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Semi-quantitative method for the assessment of focal lesions in parathyroid scintigraphy with relation to histopathology: a prospective study

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Abstract

BBACKGROUND: The aim of this paper was to analyse our own semi-quantitative method of assessing focal lesions localised in pre-operative diagnostic scintigraphy of primary hyperparathyroidism (PHPT) using ^{99m}Tc-MIBI with washout and comparing these data with the result of the histopathological examination (HP).
MATERIAL AND METHODS: A total of 40 (37 female, 3 male, average age 58.7 years) patients with a suspicion of PHPT were enrolled for prospective analysis. Dual phase planar and SPECT/CT examination with ^{99m}Tc-MIBI were performed. The tumour to background ratios in the 10th and 120th minute were calculated (TBR10 and TBR120) on the basis of the planar acquisition. PTH, ionised calcium and phosphate levels were measured.
Parathyroid surgery alone or combined with subtotal/total thyreoidectomy was conducted in 23 (57.5%) and 17 (42.5%) patients, respectively. A HP was performed in all patients.
RESULTS: Average concentration of PTH in the whole group was 243.95 pg/ml.
There was a statistically significant correlation between medians of PTH concentration and parathyroid histopathological results ($p = 0.01$).
A total of 45 lesions of increased uptake were found in 32 (80.0%) and 34 (85%) patients in the early phase and the delayed phase, respectively.
The post-operative material contained 20 (44.5%) parathyroid adenomas, 11 (24.5%) cases of hyperplasia, 2 (4.4%) cancers, 4 (8.9%) cases of normal parathyroid tissue, 2 (4.4%) lymph nodes and 6 (13.3%) cases of thyroid gland tissue.
The medians of TBR10 and TBR120 for lesions examined in the HP were respectively: 3.64 and 2.59 for adenoma; 3.08 and 2.18 for hyperplasia; 7.7 and 5.5 for parathyroid cancer, 4.89 and 3.16 for normal tissue and 5.26 and 2.95 for lymph nodes or thyroid gland tissue.
A high correlation coefficient of TBR10 to TBR120 in the parathyroid adenoma and parathyroid hyperplasia groups was observed with $\rho = 0.867$ and $\rho = 0.964$, respectively. The ρ correlation coefficient of TBR10 to TBR120 for normal parathyroid was 0.4.
There was a statistically significant association between the HP and TBR10 medians ($p = 0.047$), but not between histopathology and TBR120 medians ($p = 0.840$).

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CONCLUSIONS: The washout technique in pre-operative ^{99m}Tc-MIBI scintigraphy is effective in detecting lesions of the parathyroid (cancer, adenoma, hyperplasia, normal tissue of the parathyroid).
Parathyroid cancers in semi-quantitative analysis were characterised by a slightly higher TBR. However, it is impossible to differentiate lesions based on this data.
Histopathology results are significantly associated with TBR and PTH.

KEY words: hyperparathyroidism, adenoma, localization, nuclear scanning, sestamibi

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Background

Primary hyperparathyroidism (PHPT) causes a disturbance in the metabolism of calcium due to excessive secretion of PTH. It affects 1 in 500 women and 1 in 1000 men, usually between the fifth and seventh decade of life. Approximately 80% of cases of this disease are a result of a solitary parathyroid adenoma. The success rate in surgical treatment is high on condition that localisation diagnostics are accurate [1].

The diagnosis of primary hyperparathyroidism is based on clinical, laboratory assessment and imaging modalities such as ultrasonography and scintigraphy. In the majority of cases, a single not palpable focal lesion is seen, quite often on ultrasonography, but it should be verified in scintigraphy [2, 3]. Surgical intervention is conditional upon visualization of the lesion with the increased metabolic activity. It may happen that identifying a lesion is not a guarantee of success in surgery. After a histopathology examination the result may show no parathyroid tissue, even if all preoperative data was collected and surgical procedures were followed [4].

Parathyroid scintigraphy is a very important diagnostic tool when suspecting parathyroid adenoma. It is performed with the use of ^{99m}Tc-MIBI (2-methoxy-isobutyl-isonitril). This compound is treated by transport proteins as a xenobiotic. Depending on protein activity this tracer may be washed out, remain stable or be retained by transport proteins in the cell [5].

Contemporary methods of diagnostics imaging allow an increasing degree of quantification of the occurring pathologies. Different protocols of parathyroid scintigraphic examination are used for semi-quantitative assessment of lesions, among them dual phase examination (washout technique) [6].

Various techniques have been used in parathyroid research to assess metabolic activity of focal lesions, but few authors have analysed the relationship between scintigraphic image data and the results of the histopathological examination in a prospective study [7].

The aim of this paper was to analyse our own semi-quantitative method of assessing focal lesions localised in pre-operative diagnostic scintigraphy of PHPT using ^{99m}Tc-Sestamibi with washout and comparing these data with the result of the histopathological examination.

Material and methods

A total 40 patients aged 27 to 81 (mean 58.4 years) with a suspicion of PHPT were enrolled for the prospective study and examined using parathyroid scintigraphy. 37 of the patients (92.5%) were female and 3 were male (7.5%). Subsequently, on the basis of a positive scintigraphy which confirmed the focal lesion of increased metabolic activity, they were operated on in two surgical wards that collaborated with the Department of Nuclear Medicine. All patients expressed their written consent for participation in the study.

On the day of scintigraphy, parathormone (PTH) concentration, ionised calcium and inorganic phosphate were measured in patients on an empty stomach.

All patients had planar scintigraphy of the parathyroid and a SPECT/CT scan 10 minutes and two hours from administering 720M Bq of ^{99m}Tc-MIBI. The washout technique was used (one tracer, two phases). Mean time between phases was 127.24 min.

The examination was performed using a gamma camera GE INFINIA Hawkeye 4 with a LEHR (Low Energy High Resolution) collimator and 2.0 zoom. The field of vision included the neck and mediastinum in a posterior-anterior projection. A 256 × 256 pixel matrix was used. Planar acquisition was conducted up to the point of obtaining 700 kcounts. The energy window was 140 keV ± 5%.

A macro function was created for planar acquisition, which enabled standardising calculations by selecting an appropriate background region of interest for the identified focal lesions. An automatic calculation of the tumour to background counts ratio was obtained for early and delayed phase (TBR 10 and TBR 120). Moreover, the method allowed obtaining a repeatable distance between the background and the tumour in all described locations and differentiating size and contour of background from the size and contour of the tumour.

Four identical macro functions for superior and inferior parathyroid on the right and left side were computed. All data were automatically adjusted for radioactive decay according to the decay rate of ^{99m}Tc (Figure 1, 2).

The results of scintigraphy were prospectively consulted with a team of surgeons before surgical treatment. Parathyroidectomy was performed in 23 (57.5%) patients, whilst in 17 (42.5%) patients surgery additionally involved complete or partial thyroidectomy. The rationale for expanding the procedure into the thyroid gland were concomitant focal lesions. After the procedure, removed tissue was secured and after recording its location transferred to two pathology departments that cooperated with the Division of Nuclear Medicine. At further stages of the study,the results of the histopathological examination were retrospectively analysed and compared with biochemical data and scintigraphic findings.

In 27 patients, PTH assays were performed after the surgical procedure. No intra-operative PTH assays were performed.

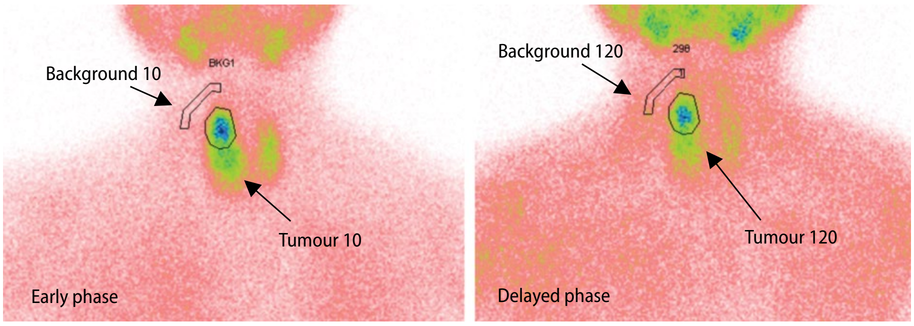

Figure 1. Example of a focal lesion and automatically determined background in the projection of the right superior pole of the thyroid lobe in early and delayed phase, TBR 10 = 6.661, TBR 120 = 3.992. Adenoma of superior right parathyroid in a histopathological examination of a 73-year-old female patientutomatic

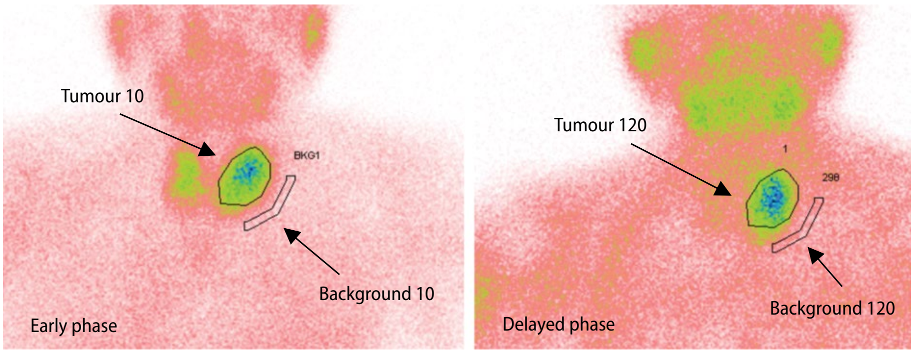

Figure 2. An example of a focal lesion and automatically determined background in the projection of the left thyroid lobe in early and delayed phase, TBR 10 = 13.112, TBR 120 = 9.027. Parathyroid cancer in a histopathological examination of a 73-year-old female patient

The normality of distribution for continuous variables was examined by the Kolomogorov-Smirnov test. Correlations between variables were examined with the Spearman test. The Wilcoxon test was used for comparing pairs of dependent observations while larger groups of independent observations were compared using the Kruskal-Wallis test. Statistical analysis was performed with IBM SPSS 23, the threshold for statistical significance was $p < 0.05$.

Results

Scintigraphy revealed 45 lesions of focally increased accumulation of the radiopharmaceutical. Two foci were found in three patients, three foci in one patient.

A foci of pathological tracer accumulation were found in 32 (80.0%) patients in the early phase and 34 (85.0%) patients in the delayed phase. A positive result in both phases of planar acquisition was recorded in 37 (92.5%) patients and negative in 3 patients (7.5%); however, the SPECT/CT result was positive in the latter group.

Average concentrations in the whole group were as follows: PTH 243.95 pg/ml (reference range15–65 pg/mL), ionised calcium 1.49 mmol/L (reference range 1.05–1.35 mmol/L), phosphate 0.9 mmol/L (reference range 0.87–1.45 mmol/L). Detailed data are presented in Table 1.

45 (97.82%) lesions that were observed on scintigraphy and removed during surgery were assessed histopathologically. This group comprised 20 (44.5%) parathyroid adenomas, 11 (24.5%) cases of parathyroid hyperplasia, 2 (4.4%) parathyroid cancers, 4 (8.9%) cases of normal parathyroid tissue, 2 (4.4%) lymph nodes and 6 (13.3%) cases of thyroid gland tissue.

Table 1. Biochemical findings in the whole group before surgery

Data	Min	Max	Average (± SD)	Median (Q25–Q75)	p*
Parathormone [pg/mL]	662.21	1699	243.95 (± 317.5)	141 (103–236.9)	0.004
Ionised calcium [mmol/L]	11.19	1.9	1.49 (± 0.17)	1.46 (1.35-1.62)	0.449
Phosphorus [mmol/L]	00.5	2.6	0.9 (± 0.36)	0.8 (0.7-0.97)	0.009

*p-value for normal distribution; SD — standard deviation

The histopathology of the patient with three focal lesions on scintigraphy revealed presence of thyroid gland tissue in each of the specimens. In patients with two focal lesions the histopathological examination revealed parathyroid hyperplasia and lymph node tissue; normal parathyroid and lymph node tissue; parathyroid adenoma and thyroid gland tissue, respectively.

The correlation between medians of preoperative PTH concentration and abnormal histopathological results was statistically significant

Table 2. Parathormon (PTH) values with corresponding histopathological diagnosis

Histopathological diagnosis	Parathyroid cancer	Parathyroid adenoma	Parathyroid hyperplasia	Normal parathyroid	Other (thyroid, lymph node)
PTH [pg/mL] Median (Q25–Q75)	339.75 (306.88–372.63)	173.10 (119.15–354.70)	125.8 (98.2–140.2)	130.8 (118.75–140.95)	103 (84.78–141.3)

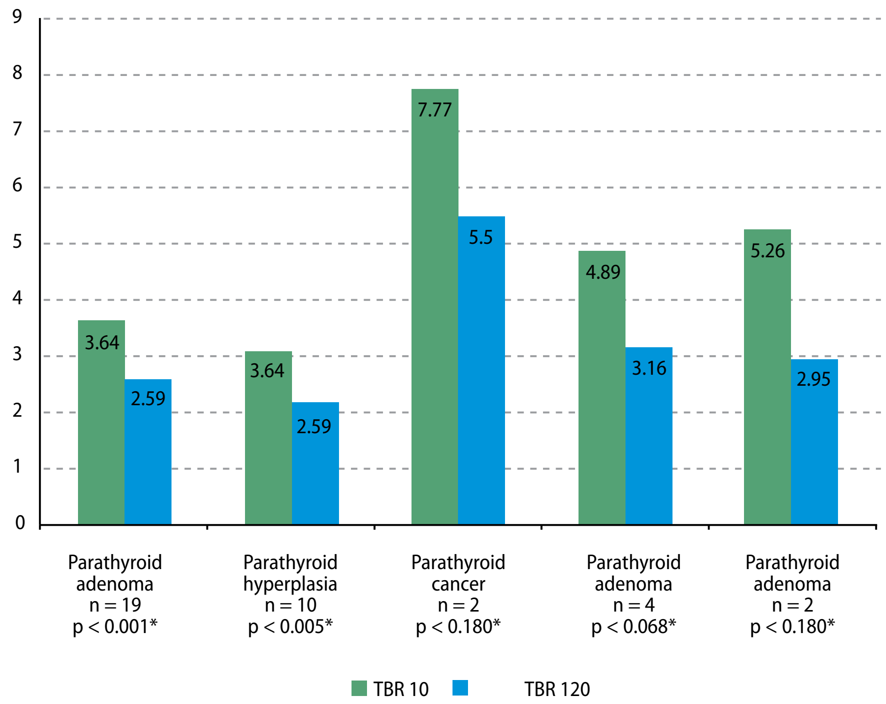

Figure 3. Median of TBR coefficients in the 10th and 120th minute of parathyroid scintigraphic examination and corresponding histopathological diagnoses; *statistical significance $\alpha = 0.05$

($p = 0.008$). After including post-operative material with normal parathyroid tissue the result was still statistically significant ($p = 0.01$).

Out of 37 patients with a positive result of the planar examination the decrease of PTH concentration was found in 25 out of 26 assays; in one case PTH concentration after surgery did not fall. The decrease of biochemical markers after surgery was recorded in 1 of 3 cases with a negative result of the planar examination. Both surgical centres did not have the possibility of intraoperative assessment of PTH concentration and hence these measurements were performed postoperatively. Postoperative PTH assays were not performed in 13 patients.

Histopathologically, 35 lesions identified on scintigraphy were verified as true positive (TP) and proved to be adenoma (19 cases), hyperplasia (10 cases), cancer (2 cases) and normal parathyroid gland tissue (4 cases). Normal parathyroid glands were considered as TP because they were visible on a scan and appeared to be visually dubious for the surgeon.

Histopathological verification revealed five lesions positive in planar examination but negative on HP (false positive, FP), five lesions not found in planar examination of which two lesions were an adenoma and hyperplasia, respectively (false negative, FN), three were normal thyroid gland tissue (true negative, TN). Lesions not found in planar examination could not serve for TBR calculation on a planar scan.

There were three other lesions without a TBR result. Two lesions were visible on the planar scan and mentioned in the descriptive section of the scintigraphy report but they were not indicated as parathyroid abnormality in the definitive report conclusions. HP of those lesions confirmed thyroid gland tissue and lymph node, respectively. The last lesion without related TBR bordered parathyroid hyperplasia. Specific calculation was abandoned due to overlap between both lesions. This lesion was HP verified as lymph node. Altogether 37 TBR ratio were calculated.

The total sensitivity of the method was estimated to be 94.6%, with a specificity of 37.5%, positive and negative predictive value of 87.5% and 60.0%, respectively and an accuracy of 84.4%.

Figure 3 presents the median of tumour/background coefficients TBR 10 and TBR 120 obtained during planar scintigraphy, corresponding histopathological diagnoses and the statistical relationships between them.

A high correlation coefficient of TBR 10 to TBR 120 in the parathyroid adenoma and parathyroid hyperplasia groups was observed, with $\rho = 0.867$ and $\rho = 0.964$, respectively. The ρ correlation coefficient of TBR 10 to TBR 120 for normal parathyroid was 0.4.

The analysis did not include cases of parathyroid cancer due to their small number (two cases).

As regards TBR medians for all five HP diagnoses, statistical significance was found for TBR 10 medians (p = 0.047), but not for TBR 120 medians (p = 0.840).

When the relationship between the subgroup of abnormal (cancers, adenomas and hyperplasias) HP diagnoses and the subgroup that included normal parathyroid tissue and other HP diagnoses was examined, the result remained statistically significant for TBR 10 medians (p = 0.021) but not for TBR 120 medians (p = 0.604). Unfortunately, there were very few patients with normal parathyroid and conclusions drawn from these data may be overestimated.

Discussion

Quantitative approach to the analysis of the results in nuclear medicine has a long-standing tradition, particularly as far as planar examination is concerned. The assessment of tumour size and intensiveness of tracer accumulation are especially important in oncology. Researchers have sought a relationship between the obtained images and their quantitative assessment in hope that there would be a possibility of using such information in clinical practice. The radiotracer uptake is usually associated with a specific metabolic feature specified in the scintigraphic examination. It may be related to, for example, osteoblastic activity in the bone, activity of renal parenchyma, or, as in parathyroid scintigraphy, metabolic activity of a parathyroid tumour.

In this study, performed with dual-phase ^{99m}Tc-MIBI scintigraphy, we present a method of calculating the tumour-to-background ratio (TBR), based on the assumption that the number of counts in the background region is subtracted from the number of counts in the tumour region, depending on the contour and size of the tumour and its location. It should also be noted that the distance between the region of the tumour and the region of the background remains constant. In addition, a correction was introduced in the delayed phase to adjust for radioactive decay of the ^{99m}Tc isotope. The authors of the present study did not find a similar approach in the literature, although there have been attempts at evaluating the metabolic activity of the tumour as measured by the tumour/background ratio. The diagnostics of PHPT usually identifies adenoma, hyperplasia and cancer cases. The correlation between TBR 10 and TBR 120 in patients with adenoma or hyperplasia was much higher than for normal parathyroid: $\rho = 0.867$, $\rho = 0.964$ and $\rho = 0.400$, respectively.

Little information has been found when searching for semi-quantitative data on the metabolic activity of histopathologically normal parathyroid, thyroid gland and lymph node tissue [7]. The present study isolated five histopathological diagnosis groups. This allowed conducting a semi-quantitative analysis based on the histopathological diagnosis, which is undoubtedly an advantage of the presented analysis.

Cheon et al. presents a retrospective attempt at differentiating between benign and malignant lesions on the basis of double phase scintigraphy with ^{99m}Tc-MIBI in patients with PHPT. The findings were evaluated using a four-point visual scale based on the comparison of tracer accumulation in the submandibular gland and thyroid gland as opposed to the parathyroid. The high uptake of radiotracer in the delayed phase and small difference in radioactivity between early and delayed uptake were among the combinations of different factors that proved useful in determining the highest possible positive predictive value for detecting a neoplastic lesions [8].

In an earlier publication, Takebayashi et al. used a retrospective semiquantitative analysis to correlate the results of the histopathological examination with double phase ^{99m}Tc-MIBI scintigraphy in primary and secondary hyperparathyroidism. They demonstrated an association between uptake of oncophilic tracer and the size of the tumour and its histological structure (chief cells and oxyphilic cells). The analysis was based on the parathyroid-to-thyroid counts ratio. There was no significant association between data describing early and delayed image in any of the 11 cases of PHPT [7].

Qiu et al. performed a retrospective analysis of planar scintigraphic images of patients with PHPT obtained using the double phase method, also used by the authors of this paper. A positive result was defined as increased accumulation of ^{99m}Tc-MIBI in the delayed phase when compared to the early phase. A negative result was defined as lack of ^{99m}Tc-MIBI uptake when compared to the background. Only visual assessment was used, without a numerical scale [5].

The analysis of literature demonstrated that the rate of positive results in the double phase planar scintigraphy had been steadily increasing. In 1999 Takebayashi et al. reported 52.4% positive planar examinations, in 2001 Scheiner et al. reported 64.5%, in 2012 Akbaba et al. obtained 67.3%, whereas papers published in 2014 by Noda et al. and Qiu et al. give 85.2% and 71.31%, respectively [2, 7, 9, 10].

In the present study, planar examinations were positive in 92.5% of patients. Close cooperation with surgeons (feedback after surgery), the author's considerable experience and scintigraphy acquisition parameters might have all played a role in achieving such high rate of positive examinations.

The authors of the present study have observed that the medians of pre-operative PTH concentrations in patients with PHPT range from 83 to 434 pg/mL [11–15]. Cheon et al. observed that there is a statistically significant difference between PTH concentrations in blood serum of patients with parathyroid adenoma and with parathyroid cancer. Patients with a confirmed parathyroid cancer usually have a higher concentration of PTH in blood serum. This is consistent with our observations and with findings in subject literature [8, 16–18].

In this study, the median of PTH concentrations was 141 pg/mL, which does not diverge from the results presented in Wei et al.'s meta-analysis [19]. Cancers of the parathyroid gland are usually characterised by higher PTH concentration. In our case the medians of PTH concentrations for parathyroid cancer were also the highest and differed significantly from other histopathological diagnoses [20].

In the meta-analysis by Wei et al. from 2015,18 publications about parathyroid scintigraphy were evaluated. The authors compared different scintigraphic modalities that used ^{99m}Tc-MIBI (planar examination, SPECT-CT, SPECT) to investigate their usefulness for minimal invasive parathyroidectomy in patients with PHPT. They concluded that planar examinations on average had a sensitivity of 63% (95% CI: 51–74%) and a positive predictive value of 90% (95% CI: 96–99%) [19]. Sensitivity of double phase examination in the cited publications ranged from 44% to 87.5% when using a 128 × 128 matrix and 59.18% to 76%. When using a 256 × 256 matrix for planar examination [14, 21–23].

By following the algorithm developed by the authors a sensitivity of 94.6% was achieved in the presented method. Positive predictive value was 87.5%, which is similar to average values in the literature. Moreover, it is important to mention that owing to the prospective process of patient enrolment and to histopathological confirmation as the gold standard it was possible to assess specificity, negative predictive value and accuracy of the method.

Currently the only possibility of calculating these parameters is planar examination since SPECT requires a much more advanced mathematical approach that would entail measuring counts in a 3D environment. The task presents an additional obstacle due to the close vicinity of the thyroid gland which affects the precision of the examination (pinpointing voxel position) [24]. In these circumstances proposing a relatively simple, repeatable method of focal lesion metabolic activity assessment, as is the case with TBR, allows a much more precise differentiation of these foci.

Conclusions

The washout technique in pre-operative ^{99m}Tc-MIBI scintigraphy is effective in detecting lesions of the parathyroid (cancer, adenoma, hyperplasia, normal tissue of the parathyroid).

Parathyroid cancers in semi-quantitative analysis were characterised by a slightly higher TBR. However, it is impossible to differentiate lesions based on this data.

Histopathology results are significantly associated with TBR and PTH.

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