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ORIGINAL ARTICLE

Comparison of hyperparathyroidism types and utility of dual radiopharmaceutical acquisition with Tc99m sestamibi and ^{123}I for localization of rapid washout parathyroid adenomas

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Abstract

Summary Tc99m-sestamibi dual-time imaging is a standard tool for localization of adenomas/hyperplasia in hyperparathyroidism. We investigated the degree and causes of localization failure among different types of hyperparathyroidism. Pre-operative parathyroid hormone levels and size of the gland were major determinants of Tc99m-sestamibi positivity; ^{123}I scan may be helpful in localization failures.

Introduction Tc99m-sestamibi dual-time imaging is a standard tool for localization of adenomas/hyperplasia in hyperparathyroidism. However, parathyroid adenomas/hyperplasia has been reported to washout as fast as normal thyroid tissue ("rapid washout") which may lead to diagnostic failure. We aimed to evaluate the determinants of rapid washout and to determine the role of subtraction imaging for detection of parathyroid adenomas/hyperplasia with rapid washout.

Methods Retrospective analysis of patients with hyperparathyroidism who have undergone Tc99m-sestamibi dual-time imaging and parathyroid surgery. Rapid washout was correlated to the type of hyperparathyroidism in surgically confirmed cases. Biochemical and pathological data were reviewed.

Results A total of 135 hyperparathyroidism patients met the inclusion criteria. Ninety-six (72%), 29 (21%), and 10 (7%) had primary, secondary, and tertiary hyperparathyroidisms, respectively. Rapid washout was identified in 28/87 glands (32%), 14/53 glands (26%), and 1/16 glands (6%) with primary, secondary, and tertiary hyperparathyroidisms, respectively. Glands that were positive on late-phase Tc99m-sestamibi scans were significantly large being 1.7 (IQR 1.4–2.3) vs. 1.45 (IQR 1–2) cm ($p = 0.003$). High parathyroid hormone levels (PTH) were associated with early-phase Tc99m-sestamibi positivity in both primary ($p = 0.01$) and secondary hyperparathyroidism ($p = 0.03$) but not with last phase ($p = 0.11$, $p = 0.37$, respectively). Correlative imaging with subtraction scintigraphy was positive in 14/16 (87.5%) parathyroid adenomas.

Conclusion Pre-operative PTH levels and size of the gland were major determinants of Tc99m-sestamibi positivity on early-phase Tc99m-sestamibi scans, whereas size is an independent predictor of late-phase Tc99m-sestamibi positivity. Subtraction scintigraphy might be a useful tool in suspected cases of rapid washout adenomas/hyperplasia.

Keywords Hyperparathyroidism · Parathyroid adenomas · Rapid washout · PTH

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Introduction

In patients with hyperparathyroidism, apart from finding an experienced parathyroid surgeon, an accurate localization of hyper-functioning parathyroid gland(s) is essential for optimal surgical outcomes [1]. This is especially true in cases with failed initial parathyroid surgery where the presence of ectopic parathyroid glands is a possibility [2]. In general, technetium-99m-hexakis-isobutyl-isonitrite (Tc99m-sestamibi) is the preferred imaging modality of choice for initial pre-operative localization of hyperfunctioning parathyroid tissue in patients with biochemical hyperparathyroidism [3]. Tc99m-sestamibi imaging, first introduced by *Coakley* et al. in 1989, became rapidly the standard for diagnosis of hyperparathyroidism due to favorable results, superior image quality, better detection sensitivity, and more favorable dosimetry in comparison with previously used 201-thallium [4–6].

Tc99m-sestamibi is a monovalent lipophilic cation that passively diffuses through cell membrane with temperature-dependent and non-saturable transport and localizes mostly in the mitochondria due to its negative inner membrane potential [7]. Hence, 90% of Tc99m-sestamibi uptake is associated with mitochondrial load in uptaking cells—the higher the mitochondrial load, the higher the uptake is. The classical single-tracer, dual-phase method with Tc99m-sestamibi has wide-range sensitivity (55–94%) in localizing lesions in hyperparathyroidism [8, 9]. Parathyroid images were typically acquired at approximately 10–20 min and 2 h after administration of Tc99m-sestamibi scan in early and late phases of the scan, respectively. Since Tc99m-sestamibi accumulates in thyroid and parathyroid tissue, the localization of parathyroid adenoma depends on the difference between Tc99m-sestamibi washout form thyroid and parathyroid glands with classic early Tc99m-sestamibi washout from thyroid and late from parathyroid glands. This pattern occurs in 70–75% of cases. However, in some cases, Tc99m-sestamibi washout from parathyroid adenoma/tumor and thyroid gland occurs at the same time. This phenomenon called rapid washout, and it may lead to equivocal findings or diagnostic failure. The exact cause of rapid washout is still unclear, and proposed mechanisms are related to number of mitochondria-rich cells, degree of angiogenesis, percentage of ill formed blood vessels, high mitotic activity, PTH, calcium, phosphorus levels, effects of some medications, and the patients' weight [10, 11]. In late-phase Tc99m-sestamibi scintigraphy, classic pattern of Tc99m-sestamibi retention by parathyroid adenomas/hyperplasia and washout from thyroid occurs in 60–75% of the cases. However, in some cases, parathyroid adenoma/hyperplasia can be missed due to radiotracer rapid washout. There is very limited literature on rapid Tc99m-sestamibi washout and correlation to the type of hyperparathyroidism.

In this retrospective analysis, we sought to determine the correlation of rapid washout of Tc99m-sestamibi with the type of hyperparathyroidism and the utility of dual radiopharmaceutical acquisition with ^{123}I-Tc99m-sestamibi subtraction imaging for detection of parathyroid adenomas/hyperplasia with rapid washout. We also analyzed the correlation of other biochemical parameters such as calcium and PTH levels with the Tc99m-sestamibi positivity.

Materials and methods

Study design

We conducted a retrospective chart review of adult (≥ 18 years) patients with primary/secondary/tertiary hyperparathyroidism who had Tc99m-sestamibi parathyroid imaging for evaluation and subsequently proceeded to parathyroid surgery at the Washington Hospital Center/Georgetown University from January 1, 2012 to December 31, 2013. One nuclear medicine physician with more than 12-year experience blindly reviewed the Tc99m-sestamibi images. Rapid washout was defined as an area of Tc99m-sestamibi activity on the initial images that did not show any significant retention on delayed images. We also evaluated the utility of ^{123}I-Tc99m-sestamibi subtraction scan in selected patients who had either a negative delayed phase Tc99m-sestamibi or negative scans (both early and delayed phase negative on Tc99m-sestamibi) and correlated the findings with histopathological findings of surgically removed parathyroid glands. The same nuclear medicine physician blindly reviewed the subtraction scan imaging.

Imaging technique

For the parathyroid scanning, a dual-phase single isotope protocol was adopted using 25 mCi of the Tc99m -sestamibi. Initial phase (5–10 min post injection) consisted of pinhole images of the neck in the anterior, right anterior oblique and left anterior oblique projections followed by SPECT-CT of the neck and chest. Delayed phase (2 to 2.5-h post injection) consisted of pinhole images in the anterior, right anterior oblique, and left anterior oblique projections.

In cases of suspected rapid washout and negative Tc99m-sestamibi on both early and delayed phases, patients were re-scanned using the dual isotope subtraction scan on a separate date. For this technique, 200–400 mCi of ^{123}I was administered and patient returned approximately 24 h later for imaging. Pinhole images of the neck in the anterior, right anterior oblique and left anterior oblique projections were performed for ^{123}I imaging. While maintaining the patient in one of the preferred position, Tc99m-sestamibi was injected and pinhole image using a Tc99m window in that preferred projection was performed. Digital subtraction of ^{123}I imaging from Tc99m-sestamibi images was performed utilizing Medview software (Medimage, Ann Arbor, MI, USA). An area of uptake on the Tc99m sestamibi that was not seen on subtraction scan image was considered discordant and indicative of parathyroid adenoma or hyperplasia with rapid washout of Tc99m sestamibi.

Surgical technique and biochemical assays

Surgical treatment included minimally invasive parathyroidectomy, unilateral exploration, bilateral exploration with

Table 1 Baseline characteristics of patients with hyperparathyroidism

Parameter	Primary HPTH	Secondary HPTH	Tertiary HPTH	*p* value
Median age (years)	62 (IQR 54–68)	48 (IQR 42–65.5)	41.5 (IQR 35–55.5)	0.0003
Pre-operative PTH levels (pg/ml)	142 (IQR 110–240.3)	955 (IQR 1865–2448)	1394 (IQR 949–2613)	< 0.0001
Pre-operative calcium levels (mg/dl)	10.9 (IQR 10.35–11.42)	9.34 (IQR 8.75–9.87)	10.4 (IQR 9.4–11.3)	< 0.0001
Post-operative PTH levels (pg/ml)	21.45 (IQR 12.95–35.25)	77 (IQR 56.08–272.3)	92.5 (IQR 29.5–163.8)	< 0.0001
Post-operative calcium levels (mg/dl)	9.02 (IQR 8.25–9.48)	8.55 (IQR 7.69–9.55)	8.09 (IQR 7.38–8.95)	0.0894

All the parameters are mentioned in median and interquartile ranges

N total number of glands analyzed, *IQR* interquartile range, *HPTH* hyperparathyroidism, *PTH* parathyroid hormone

hemithyroidectomy, and/or near-total thyroidectomy. Thyroid surgery was performed in addition to parathyroid surgery in cases of thyroid nodules (when appropriately indicated). Intraoperative assays of serum PTH before and after tumor resection were performed. We used third-generation PTH assay to measure the PTH levels. A decrease in blood parathyroid hormone level of 50% or more was considered evidence of curative surgery.

Data collection

All available medical records including surgical report, pathology report, and pre- and post-surgical biochemical workups for hyperparathyroidism were reviewed. The diagnosis of parathyroid adenoma or hyperplasia was based primarily on the pathology report. We used the size criteria based on analysis of surgical specimens for accurate analysis of correlation between the adenoma size and Tc99m -sestamibi uptake.

Data analysis

Continuous variables were expressed as mean ± standard error (SE) and categorical and interval variables as frequencies or median and interquartile range (IQR). To compare the groups' means, *t* test, ANOVA test, and Brown–Forsythe test were used, appropriately. A two-tailed Student's *t* test and Mann–Whitney *U* test were used for intergroup comparisons of normally distributed and non-normally distributed continuous data, respectively. For categorical variables, we used Pearson's chi-squared test. All analyses were performed with GraphPad Prism Software version 7.0a (GraphPad Software, San Diego, CA). Difference between groups of patients was considered significant with $p < 0.05$. The corresponding author's (K.K) institutional review board approved the study.

Results

A total of 135 hyperparathyroidism patients (males 41; females 94) with 220 adenomas/hyperplasia met the selection criteria. Seventy-two percent of those patients ($n = 103$ glands in 96 patients) had primary hyperparathyroidism, 21% ($n = 94$ glands in 29 patients) had secondary hyperparathyroidism, whereas the remaining 7% ($n = 23$ glands in 10 patients) were diagnosed with tertiary hyperparathyroidism. Baseline characteristics of all the three groups are summarized in Table 1.

In primary, secondary, and tertiary hyperparathyroidisms, 87/103 (84%), 53/94 (56%), and 16/23 (69%) glands were positive on early-phase Tc99m-sestamibi imaging. Among these patients with positive early-phase Tc99m-sestamibi imaging, negative delayed phase (rapid washout) was identified in 32% (28/87), 26% (14/53), and 6% (1/16) of the glands in primary, secondary, and tertiary hyperparathyroidisms, respectively (primary vs secondary, $p = 0.52$; primary vs tertiary, $p = 0.03$; secondary vs tertiary, $p = 0.08$) (Table 2) (Fig. 1). On the other hand, no uptake of Tc99m sestamibi was identified on both early and delayed

Table 2 Tc99m-sestamibi uptake in early-/late-phase Tc99m-sestamibi scans and rapid washout comparison in primary, secondary, and tertiary hyperparathyroidisms

Tc99m-sestamibi scan uptake	Primary HPTH ($n = 103$ glands)	Secondary HPTH ($n = 94$ glands)	Tertiary HPTH ($n = 23$ glands)
Positive on early and late-phase scan (no rapid washout)	59 (57.3%)	39 (41.5%)	15 (65.2%)
Positive on early phase only (rapid washout)	28 (32.1%)^	14 (26.4%)^	1 (6.3%)^
No uptake on early or delayed phase	16 (15.5%)	41 (43.6%)	7 (30%)

HPTH hyperparathyroidism

^Percentage calculated based on the number of glands that had early-phase positivity (denominator)

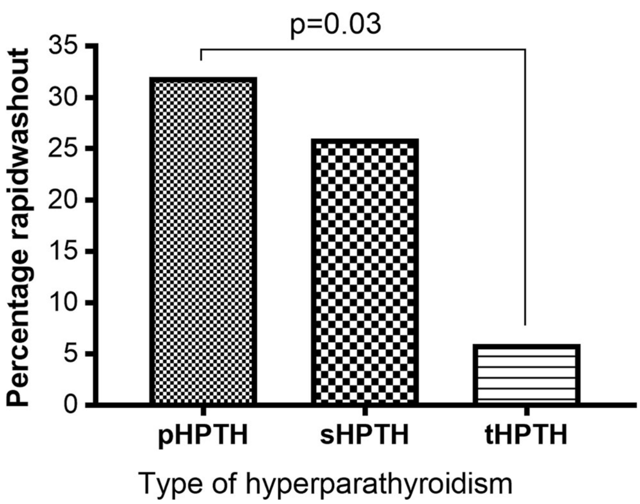

Fig. 1 Frequency of rapid washout in groups of primary, secondary, and tertiary hyperparathyroidisms. Significant difference was noted between primary and tertiary hyperparathyroidisms ($p = 0.03$), whereas no significant difference was noted between primary and secondary hyperparathyroidisms ($p = 0.52$) and secondary and tertiary hyperparathyroidisms ($p = 0.08$)

phases in 15.5% (16/103), 43.6% (41/94), and 30% (7/23) of the glands in primary, secondary, and tertiary hyperparathyroidisms, respectively (primary vs secondary, $p < 0.001$).

Median PTH levels for primary, secondary, and tertiary hyperparathyroidisms were 142 pg/ml (IQR 110–240.3), 955 pg/ml (IQR 1865–2448), and 1394 pg/ml (IQR 949–2613), respectively ($p < 0.001$). In glands with primary hyperparathyroidism**,** though PTH levels correlated with early-phase Tc99m-sestamibi positivity ($p = 0.01$), no such correlation between delayed phase and 99mTc-sestamibi positivity was noticed ($p = 0.11$) (Fig. 2). Similar results were seen in glands with secondary hyperparathyroidism ($p = 0.03$ in early-phase positivity, $p = 0.37$ in delayed phase positivity). We could not analyze the correlation in glands with tertiary hyperparathyroidism due to small sample size in the cohort. Among 16 adenomas with rapid washout 99mTc-sestamibi scan, 87.5% ($n = 14$ adenomas) were discordant on subsequent dual isotope subtraction imaging and diagnostic of parathyroid origin (Table 3). Parathyroid adenomas that were positive on late-phase Tc99m-sestamibi imaging were significantly large being 1.7 cm (IQR 1.4–2.3) vs. 1.45 cm (IQR 1–2) ($p = 0.003$). Similar size correlation with early-phase Tc99m-sestimibi positivity was noted, with the average size of positive and negative scan being 1.7 cm (IQR 1.3–2.1) and 1.3 cm (IQR 0.8–2), respectively ($p = 0.006$) (Fig. 3). On the contrary, we did not notice any significant correlation between pre-operative calcium levels and Tc99m-sestamibi radiotracer retention in both early [10.5 mg/dl (IQR 9.45–11.1) vs. 10.75 mg/dl (IQR 9.9–12.58), ($p = 0.54$)] and late-phase scans [10.4 mg/dl (IQR 9.4–10.7) vs. 10.4 mg/dl (IQR 10–11.3), ($p = 0.52$)].

Discussion

Tc99m-sestamibi is a standard tool for localization of adenomas/hyperplasia in hyperparathyroidism designed on the difference between thyroid and parathyroid tissue radiotracer washout on early and late phases of scintigraphy. In our study, we found a significant association of type of hyperparathyroidism with rapid washout. Primary hyperparathyroidism had higher percentage of rapid washout (32%) as compared to that of tertiary hyperparathyroidism (6%). This is in contrast from the previous studies that have concluded that rapid washout in adenomas and hyperplasia was in the range of 8–40% and 75%, respectively [12–14]. However, it is important to note that the previous studies suffered from very small sample size. One of the plausible explanations for less rapid washout in secondary and tertiary hyperparathyroidism might be the presence of higher number of oxyphil cells in the later [15]. These oxyphil cells contain high number of mitochondria, which have high affinity of Tc99m -sestamibi radiotracer uptake leading to less degree of washout as seen in secondary and tertiary hyperparathyroidism in our study. Chief cells are the predominant cell type in the parathyroid glands of young, healthy subjects, and this number gradually decreases with age as they get transformed into oxyphil cells [16]. This transformation of chief

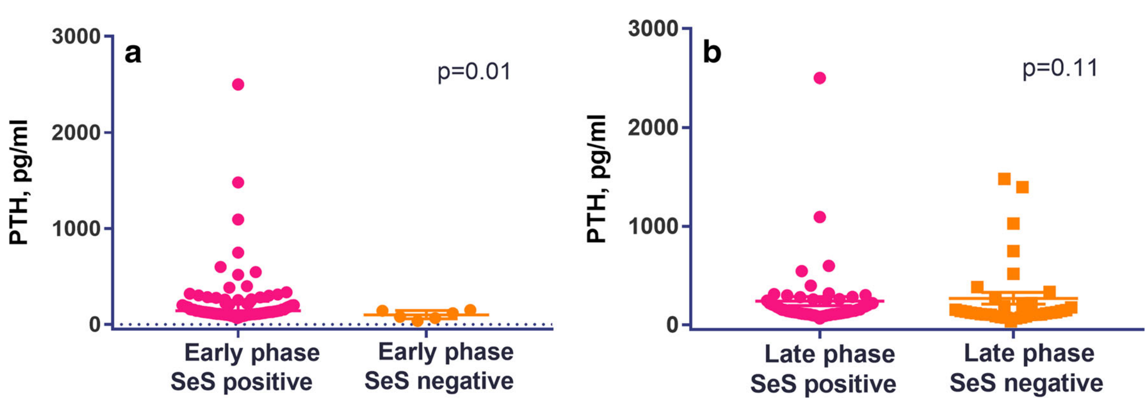

Fig. 2 Association of median PTH levels with early-phase (**a**) and late-phase (**b**) Tc99m-sestamibi imaging in primary hyperparathyroidism

Table 3 Tc99m-sestamibi uptake in early-/late-phase scans and comparison with rates of detection with ^{123}I-Tc99m-sestamibi dual isotope scintigraphy

Tc99m-sestamibi scan uptake	Total glands analyzed	% Positive on SS	Comments
Rapid washout	16 (100%)	14 (87.5%)	87.5% adenomas with rapid washout were identified on SS
Negative on early and late scan	9 (100%)	0 (0%)	Adenomas not identified on 99mTc-sestamibi scan were also not identified on SS

SS subtraction study

cells to oxyphil cells is known to occur at a higher degree in patients with chronic kidney disease [17]. This may explain the lesser degree of rapid washout in tertiary hyperparathyroidism, which is commonly seen in chronic kidney disease.

In addition, we demonstrated that size of the parathyroid adenoma/hyperplasia is directly related to early- and late-phase uptakes on 99mTc-sestamibi scans—smaller adenomas were more often missed on early and late-phase scans. A study by Neumann et al. [12] has concluded that majority of adenomas that were greater than 600 mg were positive on 99mTc-sestamibi scans and adenomas less than 350 mg were more likely to be missed. Another study has showed that weight of adenoma greater than 1 g was associated with sensitivity greater than 95% [18]. In our study, rather than weight, we used the size criteria as it is easy to determine the size of the adenoma by pre-operative imaging studies. Again, this increased uptake in larger glands might be secondary to the presence of more number of mitochondria rich oxyphilic cells, which is an important factor for Tc99m-sestamibi uptake [19, 20]. We also found that high PTH levels were associated with positive uptake in early-phase Tc99m-sestamibi scans but not in late-phase scans. A small number of oxyphil cells in some adenomas may account for rapid washout [21]. This correlation Tc99m-sestamibi uptake with PTH levels has been proposed by some authors [22–26] but not others [10, 14]. These controversial results of the role of PTH and adenoma size on the uptake and accumulation of radiotracer in parathyroid lesions require the roles of other factors to be taken into consideration. One of such factors is the changes in serum calcium levels. Elevated calcium level has been shown to be significant for Tc99m-sestamibi uptake [27, 28], which again is contradicted by few studies [10, 26]. Some authors have found significant correlation only for early phase of scintigraphy [29]. Some authors debated that increased calcium concentration in mitochondria can block Tc99m-sestamibi uptake by mitochondria [7]. In our study, we did not find any significant association between pre-operative calcium levels and early/late Tc99m-sestamibi uptake. Hence, we think that the uptake of the radiotracer by the parathyroid glands is dependent of multiple factors. For instance, Lane MJ et al., reported that increased tissue perfusion is an important determinant factor in the uptake and retention of radiotracer [30]. In addition, the varied timing of acquisition of late-phase scan might also explain the contradictory results obtained in various studies.

Dual acquisition of Tc99m-sestamibi and ^{123}I has been shown to be better in comparison to single trace dual-phase Tc99m-sestamibi with sensitivity ranging from 70 to 94% depending upon imaging protocols and histology [6, 8, 31–33]. Adding ^{123}I as a thyroid tracer is helpful to distinguish thyroid from parathyroid uptake of Tc99m-sestamibi since thyroid nodules can account for about 20–30% of false positive parathyroid scans [32, 34]. This technique can be helpful in detection of adenomas with rapid washout. However, utility of dual Tc99m-sestamibi and ^{123}I acquisition with focus on parathyroid rapid washout has been not investigated thus far, which we did in our study. In our study, dual isotope imaging as an additional diagnostic tool was positive in 87.5% of

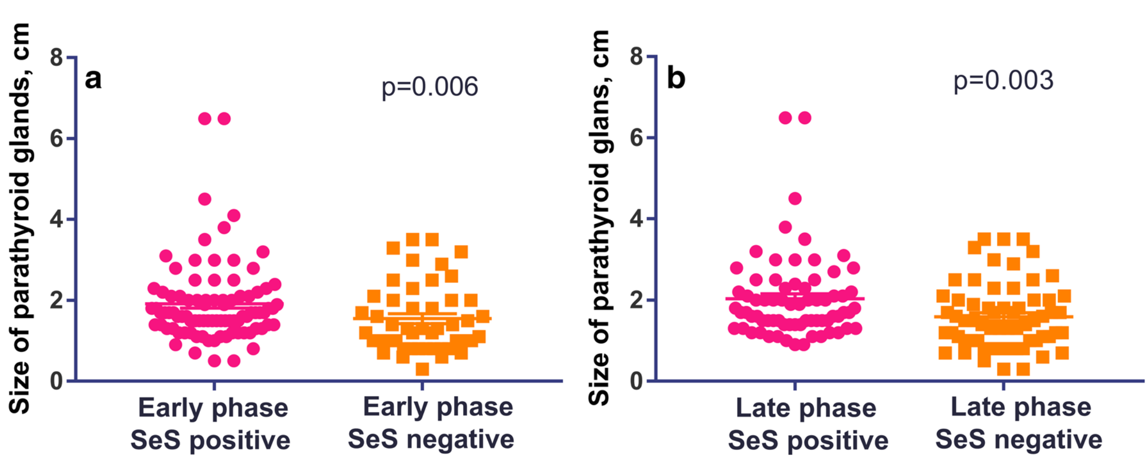

Fig. 3 Association of the size of the glands with early-phase (**a**) and late-phase (**b**) Tc99m-Sestamibi uptake

parathyroid adenomas/hyperplasia with rapid washout but was not effective in cases that were negative on both early- and late-phase Tc99m-sestamibi scintigraphies. The later finding might guide the different approach in terms of dual Tc99m-sestamibi and ^{123}I acquisition application in practice.

Study limitations are inherent to retrospective study design and small sample size in tertiary hyperparathyroidism. However, it is important to note that our study cohort resembles the normal distribution in the incidence of primary, secondary, and tertiary hyperparathyroidisms in general population. Since this was a retrospective chart review, the decision to perform the additional dual isotope scan was made by the individual reviewing the scan rather than the investigator itself. However, during the chart review, all the scans were re-reviewed to assure that the defined criteria of rapid washout were met. The other limitation is lack of data on oxyphil cell count in parathyroid adenomas/hyperplasia scintigraphy. Nonetheless, to the best of our knowledge, in English literature, this is the first study to determine the association of type of hyperparathyroidism and rapid washout in Tc99m-sestimibi imaging.

Conclusions

Higher rates of rapid washout were seen in primary hyperparathyroidism followed by secondary and tertiary kind. Pre-operative PTH levels and size of the gland were major determinants of Tc99m-sestamibi positivity on early-phase Tc99m-sestamibi scans, whereas size is an independent predictor of late-phase Tc99m-sestamibi positivity. Tc99m sestamibi and ^{123}I scintigraphy dual isotope imaging might be useful tool in confirmation of parathyroid origin of the disease in suspected cases of rapid washout. Future studies should include cytological analysis of adenomas/hyperplasia so that the possible explanation of direct association of oxyphil cell count with Tc99m-sestamibi uptake can be answered with accuracy.

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Compliance with ethical standards

The corresponding author's (K.K) institutional review board approved the study.

Conflict of interest None.

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