Parathyroid nuclear scan. A focused review on the technical and biological factors affecting its outcome

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Summary

***Objective*. Technetium Parathyroid Scintigraphy (TS) is the most popular noninvasive localization procedure in patients with primary hyperparathyroidism (PHPT). Awareness of various factors involved in technetium uptake helps understand the outcome of TS.**
***Methods*. We utilize a case of changing TS scans in a patient to review the literature on the various biological and technical factors involved in technetium uptake by the abnormal parathyroid tissue. A 56 year female was diagnosed with PHPT and osteopenia. An initial scan using ^{99m}Tc-Tetrofosmin showed no definite areas of abnormal parathyroid tissue. Patient refused surgical exploration, was started on Bisphosponates and subsequently monitored. Five years later she suffered fracture of her right wrist. A repeat TS using ^{99m}Tc-Sestamibi revealed hypervascular parathyroid lesion in the right lower neck. She underwent successful removal of a right lower parathyroid adenoma.**
***Results*. Technical factors like the type of Tc isotope used, imaging techniques and biological factors like biochemical parameters (calcium, vitamin D levels), adenoma size, content of oxyphilic cells, vascularity can affect the outcome of the scan.**
***Conclusion*. Clinicians should be aware of technical and biological factors that could result in negative scan in parathyroid nuclear scintigraphy.**

KEY WORDS: primary hyperparathyroidism; parathyroid nuclear scintigraphy; technetium tetrofosmin; technetium sestamibi.

Introduction

Technetium nuclear scintigraphy (TS) is the most popular procedure to localize abnormal parathyroid glands in patients with primary hyperparathyroidism (PHPT). The two radio-pharmaceuticals used are ^{99m}Tc-Sestamibi and ^{99m}Tc-Tetrofosmin. Despite its limitations and variable accuracy TS along with pre-operative ultrasound has an established role in centers which perform large volume parathyroid surgery (1, 2). However there are technical and biological factors that affect the uptake of the ^{99m}Tc in the parathyroid adenoma and potentially affect the sensitivity and specificity of scan. We present a patient with PHPT whose initially negative scan converted to a positive scan five years later. We then review published data about the biological and technical factors that could possibly lead to such conversion.

Case report

A 63 year old Caucasian woman was evaluated in 2005 for high normal calcium 10.2 mg/dl (8.5-10.5), elevated PTH (72 pg/ml) and low bone mineral density (BMD) in the spine (T-score -1.5) and the hip (T-score -1.3). Information on forearm bone density was not available. She had no problems attributable to parathyroid disease. Her daily total calcium intake was approximately 2500mg including diet and supplements and 400-800 IU vitamin D/day from Multivitamins. Her examination was normal. The initial laboratory test results are listed in Table 1. A ^{99m}Tc scan using ^{99m}Tc-Tetrofosmin showed no definite areas of abnormal uptake to suggest possible sites for abnormal parathyroid tissue (Figure 1). Neck Ultrasound (US) did not reveal enlarged parathyroid lesions. Patient refused surgical intervention. She was started on Risedronate 35mg/week and was monitored with periodic labs. During the subsequent six year period her calcium was in the upper limits of normal range and bone turnover markers were stable. In January 2010, the spinal and hip BMD were stable but T-score in her left forearm was -2.9. In December 2010 she suffered a Colles' fracture of the right wrist and underwent parathyroid surgery. A repeat scan using ^{99m}Tc-Sestamibi showed a hypervascular parathyroid lesion in the right lower neck (Figure 2). US revealed a 1.56 x 0.35 x 0.33 cm hypoechoic nodule inferior to the lower pole of the right thyroid lobe with hyperechoic rim and increased color flow Doppler signal. At surgery she underwent a four gland exploration leading to excision of right lower parathyroid adenoma weighing 100mg and consisting of oxyphil cells (90%)

Table 1 - Laboratory values of patient 2005 to 2011.

Lab (normal range)	2005 (Negative Tc-scan)	2006	2006	2007	2007	2008	2010	2011 (Positive Tc scan)	2011 postop	2011 follow up
Calcium (8.5-10.5mg/dl)	10.4	10.2	10.5	10.3	9.4		10.5	10.6		9.8
Albumin (4g/dl)	4.7		5		4.7			4.8		
Ionized Calcium (1.08-1.30 mmol/L)							1.38	1.38		1.28
PTH (10-60 pg/ml)	72	68	83	90	116	67	94	74	<4	53
Phosphorus (2.5-4.5 mg/dl)	3.6	2.7	2.8					3.5	5	4.1
Magnesium (1.7-2.6 mg/dl)	2.2							2.3	1.8	2.1
25OH Vit D (ng/ml)	37.6		40.3	32.7	33.4	48.2		51.2	49.2	45.8
24 hr urine calcium (100-300mg)								236.3		
Urine NTX (14.4-70 nM/mM Cr)	70.1	21.5		16.7			46.3			12.6

and pockets of clear cells. Her calcium and PTH levels normalized after surgery (Table 1).

Discussion

Our case provided the unique opportunity to compare two different radio-pharmaceuticals of ^{99m}Tc based scans in the natural history of PHPT. Multiple factors could explain the conversion of the TS from a initial negative scan to a positive scan including disease progression, increase in size and vascularity of the adenoma, change in radio-pharmaceuticals of ^{99m}Tc and variability in technique of the two scans.

We now review the biological and technical factors that can potentially affect the outcome of TS:

I. ***Biological factors affecting TS***:
Sestamibi and Tetrofosmin are monovalent lipophilic cations that diffuse passively down an electro-chemical gradient through cell membranes and accumulate almost exclusively in mitochondria of parathyroid lesions. A normal parathyroid gland does not take up Sestamibi or Tetrofosmin. The exact mechanism of its selective uptake in abnormal parathyroid glands remains debatable. High mitochondrial activity is considered to be the major component of tracer uptake by human parathyroid tissue in patients with PHPT (3). The following factors have been reported to be associated with negative scans.

a. *Biochemical factors:*

i. Serum calcium level
Higher preoperative calcium levels are more likely to be observed in patients with positive scans. In a study of 102 patients, more than 95% of those with plasma calcium greater than 11.3 mg/dL had a positive scan as compared with 60% of those with lesser values (4).

ii. Serum PTH level
A significant correlation was noted between the uptake and preoperative PTH levels. Higher PTH values are more likely observed in patients with positive scans (5). A serum PTH level greater than 160 pg/mL correlated with positive scans in 93% as opposed to 57% in those with lower levels (4). This correlation was not observed by others and the overlap of PTH levels in positive and neg-

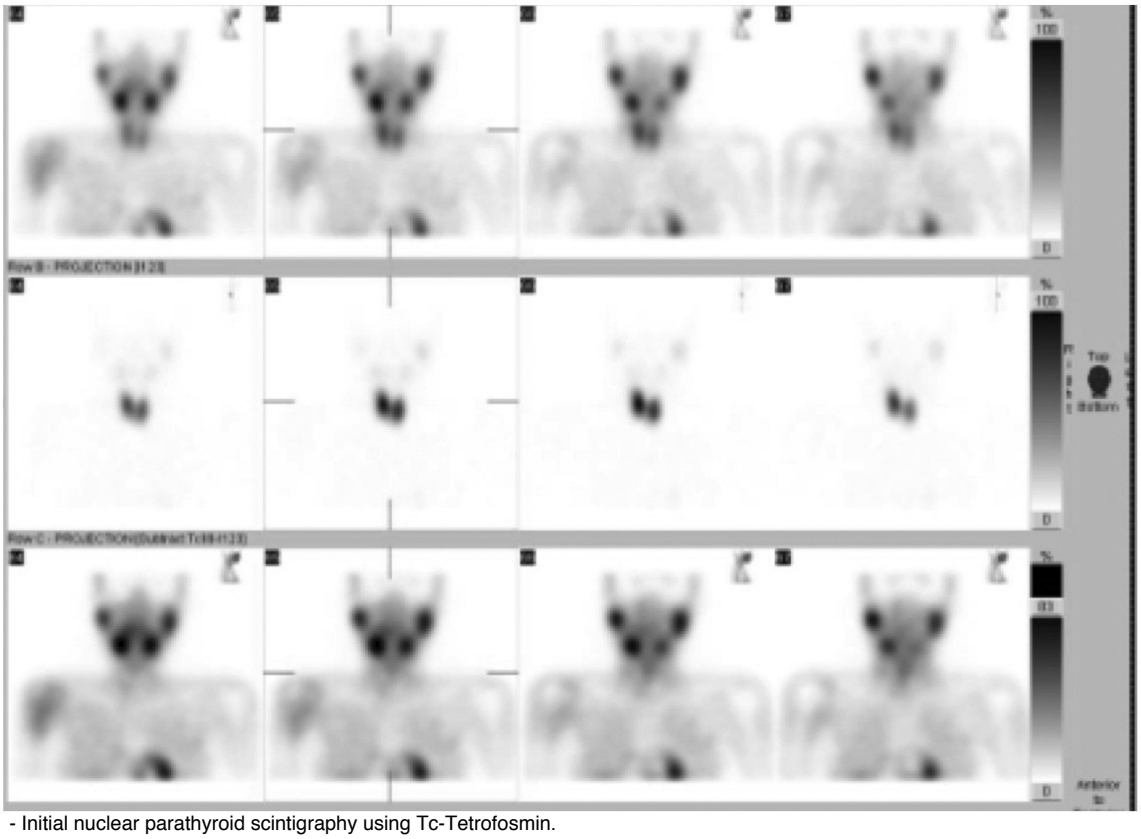

Figure 1 - Initial nuclear parathyroid scintigraphy using Tc-Tetrofosmin.

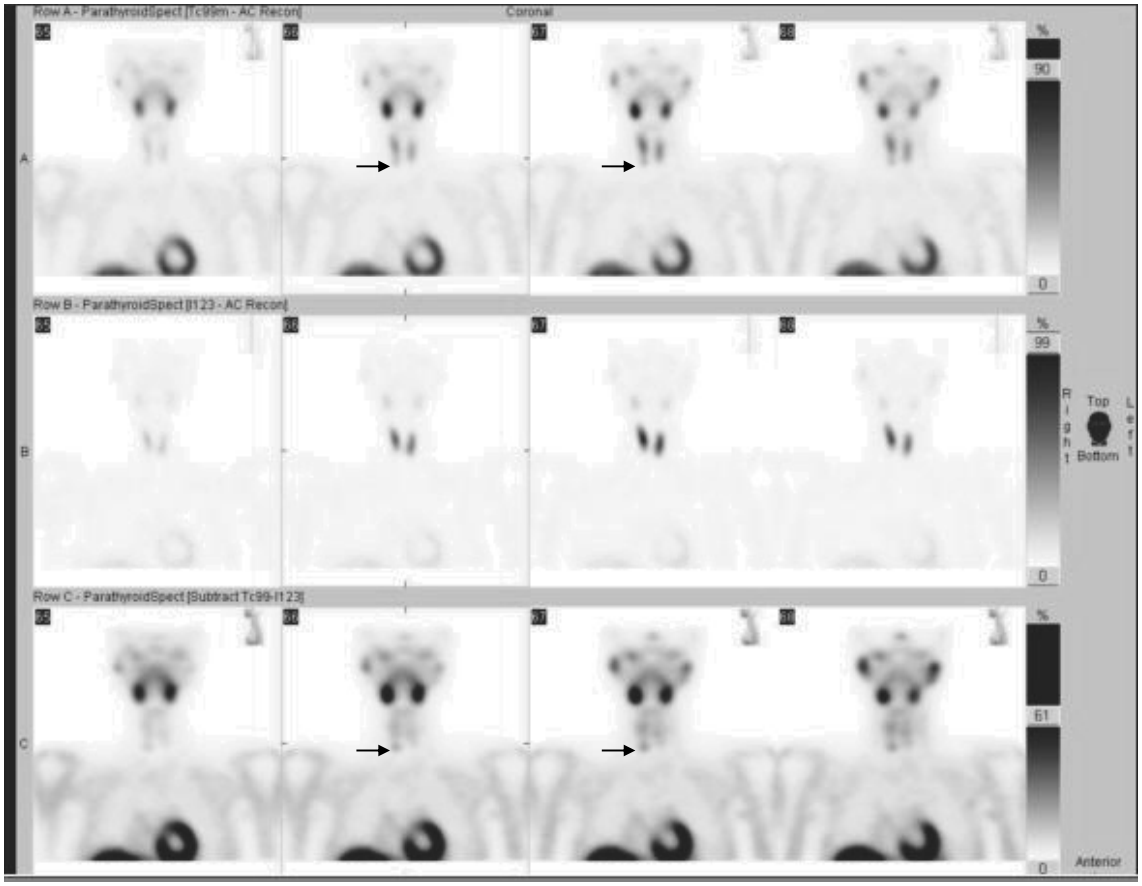

Figure 2 - Second nuclear parathyroid scintigraphy using Tc-Sestamibi (arrows point to abnormal right lower parathyroid).

ative scans does not change the likelihood of positive or negative scanning (6, 7)

iii. Serum vitamin D level
Patients with vitamin D deficiency more likely have positive scans. In a study of 421 consecutive primary hyperparathyroid patients, those with cholecalciferol levels <25 ng/mL had PTH levels and adenoma weight higher than those with normal vitamin D and were eight times more likely (OR 7.86; 95% CI, 4.78-12.93; P < .001) to have a positive scan after adjusting for age and sex (8). Suboptimal vitamin D nutrition may stimulate parathyroid adenoma growth by a mechanism unrelated to hypocalcemia or 1,25-dihydroxyvitamin D deficiency and reduce the calcemic response to PTH, so that a higher PTH level and more parathyroid cells are needed to maintain the increased set-point that is characteristic of the disease (9).

iv. Calcium Channel Blockers
The use of calcium channel blockers (CCBs) may interfere with ^{99m}Tc-Sestamibi uptake by parathyroid cells and reduces the sensitivity of the scan. Friedman et al found that the odds ratio for a negative scan was about two fold higher in patients taking CCBs than who were not. (OR 2.88, 95% CI, 1.03-8.10; p 0.045) (10).

b. *Biological factors:*

i. Size - Although size is thought to be an important factor to affect the positivity of a TS, it is clearly not the sole factor involved.

ii. Parathyroid adenoma cell content
As oxyphil cells have a higher mitochondrial content compared to the clear cell, they are more likely to uptake Technetium isotopes. The presence of oxyphil cells within the parathyroid adenomas is associated with a positive 99mTc-Sestamibi scan (11). In a report by Erbil et al., an adenoma weight >600 mg and an oxyphil cell content >20% increased the rate of obtaining a positive sestamibi scan result by 10- and 4-fold respectively (12).

iii. P glycoprotein and MDR gene products
The uptake of tetrofosmin and of sestamibi into parathyroid adenoma cells depends on the activity of the P-glycoprotein (P-gp) coded on the multidrug resistance (MDR1) gene, which functions as an ATP-dependent efflux pump, preventing the accumulation of lipophilic, cationic radiopharmaceuticals, including Tetrofosmin and Sestamibi (13). P-gp expression in parathyroid adenomas has been postulated to be another important factor influencing 99mTc-MIBI and Tc-TF uptake in parathyroid adenomas. In one study, 71% (10 of 14) of adenomas with strong P-gp membrane positivity had negative imaging and 70% (45 of 64) with negative P-gp membrane expression (p=0.006) had a positive scan (14).

iv. Multi-gland disease
A significant limitation of nuclear parathyroid scanning is the detection of all diseased parathyroid glands consistently. In the study by Siperstein et al., the accuracy of Sestamibi scan was 49% (73/150) in multi-gland disease (1). Similarly, the accuracy of ^{99m}Tc Sestamibi was only 30% in a group of 21 patients with double adenomas identified in a cohort of 287 PHPT patients (15). A possible explanation in these scenarios include preferential uptake of sestamibi by one abnormal parathyroid gland compared to the others.
Some of these factors and likelihood of ^{99m}Tcc scan positivity are summarized in Table 2.

II. Technical factors:

a. *Evolution of TS:*
Technical aspects for TS have evolved in recent years. The first radionuclide imaging technique widely used in the 1980s for hyper-functioning parathyroid localization was thallium-201 (^{201}Tl) scintigraphy. Since ^{201}Tl was taken up by both the thyroid and parathyroid, it was used in conjunction with ^{99m}Tc pertechnetate, which is taken up only by the thyroid (16). The ^{99m}Tc scintigram then was digitally subtracted from the ^{201}Tl scintigram to allow parathyroid localization. In 1989, Coakley and colleagues reported the use of ^{99m}Tc Sestamibi for parathyroid scintigraphy (17). It was a serendipitous discovery as ^{99m}Tc was predominantly used in cardiac stress testing during those days. The new radionuclide rapidly replaced ^{201}Tl because of superior image quality, more favorable dosimetry, and improved detection sensitivity (18). Variations of this basic methodology have since been used in practice which includes single-isotope dual-phase imaging and dual-isotope subtraction imaging.
The single-isotope dual-phase (early and delayed phase) scintigraphic technique was suggested by Taillefer et al based on the observation that ^{99m}Tc-Sestamibi washes out more rapidly from the thyroid gland than from hyperfunctioning parathyroid glands (19). The neck is imaged at 5 minutes and 120 minutes after ^{99m}Tc-Sestamibi administration. The “differential washout” phenomenon improves target-to-background activity so that abnormal parathyroid tissue should become more visible on the delayed images. In the dual agent method thyroid images obtained with Iodine-123 (^{123}I) or ^{99m}Tc pertechnetate are subtracted from the images obtained with ^{99m}Tcc Sestamibi thereby revealing persistent isotope uptake in the parathyroid adenoma.

b. *Imaging techniques in TS:*
These changes in Tc agents were followed by improved imaging methods. Planar imaging (2 dimensional) was followed by tomographic (3 dimensional) imaging. The advantages of single photon emission computed tomography (SPECT) over planar imaging included an enhanced contrast, 3-dimensional localization, and estimation of lesion size. SPECT was found to further increase the sensitivity of parathyroid imaging from 87% (as in planar scintigraphy) up to 95% (20). The introduction of hybrid SPECT/CT, an instrument that physically couples a SPECT camera with a CT in a single integrated unit offers the potential advantage of better anatomically defining the location of scintigraphic findings that are identified on SPECT images. Another addition to parathyroid imaging has been the 4D-CT also referred to as multidimensional CT. Its difference compared to a 3D CT is the fourth dimension with contrast enhancement. Parathyroid adenomas typically enhance avidly on early-phase imaging, and the hyper-enhancement persists despite a long delay after contrast administration. The degree of early enhancing and slow washout of contrast correlates with metabolic activity of the parathyroid adenoma. This characteristic gives 4D-CT the double advantage of demonstrating gland functionality and excellent anatomy of the gland and its surrounding structures.

c. *Isotope-Tracers of Technetium*:
^{99m}Tc-Sestamibi and ^{99m}Tc-Tetrofosmin are both used in TS. Often, the choice of imaging agent depends on its availability, which agent is used for cardiac stress testing in the institution and the experience of the physician.

Table 2 - Biochemical and biological factors affecting the likelihood of positive TS.

Factor	Higher Likelihood of Positive Tc scan	Lower Likelihood of Positive Tc scan
Calcium level (mg/dl)[4]	Greater than 11.3	Lesser than 11.3
PTH level (pg/ml)[4]	Greater than 160	Lesser than 160
25 Hydroxy Vitamin D (ng/dl)[8]	Lesser than 25	Greater than 25
Use of Calcium Channel Blocker [10]	Non-use of CCB	Use of CCB
Mean weight of Adenoma (mg)[12]	1434 $\pm$ 403	480 $\pm$ 156
Oxyphil cell content[12]	Greater than 20%	Lesser than 20%

Table 3 - Summary of the studies comparing Tetrofosmin and Sestamibi.

Author & Year	Type of Study	PHTP patients (n)	Type of Scan technique	Results
Aigner et al 1996[23]	Prospective	10	Single agent dual phase	Sensitivity of Tetrofosmin comparable to Sestamibi
Giordano et al 1997[21]	Prospective	93	Single agent dual phase & Per-technetate subtraction	Correct result 88% (S) vs 59% (T) (P=0.016)
Wakamatsu et al 2001[22]	Prospective	25	Dual agent Subtraction; Parallel hole collimater	SGD: 63.2% (T) vs 68.4% (S) MGD: 41.7% (T) vs 41.7%(S)
A C Froberg et al 2002[24]	Retrospective	8	Single agent dual phase; Planar images	8/8 cases: 100% (S) 2/8 cases: 25% (T)

**T= Tetrofosmin; S=Sestamibi

Giordano et al compared the retention characteristics of these two tracers and Tc-pertechnetate in euthyroid subjects and found that Tc-Tetrofosmin had a lower early thyroid uptake than ^{99m}Tc-Sestamibi (2.26+0.52 vs. 2.01+0.49, respectively; p<0.002) as well as lower retention (1.4+0.37 vs. 1.65+0.58, respectively; p<0.002) (21). This finding provided an objective basis for the poorer results of ^{99m}Tc-tetrofosmin in single agent dual phase parathyroid scintigraphy. However Wakamatsu et al found that the two isotopes had similar sensitivities in the dual agent subtraction technique: 51.2% (Tetrofosmin) versus 53.5% (Sestamibi) in overall sensitivities, 63.2% vs 68.4% (single gland disease), 41.7% versus 41.7% (multi-gland disease)(22). Table 3 summarizes the studies comparing Tetrofosmin and Sestamibi (23, 24).

In the index case described serum biochemical markers were comparable during both the scans. It is possible that the adenoma increased in size, vascularity and had accrued more oxyphil cells along with changes in the cell surface glycoproteins in the 5 year time period. However these factors are impossible to evaluate and objectively compare. Lack of information on the forearm bone density during the initial scan makes it difficult to say with certainty whether her osteoporosis had worsened. Addition of CT to SPECT imaging during the second scan did not contribute to the conversion in our case as the adenoma was clearly visible even on the initial SPECT images (Figure 2). The biggest technical factor that was different between the two scans was the type of isotope tracer used. The differences in tumor localization ability between Tetrofosmin and Sestamibi was compared in a prospectively maintained database of sporadic PHPT patients from 2004-2006 at the Cleveland Clinic (Institution quality outcome survey, internal data not previously published). The patients were divided into two groups depending on the isotope used (Sestamibi (n=262) & Tetrofosmin (n=83) and the accuracy of localization was adjusted to age, gender, BMI and gland size. Sestamibi and Tetrofosmin didn't show any difference in overall accuracy when a single adenoma or multigland hyperplasia was noted. However when the scan showed a single gland, Tetrofosmin was significantly less accurate in orienting the surgeon to the diseased gland than Sestamibi (Tetrofosmin 64%, Sestamibi 79%; χ^2 test 10.3; p 0.01). This led to a change of practice at the Cleveland Clinic where Tc-Sestamibi is routinely used for pre-operative localization.

Conclusion

Changing TS from negative to positive is an interesting phenomenon and the various biological and technical factors help us understand the process involved in ^{99m}Tc-isotope uptake by abnormal parathyroid cells. It is important to emphasize that diagnosis of PHPT is made on clinical and biochemical data. TS is not a diagnostic tool. Its imaging capabilities are limited and the surgeon's skill is the ultimate "localizing test". By understanding the technical and biological factors involved in imaging and possibly manipulating some or all of them in the future, the accuracy of these scans may

markedly improve. Clinicians should be aware of technical and biological factors that could result in negative scan in TS.

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