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Original Article

Clinical impact of SPECT-CT in the diagnosis and surgical management of hyper-parathyroidism

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Abstract: Hyper-functioning parathyroid glands with autonomous overproduction of PTH is the most frequent cause of hypercalcemia in outpatient populations with primary hyper-parathyroidism. It is generally caused by a solitary adenoma in 80%-90% of patients. Despite the various methodologies that are available for preoperative localization of parathyroid lesions, there is still no certain preoperative imaging algorithm to guide a surgical approach prior to the management of primary hyper-parathyroidism (P-HPT). Minimally invasive surgery has replaced the traditional bilateral neck exploration (BNE) as the initial approach in parathyroidectomy at many referral hospitals worldwide. In our study, we investigated diagnostic contributions of SPECT-CT combined with conventional planar scintigraphy in the detection of hyper-functioning parathyroid gland localization, since planar imaging has limitations. We also evaluated the efficacy of preoperative USG in adding to initial diagnostic imaging algorithms to localize a parathyroid adenoma. Methods: A total of 256 consecutive surgically naive patients with hyper-parathyroidism diagnosis were included in the following preoperative localization study. The study consisted of 256 consecutive patients with HPT, with a selected 154 patients who had neck surgery with definitive histology reports. All patients had 99mTc-methoxyisobutylisonitrile (99mTc-MIBI) double-phase scintigraphy. The SPECT-CT procedure, combined with standard 99mTc-MIBI planar parathyroid scintigraphy with a pinhole and parallel-hole collimator to evaluate whether the SPECT-CT procedure was able to provide additional information in the localization of the pathology, caused hyper-parathyroidism in both P-HPT and S-HPT. Results: In the 154 P-HPT patients, 168 lesions (142 adenomas including 2 intrathyroidal and 2 double adenoma, 2 carcinoma, and 22 hyperplastic glands (four patients had MEN I, each with four hyperplastic glands)), were found at surgery. SPECT-CT detected more lesions than planar imaging in P-HPT (97.8% vs. 87.6%). SPECT-CT detected all adenomas and increased sensitivity, particularly in small lesions. Regardless of their size, the number of detected hyperplastic glands by SPECT-CT was remarkably higher than planar imaging.

Keywords: Hyper-parathyroidism, parathyroid adenoma, parathyroid scintigraphy, SPECT-CT, minimally invasive parathyroidectomy

Introduction

Primary hyper-parathyroidism (P-HPT) is the most common cause of hypercalcemia and is characterized by an increased parathyroid hormone (PTH) level which is usually caused by a single hyperfunctioning parathyroid gland (85-96% of cases). Other less frequent causes include parathyroid hyperplasia, multiple adenoma, and parathyroid carcinoma (< 1%) [1-3]. Hypercalcemia is usually incidentally identified through routine biochemical laboratory testing rather than clinical symptoms of hypercalcemia in patients with P-HPT [3, 4].

Patients with symptomatic hyper-parathyroidism or individuals with asymptomatic hyper-parathyroidism that satisfies certain criteria have indications for parathyroidectomy that offers an enduring cure [2, 5-7]. The success rate of bilateral neck exploration is higher than 95% when it is performed by an experienced endocrine surgeon [8, 9]. However, nowadays there is a new trend in surgery methods called minimally invasive parathyroidectomy (MIP) which is a more selective surgical approach [9, 10]. Precise pre-operative localization is an essential prerequisite for this targeted excision method's success.

Despite currently available advanced methodologies for the localization of parathyroid lesions, there is no consensus on the best preoperative imaging protocol to use as guidance

management of primary hyper-parathyroidism (P-HPT).

The superior parathyroid glands originate from the endoderm of the third pharyngeal pouch. The inferior ones originate from the endoderm of the fourth pharyngeal pouch during the sixth week of gestation and migrate toward the mediastinum. Normally, there are four parathyroid glands, but in a small number of cases (approximately 10%) individuals may have more (between five and seven) glands, and some of cases may have less than four parathyroid glands (2-3%).

The advent of accurate preoperative localization, along with intraoperative PTH measurement, has allowed surgeons to perform a more focused surgical approach. This targeted approach is associated with minimal dissection and decreased risk of bilateral recurrent laryngeal nerve injury. In addition to decreasing post-operative pain and shortening the length of stays in the hospital, it has replaced previous bilateral neck exploration procedures in the surgical treatment of primary hyper-parathyroidism at many medical centers worldwide [11-14]. Successful preoperative lesion localization is crucial and preoperative 99mTc-methoxyisobutylisonitrile (99mTc-MIBI) is one of the primary standard methods that provides this prime prerequisite. SPECT-CT (Single photon emission computed tomography-computed tomography) enables having a high spatial resolution 3D (three-dimensional) image that improves overall diagnostic confidence of parathyroid lesions.

Material and methods

Between January 2006 and August 2013, 256 consecutive surgically naïve patients with hyper-parathyroidism diagnoses underwent the following localization studies before having a parathyroidectomy. Of these, a select group of 154 patients (30 male and 124 female, age rage: from 15 to 86 y, mean, 53.76 ± 17 y), who underwent surgery and had definitive histology are included in this study. All patients underwent conventional 99mTc-methoxyisobutylisonitrile (99mTc-MIBI) double-phase scintigraphy combined with the neck SPECT-CT procedure, using a γ-camera with a pinhole and parallel-hole collimator. Ultrasonography (USG) was performed on all patients to evaluate the clinical utility of adding ultrasonography (USG) to scintigraphy-based imaging.

After injection, at the 20 and 120 minute marks, planar imaging and SPECT-CT were performed. Planar images (early and delayed), SPECT, and SPECT-CT image sets were evaluated for adenoma localization at the neck and thorax. Surgical location served as the standard.

Positive and negative predictive values, sensitivity, and specificity values of each method were calculated. This analysis indicates that even diagnostic contribution gained by adding ultrasonography to SPECT-CT does not change the statistical results, and USG guidance is valuable especially throughout the operation.

The data was collected and analyzed retrospectively through reviewing patients' hospital charts. All imaging, pathology and biochemical results, and surgery data were recorded. Complete cure of P-HPT was confirmed with the patient's postoperative normalized serum calcium levels within 3 weeks.

The preoperative baseline mean serum total calcium value was evaluated (11.13 ± 1.02 mg/dl). Serum calcium levels were recorded as postoperative immediate (10.62 ± 1.43 mg/dl ($p = 0.006$), and as postoperative 3rd week (9.24 ± 0.79 mg/dl ($p < 0.001$). The preoperative mean serum PTH value was 434.17 ± 550.22 pg/ml. PTH values were recorded as postoperative (immediate 34.69 ± 28.50 pg/ml ($p < 0.001$), and postoperative (2-3 week's 91.21 ± 81.86 pg/ml ($p < 0.001$).

Imaging protocol

99mTc-sestamibi (925-1,110 MBq) was injected intravenously (IV) into all patients. At 20 and 120 minutes after injection (10 minutes anterior, 35 degree right anterior oblique, and 35 degree left anterior oblique), (LAO) planar images were acquired in a 128 × 128 matrix, with the 140 keV photo-peak using a low-energy, high-resolution (LEHR) parallel collimator.

Thorax images were obtained in the supine position with a LEHR collimator, after 20 minutes of IV injection of 700 MBq 99mTc-methoxyisobutylisonitrile (99mTc-MIBI). Planar images were obtained over a 5-minute period, the first

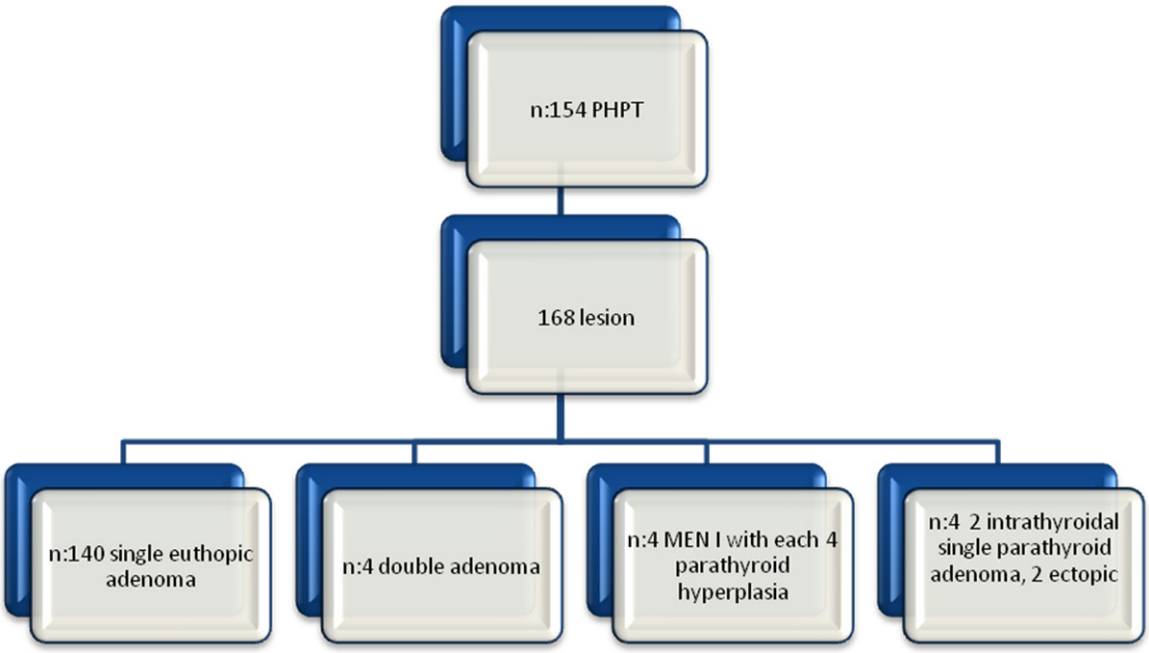

Figure 1. Diagram of patient distribution.

one at an early interval (20 minutes after injection) and the second one at a later interval (120 minutes after injection) (128 × 128 matrix).

SPECT was obtained after planar images (128 × 128 matrix, 128 stops, 20 seconds per stop for early and 30 seconds per stop for delayed acquisition).

Statistical analysis

Positive predictive value (PPV = number of true positive results divided by the number of true positive results + number of false positive results), negative predictive value, (NPV = number of true negative results divided by the number of true negative results + false negative results), sensitivity (true positive results number divided by the number of true positive results + false negative results) and specificity (true negative results number divided by the number of true negative results + false-positive results number), were calculated for localization. Surgical location was accepted as the gold standard. Statistical tests were two sided and considered to be statistically significant at a P value of 0.05 or less.

Results

In the 154 P-HPT patients, 168 lesions (144 single adenomas including 2 intrathyroidal and 2 ectopic adenoma, 4 double adenoma and 16 hyperplastic glands (four patients had MEN I, each with four hyperplastic glands)) were found at surgery. Ectopic adenoma accounted for 1.19% of all cases, and all ectopic adenomas were solitary (**Figure 1**).

In identifying parathyroid adenoma, SPECT-CT is a more sensitive method than the planar imaging method in P-HPT (97.9% vs. 87.7%). SPECT-CT increased overall sensitivity particularly in light weight adenomas. SPECT CT identified 28% of lesions which were not detected on planar imaging, and also determined more hyperplastic glands, regardless of the size. SPECT-CT improved image quality and resolution, and increased the accuracy rate of lesion localization both in eutopic and ectopic glands. There was no false positive finding either with the planar or with SPECT/SPECT-CT imaging. SPECT precisely identified the localization of lesions (confirmed by surgery) in 97.9% of the single adenoma patients and in 81.5% of multigland disease patients, whereas planar imaging showed the location of lesions in 89.5% and 57.9%, respectively. In 9.2% of all patients only SPECT-CT was able to determine the lesion. In patients with hyperplastic glands (MEN I patients), SPECT-CT revealed about 7% more lesions than planar images.

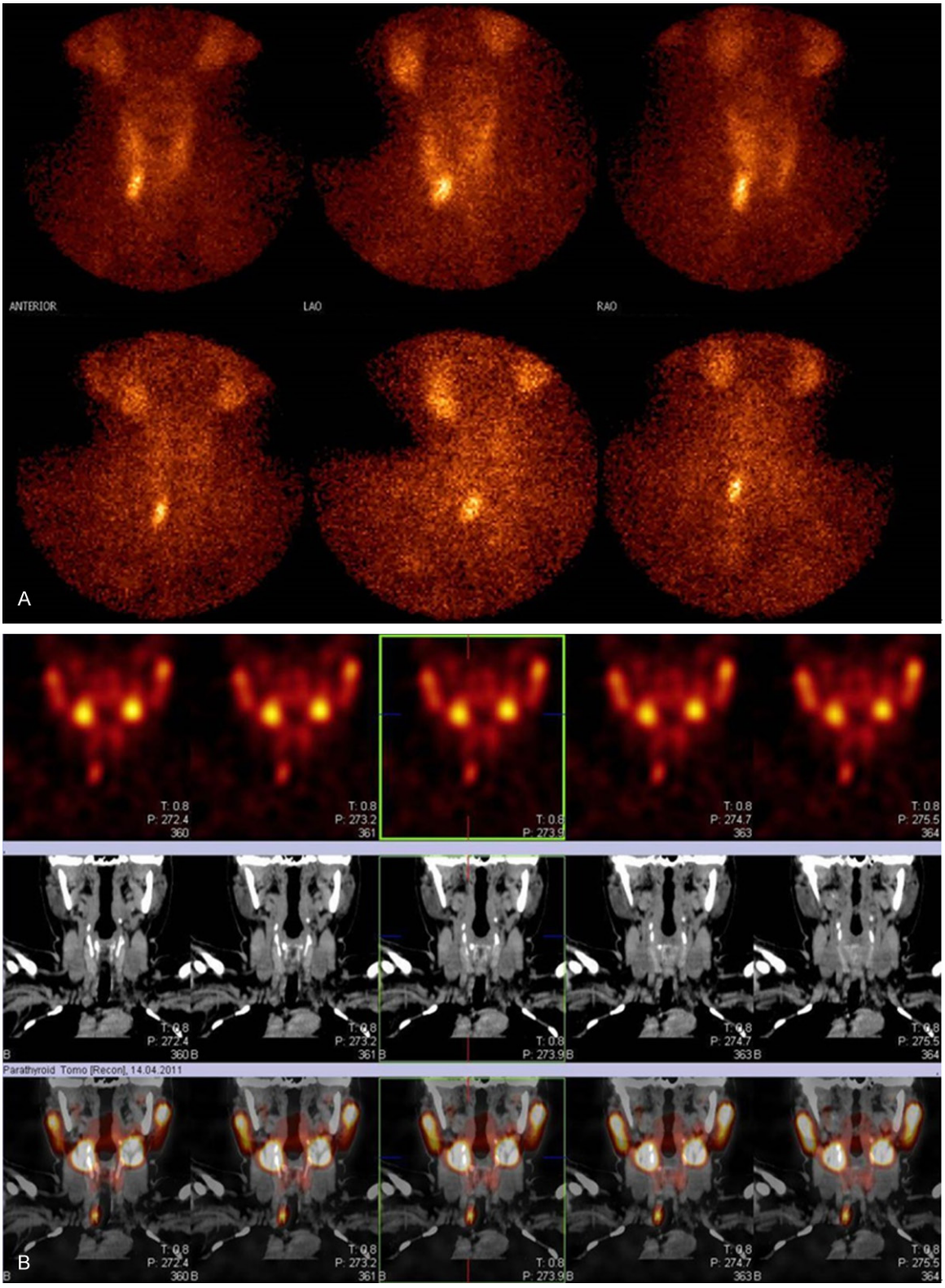

Figure 2. A: Right inferior parathyroid adenoma with early and delayed washout planar images. B: Coronal SPECT/CT images from a delayed phase in a patient with a right inferior parathyroid adenoma confirmed at surgery.

The mean patient follow-up, as defined by the date of the last serum calcium measurement, was three months.

For all imaging methods, overall sensitivity was 61% while specificity was 99.2% for localization of lesions. PPV and NPV were 81% and 97%, respectively. The best results in the matter of overall sensitivity were gained with dual phase studies that included SPECT-CT (92.6%). Regarding sensitivity, early SPECT-CT combined delayed planar imaging or SPECT was significantly better ((P = 0.003), PPV (P = 0.01)) than other scintigraphic imaging combinations. Early + delayed SPECT-CT (dual phase) had better statistical results than dual phase SPECT (P = 0.012) on the subject of sensitivity.

All dual phase imaging (SPECT-CT, SPECT, and planar) results were statistically superior to single phase imaging methods (early or delayed imaging) in means of sensitivity and PPV. The combination of early phase SPECT-CT with any delayed imaging protocol was superior to dual phase planar imaging or SPECT for sensitivity and positive predictive value.

The localizations of the 142 single adenomas were as follows: 38 were left inferior, 36 were right inferior (**Figure 2**), 22 were right inferior-posterior, 20 were left superior, 12 were right superior, 10 were left inferior-posterior, 2 were right intra-thyroidal, and 2 were mediastinal.

Dual phase SPECT-CT (Dual phase) had better statistical results than dual phase SPECT (P = 0.012) on the subject of sensitivity.

Patient's identities were hidden before evaluation. All image sets (early SPECT, early SPECT-CT, delayed SPECT, delayed SPECT-CT, and early and delayed planar images) were evaluated individually. After the first evaluation of each individual image, all images sets were evaluated for every patient. Overall sensitivity for localization of dual phase SPECT-CT and/or planar imaging modality was 93% with an accuracy of 97%. Single phase early or delayed planar images sensitivity ranged between 43% and 49%. The sensitivity for the dual phase studies that included early SPECT-CT was 78%. PPV of single phase delayed planar, SPECT, or SPECT-CT studies ranged from 71% to 74%. Dual phase studies that included early SPECT-CT PPV improved to 86%-93%. The specificity values of all modalities were greater than 99.0%, and values for NPV were equal to or greater than 98%. Enhanced image quality and resolution, provided by SPECT-CT, allowed the determination of the exact location of lesions in eutopic and ectopic sites. There was not any false-positive finding in the SPECT-CT or planar images. The precise location of lesions that were found at the surgery was accurately predicted by SPECT in 96.8% of P-HPT patients and in 82.2% of S-HPT patients. The cause of hyperparathyroidism was correctly predicted, in 89.2% of P-HPT patients and 57.6% of S-HPT patients, by planar imaging. In 9.2% of all patients only SPECT-CT was able to determine the lesion. In patients with hyperplastic glands (MEN I patients) SPECT-CT revealed about 7% of more lesions than planar images.

The SPECT-CT protocol seems quite reliable and is a sensitive method in the diagnostic imaging algorithm of hyperparathyroidism. We suggest using SPECT-CT protocol as a complementary method to planar parathyroid scintigraphy whenever possible, selectively in P-HPT patients but extensively in S-HPT patients.

We evaluated the value of ultrasonography with respect to proportion of correct localization in patients who underwent preoperative sintigraphic imaging versus patients who had the addition of preoperative ultrasonography. The addition of ultrasonography to SPECT-CT did not significantly affect the correct preoperative localization rate (p = 0.30).

The overall results of this study indicate that there is significant value in adding SPECT-CT to initial diagnostic imaging algorithms to localize a parathyroid adenoma preoperatively.

Discussion

The advent imaging modalities with highly dependable accuracy rates, as our study results demonstrate (97.9% in P-HPT), enable the localization of parathyroid tissue and have allowed surgeons to perform a minimalized selective surgery approach. Early evaluation opportunities for the success of surgery during operation through intraoperative quick PTH measurement gives courage to perform selective surgical excision of the hyperfunctioning parathyroid through a small cervical incision via so-called minimally invasive parathyroidectomy (MIP),

which is associated with decreased surgical complications [12, 13]. Precise pre-operative localization is an essential prerequisite for successful MIP. Embriologic descent of parathyroid glands cause a more posterior localization of superior parathyroid glands than inferior glands and surgery is usually more complicated than inferior parathyroid lesions because of the adjacent localization with the recurrent laryngeal nerve. Preoperative accurate information of location eases exploration. This investigation directly compared scintigraphic imaging techniques, which are possible to evaluate separately, and report statistically significant differences in localization. Although the study data demonstrate a trend toward higher sensitivity and PPV for SPECT rather than planar imaging with pinhole [15-22], the difference was not statistically significant. Dual phase SPECT-CT has become indispensable in our department. It provides a detailed anatomic location and is statistically significantly superior to single phase SPECT, SPECT-CT, single and dual phase standard (without pinhole) planar imaging [23-25], especially in posterior glands (i.e. superior glands in the tracheoesophageal groove) or ectopic localized lesions.

This analysis indicates that even diagnostic contributions gained by adding ultrasonography to SPECT-CT does not change the statistical results [26]; USG guidance is valuable especially throughout operation.

Conclusion

In the era of minimally invasive surgical approaches, it is increasingly becoming important to ascertain the precise localization of lesions. Although a wide variety of imaging methods has been used to diagnose the location of parathyroid adenomas, we suggest considering using a dual-phase imaging method, combined with early SPECT-CT whenever possible, as a contributory component of the preoperative imaging algorithm of patients with hyperparathyroidism.

Further studies are required in order to confirm the findings that preoperative accurate localization of parathyroid lesions cause hyper-parathyroidism. Especially prospective or randomized controlled studies are important to the future direction that will ultimately lead to improved outcomes for individuals with HPT.

Disclosure of conflict of interest

None.

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