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Original Research

The Effectiveness of Preoperative Ultrasonography and Scintigraphy in the Pathological Gland Localization in Primary Hyperparathyroidism Patients

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Abstract

Objectives: Primary hyperparathyroidism (pHPT) is a common disease, and its curative treatment is surgical. Nowadays, preoperative localization studies have become standard before surgical treatment, and the first stage imaging methods are ultrasonography and/or scintigraphy. With the contribution of these studies to the localization of the pathological gland, focused surgery has become the first standard of choice. In this study, we aimed to evaluate the efficacy of ultrasonography and scintigraphy in the preoperative localization of the pathologic gland or glands in patients who underwent surgical treatment and cure for pHPT.

Methods: In this study; the data of the biochemically diagnosed pHPT patients, who had Tc 99m-MIBI scintigraphy and/or ultrasonography for localisation preoperatively, were evaluated retrospectively. The lesion, which was positive in USG or scintigraphy for localization, was evaluated according to the neck side or neck quadrant, and the results were compared with intraoperative localization findings. The effectiveness of both methods and combinations was evaluated with the localization rates, sensitivity and positive predictive values (PPV). The three methods were compared with the Youden index (J).

Results: The mean age of 380 patients included in this study was 54.8±12.8 years (20-83). Three hundred eight of them were female, and 72 were male. Scintigraphy was performed in 339 patients, USG was performed in 344 patients, and both USG and scintigraphy were performed in 306 patients. One hundred twenty patients (32%) underwent bilateral neck exploration (BNE), and 260 patients (68.4%) underwent minimally invasive parathyroidectomy (MIP) (unilateral exploration or focused surgery). Single adenoma was detected in 358 (94%), double adenoma in 10 (3%) and hyperplasia in 12 (3%) patients.

Localization rates of USG, scintigraphy, USG and scintigraphy combinations were 53%, 74%, 75%; their sensitivity was 56%, 85%, 89%; PPDs were 90%, 86%, 83%. The efficiency of scintigraphy is higher than USG (J: 0.743 vs 0.527). The contribution of scintigraphy to USG in combination with USG was limited (J: 0.743 vs 0.754).

The localization rates of USG, scintigraphy, USG and scintigraphy combinations were 46%, 64%, 66%; their sensitivity was 51%, 83%, 88%; PPDs were 79%, 74%, 73%. The efficiency of scintigraphy is higher than that of USG (J: 0.64 vs 0.427). The contribution of scintigraphy to USG in combination with USG was limited (J: 0.64 vs 0.66).

Conclusion: In patients with pHPT, scintigraphy is a more effective method for USG as the first step preoperative imaging and should be preferred as the first method if there is no contraindication. A combination of scintigraphy with USG may contribute minimally to the efficacy of scintigraphy. It may be advantageous for early detection of the pathologic gland in patients with incompatible two imaging and initiating surgery on the positive side of the first scintigraphy. Scintigraphy and USG methods may allow successful MRP surgery in the majority of patients with pHPT.

Keywords: Gland localisation; Primary hyperparathyroidism; scintigraphy; ultrsonography.

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Primary hyperparathyroidism (pHPT) is one of the most common endocrine diseases and the most common cause of hypercalcemia in outpatient clinics. The diagnosis of pHPT is made biochemically and the only curative treatment is surgery.[2] Bilateral neck exploration (BNE) was the standard surgical approach in the treatment of pHPT for many years in the past, and the surgical cure rate has been achieved above 95% in experienced centers.[3]

In the last quarter of the last century, USG and scintigraphy have been used for parathyroid imaging,[4, 5] and parallel to the rapid development of technology, both these methods have been developed, and new imaging methods have been identified.[6, 7] In addition, the use of intraoperative assistive methods, such as intraoperative parathyroid hormone (ioPTH) has increased gradually.[8] 80-85% of pHPTs are due to a single adenoma and the only excision of the enlarged gland is sufficient for treatment.[9] Based on that the disease is often a single gland disease; there has been a shift to MIP from BNE in parathyroid surgery with the contribution of preoperative imaging and intraoperative assistive methods. Although BNE is currently the gold standard therapy in the treatment of pHPT, MIP has become the standard treatment option in selected patients with positive imaging.[10]

The cure rate in selected patients with MIP was similar to that of BNE. It has been reported that patients with MIP have less total complication rates, shorter operative time, lower postoperative pain, less analgesic requirement, shorter hospital stay, and better cosmetic outcome and less fibrosis in the early period than BNE.[11,12]

The contribution of preoperative imaging methods to BNE is limited and it is possible to apply it without the need for any imaging method.[7] However, to perform MIP, the location of the pathological gland needs to be localized with preoperative imaging.[6] MIP is the first choice in the treatment of pHPT in patients in whom the preoperative enlarged solitary adenoma can be localized. Since every patient with sporadic pHPT for surgical indications is a potential MIP candidate, preoperative imaging methods are standard.[6] USG and MIBI scintigraphy are widely used as first-line imaging and are often combined.[7]

In our clinic, the combination of preoperative MIBI and USG is also routinely performed as first-line imaging. In this study, we aimed to evaluate the efficacy of ultrasonography and scintigraphy to localize the pathological gland alone and also in combination in patients who were undergoing surgical treatment for pHPT.

Methods

Data of patients who underwent surgery for the diagnosis of pHPT (AI, MU) between 2000 and 2015 were reviewed retrospectively with the approval of the local ethics committee. Preoperative imaging methods, intraoperative findings and postoperative pathologic results of the patients were evaluated (Table 1). All patients underwent preoperative sestamibi (MIBI) scintigraphy and/or ultrasonography. Scintigraphy was performed as planer MIBI or MIBI SPECT (single photon emission scintigraphy). All symptomatic patients who accepted surgery and those with asymptomatic pHPT and surgical indications were operated. For the surgical indication of asymptomatic patients, the latest versions of the guidelines of the international working group, first published in 1990 and then updated in 2002, 2008, 2013, were considered.[13–16]

Both sides of the neck were explored with a standard cervical Kocher incision in bilateral exploration. In focused surgery (FC), the sternocleidomastoid (SCM) was incised 2-3 cm from the anterior edge of the muscle; only the enlarged gland was explored with access between the anterior edge of the SCM and lateral edge of the infrahyoid muscles and the other gland on the same side was not observed. In unilateral neck exploration (UNE), as in FC, it was entered at the anterior edge of the SCM through a 2-3 cm incision made laterally or with a Kocher incision in the midline, and the enlarged gland on one side of the neck and normal gland on the same side were explored. Both methods were defined as MIP.[17,18]

FC or UNE was applied to patients with positive two imaging, and UNE was applied to patients with positive single imaging. BNE was performed in patients in whom two

Table 1. Demographic profile, preoperative imaging modalities, intervention types aand pathology results

	n (%)
Mean age + SD (min-max)	54.8+12.8 (20-83)
Gender	
Female	308 (81)
Male	72 (29)
Preoperative imaging	
USG	344 (91)
Scintigraphy	339 (89)
USG+Scint	306 (81)
Surgeries	
BNE	120 (32)
UNE or FS	260 (68)
Pathology	
Simple adenoma	358 (94)
Double adenoma	10 (3)
Hyperplasia	12 (3)

SD: standard deviation; USG: ultrasonography; Scint: scintigraphy; BNE: bilateral neck exploration; UNE: unilateral neck exploration; FS: focused surgery.

views were negative or two images were discordant. When the pathological gland could not be detected on the side where the imaging was positive in FC or UNE, two normal glands or two enlarged glands were observed; it was switched to BNE. In order to return to BNE, the lateral incision was extended from the midline to the other side and converted to a standard Kocher incision.

This study included patients with pHTP with at least one preoperative visualization method who had undergone first surgery or persistent and had cured by the second operation. Although preoperative USG and scintigraphy were applied to all patients, the examination results of some of the patients who were examined outside our center could not be reached. The only imaging study available for these patients was evaluated. Patients with pHPT whose data were not available, patients with recurrent and persistent pHPT, patients with secondary and tertiary hyperthyroidism, and pregnant patients were excluded from the study. 380 of 402 patients with pHPT operated during this period were included in the study. The recurrence of hypercalcemia was defined as persistent in the first six months postoperatively and recurrent disease after six months.

Preoperative imaging methods were evaluated by dividing the neck into two sides as right and left sides and four quadrants as right lower, right upper, left lower and left upper. In USG detection of the lesion, which is suspicious or consistent with one or multiple parathyroid pathologies was considered as positive and no lesion detection as negative. One or multiple abnormal MIBI retention on scintigraphy was considered as positive and no retention as negative.

Preoperative imaging findings were compared with intraoperative findings. Intraoperatively enlarged parathyroids were confirmed by frozen examination or paraffin section histopathological examination. If a single adenoma was detected on the USG and scintigraphy in the solitary scintigraphy with MIBI involvement, in the side or quadrant where abnormal lesion detected in the USG, it was evaluated as positive in the presence of multiple gland disease with MIBI or USG findings and confirmed intraoperatively at the same locations. In the combination of USG and scintigraphy, one true positive imaging was considered as sufficient. Although preoperative imaging revealed a single gland in different locations or a single focus in imaging, preoperative imaging was considered to be false positive when multiple gland disease was detected. Negative imaging for single or multiple gland disease was evaluated as false negative. The localization rates of the pathological glands, sensitivities and positive predictive values (PPV) were calculated for USG and scintigraphy. Sensitivity is the probability that the test is positive for the pathological gland or the rate at which it can detect the pathological gland. PPV expresses the accuracy rate of the positive test; in other words, how much PPV can show the pathological gland when the test is positive.

Localization rate: 100xTP (n)/Total (n)), Sensitivity: TP/(TP+FN), PPV: TP/(TP+FP). The efficacy of USG, scintigraphy and the combination of the two tests were compared with the Youden Index (J). The test with higher J value, calculated as J=1- (FN+FP) formula, was considered to be more effective.

Results

Ultrasonography

The localization rates of USG according to neck side and neck quadrant were 53% and 46%, respectively; sensitivity was 56%, 51%; PPV was 90% and 79% (Tables 2, 3).

Table 2. Preoperative localization rates of the imaging methods according to the neck side (right, left)

	Total, IM	LR, (%)	TP	FP	FN	Sensitivity, (%)	PPV, (%)	Youden index
USG	344	53	181	19	144	56	90	0.527
Scintigraphy	339	74	252	41	46	85	86	0.743
USG+Scintigraphy	306	75	231	47	28	89	83	0.754

IM: imaging method; LR: localization rate; USG: ultrasonography; TP: true positive; FP: false positive; FN: false negative; PPV: positive predictive value.

Table 3. Preoperative localization rates of the imaging methods according to the neck quadrants (lower and upper right, lower left and upper)

	Total IM	LR, (%)	TP	FP	FN	Sensitivity, (%)	PPV, (%)	Youden index
USG	344	46	157	43	154	51	79	0.427
Scintigraphy	339	64	217	76	46	83	74	0.64
USG+Scintigraphy	306	66	202	76	28	88	73	0.66

IM: imaging method; LR: localization rate; USG: ultrasonography; TP: true positive; FP: false positive; FN: false negative; PPV: positive predictive value.

Scintigraphy

Localization rates of scintigraphy were 74%, 64%; sensitivity was 85%, 83%; PPV was 86% and 74% (Tables 2, 3).

Combination of Scintigraphy and Ultrasonography

Localization rates of scintigraphy and USG were found to be 75%, 66%, sensitivity 89%, 88%, PPV 83% and 73%, respectively, relative to the neck side and neck quadrant (Tables 2, 3).

Comparison of the Efficiency of Imaging Methods

The efficiency of scintigraphy according to the side of the neck was higher than that of the USG (J: 0.527 vs 0.743). Although scintigraphy had a localization rate of 21% and a sensitivity of 29% higher than USG, PPV was 4% lower than USG (86% vs 90%, respectively) (Table 2). Combination of scintigraphy with USG showed a 1% increase in localization rate and 4% increase in sensitivity compared to scintigraphy. The PPV ratio decreased by 3% (PPV: 83% vs 86%, respectively: J: 0.754 and 0.743).

The efficiency of scintigraphy according to the quadrant of the neck was higher than the USG (J: 0.427 vs 0.64). Although scintigraphy had a localization rate of 20% and a sensitivity of 32% higher than USG, PPV was 5% lower than USG (74% vs 79%, respectively) (Table 3). Combination of scintigraphy with USG increased the localization rate by 2% and sensitivity by 5% compared to scintigraphy. The PPV ratio was similar (PPV: 73% vs 74%, J: 0.66 vs 0.64, respectively).

Discussion

Today, MIP has become the standard in parathyroid pathologies that can be localized with preoperative imaging methods and new imaging methods in pHPT. Sensitivity and PPV of imaging methods in pHPT are the variables that show the accuracy of the tests to determine the localization of pathological glands. The most commonly used imaging methods for imaging in pHPT are USG, scintigraphy, or a combination of these.[7]

USG is an inexpensive, widely available, portable, radiation-free imaging technique with good anatomical resolution. In the literature, the sensitivity of conventional USG varies between 49-89%, and PPV varies between 78-98%.[19–25] In the meta-analysis of 19 studies, the combined sensitivity was 76% and PPV was 93%.[26]

In our study, the rate of localization of the pathological gland according to the neck side was 53%, the sensitivity rate was 56% and the PPV rate was 90%. In the other two studies, the localization rates were 77% and 94% by USG, while these rates decreased to 66% and 87% according to the quadrant of neck, respectively.[20, 27]

Sensitivity and PPV of USG and scintigraphy in pHPT may be affected by many factors. In our study, although the sensitivity rates were within the limits of the literature, it was noteworthy that they were in the lower limits. The factors that could affect the localization of the pathological gland were not evaluated in this study. However, one of the factors affecting the low sensitivity rate may be the experience of the radiologist. It may be related to the lack of experience of endocrine USG by radiologists who perform the ultrasound of patients referred to our center from other centers and young trainee radiologists who generally perform USG in our center, which is a training and research hospital. The sensitivity and PPV of the USG performed by an experienced radiologist or experienced surgeon increase.[20, 28] Referral of patients with negative or incompatible imaging to our center may also contribute to this situation. Multinodular goiter, posterior or intrathyroidal lesions of the thyroid, ectopic localizations, small glands and multiple gland diseases and obesity of the patient decrease sensitivity.[9, 19, 24, 26, 27, 29–31]

Although thyroid nodules decrease the sensitivity of USG, 29-51% additional thyroid pathology is present in patients with pHPT and thyroid pathologies can be evaluated with USG.[31]

Sestamibi is frequently used in parathyroid scintigraphy and some different protocols can be used in scintigraphy. Sensitivity rate is 44-89% and the PPV rate is 74-100% concerning localization of the pathological gland by scintigraphy.[19, 21, 22, 24, 25, 32]

In the meta-analysis of the nine sestamibi SPECT study, the combined sensitivity rate was 79%, and the PPV rate was 91%.[26]

In our study, the rate of localizing the pathologic gland was 74%, sensitivity 85%, and PPV 86% according to the neck side of the scintigraphy. According to the quadrant, the localization rate decreased to 64%; sensitivity was 83% without being affected much, PPV decreased to 74%. In the literature, it was reported that quadrant localization concerning lateralization decreased from 70% to 58% in Al-Kurd et al.'s study and from 52% to 42% in Atkisson et al.'s study.[27, 28] One of the main reasons for high sensitivity and PPV in scintigraphy is that scintigraphy is not operator-dependent like USG. However, many factors may affect the sensitivity of scintigraphy. In the literature, the patient's being symptomatic, preoperative higher calcium level, higher PTH value, vitamin D deficiency, higher oxyphil cell ratio in adenoma, inferior neck adenoma, thyroid suppression, parathyroid stimulation are the factors that increase the sensitivity of scintigraphy. The use of calcium channel blocker, multinodular goiter, small parathyroid adenoma, and multiple gland disease are factors that decrease sensitivity.[29, 30, 33]

There is no generally accepted algorithm for the use of USG or scintigraphy as the first-line test in the imaging of pHPT.[7, 29] In some studies, it was found that the pathological gland could detect the USG and the first USG must be selected,[27, 34, 35] others had higher efficacy of scintigraphy and scintigraphy was recommended as the first test.[21] In some studies, the combination of scintigraphy and USG has been suggested to increase the sensitivity, and the use of these methods in combination was recommended.[19, 36] Many centers now combine two imaging modalities.[25, 29]

Although these methods have been used in our center in combination and the localization rate and sensitivity of scintigraphy according to USG both neck side and quadrant are significantly higher, PPV decreases slightly. Our results suggest that scintigraphy is more effective in localization than USG. When scintigraphy is combined with USG, the sensitivity increases, but PPV decreases slightly. It can be said that the combination of scintigraphy with USG makes a small contribution to localization. However, the contribution of USG may be more significant when performed by an experienced radiologist. The combination of SPECT or SPECT/CT with USG by an experienced ultrasonographer before the first intervention is reported to be the optimal combination option.[37] Kluijfhout et al. proposed scintigraphy as SPECT-CT as the first imaging method. Sensitivity did not increase, and PPV significantly decreased compared to SPECT scintigraphy when USG applied before SPECT scintigraphy and when two methods were combined. It has been reported that USG is significantly better to confirm scintigraphy findings after SPECT scintigraphy.[21] When both imaging methods are combined, MRP can be performed with a high success rate without intraoperative PTH in patients with both positive and compatible imaging results.[19] In our study, surgical curing with MRP was achieved in 2/3 of the patients with the contribution of imaging methods.

Although there is a sufficient number of case in this study, given that this study is retrospective and the lack of scintigraphy and USG findings in some patients and the failure to elaborate scintigraphic application methods can be considered as the main limitations of our study.

Conclusion

In conclusion, scintigraphy is a more effective method for USG for first-stage preoperative imaging in patients with pHPT and the scintigraphy should be primarily preferred in the absence of contraindications. The combination of scintigraphy with USG may contribute minimally to the effectiveness of scintigraphy. In patients with incompatible two imaging and undergoing BNE, starting surgery from the scintigraphy positive part may be advantageous in the early detection of the pathological gland. Scintigraphy and USG methods may allow successful MRP surgery in the majority of patients with pHPT.

Disclosures

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