The Role of the Experience of Nuclear Medicine Physician on Selection of Patients for Minimally Invasive Parathyroidectomy: Institutional Experience

Minimal İnvazif Paratiroidektomi İçin Hasta Seçiminde Nükleer Tıp Hekim Deneyiminin Rolü: Bölüm Tecrübemiz

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ABSTRACT Objective: To evaluate the possible role of the reporting nuclear medicine physician's experience on the results of the parathyroid scintigraphy (PS). **Material and Methods:** Patients with primary hyperparathyroidism (n=157) who were undergone a presurgical dual phase 99mTc-MIBI PS and cured with surgery were included in the study. The parathyroid scintigraphies were evaluated retrospectively and classified according to the results-conclusion sections. Adenoma, washout adenoma, indeterminate adenoma, double adenoma/hyperplasia and hyperplasia were defined. The experience of the nuclear medicine physicians was ascertained according to the date of the reports and the reporting physicians were grouped as residents (residents who are about to complete residency, senior residents) and specialists. The statistical analyses were performed using the final pathological results. **Results:** The parathyroid scintigraphies were negative in 23 patients. The final diagnosis was adenoma in 19 and hyperplasia in 4 cases. There were 113 true positive cases among 134 MIBI positive patients. There was not any statistically significant difference between reviewers in the whole group according to the experience. The diagnosis was adenoma in 108 patients. The results were true positive in 91.6% and 72.2% of the patients reported by the specialists and the residents, respectively. The results were significantly different (p=0.007). **Conclusion:** The specialists localized the adenomas more reliably than the residents. The endocrine surgeon, using a minimally invasive surgery, can detect an adenoma in the right place in 92% of the cases whenever the PS indicates an adenoma and reported by a nuclear medicine specialist.

Key Words: Technetium Tc 99m sestamibi; parathyroid neoplasms; diagnosis; radionuclide imaging

ÖZET Amaç: Tanısal testlerde doğru teşhis için yorumcunun deneyimi önemlidir. Nükleer tıp alanında, özellikle de paratiroid sintigrafilerinin yorumlanmasında hekim deneyimi konusunda çalışma bulunmamaktadır. Bu çalışmada deneyim farkının tetkik sonuçlarına yansımasını araştırmayı hedefledik. **Gereç ve Yöntemler:** Primer hiperparatiroidi tanısı almış, Tc-99m MIBI paratiroid sintigrafisi ile dual-faz görüntüleme yapılmış ve cerrahi tedavi sonrası normokalsemi sağlanmış 157 hasta bu geriye dönük çalışmaya dâhil edildi. Hastalara ait paratiroid sintigrafileri, boyun ultrasonografisi ve cerrahi-patoloji bilgilerine ulaşıldı. Paratiroid sintigrafisi raporları sonuç kısımlarına göre sınıflandı; hastalarda adenoma, "washout adenom", şüpheli adenom, çift adenom veya hiperplazi bildirilmişti. Raporlama tarihlerine bakılarak değerlendiren hekimler uzman/kıdemli asistan olarak sınıflandı. İstatistiksel analizler rapor sonuçları patoloji sonuçları ile karşılaştırılarak yapıldı. **Bulgular:** Paratiroid sintigrafisinde 23 hastada hiçbir lezyon bildirilmemişti. Bu hastaların 19'unda adenom, dördünde ise hiperplazi saptanmıştı. Hastaların 21'inde ultrasonografi yapılmış ve yedisinde lezyon doğru olarak bulunmuştu. Toplam 134 MIBI pozitif vakadan 112'si doğru pozitifti. Hastaların 99'unda adenom, 9'unda "washout adenom, 10'unda şüpheli adenom, 9'unda çift adenom/hiperplazi ve 7'sinde hiperplazi bildirilmişti. Gruplar arasında istatistiksel olarak anlamlı bir fark yoktu. Paratiroid sintigrafisi ile kesin adenom tanımlanmış hastalar değerlendirildiğinde (99 adenom ve 9 washout adenom) kıdemli asistanlar vakaların % 72,2'sinde doğru pozitif yorum yaparken, uzmanlar vakaların %91,6'sında doğru pozitif sonuca ulaşmıştı. İki grup arasında izlenen fark istatistiksel olarak anlamlıydı (p=0.007). **Sonuç:** Nükleer tıp uzmanlarının paratiroid adenomu lehine değerlendirdikleri vakalar kıdemli asistanlara göre daha yüksek doğruluktaydı. Tc-99m MIBI dual faz paratiroid sintigrafisi bir nükleer tıp uzmanı tarafından yorumlanır ve bir adenom bildirilirse endokrin cerrahı minimal invazif yöntem kullanarak vakaların %92'sinde tanımlanan alanda adenomu bulacaktır.

Anahtar Kelimeler: Teknesyum Tc 99m sestamibi; paratiroid tümörleri; tanı; radyonuklit görüntüleme

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Surgical excision of the hypersecreting parathyroid gland(s) should be performed to normalize serum calcium levels in symptomatic patients.[1] It may also be carried out in some asymptomatic patients to improve bone mineral density and to decrease progression of the disease.[2] Bilateral neck exploration, which was defined more than 80 years ago, is a standard and successful surgical treatment in the hands of an experienced parathyroid surgeon and does not necessitates imaging before the surgery.[1] Some imaging methods like neck ultrasonography (US) and parathyroid scintigraphy (PS) for the detection of abnormal glands in primary hyperparathyroidism (PHPT) were introduced since then.[3]

Surgical approach of unilateral neck exploration gained access in patients with unilateral disease on preoperative imaging with PS[4] and US.[5] Recently, minimally invasive radioguided parathyroidectomy has gained popularity over traditional bilateral neck exploration since this technique is also successful, decreasing costs and hospital stay.[7]

US is one of the most widely used imaging technologies for parathyroid lesions. It is very subjective test and highly dependent to the operator.[1] The sensitivity of the study ranged from 44% to 87 % in different studies.[7-9] The sensitivity of computerized tomography (CT) and magnetic resonance imaging (MRI) for the detection of parathyroid lesions is also low and varies between 46-80% and 50-90% respectively.[10,11]

Tc-99m MIBI is the most widely preferred agent for PS [1] and becoming the most important parameter for the decision of minimally invasive parathyroidectomy. The declared sensitivities and the specificities for dual-phase study using Tc-99m MIBI as a radiopharmaceutical are between 68%-95% and 75%-100% respectively. The percentages are higher in studies with additional anterior oblique pinhole images and SPECT studies.[12-14] Many factors were studied to demonstrate any possible effects on cellular MIBI uptake and retention until today. The weight, size and volume of the adenoma, oxyphil cell numbers, amount of mitochondria, Pgp expression and parathyroid hormone levels are some examples.[15-18]

It is very well known that US for the evaluation of parathyroid glands is dependent to the performer.[1] Some nuclear medicine studies were also known to be dependent to the observers and to the technique.[19,20] Interestingly, there isn't any study in the literature concerning the influence of different interpreters on PS results.

In this retrospective study we analyzed the PS results of a patient group who were undergone surgical treatment for hyperparathyroidism and proved to have a parathyroid adenoma or hyperplasia histologically. The aim of this study was to analyze the results of these PS studies and to find the role of the experience of the interpreters and the role of the new versus old gamma camera systems on diagnostic accuracy of PS studies.

MATERIAL AND METHODS

PATIENTS

The patients with primary hyperparathyroidism who became normocalcemic following surgical treatment between the years 2000-2009 and imaged with a dual phase 99mTc-MIBI study for the diagnosis were included in this study.

DATA COLLECTION

The surgical methods (partial or total parathyroidectomy with or without thyroidectomy) and the pathology reports (the cytology, the sites of adenoma/adenomas or hyperplasia) were obtained from patient files. The PS and US (if performed) reports were also obtained from patient files. The pathologic gland localization was defined according to the side as left or right and according to the site as superior or inferior in both MIBI scans and US studies. The localizations of ectopic glands were also defined in PS.

THE INTERPRETERS AND THE INSTRUMENTS

The reporting nuclear medicine physicians and the gamma cameras used for imaging were determined for each PS study.

There were 10 different reporting nuclear medicine physicians and they were classified according to their expertise level for each report. The reporting nuclear medicine physicians were either

a senior resident (an assistant doctor at nuclear medicine department for at least 3 and a half years), or a specialist (the medical doctors who were completed the prescribed theoretical and practical training in nuclear medicine department for at least 4 years). Some reporters evaluated the PS studies both as a senior resident and as a specialist during the time period of the selected studies. The studies were also grouped according to the gamma cameras by which the images were obtained. The images were obtained with a GE gama camera (Camstar XR/T 3000, General Electric, Milwaukee, WI, USA) until March of 2006 and with Philips gamma cameras (Forte Gamma Camera System, SPECT, ADAC Laboratories, Milpitas, CA, USA) there after.

DUAL PHASE SCINTIGRAPHY

The radiopharmaceuticals used for imaging and the imaging protocols were standard for the study period. The PS was obtained following the intravenous injection of 555 MBq of 99mTc-MIBI. Early pinhole anterior and both anterior oblique images were obtained 15 minutes after the injection. Late pinhole images of the neck and a planar mediastinal image were obtained 2-3 hours after the injection. The early pinhole images were obtained for 150.000 counts at 256x256 matrixes. The late pinhole images were obtained for the same time period with early images. The mediastinal planar images of 10 minutes at 256x256 matrixes were obtained to evaluate a possible ectopic gland with a low energy all purpose collimator. The oblique images were obtained at 45° right anterior oblique and 45° left anterior neck projections.

CLASSIFICATION OF PS STUDIES

All the reports were classified retrospectively according to the results/conclusions section. The reports were negative, indeterminate or positive for parathyroid lesions. The reports were negative whenever a focal activity both on early and late images were absent. The scintigraphic study was classified as indeterminate for parathyroid adenoma (InAD) if there was a thyroid nodule at the same localization on thyroid scintigraphy or by US. The studies were also classified as InAD if the early study is negative and a mild activity was detected on the late images or if there is only a very faint activity both on early and late images. Finally, any activity which was discriminated from the surrounding thyroid gland by the presence of a demarcation line around it was also accepted as an InAD. The reports were positive if an activity or activities were present at early images which were persisted at late images following washout from thyroid gland. The positive studies were reported as an AD if only one activity was present, as a dAD-HP if two activities were present and finally as a HP if three or more activities were present. The activities that are present on early images but not detected on late images were reported as awAD in the absence of a thyroid nodule in that localization by US and/or thyroid scintigraphy.

STATISTICAL ANALYSIS

The patient group in this study was constituted from clinically and/or biochemically proven hyperparathyroid patients. So, there was not any true negative patient in the study group and we could not calculate the sensitivity, specificity and likelihood ratios for the whole group. Chi-square test was used to analyze the presence of any statistically significant difference of PS results between the senior residents and specialists. It was also used for the establishment of differences between individual reviewers and between the different camera systems.

RESULTS

There were a total of 157 patients (27 men, 130 women). The mean age of the patients were 55.6±11.2 (min:22, max:84). Partial parathyroidectomy (minimally invasive parathyroidectomy) was performed in 147 (94 %) patients using an intraoperative gamma probe to localize the lesion or lesions using quick PTH test (for the last 3 years) to confirm the complete resection of the involved gland or glands. Total parathyroidectomy was performed in the rest. If present, total or subtotal thyroidectomy was also performed for the nodular thyroid disease.

The scintigraphic study was negative in 23 patients (14.6 %). Parathyroid hyperplasia (4 patients) and parathyroid adenoma (19 patients) were the final diagnosis in these patients. The US was true po-

sitive in 7 and false positive in 2. It was also negative in 12 of these patients. US was not performed in the remaining two. The adenoma was at right lower in 11, at left lower in 5 patients. It was detected at left upper in 1 patient and right upper in another. The site of adenoma was unclear in one patient. The localization of MIBI negative parathyroid adenomas was at lower poles in 88.9 % of the patients.

The scintigraphy was positive in 134 patients (85.4 %). The scintigraphic results were correct in 113 of them (84 %). The MIBI results of the whole study group with respect to the pathology were summarized in Table 1.

The diagnosis with MIBI was an AD in 99 of the patients (63.1 %). Eighty-five of them were true positives (86 %). MIBI was false positive for AD in 14 and the final diagnosis was hyperplasia in 10 and an adenoma at a different localization in 4 patients. The US result was also true positive in 62 of these 99 patients (59 adenomas, 3 hyperplasia). The results were false positive in 30 patients (an adenoma on the wrong localization in 26 patients and a false diagnosis of an adenoma instead of a hyperplasia in 4). US was not performed in 6 patients and it was negative in one patient. Among the patients with false positive MIBI results, the neck US was true positive in 7, was also false positive in 5 and not performed in 2 patients.

TABLE 1: Documentation of the parathyroid scintigraphy results with respect to the pathology.

	Final Diagnosis (Pathology)			
		Adenoma		
MIBI Results	Hyperplasia	Site true	Site false	Total
MIBI Negative	4		19	23
MIBI Positive				
AD	10	85	4	99
wAD	1	7	1	9
InAD	2	7	1	10
dAD-HP	4	4	1	9
HP	5		2	7
Total	26	124	7	157

* AD: Adenoma, wAD: washout adenoma, InAD: Indeterminate adenoma, dAD-HP: Double adenoma or hyperplasia, HP: Hyperplasia

The diagnosis on MIBI was a wAD in 9 patients. Seven of them were true positives. One of the false positive lesions was excised from the contralateral side and the final diagnosis in the other patient was hyperplasia. The US was true positive in 5 patients including the patient with a false positive MIBI result on the contralateral side of the adenoma. It was negative in two adenomas and false positive in one adenoma (incorrect side) and one hyperplasia (only an adenoma was reported).

Seven patients (4.5 %) were diagnosed to have hyperplasia of the parathyroid glands scintigraphically. Five of them were true positives. Adenomas of the right and left lower poles were detected pathologically in the remaining two patients. The neck US detected the 3 out of five hyperplasia. It was negative in one and suggestive of an adenoma in the last patient with hyperplasia. The neck US was also negative in one and false positive for the localization in the other patient diagnosed to have adenomas pathologically.

The diagnosis was dAD-HP in 9 patients (5.7 %). Eight of them were true positives (4 hyperplasia and 4 adenomas). The MIBI study was false positive in the last patient. Normal parathyroid glands were diagnosed on MIBI positive sites on histological examination (US was not performed in this patient) in this patient. The US was true positive in two, negative in one and suggesting an adenoma in the last with hyperplasia. It is true positive in 2, false positive in the remaining 2 patients with the diagnosis of adenoma.

The diagnosis was InAD in 10 of the patients (6.4 %). The reports were indeterminate in 7 patients because of the absence of a focal activity at early images although there was a faint uptake at late images. It was indeterminate in two because of the presence of a thyroid nodule at the same localization with the suspected adenoma. Finally, in one patient, although the activity is same with the surrounding tissue a clear demarcation line was detected surrounding the InAD. The final diagnosis was an adenoma in 8 patients. A parathyroid adenoma was diagnosed on the same site in seven patients (true positives), on the opposite side in one

patient. The final diagnosis was hyperplasia in two patients and MIBI scintigraphy was suspicious for an adenoma in these patients. The neck US detected the 2 patients with parathyroid adenoma with the correct localization (in one MIBI was incorrect for the localization). The side was incorrect in one patient and the US was negative for any parathyroid lesion in the rest.

Five different reporting physicians reported the PS of 126 patients (min 18, max 36 reports per reviewer). The ratios of true positive MIBI results according to the reviewers were 13/19, 13/22, 13/18, 28/36 and 24/31. There was not any statistically significant difference between the reviewers (chi-square, p= 0.56). Five other reporters reported the remaining 31 studies.

The whole reports (157) were used for the other tests. Six of the reporting physicians were females and 4 were males. The reporting physicians of male gender reported a total of 94 patients and the results were true in 69 patients (73.4 %). Female physicians reported a total of 63 patients and the results were true in 43 (68.2 %). There was not any statistically significant difference according to the genders of reviewers (chi-square, p= 0.48). In 53 cases (33.8 %) the reporting physician was a resident at the time of the study. The results were true with respect to the pathology in 34 of them (64.1 %). The specialists evaluated the rest of the studies (104 studies). The results were true positives in 78 patients (75 %). There was not any statistically significant difference between the senior residents and the specialist although the specialist localized the parathyroid lesions in more then 10 % of the patients (chi-square, p= 0.15).

The adenoma cases without any suspect (99 AD + 9 wAD, a total of 108 patients) on PS were also tested separately for the effect of the experience on results. Thirty-six of them (33.3 %) were reported by the senior residents and an adenoma was excised in 26 of them (72.2 %). Seventy-two cases (66.7 %) were reported by the specialists and an adenoma was excised in 66 of them (91.6 %) providing normocalcemia postoperatively. The difference was significant (chi-square, p= 0.007) and the true positive rates were higher whenever the result was interpreted as an adenoma by a specialist.

For imaging, new gamma camera systems were used with the beginning of March 2006 in 23 patients (14.6 %). The rest were imaged with the old systems, which were used until the beginning of March 2006. The MIBI results were true in 69.4 % of the patients (93/134) who were imaged with the old systems and the results were true in 82.6 % of the patients (19/23) imaged with the new systems. There was not any statistically significant difference of the MIBI results according to the imaging systems (chi-square, p= 0.19). The same was true for the adenoma group. The results were true in 84.3 % (75/89) with the older and 89.5% (17/19) with the newer systems and the difference was not significant (p= 0.73).

DISCUSSION

The specialists located the adenomas (excluding the HP, dAD-HP, InAD and negative cases) more accurately than the senior residents (p= 0.007). The PS studies interpreted by a specialist and indicating an adenoma is a highly reliable method. On the other hand there was not any statistically significant difference between observers of different experience levels in the whole group including HP, dAD-HP and InAD subgroups. We think that this finding is secondary to the low sensitivity of PS in parathyroid hyperplasia. Nevertheless, planar dual phase MIBI parathyroid scintigraphy correctly localized the site of the adenoma in 91.6% of the patients whenever the result of the test is suggestive for an adenoma and the test was reviewed by a nuclear medicine specialist. This finding indicates that an endocrine surgeon could find the adenoma on the pointed site in about 92% of the cases. On the other hand, it will be wise for the nuclear medicine specialists to reevaluate the PS studies which were reported by senior residents. This reevaluation before the approval of the reports will be very important to achieve a good practice.

The studies investigating the role of the experience of the nuclear medicine physicians in evaluating PS were lacking in the literature. This is not

true for the neck US in which the skill and the experience of the ultrasonographer was declared to be one of the most important parameters that determine the accuracy of the test in detecting parathyroid lesions.[1,21] The neck US was also reported to be affected by the presence of multiglandular disease or hyperplasia[22,23] and the presence of recurrent disease or previous surgery.[24] Our findings about the importance of experience of reviewers in evaluating PS studies justifies the prediction of Clark et al about minimally invasive parathyroidectomy; "experienced nuclear medicine physicians may be the most important factor to achieve maximum success".[21] Minimally invasive surgery can be carried out for these patients confirming the success of the surgery by quick PTH test. A classic bilateral neck exploration can be performed for the rest of the patients (8%). A recommended algorithm for patients with primary hyperparathyroidism is represented in Figure 1.

There was not any statistically significant difference in the detection of parathyroid lesions with PS between the individual reviewers of the equal experience levels (chi-square, p= 0.56). This is the advantage of PS over some other nuclear medicine studies like brain perfusion SPECT and myocardial perfusion SPECT, which were demonstrated to be dependent on the reviewers.[26,27] A poor correlation between observers was also demonstrated for bone scans.[28] So, the interpretation of a parathyroid scintigraphy was not dependent to the reviewer in contrast to the other scintigraphic studies as long as the reporting physician is a specialist. This was an obvious advantage of PS.

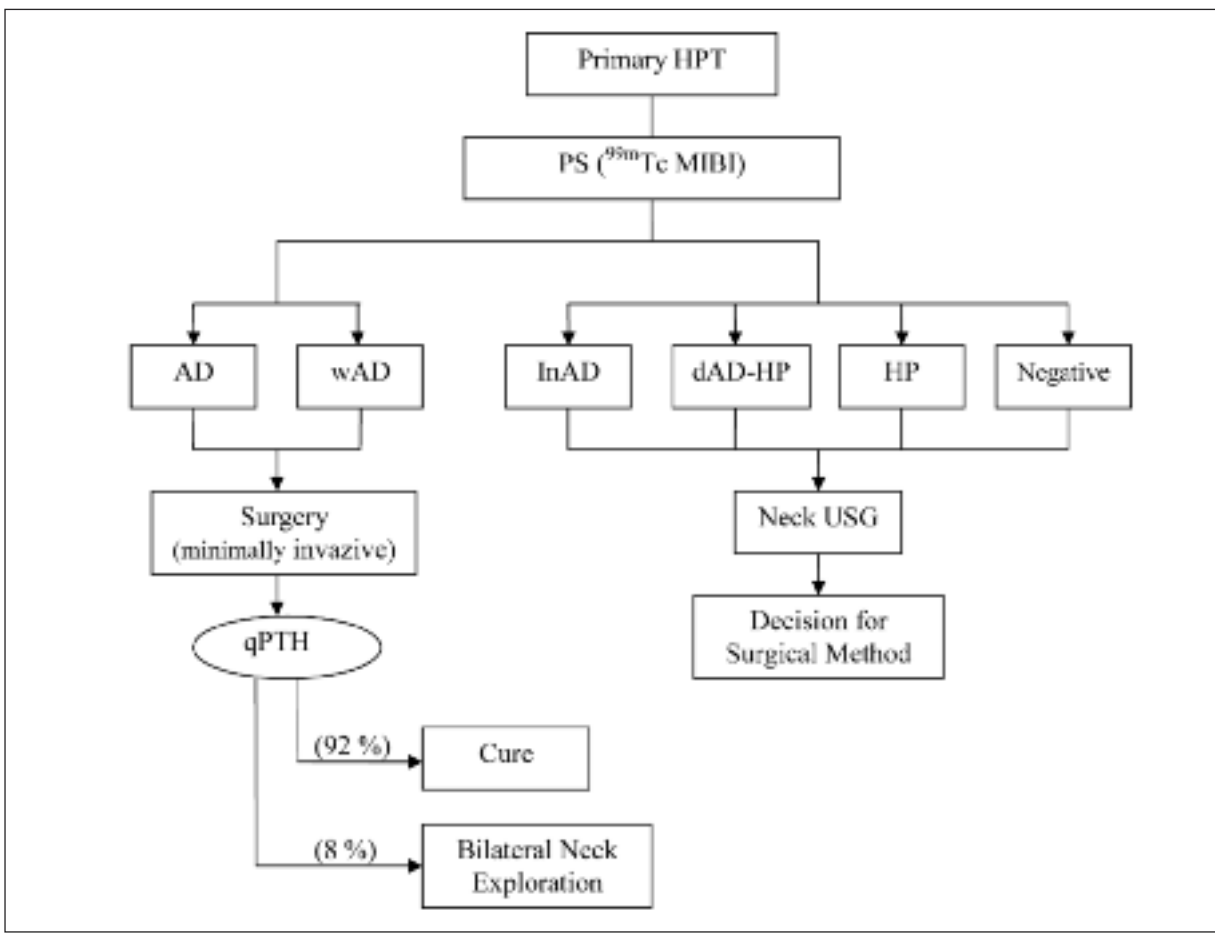


FIGURE 1: An algorithm for the evaluation of patients with primary hyperparathyroidism (using the parathyroid scintigraphy as a first-line diagnostic procedure)*
HPT: hyperparathyroidism, PS: parathyroid scintigraphy, AD: Adenoma, wAD: washout adenoma, InAD: Indeterminate adenoma, dAD-HP: double adenoma or hyperplasia, HP: hyperplasia, qPTH: quick parathyroid hormone

It is also known that the accuracy of the parathyroid scintigraphy changes according to the used techniques. Many imaging techniques were investigated until now like SPECT and pinhole studies or subtraction studies. In our study we analyzed the results with respect to the old and the new camera systems. There was not any statistically significant difference between the old and the new systems. So, the current technology gamma camera systems with higher spatial resolution did not seem to have any improvements on parathyroid lesion detection.

The final diagnosis was a parathyroid adenoma in 82.6 % and hyperplasia in 17.4% of the cases with negative MIBI results. The MIBI negative lesions were excised from lower sites of the lobes in about 90% of the cases. The neck US, when performed in MIBI negative cases could localized the lesions in 33.3% (7/21) of the patients correctly. In patients with primary hyperparathyroidism in whom both PS and neck US are negative it would be wise to start from lower lobes for exploration during surgery.

As a conclusion;

The specialists' reports were more reliable than the senior residents in determining the lesions when an adenoma was declared by a dual phase 99mTc-MIBI parathyroid scintigraphy. PS alone as a diagnostic test, when suggestive of an adenoma and evaluated by a specialist seems to be sufficient for presurgical localization, decreasing the need for bilateral neck exploration to about 8%.

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