): Abnormal gland(s) were found in the anterior mediastinum (n=8), in the posterior mediastinum (n=12), in the tracheoesophageal groove or retroesophageal space (n=19), on intrathymic (n=5), near the carotid artery bifurcation (n=1), and within the thyroid gland (n=2). On pathologic examination the average size of the adenoma was 17 mm (range, 7 mm to 66 mm), and average weight was 1930 mg (range, 83 mg to 46300 mg).

No patient was lost to follow-up. 57 patients (98.3%) were cure during a median follow-up period of 48 months (range 12 to 216). 53 patients had normal PTH levels. 7 patients required postoperative calcium supplementation for 2 to 5 months, and all were normocalcemic at the time of the last clinic visit. Transient recurrent laryngeal nerve palsy occurred in 2 patients. In this series, no patient developed neck hematomas or persistent hypoparathyroidism or had permanent recurrent laryngeal nerve injuries. One patient (1.7%) developed hypercalcemia 2 years after surgery.

Comparison of groups 1, 2, and 3

There were 37 patients in Group 1, 15 patients in Group 2 and 6 patients in Group 3. Both sex groups were comparable regarding median age (56 years for women, 58 years for men, p=0.42). Patient enrollment and assessment in groups was summarized in Table 2 and 3.

Patients in Group 1 (n=37) underwent BNE under general anesthesia because a double negative preoperative localization studies. The anatomic distribution of abnormal gland(s) was: anterior mediastinum (n=5), posterior mediastinum (n=7), the tracheoesophageal groove or retroesophageal space (n=15), intrathymic (n=3), and near the carotid artery bifurcation (n=1), intra thyroid (n=1). No Unsuccessful cervical exploration occurred. The exploration of the different cervical spaces averaged 92 min (range, 35 min to 182 min). Patients in Groups 2 and 3 (n=21) underwent minimally invasive parathyroidectomy by unilateral neck exploration under local anesthesia with intraoperative dosage of 1 PTH to 84 PTH. Three patients in this group required conversion to BNE under general anesthesia because of failure of a significant decrease in intraoperative quick PTH assay (n=2) after excision of the adenoma. In one patient, frozen section study revealed hyperplastic parathyroid glands on the same side, and the procedure was extended to a bilateral exploration. The anatomic distribution of abnormal gland(s) was: Anterior mediastinum (n=3), posterior mediastinum (n=5), in the tracheoesophageal groove or retroesophageal space (n=4) intrathymic (n=2), and intra thyroid (n=1). The mean operative time was 13 min (range, 7 min to 39 min).

Comparison between Groups 1 and 2 yielded significant differences in pathology findings: 13% of patients in group 2 had a polyglandular disease compared to 49% of patients in Group 1 (p=0.004). Comparison between Groups 1 and 3 showed significant differences in anatomic localization as there were 86% and 17% of atypical localizations respectively (p<0.001). Comparison between Groups 2 and 3 showed significant differences in sex (p=0.046) and anatomic localization (p<0.001). 53% of male patients were in Group 2 and zero (0%) patient in Group 3. There were 17% of atypical localizations in Group 3 compared to 93% of patients in Group 2.

Discussion

In this study, we found that ectopic localizations (86%) and polygland diseases (49%) were independently associated with double negative preoperative US and MIBI Scan in PHPT. Our experience corroborates several reports of a significantly increased incidence of MGD (21.7% to 84%) in patients with double negative imaging in patients with PHPT [19,29,32,34]. In our series, BNE was performed if no positive result was seen in any imaging technique. These patients typically required BNE (more extensive surgery) for suitable disease control. In our patients, there was no difference in the rates of common postoperative complications between groups. Additionally, while previous studies have associated nonlocalizing hyperparathyroidism with lower cure rates [31], cure rates at our institution have been comparably high between patients with nonlocalized and localized disease at 98.3% and 98.9%, respectively. In contrast, some authors, found a markedly decreased cure rate of 89% in patients with both a negative MIBI scan and a negative ultrasound [30,31]. Gland size in our series was smaller in patients with negative US and/or negative ^{99m}Tc sestamibi compared to those with positive imaging without reaching statistical significance.

In our series, 87% of patients in Group 2 and 83% of patients in Group 3 had a single adenoma and underwent parathyroidectomy by MIP with intraoperative dosage of 1-84 PTH. A unilateral MIP procedure was successful after an intra-operative PTH drop of at least 50% of its initial value to confirm the absence of other abnormal glands. The usefulness of IOPTH in MIP was also validated by many other authors [9,36-39]. At our institution, US and MIBI scans are most often used to localize hyperfunctioning gland(s). Previous studies have suggested the sensitivities for MIBI and US to range from 54% to 88% and 59% to 92.5% respectively [6,9,35]. Combining these two imaging modality increases the sensitivity of localization. In this series, 8% of patients undergoing initial surgery for PHPT failed to localize on pre-operative imaging (double negative). Previous studies show rates of 14% to 32% [18,33-35]. The precise reasons for equivocal or negative studies remain unclear. The successful identification of a parathyroid adenoma with ultrasound is dependent on the operator's proficiency, neck girth, lesion size, presence of thyroid disease and ectopic gland [8,9,17,23,27,28]. In our series, among the patients with negative US, 88% had abnormal parathyroid gland(s) situated in AL. ^{99m}Tc-MIBI SPECT/CT scans has difficulty localizing adenomas when thyroid nodules are present, when parathyroid adenomas are small, or if there is multigland disease and the degree of necrosis and apoptosis. Other factors include accuracy of imaging modality, imaging technique, and the discipline and experience of the interpreter [40-47]. Some authors demonstrated that radionucleotide retention in 99mTc sestamibi scans is related to oxyphil cell content and a pathologic study by others showed a higher proportion of chief cells in the glands of patients with nonlocalizing scan [33]. Singer et al. [42] found that centers that perform a high volume of MIBI imaging may achieve higher levels of scan sensitivity (82% within their institution versus 67% at outside facilities). Interpretation of the imaging may also vary based on the level of experience of the physician who is interpreting the film as well as their specialty (surgeon *vs.* radiologist). Adenoma weight of more than 600 mg and oxyphil cell content of more than 20% were independent factors for a positive MIBI scan for some authors [40]. Several studies have reported lower preoperative PTH and calcium levels in patients with nonlocalized PHPT [44]. While our series uncovered no difference in preoperative calcium and PTH levels in patients with double negative imaging. Some authors showed that negative MIBI scan was associated with an increased rate of multiglandular disease and a lower cure rate [31]. In contrast to this finding, other studies did not find any association between negative MIBI scan and mutliglandular disease; Their et al. [37], identified a single adenoma in 94.2% of patients. Our study showed that the rate of multiglandular disease in patients with negative MIBI was 44% but success cure rate was not affected.

Recently, various imaging modalities such as 4D-CT, PET/CT, and MRI have been used with mixed success. 4D-CT is traditionally reserved for patients with unclear SPECT/CT results with a continued suspicion for adenoma [24,29]. Some authors recommend reserving 4D-CT for certain situations such as cases with ectopic glands, especially in patients suspected to have adenoma but have unidentified lesions on initial imaging. However, 4D-CT has been shown to miss smaller adenomas as well and may not be the best alternative [17]. Historic cure rates for parathyroidectomy before the introduction of preoperative imaging were approximately 95%; as our study demonstrates, cure rates continue to be high regardless of preoperative imaging status. The only localization required for a patient with primary hyperparathyroidism is the localization of an experienced endocrine surgeon [29].

There are limitations to our study. This series is limited by its retrospective nature and the small sample size. Unfortunately, it not possible to perform a prospective randomized control trial in which patients are randomized to be localized or nonlocalized.

Conclusion

According to our results, US and MIBI must be performed preoperatively in PHPT in order to realize a MIP. Nonlocalization of parathyroid glands was not associated with decreased surgical cure rate or increased surgical morbidity. BNE is the treatment of choice with double nonlocalizing disease. MIP with intraoperative dosage of 1 to 84 PTH is the treatment of choice when US and/or MIBI was positive (more than 83% of patients had one adenoma).

References

1. Bilezikian JP, Silverberg SJ. Clinical spectrum of primary

hyperparathyroidism. Rev Endocr Metab Disord 2000;1(4):237-45.

2. Ruda JM, Hollenbeak CS, Stack BC Jr. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. Otolaryngol Head Neck Surg. 2005;132(3):359-72.
3. Calò PG, Medas F, Loi G, Erdas E, Pisano G, Nicolosi A. Feasibility of unilateral parathyroidectomy in patients with primary hyperparathyroidism and negative or discordant localization studies. Updates Surg. 2016;68(2):155-61.
4. Kaplan EL, Yashiro T, Salti G. Primary hyperparathyroidism in the 1990s. Choice of surgical procedures for this disease. Ann Surg. 1992;215(4):300-17.
5. Allendorf J, DiGorgi M, Spanknebel K, Inabnet W, Chabot J, Logerfo P. 1112 consecutive bilateral neck explorations for primary hyperparathyroidism. World J Surg. 2007;31(11):2075-80.
6. Johnson NA, Carty SE, Tublin ME. Parathyroid imaging. Radiol Clin N Am. 2011;49(3):489-509.
7. Sukan A, Reyhan M, Aydin M, Yapar AF, Sert Y, Canpolat T, et al. Preoperative evaluation of hyperparathyroidism: The role of dual-phase parathyroid scintigraphy and ultrasound imaging. Ann Nucl Med. 2008;22(2):123-31.
8. Lee L, Steward DL. Techniques for parathyroid localization with ultrasound. Otolaryngol Clin North Am. 2010;43(6):1229-39.
9. Chapuis Y, Fulla Y, Bonnichon P, Tarla E, Abboud B, Pitre J, et al. Values of ultrasonography, sestamibi scintigraphy, and intraoperative measurement of 1-84 PTH for unilateral neck exploration of primary hyperparathyroidism. World J Surg. 1996;20(7):835-9.
10. Chen H, Mack E, Starling JR. A comprehensive evaluation of perioperative adjuncts during minimally invasive parathyroidectomy: Which is most reliable? Ann Surg. 2005;242(3):375-80.
11. Kiriakopoulous A, Linos D. Accuracy and role of surgeon-performed intraoperative ultrasound in minimally invasive open parathyroidectomy. World J Endocr Surg. 2009;1(1):23-6.
12. Goldstein RE, Carter WM 2nd, Fleming M, Bumpous F, Lentsch E, Rice M, et al. Unilateral cervical surgical exploration aided by intraoperative parathyroid hormone monitoring in patients with primary hyperparathyroidism and equivocal Sestamibi scan results. Arch Surg. 2006;141(6):552-9.
13. Adil E, Adil T, Fedok F, Kauffman G, Goldenberg D. Minimally invasive radioguided parathyroidectomy performed for primary hyperparathyroidism. Otolaryngol Head Neck Surg. 2009;141(1):34-8.
14. Grant CS, Thompson G, Farley D, van Heerden J. Primary hyperparathyroidism surgical management since the introduction of minimally invasive parathyroidectomy: Mayo Clinic experience. Arch Surg. 2005;140(5):472-8.
15. Lal A, Chen H. The negative sestamibi scan: Is a minimally invasive parathyroidectomy still possible? Ann Surg Oncol. 2007;14(8):2363-6.
16. Stawicki SP, Chaar ME, Baillie DR, Jaik NP, Estrada FP. Correlations between biochemical testing, pathology findings and preoperative sestamibi scans: A retrospective study of the Minimally Invasive Radioguided Parathyroidectomy (MIRP) approach. Nucl Med Rev Cent East Eur. 2007;10(2):82-6.
17. Kedarisetty S, Fundakowski C, Ramakrishnan K, Dadparvar S. Clinical value of Tc99m-MIBI SPECT/CT versus 4D-CT or US in management of patients with hyperparathyroidism. Ear Nose Throat J. 2019;98(3):149-57.
18. Payne SJ, Smucker JE, Bruno MA, Winner LS, Saunders BD, Goldenberg D. Radiographic evaluation of non-localizing parathyroid adenomas. Am J Otolaryngol. 2015;36(2):217-22.
19. Wachtel H, Bartlett EK, Kelz RR, Cerullo I, Karakousis GC, Fraker DL. Primary hyperparathyroidism with negative imaging: A significant clinical problem. Ann Surg. 2014;260(3):474-80.
20. Hughes DT, Sorensen MJ, Miller BS, Cohen MS, Gauger PG. The biochemical severity of primary hyperparathyroidism correlates with the localization accuracy of Sestamibi and surgeon-performed ultrasound. J Am Coll Surg. 2014;219(5):1010-9.
21. Royal RE, Delpassand ES, Shapiro SE, Fritsche Jr HA, Vassilopoulou-Sellin R, Sherman SI, et al. Improving the yield of preoperative parathyroid localization: technetium Tc^{99m}-sestamibi imaging after thyroid suppression. Surgery. 2002;132(6):968-74.
22. Burke JF, Naraharisetty K, Schneider DF, Sippel RS, Chen H. Early-phase technetium-99m sestamibi scintigraphy can improve preoperative localization in primary hyperparathyroidism. Am J Surg. 2013;205(3):269-73.
23. Gayed IW, Kim EE, Broussard WF, Evans D, Lee J, Broemeling DL, et al. The value of ^{99m}Tc-sestamibi SPECT/CT over conventional SPECT in the evaluation of parathyroid adenomas or hyperplasia. J Nucl Med. 2005;46(2):248-52.
24. Schwartz IE, Capra GG, Mullin DP, Johnson TE, Boswell GE. Parathyroid computed tomography angiography: Early experience with a novel imaging technique in primary hyperparathyroidism. Otolaryngol Head Neck Surg. 2019;161(2):251-6.
25. Liu Y, Dang Y, Huo L, Hu Y, Wong O, Liu H, et al. Preoperative localization of adenomas in primary hyperparathyroidism: The value of 11c-choline PET/CT in patients with negative or discordant findings on ultrasonography and ^{99m}Tc-sestamibi SPECT/CT. J Nucl Med. 2020;61(4):584-9.
26. De Feo ML, Colagrande S, Biagini C, Tonarelli A, Bisi G, Vaggelli L, et al. Parathyroid glands: Combination of (99m)Tc MIBI scintigraphy and US for demonstration of parathyroid glands and nodules. Radiology. 2000;214(2):393-402.
27. Adkisson CD, Koonce SL, Heckman MG, Thomas C. Predictors of accuracy in preoperative parathyroid adenoma localization using ultrasound and Tc-99 m-sestamibi: A 4-quadrant analysis. Am J Otolaryngol 2013;34(5):508-16.
28. Bergenfelz AOJ, Wallin G, Jansson S, Eriksson H, Mårtensson H, Christiansen P, et al. Results of surgery for sporadic primary hyperparathyroidism in patients with preoperatively negative sestamibi scintigraphy and ultrasound. Langenbecks Arch Surg 2011;396(1):83-90.
29. Vuong C, Frank E, Simental AA, Han P, Perez H, Staton M, et al. Outcomes of parathyroidectomy for primary hyperparathyroidism with nonlocalizing preoperative imaging. Head Neck. 2019;41(3):666-11.
30. Dy BM, Richards ML, Vazquez BJ, Thompson GB, Farley DR, Grant CS. Primary hyperparathyroidism and negative Tc99 sestamibi imaging: To operate or not? Ann Surg Oncol. 2012;19(7):2272-8.
31. Elaraj DM, Sippel RS, Lindsay S, Sansano I, Duh QY, Clark OH, et al. Are additional localization studies and referral indicated for patients with primary hyperparathyroidism who have negative sestamibi scan results? Arch Surg. 2010;145(6):578-81.
32. Chan RK, Ruan DT, Gawande AA, Moore FD Jr. Surgery for hyperparathyroidism in image-negative patients. Arch Surg. 2008;143(4):335-7.
33. Mihai R, Gleeson F, Buley ID, Roskell DE, Sadler GP. Negative imaging studies for primary hyperparathyroidism are unavoidable: Correlation of Sestamibi and high-resolution ultrasound scanning with histological analysis in 150 patients. World J Surg. 2006;30(5):697-704.
34. Chiu B, Strugeon C, Angelos P. What is the link between nonlocalizing setsamibi scans, multigland disease, and persistent hypercalcemia? A study of 401 consecutive patients undergoing parathyroidectomy. Surgery. 2006;140(3):418-22.

35. Amin AL, Wang TS, Wade TJ, Quiroz FA. Nonlocalizing imaging studies for hyperparathyroidism: Where to explore first? J Am Coll Surg. 2011;213(6):793-9.

36. Calò PG, Pisano G, Loi G, Medas F, Tatti A, Piras S, et al. Surgery for primary hyperparathyroidism in patients with preoperatively negative sestamibi scan and discordant imaging studies: The usefulness of intraoperative parathyroid hormone monitoring. Clin Med Insights Endocrinol Diabetes. 2013;6:63-7.

37. Their M, Nordenström E, Bergenfelz A, Westerdahl J. Surgery for patients with primary hyperparathyroidism and negative sestamibi scintigraphy-a feasibility study. Langenbecks Arch Surg. 2009;394(5):881-4.

38. Alvarado R, Meyer-Rochow G, Sywak M, Delbridge L, Sidhu S. Bilateral internal jugular venous sampling for parathyroid hormone determination in patients with nonlocalizing primary hyperparathyroidism. World J Surg. 2010;34(6):1299-303.

39. Khan AA, Khatun Y, Walker A, Jimeno J, Hubbard JG. Role of intraoperative PTH monitoring and surgical approach in primary hyperparathyroidism. Ann Med Surg (Lond). 2015;4(3):301-5.

40. Erbi YL, Kapran Y, Issever H, Barrbous U, Adalet I, Dizdaroglu F, et al. The positive effect of adenoma weight and oxyphil cell content on preoperative localization with ^{99m}Tc-sestamibi scanning for primary hyperparathyroidism. Am J Surg. 2008;195(1):34-9.

41. Carpentier A, Jeannotte S, Verreault J, Lefebvre B, Bisson G, Mongeau CJ, et al. Preoperative localization of parathyroid lesions in hyperparathyroidism: relationship between technetium-99m-MIBI uptake and Oxyphil cell content. J Nucl Med. 1998;39(8):1441-4.

42. Singer MC, Pucar D, Mathew M, Terris DJ. Improved localization of sestamibi imaging at high-volume centers. Laryngoscope. 2013;123(1):298-301.

43. Torregrosa JV, Fernandez-Cruz L, Canalejo A, Vidal S, Astudillo E, Almaden Y, et al. (99m)Tc-sestamibi scintigraphy and cell cycle in parathyroid glands of secondary hyperparathyroidism. World J Surg 2000;24(11):1386-90.

44. Pons F, Torregrosa JV, Fuster D. Biological factors influencing parathyroid localization. Nucl Med Commun. 2003;24(2):121-4.

45. Turgut B, Elagoz S, Erselcan T, Koyuncu A, Dokmetas H, Hasbek Z, et al. Preoperative localization of parathyroid adenomas with technetium-99m methoxyisobutylisonitrile imaging: Relationship with P-glycoprotein expression, oxyphilic cell content, and tumoral tissue volume. Cancer Biother Radiopharm. 2006;21(6):579-90.

46. Peters G, Kulbersh B, Mantle B, Well W, Grizzle W, Rosenthal E. Role of microvascular density in nonlocalizing parathyroid Sestamibi scans. Laryngoscope. 2007;117(12):2163-8.

47. Bhatnagar A, Vezza PR, Bryan JA, Atkins FB, Ziessman HA. Technetium-99m-sestamibi parathyroid scintigraphy: effect of P-glycoprotein, histology and tumor size on detectability. J Nucl Med. 1998;39(9):1617-20.