PARATHYROID CANCER – OCCURRENCE, DIAGNOSIS, TREATMENT

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Primary hyperparathyroidism and its causes

By secreting parathormone (PTH), parathyroid glands regulate the level of calcium concentration in blood serum. The regulation is based on a feedback, i.e. an increase in calcium level will inhibit PTH secretion whereas a decrease will stimulate the same. In normal conditions the concentration of ionized calcium Ca²⁺, being 4 mg/dl (1 mmol/l) in blood serum, maintains 50% of maximum parathormone secretion and is called PTH secretion control point. A decrease in blood serum calcium level will lead after a few seconds to an increase in PTH secretion through weaker activation of the calcium-sensing receptor (CASR) on parathyroid cell surface (1, 2, 3).

Primary hyperparathyroidism (PHP) is characteristic for excessive parathormone secretion. This condition leads to hypercalcemia, hypophosphatemia, hypercalciuria, urolithiasis, bone defect and subperiosteal resorption, resulting in bone cysts (osteitis fibroso-cystica) (4-10).

Idiopathic hyperparathyroidism is caused most often by a single or multiple parathyroid adenoma (3, 7-13). Single parathyroid adenoma causes idiopathic hyperparathyroidism in 85% of patients (14). Multiglandular hyperparathyroidism is found in the other 15% of patients (3, 15). The changes include hypertrophy, multiple adenomatosis and polycyclic hyperparathyroidism, usually having hereditary background (16, 17). Idiopathic hyperparathyroidism (IHP) may also be caused, although very rarely, by parathyroid cancer (PC) (1, 6, 18, 19, 20).

Epidemiology of parathyroid cancer

Although described for the first time about 100 years ago by de Quervain (1904), parathyroid cancer is still a diagnostic and therapeutic challenge (18-21). As various authors report, the tumor is found in 0.4-5.2% of all patients treated for idiopathic hyperparathyroidism, covering approx.0.2% of all malignant tumors within endocrine system (7-13, 20-26) (tab. 1).

It is assumed in Europe and USA that parathyroid cancer is found in less than 1%, and in Japan approx. 5%, of all IHP cases (8-13, 18). The disease is so rare that even chief medical centers of the world are not able to provide rich enough material (14, 18-27). It is not at all easy to define the frequency of primary parathyroid cancer due to non-explicit histologic criteria, and the disease is more often diagnosed than it indeed occurs (9, 20, 24, 25). Reports in the world literature have presented about 700 cases of parathyroid cancer so far (14, 19, 23, 27). According to “National Cancer Registry Database” (USA), the frequency of PC is 0.005% as compared to other registered malignant tumors (18, 19, 27, 28). PC occurs most often in adults between 45 and 65 years of age (17), although it is sometimes found in young people (below 19 years of age) or in the elderly (over 81) (1, 29). Among the patients, proportion of men to women is observed to range from 1:1 to 1:10 (12, 17-19, 30, 31).

The proportion is different for hyperparathyroidism. This condition is found four times more often in women (12, 19, 28, 32-34). Primary PC is far more frequently found in groups with familial type of hyperparathyroidism (1, 35-41).
Pathogenesis and clinical picture of parathyroid cancer

Over the last 20 years a number of reports have appeared containing clinical analysis of PC patients (tab. 2).

The period between the onset of first symptoms and surgical treatment is 3-24 months (mean 9.4) (13, 42-48).

Wiseman et al (49) observed that PC occurred most often in lower parathyroid glands (69.2%). Cohn et al (50) report that 88.9% of PC cases occurred in right lower parathyroid glands (tab. 3). Furthermore, some authors describe rare cases of ectopic localization of PC, e.g. within upper mediastinum (16, 50).

The tumors are found to measure 5-56 mm in their longest dimension (7, 24, 49). However, both Clayman et al (28) and Hundahl et al (19) report that approx. 60% of their study tumors exceeded 30 mm.

Macroscopically, parathyroid cancer is usually characterized by the presence of adhesions with adjacent structures and invasion into thy-

### Table 1. Frequency of occurrence patient with parathyroid cancer (PC)

<table>
<thead>
<tr>
<th>Author</th>
<th>Period</th>
<th>Number of patients with PHPT</th>
<th>Number of patients with PC</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang et al. (24)</td>
<td>1992-2003</td>
<td>168</td>
<td>8</td>
<td>4.7</td>
</tr>
<tr>
<td>Schantz and Castleman (20)</td>
<td>1930-1972</td>
<td>1200</td>
<td>70</td>
<td>5.8</td>
</tr>
<tr>
<td>Favia et al. (26)</td>
<td>1980-1996</td>
<td>290</td>
<td>16</td>
<td>5.2</td>
</tr>
<tr>
<td>Shortell et al. (35)</td>
<td>1958-1990</td>
<td>186</td>
<td>11</td>
<td>5.9</td>
</tr>
<tr>
<td>Pelizzo et al. (21)</td>
<td>1980-2000</td>
<td>478</td>
<td>17</td>
<td>3.6</td>
</tr>
<tr>
<td>Cohn et al. (50)</td>
<td>1942-1984</td>
<td>301</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Agarwal et al. (7)</td>
<td>1990-2004</td>
<td>100</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Klempeter et al. (57)</td>
<td>1975-2004</td>
<td>583</td>
<td>23</td>
<td>3.9</td>
</tr>
</tbody>
</table>

### Table 2. Parathyroid cancer (PC) – clinical and laboratory profile

<table>
<thead>
<tr>
<th>Author</th>
<th>Period</th>
<th>Number of patients with PC</th>
<th>M:W</th>
<th>Age</th>
<th>Average size of tumors (mm)</th>
<th>Average level of Ca (mmol/l)</th>
<th>Average level of PTH (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohn et al. (50)</td>
<td>1942-1984</td>
<td>9</td>
<td>1:2</td>
<td>48, 19-64 35</td>
<td>3.5</td>
<td>371</td>
<td></td>
</tr>
<tr>
<td>Sandelin et al. (53)</td>
<td>1958-1990</td>
<td>11</td>
<td>1:10</td>
<td>54, 35-71 30</td>
<td>3.8</td>
<td>722</td>
<td></td>
</tr>
<tr>
<td>Hundahl et al. (19)</td>
<td>1985-1995</td>
<td>286</td>
<td>1:1</td>
<td>54, 14-88 33</td>
<td>3.5</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Cordeiro et al. (31)</td>
<td>1995-2000</td>
<td>4</td>
<td>1:1</td>
<td>44, 22-64 45</td>
<td>3.7</td>
<td>560</td>
<td></td>
</tr>
<tr>
<td>Pelizzo et al. (21)</td>
<td>1980-2000</td>
<td>17</td>
<td>1:1,1</td>
<td>57, 30-83 31</td>
<td>3.3</td>
<td>391</td>
<td></td>
</tr>
<tr>
<td>Kirby-Bott et al. (45)</td>
<td>1991-2002</td>
<td>7</td>
<td>2,5:1</td>
<td>44, 25-70 -</td>
<td>3.5</td>
<td>355</td>
<td></td>
</tr>
<tr>
<td>Kebebew et al. (33)</td>
<td>1966-1999</td>
<td>18</td>
<td>2,6:1</td>
<td>46, 23-63 -</td>
<td>3.4</td>
<td>702</td>
<td></td>
</tr>
<tr>
<td>Chang et al. (24)</td>
<td>1992-2003</td>
<td>8</td>
<td>1,7:1</td>
<td>58, 36-82 22</td>
<td>2.9</td>
<td>623</td>
<td></td>
</tr>
<tr>
<td>Agrawal et al. (7)</td>
<td>1990-2004</td>
<td>4</td>
<td>1:3</td>
<td>37, 22-56 21</td>
<td>3.3</td>
<td>922</td>
<td></td>
</tr>
<tr>
<td>Wiseman et al. (49)</td>
<td>1970-2000</td>
<td>13</td>
<td>2,6:1</td>
<td>48, 23-63 28</td>
<td>-</td>
<td>764</td>
<td></td>
</tr>
<tr>
<td>Kleinpetter et al. (57)</td>
<td>1975-2004</td>
<td>23</td>
<td>1:1,5</td>
<td>54, 26-81 -</td>
<td>3.2</td>
<td>290</td>
<td></td>
</tr>
<tr>
<td>Dpt of General Surgery in Bytom</td>
<td>1983-2007</td>
<td>19</td>
<td>1,2:2</td>
<td>56, 27-77 19</td>
<td>3.5</td>
<td>313,4</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. Localization of parathyroid tumors

<table>
<thead>
<tr>
<th>Localization of primary parathyroid tumors</th>
<th>Wiseman et al. (49) n=13</th>
<th>Cohn et al. (50) n=9</th>
<th>Dpt of General Surgery in Bytom n=19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper right (%)</td>
<td>15,4</td>
<td>11,1</td>
<td>15,8</td>
</tr>
<tr>
<td>Upper left (%)</td>
<td>15,4</td>
<td>0</td>
<td>15,8</td>
</tr>
<tr>
<td>Lower right (%)</td>
<td>53,8</td>
<td>55,6</td>
<td>26,3</td>
</tr>
<tr>
<td>Lower left (%)</td>
<td>15,4</td>
<td>33,3</td>
<td>36,8</td>
</tr>
<tr>
<td>Different (%)</td>
<td>0</td>
<td>0</td>
<td>5,3</td>
</tr>
</tbody>
</table>
roid gland, whereas the parathyroid is hard in consistency and surrounded with fibrous capsule (13). Histopathological examinations performed during operative procedure rarely enable explicit assessment of malignancy or diagnosis of PC (12, 18, 34, 44, 55, 71-86). Histopathological diagnosis on postoperative material is also difficult, whereas “final” result is ambiguous and raises doubts among clinicians (12, 44, 51).

In 1973 Schantz and Castelman (20) described histopathological criteria for diagnosing parathyroid cancers. They included fibrous trabeculas, invasion into capsule and vessels, the presence of numerous mitotic forms.

“Classical” features of histopathological picture of PC, like the presence of mitotic forms, trabecular arrangement of cells, capsule invasion, signs of fibrosis or vessel invasion, are found in a very high percentage (even up to 100%) of the removed tumors (tab. 4).

Some authors believe that malignancy of parathyroid tumors is manifested most reliably by the presence of fibrous septa together with capsule hyalinization showing blurred architecture (otherwise clearly lobulated) and the presence of necrotic focuses (13, 28).

It has many times been documented that high mitotic activity of cells occurs more commonly in poorly differentiated tumors (11,25). However, a large number of mitotic forms can also be observed in adenomas or parathyroid gland hyperplasia (20, 50). It is widely accepted now that a definite diagnosis of PC can only be made when thyroid or other tissues are locally invaded, tumor metastases are seen in regional lymph nodes and remote metastases are evident (33).

Immunohistochemical examinations, tumor markers (MiB-1) or DNA cytometric analysis have only limited significance for the diagnostics of patients with parathyroid cancer (59). The presence of MiB-1 in patients with parathyroid tumor can indicate a malignant process only and has little effect on postoperative observation or control of the patients (44, 59).

On the other hand, it is useful to know histological grade of tumor malignancy and its cellular ploidy in order to assess further course of the disease (60). HRP2 gene mutation was detected in a majority of patients with PC and familial idiopathic hyperparathyroidism. The presence of mutated HRP2 gene is believed to increase the risk of malignant parathyroid tumor formation (1, 61).

Moreover, patients with PC are observed to show hyperexpression of calcium-sensing receptor (CASR), D1-cycline (CCND10) and Ki-67 (27, 60), loss of heterozygocity (LOH) in chromosome 1 region (containing HRPT2 gene), chromosome 11 containing MEN1 gene and RB gene (Retinoblastoma), the latter being a cell growth cycle regulator having an effect on p53 suppressor gene (2, 28, 59).

The above data indicate that final histopathological diagnosis of PC is very difficult and that macroscopic and microscopic features of the tumor should be assessed jointly in correlation with clinical data (9, 18, 25, 37).

It also seems reasonable to believe that a reliable diagnosis of PC can only be made basing on clinical course of the disease - local recurrence, metastases to regional lymph nodes and/or remote metastases (53).

Symptoms of PECE are first of all caused by hyperproduction of parathormone (PTH) and metabolic outcome of hyperparathyroidism. Only in later stage are they connected with the presence of the tumor mass and its metastases (32, 56).

As I already mentioned, an excess of PTH will lead to increased level of calcium in blood serum, disorders in skeletal system, digestive system and kidneys, leading finally to renal failure or uremia in extreme cases (6, 12, 13).

<table>
<thead>
<tr>
<th>Table 4. Parathyroid cancer (PC) – histopathology examination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histopathology characteristic</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Presence of mitotic forms (%)</td>
</tr>
<tr>
<td>Trabecular arrangement of cells (%)</td>
</tr>
<tr>
<td>Capsule invasion (%)</td>
</tr>
<tr>
<td>Signs of fibrosis (%)</td>
</tr>
<tr>
<td>Vessel invasion (%)</td>
</tr>
</tbody>
</table>
Clinical picture of such patients includes some non-characteristic problems e.g. nausea, vomiting, abdominal pain, loss of body weight, constipation, anemia, heart disrhythmia, muscular pains, polyneuropathy, depression or other psychic disturbances (13, 19).

PC patients demonstrate much higher frequency of renal or skeletal diseases as compared with those suffering from benign forms of hyperparathyroidism (4, 22, 47). Moreover, such patients often have advanced stages of skeletal destruction including osteoporosis or osteitis fibroso-cystica (40).

The conditions are found in up to 91% of all patients with PC diagnosis (13, 47). Renal problems are somewhat less common (found in approx. 60% of PC patients) (12, 33) and appear as renal colic, polyuria or polydipsia (66).

Renal failure is found more often in PC patients than in those with benign forms of hyperparathyroidism (15, 39). Interrelationship between skeletal and renal problems is found in approx. 50% of patients (9, 13, 44).

Shortell et al (35) report urolithiasis as the main complaint in 27% of their patients. Shane et al (12) detected renal problems in 60% of their patients and skeletal problems, including intraosseous resorption (resulting in bone cysts), osteitis fibroso-cystica or subperiosteal resorption, in 50%. Wynne et al. (13) observed complications connected with urolithiasis in 56% of their patients, and skeletal problems in 91% (tab. 5).

PC patients can also have periodic gastrointestinal troubles connected mainly with chronic peptic ulcer disease, chronic or acute pancreatitis (22, 28, 40).

Very high levels of parathormone and calcium concentration in blood serum accompanied by problems connected with urinary or skeletal systems and by palpable neck tumor may suggest the presence of parathyroid cancer (28, 57). Such relationship was shown by Shane et al. (12) in 35% and Schantz and Castleman (20) in 31%.

To obtain correct diagnosis as well as assessment of treatment and prognosis for PC patients it is useful to measure parathormone and calcium concentrations in blood serum together with urea concentration and creatinine in kidneys before the primary operation, immediately after the operation and at later follow-up visits (12, 50, 57).

Total calcium concentration in PC patients’ blood serum is usually significantly higher than normal, and its level often exceeds 3.5 mmol/l, whereas PTH concentration is usually ten to twenty times higher than the upper normal range (13, 21, 24, 57).

Immediately after the operation PTH level falls sharply, then is falling slowly for some time to finally reach the plateau (7, 12, 58). Most patients develop hypocalcemia, but come to normal in a few months upon calcium and vit.D therapy (9, 21, 29).

Schantz and Castleman (20) describe high concentrations of calcium in their study groups before the operation.

Levin et al (48) report that preoperative total calcium concentration exceeded 2.75 mmol/l in 80% of their group consisting of 11 patients. Wynne et al. (13) observed that most patients had high calcium levels and significantly high PTH levels in blood serum. Similar results were

Table 5. Profile of patients with parathyroid cancer (PC)

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Only skeletal problems (%)</td>
<td>18</td>
<td>91</td>
<td>30</td>
<td>100</td>
<td>26</td>
<td>55</td>
<td>50</td>
<td>84</td>
</tr>
<tr>
<td>Only urolithiasis (%)</td>
<td>27</td>
<td>56</td>
<td>50</td>
<td>50</td>
<td>48</td>
<td>60</td>
<td>61</td>
<td>68</td>
</tr>
<tr>
<td>Skeletal problems and urolithiasis (%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>74</td>
</tr>
<tr>
<td>Gastrointestinal troubles and chronic or acute pancreatitis (%)</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>25</td>
<td>30</td>
<td>-</td>
<td>6</td>
<td>42</td>
</tr>
<tr>
<td>Arterial hypertension (%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>-</td>
<td>67</td>
<td>47</td>
</tr>
<tr>
<td>Other (%)</td>
<td>17</td>
<td>60</td>
<td>50</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>42</td>
</tr>
<tr>
<td>Absence (%)</td>
<td>27</td>
<td>7</td>
<td>-</td>
<td>-</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td>11</td>
</tr>
</tbody>
</table>
obtained by Kleinpeter et al. (57) when testing
their group consisting of 23 patients.

Preoperative diagnosis of parathyroid cancer
occurs rarely. However, a suspicion of ma-
lignant origin of IHP is fairly frequent as it is
based on clinical features like persistent hy-
percalcemia (over 3.5 mmol/l), very high level
of PTH and the presence of palpable neck tu-
mor (4, 18, 39, 40).

Pathogenesis of parathyroid cancer (PC) is
not fully recognized. There are many concepts
as to risk factors connected with development
of this tumor, but none of them has been well
confirmed (11, 33).

However, it has been documented that ra-
dioactive induction can cause malignant trans-
formation in parathyroid glands (21, 34, 35).

Risk factors connected with thyroid cancer
occurrence include also some hereditary dis-
ases like family idiopathic hyperparathyroid-
ism (FIHP), polyendocrine adenomatosis syn-
dromes (MEN1, MEN2A), hereditary syndrome
consisting of hyperparathyroidism and maxillairy or mandibular tumors (HPT-JT) (6,
16, 36, 37, 38, 61).

Parathyroid cancer is a tumor showing hor-
monal activity and secreting parathormone
(PTH). Clinical picture bears strong relation
to the increasing process of hypercalcemia in
result of PTH hypersecretion (4, 21, 39-44). PC
showing no hormonal activity is very rare and
is usually asymptomatic (8, 45, 46). There are
14 cases of this type reported in the literature
(18, 45). Such patients are usually operated too
late, when the disease process has become well
advanced (1).

There are often conflicting opinions as to dia-
agnostic criteria, optimal management and pro-
gnosis for PC patients (19, 56). Clinical symp-
toms of the tumor are similar to symptoms ty-
pical for parathyroid adenoma, the latter being
much more common. Chance the preoperative
diagnostic procedure is far from easy (41).

PC patients have often the symptoms of hy-
perparathyroidism, but more intense than
those occurring in benign cases (6, 39, 41).

Calcium and parathormone levels in blood
serum are higher in PC patients than in those
with parathyroid adenoma (12, 13, 48).

Incidence and mortality connected with PC
are chiefly caused by metabolic consequences
of the disease rather than by malignant pro-
gress of the tumor, the latter playing a sec-
ondary role (7, 18, 43-47). Excessive PTH secre-
tion by the tumor may lead to death due to
symptoms of severe hyperparathyroidism and
hypercalcemia (4, 13, 48).

Preoperative impairment of kidney func-
tions can be observed in approx. 40-48% of pa-
tients and is connected with renal parenchy-
ma destruction process. This aspect should be
given special attention because the patients
may even require a therapy by extracorporeal
dialysis (9).

After PC operation, the patients usually die
because of renal failure, heart dysrhythmia or
acute pancreatitis (31). Death caused by hy-
percalcemic crisis occurs very rarely (16).

Diagnostics of parathyroid cancer

Preoperative detection of parathyroid can-
cer is difficult. However, a palpable tumor wi-
in the neck (30-76%) (18) with concomitant
acute clinical course of hyperparathyroidism
must arouse suspicion (51). The patients often
suffer from symptoms related to bone destruc-
tion, most often including undefined back
pain (approx. 10% of patients) (11, 34).

Metabolic disorders are usually more severe
when compared to patients with idiopathic hy-
perparathyroidism caused by benign tumors (43).

Parathormone concentration in blood serum
is often two to ten times higher than normal,
and total calcium concentration often exceeds
3.5 mmol/l (8, 13).

Moreover, there are symptoms of recurrent
peptic ulcer disease and chronic pancreatitis
in approx. 5% of PC patients (5, 21). Other
symptoms, like muscular weakness, loss of ap-
petite, constipation, nausea, vomiting, polyuria,
polydipsia, polynephropathy, arterial hyperten-
sion, loss of body weight or coptosis, are much
rarer (31).

Symptomatic hypercalcemia or skeletal le-
isons like osteitis fibroso-cystica are not charac-
teristic because they occur also in other mali-
gnant diseases accompanied by osteolytic me-
tastases to bones (44). Differentiation between
IHP and advanced PC is still more perplexing if
the latter has ectopic localization (6, 34).

Laboratory examinations used for diagno-
stics of parathyroid tumors include chiefly te-
sts on calcium concentration in blood serum,
calcium content in urine and PTH concentration (6, 34, 58).

Size and localization of parathyroid glands can be best assessed through imaging examinations (11), such as:
- ultrasonography (USG),
- radioimmunoassay and radio-isotope tests - scintigraphy with oncophilic marker (Tc-MIBI),
- X-ray examination, selective arteriography and computer tomography (CT),
- thermography and lymphography,
- nuclear magnetic resonanse (NMR).

However, neither imaging examinations nor scintigraphy enable differentiation between parathyroid cancer and adenoma (4, 40, 62, 52).

Aspiration biopsy (BAC) is not recommended because cytological diagnosis of PC is very difficult (18, 27), whereas mistakes at sampling can lead to false negative results and increase the risk of introducing cancer cells in needle insertion canal (18).

Intra-operative identification of parathyroid glands and differentiation between normal and abnormal basing on their position, shape, contour, size, compactness or vascularization are often difficult and require a surgeon with very extensive experience (13).

As compared to benign adenoma, parathyroid cancer has much harder consistency and more irregular shape (8). Parathyroid adenoma is usually soft, round or oval and reddish-brown in color. Parathyroid glands affected by PC are usually 3.1-3.5 cm in their longest dimension, whereas in case of adenoma the size is usually approx. 1.5 cm (19). Malignant lesion is usually surrounded with a hard, fibrous, grey-whitish capsule, and adjacent tissues are invaded (8, 13).

Intra-operative identification of parathyroid glands and differentiation between normal and abnormal basing on their position, shape, contour, size, compactness or vascularization are often difficult and require a surgeon with very extensive experience (13).

As compared to benign adenoma, parathyroid cancer has much harder consistency and more irregular shape (8). Parathyroid adenoma is usually soft, round or oval and reddish-brown in color. Parathyroid glands affected by PC are usually 3.1-3.5 cm in their longest dimension, whereas in case of adenoma the size is usually approx. 1.5 cm (19). Malignant lesion is usually surrounded with a hard, fibrous, grey-whitish capsule, and adjacent tissues are invaded (8, 13).

Intra-operative histopathological examination has little value as the differences between adenoma and highly differentiated cancer are very difficult to catch even for an experienced pathomorphologist (7, 28, 49). It is likewise difficult to diagnose postoperative material on histopathological basis (12), whereas „final” result is often ambiguous and doubtful for clinicians (11, 25, 50).

Auxiliary methods used by the surgeon to support intra-operative identification of parathyroid glands can include tests on PTH concentration or concentration gradient in jugular vein blood (SVS), intra-operative USG or radio-isotope techniques and gamma camera (34).

Some authors claim that the presence of PC can only be finally confirmed by the development of local recurrence or remote metastases together with persistent hyperparathyroidism (9, 51, 52). This is one more proof that making an accurate diagnosis of PC is an extremely difficult task.

**Treatment for parathyroid cancer**

Treatment of choice used for PC patients is surgical procedure. Radical removal of the tumor in tissue block during the first operation gives a biggest chance for successful cure (8, 11, 16, 53). It is recommended to remove the tumor en-bloc with thyroid lobe and isthmus on the lesion side (19, 33). The important thing is that the capsule should be left intact in order to prevent scatter of the cancer cells (21, 54). The operation includes removal of lymph nodes on the lesion side, together with neck muscles if affected by invasion (35, 55). If only PC is suspected, all parathyroid glands should be inspected for assessment as it quite often happens that malignant tumor is accompanied by adenoma or proliferation (16, 42).

A course of radiotherapy is decided usually as adjuvant treatment following surgery when the tumor mass must be reduced due to considerable advancement of the disease (13, 45, 49). Chemotherapy is nowadays used at the level of clinical examinations (13, 51).

Radioguided parathyroid surgery (MIRP) can be a very useful method of treating PC, in particular if local recurrence or metastases to other body parts are detected. This method is usually much more accurate and less invasive than “standard” surgical treatment (6).

Other methods, such as transcutaneous injection of ethanol, laser therapy or radio-frequency wave ablation, have limited value (56).

During postoperative period most patients develop hypocalcemia indicating intensive mineralization process in bone tissue (“hungry bone” syndrome) (12, 18). Postoperative monitoring is based on testing calcium and PTH concentrations in blood serum. The disease can recur even several dozen of years after the primary treatment (7, 12, 32).

Overall, a 5-year survival rate is observed after PC surgery in 50-86% of patients (13, 19). During the 5-year period postoperatively most deaths are caused by recurrence of the hormonally active parathyroid cancer and related metabolic disturbances (7, 27, 41).
Percentage of PC recurrences is 50-78% (11). They are observed most often 3-5 years after the first operation (54). Late results are improved by a possibility that resection of local recurrences can be repeated (11, 35, 55, 57). It is not difficult to take such decision as PC shows low aggressiveness and slow growth (14, 50, 58).

However, the assessment of PC surgical treatment is difficult and requires that patients should be monitored continually even after radical surgery. Diagnosis of a recurrence is based on redevelopment of hypercalcemia (59). Patients with polyadenomatosis syndromes (MEN1, MEN2A or FIHP) are at highest risk of developing hyperparathyroidism recurrence (6, 16, 36, 38, 60). The recurrence is local in most cases (21, 36, 61) and rather difficult to localize because of its possibly very small size or multifocal character (13). Remote metastases are detected in 25% of patients on average, chiefly in lungs but also in bones, liver or brain (11, 41, 53).

Enforced diuresis together with drugs to reduce calcium levels (calcitonin, diphosphate or mithramycin) are often found useful in surgery-resistant hypercalcemia (11, 21, 56).

Operation is a treatment of choice both for primary tumor and for recurrences of the disease (11, 21, 54). Operative treatment has also a relieving effect on metabolic consequences of hypercalcemia, thus playing a role in extending patients’ survival. Pharmacotherapy is used for non-operative lesions or in unsuccessful surgical management to reduce the level of calcium in blood serum (12, 55).

The most effective treatment for parathyroid cancer is radical en-bloc resection of the tumor during primary operation (8, 23) possibly followed by adjuvant teleradiotherapy on the tumor site (21, 33, 55). Such management gives a chance that the condition will be completely cured (8, 31, 32). However, it is important to note that most operations are scheduled for IHP of unclear etiology (benign or malignant lesion), and therefore the ability to make a correct diagnosis intra-operatively basing on macroscopic features is a necessity (7, 37). Parathyroid cancer may be confirmed by invasive growth of the lesion originating from parathyroid gland together with increased regional lymph nodes (1, 15, 26).

On the other hand, neither macroscopic inspection nor even immediate histopathological examination will give a satisfactory answer to the question whether the increased parathyroid gland is or is not malignant (12, 57). Therefore the diagnostic procedure should consider both clinical and intra-operative pictures but also doubts that might be raised during examinations for malignancy (24, 45, 56).

If the result of postoperative microscopic examination indicates malignant lesion and/or if hypercalcemia persists after the operation, another imaging examinations and perhaps a reoperation are recommended (12).

Bilateral exploration of neck is essentially important because there may be a benign adenoma or proliferation of other parathyroid glands besides a malignant tumor. There are also some reports describing both parathyroid and thyroid cancers at the same time (16).

To distinguish between an atypical adenoma and malignant tumor is not easy at all, and requires an enormously experienced histopathologist (7, 50).

In recent years there have been some reports on successful results of adjuvant therapy used for neck region in order to reduce the frequency of local recurrences (13, 18, 28) or to extend PC patients’ survival time (21, 28, 45). Other authors have described successful results of radiotherapy used for the purpose of relieving the symptoms of intense hypercalcemia (13, 56).

Chow et al. (76) present the results of adjuvant radiotherapy as used in PC patients in order to eliminate early local recurrence after surgical treatment. However, adjuvant radiotherapy is now considered highly controversial (57). Chemotherapy is not used any more either as it turned out to be ineffective (1, 21, 32).

Parathyroid cancer has typically a tendency to develop local recurrence and to spread both by lymphatic system and by blood (19, 26, 41). Metastases are observed in 15% of patients on average in neck regional lymph nodes, and in 10-40% of patients in remote places, chiefly lungs, liver and bones (12, 20, 53). The lesions can manifest even a few years after surgical treatment (18, 35). Parathyroid cancer recurrences are observed 2-3 years on average after the operation in approx. 50-78% of patients (11, 54).

Therefore PC patients require close follow-up for many years in aspect of possible local recurrence or remote metastases (41).
Table 6. Results of operating treatment patients with parathyroid cancer (PC)

<table>
<thead>
<tr>
<th>Centre</th>
<th>Time of observation</th>
<th>Number of patients with PC</th>
<th>5-years survival</th>
<th>10-years survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hundahl et al. (19)</td>
<td>1985-1995</td>
<td>46</td>
<td>86</td>
<td>49</td>
</tr>
<tr>
<td>Wynne et al. (13)</td>
<td>1955-1991</td>
<td>14</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Dpt of General Surgery in Bytom</td>
<td>1983-2007</td>
<td>19</td>
<td>89,5</td>
<td>79</td>
</tr>
</tbody>
</table>

It seems that to make a reliable diagnosis of parathyroid cancer recurrence it is necessary to assess the growth of both parathormone and ionized (or total but rather rarely) calcium levels in blood serum (47, 51). Local recurrence is observed in approx. 30-45% of patients (21, 36). If detected, the best method of treatment should always be a reoperation (14, 33). The aim of any reintervention is to reduce the mass of tumor and to normalize the concentration of calcium in blood serum (18). The procedure should be preceded by careful diagnostic examinations to localize the recurrence and possibly exclude remote metastases (18, 61, 62, 81).

In selected cases it is possible to remove surgically single metastases from bones or even to perform extensive resection of lung parenchyma if multiple lesions have developed (22, 23, 36).

In advanced cases, the cause of death is usually connected with the consequences of severe hypercalcemia (27, 37). Therefore total survival time of patients can be prolonged by a therapy enabling resorption of calcium from bones and reduction of its concentration in blood (7, 12, 31, 56). Such management results in long-term survival of patients in spite of even generalized malignant process (21, 35, 54).

Hundahl et al. (19) report that 86% of their 286 PC patients survived five years, and 49% survived ten years postoperatively. Clayman et al (28) observed five-year survival rate in 85% of their patients, and ten-year survival rate in 77%. Similar observations were made by other authors (13, 19) (tab. 6).

Kleinpeter et al. (57) and Wynne et al. (13) observed recurrence of the malignant disease in 22-60% of their patients, whereas Kebebew et al (11) in 50-78%.

After surgical procedure for thyroid cancer, the patients make far less complaints related to skeletal system or kidneys (12, 29, 33), and nephrolithiasis rate is reduced by 90% (58).

Prognosis for PC patients after surgical procedure is uncertain (7, 11, 34). Clinically, a part of such patients can be considered as cured, but the other part gradually develop recurrences (14, 55, 57).

The size of primary tumor seems to have no connection with postoperative prognosis. This is confirmed by experiences described by Clayman et al. (28) and Hundahl et al. (19).

Many authors believe that prognostic factors influencing survival rate in PC patients remain unclear (19, 28, 43). Furthermore, the diagnosis of parathyroid cancer is often made as late as after a malignant recurrence has developed (15, 23). It is also quite often noted that a mild course of postoperative period has no relation to the primary lesion degree of advancement (7, 33, 50). Some patients have persistent hypercalcemia accompanied by metabolic disorders that may even lead to death (12, 28, 41). Patients with malignant scatter should first of all be treated for hypercalcemia as this is a life-threatening condition (22, 34, 47). Let us hope that the research on immunotherapy connected with human peptide PTH will produce some new, more effective, methods of treating patients with PC scatter.

REFERENCES


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