

Original article

The Histopathological Findings of Operated Tumors of the Parathyroid Glands and Patient Data: A Single Centre Experience

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Abstract

Introduction: Parathyroid proliferative disorders include adenoma, hyperplasia and carcinoma. Adenoma and hyperplasia are more commonly found in women, while carcinoma, which is very rare, is equally common in both sexes. The aim of this study was to analyze parathyroid tumors location and histopathology and to compare differences between the sexes. Tumors were surgically removed at the University Hospital Centre Osijek between 2016 and 2019.

Patients and Methods: Patients of both sexes who underwent parathyroidectomy for parathyroid tumor at the University Hospital Centre Osijek between 2016 and 2019 were included in the study. Parathyroid tumor samples were histologically analyzed, and their size and histopathology were noted. Existing documentation on patients with parathyroid tumor was used. Analyses were done on archived histologic material stained with hematoxylin and eosin.

Results: Overall, 19 samples of parathyroid tumor were included in this study. Tumors of the parathyroid glands were most commonly localized on the lower left parathyroid (8 cases, 42%), and least commonly on the upper right parathyroid (2 cases, 11%). The most common disorder was adenoma (11 cases, 58%), followed by hyperplasia, while no cases of cancer were diagnosed. Women underwent tumor operations more frequently than men (17 versus 2 cases). There was no correlation between histopathology of parathyroid tumor and sex (Fisher's exact test, $p = 1$) or between tumor location and sex (Fisher's exact test, $p = 1$).

Conclusion: The most common locations of tumors of the parathyroid glands were the inferior glands; the most common location was the left inferior parathyroid gland and the most common disorder was adenoma. Women were operated on more frequently than men.

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Introduction

Parathyroid glands are 4 nodular structures located behind every pole of the thyroid gland. They are separated from thyroid gland tissue by a fibrous capsule (1). Their size is mostly around 5 x 3 x 1 mm, and they weigh up to 50 mg (2). On rare occasions, the number of parathyroid glands can vary from 1 to 12 parathyroid glands (3). Due to embryonic development, inferior parathyroid glands are most frequently located ectopically. Common ectopic locations are within the thymus, the mediastinum and the thyroid gland, but they are also rarely found within the vagus nerve, the pharynx and the esophagus (4). The main function of parathyroid glands is calcium homeostasis. Parathyroid hormone increases serum calcium by increasing renal tubular reabsorption of calcium, bone resorption and by indirectly increasing vitamin D levels, which leads to increased intestinal calcium absorption. Parathyroid hormone excretion is regulated by ionized calcium levels, extracellular phosphate levels and vitamin D (5).

Chief cells, adipocytes and oxyphil cells make up the parathyroid gland parenchyma. Chief cells produce and secrete parathyroid hormone (6). Oxyphil cell function is not fully understood. They are considered to secrete parathyroid hormone in secondary parathyroid hyperplasia (7). Hematoxylin and eosin stain is used to observe parathyroid gland structure, while immunochemistry is used to identify molecular markers (8).

Parathyroid gland dysfunction can have different causes. Increased secretion of parathyroid hormone from at least one parathyroid gland leads to primary hyperparathyroidism. It is mostly caused by a single adenoma, but can be caused by multiple adenoma, hypertrophy of all 4 parathyroid glands, and rarely by carcinoma (9). Secondary hyperparathyroidism is a condition of parathyroid hormone oversecretion in response to abnormally low calcium in the blood due to other pathological processes, such as kidney failure, gastrointestinal malabsorption, or

vitamin D deficiency. Parathyroid hyperplasia caused by prolonged hypocalcemia, which is seen mostly in chronic kidney failure, is defined as tertiary hyperparathyroidism (10, 11). Hypoparathyroidism is a rare disorder that occurs after damage to or removal of parathyroid glands, for example during thyroidectomy (12). Pseudohypoparathyroidism occurs when the body, and especially the kidneys, develops resistance to the parathyroid hormone (13).

Parathyroid proliferative disorders include adenoma, hyperplasia and carcinoma. These usually manifest as primary hyperparathyroidism (2). Parathyroid adenoma usually occurs between the ages of 50 and 70. Microadenomas usually do not have a capsule. Larger adenomas have a thin fibrous capsule and can have cystic degeneration in the tumor. Their average weight is one gram. Macroscopically, the adenoma is smooth, soft and reddish-brown in color, in contrast to the yellow-brown of a normal parathyroid gland (2). There may be normal parenchyma of a parathyroid gland around the edge. Histologically, there is a population of enlarged cells, glandular architecture with secretions, atrophy or compression of parathyroid gland tissue (14, 15). Parathyroid hyperplasia usually occurs as a result of calcium deficiency, mostly due to chronic kidney disease. All 4 parathyroid glands are enlarged. In certain cases where glands are unevenly enlarged, they may be mistaken for adenoma. Resection will not resolve the problem in such case (2). Histologically, there is parenchymal fat accumulation and nodular distribution of chief and oxyphil cells (14, 15).

Parathyroid carcinoma is mostly seen in middle-aged patients. Risk factors include hereditary syndromes such as MEN 1 and MEN 2 (multiple endocrine neoplasia type 1 and type 2), familial isolated hyperparathyroidism, neck radiation and chronic kidney disease. Parathyroid hormone and calcium are more increased than in adenoma. In addition to the usual hypercalcemia symptoms such as nausea, vomiting, ulcers, pancreatitis, depression and

languor, there are also special symptoms of the disease, such as osteoporosis, subperiosteal bone resorption and pathological fractures. Using ultrasound, carcinoma is identified as a mass, usually in inferior poles of the thyroid, with a size greater than 3 cm (16, 17). Histologically, carcinomas look very similar to adenomas, which is why it is difficult to diagnose the disease with only histological analysis. Histological features of parathyroid carcinoma are thick fibrous capsule, adherence to surrounding tissue, vascular and capsular invasion, necrosis and increased mitotic activity (18). Immunohistochemical methods help differentiate carcinoma from adenoma. The only unequivocal criterion for carcinoma are metastases (16).

Ultrasound and technetium Tc 99m sestamibi scintigraphy scan are most commonly used for localization of parathyroid tumor. SPECT (single-photon emission computed tomography) allows a 3-dimensional image. Scintigraphy and SPECT combined have up to 98% sensitivity for detection of parathyroid adenoma (2). Detection of parathyroid glands by imaging methods is of no importance for primary hyperparathyroidism confirmation. Other localization techniques include MRI (magnetic resonance imaging), CT (computerized tomography) and venous parathyroid hormone sampling (19).

Parathyroidectomy is the only definitive treatment of primary hyperparathyroidism. Observation and pharmacological therapy are less effective and less cost-effective than surgery, even in asymptomatic patients (19 - 21). According to the Guidelines of the American Association of Endocrine Surgeons, parathyroidectomy is indicated in all patients with symptomatic primary hyperparathyroidism; when the serum calcium level is more than 1 mg/dL (0,25 mmol/L) above normal, regardless of whether objective symptoms are present or absent; when there is objective evidence of renal involvement, including silent nephrolithiasis, nephrocalcinosis, hypercalciuria, or impaired renal function; in patients with primary hyperparathyroidism and osteoporosis;

when primary hyperparathyroidism is diagnosed in patients aged 50 or younger; in patients with parathyroid cancer; in patients who are unable or unwilling to comply with observation protocols; in patients with neurocognitive and/or neuropsychiatric symptoms that are attributable to primary hyperparathyroidism. Many different surgical methods to streamline parathyroidectomy and reduce the risk of complications have been developed; they are collectively termed minimally invasive parathyroidectomy (MIP). The most commonly used auxiliary method that significantly increases surgery success is intraoperative parathyroid hormone measurement (IPM). If, during minimally invasive parathyroidectomy, intraoperative parathyroid hormone measurement indicates residual hypersecreting tissue, conversion to bilateral exploration (BE) is necessary. Minimally invasive parathyroidectomy has the most success with solitary adenoma (19). Preventive measures and routine monitoring of serum calcium, creatinine and bone density are recommended in asymptomatic patients that do not meet the criteria for surgery (22).

The aim of this cross-sectional study with historical records was to investigate parathyroid tumors that were surgically removed at the University Hospital Centre Osijek between January 2016 and March 2019. The aim was also to review tumor location and histopathology and to compare differences between sexes.

Patients and Methods

Patients of both sexes who underwent parathyroidectomy for parathyroid tumor at the University Hospital Centre Osijek between January 2016 and March 2019 were included in the study. Data were obtained for 19 patients. In the Clinical Department of Pathology and Forensic Medicine, parathyroid tumor samples were histologically analyzed; their size and level of histopathological tumor differentiation were noted. Existing documentation on patients with parathyroid tumor of the Clinical Department of Pathology and Forensic Medicine and the Department of Maxillofacial Surgery was used.

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Analysis was done on archived histologic material stained with hematoxylin and eosin. Approval of the institutional ethical committee for this study was obtained from Faculty of Medicine Osijek.

Statistical analysis

Statistical analysis was done using MedCalc Statistical Software version 18.9. Normal distribution of variables was tested using the Kolmogorov-Smirnov test. Comparisons between nominal variables due to the small number of samples were made using Fisher's

Table 1. Parathyroid tumor location in both sexes

	Right inferior parathyroid gland	Left inferior parathyroid gland	Right superior parathyroid gland	Left superior parathyroid gland	
Female	5 (26%)	8 (42%)	2 (11%)	2 (11%)	p = 1 *
Male	1 (5%)	0	0	1 (5%)	
Total	6 (31%)	8 (42%)	2 (11%)	3 (16%)	

* Fisher's exact test

Parathyroid tumor location was observed. Table 1 shows that parathyroid tumors were predominantly located on inferior parathyroid glands (14 cases, 74%) in comparison with superior parathyroid glands (5 cases, 26%). The most common location of the tumor was the left inferior parathyroid (8 cases, 42%). There were 6 cases (31%) of right inferior, 3 cases (16%) of left

exact test. Alfa = 0.05 was set as the level of statistical significance.

Results

Data were obtained for 19 patients diagnosed with parathyroid tumor. In regard to histopathology, the studied sample included only adenoma and hyperplasia.

Women underwent parathyroid tumor operations more often than men. Of total of 19 samples, there were 2 (11%) male samples, and 17 (89%) female samples.

superior and 2 cases (11%) of right superior parathyroid gland involvement.

Of the 2 obtained samples of parathyroid tumor in men, one was located on the right inferior and one on the left superior parathyroid gland. In regard to histopathology, one sample was of hyperplasia, and the other was of parathyroid adenoma.

Table 2. Distribution of parathyroid gland tumor in both sexes by histopathological diagnosis

	Adenoma	Hyperplasia	Undetermined disorders of parathyroid tissue	
Female	10 (53%)	3 (16%)	4 (21%)	p = 1 *
Male	1 (5%)	1 (5%)	0	
Total	11 (58%)	4 (21%)	4 (21%)	

* Fisher's exact test

In our research, we examined the distribution of parathyroid tumor by histopathological diagnosis. The most common parathyroid tumor was adenoma. In regard to histopathology, 11 samples (58%) were determined as adenoma, 4 samples (21%) as hyperplasia and 4 samples (21%) as undetermined disorders of parathyroid

tissue (Table 2). In four cases termed as "undetermined disorders of parathyroid tissue", due to damaged samples, it was not clear whether the tissue histopathology matched adenoma or hyperplasia.

Although women exhibited more adenoma compared to hyperplasia than men, there is no correlation between histopathology of parathyroid tumor and sex (Fisher's exact test, $p = 1$). Likewise, even though there were more inferior parathyroid tumors in regard to superior in women when compared to men, there is also no correlation between tumor location and sex (Fisher's exact test, $p = 1$). Statistical analysis is not valid because the male data sample was small.

Discussion

Parathyroid tumors include adenoma, hyperplasia and carcinoma. They most often present as primary hyperparathyroidism. Parathyroidectomy is the only definitive treatment. From 1925, when Felix Mandl performed the first successful parathyroidectomy in Vienna, many surgical techniques have been developed that have become less and less invasive (23). Minimally invasive parathyroidectomy is a relatively new technique that is used increasingly commonly in parathyroid adenoma treatment. Its success depends on imaging of the tumor. Ultrasound, technetium Tc 99m sestamibi scintigraphy scan, and intraoperative parathyroid hormone measurement can aid the success of the operation. The most common parathyroid tumor locations are inferior parathyroid glands, with frequency of occurrence from 70 to 86.7% (24 - 26). In our study, tumor was likewise most commonly located on inferior parathyroid glands. According to our study, the most common parathyroid tumor location was the left inferior parathyroid gland, which was also the case in El-Hady's and Usta's studies (24, 25). Minimally invasive parathyroidectomy decreases the risk of postoperative hypocalcemia, the length of procedure, the length of hospital stay and overall treatment cost (27). Primary hyperparathyroidism is more often found in women (10). In the conducted study, women were also more affected by parathyroid tumors.

The most common parathyroid gland tumor is adenoma (80-85%), which is followed by

hyperplasia (15%), and carcinoma, which is extremely rare (2). In our study, a similar distribution was seen, but there were no cases of carcinoma. Depending on the literature, carcinoma represents from under 1% to 5% of cases of parathyroid tumor (28-30). Diagnosing carcinoma is not simple. There are no special clinical manifestations and histology is ambiguous. Clinical manifestations can be more extreme than with other causes of primary hyperparathyroidism (16). Atypical parathyroid adenoma or parathyroid neoplasm of uncertain malignant potential is a special histological entity that does not meet all the criteria for carcinoma. Its course is more benign, it is less aggressive than parathyroid carcinoma, and it has a greater 5-year survival rate (31, 32). In the same period, three patients had parathyroidectomy for multi-gland hyperplasia due to secondary hyperparathyroidism (results not shown). All three of them had chronic kidney failure and were on a hemodialysis program.

In the conducted study, primary hyperparathyroidism was the most common clinical diagnosis, followed by secondary hyperparathyroidism. Primary hyperparathyroidism occurs in over 2% of the population older than 55 (33). It is usually caused by solitary adenoma, but can also be caused by multiple adenomas, hypertrophy and carcinoma. Risk factors include neck radiation, lithium intake or hereditary factors such as MEN 1 and MEN 2 syndromes (8). It manifests as hypercalcemia with increased or normal level of parathyroid hormone. Patients usually have no symptoms, but in symptomatic patients, it manifests as fatigue, weakness, depression, gastroesophageal reflux and bone pain. In the advanced stage, it can manifest as skeletal disease, nephrolithiasis and cardiovascular disease (10).

In secondary hyperparathyroidism, there is normal parathyroid hormone secretion as a response to chronically low calcium levels. Low calcium levels are caused by malabsorption, vitamin D deficiency, kidney failure and taking certain medication, such as thiazide diuretics. Serum calcium level is low or normal, and parathyroid hormone level is normal. In tertiary

hyperparathyroidism, after an initial stimulus, parathyroid glands become autonomous, and parathyroid hormone levels and calcium levels resemble primary hyperparathyroidism. Clinical symptoms of secondary hyperparathyroidism depend on the underlying cause (8, 34).

Our study did not show a correlation between sex and tumor location, or between sex and type of tumor. To our knowledge, no study has so far analyzed the correlation between sex and tumor location. Only 2 male samples were analyzed, which was not sufficient for making an adequate statistical analysis. Corresponding to the correlation between sex and tumor location, it is known that adenoma is found 3 times more often in women than in men (18, 35). In the study by Cvasciuc (36), patients with parathyroid adenoma were predominantly female, and there was a similar female-to-male ratio in regard to adenoma and hyperplasia. Carcinoma affects both sexes equally commonly (16).

It is important to note that these are data collected from patients who were subjected to parathyroidectomy at our University Hospital Centre. Not all patients with primary or secondary hyperparathyroidism are operated on, so this study can in no way present the prevalence of hyperparathyroidism in the area gravitating to the University Hospital Centre in

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Osijek. The sizes of tumors in samples from this area were 0.7-2.2 cm (results not shown).

The main limitation of the study was its small sample, which is probably the reason why there were no cases of carcinoma. If the sample were larger, carcinoma frequency could have been assessed. The aim of this study was to review the possible connection between sex and parathyroid tumor histopathology or location, but only 2 male samples were obtained, which was not sufficient for making a statistical analysis.

To conclude, the study shows that women are operated on for tumors of the parathyroid gland more often, which most commonly manifest as adenomas. Parathyroid tumors were more frequently located in inferior parathyroid glands, and the most common location was the left inferior parathyroid gland.

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