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**Title:** Ectopic and Eutopic Located Parathyroid Lesions: Do They Behave Differently? How Can We Monitorize Them? What Can We Look for?

**Running Head:** Ectopic and Eutopic Parathyroid Lesion Imaging

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**Abstract**

**Objective:** Hyperparathyroidism (HPT), is a frequent endocrine disorder that progress with increase in parathormone (PTH) synthesis and secretion from chief cells in one or more glands. The common methods used for imaging of parathyroid adenomas are USG and MIBI scintigraphy. We aimed to investigate the determination characteristics and availability of MIBI scintigraphy technique for determination of eutopic and ectopic localized parathyroid adenomas.

**Methods:** This is a retrospective data search study. 59 Patients with primary HPT diagnosis between 2002 and 2010 by parathyroid scintigraphy with Tc99m MIBI, imaging with dual phase-dual isotope technique and reported as parathyroid adenoma enrolled in this study. In order to determine radiopharmaceutic retention, the early parathyroid-to-thyroid ratio (early PT/T), the late parathyroid-to-thyroid ratio (late PT/T), the early-to-late ratio (E/L) and the retention index (RI) were calculated.

**Results:** Lesions were divided into two groups: ectopic (n=28), and eutopic (n=37) localization. When biochemical parameters are compared, there was not statistically significant difference in physiological parameters excluding PTH levels. We determined that the level of PTH is the only biochemical parameter that directly associated with positivity of MIBI. Moreover, our findings revealed that E/L is negatively correlated with Ca+2 and P whilst RI exhibited a positive association with Ca+2 and P in ectopic group.

**Conclusion:** We concluded that MIBI is, currently, the best imaging method to diagnose parathyroid adenomas. The ideal imaging protocol should include a combination of single photon emission computerized tomography (SPECT) study that is not prolonged over 1 hour with an early and a late planar (15 minutes and 2 hours, respectively) imaging.

**Keywords:** Parathyroid, ectopic, MIBI, imaging



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**INTRODUCTION**

Hyperparathyroidism (HPT) is a frequent endocrine disorder that progress with increase in parathormone (PTH) synthesis and secretion from chief cells in one or more glands. It is divided into three etiological classes as primary, secondary and tertiary.

Primary hyperparathyroidism (PHPT), is due to excessive autonomous secretion of PTH from one or more parathyroid gland. In the fifth, sixth and seventh decades of life yearly incidence is reported as 1/500 for women and 1/2000 for men. In 80-90% of patients one adenoma is monitored and on the other hand, in 5-10% of patients double adenomas and 10-15% of patients four gland hyperplasia was found (1).

Diagnosis of the disease can be made clinically by measurement of serum PTH, $Ca^{+2}$ and phosphorus (P) levels. There is no need for imaging techniques in diagnosis stage. In the treatment, some of the asymptomatic patients and all symptomatic patients are treated primarily by surgery. Surgery selection criteria of PHPT presented at Table 1 (2). Early surgical resection using minimally invasive parathyroidectomy (MIP) technique is becoming a more common used practice. Because of this trend in approach for HPT patients, the determination of number and localization of parathyroid glands that causes the disease is becoming more important (3).

The most common methods used for imaging of parathyroid adenomas are ultrasonography (USG) and Tc-99m sestamibi scintigraphy (MIBI). Sensitivity of USG and MIBI for detecting parathyroid adenomas varies between 80% (77-83) and 84% (80-87) (4). In different study, it was reported that MIBI is more sensitive than USG for detecting parathyroid adenoma (5). It was shown that MIBI is an eminent method for determination of localization of parathyroid adenomas preoperatively and it can give certain information to the surgeon for adenomas which cannot be detected with standard radiological procedures (3). Consequently, both USG and MIBI have high sensitivity for solitary parathyroid adenoma, however negative imaging studies can be made inevitably (6). We aimed to investigate determination characteristics and availability of MIBI imaging for determination of eutopic and ectopic localized parathyroid adenomas.



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## METHODS

### *Patients*

Patients with PHPT diagnosis between 1 January 2002 and 30 August 2010 by parathyroid scintigraphy with MIBI, imaging with dual phase-dual isotope technique and reported as parathyroid adenoma enrolled in this study. We retrospectively scanned the data of 387 patients who were referred for MIBI imaging for evaluation of parathyroid adenoma. From the hospital patient record and automation system; PTH, $Ca^{+2}$, P, urea, creatinine values and USG data of all patients during scintigraphy were obtained. Surgery notes and pathology results of all parathyroidectomy patients were also found from medical records and were added to the study. The cases that has missing biochemical parameters and pathological confirmation were left out of the study. Images were evaluated for compliance with the Turkish Society of Nuclear Medicine Parathyroid Scintigraphy Procedure Guideline (7) and Europe Nuclear Medicine Society (EANM) standard imaging protocol (8). Images which did not match the protocol, were not optimal due to patient movement or other reasons and reported as suspicious were left out of the study. Finally, 59 patients were included in the study whose ages were between 20 and 82 (mean age= 53,3; median age=48) and comprised 14 males (24%) and 45 females (76%). The whole process of patient selection is given in Figure 1. Lesions in each imaging were divided into two groups: ectopic and eutopic localization.

### *The Consent Statement of The Subject And Ethical Approval*

All of cases has been informed about process and consequences of the procedure before the scintigraphy protocol. All patient data is allowed to be used in scientific studies. This study was approved by the local ethics board (TUTFEK2009/139).

### *Imaging protocol*

In all studies, after giving 20-25 mCi Tc99m MIBI to the patient, at 15.minute and 2.hour planar imaging were made and after the complete MIBI washout 5 mCi Tc99m pertechnetate were given and thyroid scintigraphy was performed. All MIBI images were obtained from Philips BrightView gamma camera (Philips Medical Systems, Cleveland, USA) and Siemens E.CAM gamma camera (Siemens Healthcare GmbH., Erlangen, Germany). In addition early (1. hour) single photon emission computerized tomography (SPECT) and 4. hour planar MIBI imaging (if needed) was performed. Due to the anatomical definition (9), adenomas which were posterior to bilateral lower and upper thyroid lobes adjacent to the thyroid gland were accepted as eutopic; adenomas which were out of these areas were accepted as [Neck, mediastinum and intrathyroidal. (All intra-

thyroid lesions were confirmed as parathyroid adenomas pathologically)] ectopic.

Following visual assessment of the image, in order to determine radiopharmaceutic retention and excretion in early and late phases of dual phase imaging protocol, counting was made after drawing same sized region of interest (ROI) around lesion for each phase from early and late images of all lesions (15. minute and 2. hour). Base activity counting was made without changing ROI sizes, for cases with one adenoma from symmetric thyroid tissue and for cases with bilateral adenoma from shoulder muscle tissue abroad. For ectopic and eutopic lesions, four different scintigraphic parameters were calculated. The early parathyroid-to-thyroid ratio (early PT/T), the late parathyroid-to-thyroid ratio (late PT/T), the early-to-late ratio (E/L) and the retention index (RI) were calculated as follow:

**PT/T=**parathyroid/thyroid

**E/L=**Early/Late

**RI=** [(Late PT/T)-(Early PT/T) ]/(Early PT/T) x 100

**Statistical Analysis**

Statistical correlation between scintigraphic parameters and three biochemical parameters that were serum PTH, calcium and phosphor levels was evaluated. For ectopic and eutopic localized lesions, statistical differences for these parameters were tested. Statistical analysis was made with AXA507C775506FAN3 serial numbered STATISTICA AXA 7.1 statistical program. Compliance with the normal distribution of data that can be measured was made with Kolmogorov Smirnov test and as it does not show compliance Mann Whitney U test was used for comparing groups. Also t test was applied when assuming the normal distribution assumption. For evaluation of the relation between variables Spearman rho correlation analysis was used. For definitive statistics Median (interquartile range (IQR)). values and mean ±standard deviation was given. $p<0.05$ was considered to represent a significant difference for all statistics.

**RESULTS**

59 patients were included in the study. The mean age of patients for ectopic group was 55,43 ±15.23 years and, it was 51,62±11,33 in the eutopic group. Of the 65 identified lesions, 28 were (43%) ectopic, and 37 were (57%) eutopic. 54 have one adenoma, four have double adenomas and one has three parathyroid adenomas (91.5%, 6.8%, 1,7%, respectively). According to localization 28 adenomas were determined as ectopic and 37

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of the adenomas as eutopic.

When biochemical parameters are compared in between two patients` groups with either eutopic or ectopic parathyroid adenoma, there was not statistically significant difference excluding PTH levels (Table 2). Since PTH data were non-normally distributed, we described PTH levels with the median and interquartile range. PTH levels ranged from 65 to 2500 pg/mL, with a median of 222 pg/mL (25th percentile: 160 pg/mL; 75th percentile: 561 pg/mL) for ectopic group. For eutopic group, PTH levels ranged from 73 to 1222 pg/mL, with a median of 151 pg/mL (interquartile range (IQR): 119 to 303 pg/mL). Since all other parameters fit the normal distribution, they were expressed as mean ± SD. Mean $Ca^{+2}$ levels were 10,53 ± 1,51 mg/dL and 10,68± 0,998 mg/dL for ectopic and eutopic group, respectively.

If we look at the association between scintigraphic and biochemical parameters in ectopic group, a positive and medium level association was determined between RI and $Ca^{+2}$ and P levels which was statistically remarkable. In addition, although an association of the RI with PTH level was at a positive direction, it was weak and statistically non-significant (Table 3). Moreover, there was statistically significant relationship between Early PT/T rate and $Ca^{+2}$ value which was at a negative direction and medium level. Although, the association between P and PTH levels was similarly negative, it was not statistically remarkable. On the other hand, the late PT/T values were not significantly affected by biochemical parameters.(Table 3). Furthermore, we determined a negative association of E/L values with $Ca^{+2}$ and P levels which was statistically significant whilst there was not a remarkable relationship between the E/L values and PTH levels, although it was very weak but similarly negative (Table 3).

At the same time, our assessment revealed that scintigraphic parameters including RI, Early PT/T, Late PT and E/L are not significantly affected by biochemical values such as $Ca^{+2}$, P and PTH in eutopic group (Table 4).

**DISCUSSION**

Since the success of minimally invasive parathyroidectomy is highly correlated with the correct location of the adenoma, preoperative imaging techniques have become more important in recent years. A variety of scintigraphic methods were improved for preoperative pinpoint of hyperfunctional parathyroid glands in past decade. Although, there are few researchers directly compared the reliability of different methods, a clear protocol has not been improved yet for MIBI parathyroid scintigraphy in medical literature. Comparison between different methods revealed that any method is not significantly better than the other.

The majority of studies on parathyroid scintigraphy compare sensitivity of SPECT and planar imaging systems.

Although the sensitivity is higher in SPECT (% 11-20) than planar imaging in the number of studies, difference between them is not statistically significant (10). Moreover, two studies suggested that there is no difference between using either SPECT or planar imaging (11, 12).

The current hot topic for researchers is to improve scintigraphy revealing parallel changes in positive invasion patterns with both biochemical and pathological processes. We also focused on two main targets. The first target is to determine whether there is any difference between ectopic and eutopic parathyroid adenomas considering radiopharmaceutical absorption and elimination by early and late imaging and to develop easy obtainable and repeatable parameter to use in choosing the most suitable imaging protocol for an every single patient. Secondly, we aimed to evaluate the plausible association of scintigraphic results obtained by MIBI parathyroid scintigraphy in patients` groups (having either ectopic or eutopic parathyroid adenomas) with biochemical parameters that are routinely studied in the same patients` groups and to assess whether these biochemical parameters differ due to localization of parathyroid adenomas.

The main principle of MIBI parathyroid imaging is based on differences in the amount and duration of radiopharmaceutical absorption by parathyroid and thyroid tissues. Moreover, the amount of radiopharmaceutical absorption by parathyroid tissue positively correlates with the weight and size of the parathyroid gland and how the parathyroid gland is functional (13, 14). Therefore, the rate of PT/T obtained from interested areas including adenoma and neighbouring normal tissue will reveal us the amount of absorption of radiopharmaceutics by lesion. Common consensus in nuclear medicine literature is that the rate of PT/T increases by time after MIBI injection (15). In consist with this consensus; we determined a significant difference between the values of early PT/T and late PT/T in both eutopic and ectopic groups whereas the enhancement in PT/T values was more remarkable in late period. Therefore, we suggest that the use of prolonged scintigraphic imaging (2 hours or 4 hour in special cases) will advance the sensitivity and specificity of this imaging method by improving an identification of parathyroid adenomas and its differential diagnosis from thyroid nodules. However, it should be beared on mind that early imaging at 15 minutes is essential to catch parathyroid adenoma with multi drug resistance gene encoding P-glycoprotein that causes early elimination of MIBI from parathyroid adenoma (16, 17). We suggest that the ideal imaging protocol should include both early and late imaging.

The intact PTH level reveals the functional condition of parathyroid gland. The association was suggested between MIBI absorption in parathyroid adenoma and the amount of oxyphilic cells consisting of a number of mitochondria. These cells also synthesis PTH which may be possible involved in the pathophysiology of HPT.

Therefore, the relationship can be postulated between the absorption of MIBI and PTH levels. In this study, we did not find any significant association between PTH level and RI, mean of Early PT/T or Late PT/T values in both two groups. Other studies presented different findings on association of MIBI absorption with PTH levels regarding the same scintigraphic parameters including RI, Early PT/T or Late PT/T values in parathyroid adenomas. In 2016, Koberstein et al. and in 2018 Beheshti et al., suggested a positive correlation between serum PTH values and positive MIBI scan (18, 13). Similarly, Hung et al., revealed that the sensitivity of test reaches at %100 when the level of serum intact PTH is over 200 pg/ml (19).

Moreover, Siegel et al., that suggest a positive correlation between the PTH values and gland`s weight studied for the determination of a threshold of PTH level enabling to take positive imaging in 2006 (20). In their study, the mean PTH level was calculated as 367 pg/ml (normal range: 46–3231 pg/ml) for a real positive imaging whilst it was determined as 148 pg/ml (normal range: 46–390 pg/ml) for pseudo negative and positive imaging which difference was found statistically significant (20).

In contrast, Melloul et al., postulated no correlation between MIBI absorption and PTH levels in parathyroid adenomas (21). Although we did not determine any correlation between PTH level and scintigraphic parameters, significant differences were found in the mean PTH values between two patient groups. By considering that there is an association between gland function and cellular response, PTH levels were higher in ectopic group; we hypothesized that there may be changes in the number of receptor and their function that differ cellular response to PTH in this group. Further studies will clarify that whether the same possible molecular or cellular change is also a cause of ectopic location of parathyroid gland or not.

When we focus on the association of RI, PT/T or E/L rates with $Ca^{+2}$ and P, any significant association was not detected between these parameters in eutopic group suggesting that the levels of $Ca^{+2}$ and P associate, at least partially, with MIBI absorption independent of PTH and this association should be considered prior to scintigraphic imaging. We proposed that the difference regarding RI and E/L rates in between two patient groups may be caused by structural differences (receptor structure or sensitivity) at cellular level in glands revealing unique embryological migration. These structural differences may also explain behavioral difference seen at late embryonic period. More advanced research needs to be conducted to assess whether this hypothesis is true or false.

There are a few previous studies on determination of association between $Ca^{+2}$ and P levels and positivity for MIBI. Findings published in 2008 by Erbil et al., suggested that there was no correlation between the parameters (including the values of PTH and $Ca^{+2}$, weight of gland) and ectopic localization of parathyroid adenoma (22). In the same study, the association was postulated between the weight of gland and positivity of USG and MIBI. A study conducted on the determination of MIBI absorption and the volume of tumor and biochemical markers (PTH, $Ca^{+2}$, P) by Çermik et al., revealed that MIBI absorption is higher in late phase in comparison to early phase (23). Moreover, an increase in the weight of gland and serum PTH level was found in all parathyroid adenomas compared with the normal whilst there was no statistically significant correlation between the phase of imaging, volume of lesions and levels of $Ca^{+2}$ and PTH (23). Çermik et al., also suggested that MIBI absorption is not always correlated with the content of oxyphilic cells and additionally postulated that the amount of oxyphilic cells is not only factor affecting absorption of MIBI (23). Conversely, in 2012, Ciappuccini et al. showed that the adenoma size, serum calcium levels and serum PTH levels are most likely affects the result of MIBI scintigraphy (24).

We secondly aimed to determine any differences between ectopic and eutopic-parathyroid adenomas regarding four scintigraphic and three biochemical parameters. In addition, we also purposed to study that whether any of these parameters could be a marker to be focused on when we need to take images of ectopic parathyroid adenoma. In conclusion, we found a statistically significant difference only in PTH levels (p= 0,027) in between patient groups when we regard analysis of results obtained by seven parameters. When we searched the scientific literature for this purpose, we could not find any study investigating scintigraphic or biochemical tools to predict ectopic adenoma before imaging. The study of Koberstein et al.in 2016 shows that MIBI SPECT is useful imaging tool for both of the two groups (18). Liddy et al. compared ability of USG and MIBI scintigraphy in 2016, and found that MIBI images are more sensitive and accurate for detecting ectopic adenomas (5). In current study, since the all included cases were positive for adenoma, we did not investigate efficacy of MIBI scanning on detecting adenomas. We only investigated whether biochemical and scintigraphic parameters have changed according to localization of adenomas. Our findings are consisted with previously reported results on $Ca^{+2}$ values whilst they are controversial when we consider the level of PTH in the same study performed on the changes on parameters due to lesion localization (22). We suggest that these differences in results may be due to different features of patient`s population included in the study. A population included in a study conducted by Erbil et al., were agreed to be operated for their parathyroid adenomas. However, our patient population was included individuals that were randomly evaluated for any parathyroid adenoma due to PHPT.

Moreover, we evaluated all patients with or without indication for parathyroid operation. Differences between two studies may be caused by changes in parameters regarding an age, a metabolic condition and the level of PTH in between two patients group.

Furthermore, another study evaluating PHPT, the incidence of parathyroidectomy and the association of PHPT with age and gender was conducted by Richerta et al., based on a population of patients taken from Switzerland (25). They suggested that the incidence of PHPT significantly elevates by age and the difference between two genders becomes clearer by the increase in age (24). The incidence of parathyroid adenomas starts enhancing at the age of forties and reaches at significantly increased rates when patients are over 65 and eventually make a peak after the age of 80. This alteration appearing with age may explain the difference between the results of the studies.

**CONCLUSION**

By considering all mentioned information, we concluded that MIBI scanning is, currently, the best imaging method for localization of parathyroid adenomas. The ideal imaging protocol should include a combination of SPECT study that is not prolonged over 1 hour with an early and a late planar (15 minutes and 2 hours, respectively) imaging. We determined that the level of PTH is the only biochemical parameter that directly associated with positivity of MIBI. Moreover, our findings revealed that the rate of E/L is negatively correlated with $Ca^{+2}$ and P whilst RI exhibited a positive association with $Ca^{+2}$ and P. Previous studies also suggested that the content of oxyphilic cells is not a single and the most important parameter affecting MIBI absorption.

The biochemical parameters including $Ca^{+2}$ and P levels are not clearly predictive for scintigraphy results and the localization of adenomas. However, serum PTH values should be considered in ectopic parathyroid adenomas prior to scintigraphic imaging. The possibility of ectopic parathyroid adenomas should be beared in mind especially the blood levels of PTH are high.

Imaging protocols and radionuclides used for imaging of parathyroid gland have changed and different protocols were developed by researchers by the time. Currently, Tc99m MIBI is commonly used as a chosen radiopharmaceutical agent for imaging of parathyroid and thyroid tissues. The principle of imaging by Tc99m MIBI is based on the differences in the mechanisms and amount of radiopharmaceutical agent`s uptake by

parathyroid and thyroid glands and its duration of elimination from these tissues. Specialists in nuclear medicine that are responsible for performing imaging and analysis of its results should be careful and consider uptake and elimination principles of Tc99m MIBI when they decide the use of either planar or SPECT imaging method.

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**Table 1.** Current Recommendations for Surgery in Asymptomatic PHPT (2)

| | |
|---|---|
| Serum calcium (>upper limit of normal) | 1.0 mg/dL (0.25 mmol/L) |
| Skeletal | A. BMD by DEXA: T-score < −2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius* |
| | B. Vertebral fracture by x-ray, CT, MRI, or VFA |
| Renal | A. Creatinine clearance < 60 cc/min B. 24-h urine for calcium >400 mg/d (>10 mmol/d) and increased stone risk by biochemical stone risk analysis** C. Presence of nephrolithiasis or nephrocalcinosis by x-ray, ultrasound, or CT |
| Age, y | <50 |

BMD: Bone Mineral Dansity, DEXA: Dual Energy X-ray Absorbsiometry, CT: Computarized Tomography, MRI: Magnetic Resonace Imaging, VFA: vertebral fracture assessment

*Consistent with the position established by the ISCD, the use of Z-scores instead of T-scores is recommended in evaluating BMD in premenopausal women and men younger than 50 y

**Most clinicians will first obtain a 24-hour urine for calcium excretion. If marked hypercalciuria is present (>400 mg/d [>10 mmol/d]), further evidence of calcium-containing stone risk should be sought by a urinary biochemical stone risk profile, available through most commercial laboratories. In the presence of abnormal findings indicating increased calcium-containing stone risk and marked hypercalciuria, a guideline for surgery is met.



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**Table 2.** Assessment of difference in between two study groups regarding parameters listed below

| | RI | Early PT/T | Late PT/T | E/L | PTH (pg/mL) | $Ca^{+2}$ (mg/dL) | P (mg/dL) |
|---|---|---|---|---|---|---|---|
| Ectopic | 17,8±17,5 | 1,1±0,4 | 1,16±0,2 | 0,8±0,1 | 222 (IQR=160-561) | 10,53±1,51 | 2,6±0,8 |
| Eutopic | 20,2±24,9 | 1,2±0,4 | 1,3±0,3 | 0,8±0,1 | 151 (IQR=119-303) | 10,68±0,998 | 3±0,8 |
| p | 0.865 | 0.175 | 0.803 | 0.219 | **0.001** | 0.102 | 0.075 |

RI: Retention Index, PT: Parathyroid, T: Thyroid, E: Early, L: Late, PTH: Parathyroid hormone, $Ca^{+2}$: Calcium, P: Phosphorus. IQR: Interquartile range. $p<0.05$ was considered to represent a significant difference for all statistics.



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**Table 3.** Associations between parameters in a group of patients with ectopic parathyroid adenomas

| | $Ca^{+2}$ | P | PTH |
|---|---|---|---|
| RI | **rho = 0,325, p= 0,013** | **rho = 0,410, p= 0,003** | rho = 0,143, p= 0,272 |
| Early PT/T | **rho = -0,403, p= 0,002** | rho = -0,268, p= 0,058 | rho = -0,126, p= 0,332 |
| Late PT/T | rho = -0,188, p= 0,158 | rho = -0,085, p= 0,555 | rho = -0,077, p= 0,556 |
| E/L | **rho = -0,311, p= 0,017** | **rho = -0,318, p= 0,023** | rho = -0,058, p= 0,658 |

RI: Retention Index, PT: Parathyroid, T: Thyroid, E: Early, L: Late, PTH: Parathyroid hormone, $Ca^{+2}$: Calcium, P: Phosphorus, rho: Spearman's rank correlation coefficient, p: level of significance. p<0.05 was considered to represent a significant difference for all statistics.

**Table 4.** Associations between parameters in a group of patients with parathyroid adenomas that are located at eutopic position

| | $Ca^{+2}$ | P | PTH |
|---|---|---|---|
| RI | rho = 0,200, p= 0,131 | rho = 0,101, p= 0,480 | rho = 0,065, p= 0,618 |
| Early PT/T | rho = -0,074, p= 0, 580 | rho = -0,267, p= 0,058 | rho = -0,072, p= 0,584 |
| Late PT/T | rho = 0,145, p= 0,279 | rho = -0,240, p= 0,090 | rho = 0,012, p= 0,929 |
| E/L | rho = -0,200, p= 0,131 | rho = -0,101, p= 0,480 | rho = -0,065, p= 0,618 |

RI: Retention Index, PT: Parathyroid, T: Thyroid, E: Early, L: Late, PTH: Parathyroid hormone, $Ca^{+2}$: Calcium, P: Phosphorus. rho: Spearman's rank correlation coefficient, p: level of significance. p<0.05 was considered to represent a significant difference for all statistics.



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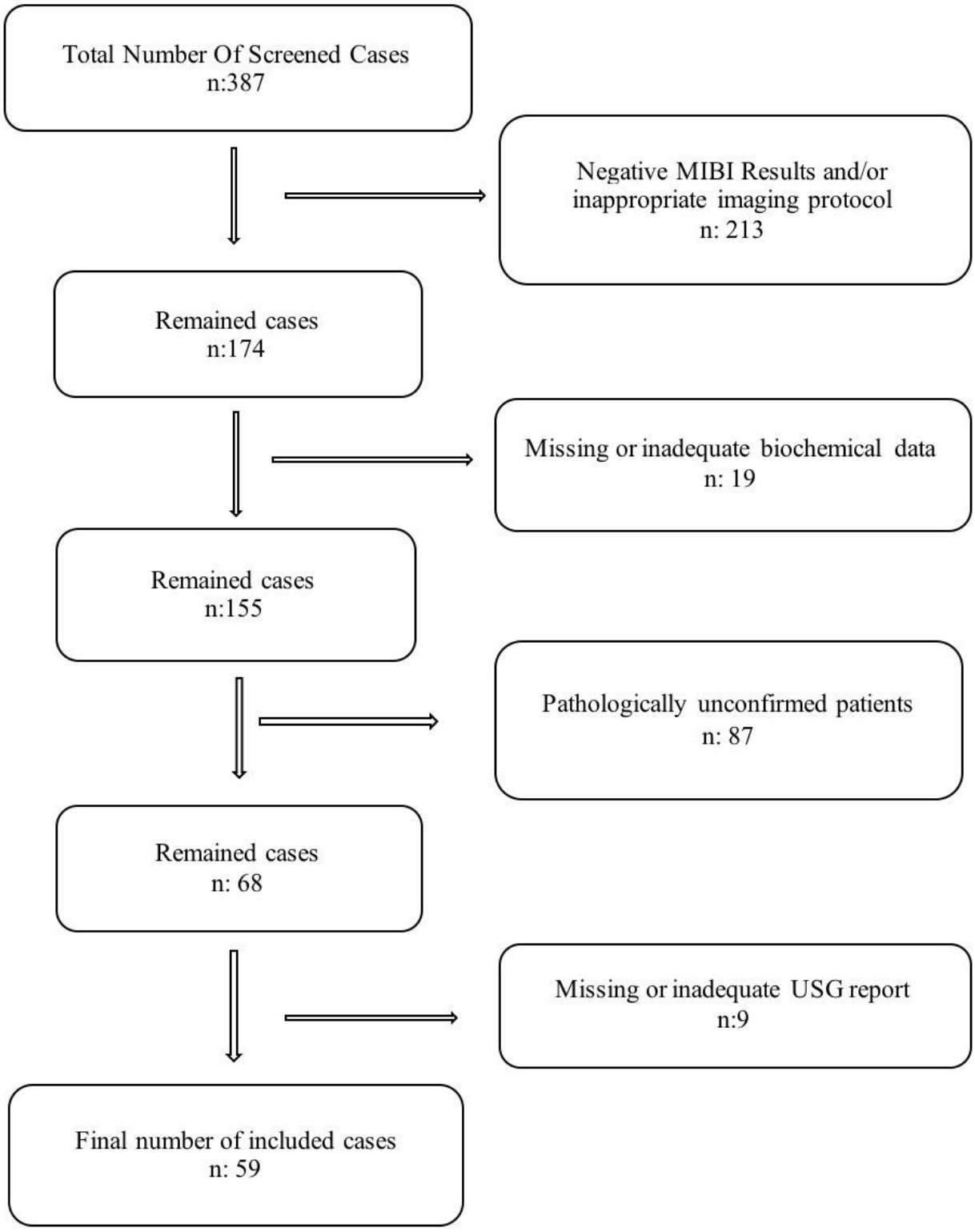


**Figure 1**

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