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Evaluation of the minimally invasive parathyroidectomy in patients with primary hyperparathyroidism: A retrospective cohort study

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HIGHLIGHTS

- We examined diagnostic accuracy for 48 patients with primary hyperparathyroidism.
- All 39 patients in the MIBI-positive group were diagnosed with a single adenoma.
- The preoperative diagnostic accuracy in MIBI-negative patients was only 50%.
- We advise minimally invasive parathyroidectomy is avoided in MIBI-negative patients.

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ABSTRACT

Introduction: An accurate differential diagnosis between single adenoma (SA) and multiglandular disease (MGD) remains difficult in Technetium-99m sestamibi scintigraphy (MIBI)-negative patients with primary hyperparathyroidism (PHPT). The aim of the present study was to evaluate the minimally invasive parathyroidectomy (MIP) in patients with PHPT.

Methods: Clinical records of 48 patients who underwent neck exploration between November 2002 and June 2012 in Kochi Medical School Hospital were reviewed retrospectively to identify candidates that underwent for MIP which was defined as the selective removal of a SA using less invasive surgery.

Results: The preoperative detection rate of lesions using ultrasonography, MIBI, computed tomography, and magnetic resonance imaging was 90%, 83%, 76%, and 55%, respectively. Although all 39 patients in the MIBI-positive group were diagnosed with an SA and subsequently underwent curative MIP, 3 patients in MIBI-negative group ($n = 6$) were MGD, who underwent neck exploration. Preoperative mean intact parathyroid hormone (419 pg/ml vs. 149 pg/ml; $P < 0.01$) and alkaline phosphatase levels (746 U/l vs. 277 U/l; $P < 0.01$) were significantly higher in the SA than MGD group.

Conclusions: In MIBI-negative patients with indications for surgery, MIP should not be carried out without a clear localization of SA, or in MGD.

1. Introduction

Primary hyperparathyroidism (PHPT) is a generalized disorder of calcium, phosphate, and bone metabolism caused by increased secretion of parathyroid hormone. PHPT is a relatively common disease, with an estimated prevalence of 0.3% of the population [1]. In approximately 80% of PHPT cases, a benign single adenoma (SA) is responsible, whereas multiple adenomas, parathyroid hyperplasia, and parathyroid cancer account for approximately 5%, 15%, and <1% of cases, respectively [2].

Traditionally, symptomatic PHPT presents various symptoms of hypercalcemia, such as fatigue, nausea, dysorexia, peptic ulcer disease, diarrhea, changes in mental status, recurrent kidney stones, and bone discomfort or evidence of bone loss [1].

The traditional gold standard surgical treatment for PHPT is bilateral neck exploration (BNE) to identify all parathyroid glands and remove the adenomas. Based on the assumption that most cases of PHPT are due to an SA, curative excision of the affected

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gland following unilateral neck exploration (UNE), including identification of the ipsilateral normal parathyroid, was explored in the early 1980s as a new treatment for PHPT. Recently, minimally invasive parathyroidectomy (MIP) with adequate preoperative imaging for the selective removal of a SA has replaced BNE or UNE [3–5]. To improve the cure rate, patients must be carefully selected for MIP to ensure that only SA exists and to exclude multiglandular disease (MGD), including hyperplasia and multiple adenomas. Specifically, MIP is indicated in selected patients with PHPT caused by an SA.

Ogo et al. [6] suggested that surgical indications for asymptomatic PHPT should be determined in general according to the revised guidelines of the Fourth International Workshop on the Management of Asymptomatic PHPT, which provides recommendation for a surgical approach along with monitoring those who do not undergo parathyroid surgery [7]. Surgery is always an option because it is the only definitive therapy for PHPT, while surgery is not mandatory in some patients with asymptomatic disease. In addition, it is desirable that technetium-99m sestamibi (MIBI) scintigraphy be performed whenever possible, because this modality plays an important role in determining whether surgery is appropriate [6]. MIBI has proved to be one of the most reliable modalities for the localization of affected parathyroid glands, including differential diagnoses between SA and MGD. Unfortunately, obtaining an accurate differential diagnosis between SA and MGD in MIBI-negative patients remains difficult. The aim of the present retrospective study was to evaluate the characteristics of patients with PHPT who underwent MIP.

2. Patients and methods

The clinical records of 49 consecutive patients who underwent primary parathyroidectomy for PHPT between November 2002 and June 2012 in Kochi Medical Hospital were reviewed retrospectively (Fig. 1). One patient with cancer was excluded, but the remaining 48 patients (44 with SA and four with MGD) were included in the study. Medical records were obtained for all 48 patients, including information regarding the patients' clinical condition, laboratory data for intact parathyroid hormone (iPTH; upper limit of normal (ULN) 65 pg/mL), serum calcium (s-Ca; ULN 10.4 mg/dL), phosphate (ULN 5.3 mg/dL), and alkaline phosphatase (ALP; ULN 340 U/L) and diagnostic imaging for MIBI, ultrasonography (US), computed tomography (CT), or magnetic resonance imaging (MRI). Unfortunately, data regarding creatinine clearance (CCr) and bone mineral density (BMD) are incomplete because these parameters were not measured in all patients in this series.

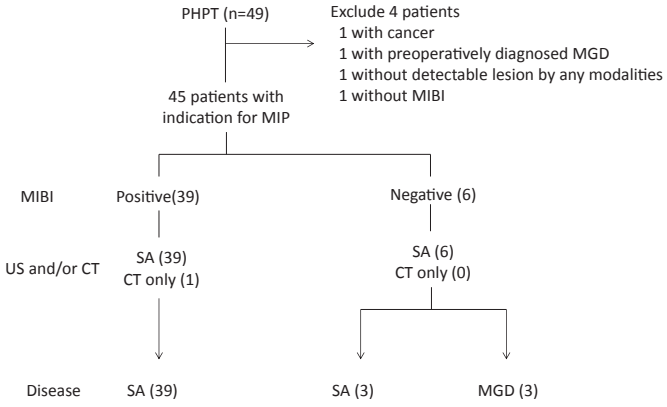

Fig. 1. Flowchart showing patient disposition in the present study. PHPT, primary hyperparathyroidism; SA, single adenoma; MGD, multiglandular disease; MIBI, technetium-99m sestamibi scintigraphy; MIP, minimally invasive parathyroidectomy; US, ultrasound; CT, computed tomography.

In Kochi Medical Hospital, MIP is indicated for patients who are diagnosed preoperatively as having an SA. In contrast, BNE is indicated in patients diagnosed preoperatively with MGD. Although defining the term "cure" after surgery is difficult, in the present study we defined a "cure" as restoration of both iPTH and s-Ca levels to within the normal range with no re-elevations for >1 year of follow-up. To perform MIP, mini-cervicotomy on midline or just above the tumor is made according to a precise preoperative localization of the adenoma. After an intraoperative confirmation of tumor, an adequate resection is performed, resulting in less invasive surgical procedure.

This study was fully compliant with the STROBE criteria [8], registering to the Research Registration (Research Registration Unique Identifying Number, researchregistry491). The approval of ethical review board in our institution was waivered according to the Ethical Guideline for Clinical Research issued by Ministry of Health, Welfare and Labor, Japan.

Data are presented as the mean ± SD. The significance of differences was evaluated using unpaired Student's *t*-test. Two-tailed $P < 0.05$ was considered significant.

3. Results

3.1. Study patients

The present cohort was comprised of 37 women and 11 men, with a mean (range) age of 61 ± 15 (19–87) years. All 48 patients were evaluated preoperatively by US, and MIBI, CT, and MRI were further performed in 47 (98%), 33 (69%), and 11 (23%) patients, respectively. The preoperative detection rate of lesions using US, MIBI, CT, and MRI was 90%, 83%, 76%, and 55%, respectively. In the final diagnosis, 44 patients were found to have an SA and only four had MGD.

Of the 48 patients in the study, 45 (94%) were selected as candidates for MIP (Fig. 1). Three patients were deemed not suitable for MIP: one with a preoperative diagnosis of MGD (final diagnosis MGD), one without detectable PHPT lesions regardless of the imaging modality used (final diagnosis SA), and one who had not undergone preoperative MIBI (final diagnosis SA). The 45 patients who underwent MIP were divided into two groups: an MIBI-positive group (n = 39) and an MIBI-negative group (n = 6). All 39 patients in the MIBI-positive group were diagnosed with an SA and subsequently underwent curative MIP. In the MIBI-negative group, three patients had a final diagnosis of MGD, which would normally exclude MIP. Of these three patients with MGD, two underwent UNE because we suspected MGD on the basis of intraoperative findings. However, one patient was treated with MIP alone because we had no suspicions of MGD during surgery and this patient refused to undergo further radical surgery, such as UNE or BNE, after the initial operation.

3.2. Patient characteristics and preoperative findings of patients with an SA and MGD

Preoperative characteristics and symptoms of patients with an SA and MGD are given in Table 1. There were 44 patients (nine men, 35 women) in the SA group and four patients (two men, two women) in the MGD group. The incidence of palpable neck tumor in the SA and MGD groups was 18% and 0%, respectively. Based on their preoperative symptoms, 75%, 11%, and 14% of patients in the SA group were classified as having chemical type, stone type, and bone type PHPT, respectively, compared with 75%, 25%, and 0%, respectively, in the MGD group (see Table 1). None of the patients

Table 1
Preoperative characteristics and symptoms in patients with single adenoma (SA) or multiglandular disease (MGD).

	SA (n = 44)	MGD (n = 4)
Age (years)	63 ± 11	60 ± 16
No. men/women	9/35	2/2
Symptoms		
Neck tumor palpable	8 (18%)	0 (0%)
Chemical type[a]	33 (75%)	3 (75%)
Abdominal pain	1	1
Joint pain	1	0
Depression	1	0
Nausea or loss of appetite	9	0
Asymptomatic	21	2
Stone type[b]	5 (11%)	1 (25%)
Bone type[c]	6 (14%)	0 (0%)

Data are given as the mean ± SD or as the number of patients in each group, with percentages in parentheses.
[a] Chemical type, patients are diagnosed on the basis of a blood test only; they do not have any urinary tract stones or symptoms on bones and tend to be in the early stages of the disease.
[b] Stone type, patients have urinary tract stones.
[c] Bone type, patients have bone symptoms such as pathological fractures or brown tumor.

with MGD had any family history suggestive of multiple endocrine neoplasia type 1 (MEN1) with PHPT, pituitary tumor, and/or pancreatic tumor.

Preoperative laboratory data of mean iPTH, ALP, s-Ca, and phosphate in the SA and MGD groups are shown in Fig. 2. Before surgery, mean iPTH (Fig. 2a) and ALP (Fig. 2b) levels were significantly higher in the SA than MGD group, but there were no significant differences in s-Ca (Fig. 2c) and phosphate (Fig. 2d) levels between the two groups.

3.3. Characteristics of MIBI-positive and -negative patients

Of the 45 patients who underwent MIP, 39 (87%) were MIBI positive. These patients were found to have a large single gland, compatible with SA, by preoperative US, CT, and/or MRI. Consequently, all these patients underwent curative MIP and the final diagnosis in all cases, based on histological examination, was SA. In MIBI-positive patients, the preoperative diagnostic accuracy was confirmed to be 100%.

The remaining six patients (13%) were MIBI negative (Fig. 1). Table 2 lists the preoperative findings in MIBI-negative patients. All six MIBI-negative patients were >50 years of age and had been diagnosed preoperatively as SA on the basis of US results. Three of these six patients (50%) were found to have been correctly diagnosed as SA after undergoing curative MIP, whereas the final diagnosis for the remaining three patients was MGD, and so two parathyroid glands were removed from these patients. Undoubtedly there are limitations to the accuracy of diagnoses based on imaging modalities. Another reason for the misdiagnosis of MGD as SA is that all concentration may be focused on a single enlarged gland in MGD, missing other small lesions, not only during preoperative imaging, but also on intraoperative US. For example, in one MIBI-negative patient, intraoperative US did not detect MGD because we misdiagnosed a neurogenic tumor near the thyroid as SA (Fig. 3). In the MIBI-negative group, although preoperative mean iPTH ($P = 0.311$), s-Ca ($P = 0.167$), and ALP ($P = 0.336$) levels tended to be lower in MGD than SA patients, the differences failed to reach statistical significance.

4. Discussion

MIBI and US are the most widely accepted methods for the preoperative localization of PHPT. Previous *meta*-analyses reported sensitivities and specificities of 68%–95% and 75%–100%, respectively, for MIBI [9] and 34%–92% and 92%–97%, respectively, for US [10]. Combining MIBI and US may increase the sensitivity further to 95% [11]. The preoperative sensitivity of US, MIBI, CT, and MRI was 90%, 83%, 76%, and 55%, respectively, which is comparable to the values reported previously [9–11]. In addition, the preoperative sensitivity of combining MIBI and US in the present study was 93% (42/45), which is also comparable to the value reported previously [11].

Combinations of various diagnostic imaging modalities, especially MIBI and US, may improve the accuracy of SA diagnosis [3,12,13]; however, the possibility remains of misdiagnosing MGD as SA. Indeed, for patients with a negative MIBI scan, preoperative localization of the affected gland and exclusion of MGD is incredibly difficult, with the diagnostic accuracy of US in patients with a negative MIBI scan reported to be 43% in a retrospective study on a large patient cohort [14].

In the present study, MIBI remained the most reliable imaging modality for diagnosing SA in PHPT patients. In our series of 48 patients with benign PHPT, all 39 MIBI-positive patients were found to have an SA, in agreement with preoperative US, CT and/or MRI results. These patients underwent MIP and were completely cured. Therefore, the findings of the present study suggest that MIP is a valuable therapeutic option for patients with SA diagnosed preoperatively using a combination of MIBI and other imaging modalities, such as US, CT, and/or MRI.

Conversely, in MIBI-negative patients, the preoperative diagnostic accuracy using conventional imaging modalities such as US, CT, and/or MRI in addition to MIBI was only 50%. Not surprisingly, there are diagnostic limitations with all imaging modalities. Indeed, three patients with MGD in the present study were misdiagnosed as SA because we focused on a single enlarged gland, missing other small lesions, not only on preoperative imaging, but also with intraoperative US. Of the three patients with MGD, two underwent UNE because MGD was suspected on the basis of intraoperative findings. However, one patient was treated with MIP alone because we had no suspicions of MGD during surgery and this patient refused to undergo further surgery, either UNE or BNE, even after the final diagnosis had been made. Therefore, more care needs to be exercised during surgery to ensure that MGD is not missed, particularly in MIBI-negative patients.

Recent reports suggest that single-photon emission computed tomography (SPECT) may improve the sensitivity and anatomical definition of imaging in patients for whom the MIBI planar images are difficult to interpret [15–19]. Therefore SPECT imaging may be helpful for the detection of smaller parathyroid adenomas in the thyroid bed and for improved delineation of subtle parathyroid adenomas located behind the thyroid gland. The sensitivity of SPECT for the detection of parathyroid adenoma reportedly ranges from 87% to 95%, which is higher than the sensitivity of MIBI [15–19]. Conversely, the sensitivity of SPECT for the detection of parathyroid hyperplasia is lower than that for the detection of adenoma, ranging from 53% to 67%, because the accumulation of the MIBI signal is much lower in hyperplastic glands than in adenoma [15–19]. Because most MGD is hyperplastic in nature, the sensitivity of SPECT is limited for the diagnosis of MGD and so SPECT may not adequately exclude MGD in PHPT patients [15–19]. Taking this into consideration along with the results of the present study, although indications for surgery in MIBI-negative patients have been determined, it is recommended that criteria other than those based on imaging studies should also be taken into account.

In 2011, the Fourth International Workshop on the Management of Asymptomatic PHPT convened to discuss the management of asymptomatic PHPT patients [7]. This panel determined that the criteria for surgical indications were elevated serum calcium

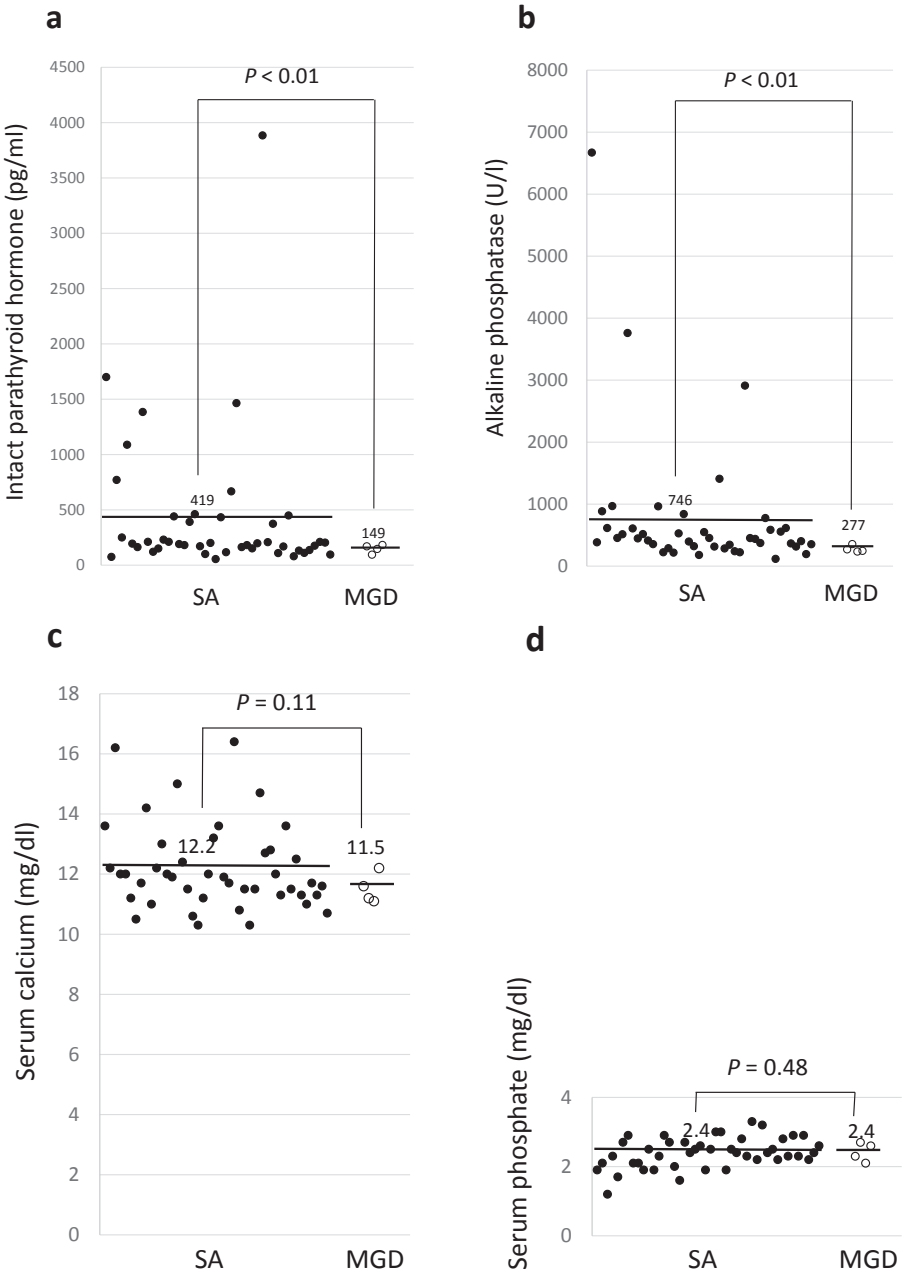

Fig. 2. Preoperative laboratory data showing mean (a) intact parathyroid hormone (iPTH), (b) alkaline phosphatase (ALP), (c) serum calcium (s-Ca), and (d) phosphate levels in patients with a single adenoma (SA) and multiglandular disease (MGD). Data show values in individual patients, with the horizontal line and the numbers indicating median. Both iPTH and ALP levels were significantly higher in the SA than MGD group. However, there were no significant differences in s-Ca or phosphate between the two groups.

Table 2
Preoperative findings of patients with negative technetium-99m sestamibi scintigraphy scans.

No.	Age (years)	Gender	Disease[a]	Symptoms[b]	iPTH (pg/mL)	Ca (mg/dL)	Phosphate (mg/dL)	ALP (U/L)	US[c]
1	79	F	MGD	Stone type	183	12.2	2.6	247	SA
2	58	M	MGD	Asymptomatic	95	11.2	2.7	356	SA
3	56	M	MGD	Pancreatitis	147	11.1	2.1	235	SA
4	61	F	SA	Vomiting	432	13.6	2.5	548	SA
5	85	F	SA	Bone type	1384	11.7	2.1	3761	SA
6	58	F	SA	Bone type	130.9	12.5	2.3	556	SA
P-value (*t*-test)					0.311	0.167	0.488	0.336	

PTH, intact parathyroid hormone; ALP, alkaline phosphatase; MGD, multiglandular disease; SA, single adenoma.
[a] Final disease diagnosis.
[b] Patients with “stone type” symptoms have urinary tract stones; those with “bone type” symptoms have symptoms such as pathological fractures or brown tumor.
[c] Preoperative diagnosis based on ultrasound (US) imaging.

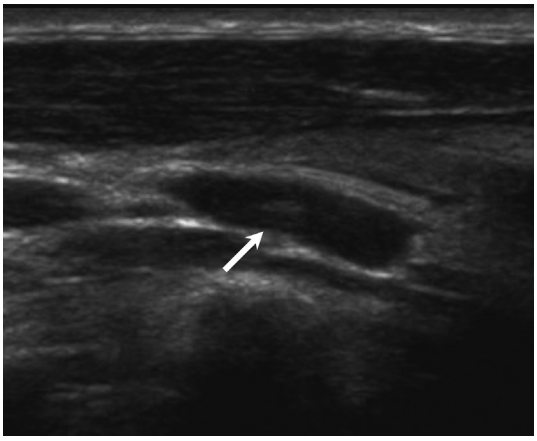

Fig. 3. Intraoperative ultrasound findings in a patient with negative technetium-99m sestamibi scintigraphy scans. This patient (No. 2, Table 2) had multiglandular disease, but the neurogenic tumor near the thyroid was misdiagnosed as SA.

concentrations (1.0 mg/dL more than the ULN), reduced CCr (<60 mL/min), reduced BMD (T-score less than −2.5 at any site and/or previous fracture fragility), and younger patient age (<50 years) [7]. The results of the present study reveal that there are no significant differences in symptoms between patients with SA and those with MGD in the group of MIBI-negative patients, but mean s-Ca concentrations in the three patients with SA tended to be higher than in the three patients with MGD (12.6 vs 11.5 mg/dL, respectively), and this may be a useful marker for the differential diagnosis of SA and MGD, as recommended by the Workshop criteria [7]. Further, the findings of the present study suggest that in addition to s-Ca, iPTH and ALP levels may be potential predictors in the differential diagnosis of SA and MGD in MIBI-negative patients. This is supported by the findings of Khorasani et al. [20], who reported that mean iPTH concentrations in patients with PHPT were significantly higher for those with MIBI positive than negative scans (589 + 373 vs 319 + 247 pg/mL, respectively). Hughes et al. [21] reported that MIBI and US had higher localization rates and positive predictive value for PHPT with increasing preoperative s-Ca and iPTH levels. Together, these findings indicate that the biochemical severity of PHPT may be correlated with the localization accuracy of MIBI and US. Unfortunately, however, there were no positive predictive values in MIBI-negative patients in the present study because the differences in potential biochemical markers (i.e. iPTH, s-Ca, and ALP) between SA and MGD did not reach statistical significance.

Even if patients are diagnosed preoperatively as SA using other imaging modalities, the possibility of MGD should be kept in mind and care taken during surgery to identify findings suggestive of MGD. In addition, even if there is only a slight suspicion of MGD, MIP should be switched to more radical surgery, such as UNE or BNE. Interestingly, more invasive surgery is required for MGD than SA even though the severity of the symptoms due to hyperthyroidism in MGD is milder than in SA because almost all MGD is hyperplastic. More aggressive surgery is required for patients with MGD because of the multiple locations of disease, rather than because of the hyperplastic nature of MGD as opposed to the adenoma in SA. However, in contrast with SA, in which there is high cellular activity, surgical indications for MGD with mild symptoms should be approached cautiously. In the present study, none of the patients with MGD had a family history suggesting MEN1.

We recognize the following limitations of the present study. First, this study includes the errors and biases inherent in a retrospective study design. Second, the number of patients with MIBI-negative hyperparathyroidism is only six patients, and only four patients have MGD. Further studies with adequate statistical power and a larger number of patient subgroups are needed to examine the methods for a more accurate preoperative diagnosis of MGD in MIBI-negative patients.

5. Conclusion

The preoperative diagnostic accuracy using conventional imaging modalities such as US, CT, and/or MRI in MIBI-negative patients was only 50%. In addition, we could not identify positive predictive values in these patients. Therefore, in MIBI-negative patients with indications for surgery, MIP should be avoided and UNE or BNE performed instead.

Ethical approval

Not applicable.

Role of funding source

No authors received any funding.

Author contribution

Toriie S. contributed for the drafting of manuscript.

Sugimoto T. contributed for the study design, analysis and interpretation of data and drafting manuscript.

Hokimoto N. contributed for the acquisition of data.

Funakoshi T. contributed for the acquisition of data.

Ogawa M. contributed for the acquisition of data.

Oki T. contributed for the acquisition of data.

Dabanaka K. contributed for the acquisition of data.

Namikawa T. contributed for the drafting of manuscript and critical revision.

Sakurai A. contributed for the drafting of manuscript and critical revision.

Hanazaki K. contributed for the drafting of manuscript and critical revision.

Conflicts of interest

All authors have no conflicts of interests to disclose.

Consent

Written informed consent was obtained from each patients.

Guarantor

Tsutomu Namikawa, M.D., Ph.D.

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