PARATHYROID CARCINOMA – DIAGNOSIS AND SURGICAL TREATMENT A 24-YEAR EXPERIENCE

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The aim of the study was to evaluate the clinical, surgical and pathological prognostic factors of postoperative disease progression in parathyroid cancer patients.

Material and methods. This is a retrospective study of 19 patients operated on between 1983 and 2007 for parathyroid cancer at the Department of General Surgery of the Silesian Medical University constituting 4.6% of the total 416 patients operated on during that time for primary hyperparathyroidism.

Results. The study is based on a group of 7 (27%) men and 12 (63%) women aged 27 – 77 (av. 56). On admission, serum calcium levels exceeding 3.5 mmol/L were observed in 11 (58%) patients with parathyroid cancer and in 4 (1%) of the 397 patients with benign changes. Serum parathormone (PTH) levels higher than 450 pg/ml were found in 9 (47.4%) and 11 (2.8%) patients, respectively. Whenever parathyroid cancer was suspected, an en bloc resection of the parathyroid tumor including a wide margin of adjacent tissue was performed. Ipsilateral thyroid lobectomy was performed on 14 patients but in 5 cases total thyreoidectomy was required. 14 (73.7%) patients underwent either ipsilateral (11x) or bilateral (3x) lymphadenectomy. Within the group of 19 patients a total of 41 operations were required, including 4 operations in other medical centers. Three patients underwent adjuvant radiation therapy. The cumulative postoperative 5-, 10- and 15-year survival rate for the 19 parathyroid cancer patients was 95%, 82.5% and 62% respectively. Local and/or regional recurrences as well as remote metastases were found in 7 and 6 patients, respectively. Of the former group six patients are still alive after 3, 7, 9, 10, and – in two cases – 12 years (the 7th patient died 14 years after the first operation). Of the latter group three patients died of cancer dissemination 5, 7 and 8 years after the initial operation, but three others are still alive after 7, 10 and 14 years while still displaying the disease symptoms. Six patients, all of whom underwent one-stage resection of parathyroid glands and both ipsilateral thyroid lobectomy and lymphadenectomy, are still alive 8, 10, 11, 13, 14 and 21 years after with no evidence of the disease.

Conclusions. 1. Parathyroid cancer should always be suspected while dealing with primary hyperparathyroidism in patients with significantly elevated serum calcium and PTH levels. 2. Ipsilateral lymphadenectomy is advocated for parathyroid cancer patients already during the initial operation. 3. In order to avoid parathyroid cancer relapse even many years after the surgery, periodic checks are recommended for the rest of the patients’ lives.

Key words: primary hyperparathyroidism, parathyroid cancer

During the last hundred years, since the first mention of a patient suffering from parathyroid cancer (PC) appeared, only about 700 cases have been described (1, 2). This is a rare malignant phenomenon and in most series the incidence of PC ranged from 0.4 to 5.2% of the patients with primary hyperparathyroidism (1-4). The natural history of parathyroid cancer-induced hyperparathyroidism often includes skeletal and renal complications or even death. It has been confirmed in several studies that an en block operation is the only procedure offering a chance of recovery and that neither radio- nor chemotherapy provided any benefit for such patients. However, histopathological findings do not always
help to distinguish between benign and malignant parathyroid tumors (1, 2, 3). Therefore, there is a need for more precise diagnostic and prognostic criteria for the purpose of limiting the discrepancies between the expected and the actual clinical course and prognosis in patients operated on for parathyroid tumors.

The aim of our study was to evaluate the clinical, surgical and pathological prognostic factors of postoperative disease progression of PC determined retrospectively within a single institution.

MATERIAL AND METHODS

This is a retrospective study of 19 patients operated on between 1983 and 2007 for parathyroid cancer. Two of them were admitted with recurrence – two and three years after an operation in other medical centers. They constituted 4.6% of the 416 patients operated on at that time for primary hyperparathyroidism. Consequently, we evaluated 397 patients operated on in the same time period for primary hyperparathyroidism (326 for adenoma and 71 for hyperplasia) and carried out a comparison with the PC group. Among the hyperparathyroidism patients we found two with MEN-2A syndrome (adenoma 1x, hyperplasia 1x) and one with HPT jaw tumor syndrome (adenoma).

Patients were identified based on the operation protocols and histopathological findings in accordance with the proposal made by Schantz and Castelman.

In all patients the diagnostic management consisted of clinical evaluation of hyperparathyroidism, biochemical screening including serum parathyroid hormone level and renal function evaluation (serum calcium, creatinine, potassium, inorganic phosphorus levels), preoperative localizing procedures (neck ultrasonography, computed tomography scans of the neck and mediastinum, Technetium $^{99m}$Tc sestaMIBI scintigraphy, as well as magnetic resonance imaging in 3 patients).

All patients were operated on under general anesthesia. After collar skin incision, strap muscles were retracted laterally and the area from the sternal notch to the upper part of the thyroid cartilage was exposed to visualize all the parathyroid glands. The pathologically changed parathyroids (one or more) were completely removed. If glandular hyperplasia was revealed, three parathyroids were removed completely and 2/3 of the fourth. If parathyroid cancer had been suspected, every patient had an en block resection of the parathyroid tumor including a wide margin of adjacent tissue. Ipsilateral thyroid lobectomy with isthmus was performed in 14 patients, but in 5 cases total thyroidectomy was required. 14 (73.7%) patients underwent either ipsilateral (11x) or bilateral (3x) lymphadenectomy. Within the group of 19 patients a total of 41 operations were required, including 4 operations in other medical centers (six patients underwent one reoperation, three had two, one – three, and one – seven). Three patients underwent adjuvant radiation therapy (60 Gy in 30 sessions – 1x, 54Gy in 27 sessions – 2x). None of the patients were treated with chemotherapy.

Following their discharge from hospital, the patients were seen at least once every 3 months within the first 5 years, and once every six months thereafter. Physical examination as well as laboratory tests were performed. Serum calcium and/or PTH increase were considered as pathognomonic for the disease recurrences. Subsequently in such patients localizing procedures were performed such as ultrasonography or computed tomography imaging of the neck and, if necessary, the chest, as well as scintigraphy.

In order to confirm the dates of death, if any, the data were verified at Regional Station of Public Records Department for Telecommunication and Computer Science, Ministry of Home Affairs and Administration in Katowice and at Medical Center of Analyses and Statistics, Silesian Center of Public Health in Katowice.

Statistical analysis

Data from case reports were entered into a Microsoft spreadsheet Excel 2003 to obtain a data base which could be analysed according to a standard statistical procedure. In case of normally distributed variables, two mean values were compared using Student’s t-test for non-combined variables, whereas three or more groups were compared by multimean homogeneity test in single classification. In case of variables showing other than normal
distribution, Mann-Whitney U-test was used.

Survival curves were determined using the Kaplan-Meier estimator using a StatSoft program STATISTICA. F Cox test was used to compare two groups, and a chi-square test to compare more than two groups. In order to establish which independent factors had a jointly significant effect on the overall survival rate, we performed Cox's multivariate regression analysis.

RESULTS

There were 7 (27%) men and 12 (63%) women aged 27-77 years (av. 56) treated for parathyroid cancer. Most of them – 16 (84%) – complained of myalgia and/or arthralgia. Osteoporosis was observed in 16 patients. Nephrolithiasis was present in 13 (68%) of the 19 patients. Gastric or duodenal ulcers occurred in 8 (42%) patients, polydipsia and/or polyuria in 4 (21%), weakness in 3 (16%) polyneuropathy in 2 (11%). Severe renal dysfunction was present in 3 patients. Two treated patients observed weight loss, another two suffered from depression and further two complained of nausea and/or vomiting and anorexia. No complaints were reported from two others. A palpable cervical mass was found in 8 (42%) of the admitted patients.

The left lower parathyroid gland was affected in 7 (37%) patients, the right lower one in 4 (21%), the right upper one in 3 (16%) and the left upper one also in 3. In two cases parathyroid cancer was found in the ectopic glands (upper mediastinum, cervical thymus). The mean tumor size was 19 mm (ranging from 5 mm to 56 mm).

Histologic and cytologic examinations of all tumors showed fibrosis in 18 (95%), mitoses in 18, vascular invasion in 15 (80%), capsular invasion also in 15 and nuclear atypia in 13 (70%). The comparison of the histologic and cytologic features of parathyroid cancer and adenoma groups revealed that fibrosis (p<0.001), mitoses (p<0.001), vascular (p<0.001) and capsular invasion (p<0.001) as well as nuclear atypia (p<0.001) were significantly more frequent in the former group of tumors.

Biochemical abnormalities, including hypercalcemia, elevation of serum PTH and renal function parameters were present at hospital admission and during follow-up after surgery (tab. 1). Serum calcium levels higher than 3.5 mmol/L were observed on admission in 11 of the 19 (58%) patients with parathyroid cancer and in 4 (1%) of the 397 patients with benign diseases. Serum PTH levels higher than 450 pg/ml were present in 9 patients (47.4%) with cancer (ranging between 479-1732 pg/ml) and in 11 (2.8%) with benign diseases (ranging 456 -1161 pg/ml).

The cumulative postoperative 5-, 10- and 15-year survival rate for the 19 parathyroid cancer patients was 95%, 82.5% and 62% respectively.

<table>
<thead>
<tr>
<th>Serum examination</th>
<th>Time to operation</th>
<th>Benign lesions (n=397)</th>
<th>Parathyroid cancer (n=19)</th>
<th>P</th>
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<tr>
<td></td>
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<td>average ±SD</td>
<td>average ±SD</td>
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<tr>
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<td>164 138</td>
<td>313 381</td>
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<td></td>
<td>up to 30 days</td>
<td>21 14.1</td>
<td>40 28</td>
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<tr>
<td></td>
<td>after 5 years</td>
<td>23 10</td>
<td>79 103</td>
<td>0</td>
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<tr>
<td>Calcium</td>
<td>before</td>
<td>2.8 0.3</td>
<td>3.5 1.2</td>
<td>0</td>
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<td></td>
<td>up to 30 days</td>
<td>2.1 0.1</td>
<td>2.2 0.4</td>
<td>NS</td>
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<td>after 5 years</td>
<td>2.2 0.1</td>
<td>2.6 1.6</td>
<td>NS</td>
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<tr>
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<td>92 41</td>
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<td>4.3 0.4</td>
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<td>4.4 0.7</td>
<td>4.6 0.5</td>
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<td>1.1 0.3</td>
<td>NS</td>
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<td></td>
<td>up to 30 days</td>
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<td>NS</td>
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<td></td>
<td>after 5 years</td>
<td>1.2 0.1</td>
<td>1.2 0.5</td>
<td>0.036</td>
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</table>
Local and/or regional recurrences as well as remote metastases were found in 7 and 6 patients respectively. Of the former group six patients are still alive 3, 7, 9, 10, and in two cases – 12 years after the initial operation. The seventh patient died 14 years after the initial operation, following radiation therapy (60 Gy) and a successive (seventh) operation. He died of multiorgan failure in the 35th postoperative day.

Bone (3 cases) as well as pulmonary (2 cases), mediastinal (3 cases) or retroperitoneal (1 case) metastases were found in the latter group of six patients. Three of them died of cancer dissemination 5 (in which case four parathyroid glands were affected), 7 and 8 years after the initial operation, but three others are still alive after 7, 10 and 14 years with existing disease symptoms. The first two were treated with Sr89 therapy for the bone metastases whereas the third one underwent solitary femur metastasectomy.

Six patients are still alive 8, 10, 11, 13, 14 and 21 years after the initial operation with no evidence of disease. All of them underwent one-stage resection of parathyroid glands and both ipsilateral thyroid lobectomy and lymphadenectomy.

Postoperatively, two patients required oral calcium and vitamin D substitution due to prolonged hypocalcaemia.

Cox’s proportional hazard ratio revealed that in the group of patients treated surgically for primary hyperparathyroidism the presence of parathyroid cancer was an independent, unfavourable prognostic factor (tab. 2).

Within the group of primary hyperparathyroidism patients, serum parathormon levels were significantly higher in parathyroid cancer patients than in those with benign lesions, both at hospital admission (p<0.05) and during follow-up studies (after 30 days p<0.05 and after 5-years p<0.05) (fig. 1a). Similarly, in the former group of patients, serum calcium levels were significantly elevated in comparison to the latter (p<0.05; p<0.05) (fig. 1b). However, no significant differences of serum parathormon (p=0.80; p=0.89; p=0.99) (fig. 2a) and serum calcium (p=0.76; p=0.85; p=0.91) (fig. 2b) levels were found between the adenoma and hyperplasia groups of patients, at hospital admission or during follow-up studies (30 days and 5 years), respectively.

**DISCUSSION**

The diagnosis and treatment of parathyroid cancer pose a great challenge for surgeons specialising in endocrine surgery (5, 6). As the results of histological and laboratory examinations do not always make it possible to distinguish between malignant and benign parathyroid tumours or to predict later results of the treatment, the most important factors used to evaluate the nature of these neoplasms are still intraoperative appearance, the degree of surrounding tissue invasion, the necessary extent of the surgical procedure and relapse occurrence (6-13).

This series presents one institution’s experience with patients operated on for parathyroid cancer. It seems that the high incidence of cancer in our institution is due to many years’ cooperation with endocrine specialists in this domain and selective referral of hyperparathyroidism patients to our centre, whose activity covers an area inhabited by ca 5-6 million people.

In the years 1996-2000 we observed a rather strange phenomenon of growth of parathyroid cancer morbidity (1.8 cases per year) in comparison to 0.6 – between 1991 -1995 and 0.4 in 2001-2007. We have no definite evidence,
but it seems that, especially as we observed a similar growth of thyroid cancer morbidity as well, it could be related to the Chernobyl disaster (14).

Although identifying parathyroid cancer before surgery is very difficult, the surgeon should always bear in mind the possibility of its presence. Similarly to others, we recommend a detailed interview with the patient as well as checking for palpable neck masses and laboratory disorders (serum calcium >3.5 mmol/L and PTH >450 pg/ml) which could suggest parathyroid cancer (15, 16). In our experience, whenever cancer is suspected preoperatively, an ultrasound of the neck and computer tomography imaging is mandatory. Both can help to determine the extent of the tumor as well as provide valuable information for surgical planning.

In our view, preoperative fine-needle aspiration is not recommended, as it may result in cancer cell implantation to the adjacent structure. Moreover, the histopathological value of the procedure is rather doubtful (17).

Similarly to others, in the treatment of patients with parathyroid cancer we recommend an en block resection of the affected parathyroid gland with adjacent structures. During the operation identification of all the parathyroid glands is necessary, because, as was the case with one of our patients, malignant changes may be diagnosed in others. Adenoma or hyperplasia may also co-exist, as was the case in five of our patients (adenoma 2x, hyperplasia 3x) (18, 19, 20).

Apart from the two patients admitted for recurrences, a frozen section allowed us to diagnose parathyroid cancer with certitude in
only one out of seventeen people. Among the remaining patients, the probability of cancer, hyperplasia or adenoma was diagnosed in six, five and six patients, respectively. Paraffin examination revealed parathyroid cancer in all cases. Therefore, if the surgeon is in doubt regarding the nature of the lesions during the first attempt, he should, despite negative frozen section results, perform as extensive an operation as possible in order to avoid another operation in a short time (21, 22). We fully agree with this view – a complementary procedure, within 2-3 weeks, was required in four of our patients, following a paraffin cancer examination. During the first operation, the surgeon already saw intraoperatively the characteristics typical of malignant lesions but he chose not to expand the operation without absolute certitude as well as histopathological verification.

Moreover, although the incidence of cervical lymph node metastasis is about 15-30% (3, 7, 23, 24), we advocate ipsilateral lymph nodes dissection as a routine procedure during the first operation. Six of our patients had one-stage ipsilateral lymphadenectomy during the first procedure (or during the second attempt within 2-3 weeks) and all are still alive (8, 2x12, 13, 14, 21 years after), four of them without evidence of disease.

The 5-year survival of our group of parathyroid cancer patients was similar to other groups of PC patients, but the 10-year observations are somewhat better (5, 7, 11, 21). It seems, that ipsilateral lymphadenectomy, performed as quickly as possible, ideally already during the first procedure, can be responsible for the improvement of the 10-year results.

Our observation confirms other reports that most tumors (50-78%) recurred within 2-3 years after the first parathyroid cancer operation (7, 22, 24, 25). However, in three of our patients primary recurrences were identified 5, 6 and even 13 years after the surgical treatment. Therefore, in the postoperative period we recommend periodic checks for the rest of the patients’ lives – every three months for the first five years and every 6 months thereafter. Like others, we recommend USG of the neck, serum PTH and calcium levels monitoring and, facultatively, computed tomography imaging (23), which makes sense as parathyroid cancers grow slow, and patients die mainly from metabolic complications (6, 16).

Some authors advocate adjuvant radiotherapy based on reported benefits in locoregional control of the disease. However, most of them did not observe any profits as was the case with chemotherapy (3, 11, 26-30).

In our experience based on three of our patients, who received adjuvant radiotherapy, two are still alive and the third died 11 years after the first operation. The first of the living patients received one-stage resection of the parathyroid tumour, total thyreoidectomy and bilateral lymphadenectomy. He has had no relapse for 21 years. The second patient after the third reoperation for locoregional relapse (lymphadenectomy was performed during the second one) is still alive after 14 years with no evidence of the disease. The third one died of disease dissemination having undergone radiotherapy albeit very late – only before the seventh operation.

CONCLUSIONS

1. Surgeons dealing with primary hyperparathyroidism should always bear in mind the possibility of parathyroid cancer when patient’s serum calcium and PTH levels are significantly elevated.
2. In parathyroid cancer patients we advocate ipsilateral lymphadenectomy, already during the first operation.
3. In order to avoid parathyroid cancer relapse even many years after the surgery, we recommend periodic checks for the rest of the patients’ lives.

REFERENCES