MORPHOLOGY, PHYSIOLOGY AND PATHOPHYSIOLOGY

MORPHOLOGICAL CRITERIA FOR SPORADIC MULTIPLE PARATHYROID GLAND DISEASE

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ABSTRACT

Background. *There are no specific morphological signs for sporadic multiglandular disease (MGD) in primary hyperparathyroidism (PHPT).*

The aim of the study. *To study the structure of the morphological substrate of primary, secondary and tertiary hyperparathyroidism and to assess the effectiveness of morphological criteria in the diagnosis of sporadic multiglandular disease in primary hyperparathyroidism.*

Methods. *The study included 69 patients; 18 patients with PHPT and sporadic multiglandular disease ($n_{preparation}$ = 31) formed the main group, 51 patients ($n_{preparations}$ = 104) – the comparison group. The comparison group was divided into 3 subgroups: 1) patients with PHPT and solitary parathyroid gland (PTG) lesions – 26 patients ($n_{preparations}$ = 26); 2) patients with secondary hyperparathyroidism (SHPT) – 15 patients ($n_{preparations}$ = 48); 3) patients with tertiary hyperparathyroidism (TGPT) – 10 patients ($n_{preparations}$ = 30).*

Results. *The morphological structure of the comparison groups is homogeneous: group 1 is represented by parathyroid adenoma (26 (100 %)), groups 2 and 3 – by hyperplasia (48 (100 %) and 30 (100 %), respectively). Most of the PTG specimens of the main group are represented by hyperplasia (25 (80 %)), and in 1/5 cases – by adenomas (6 (19.4 %)). Sporadic multiglandular disease in PHPT was characterized by a predominant frequency of detecting the absence of a capsule and a rim of unchanged tissue, as well as the presence of adipocytes ($p_{\chi 2} < 0.01$). Components of the PTG morphological structure make it possible to identify changes specific to the sporadic multiglandular disease in PHPT, with a diagnostic efficiency of 76.5–90.3 %.*

Conclusion. *Sporadic multiglandular disease in any clinical variant of hyperparathyroidism is characterized by a high prevalence of hyperplasia – 80 % in PHPT and 100 % in SHPT and TGPT. The following morphological criteria for sporadic multiglandular disease in PHPT have been established: the presence of adipocytes in the PTG parenchyma (diagnostic efficiency (DE) – 90 %)); absence of a capsule (DE = 78 %) and a rim of unchanged gland tissue (DE = 76 %).*

Key words: *pathological assessment, sporadic multiglandular disease, hyperparathyroidism*

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МОРФОЛОГИЧЕСКИЕ КРИТЕРИИ МНОЖЕСТВЕННОГО ПОРАЖЕНИЯ ОКОЛОЩИТОВИДНЫХ ЖЕЛЕЗ ПРИ ПЕРВИЧНОМ ГИПЕРПАРАТИРЕОЗЕ

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РЕЗЮМЕ

Обоснование. *Специфических морфологических признаков множественного поражения околощитовидных желез (ОЩЖ) при первичном гиперпаратиреозе (ПГПТ) нет.*

Цель исследования. *Изучить структуру морфологического субстрата первичного, вторичного и третичного гиперпаратиреоза и оценить эффективность морфологических критериев в диагностике множественного поражения околощитовидных желез при первичном гиперпаратиреозе.*

Методы. *В исследование включены 69 пациентов, из которых основную группу составили 18 пациентов с ПГПТ и множественным поражением ОЩЖ ($n_{препаратов} = 31$), группу сравнения – 51 пациент ($n_{препаратов} = 104$). Группа сравнения была разделена на 3 подгруппы: 1) с ПГПТ и солитарным поражением ОЩЖ – 26 пациентов ($n_{препаратов} = 26$); 2) с вторичным гиперпаратиреозом (ВГПТ) – 15 пациентов ($n_{препаратов} = 48$); 3) с третичным гиперпаратиреозом (ТГПТ) – 10 пациентов ($n_{препаратов} = 30$).*

Результаты. *Морфологическая структура групп сравнения однородна: 1-я группа представлена аденомой ОЩЖ (26 (100 %)), 2-я и 3-я группы – гиперплазией (48 (100 %) и 30 (100 %) соответственно). Большинство препаратов ОЩЖ основной группы представлены гиперплазией (25 (80 %)), а в 1/5 случаев – аденомами (6 (19,4 %)). Для множественного поражения ОЩЖ при ПГПТ было характерно преобладание частоты выявления отсутствия капсулы и ободка неизменённой ткани, а также наличие адипоцитов ($p_{\chi^2} < 0,01$). Структурные компоненты морфологического строения ОЩЖ позволяют выявить изменения, характерные для множественного поражения ОЩЖ при ПГПТ, с диагностической эффективностью 76,5–90,3 %.*

Заключение. *Множественное поражение ОЩЖ при любом клиническом варианте гиперпаратиреоза характеризуется высокой частотой преобладания гиперплазии – 80 % при ПГПТ и 100 % при ВГПТ и ТГПТ. В качестве морфологических критериев множественного поражения ОЩЖ при ПГПТ установлены: наличие адипоцитов в паренхиме железы (диагностическая эффективность (ДЭ) – 90 %); отсутствие капсулы (ДЭ = 78 %) и ободка неизменённой ткани железы (ДЭ = 76 %).*

Ключевые слова: *патоморфологическая оценка, множественное поражение околощитовидных желез, гиперпаратиреоз*

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INTRODUCTION

Primary hyperparathyroidism (PHPT) is a common endocrinological disease caused by adenoma of a single parathyroid gland (PTG) in 80–85 % of cases (solitary lesion of the PTG), lesions of more than one PTG in 20–25 % (hyperplasia of all glands or double adenomas (double adenomas – multiple PTG lesions), and less than 1 % is caused by cancer of the PTG [1, 2].

The actual incidence of multiple PTG lesions in PHPT is difficult to estimate, as detection depends on the surgical approach of a particular clinic (selective single PTG excision under intraoperative monitoring of intact parathyroid hormone or routine bilateral neck revision), the alertness and experience of the operating surgeon, and the experience of the pathologist to differentiate the pathomorphological basis of hyperparathyroidism from normal PTG tissue [3].

There are no specific morphological signs of multiple lesions of the PTG at the PHPT, histological examination is limited to the determination of the substrate – adenoma or hyperplasia.

The complexity of classifying PTG adenoma from hyperplasia lies in their minor morphological differences. Distinguishing features of hyperplasia as opposed to adenoma comprise the absence of capsule and rim of unchanged PTG tissue, heterogeneous cellular composition with the presence of adipocytes and diffuse proliferative process with the growth of all cellular elements [4–7].

The use of Sudan III staining for fat cell detection has been previously recommended to help distinguish the pathomorphological basis of hyperparathyroidism. Both normal PTG morphological structure and hyperplasia are characterised by the presence of fat droplets in the main cells, while they are few or absent in hyperfunctioning adenoma cells [8].

Adenoma is considered to be a monoclonal true tumour, whereas hyperplasia is characterised by polyclonal growth that develops under the influence of external factors [9, 10]. This is the reason why during hyperplasia there is synchronous enlargement of all PTGs [4]. Revealing hyperplasia after selective parathyroidectomy is associated with a high risk of persistence or recurrence of hyperparathyroidism [11].

THE AIM OF THE STUDY

To study the structure of morphological substrate of primary, secondary and tertiary hyperparathyroidism and to assess the effectiveness of morphological criteria in the diagnosis of sporadic multiglandular disease in primary hyperparathyroidism.

MATERIALS AND METHODS

A single-centre prospective study of a continuous sample consisted of 100 cases of surgically treated patients with PHPT, secondary hyperparathyroidism (SHPT), undergoing renal replacement therapy (RRT), haemodialysis (HD), and tertiary hyperparathyroidism (THPT), undergoing RRT after kidney transplantation (KT), in the thoracic surgical department of the Irkutsk Regional Clinical Hospital in 2020–2021. The inclusion criterion was the indication for surgical treatment for diagnosed PHPT, SHPT and THPT. Exclusion criteria were age below 40 years in those diagnosed with PHPT and multiple PTG lesions, as well as suspected hereditary PHPT.

According to the criteria, 69 patients were included in the study, of which 18 patients with PHPT and multiple PTG lesions formed the main group ($n_{preparation}$ = 31) and 51 patients ($n_{preparations}$ = 104) – the comparison group. The comparison group was divided into 3 subgroups: 1) patients with PHPT and solitary PTG lesion – 26 patients ($n_{preparations}$ = 26); 2) patients with SHPT – 15 patients ($n_{preparations}$ = 48); 3) patients with THPT – 10 patients ($n_{preparations}$ = 30). Control group – 5 preparations of unchanged PTG tissue sampled as a result of intraoperative biopsy of intact PTG from patients with solitary lesions of the PTG in PHPT, recognized by a pathologist as normal PTG tissue.

Sporadic multiglandular disease in PHPT was deemed to be the removal of more than one pathologically altered parathyroid gland or detection of persistence after removal of at least one pathologically altered parathyroid gland.

The object of the study was PTG preparations obtained as a result of surgery. Standard morphological study of hematoxylin-eosin stained preparations was performed by light microscopy in 10 fields of view. This phase evaluated the efficacy of morphological criteria in the diagnosis of sporadic multiglandular disease in PHPT.

The first step was to categorize all PTG tissue preparations into three groups depending on the pathomorphological changes: adenoma, hyperplasia, and normal PTG structure. Adenoma criteria: presence of a rim of unchanged gland tissue, whose cells are in the inactive phase (light main), and a capsule that surrounds a single tumour nodule with a homogeneous cellular composition of the parenchyma, represented by a single cell type; absence of adipocytes in the parenchyma. Hyperplasia criteria: absence of unchanged tissue rim and capsule; heterogeneity of cellular composition of parenchyma and presence of adipocytes in it; formation of cell nodules with clear connective tissue borders. In the second step, three types of hyperplasia were distinguished to clarify the nature of hyperplasia: diffuse, diffuse-nodular and nodular [12]. Diffuse type of hyperplasia is characterised by a uniform increase in the number of cells of the whole gland parenchyma with preservation of the normal lobular structure. In the diffuse nodular type of hyperplasia the lobular structure of the gland parenchyma is disturbed with the formation of multiple encapsulated nodules of cells. Nodular ("pseudo-adenoma", according to the authors) type of hyperplasia is represented by a single large nodule of uniformly proliferating parenchymatous cells resembling an adenoma in PHPT and predominating over the rest of the diffusely hyperplastic PTG tissue.

Being based on the literature data concerning the PTG pathological morphology, the following structural components were used to assess the pattern of PTG morphological changes in different types of hyperparathyroidism (Table 1).

Statistical analysis of data was performed using Statistica 10.0 for Windows software package (StatSoft Inc., USA; license No. AXAR402G263414FA-V). Categorical are presented as number of observations and frequency as a percentage with 95 % confidence interval. Statistical significance was determined using Pearson's chi-square test (χ^2), Fisher's exact test. Differences were considered statistically significant at $p < 0.05$.

All patients signed informed consent to participate in the study. The study was approved by the Biomedical Ethics Committee of Irkutsk Scientific Centre of Surgery and Traumatology (protocol No 9 dated of 09.11.2012).

RESULTS

Table 2 shows the structure of morphological changes of PTG in the main group and comparison groups.

Table 2 reveals that the morphological picture of the comparison groups was homogeneous: group 1 was represented by PTG adenoma, groups 2 and 3 by hyperplasia. The majority of PTG preparations in the main group were represented by hyperplasia, and in 1/5 cases by adenomas. Among 61 PTG preparations of PHPT patients, 25 of 31 preparations (80.6 (62.5–92.5) %) of the main group

TABLE 1

STRUCTURAL COMPONENTS OF THE PARATHYROID GLAND MORPHOLOGY

PTG segments	Components	Assessment
Stroma	Capsule	Presence/absence
	Unchanged tissue rim	Presence/absence
Parenchyma	Uniformity of cellular composition	Yes/No
	Predominant cell type	• main active (dark) • main inactive (light)
	Presence of adipocytes	Yes/No
	Presence of cell nodules with clear connective tissue boundaries	Yes/No

TABLE 2

STRUCTURE OF MORPHOLOGICAL CHANGES IN PARATHYROID GLANDS IN THE MAIN GROUP AND THE COMPARISON GROUPS

Study groups	Morphological characteristics	
	Morphological basis	Number of preparations, *n* (%)
Main group: $n_{patients}$ = 18 (100) $n_{preparations}$ = 31 (100)	Hyperplasia	25 (80.6)
	Adenoma	6 (19.4)
Comparison Group 1: $n_{patients}$ = 26 (100) $n_{preparations}$ = 31 (100)	Adenoma	26 (100)
	Biopsy: normal structure	5 (100)
Comparison Group 2: $n_{patients}$ = 15 (100) $n_{preparations}$ = 48 (100)	Hyperplasia	48 (100)
Comparison Group 3: $n_{patients}$ = 10 (100) $n_{preparations}$ = 30 (100)	Hyperplasia	30 (100)

and 0 of 30 preparations (0 (0–11.5) %) of the comparison group 1 had hyperplasia ($p < 0.01$; χ^2 test).

Figure 1 shows a microphotograph of the normal PTG morphological structure.

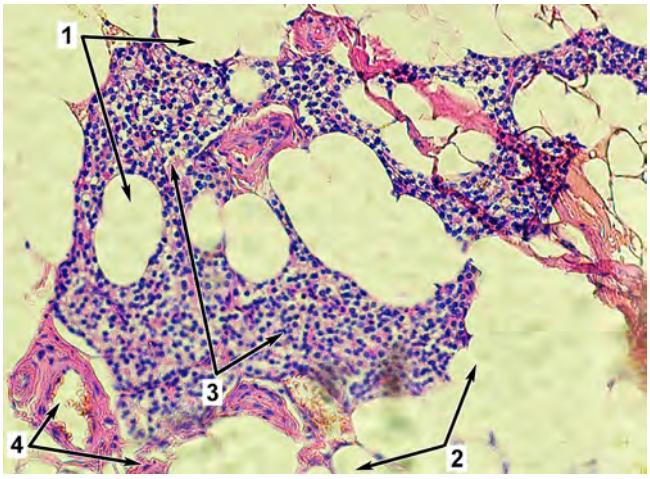

FIG. 1.
Microphotograph. Normal morphological structure of parathyroid gland tissue. Hematoxylin-eosin staining, magnification × 20.
1 *– adipocytes;* **2** *– connective tissue capsule;* **3** *– main light cells;* **4** *– vessel*

The normal morphological structure was characterised by the location of PTG tissue surrounded by adipocytes of adipose tissue. The gland was separated from the latter by a barely visible thin connective tissue capsule, which gave off tracts deep into the stroma, forming a lobular structure. The main cellular stroma consists of inactive (light-coloured) principal cells with light transparent cytoplasm and clear nuclei, grouped in the form of lobules, between which adipocytes and vessels are located.

The frequency of detection of stroma and parenchyma components of preparations in adenoma and hyperplasia was analysed using the selected structural parameters (see Table 1) (Table 3).

According to Table 3, the frequency of detection showing absence of capsule and rim of unchanged tissue was statistically significantly predominant in hyperplasia compared to adenoma ($p < 0.01$). There was no statistical significance of the frequency of the predominant cell type when comparing adenomas and hyperplasias ($p > 0.05$). The frequency of adipocyte detection was statistically significantly predominant in hyperplasia compared to adenomas ($p < 0.01$). Therefore, the structural components of PTG stroma and parenchyma as classical pathomorphological criteria allowed to distinguish adenoma from hyperplasia quite accurately.

TABLE 3

THE FREQUENCY OF DETECTION OF THE COMPONENTS OF STROMA AND PARENCHYMA OF PARATHYROID GLANDS PREPARATIONS DEPENDING ON THE PATHOMORPHOLOGICAL BASIS, *n* (%), [95% CI]

PTG components			Pathomorphologic basis		$p_{\chi 2}$
			denoma, *n* = 32 (100 %)	AHyperplasia, *n* = 103 (100 %)	
Stroma	Capsule	Yes	26 (81.2) [63.5–92.7]	14 (13.6) [7.6–21.7]	**< 0.01**
		No	6 (18.8) [7.2–36.4]	89 (86.4) [78.2–92.3]	
	Unchanged tissue rim	Yes	23 (71.8) [53.2–86.2]	–	**< 0.01**
		No	9 (28.2) [13.7–46.7]	103 (100) [96.4–100.0]	
Parenchyma	Predominant cell type	Main active (dark)	27 (84.3) [67.2–94.7]	78 (75.7) [66.2–83.6]	> 0.05
		Main inactive (light)	5 (15.6) [5.2–32.7]	25 (24.3) [16.3–33.7]	
	Presence of adipocytes	Yes	–	103 (100) [96.4–100.0]	**< 0.01**
		No	32 (100) [89.1–100.0]	–	
	Presence of cell nodules with clear borders	Yes	–	62 (60.1) [50.0–69.7]	**< 0.01**
		No	32 (100) [89.1–100.0]	41 (39.8) [30.2–49.9]	

TABLE 4

THE FREQUENCY OF DETECTION OF THE COMPONENTS OF STROMA AND PARENCHYMA OF PARATHYROID GLANDS PREPARATIONS OF THE MAIN AND COMPARISON GROUPS, *n* (%), [95% CI]

PTG components			Main group, 31 (100 %)	Comparison group 1, 26 (100 %)	Comparison group 2, 48 (100 %)	Comparison group 3, 30 (100 %)
Stroma	Capsule	Yes	6 (19.3) [7.4–37.4]	**20 (76.9) [56.3–91.0]**	6 (12.5) [4.7–25.2]	14 (46.6) [28.3–65.6]
		No	**25 (80.4) [62.5–92.5]**	6 (23.1) [8.9–43.6]	**42 (87.5) [74.7–95.2]**	**16 (53.4) [34.3–71.66]**
	A rim of unaltered tissue	Yes	5 (16.1) [5.4–33.7]	**18 (69.2) [48.2–85.6]**	–	–
		No	**26 (83.9) [66.2–94.5]**	8 (30.8) [14.3–51.1]	**48 (100) [92.6–100.0]**	**30 (100) [88.4–100.0]**
Parenchyma	Predominant cell type	Main active (dark)	30 (96.7) [83,3–99,9]	21 (80.7) [60.6–93.4]	36 (75) [60.4–86.3]	18 (60) [40.6–77.3]
		Main inactive (light)	1 (3.3) [0.1–16.7]	5 (19.3) [6.5–39.3]	12 (25) [13.6–39.6]	12 (40) [22.6–59.4]
	Presence of adipocytes	Yes	25 (80.4) [62.5–92.5]	–	48 (100) [92.6–100.0]	30 (100) [88.4–100.0]
		No	6 (19.3) [7.4–37.4]	**26 (100) [86.7–100.0]**	–	–
	Presence of cell nodules with clear boundaries	Yes	1 (3.3) [0.1–16.7]	–	**35 (72.9) [58.1–84.7]**	**26 (86.6) [69.2–96.2]**
		No	30 (96.7) [83.3–99.9]	26 (100) **[86.7–100.0]**	13 (27.1) [15.2–41.8]	4 (13.4) [3.7–30.7]

Note. Statistically significant results by χ^2 criterion (Fisher's exact test), $p < 0.05$, are shown in bold.

Table 4 shows the frequency of detection of PTG stroma and parenchyma components in the main group and in the comparison groups.

According to Table 4, the frequency of detection of capsule absence in surgical preparations significantly prevailed in the main group and in comparison groups 2 and 3 in comparison with comparison group 1 ($p < 0.01$). Moreover, the frequency of capsule detection was statistically significantly higher in comparison group 3 compared to the main group and comparison group 2 ($p < 0.05$). The capsule absence allows to distinguish the PTG pathology of multiple lesions in PHPT and SHPT patients undergoing RRT HD compared to solitary lesions in PHPT and multiple lesions in THPT patients undergoing RRT KT.

Figure 2 shows a microphotograph of the PTG adenoma morphological structure.

The frequency of detection of rim absence was statistically significantly predominant in the main group and comparison groups 2 and 3 compared to comparison group 1 ($p < 0.01$). Additionally, the frequency of capsule absence detection was statistically significantly prevalent in comparison groups 2 and 3 compared to the main group ($p < 0.01$). Similar to the capsule, detection of the absence of a rim of unchanged PTG tissue allows us to distinguish gland pathology in multiple lesions, in PHPT and SHPT patients undergoing RRT HD, compared to solitary lesions in PHPT and multiple lesions in THPT in patients undergoing RRT KT.

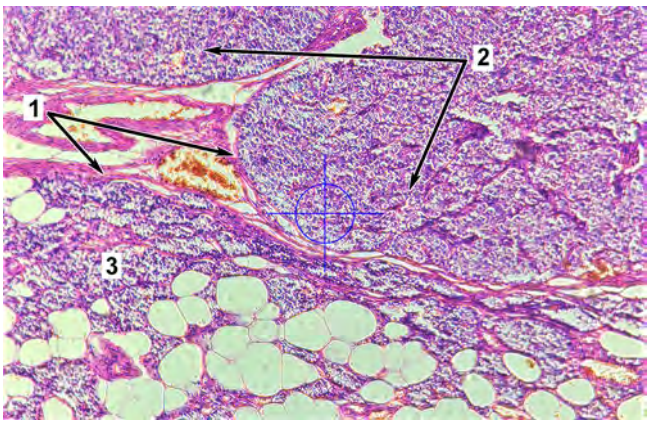

FIG. 2.

Microphotograph. Morphological structure of parathyroid adenoma at the border of adenoma and the "rim" of normal parathyroid tissue. Hematoxylin-eosin staining, magnification × 10. **1** *– connective tissue capsule;* **2** *– parenchyma of the adenoma, represented by a homogeneous cellular composition with a predominance of active (dark) main cells and the absence of adipocytes;* **3** *– stroma of the "island" of unchanged parathyroid tissue*

The frequency of prevalence of major active PTG cells was statistically significantly prevalent in the main group compared to all comparison groups (1, 2 and 3) ($p < 0.05$). In contrast, no statistically significant frequency of prevalence of active or inactive main PTGs was found by comparing comparison groups 1, 2 and 3 with each other ($p > 0.05$). In our sample, the predominance of major active cells appeared to distinguish the glandular pathology of multiple PTG lesions in patients with PHPT from other types of hyperparathyroidism.

The frequency of adipocyte detection in the gland parenchyma was statistically significantly predominant in the main group compared to comparison group 1 ($p < 0.01$). Additionally, the frequency of adipocyte detection in PTG parenchyma was statistically significantly predominant in comparison groups 2 and 3 compared to comparison group 1 ($p < 0.01$). Detection of adipocytes in the gland parenchyma allows to distinguish the pathology of multiple PTG lesions in any type of hyperparathyroidism from solitary ones in PHPT.

The frequency of cell nodule detection in the gland parenchyma was statistically significantly predominant in both comparison group 2 and comparison group 3 as compared to both the main group and comparison group 1 ($p < 0.01$). However, there was no statistically significant predominance of cell nodules in comparison group 2 compared to comparison group 3 ($p > 0.05$). Cell nodule formation appeared to be characteristic of multiple lesions in SHPT and THPT and distinguishes it from the pathology in PHPT.

TABLE 5

THE FREQUENCY OF DETECTION OF DIFFERENT TYPES OF HYPERPLASIA IN THE MAIN GROUP AND IN THE COMPARISON GROUPS 2 AND 3, *n* (%), [95% CI]

Study groups	Type of hyperplasia	Quantity
Main group 25 (100) [86.2–100.0]	Diffuse	**21 (84.0) [63.9–95.4]**
	Diffuse nodular	4 (16.0) [4.5–36.0]
Comparison group 2 48 (100) [92.6–100.0]	Diffuse	13 (27.0) [15.2–41.8]
	Diffuse nodular	**29 (60.4) [45.2–74.2]**
	Nodular	6 (12.6) [4.7–25.2]
Comparison group 3 30 (100) [88.4–100.0]	Diffuse	4 (13.4) [3.7–30.7]
	Diffuse nodular	12 (40.0) [22.6–59.4]
	Nodular	**14 (46.6) [28.3–65.6]**

Note. Statistically significant results by χ^2 criterion (Fisher's exact test), $p < 0.05$, are shown in bold.

Table 5 shows the frequency of detection of different types of hyperplasia in the main group and in comparison groups 2 and 3.

According to Table 5, the incidence of diffuse hyperplasia was statistically significantly predominant in the main group compared to comparison groups 2 and 3($p < 0.01$). There was no statistically significant predominance of the diffuse hyperplasia incidence in comparison group 2 as compared to comparison group 3 ($p > 0.05$).

Figure 3 shows a microphotograph of the morphological structure of PTG hyperplasia (diffuse hyperplasia).

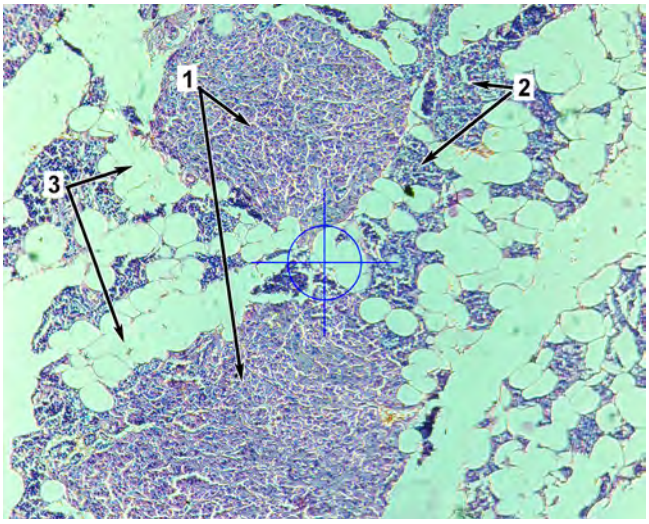

FIG. 3.

Microphotograph. Diffuse hyperplasia of the parathyroid gland. Hematoxylin-eosin staining, magnification × 10. **1** *– main dark cells;* **2** *– main light cells;* **3** *– adipocytes*

The frequency of diffuse nodular hyperplasia cases was statistically significantly higher in comparison group 2 as compared to the main group ($p < 0.01$). There was no statistically significant predominance of the diffuse nodular hyperplasia incidence in comparison group 2 as compared to comparison group 3 ($p > 0.05$).

Figure 4 shows a microphotograph of the morphological structure of PTG hyperplasia with nodule formation (diffuse nodular hyperplasia).

The frequency of detection of nodular hyperplasia was statistically significantly higher in comparison group 3 as compared to the main group and comparison group 2 ($p < 0.01$).

Figure 5 shows a micrograph of the morphological structure of PTG hyperplasia with nodule formation (nodular hyperplasia).

By comparing the histological examination data and surgical outcomes, the results of diagnostics of morphological signs of multiple PTG lesions in PHPT using the selected structural criteria were obtained (Table 6).

By comparing the data of the histological study and the results of the surgery (Table 6) the operative

characteristics of the structural components of the morphological structure of the gland in diagnosing the pathology of multiple PTG lesions in PHPT were calculated (Table 7).

Table 7 shows that the structural components of the PTG morphological structure allow us to diagnose changes characteristic of multiple PTG lesions in PHPT with a diagnostic efficiency of 57.9–90.3 %.

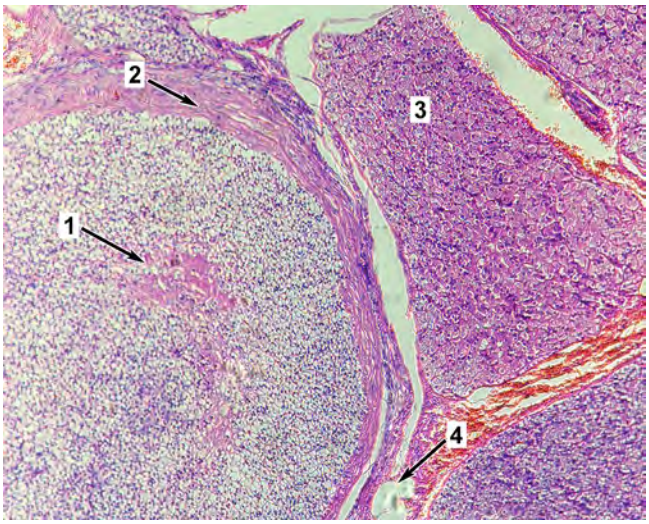

FIG. 4.
Microphotograph. Diffuse-nodular hyperplasia of the parathyroid gland. Hematoxylin-eosin staining, magnification × 10. **1** *– node of the main light cells;* **2** *– connective tissue border;* **3** *– the main parenchyma of dark smooth cells;* **4** *– adipocytes*

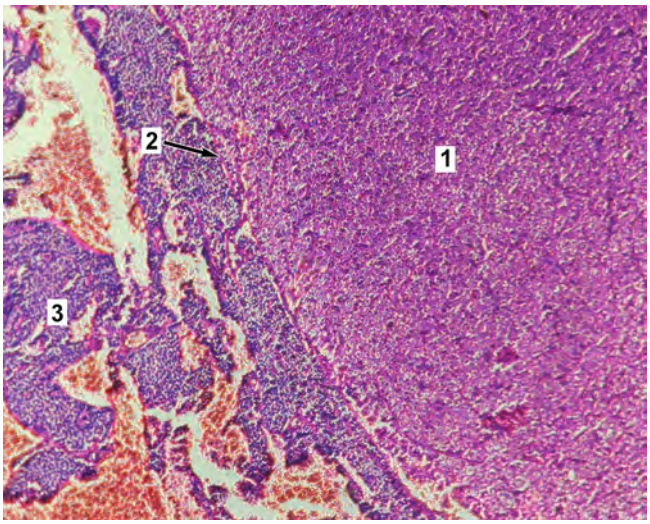

FIG. 5.
Microphotograph. Nodular hyperplasia of the parathyroid gland. Hematoxylin-eosin staining, magnification × 10. **1** *– area of nodular hyperplasia from the main light cells;* **2** *– connective tissue border;* **3** *– main parenchyma of dark smooth cells*

TABLE 6

RESULTS OF STUDY OF MORPHOLOGICAL SIGNS OF MULTIGLAND PARATHYROID DISEASE IN PRIMARY HYPERPARATHYROIDISM USING SELECTED STRUCTURAL CRITERIA

Results	True positive	False positive	False negative	True negative
Capsule absence	25	6	6	20
Rim of unchanged tissue absence	26	8	5	18
Predominance of main active cells	30	21	1	5
Presence of adipocytes	25	0	6	26

TABLE 7

OPERATIONAL CHARACTERISTICS OF THE COMPONENTS OF THE MORPHOLOGICAL STRUCTURE OF THE PARATHYROID GLAND IN THE DIAGNOSIS OF MULTIGLANDULAR PARATHYROID DISEASE, % (95% CI)

Characteristics	DSE	DSP	DE	PPV	NPV
Capsule absence	80.6 (62.5–92.5)	76.9 (56.3–91.0)	78.7 (66.5–81.6)	80.6 (62.5–92.5)	76.9 (56.3–91.0)
Rim of unchanged tissue absence	83.8 (66.2–94.5)	69.2 (48.2–85.6)	76.5 (69.4–80.9)	76.4 (58.8–89.2)	78.2 (56.3–92.5)
Predominance of main active cells	96.7 (83.3–99.9)	19.2 (6.5–35.3)	57.9 (42.5–64.2)	58.8 (44.1–72.4)	83.3 (35.8–99.5)
Presence of adipocytes	80.6 (62.5–92.5)	100.0 (86.7–100.0)	90.3 (87.5–99.9)	100.0 (86.7–100.0)	81.2 (63.5–92.7)

Note. DSE – diagnostic sensitivity; DSP – diagnostic specificity; DE – diagnostic efficiency; PPV – positive predictive value; NPV – negative predictive value.

DISCUSSION

Thus, in our sample, the majority of PHPT patients with multiple PTG lesions had hyperplasia as the morphological substrate and 1/5 had adenomas.

Previously, we retrospectively analysed the case histories of 62 patients suffering from PHPT with both solid and multiple PTG lesions (44 and 18 patients, respectively), assessing surgical outcomes and PTG morphology [13]. Multiple PTG lesions were found to be the main cause of disease persistence (16 %) [13]. The structure of the morphological substrate was heterogeneous: with a solitary PTG lesion – 52.2 % adenomas and 40.9 % hyperplasias, with multiple – 22.1 % adenomas, 72.2 % hyperplasias [13, 14]. Among 18 patients in the main group, persistence was observed in 8 out of 14 (57 %) with the morphological substrate of PTG hyperplasia and in 2 out of 4 (50 %) with adenoma ($p_{\chi 2} > 0.05$) [13, 14]. The heterogeneity of the morphological structure and its lack of influence over the outcome of surgical treatment in PHPT with solitary and multiple PTG lesions dictated this study.

The question was posed: are there pathomorphological features of multiple PTG lesions and can routine microscopy distinguish between them?

In our sample of PHPT patients with multiple PTG lesions, a heterogeneous morphological structure with a prevalence of hyperplasia of 80 (62–92) % and a hyperplasia to adenoma ratio of 4:1 was revealed. In other clinical variants of hyperparathyroidism the morphological structure was homogeneous: in PHPT with solitary lesion of PTG – adenoma (100 (86–100) %), in SHPT and THPT – hyperplasia (100 (92–100) % and 100 (88–100) %, respectively).

Morphological structural criteria known in the literature to distinguish hyperplasia and PTG adenoma [4–7] allowed us to establish that multiple glandular lesions in PHPT compared to solitary ones were characterised by a predominant frequency of absence of capsule and rim of unchanged tissue, presence of adipocytes in the parenchyma and main active (dark) cells. The diagnostic efficiency of these criteria in detecting sporadic multiglandular disease in PHPT was 57–90 %. The following criteria were found to be most effective: presence of adipocytes (90 %), absence of capsule (78 %) and rim of unchanged glandular tissue (76 %).

CONCLUSION

Sporadic multiglandular disease in any clinical variant of hyperparathyroidism is characterised by a high frequency of predominance of the morphological substrate in the form of hyperplasia – 80 % (62–92 %) in primary hyperparathyroidism and 100 % (92–100 % and 88–100 %, respectively) in secondary and tertiary hyperparathyroidism. The following morphological criteria of multiple PTG lesions in primary hyperparathyroidism were established: presence of adipocytes in the gland parenchyma (DE = 90 %), absence of capsule (DE = 78 %) and rim of unchanged gland tissue (DE = 76 %).

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Conflict of interest

The authors declare no apparent and potential conflicts of interest related to the publication of the present article.

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