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Parathyroid Carcinoma in Patients that Have Undergone Surgery for Primary Hyperparathyroidism

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Abstract. *Background/Aim: Parathyroid carcinoma is a rare clinical entity, which represents one of the main reasons, why surgery should be performed in specialized centres. Preoperatively, it is very difficult to distinguish between benign and malignant hyperparathyroidism. Patients and Methods: During the years 1996-2016, we performed 2,220 operations in 2,075 patients with a diagnosis of primary hyperparathyroidism. Results: Among these 2,220 operations, there were 16 operations for parathyroid carcinoma. These 16 operations, including reoperations, were performed in four patients. Two patients had no reoperation, but another 2 patients required 14 reoperations in total. Parathyroid carcinoma was described in 0.2% of all patients with a diagnosis of primary hyperparathyroidism. The number of operations was 0.73% of all operations of primary hyperparathyroidism in years 1996-2016. Conclusion: Prognosis of parathyroid carcinoma is quite favourable, patients evidence a long-term survival rate after the primary operation. However, every reoperation increases the number of possible complications, including recurrent laryngeal nerve injury.*

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Carcinoma of the parathyroid gland is very rare, but a very serious cause of primary hyperparathyroidism. Primary hyperparathyroidism is a generalized disorder of calcium, phosphate and bone metabolism, developing on the basis of long-term overproduction of parathormone with one or more pathologically changed parathyroid glands, on the basis of parathyroid adenoma, hyperplasia or, rarely, carcinoma. Before the first operation, it is very hard to detect parathyroid carcinoma. Before the operation, patients are examined using sonography, MIBI-scintigraphy with Computed Tomography or by Magnetic Resonance Imaging. In the case of parathyroid carcinoma observed in the first operation, the "*en bloc*" resection with ipsilateral lobe of thyroid gland has to be done, because radical resection offers the only possible cure.

Materials and Methods

In this study, all patients enrolled have undergone surgery for primary hyperparathyroidism on the Third Department of Surgery, First Faculty of Medicine and University Hospital Motol, Prague between 1996 and 2016. The observation was targeted for patients with parathyroid carcinoma.

In these cancer patients, the levels of calcium and parathormone in peripheral blood were measured. The patients were examined with neck sonography and MIBI-scintigraphy. When the result was not clear, Magnetic Resonance Imaging (MRI) was also performed. All signs of disease were carefully examined and noted.

Results

Between 1996-2016 we have performed 2,220 operations (including reoperations) in 2,075 patients with diagnosis of primary hyperparathyroidism on the Third Department of Surgery, First Faculty of Medicine and University Hospital Motol, Prague. In this group, four patients with parathyroid carcinoma (mean age 60.25 years; range=59-61 years; 2 men and 2 women) were operated during the years 1996-2016 (Table I).

Among these 2,220 operations, there were 16 operations for parathyroid carcinoma. These 16 operations, including reoperations, were performed in these four patients. All pathological tissues were examined by an experienced pathologist.

The whole series comprised of biochemically, surgically and histologically proven PHPT during a period of 43 years (1970-2013). From the whole group the patients who underwent parathyroidectomy 93% had an adenoma (chief-cells) and 7% of patients had hyperplasia.

From these patients, 85.26% were females and 14.74% were males. Mean age of patients was 60.52±8.25 years. 26.98% had renal syndrome, 46.03% had bone syndrome, 7.03% had gastroduodenal ulcer, 2.04% had pancreatitis, 24.94% had cholecystolithiasis, 9.98% suffered from psychiatric disorders, 53.97% had arterial hypertension and only 11.11% had no signs of another disease in their medical history. The mean value of total calcium before the operation was 2.76±1.11 mmol/l, mean value of intact parathormone before the operation was 19.53±11.48 pmol/l.

So, the parathyroid carcinoma was described in 0,2% of all patients with the diagnosis of primary hyperparathyroidism. The number of the operations was 0,73% of all operations of primary hyperparathyroidism in years 1996-2016. In two patients, reoperations were necessary. The mean age by the first operation was 60.25 years. All patients survived and currently are around 8 years after the primary diagnosis.

Case 1: A 58-year old man with bone and renal syndrome was indicated for operation for the diagnosis of primary hyperparathyroidism. Pathologically enlarged parathyroid gland was localized by sonography and CT examination behind the right lobe of the thyroid gland. Before the operation, the parathormone level was 90.09 pg/ml and calcium level was 3.23 mmol/l. By the first operation, the right lobe of thyroid gland together with two pathologically enlarged parathyroid glands were removed. After the operation, the calcium levels decreased to 2.05 mmol/l. After the operation, the patient was without complications. Paraesthesia was intermittent with a good reaction on the oral calcium supplements. The patient was dismissed to home care four days after the operation. The final histological examination was: parathyroid carcinoma and adenoma. In 48 months after the first operation, the calcium level increased to 3.1 mmol/l and parathormone level was 23.83 pmol/l. Repeated scintigraphy showed pathological parathyroid gland in mediastinum. The patient was indicated for reoperation. It included partial sternotomy and thymectomy. After the operation, the level of blood calcium was 2.92 mmol/l and level of intact parathormone was 21.54 pmol/l. Thus, the decrease in the calcium level was not significant. We have performed a CT scan, where the pathologically changed parathyroid gland was found at the site of the original parathyroid carcinoma. The neck revision was made and during the operation, the carcinoma was found. Post-operative course was without complications, the level of blood calcium decreased to normal values. In 58 months after the primary operation, there was again a marked increase in calcium and parathormone levels. The MIBI-scintigraphy with Computed Tomography was performed, where three focuses have been found (Figures 1 and 2). The first focus has been found in the lateral pole of the scar in a subcutaneous tissue – it was palpable. The second one was found close to the inferior left pole of the thyroid gland. The last one was found at the site of the original parathyroid carcinoma, posterior to the right common carotid artery. Patient was indicated for reoperation and preoperatively the subcutaneous metastasis was verified and removed as well as the right lobe of the thyroid gland (Figure 3). Partial resection of the carcinoma relapse posterior to the right common carotid artery was performed, due to its oesophageal infiltration. Post-operatively, the parathormone level decreased to normal values as well as blood calcium. The post-operative course was complicated by bilateral paresis of the recurrent laryngeal nerve. Patient was repeatedly examined by an ENT specialist, with the result of sufficient glottis diameters. Due to oesophageal tumor infiltration, the patient was treated by neck radiotherapy. Due to a subsequent respiratory insufficiency, the tracheostomy and unilateral glottis ablation was necessary to perform. 76 months after the primary operation, the closure of tracheostomy was performed. Currently, *i.e.* 10 years after the primary operation, the patient has no complications.

Table I. *Overview of the first operations in patients.*

Gender	Age	Year of operation	Serum Ca (mmol/L)	Plasma PTH (pmol/L)	First operation
Man	58	2005	3.47	90.09	CA, ADE, LOB
Woman	61	2004	3.47	90.48	CA
Woman	61	2008	3,18	25,18	CA, LOB
Man	61	2014	3,01	108,7	CA, LOB

CA: Carcinoma removal; ADE: adenoma removal; LOB: ipsilateral thyroid lobectomy.

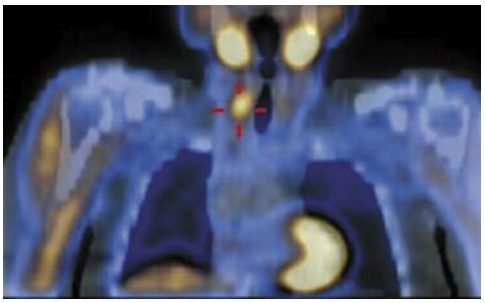

Figure 1. *Lower right hyperplastic parathyroid gland, evaluated as a parathyroid adenoma, indicated to surgical removal.*

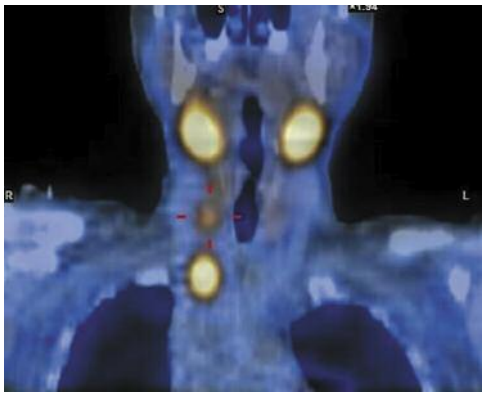

Figure 2. *Reoperation in patient from Figure 1. Relapse is present on the neck, in upper mediastinum, with the necessity of partial sternotomy.*

Case 2: A 61-year old woman with cholecystolithiasis, gastroduodenal ulcers and primary hyperparathyroidism was admitted to our hospital. The pathological enlargement of the lower left parathyroid gland was verified sonographically and scintigraphically. Preoperative level of parathormone was 90.48 pg/ml, whereas preoperative level of blood calcium was 3.47 mmol/l. The pathologically changed parathyroid gland was removed. The post-operative course was without any complications. The patient was released home on the fourth post-operative day. Histological examination revealed a parathyroid adenocarcinoma. After two months, the level of blood calcium was 2.33 mmol/l and the level of intact parathormone was 27,64 mmol/l. On MIBI scintigraphy, the focus was found on the left site. However, CT or PET scan did not verify relapse. Even though, the patient was indicated for reoperation – an "*en bloc*" resection. The neck revision together with left thyroid lobectomy was performed. Histological examination revealed a relapse of the parathyroid carcinoma in the inferior thyroid artery pedicle. Currently, *i.e.* 84 months after the primary operation, the patient is without any problem and the calcium levels are normal.

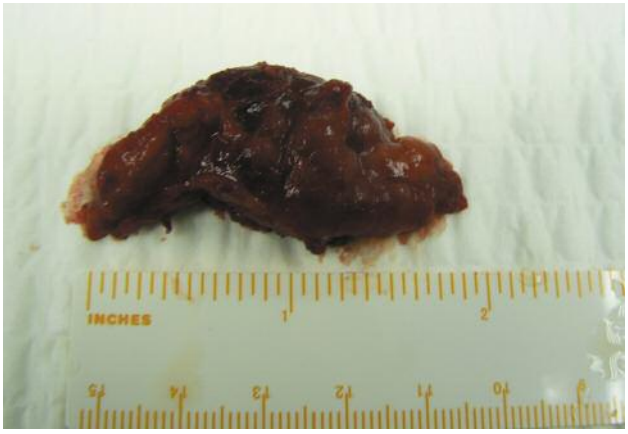

Figure 3. *Removed tumour from the approach that included the partial sternotomy. Patient from Figures 1 and 2.*

Case 3: A 61-year old woman with cholecystolithiasis and otherwise asymptomatic hypercalcaemia has been diagnosed with primary hyperparathyroidism. The pathologically changed parathyroid gland was found inside the right lobe of the thyroid gland, according to sonoghraphy, MIBI and CT scan. Preoperative level of parathormone was 25.18 pmol/l and blood calcium level was 3.18 mmol/l. Due to intrathyroid localization of the pathologically changed parathyroid tissue, right thyroid lobectomy, was performed. During the operation, any other pathologically changed parathyroid glands were not found. After the operation, no complications occurred. Histologically, we identified a parathyroid carcinoma due to thyroid lobectomy. After the operation, the calcium level normalized to 2.22 mmol/l. After 22 months, the level of blood calcium increased to 3.15 mmol/l. We performed SPECT/CT where the relapse at the site of thyroid lobe removal was described. The block resection and debulking of the particular site was performed. Post-operatively, the level of blood calcium decreased to 2.74 mmol/l. After 28 months from the primary operation, the level of blood calcium increased to 3.28 mmol/l. The site was reoperated, debulking was performed. Post-operatively, the level of blood calcium was almost the same as before the operation. Thirty-two months after the primary operation, the calcium levels persisted around 3 mmol/l. A radio-navigated operation was performed consisting of debulking only. The level of blood calcium decreased to 2.84 mmol/l. The operation was complicated with peroperative bleeding from the right internal jugular vein. Post-operatively, the patient was without complications, and was released home in a good

condition. After 44 months from the primary operation, there was another increase in total calcium level to 3.3 mmol/l and an increase of intact parathormone to 37.21 pmol/l. The revision was performed and the relapse was removed along with the wall of the internal jugular vein. Preoperatively, the calcium did not decrease. According to control SPECT/CT, there was a relapse posterior to sternoclavicular joint, which was subsequently removed from partial sternotomy. During the operation, the calcium levels were 3.09 mmol/l and the level of intact parathormone was 17.17 pmol/l. After 66 months from the primary operation, the relapse tissue on the right side was removed, reaching the level of blood calcium 3.43 mmol/L and the level of intact parathormone 32.33 pmol/L. After 70 months from the primary operation, the level of blood calcium was 4.24 mmol/l, the level of intact parathormone was 88.1 pmol/l. The debulking was performed. Post-operatively, the calcium level was 3.88 mmol/l. She was treated conservatively – by cytostatics (Mimpara), then the decrease of calcium levels to 3.00 mmol/l was reached. The patient is currently 84 months after the primary operation. She underwent 10 operations for parathyroid carcinoma. The relapse of the disease persists.

Case 4: 61-year old male patient with a medical history of bone syndrome and laparoscopic cholecystectomy was admitted to our hospital. The total blood level of calcium was 3.01 mmol/l, the level of intact parathormone was 108.7 pmol/l. By a 99 mTc MIBI SPECT/CT, the pathologically changed lower left parathyroid gland was localized. On the parietal pleura, an accumulation of the signal was also present. Preoperatively, the parathyroid carcinoma with metastasis was suspected. The ipsilateral lobectomy of thyroid gland together with parathyroidectomy of the affected parathyroid gland was performed. During the operation, the level of intact parathormone decreased to 18.17 pmol/l. Post-operative course was without complications. The level of blood calcium post-operatively was 2.28 mmol/l. Histologically, the adenocarcinoma was verified. A month later, the third rib resection was performed due to tumor infiltration, prominent to pleural cavity. The calcium level postoperatively was 1.98 mmol/l. Histologically, a brown tumor of hyperparathyroidism aetiology was found, not metastasis. Currently, patient is 12 months after the operation and has no relapse or complications.

Discussion

Parathyroid carcinoma is a very rare endocrine disease resembling an important cause of primary hyperparathyroidism. The incidence of parathyroid carcinoma as a primary cause of primary hyperparathyroidism is reported around 1%. For example, Wang and Gaz found 28 such patients among 1,200 patients, *i.e.* 2.3% (1). Sandelin *et al.* found 6 patients with parathyroid carcinoma among 1,650 patients with primary hyperparathyroidism, *i.e.* 0.3% (2). In our cohort, they occurred in 0.2%. Different incidences among particular centres can be partially explained with different histological criteria for recognizing the parathyroid carcinoma (3). From a genetic point of view, the parathyroid carcinoma can occur as a solitary finding in the isolated familial hyperparathyroidism or as a part of multiple endocrine neoplasia type I (MEN-1) (4). The central role in the molecular pathogenesis of parathyroid carcinoma is played by a mutation in a tumor-supressor gene *hrpt2* (cdc73) (5, 6). Other genetic changes have been also found: the mutations of men1 gene, loss of heterozygosity (LOH) in locus for retinoblastoma and overexpression of cyclin D1 (7). Some patients hadradiotherapy of the neck region in their medical history (8). In our four cases, we did not observe a correlation with radiotherapy neither in parathyroid adenomas nor in carcinomas (9, 10). Some authors have described an increased simultaneous occurrence of parathyroid carcinoma and adenoma in one patient (11, 12).

Interestingly, in parathyroid adenoma women are affected more often whereas in case of parathyroid carcinoma, the ratio of men and women is 1:1 (13). The patients with parathyroid carcinoma are generally slightly younger than patients with a benign primary hyperparathyroidism.

Clinically, it is almost impossible to differentiate between severe benign primary hyperparathyroidism and carcinoma (1). The primary diagnosis of parathyroid carcinoma, based solely on the clinical picture is thus very severe and in many cases possible only based on the histological picture. In one of our patients, preoperatively the parathyroid carcinoma was suspected, on the basis of lung metastasis finding (subsequently disproved).

One of the possible leads could be the significantly increased level of blood calcium and parathormone levels, sometimes also the palpation findings on the neck. Preoperatively increased level of calcium is not connected with increased mortality, but with a parathyroid carcinoma suspicion (11). In many patients, a palpable tumor on the neck has been reported (1). Approximately in 10 % of patients, the parathyroid carcinoma is hormonally inactive (14).

In our 4 patients, we observed both higher calcaemia and a high level of parathormone in blood. In our sample, we observed a palpable resistance on the neck corresponding to parathyroid carcinoma metastasis. Patients usually undertook neck sonography. The sensitivity of preoperative localization methods for reoperations of parathyroid carcinoma was set at 69% for sonography, 67% for CT, 93% for MRI and 79% for MIBI scintigraphy (15). The fine needle aspiration biopsy (FNAB) is not recommended, because when the parathyroid carcinoma is suspected preoperatively, the chance of positivity is low and the risk of tumor cells dissemination occurs (4, 16). In our patients, we recommend the performance of SPECT-CT in combination with MRI.

Parathyroid carcinoma can rise from any parathyroid gland, even an ectopic one. The final verification of diagnosis is often done by histological examination of the sample. The occurrence of necrotic tissue inside the tumor indicates the malignant character (17). Typical size of tumor is up to 3 cm, tough consistence, grey-white colour and important infiltration into surrounding structures (12, 18).

Surgical therapy is the most frequent option for the treatment of parathyroid carcinoma (90% of cases). Primary operation is crucial for an adequate local excision. The tumor should be removed in one block with ipsilateral thyroid gland lobectomy. However, some authors do not agree with this statement and conclude that in case of the absence of thyroid invasion, the lobectomy is not necessary (11, 19). During the operation, the surgeon should avoid the rupture of the capsule. Peroperative biopsy is necessary, because it can be the first diagnostic mark of the parathyroid carcinoma. If we would be able to reliably and reproducibly determine the diagnosis of parathyroid carcinoma, it would be preferable to perform an ipsilateral thyroid gland lobectomy together with parathyroid tissue and neck block dissection. However, due to a significant risk of such approach, it is contraindicated in case of unsure diagnosis (20).

In our four patients, we did not observe significant rigidity and fixation of parathyroid tissue to surrounding structures in the primary operation. However, we have observed rigid nodes, together with a resistance, corresponding to the metastasis of the affected lymph node in reoperations.

We performed the preoperative biopsy in all cases and the success of the operation was verified by intraoperative determination of the decrease of the intact parathormone level. Soloranzo *et al*. state that after the "*en bloc*" parathyroid carcinoma resection is the decreasing of iPTH of 50% from the baseline (21). The diagnosis of the parathyroid carcinoma is usually set after the final histological examination after the primary operation. If reoperation follows, we can assume an increased risk of recurrent laryngeal nerve injury with every other operation. Moreover, it is possible to use the radionavigation technique connected with a scintigraphy probe in order to localize the relapse of the tumor (22).

The systemic oncological treatment of parathyroid carcinoma is not yet available. Some authors assume that radiotherapy could be helpful against repeated growth of the tumor (23). In our sample, we treated a patient who underwent radiotherapy. This patient had repeated operations for relapsing parathyroid carcinoma, which included tracheostomy. In literature, a limited effect is reported from the use of chemotherapy, mainly of synthetic estrogens, 5-fluorouracil, cyclophosphamide and drugs with dacarbazine. Immunotherapy has also been described including the use of human, modified human or bovine PTH peptide, stimulating the production of anti-parathormone antibodies.

The post-operative recall is based on repeated monitoring of serum calcium levels. When considering surgery, the level of intact parathormone as an initial parameter should be determined. Patients with parathyroid carcinoma are repeatedly reoperated due to relapse. Persistent or relapsing disease occurs in 50% of cases (14). The relapse occurs in 33 months (range=1-228 months) (24). When metastases are present, they are hormonally active and thus the aim is to remove then in order to decrease the parathormone production. The surgical excision of local as well as distant metastatic lesions is the most effective method (2).

Importantly, with every reoperation, the incidence of perioperative complications increases (60%); the occurrence of paresis of recurrent laryngeal nerve reaches up to 38 % (11).

The death of patients is most often caused by uncontrolled hypercalcaemia, which leads to renal failure, heart dysrhythmias or pancreatitis (11, 19, 25). It is why the repeated surgical approach, *i.e.* the debulking of the hormonally active tissue, is necessary. The symptomatic treatment of hypercalcaemia is targeted on three main goals: hydration, calcimimetics (Cinacalcet) and bisphosphonates (26).

Generally, men have worse prognosis than women. Other unfavourable markers include diagnosis in young age, histopathologic level of differentiation and the number of mitoses, the presence of vascular invasion, lymph node affection, genetic changes of tumor cells, non-radical surgical approach including "*en bloc*" lymph node resection (24). In the majority of studies, the long-term survival rate is between 6-7 years (1, 27). In two-thirds of cases, the treatment does not have a curative effect and relapse occurs, in some cases even as distant as after 30 years.

Conclusion

Parathyroid carcinoma is a rare clinical entity, which represents one of the main reasons, why the surgery should be performed in specialized centres. Preoperatively, it is very difficult to distinguish between benign and malignant hyperparathyroidism. One such sign might be the level of blood calcium. Preoperative finding of gray-white, pathologically-enlarged and tough parathyroid gland, together with marked increase in preoperative calcium and parathormone levels should lead the surgeon to remove it "*en bloc*". During the operation, it is absolutely necessary to avoid the rupture of the tumor capsule. If the parathyroid carcinoma is verified, the possibility of repeated surgery should be presupposed. During repeated surgical interventions, it is necessary to employ all possible preoperative examination methods, including SPECT/CT, MRI or sonography, in order to localize the pathologically changed parathyroid tissue. Today, the surgical resection of tumor relapse including metastatic lesions, represent the most successful method of relapse treatment. However, every reoperation increases the

number of possible complications, including recurrent laryngeal nerve injury. The prognosis of parathyroid carcinoma is quite favourable, patients evidence a long-term survival rate after the primary operation.

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