

Technetium-99m-MIBI SPECT/CT in Primary Hyperparathyroidism

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Abstract

The novel trend toward focused parathyroidectomy requires precise preoperative localization of the parathyroid adenoma in patients with primary hyperparathyroidism (PHPT). The present study evaluated the impact of hybrid single photon emission computed tomography/computed tomography (SPECT/CT), using ^{99m}Tc-sestamibi (MIBI), on the surgical management of these patients. In a retrospective study of 36 patients with PHPT, SPECT/CT was undertaken when planar ^{99m}Tc-MIBI scintigraphy was negative or when an ill-defined focus in the neck or an ectopic site on planar views was visualized. Imaging data were compared with intraoperative findings, and the incremental value of SPECT/CT to lesion localization and surgical procedure was assessed. Three patients with both negative planar and SPECT/CT studies subsequently underwent bilateral neck exploration, with multiglandular hyperplasia diagnosed in two patients and a parathyroid adenoma in one. Of 33 patients with a positive MIBI study, parathyroid adenoma was confined to the neck in 23 patients and to the lower neck-mediastinum in 10. SPECT/CT facilitated the surgical exploration of all 10 ectopic parathyroid adenomas and 4 of 23 cervical parathyroid adenomas, the latter four either at reexploration or in patients with nonvisualization of the thyroid after thyroidectomy. SPECT/CT contributed to the localization of parathyroid adenomas in patients with PHPT and to planning the surgical exploration in 14 of 36 (39%) patients, predominantly those with ectopic parathyroid adenomas or who had distorted neck anatomy.

Bilateral neck exploration, the traditional surgical approach in patients with primary hyperparathyroidism (PHPT), is associated with a high success rate (95–98%) and low morbidity when performed by an experienced parathyroid surgeon.¹ It has been recently replaced, however, by limited surgical procedures such as unilat-

eral neck exploration,^{2,3} minimally invasive parathyroidectomy,⁴ and endoscopic surgery.⁵ These techniques are associated with decreased risk of hypoparathyroidism and recurrent laryngeal nerve injury as well as a shortened operating time and hospitalization.

Guided parathyroidectomy is feasible only with preoperative localization of a solitary parathyroid adenoma. Among the imaging modalities, ^{99m}Tc-sestamibi (MIBI)

scintigraphy (dual-phase and dual-isotope technique) was found to play an important role in detecting adenomas,⁶ with a sensitivity ranging from 85% to 95%.⁷ High diagnostic accuracy is documented when intense tracer uptake and retention in a single lesion on delayed images indicate the high probability of a solitary parathyroid adenoma. The accuracy of scintigraphy decreases in the presence of MIBI-avid thyroid nodules or previous neck surgery.^{8–10}

MIBI scintigraphy, often with complementary ultrasonography (US), is considered the imaging method of choice for localizing a parathyroid adenoma in the neck.^{3,11–13} A combined approach of preoperative computed tomography (CT) and US has been also described, with both imaging modalities, however, providing only morphologic information.^{4,14} Furthermore, US is suboptimal for assessing ectopic lesions, and CT has the lowest reported sensitivity among various modalities for diagnosing parathyroid adenoma. CT, however, may be useful in cases of deep mediastinal and paraesophageal lesions.^{11,14}

Co-registration of CT and MIBI has been reported in small series of patients. Image fusion following separate acquisition of CT and MIBI scans using radiographic and scintigraphic markers predicted the site of adenoma in five of six patients with PHPT.¹⁵ Using the same technique in a prospective study of 24 patients, CT-MIBI image fusion was found superior to MIBI-SPECT (single photon emission computed tomography) alone.¹⁶ Image-based fusion using external markers, however, may be associated with misalignment and cumbersome mathematical processing.

In contrast, hybrid morphologic CT and functional scintigraphic imaging is obtained following sequential acquisition of the two modalities on a single device. Initial studies in a small series of patients have shown that MIBI SPECT/CT, performed with this system, contributed to image interpretation and the surgery in two patients in one study¹⁷ and in four patients with mediastinal parathyroid adenomas in another.¹⁸

The aim of the present study was to assess the impact of hybrid MIBI SPECT/CT on the surgical management of a larger cohort of patients with PHPT.

MATERIALS AND METHODS

Patients

Thirty-six patients with biochemical evidence of PHPT scheduled for surgery based on National Institutes of Health (NIH) criteria were studied, including six patients with persistent hyperparathyroidism when re-exploration

was considered after failed initial surgery. The patients were routinely referred for MIBI scintigraphy at three independent medical centers and were selected for SPECT/CT study following negative planar images or if an ill-defined focus in the neck or an ectopic site was visualized. The institutional ethics committees approved the study.

The study group consisted of 11 men and 25 women with a mean age of 53 ± 16 years (range 18–81 years). Prior to surgery, the median total serum calcium was 11.3 mg/dl (range 9.8–14.1 mg/dl; normal 8.0–10.4 mg/dl), and the median serum parathyroid hormone (PTH) was 146 ng/L (range 41–577 ng/L; normal 11–64 ng/L).

Scintigraphy

Anterior planar images of the neck and chest were acquired for 15 minutes at 10 and 120 minutes after intravenous injection of 555 MBq ^{99m}Tc-MIBI using a large field-of-view gamma camera equipped with a parallel-hole collimator. SPECT/CT scans of the neck and chest were acquired after the early planar imaging. The study was performed using a dual-head variable-angle gamma camera and a low-power x-ray CT transmission system mounted on the same gantry (Millennium VG or Infinia & Hawkeye; GE Medical Systems, Carrollton, TX, USA). Transmission data were reconstructed using filtered back-projection (FBP) to produce cross-sectional attenuation images in which each pixel represents the estimated x-ray attenuation of the imaged tissue. The SPECT component of the study was then acquired in 120 projections, with a 3° angle step, in a 128 × 128 matrix, and at 20 seconds per view. Reconstruction was performed by FBP or iteratively using the Ordered Subsets Expectation Maximization technique (OSEM). The emission images, obtained in transaxial, sagittal, and coronal planes, were inherently registered to the anatomic maps using eNTEGRA or Xeleris workstation software (GE Medical Systems), with generation of hybrid images of the superimposed transmission (CT) and emission (SPECT) data.

A planar thyroid scan, used for visual subtraction of the early MIBI image, was obtained following injection of 74 MBq ^{99m}Tc-pertechnetate in patients showing MIBI uptake in the parathyroid adenoma of intensity similar to that seen in the thyroid gland or in the absence of differential washout on the delayed MIBI scan.

Image Interpretation

Scintigraphic and SPECT/CT data were evaluated independently by a team of three nuclear medicine

physicians, with differences of opinion solved by consensus. A distinct focus of increased or separate MIBI uptake in the neck or focal uptake in the mediastinum was considered positive for a parathyroid adenoma on scintigraphy. The diagnosis of the parathyroid adenoma, whether cervical or ectopic, was based on the intraoperative and pathologic findings. SPECT/CT images were analyzed for localization of the adenoma in relation to adjacent anatomic structures, and its depth in the neck or mediastinum was recorded. The presence of multinodular goiter (MNG), nonvisualization of the thyroid gland, or previous surgery was also recorded.

Patient Management

Patients with positive MIBI studies underwent focused exploration at the presumed site of the parathyroid adenoma, as determined by scintigraphy; the abnormal parathyroid gland was excised and sent for frozen section examination. In one of the three centers, an intraoperative PTH assay was used to confirm the completion of surgery, sparing the surgeon and patient the need for a frozen section. Bilateral exploration was pursued only in patients with negative imaging results. Surgical cure was defined by histopathologic confirmation of the surgically removed abnormal parathyroid tissue, with subsequent normalization of serum calcium and PTH levels.

Data Analysis

Retrospective analysis of MIBI scintigraphy and SPECT/CT studies was followed by assessment of the detectability rate and the sensitivity of these modalities, as defined by the surgical findings. SPECT/CT was considered to have improved the image interpretation when it provided precise localization with respect to the depth of the suspected lesion and its relation to adjacent structures including the thyroid gland, trachea, esophagus, thymus, spine, and sternum. Data were recorded for the whole study group and for subgroups of patients with cervical and ectopic parathyroid adenomas. The additional information provided by SPECT/CT for planning the surgical procedure was obtained from surgical and pathology reports and from interviews of the surgeons who performed the operation.

Paired nonparametric tests were used for a comparison of the serum calcium and serum PTH levels before and after surgery. A probability value of <0.05 was considered statistically significant.

RESULTS

Scintigraphy

MIBI scintigraphy identified a parathyroid adenoma in 33 patients and was negative in 3 patients. Based on scintigraphy, the parathyroid adenoma was confined to the neck in 23 patients and to the lower neck or upper mediastinum in 10 patients. No additional parathyroid adenomas and no increase in the detectability rate were documented on SPECT/CT compared with planar imaging. No false-positive cases were found in this study group.

Surgery

Altogether, 36 patients underwent surgery, including 6 patients who required reexploration. The 33 patients with positive MIBI scintigraphy underwent focused parathyroidectomy, and the 3 with a negative study underwent bilateral neck exploration. Solitary parathyroid adenomas ranging in weight from 0.150 to 12.6 g were excised from 34 patients, and 2 patients underwent subtotal parathyroidectomy for multiglandular hyperplasia, the latter observed in patients with a negative scan.

Among the 36 operated patients, the sensitivity of MIBI scintigraphy was 92% (33/36). Follow-up indicated a surgical cure in all 36 patients (100%). After surgery (on postoperative days 1–8), serum calcium levels decreased from a range of 9.8 to 14.1 mg/dl (median 11.3 mg/dl) to a range of 8.4 to 9.8 mg/dl (median 8.5 mg/dl) ($P < 0.0001$). Serum PTH levels decreased from a range of 41 to 577 ng/L (median 146 ng/L) to a range of 13 to 45 ng/L (median 24 ng/L) ($P < 0.0001$).

There were no instances of postsurgical hypoparathyroidism. Three patients had recurrent nerve injury after surgery, two of them at reexploration.

Impact of SPECT-CT on Lesion Localization and Surgery

Scintigraphic findings prior to the initial surgery or to reexploration in patients with positive studies are summarized in Table 1. SPECT/CT provided three-dimensional (3-D) topographic information that focused the surgical exploration in 14 of the 33 patients with positive MIBI scintigraphy (42%). It precisely indicated the proximity of the parathyroid adenoma to the thyroid, trachea, and esophagus in 4 of the 23 patients with cervical adenoma (17%) (Fig. 1). The four patients with cervical parathyroid adenomas in whom SPECT/CT showed an incremental value included three patients after failed

Table 1.
SPECT/CT in 33 patients with positive parathyroid planar imaging: impact on surgery.

Patient population	Site of parathyroid adenoma	Positive MIBI	Impact of SPECT/CT
Total [n = 33]	Neck	23	4
	“Lower” Ectopic	10	10
Prior to Initial Surgery [n = 27]	Neck	18	1
	“Lower” Ectopic	9	9
After Failed Surgery [n = 6]	Neck	5	3
	“Lower” Ectopic	1	1

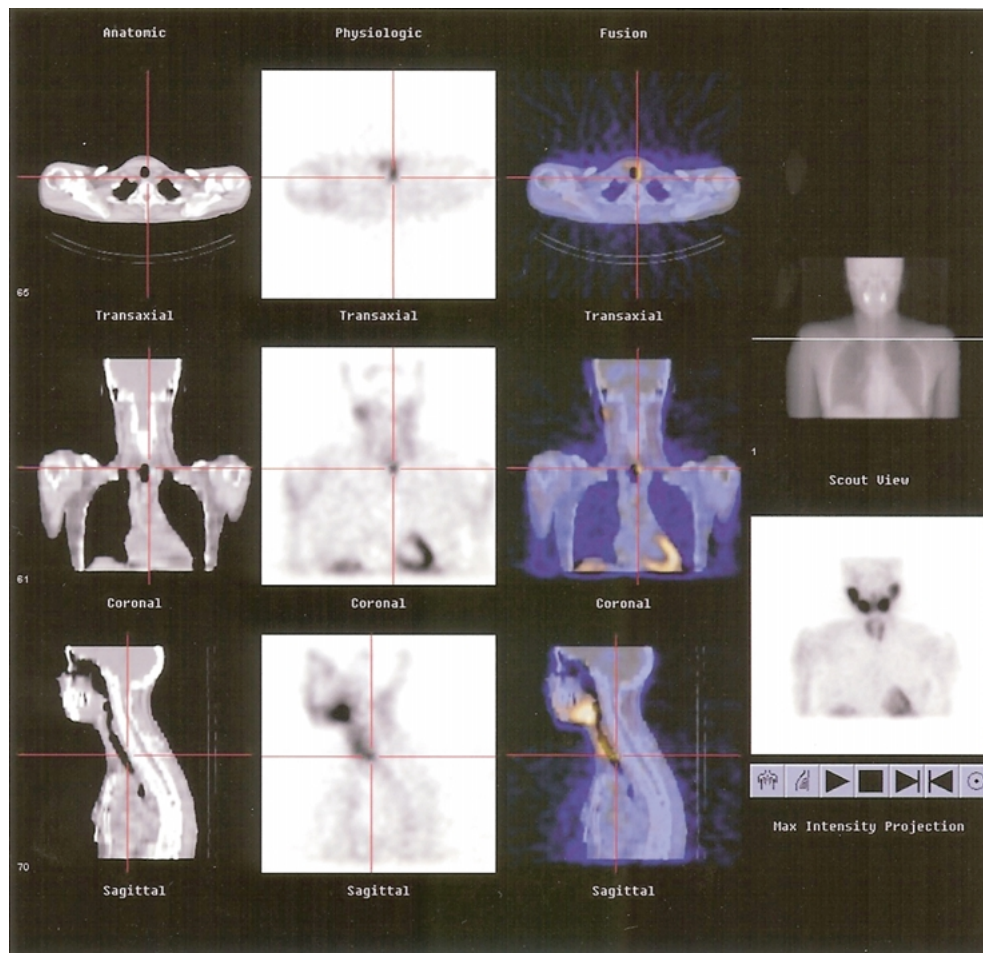


Figure 1. Hybrid methoxyisobutyl isonitrile (MIBI) single positron emission computed tomography/computed tomography (SPECT/CT) imaging after failed initial surgery in a patient with a parathyroid adenoma in the posterior paratracheal space of the neck. SPECT/CT (CT, left column; SPECT, center column; fusion, right column) with three-dimensional presentation (maximal intensity projection, bottom right) shows the precise localization of the parathyroid adenoma in the left posterior paratracheal space. The latter findings guided the surgical reexploration. A 1 cm in diameter, 0.4 g adenoma was excised.

initial surgery (one adenoma in the retroesophageal space, one adenoma in the left retrotracheal space, and a left lower parathyroid adenoma located anteriorly) as well as an additional adenoma localized to the retroesophageal space in a patient with nonvisualization of the thyroid gland after thyroidectomy.

In patients with ectopic “lower” adenomas, SPECT/CT identified the relation of the mediastinal parathyroid ade-

nomas to the trachea, esophagus, thymus, spine, or sternum and optimized the surgical procedure in all 10 patients (Fig. 2). Six of these ten adenomas were paratracheal, anterior in location at the level of the suprasternal notch or manubrium. Surgery was planned based on the SPECT/CT data, avoiding a sternotomy because of the precise localization of the adenoma. Four parathyroid adenomas were located posteriorly, with only one visual-

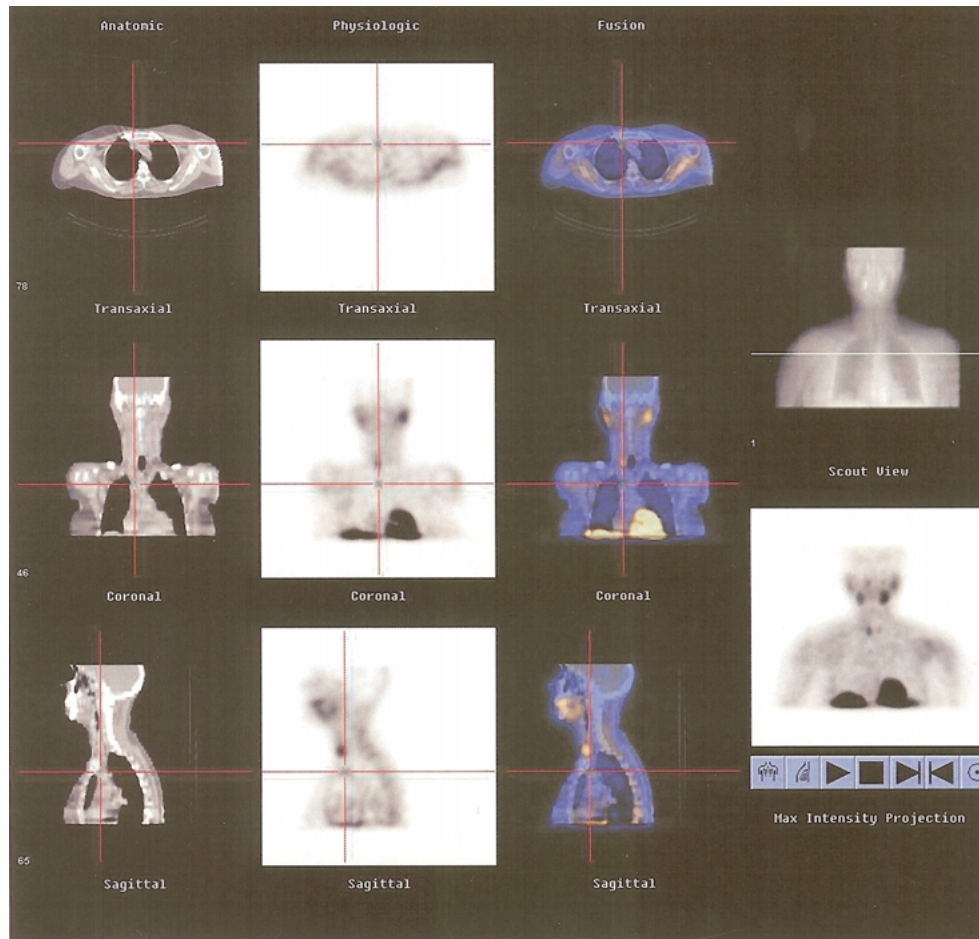


Figure 2. Hybrid MIBI imaging in a patient with an ectopic parathyroid adenoma. SPECT/CT (CT, left column; SPECT, center column; fusion, right column) with a three-dimensional presentation (maximal intensity projection, bottom right) shows the precise localization of the parathyroid adenoma in the anterior mediastinum (right off-midline). The surgical approach was planned according to these topographic landmarks. A 0.5 g adenoma adjacent to the thymus was removed.

ized on US. Surgery was planned based on the SPECT/CT data of these four adenomas, including an adenoma situated adjacent to the thymus, an adenoma in the retroesophageal prevertebral plane, and two additional lesions in the retrotracheal plane, with the location defined precisely only by the fused images.

Among the subgroup of six patients scheduled for re-exploration after failed initial surgery, SPECT/CT facilitated the surgical resection of four adenomas, including an adenoma in the retroesophageal space, an adenoma in the left retrotracheal space, an adenoma located anteriorly in the neck, and an ectopic “lower” parathyroid adenoma.

DISCUSSION

A novel trend toward focused neck exploration in patients with primary hyperparathyroidism has recently re-

placed the traditional bilateral approach owing to a decrease in operative morbidity and shortening of the hospitalization. The limited surgical procedures require, however, optimal preoperative localization studies. Planar MIBI scintigraphy has been considered the primary imaging modality for preoperative localization of the adenoma, with a sensitivity of 92% in the present study, similar to previous data in the literature.⁷ Other studies comparing planar and MIBI-SPECT support wide application of MIBI-SPECT, with increased sensitivity of 91% to 96% versus the lower sensitivity rates for planar imaging, which range from 74% to 87%.^{19–23}

No additional adenomas were detected by SPECT in our study, and therefore no improved sensitivity was documented. The anatomic landmarks of SPECT/CT, however, facilitated the surgical procedure in 14 of the 33 patients (42%) with positive scans prior to exploration.

In the neck, SPECT/CT played only a limited role in patients with cervical adenomas prior to initial surgery.

SPECT/CT provided anatomic mapping, which improved the surgical management only in special clinical settings of distorted neck anatomy after initial neck exploration, nonvisualization of the thyroid gland after thyroidectomy, or both.

In contrast, SPECT/CT improved localization and facilitated the surgical exploration of all 10 ectopic "lower" adenomas. In the present study, ectopic adenomas were documented in 10 of the 36 patients (28%). This relatively high percentage of ectopic lesions, compared to the 8% to 11% reported in the literature,^{8,24} may reflect a biased initial referral of patients and could in part be the reason for the significant benefit provided by SPECT/CT in the present study.

Ectopic parathyroid adenomas are difficult to detect by US and to differentiate from other mediastinal masses on CT.²⁵ Ectopic "upper" parathyroid glands can occur above the superior thyroid pole, below the inferior thyroid artery, or in the retropharyngeal, retrotracheal or retroesophageal space.⁸ The SPECT/CT 3-D presentation of the adenoma in these less common sites (up to 7% of all cases) with simultaneous demonstration of all anatomic structures in its vicinity may direct the surgical search and spare these patients unnecessary reexploration, particularly for parathyroid adenomas situated in the retrotracheal or retroesophageal space, as seen in the present study.

Ectopic "lower" glands can occur anywhere from the superior thyroid pole to the thymus and superior mediastinum, along the carotid sheath, or within the thyroid gland.^{26,27} Mediastinal parathyroid adenomas can be removed by mediastinoscopy,²⁸ video-assisted thoracic surgery,²⁹ or limited median sternotomy, the latter associated with an 8% to 12% incidence of complications.^{30,31} Sternotomy, however, may be avoided when SPECT/CT indicates that the anterior location of the mediastinal adenoma is at the level of the manubrium, as seen in six patients of the present study.

CT-MIBI image fusion has been previously advocated in a few studies. A mediastinal parathyroid adenoma was precisely localized following separate MIBI and CT acquisition, with radiopaque and radioactive markers placed on the patient's skin.³² Fusion of separate CT and MIBI studies indicated the localization of a solitary adenoma in five of six patients using a head-holder, a vacuum cushion, and radiographic and scintigraphic markers mounted at the head-holder and the patient.¹⁵ An incremental role of this separately performed CT-MIBI co-registration technique was documented in 24 patients, with a sensitivity of 93% compared to 31% for MIBI-SPECT alone.¹⁶ In the latter study, the poor sensitivity of

SPECT was associated with an increased incidence of MNG, which may have affected the detectability of the parathyroid adenoma. SPECT/SPECT image fusion of ^{99m}Tc-sestamibi and ^{99m}Tc-albumin, the latter as an indicator of the intravascular space, has been also described and has enabled the visualization and localization of a parathyroid adenoma situated in the aortopulmonary window.⁷

Co-registration of data obtained following acquisition of studies in separate systems is associated with misalignment and with cumbersome patient preparation and mathematic modeling. An integrated system providing hybrid SPECT/CT images had contributed to localization of two ectopic parathyroid adenomas (in the anterior and posterior mediastinum, respectively), with no impact on neck adenomas in an initial report.¹⁷ For four ectopic parathyroid adenomas described by Kaczirek *et al.*, SPECT/CT facilitated minimally invasive surgery and excluded the need for further radiologic examinations.¹⁸ In the present study, fusion of sequentially performed functional SPECT with anatomical x-ray data acquired on a single device precisely determined the topographic localization of the adenoma with respect to adjacent vital organs for all 10 ectopic "lower" parathyroid adenomas that were surgically removed.

The added value of CT in the interpretation of SPECT/CT was not evaluated in the present study. The CT component of the presently available hybrid-imaging device is of inferior resolution compared to state-of-the-art CT, the latter already known to have a lower sensitivity than other imaging modalities in the detection of a parathyroid adenoma. The CT component of the hybrid system served in this study only as a road map for anatomic localization of the focal MIBI uptake seen on SPECT.

The incremental value of SPECT/CT, combining functional and morphologic information, was not reflected in increased sensitivity but, rather, in improved planning of surgery. Although objective endpoints were not measured in this retrospective analysis, surgeons at all three medical centers independently reported the easy accessibility of the parathyroid adenoma, decreased extent and length of the surgical exploration, and the smaller size of the incision following the use of SPECT/CT for planning the surgical approach. As indicated by the surgeons, the 3-D anatomic presentation of the functioning parathyroid adenoma served as a surgical road map, directing a shorter invasive procedure, mainly in patients with upper adenomas at rare locations, such as in the retrotracheal and retroesophageal spaces. SPECT/CT allowed the avoidance of sternotomy in the case of an ectopic adenoma localized to the superior mediastinum and facili-

tated planning the surgical approach in patients with distorted neck anatomy undergoing reexploration.

CONCLUSIONS

SPECT/CT contributes to localizing parathyroid adenomas and to planning surgical strategy mainly in patients with an ectopic adenoma and in those with distorted cervical anatomy due to previous neck surgery. SPECT/CT may not be applied to patients with a well defined cervical parathyroid adenoma seen on planar MIBI scintigraphy prior to the initial surgery in the absence of associated medical conditions of the neck.

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