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Preoperative Localization of Parathyroid Lesions in Hyperparathyroidism: Relationship Between Technetium-99m-MIBI Uptake and Oxyphil Cell Content

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The aim of this study was to assess the relationship between parathyroid oxyphil cell content and early or late phases of uptake of ^{99m}Tc-MIBI, a radioisotope preferentially retained in mitochondria-rich cells. **Methods:** This study is a retrospective, single-blind analysis of all double-phase ^{99m}Tc-MIBI parathyroid scintigraphy studies performed before surgery in our institution between 1990 and 1995. A total of 18 parathyroid lesions in 14 patients were reviewed. This sample included 11 cases of primary hyperparathyroidism (8 adenomas, 1 adenocarcinoma and 2 hyperplasias) and 3 cases of tertiary hyperparathyroidism secondary to chronic renal failure. **Results:** Uptake of ^{99m}Tc-MIBI in the early phase of scintigraphy was associated with larger parathyroid lesions (1.61 ± 1.61 ml versus 0.33 ± 0.27 ml; $p < 0.02$) and higher serum calcium levels (3.00 ± 0.41 m*M* versus 2.67 ± 0.14 m*M*; $p < 0.02$). More importantly, we found that a parathyroid oxyphil cell content greater than 25% was more often associated with a positive uptake of ^{99m}Tc-MIBI in the late phase of the test (positive late uptake in 78% of lesions with a high oxyphil cell content versus 33% in lesions with an oxyphil cell content between 1% and 25% and 0% in lesions with no oxyphil cells; $p < 0.04$). **Conclusion:** These findings suggest that the late retention of ^{99m}Tc-MIBI in double-phase scintigraphy is related to parathyroid oxyphil cell content.

Key Words: hyperparathyroidism; technetium-99m-MIBI; oxyphil cells; parathyroid adenoma

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Technetium-99m-MIBI was introduced in 1989 as a novel radioisotope for parathyroid imaging. Subtraction imaging methods using this isotope in combination with ^{123}I or ^{99m}Tc-pertechnetate were initially shown to be superior to other scintigraphic or radiological techniques (*1–5*). These tech-

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TABLE 1
Characteristics of Study Patients

Age (yr)	Sex	Serum Ca (mM)	Serum PO_4 (mM)	Serum parathyroid hormone*	Volume of lesion (ml)†	Type of lesion (final diagnosis)	Oxyphil cell content
48	M	2.65	3.13‡	9.5	1.84	Tertiary (hyperplasia)	H
22	M	2.46	2.82‡	13.1	0.65	Tertiary (hyperplasia)	L
65	F	2.73	2.60‡	5.3	0.89	Tertiary (hyperplasia)	H
42	M	2.76	0.77	—	0.91	Primary (adenoma)	H
37	F	2.76	0.94	1.6	1.81	Primary (adenoma)	H
21	F	3.45	0.59	12.0	1.44	Primary (adenoma)	L
62	F	3.33	0.91	6.4	5.03	Primary (hyperplasia)	L
33	F	3.69	0.99	16.0	2.27	Primary (adenoma)	H
26	F	2.75	0.78	11.9	0.47	Primary (adenoma)	L
62	F	2.67	0.67	1.1	0.63	Primary (adenoma)	L
53	M	2.66	0.81	2.9	0.12	Primary (adenoma)	H
67	F	3.15	0.74	7.2	5.24	Primary (adenoma)	H
73	F	2.86	0.84	—	0.94	Primary (hyperplasia)§	H
72	F	3.12	0.62	3.6	1.57	Primary (adenocarcinoma)	L

*Intact or carboxy-terminal parathyroid hormone measured by radioimmunoassay and expressed as ratio over upper limit of normal.
†Volume measured using the sphere formula. In patients with parathyroid hyperplasia, the sum of all volumes is given.
‡Patient with chronic renal insufficiency.
§Recurrence of hyperparathyroidism in parathyroid tissue implanted in upper arm.
Normal values for serum calcium levels are 2.10–2.54 mM, and normal values for serum phosphorus are 0.81–1.45 mM. L = low oxyphil cell content, <25% of total number of cells; H = high oxyphil cell content, >25% of total number of cells.

niques also were recommended in cases of ectopic adenoma or postoperative recurrent hyperparathyroidism (*3,5,6*). A reduction in surgical time was associated with the combination of ^{99m}Tc-MIBI and ^{123}I in at least one study (*7*). Subsequently, Taillefer et al. (*8*) and Taillefer (*9*) introduced a double-phase ^{99m}Tc-MIBI scanning technique that proved to be equally effective and less cumbersome than other established methods. This technique is based on the tendency of parathyroid lesions to retain this radioisotope. Indeed, mitochondria-rich (oxyphil) cells were thought to be responsible for the retention of ^{99m}Tc-MIBI (*10*). However, the only study that explored this hypothesis in patients with parathyroid lesions was unable to find a positive relationship (*6*). The aim of this study was to substantiate the relationship between uptake of ^{99m}Tc-MIBI and the proportion of oxyphil cells in various parathyroid lesions in patients with hyperparathyroidism.

MATERIALS AND METHODS

This study is a retrospective analysis of all ^{99m}Tc-MIBI parathyroid scintigraphy studies performed before surgery between January 1990 and December 1995 at the Centre Universitaire de Santé de l'Estrie, Sherbrooke, Québec, Canada. All patients had clinical and biological evidence of hyperparathyroidism that was subsequently confirmed by pathologic examination of tissue sections. Our analysis included a total of 18 lesions detected in 14 patients. Most of the lesions were cervical, but 2 patients had recurrent hyperparathyroidism in parathyroid tissue implanted in the arm. Patient records were carefully reviewed, and the actual location of each parathyroid lesion was obtained from surgical notes and protocols found in the medical record of each patient.

All the imaging procedures were double-phase studies as described by Taillefer et al. (*8*), and the dose of ^{99m}Tc-MIBI was 546 ± 136 MBq (range, 370–814 MBq). Studies were reviewed by two different investigators who were not given information about the patient or the previous interpretation of the study. If there was disagreement on the interpretation, a third nuclear medicine specialist was asked to interpret the scintigram. The final interpretation was the consensus of the three opinions. Each procedure was classified as positive or negative with respect to the initial (20 min) or the late (60–180 min) phase of the radioisotope uptake. When an abnormal uptake of ^{99m}Tc-MIBI was observed, its exact location was given according to the appropriate cervical quadrant.

The surgical material was reviewed by one pathologist in a

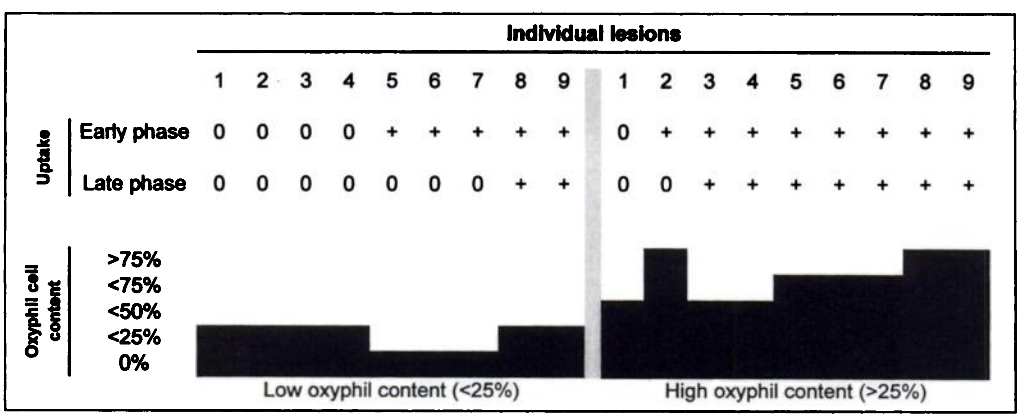

FIGURE 1. Graphic representation of each individual lesion classified according to its early and late ^{99m}Tc-MIBI radionuclide uptake and its estimated oxyphil cell content. Lesions were arbitrarily divided into low (<25%) and high (>25%) oxyphil cell content groups.

TABLE 2
Comparison of Variables According to Phase of Technetium-99m-MIBI Uptake

	Serum Ca (mM)	Serum parathyroid hormone*	Volume of lesion† (ml)	Dose (MBq)
Initial phase				
Positive	3.00 ± 0.41	8.4 ± 5.4	1.61 ± 1.61	530 ± 122
Negative	2.67 ± 0.14	7.9 ± 4.5	0.33 ± 0.27	617 ± 214
p value‡	<0.02	NS	<0.02	NS
Late phase				
Positive	2.94 ± 0.40	6.9 ± 6.2	1.34 ± 1.38	544 ± 122
Negative	2.91 ± 0.39	7.0 ±4.9	1.29 ± 1.89	555 ± 185
p value‡	NS	NS	NS	NS

*Intact or carboxy-terminal parathyroid hormone measured by radioimmunoassay and expressed as ratio over upper limit of normal.
†Volume measured using the sphere formula. In patients with parathyroid hyperplasia, the sum of all volumes is given.
‡Statistical analysis performed using Student's t-test.
Data are mean ± s.d. Normal values for serum calcium are 2.10–2.54 m*M*. NS = not significant.

single-blind fashion, and each lesion was classified as adenoma or hyperplasia according to the criteria suggested by Ghandur-Mnaymneh and Kimura (*11*). Each lesion was classified according to its oxyphil cell content (0%, 1%–25%, 26%–50%, 51%–75%, >75%) on the basis of semiquantitative assessment of the surface area covered by oxyphil cells on each section. This light microscopy evaluation of the oxyphil cell content was made for every available hematoxylin-eosin section, including frozen sections. Depending on the underlying diagnosis (adenoma versus hyperplasia), the number of sections per lesion averaged 5, ranging between 2 and 20. In case of discordance between different sections of the same lesion, the highest proportion of oxyphil cells was kept. Finally, the volume of the parathyroid lesion was estimated using the following sphere formula:

$$V = 4/3\pi(a + b + c), \qquad \text{Eq. 1}$$

in which the volume of the lesion (V) is established from the three radii (a, b and c) of each lesion.

Serum parathyroid hormone levels were expressed as time over the upper limit of normal because measurements were initially made with antibodies specific to the carboxy-terminal region and thereafter with antibodies specific to the entire intact parathyroid hormone.

Chi-square analyses were performed on categorical variables (e.g., oxyphil cell content) and two-tailed Student's t-tests were performed on continuous variables (e.g., serum calcium and the volume of the lesion). Analyses were considered statistically significant at $p < 0.05$. All data are expressed in this article as mean ± s.d.

RESULTS

Patient characteristics are shown in Table 1. A total of 14 patients with hyperparathyroidism had double-phase ^{99m}Tc-MIBI scintigraphy before surgery. Eleven patients had primary hyperparathyroidism and 3 had tertiary hyperparathyroidism secondary to chronic renal failure. All patients had increased serum calcium levels and biological evidence of hyperparathyroidism. All parathyroid adenomas (100% or 8/8) were detected and correctly lateralized using ^{99m}Tc-MIBI scintigraphy. In patients with tertiary hyperparathyroidism, ^{99m}Tc-MIBI scintigraphy was less useful, as expected, with an estimated sensitivity of 40% (for localization by side).

Taking into account the oxyphil cell content of the 18 parathyroid lesions included in this analysis, there was a clear relationship between high oxyphil cell content and late positive ^{99m}Tc-MIBI uptake (Fig. 1). Indeed, 7 of 9 parathyroid lesions (78%) with an oxyphil cell content greater than 25% had late and positive ^{99m}Tc-MIBI uptake compared with 2 of 6 lesions (33%) with an oxyphil cell content between 1% and 25% and 0 of 3 lesions (0%) with no oxyphil cells ($p < 0.04$; chi-square test). Using a different cutoff point for oxyphil cell content, late-phase uptake was positive more frequently in lesions with an oxyphil cell content greater than 50% (5/6 or 83%) than in lesions with a content less than 50% (4/12 or 33%; $p < 0.05$; chi-square test).

Although there was a slight trend for more frequently positive and early uptake in lesions with an oxyphil cell content greater than 50% (6/6 or 100%) compared with lesions with an oxyphil cell content less than 50% (7/12 or 58%), this difference was not statistically significant ($p = 0.06$). However, there were significantly more primary than tertiary hyperparathyroidism lesions with early positive ^{99m}Tc-MIBI uptake (86% versus 25%, respectively; $p < 0.02$, chi-square test). No such trend was observed with late ^{99m}Tc-MIBI uptake.

Finally, early ^{99m}Tc-MIBI uptake was associated with higher serum calcium levels ($p < 0.02$) and larger lesions ($p < 0.02$) (Table 2). None of these differences was seen in the late phase of ^{99m}Tc-MIBI scintigraphy. Of particular importance, doses of ^{99m}Tc-MIBI were not different between the two subgroups.

DISCUSSION

We have found an association between the oxyphil cell content of a parathyroid lesion and late-phase ^{99m}Tc-MIBI uptake. This finding supports the in vivo concept that ^{99m}Tc-MIBI accumulates in parathyroid lesions containing several mitochondria-rich cells and our recent observation of rapid isotopic washout in a large parathyroid adenoma that had few oxyphil cells (*10*). Although Thompson et al. (*6*) were unable to demonstrate such a relationship between oxyphil cell content and ^{99m}Tc-MIBI uptake, their study did not use double-phase ^{99m}Tc-MIBI scintigraphy, and, therefore, early and late phases of uptake were not assessed separately.

Alternatively, this study also has allowed us to demonstrate that in primary (in contrast to tertiary) hyperparathyroidism, higher serum calcium levels and larger parathyroid lesions were most likely associated with positive uptake in the first phase of ^{99m}Tc-MIBI scintigraphy. These data suggest that the larger parathyroid lesion, the higher initial uptake of ^{99m}Tc-MIBI, which concurs with data from a previous report (*12*). However, other studies have been unable to demonstrate a correlation between ^{99m}Tc-MIBI tracer uptake and volume of parathyroid lesions (*6,13*).

Although some biases could have existed because of the retrospective nature of our study, we feel that our data collection was accurate. First, we reviewed all ^{99m}Tc-MIBI scintigraphy studies performed in our institution during a well-defined period of time. Second, we reviewed the scintigraphic and pathologic data in a blind fashion with four independent expert observers (three nuclear medicine specialists and one pathologist).

CONCLUSION

Technetium-99m-MIBI uptake in the late phase of double-phase parathyroid scintigraphy is associated with a higher oxyphil cell content in parathyroid lesions (>25% or 50% of the total number of cells). No association was observed between other biological variables and the late uptake phase. On the other hand, uptake in the initial phase of the scan was associated positively with the volume of the lesion, serum calcium levels and diagnosis of primary hyperparathyroidism (parathyroid adenoma).

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Dual-Head Pinhole Bone Scintigraphy

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This article describes dual-head pinhole bone scintigraphy (DHPBS), which makes use of two opposing pinhole-collimated detectors to obtain one pair of magnified images of bone and joint at one time. The aims are to reduce scan time and solve the problem of the blind zone that is created in the background in single-head pinhole bone scintigraphy. **Methods:** DHPBS was used for normal hip and knee joints and one case each of lumbar spondylosis, vertebral compression fracture and pyoankle. The gamma camera used was a digital dual-head SPECT camera (Sopha Camera DST; Sopha Medical Vision International, Buc Cedex, France) connected to an XT data processor and a printer. Each of two opposing detectors was collimated with either a 3- or 5-mm pinhole collimator. The scan was performed 2–3 hr postinjection of 12–25 mCi ^{99m}Tc-oxidronate. Some 1500–2000 Kilocounts were accumulated at 15–40 min per pair. Anterior and posterior views were taken for the spine and hip and medial and lateral views for the knee and ankle. DHPBS images were correlated to radiographs. **Results:** DHPBS produced a pair of high-resolution bone and joint images at one time, reducing scan time by nearly half for each image. The paired DHPBS images clearly visualized both foreground and background objects, which effectively eliminated the blind zone. **Conclusion:** DHPBS can significantly improve efficiency and diagnostic acumen.

Key Words: dual pinhole scan; pinhole scan; bone imaging

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The usefulness of single-head pinhole bone scintigraphy (SHPBS) is well established (*1–7*), and it is used increasingly for diagnosing a broad spectrum of skeletal diseases. However, it has two drawbacks. One drawback is the rapid falloff of radioactivity, which creates the nonvisualization or blind zone in the periphery of the field of view, and the other is low sensitivity with prolonged scan time. SPECT is a solution for the blind zone, although its resolution needs improvement (*8,9*). Most recently, pinhole bone SPECT has been introduced to enhance image resolution and diagnostic efficacy (*10*).

The radioactive falloff is proportional to the inverse square of the distance and the function of tissue absorption (*11*). In pinhole collimation, the falloff is more acute in the peripheries of the field of view. The peripheries of the field of view include not only the outer zone of the two-dimensional field on an X-Y coordinate but also the far zone on the Z-axis or the background that lies below the detector. In SHPBS, the background structures are almost not imaged at all due both to the falloff and the out-of-focus effect. Such a blind zone can be eliminated if a pinhole-collimated detector is placed close to the background side, either the anterior or posterior, or the medial or lateral aspect of anatomical structures such as the spine, hip, knee and ankle.

We describe dual-head pinhole bone scintigraphy (DHPBS) that produced an opposing pair of two high-resolution magnified images at one time that could visualize structures in both the foreground and background and eliminated the blind zone. This method can reduce the scan time by half for each image on average. Technically, DHPBS makes use of two 3- or 5-mm pinhole collimators to collimate two opposing detectors. Any dual-head gamma camera system may be used for DHPBS provided that the gantry has space to accommodate the patient after installing cone-and-pinhole-collimator (CPC) assemblies

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