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Original

Relationship between parathyroid gland scintigraphy and its histopathology, oxyphil cell content and volume: a retrospective study

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Abstract

BACKGROUND: Mechanisms that are responsible for positive ^{99m}Tc-MIBI uptake in parathyroid glands are not clearly understood, some authors suggest there is a correlation between ^{99m}Tc MIBI accumulation and oxyphil cell content or parathyroid gland volume. The aim of our work was to assess the relationship between the pathological structure of parathyroids, their volume, oxyphil cell content and parathyroid ^{99m}Tc-MIBI retention.
MATERIAL AND METHODS: A total of 62 hyperfunctioning parathyroid glands in 46 patients were retrospectively analyzed. Preoperative ^{99m}Tc-MIBI scintigraphy was performed according to the double-phase and subtraction protocol. After surgery all glands were evaluated histologically, oxyphil cell content was assessed and volume of each excised gland was calculated.
RESULTS: Scintigraphy was positive in 41 of 62 parathyroid glands (66%). The median volume of positive glands was larger than that of negative glands (1.33 ml vs 0.7 ml, $p = 0.015$). Of the parathyroid lesions, there were 14 (22.6%) cases of nodular hyperplasia, 23 (37.1%) cases of diffuse hyperplasia, and 25 (40.3%) cases of adenomas. A high (≥ 25%) oxyphil cell content was found in 16 glands (25.8%) and a low (< 25%) oxyphil cell content in 46 (74.2%) glands. Histopathology of parathyroid glands was related to the scintigraphy result ($p = 0.002$), but not to the 99mTc-MIBI uptake pattern ($p = 0.868$). The overall result of scintigraphy was not related to the oxyphil cell content ($p = 0.797$). ^{99m}Tc-MIBI uptake pattern wasn't related to the oxyphil cell content ($p = 0.833$). In general, parathyroid lesions with low oxyphil cell content were larger than parathyroid glands with high oxyphil cell content (1.33 ml vs 0.5 ml, respectively; $p = 0.01$). The median volume of parathyroids containing a high number of oxyphil cells and having a prolonged ^{99m}Tc-MIBI retention was larger than those without prolonged ^{99m}Tc-MIBI retention (1.62 ml vs 0.3 ml, respectively; $p = 0.008$). The median volume of parathyroids with low oxyphil cells content and showing prolonged ^{99m}Tc-MIBI retention was larger than those without prolonged ^{99m}Tc-MIBI retention (1.95 ml vs 1.07 ml, respectively; $p = 0.014$).
CONCLUSIONS: Our findings suggest that a positive scintigraphy result depends on parathyroid histopathology and gland volume and does not depend on the presence of oxyphil cells. Prolonged ^{99m}Tc-retention is not related to the parathyroid gland histopathology and the presence of oxyphil cells but to the gland volume.

KEY words: parathyroid scintigraphy, ^{99m}Tc-MIBI, oxyphil cells, parathyroid adenoma, parathyroid hyperplasia, parathyroid volume

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Introduction

One of the primary methods of localizing diseased parathyroid glands is scintigraphy. There is no controversy that the sensitivity of scintigraphy (mean 83%) is superior to other imaging techniques: ultrasonography (36–76%), CT (46–55%) and MRI (50–78%) [1, 2, 3, 4]. However, there are significant differences in the sensitivity of scintigraphic studies, depending on the clinical form of hyperparathyroidism. The majority of positive results are obtained in patients with primary hyperparathyroidism 93% [5] and with a single parathyroid adenoma 82–100% [6, 7, 8]. Lower sensitivities were noted for primary hyperplasia (62%), secondary and tertiary hyperthyroidism (41%–50%) [5, 9, 10]. The reasons for such

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differences are not fully explained. The complex mechanisms responsible for the degree of radiopharmaceutical accumulation in parathyroid glands are not fully understood [11]. ^{99m}Tc-MIBI accumulates in tissues with high cellular metabolism, including enlarged parathyroid glands. Accumulation of ^{99m}Tc-MIBI may be influenced by many factors, including gland size, microscopic structure, tissue blood flow, functional status of the parathyroid, PTH and calcium levels, drugs and many others. [12]. The aim of our work was to assess the relationship between the histopathology of parathyroid glands, oxyphil cell content, gland volume and parathyroid ^{99m}Tc-MIBI retention.

Material and methods

Patients

A retrospective analysis of 62 parathyroid glands in 46 patients (34 females and 12 males with an average age of 58.4 years) was performed. The study group consisted of 35 subjects with primary hyperparathyroidism (including 6 patients with MEN1), 5 subjects with secondary hyperparathyroidism and 6 patients with tertiary hyperparathyroidism. All patients were operated, 13 patients were re-operated. The surgical procedure involved double-sided exploration of the neck with the assessment of all parathyroid glands. The size and the exact position of parathyroid glands were assessed.

Imaging techniques

In all patients prior to surgery, a double phase and subtraction scintigraphy after administration of 555–740 MBq (15-20 mCi) ^{99m}Tc-MIBI and a ^{99m}Tc thyroid scintigraphy after injection of 60 MBq ^{99m}Tc was performed. A low energy high resolution collimator was used. Images were recorded in a 128 x 128 pixel matrix. Parathyroid evaluation was started with thyroid scintigraphy, performed 10 minutes after iv administration of 60MBq ^{99m}Tc, for the purpose of subtraction of thyroid images. Subsequently, 20 min after administration of ^{99m}Tc-MIBI, an "early" image was recorded followed after 120 min by "late" image acquisition. The acquisition time was 10 minutes; approximately 1.200 kcts/picture were obtained. The parathyroid image was obtained after subtraction of ^{99m}Tc thyroid image, from an "early" image of standard two-phase ^{99m}Tc-MIBI scintigraphy. An abnormal focus of radiopharmaceutical accumulation with or without prolonged ^{99m}Tc-MIBI retention, which was positively verified surgically was assumed to be a pathologic parathyroid gland. The radiopharmaceutical retention was assessed visually. The result of ^{99m}Tc-MIBI scintigraphy was considered to be non-diagnostic in the presence of large goiter.

Histopathological examination

Surgically removed parathyroid specimens were immediately fixed in 10% neutral buffered formalin, then processed into paraffin embedded sections and stained with hematoxylin and eosin (H&E). Parathyroid lesions were classified according to histological criteria suggested by Ghandur-Mnaymneh et al. [13]. Cell types were identified as follows: chief cells, clear cells and oxyphil cells. The oxyphil cell content of each lesion was determined based on semi-quantitative assessment of the percentage of oxyphil cells on each section as proposed by Carpentier et al.: group 1: 0%, group 2: 1–25%, group 3: 26–50%, group 4: 51–75%, group 5: > 75% [14]. For statistical purposes, results were grouped into: high (> 25%) oxyphil cell content (groups 3–5) and low (≤ 25%) oxyphil cell content (groups 1–2). The parathyroid volume was calculated on the basis of histopathological measurements obtained using the formula V = (a + b + c) x 0.52

Statistical analysis

Statistical analyses were performed using STATISTICA (data analysis software system), version 12, StatSoft, Poland. The association between parameters was assessed by chi-square test (contingency tables) for categorical variables and by the Mann-Whitney test for comparison of continuous variables. For all tests, the significance threshold was set at $p \leq 0.05$.

Results

All analyzed parathyroid glands were removed surgically and verified by histopathological examination. In 5 patients (8%) ectopic glands were found intraoperatively: among them 2 parathyroid glands were located in the tracheoesophageal groove, in 2 cases the gland was found below the level of the jugular notch (Fig. 1); in one case parathyroid tissue was located inside the left lobe of the thyroid gland.

Parathyroid scintigraphy revealed 41 (66%) out of the 62 excised glands verified histopathologically. In 25 (61%) out of 41 of positive results of scintigraphy, prolonged ^{99m}Tc-MIBI retention was observed.

Histopathologically, nodular hyperplasia was found in 14 (22.6%) glands, diffuse hyperplasia in 23 (37.1%), and adenoma in 25 (40.3%) glands. 16 (25.8%) of the parathyroid lesions (including 8 cases of adenoma, 2 cases of diffuse hyperplasia and in 6 cases of nodular hyperplasia) were characterized by a high (> 25%) oxyphil cells content (Fig. 2). In this group the oxyphil cell content in 7 lesions was 26–50%, in 4 lesions 51–75% and in 5 lesions > 75%. In 46 (74.2%) parathyroid lesions (including 17 cases of adenoma, 21 cases of diffuse hyperplasia and 8 cases of nodular hyperplasia) the percentage of oxyphil cells was low (≤ 25%), of which 27 lesions had no oxyphil cells, and 19 lesions had an oxyphil content of 1–25% cells.

The histopathology of the parathyroid glands was related to the scintigraphy result ($p = 0.002$), but not to the 99mTc-MIBI uptake pattern ($p = 0.868$). 11 cases of parathyroid lesions with high oxyphil cell content had positive scintigraphy results, of which 4 cases did not demonstrate prolonged ^{99m}Tc-MIBI retention. In 5 cases, despite the presence of oxyphil cells, scintigraphy was considered to be negative. The overall result of scintigraphy was not related to the oxyphil cell content ($p = 0.797$). The ^{99m}Tc-MIBI uptake pattern was not related to the oxyphil cell content ($p = 0.833$). The median volume of scintigraphy positive glands was larger than that of scintigraphy negative glands (1.33 ml vs 0.7 ml, $p = 0.015$). The median volume of parathyroid glands with prolonged ^{99m}Tc-MIBI retention was larger than those without prolonged ^{99m}Tc-MIBI retention (1.89 ml vs 0.95 ml, respectively; ($p = 0.037$) (Tab. 1). In general, parathyroid lesions with low oxyphil cell content were larger than

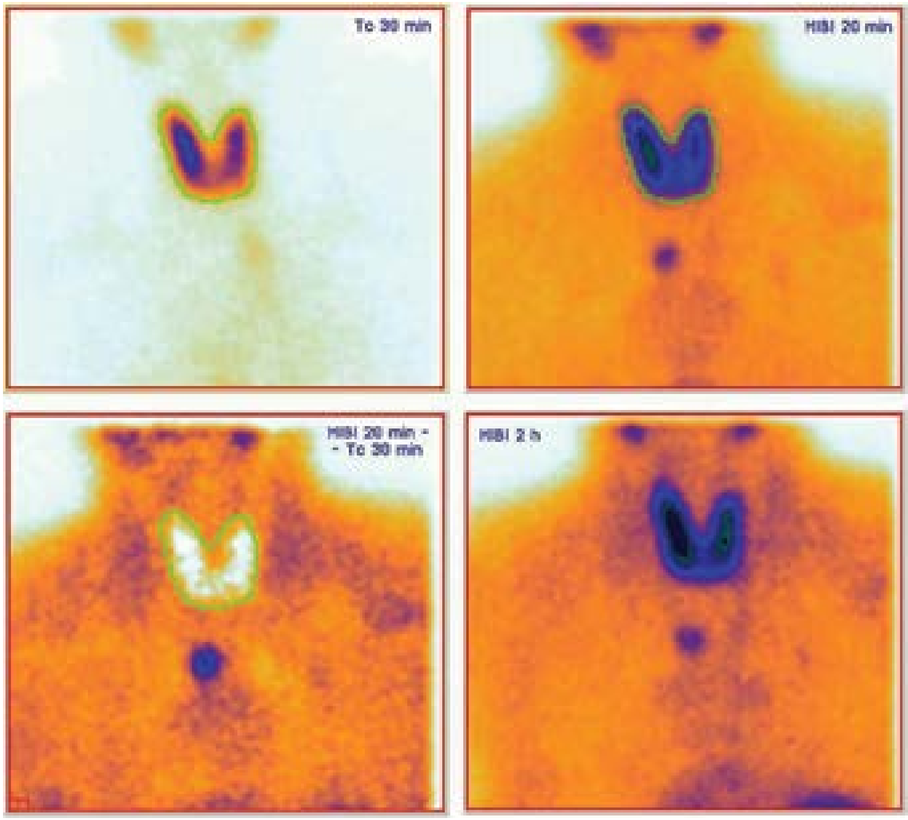

Figure 1. ^{99m}Tc-MIBI scintigraphy: ectopic parathyroid is visible below the thyroid gland; it was found below the level of the jugular notch

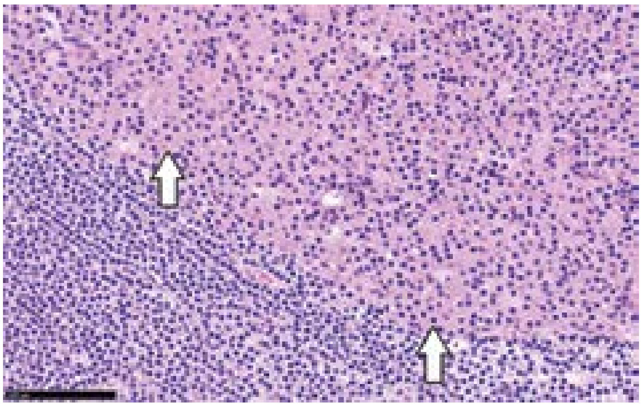

Figure 2. Parathyroid nodular hyperplasia with high (> 25%) oxyphil cell content (arrows — oxyphil cells). Scale bar: 100 μm

parathyroid glands with high oxyphil cell content (1.33 ml vs 0.5ml, respectively; $p = 0.01$). The median volume of parathyroids containing a high number of oxyphil cells and having a prolonged ^{99m}Tc-MIBI retention was larger than those without prolonged ^{99m}Tc-MIBI retention (1.62 ml vs 0.3 ml, respectively; $p = 0.008$). The median volume of parathyroids with a low oxyphil cell content and showing prolonged ^{99m}Tc-MIBI retention was larger than those without prolonged ^{99m}Tc-MIBI retention (1.95 ml vs 1.07 ml, respectively; $p = 0.014$) (Tab. 2).

Discussion

In the available literature, discussions on the nature of marker retention in the parathyroid glands include the impact of a variety of factors, including the impact of histological structure and location. A factor that unquestionably influences the sensitivity of scintigraphic studies is the parathyroid gland size. Lesions smaller than 1 cm are generally not visible in scintigraphy; however, there are cases of positive scintigraphy in smaller glands. Our current results confirmed that a positive result of scintigraphy depends mainly on the parathyroid volume. Most authors agree that there is a relationship between mass (size) and degree of marker accumulation in parathyroid glands [15, 16, 17]. Wada et al. obtained a sensitivity of 40.7% for parathyroid volume less than 0.5 cm^3. In patients with parathyroids larger than 0.5 cm^3, sensitivity was 95% [18]. Fujimoto et al. found difficulty in visualizing parathyroid glands below 300 mg [19]. Other results were obtained by Pons et al. analyzing the weight and size of glands in a group of 20 patients, there was no statistically significant difference in mean parathyroid weight in patients with positive and negative scintigraphy, but this may be due to the small sample size and patient selection [20]. Blocklet et al. on the other hand, found that the weight of the gland was related to the extent of ^{99m}Tc-MIBI accumulation in the case of adenomas, but did not find correlation in patients with parathyroid hyperplasia [21].

The second important factor influencing the visualization of the gland in scintigraphy is its location. In this study, an ectopic gland was found in 8% of excised parathyroids. This result is in

Table 1. Comparison of variables according to result of scintigraphy and ^{99m}Tc-MIBI retention pattern

	All (n=62)	Negative scintigraphy (n = 21)	Positive scintigraphy (n = 41)	P value	Positive scintigraphy (n = 41)		P value
					Prolonged retention (n = 25)	No prolonged retention (n = 16)	
Histology, n (%)							
adenoma	25 (40.3%)	5 (23.8%)	20 (48.8%)	0.002*	13 (52%)	7 (43.8%)	0.868
diffuse hyperplasia	23 (37.1%)	14 (66.7%)	9 (22%)		5 (20%)	4 (25%)	
nodular hyperplasia	14 (22.6%)	2 (9.5%)	12 (29.2%)		7 (28%)	5 (31.2%)	
Oxyphil cells, n (%)							
≤ 25% (low content)	46 (74.2%)	16 (76.2%)	30 (73.2%)	0.797	18 (72%)	12 (75%)	0.833
> 25% (high content)	16 (25.8%)	5 (23.8%)	11 (26.8%)		7 (28%)	4 (25%)	
Volume [ml]							
mean ± SD	1.75 ± 2.04	0.98 ± 0.9	2.14 ± 2.34	0.015*	2.5 ± 2.48	1.59 ± 2.07	0.037*
median (range)	1.13 (0.06-12)	0.7 (0.06-3.1)	1.33 (0.08-12)		1.89 (0.1-12)	0.95 (0.08-8.25)	

*p < 0.05

Table 2. Comparison of parathyroid volume according to the oxyphil cell content and ^{99m}Tc-MIBI retention pattern

	Low OCC (<25%)	High OCC (≥ 25%)	P value	Low OCC and PR	Low OCC and no PR	P value	High OCC and PR	High OCC and no PR	P value
n (%)	46 (74.2%)	16 (25.8%)		18 (39%)	28 (61%)		7 (43.8%)	9 (56.2)	
volume [ml]									
mean ± SD	2.02 ± 2.22	0.96 ± 1.16		2.81 ± 2.75	1.52 ± 1.67		1.7 ± 1.45	0.39 ± 0.30	
median (range)	1.33 (0.06-12)	0.5 (0.08-4.5)	0.01*	1.95 (0.1-12)	1.07 (0.06-8.25)	0.014*	1.62 (0.5-4.5)	0.3 (0.08-1.0)	0.008*

OCC, oxyphil cell content; PR, prolonged retention; *p < 0.05

agreement with the published literature. Parathyroid glands are present in the ectopic positions in about 10% of cases, occurring in various neck and mediastinal locations: from the level of the salivary glands to the level of the heart. Since the basic scintigraphic examination is performed only in the AP projection, the greater the distance from the head and the greater the thickness of the gamma radiation suppressing tissue, the smaller the number of gamma rays that are recorded. The SPECT study is helpful, but this study was of a retrospective nature and SPECT data were not available. Moreover SPECT significantly prolongs the study acquisition time and rules out subtraction. In the studied material, an ectopic position of the parathyroid gland did not noticeably affect the scintigraphy outcome: in one case, retention was not present in a parathyroid located retrosternally, while the remaining ectopic cases showed a positive scintigraphy result.

Another factor that influences the visibility and retention of the ^{99m}Tc-MIBI is parathyroid histopathology. It is well known that scintigraphy demonstrates the highest sensitivity for cases of adenomas, high sensitivity for primary hyperparathyroidism, and a lower sensitivity in secondary and tertiary hyperparathyroidism. Similarly, in the analyzed material, there was a statistically significant relationship between the scintigraphy result and the histopathologic type of parathyroid lesion. Most patients with a negative scintigraphy result had diffuse hyperplasia, whereas the most common lesion in patients with a positive scintigraphy result was parathyroid adenoma.

Due to the complex mechanism of ^{99m}Tc-MIBI accumulation in cells, it is not known which elements of the parathyroid structure are responsible for the accumulation and retention of the marker. Cinti et al. analyzed the microscopic structure of 271 parathyroid glands and described the normal structure of parathyroid glands, which consists of the chief, clear, oxyphil and transitional oxyphil cells [22]. As it is known, ^{99m}Tc-MIBI is mainly concentrated in the mitochondria, present in abundance in oxyphil cells [23]. Carpentier et al. found a correlation between ^{99m}Tc-MIBI accumulation and the oxyphil cell content [14]. Prolonged retention was found in 78% of cases with high oxyphil cell content, and in 33% of cases with a low oxyphil cell content. Glands that did not have any of the oxyphil cells showed no prolonged retention of the marker. In the analyzed material ^{99m}Tc-MIBI retention in parathyroid glands was compared in two groups: parathyroid glands containing more than 25% oxyphil cells (high oxyphil cell content) and parathyroid glands with no or less than 25% oxyphil cells (low oxyphil cell content). There was no statistically significant relationship between the presence of oxyphil cells and a positive scintigraphy result. The presence of prolonged ^{99m}Tc-MIBI retention was not associated with the presence of oxyphil cells but with the parathyroid volume. The results of Allen et al. were surprising: in the group of 114 patients with hyperparathyroidism, oxyphil cells were present in 91% secondary hyperthyroidism cases, in 69% of adenoma cases and in 55% of primary hyperplasia cases [24]. Assuming a strict dependence on ^{99m}Tc-MIBI cellular accumulation on oxyphil cell content, in the light of the data provided, the sensitivity of scintigraphy in secondary and tertiary hyperparathyroidism should be comparable or even superior to that of primary hyperthyroidism. In fact, the ^{99m}Tc-MIBI retention does not depend solely on the presence of oxyphil cells, but rather is a more complex process. This observation is confirmed by our study's results. In spite of the presence of oxyphil cells, no ^{99m}Tc-MIBI retention was observed in 4 parathyroids, and in 5 cases parathyroid glands containing oxyphil cells were not visible in scintigraphy. According to Koizumi et al there is no strict correlation between ^{99m}Tc-MIBI uptake and cellular composition [25]. They noted a positive correlation between the accumulation of ^{99m}Tc-MIBI and the presence of oxyphil cells, which is related to the high mitochondrial density compared to other cell types. However, regardless of the histological structure in the cited work, all visualized glands in 10 investigated patients were greater than 220 mg. This result confirms our observation that the ^{99m}Tc-MIBI accumulation would not depend on cellular composition but on the size and functional status of the cells.

Conclusions

Our findings suggest that a positive scintigraphy result depends on the histopathology and the volume of the parathyroid gland and does not depend on the presence of oxyphil cells. Additionally, prolonged ^{99m}Tc-retention is not related to the histopathology of the parathyroid gland and the presence of oxyphil cells, but to the gland volume.

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