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ORIGINAL ARTICLE

CT-MIBI-SPECT image fusion predicts multiglandular disease in hyperparathyroidism

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Abstract
Background To perform focused or minimally invasive surgery for hyperparathyroidism (HPT) exact preoperative localization is mandatory. Computed tomography–^{99m}Tc-sestamibi–single photon emission computed tomography image fusion (CT-MIBI-SPECT) serves this difficult task in single gland HPT to a large extent. The aim of this study was to evaluate whether CT-MIBI-SPECT image fusion is superior to MIBI-SPECT alone and CT alone in detecting abnormal parathyroid tissue in patients with multiglandular disease.
Patients and methods CT-MIBI-SPECT image fusion for preoperative localization was performed in 30 patients with multiglandular disease. There were six patients with primary hyperparathyroidism (four MEN I syndromes and two double adenomas; one of these patients has HRPT2 gene mutation), 14 with secondary, and eight with tertiary HPT, further one patient each suffering from persistent primary and persistent secondary hyperparathyroidism. In both persistent patients only one remaining gland was left from primary surgery. The results of MIBI-SPECT, CT, and CT-MIBI-SPECT image fusion were compared in these patients. The outcome and the exact predicted positions were correlated with intraoperative findings.
Results In five out of six patients with multiglandular primary hyperparathyroidism more than one gland was detected, thus multiglandular disease could be suspected preoperatively. Overall CT-MIBI-SPECT image fusion was able to predict the exact position of all abnormal glands per patient in 14 of 30 (46.7%) cases, whereas CT alone was successful in 11 (36.7%), and MIBI-SPECT alone just in four (13.3%) of 30 patients.
Conclusion Multiglandular disease in primary hyperparathyroidism can be suspected preoperatively in a high percentage of patients. Additionally, this study shows that CT-MIBI-SPECT image fusion is superior to CT or MIBI-SPECT alone in preoperative localization of all pathologic glands in patients suffering from multiglandular disease.

Keywords Hyperparathyroidism · Multiglandular disease · Localization · CT · MIBI-SPECT

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Introduction

For planned minimally invasive surgery for single gland hyperparathyroidism preoperative localization of abnormal parathyroid glands is a prerequisite. Apart from the possible detection of ectopic or additional abnormal glands in reactive multiglandular disease (MGD), preoperative localization seems to be of more or less academic interest. The standard procedure in reactive multiglandular parathyroid disease is to explore all possible sites of the parathyroid glands and to perform total parathyroidectomy with autotransplantation or subtotal parathyroidectomy [1, 2]. However, MGD in primary hyperparathyroidism (pHPT) can only be detected by intraoperative parathormone (PTH) assay if minimally invasive surgery is performed, which is nowadays the procedure of choice in over 90% of all patients with pHPT. The diagnostic criteria how to predict MGD in pHPT by intraoperative decrease of PTH levels are not well defined. The Vienna criteria seem to predict MGD best, while the Miami and the Halle criteria have a lower sensitivity and/or specificity [3]. Furthermore, problems of interpretation of intraoperative PTH kinetics may lead to undiagnosed MGD and thus result in persistent pHPT [4]. In secondary hyperparathyroidism (sHPT) remaining additional glands lead to persistence of sHPT. On the other hand, morphology alone is not always correlated with abnormal function as enlarged glands do not necessarily secrete too much PTH [5]. Ideally, in pHPT diagnosis of MGD should be available before surgery, thus preventing staged surgery with higher complication rates. The aim of this study was to investigate whether computed tomography–^{99m}Tc-sestamibi–single photon emission computed tomography (CT-MIBI-SPECT) image fusion as a new localization method with high sensitivity and specificity in single-gland hyperparathyroidism [6–10] is able to predict MGD preoperatively.

Patients and methods

In 30 consecutive patients (15 males and 15 females) with multiglandular HPT, the preoperative localization results of CT-MIBI-SPECT image fusion, CT, and MIBI-SPECT were compared with intraoperative findings.

Mean age was 44.8 years, ranging from 21 to 72 years. All 30 patients were suffering from MGD and no further selection was performed.

Technique of image fusion CT and MIBI-SPECT images were taken on separate conventional units. On a workstation these images were imported to three-dimensional reconstructions of corresponding axial CT images in order to perform CT-MIBI-SPECT image fusion. CT and radionuclide fiducial markers were attached to the patient's skin and to the immobilization system (BlueBag; Medical Intelligence, Schwabmünchen, Germany) to facilitate CT-MIBI-SPECT image fusion. Reproducible fixation of the patients' head and neck is a prerequisite for CT-MIBI-SPECT image fusion, which can be achieved with this BlueBag vacuum mattress system.

MIBI scanning with SPECT imaging was performed 10 min after intravenous administration of 370 Mbq ^{99m}Tc-sestamibi (Cardiolite, Du Pont Pharma, Germany). For CT, helical slices of the neck and mediastinum were obtained (LightSpeed QX/I General Electric, Milwaukee, MN, USA, 16 rows) after infusion of 140-ml contrast medium (Ultravist, Bayer AG, Zurich, Switzerland). CT section thickness was 1.25 mm in the early arterial phase and 2.5 mm in the parenchymal phase. In five patients just native CT studies without contrast medium were performed to avoid impairment of renal function. The CT and MIBI-SPECT datasets were then superimposed on each other by means of a special image fusion software using the paired point-matching algorithm (Framelink, Medtronic Inc., Louisville, CO, USA).

MIBI-SPECT data were evaluated preoperatively by a specialist in nuclear medicine as well as CT by a radiologist, both blinded to the CT-MIBI-SPECT image fusion. Before operation, a radiologist and a nuclear medicine specialist in the presence of the surgeon evaluated the fused datasets in order to finally plan the operation. In patients with primary or reactive hyperparathyroidism the suspected gland or glands were removed according to the preoperatively detected localization. In pHPT and patients with tertiary hyperparathyroidism (tHPT) and a normally functioning kidney allograft, cure was confirmed intraoperatively by parathormone assay (Immolite 2000, DPC-Bühlmann). If there was no conclusive result in MIBI-SPECT, CT, and CT-MIBI-SPECT image fusion, neck exploration according to the probability of possible sites by viewing the "four-dimensional" CT and ranking the visible structures according to their size and shape was planned and performed. In patients with sHPT the standard procedure—exploration of all possible sites and resection of all parathyroid glands, probably with autotransplantation of some tissue, or subtotal (3 1/2) resection—was performed.

In six cases simultaneous thyroidectomy had to be undertaken.

Patients Six patients had to be operated on for pHPT. One patient underwent reoperation for persistent pHPT suffering from MEN I syndrome. As this specific patient had only one gland left from primary surgery in the referring hospital, this patient was not counted as having MGD. A total of 14 patients were operated on for sHPT and eight patients for tHPT. One further patient had to be explored because of persistent sHPT.

Renal failure was the reason for hyperparathyroidism in 23 cases. In four patients with previous kidney transplantation graft function was normal, while in other two recipients graft function was impaired.

For 27 patients it was the first cervical operation, whereas three patients already had one previous neck operation.

Most of the patients have four glands, but all possible positions had to be taken into consideration,

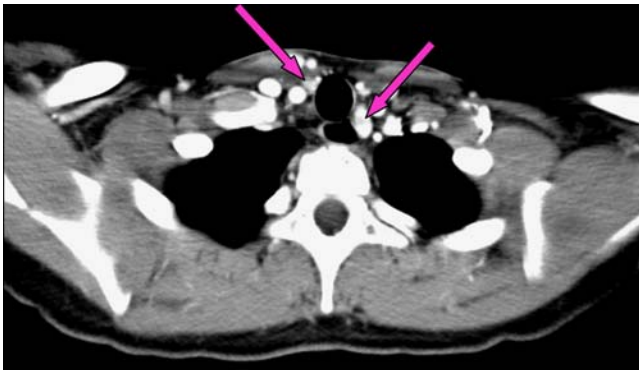


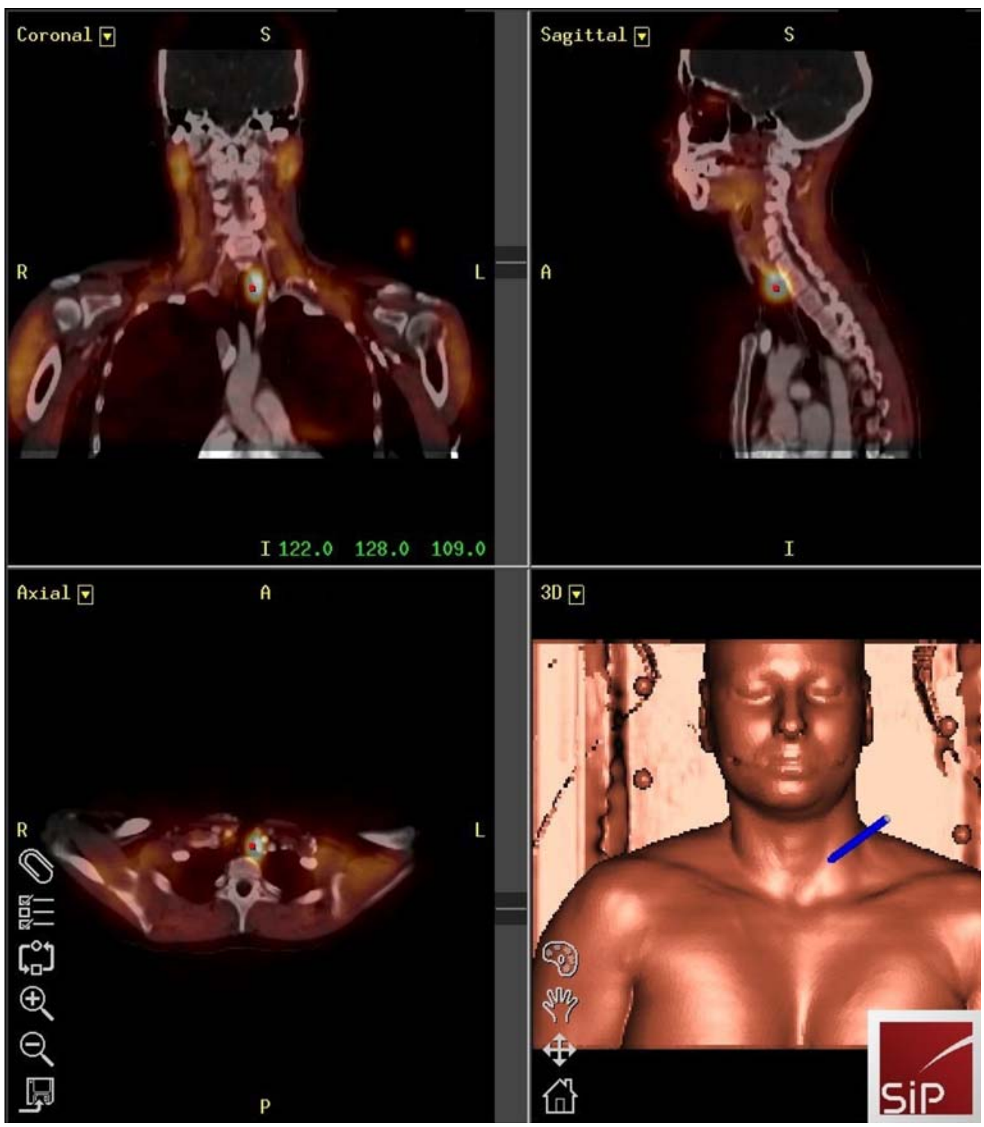
Fig. 1 CT of a patient with pHPT and multiglandular disease showing one abnormal gland on each side (*arrow*)

thus each imaging study was analyzed according to the following five possible parathyroid gland locations: right upper, right lower, left upper, left lower, and ectopic. The location of the hotspot lesion in MIBI-SPECT was correlated to anatomic landmarks in CT such as the cricoids cartilage, cervical vessels, and vertebral column, etc. If the position was outside the neck or not in anatomic vicinity of the thyroid gland, it was considered ectopic. Compared with intraoperative findings each position was expressed as true/false positive or true/false negative. If the exact positions of the abnormal glands were predicted and confirmed at surgery, an imaging result was considered true positive. Based on possible gland locations (30 patients, total 150 possible positions), sensitivity, specificity, and overall accuracy were calculated for each of the three localization procedures.

The results of CT-MIBI-SPECT image fusion were compared to those of CT or MIBI-SPECT alone.

In all patients, intraoperative electrical neuromonitoring by positioning of the needle probe over the conoidal ligament into the muscle of the vocal cord (Neurosign 100, Magstim Company, UK) was applied.

Fig. 2 Image of CT-MIBI-SPECT image fusion in a patient with pHPT and multiglandular disease, showing one enlarged left upper gland



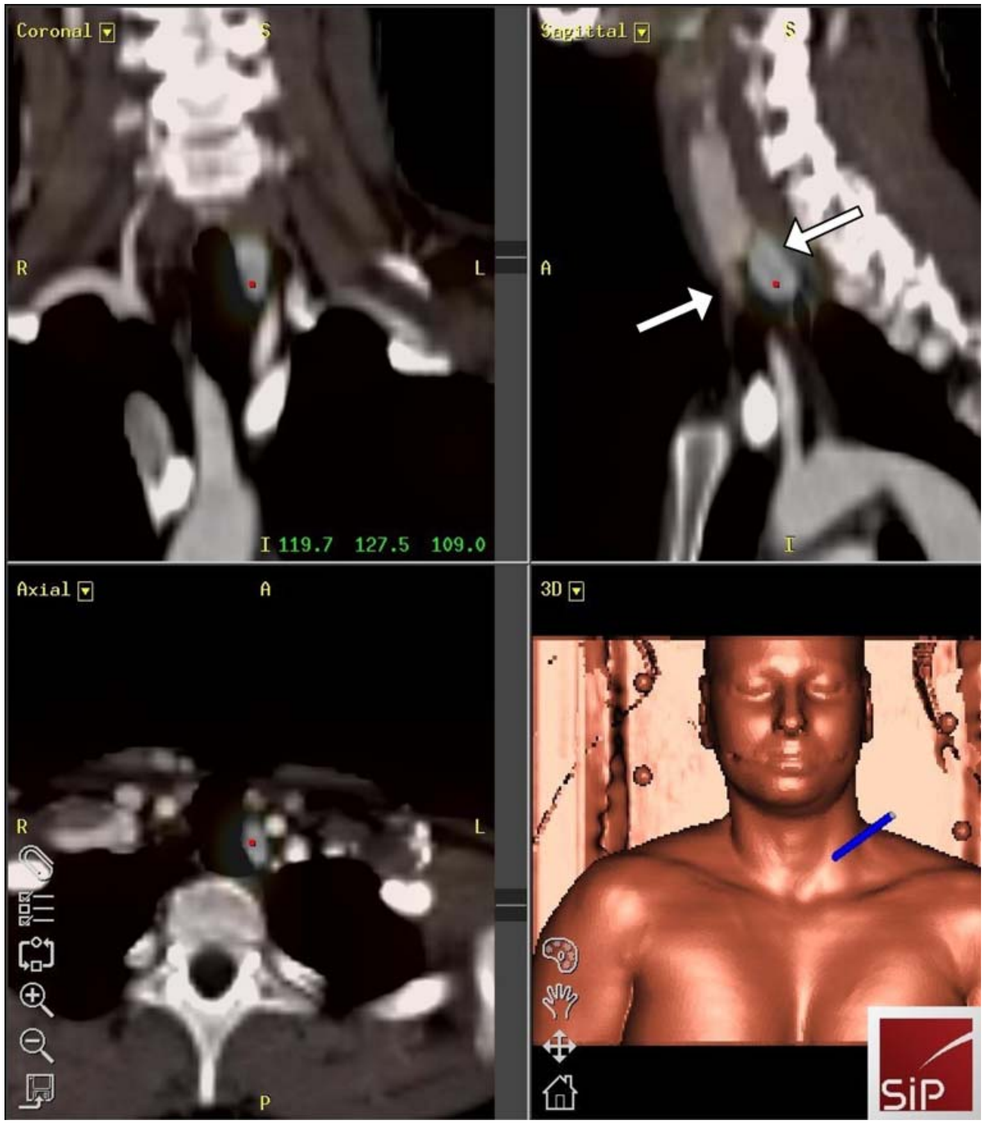


Fig. 3 Image of CT showing the upper very large adenoma and the lower adenoma in the thyreothymic ligament

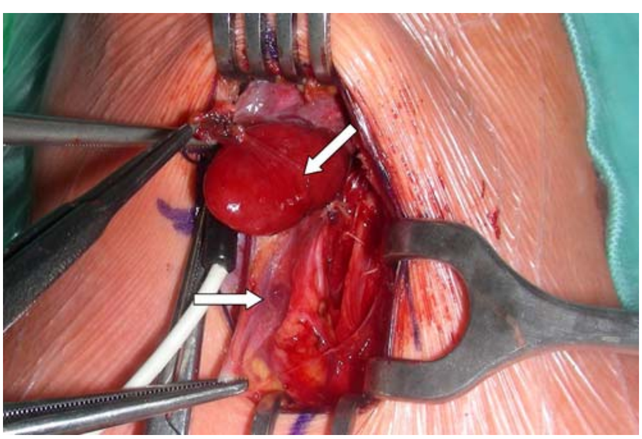


Fig. 4 Intraoperative image of the same patient showing the upper large adenoma and the lower adenoma localized within the thyreothymic ligament. Figures 1, 2, 3, and 4 are all from the same patient. pHPT with four gland disease in MEN I syndrome

In cases of pHPT and in patients with intact kidney graft function intraoperative PTH assay was used (Immolite 2000, DPC-Bühlmann). If the PTH level 10 min after removing the last gland was 50% lower than the PTH level at the beginning of anesthesia, the patient was regarded to be cured from HPT (Vienna criteria).

Results

With CT-MIBI-SPECT image fusion the exact position of all pathologic parathyroid glands per patient was predicted in 14 (47%) of 30 cases. CT alone succeeded in 11 (37%) and MIBI-SPECT alone, one of the standard imaging procedures, just in four (13%) patients (Table 1).

For diagnosis of multiglandular disease the detection of at least two abnormal glands was requested (Table 2). One patient with persistent pHPT associated with MEN I

Table 1 All abnormal parathyroid glands per patient detected (n=30)

CT-MIBI image fusion	14	(47%)
Computed tomography	11	(37%)
MIBI-SPECT	4	(13%)

syndrome, as only the fourth remaining gland had to be removed, was not counted as MGD in this series. With CT-MIBI-SPECT image fusion as well as with CT alone two abnormal glands were detected in 19 (66%) of 29 patients. MIBI-SPECT alone was successful in five (17%) cases only. With MIBI-SPECT alone it was not possible to locate at least two pathological glands per patient for diagnosis of MGD in all six patients suffering from pHPT. However, MGD was diagnosed in five of these six patients (83%) with CT-MIBI-SPECT image fusion but also CT alone (Table 3).

In four patients five ectopic glands were found intraoperatively. There was one patient with two abnormal ectopic glands. CT-MIBI-SPECT image fusion and CT alone detected both ectopic glands in this exceptional patient; with MIBI-SPECT alone just one of these glands was localized correctly. In two patients none of the preoperative localization procedures was successful in finding the abnormal ectopic parathyroid tissue. Another parathyroid gland, found intraoperatively in ectopic position, did not show any pathology, so it was counted as true negative.

Overall, CT-MIBI-SPECT image fusion showed a sensitivity of 70% and a specificity of 93% in correctly detecting the exact position of abnormal parathyroid tissue in patients with MGD (150 possible positions in 30 patients), whereas CT alone had a sensitivity of 64% and a specificity of 93%. The sensitivity of MIBI-SPECT was 33% and the specificity 90%. Overall accuracy in correctly predicting abnormal glands of CT-MIBI-SPECT image fusion was 79% whereas CT alone showed an overall accuracy of 75% and MIBI-SPECT alone of 55% (Table 4).

Being the only possibility to prove cure intraoperatively, as used in many institutions intraoperative PTH assay was performed in all six patients with MGD in pHPT and the four patients with a normally functioning kidney transplant and tHPT, showing a significant decrease in parathormone levels intraoperatively. In sHPT no intraoperative PTH assay was performed. In one patient autotransplantation of frozen preserved parathyroid tissue had to be carried out because of therapy-resistant symptomatic hypoparathyroidism. This patient suffering with sHPT had undergone subtotal parathyroidectomy. One patient had temporary nerve injury; another patient was suffering from preexisting nerve palsy. No persistent or recurrent hyperparathyroidism was diagnosed in any of the 30 patients during follow-up (mean follow-up: 47 months; 74–2 months).

Table 2 Multiglandular disease diagnosed (at least two glands per patient detected)

n=29	CT-MIBI image fusion	Computed tomography	MIBI-SPECT
pHPT (n=6):	5	5	0
sHPT or tHPT (n=22)	13	13	5
Persist. sHPT (n=1)	1	1	0
Total	19 (66%)	19 (66%)	5 (17%)

Discussion

Apart from detecting ectopic glands preoperative localization seems to be a more academic question in sHPT. In contrast, MGD in pHPT still represents a surgical challenge. MGD in pHPT is associated in a high percentage with inherited diseases and requires extensive diagnostic procedures and complex treatment. In sHPT, exploration of all possible sites and resection of all parathyroid glands with autotransplantation of some tissue or subtotal parathyroidectomy are considered the standard procedures [1]. Multiglandular disease in pHPT can be treated in different ways depending on the underlying inherited form of pHPT or on the special pathology of the glands. In MEN I syndrome subtotal parathyroidectomy (3 1/2 resection) is recommended, while in MEN II only enlarged glands must be excised [11]. Especially in MGD the experience and skill of the surgeon are important. In this study CT-MIBI-SPECT image fusion in sHPT was performed for detection of ectopic glands, while in pHPT it was performed for exact localization of abnormal parathyroid tissue. In cases of MGD in pHPT intraoperative parathormone detection is crucial since it is nowadays the only possibility to diagnose the underlying MGD when surgery is begun by a minimally invasive approach, which is currently the procedure of choice in single-gland pHPT. It is well known that not all enlarged parathyroid glands secrete too much parathormone [5]. Therefore, size and/or morphology of the glands are not the only indicator of multiple abnormally secreting glands. As intraoperative PTH assay allows diagnosis of abnormal functioning glands, the rate of MGD in pHPT diagnosed decreased since introduction of intraoperative PTH assay from 15–20% to 5–7% [12]. In our institution 7% of all patients operated on for pHPT in a period of 72 months (105 patients) were diagnosed to have MGD. However, results of intraoperative PTH detection are sometimes difficult to interpret and the cut-off levels, under which MGD in pHPT must be assumed, are not clearly defined. Therefore, it would be of great help for the surgeon to know

Table 3 Preoperative imaging studies compared to intraoperative findings in patients with pHPT and MGD

Patient (*n*=6)	Disease	CT-MIBI-SPECT image fusion	MGD diagnosed in CT-MIBI-SPECT image fusion	CT	MGD diagnosed in CT	MIBI-SPECT	MGD diagnosed in MIBI-SPECT
1	MEN I	Right upper: TP	Yes	Right upper: TP	Yes	Right upper: FN	No
		Right lower: FN		Right lower: FN		Right lower: FN	
		Left upper: TP		Left upper: TP		Left upper: FN	
		Left lower: FN		Left lower: FN		Left lower: TP	
2	MEN I	Right upper: TN	Yes	Right upper: TN	Yes	Right upper: TN	No
		Right lower: TP		Right lower: TP		Right lower: FN	
		Left upper: TN		Left upper: TN		Left upper: TN	
		Left lower: TP		Left lower: TP		Left lower: FN	
3	MEN I	Right upper: TP	Yes	Right upper: TP	Yes	Right upper: TP	No
		Right lower: TN		Right lower: TN		Right lower: TN	
		Left upper: TP		Left upper: TP		Left upper: FN	
		Left lower: FN		Left lower: FN		Left lower: FN	
4	Double adenoma; HPT-JT-syndrome	Right upper: TP	Yes	Right upper: TP	Yes	Right upper: FN	No
		Right lower: TN		Right lower: TN		Right lower: FP	
		Left upper: TP		Left upper: TP		Left upper: FN	
		Left lower: TN		Left lower: TN		Left lower: FP	
5	Double adenoma (MEN I/II neg.)	Right upper: TN	No	Right upper: TN	No	Right upper: TN	No
		Right lower: TN		Right lower: TN		Right lower: TN	
		Left upper: TN		Left upper: TN		Left upper: TN	
		Left lower: TP		Left lower: TP		Left lower: FN	
6	MEN I	Right upper: FN	Yes	Right upper: FN	Yes	Right upper: FN	No
		Right lower: FN		Right lower: TP		Right lower: FN	
		Left upper: TP		Left upper: TP		Left upper: TP	
		Left lower: TP		Left lower: FN		Left lower: FN	

TP true positive, *TN* true negative, *FP* false positive, *FN* false negative

Table 4 Comparison of CT-MIBI-SPECT image fusion, CT, and MIBI-SPECT (position prediction; blinded preoperative analysis)

n=150	CT-MIBI-SPECT image fusion (%)	Computed tomography (%)	MIBI-SPECT (%)
Sensitivity	70.3	63.7	33.0
Specificity	93.2	93.2	89.8
Positive predictive value	94.1	93.5	83.3
Negative predictive value	67.1	62.5	46.5
Overall accuracy	79.3	75.3	55.3

preoperatively whether patients with pHPT suffer from MGD or not. The requested intraoperative decrease of PTH value to exclude MGD after removing an abnormal gland differs depending on the criteria used [3, 13]. These criteria show differences in sensitivity and specificity in detecting MGD. Of those criteria the Viennese criterion (decrease of 50% of PTH level 10 min after removing an abnormal gland, compared to the value by starting anesthesia) seems to show the best relationship of sensitivity and specificity to detect MGD in pHPT [3]. There is still no imaging procedure that is able to detect normal parathyroid tissue. However, exact preoperative localization of abnormal parathyroid glands and surrounding anatomic landmarks helps planning and performing the operation [14]. MGD in pHPT may cause longer operating times and higher risk of any kind of complications. If MGD in pHPT is diagnosed, to be on the safe side, intraoperative exploration of all possible sites is still necessary. Knowledge of the exact position of the pathologic glands and of surrounding anatomic landmarks allows precise planning and performing the procedure in these cases. Furthermore, if MGD in pHPT is diagnosed preoperatively, genetic testing has to be considered in these cases, since MGD is associated in a high percentage with genetic forms of pHPT. Additionally, in MEN I syndrome neuroendocrine tumors (NET) of the thymus are seen in 20% of these patients. As these NETs have poor prognosis, transcervical thymectomy should be performed during surgery for MEN I syndrome.

MIBI-SPECT and high-resolution cervical ultrasound are considered the standard procedures for localization of abnormal parathyroid tissue [15, 16]. The analysis of the Scandinavian quality register for thyroid and parathyroid surgery [17] revealed that only three out of 93 patients with MGD in pHPT were correctly predicted with cervical ultrasound preoperatively, while no MGD was predicted with sestamibi scintigraphy. It has been shown in several studies that "four-dimensional" computed tomography is of higher sensitivity in single gland disease than MIBI-SPECT [18] but also in patients with multiglandular disease. In cases of hyperparathyroidism associated with renal dysfunction administration of CT contrast medium may not be possible and only native CT studies without "functional dimension" can be performed. Especially in these patients image fusion with MIBI-SPECT can help to compensate for that lack of information.

Our data show that CT-MIBI-SPECT image fusion, however, appears to be superior to CT or MIBI-SPECT alone in detecting correctly the exact position of pathological parathyroid glands in patients suffering from MGD as well as it was already demonstrated in several studies about single gland disease [6–10]. Furthermore, it allows predicting MGD in pHPT in a high percentage.

A crucial factor in CT-MIBI-SPECT image fusion is the precise and reproducible fixation of the patient's head and neck. It turned out that a vacuum mattress is sufficient enough to achieve stable and reproducible fixation of the patient. Further radionuclide and CT fiducial markers, to be attached to the patient's skin and to the immobilization system, are necessary for exact fusion of the imaging studies. This positioning system allows the CT-MIBI-SPECT image fusion procedure to be performed on every CT and MIBI-SPECT unit and it can be used for every new imaging technique. A workstation or navigation systems as well as the software for image fusion should be available as it is in an increasing number of hospitals for interdisciplinary, neurological, or orthopedic use. Cost for this entire immobilization system will be about €16,000 and the costs for the CT procedure were calculated to be around €60 and for the MIBI-SPECT €150.

The images can be viewed in three dimensions throughout the neck and mediastinum. The corresponding MIBI-SPECT can be superimposed over every "hotspot lesion" representing the pathological parathyroid gland. Further advantage of image fusion is that investigations can be viewed at every desktop and even in the operation theater. Thus, the surgeon can review the images immediately before surgery.

At our institution, a radiologist, a nuclear medicine specialist, and the endocrine surgeon evaluate the fused datasets in order to finally plan the operation. It is important to involve the surgeon into the interpretation of the imaging results because of his training in interpreting anatomic structures [19].

Conclusion

CT-MIBI-SPECT image fusion is a method for diagnosing MGD in pHPT preoperatively. Furthermore, this technique is superior to CT or MIBI-SPECT alone in detecting the correct position of abnormal parathyroid glands in patients suffering from MGD in all types of HPT.

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