Intraoperative diagnosis and treatment of parathyroid cancer and atypical parathyroid adenoma

G. Ippolito1, F. F. Palazzo1, F. Sebag1, C. De Micco2 and J. F. Henry1

1Department of Endocrine Surgery, La Timone University Hospital and 2Department of Pathology, Nord Hospital, Marseilles, France

Correspondence to: Professor J. F. Henry, Department of Surgery, La Timone Hospital, 264 Rue Saint-Pierre, 13385 Marseilles, France (e-mail: jfhenry@ap-hm.fr)

Background: Distinction of parathyroid cancer from atypical parathyroid adenoma (APA) at operation is difficult. The aim of this study was to determine whether parathyroid cancer and APA have different operative findings and long-term outcomes.

Methods: A retrospective review was undertaken of patients with suspicious or malignant parathyroid tumours treated between 1974 and 2005. Parathyroid cancer was defined as a lesion with vascular or tissue invasion, and APA as a neoplasm with broad fibrous bands, trabecular growth, mitosis and nuclear atypia.

Results: Twenty-seven patients with suspicious or malignant parathyroid tumours were identified. After histological review, parathyroid cancer was confirmed in 11 patients (group 1) and 16 tumours were classified as APA (group 2). The clinical presentation and operative findings of the two types of tumour were indistinguishable. At initial surgery, seven patients in group 1 underwent en bloc resection, and four had parathyroidectomy. Four of the seven patients who had en bloc resection had recurrences. No recurrences were observed in the other seven patients in group 1 at a median follow-up of 65 months. In group 2, eight patients had en bloc resection and eight had parathyroidectomy; no patient had recurrence at a median follow-up of 91 months.

Conclusion: Operative findings cannot distinguish APA from parathyroid cancer reliably. Without evidence of macroscopic local invasion, the value of en bloc resection at initial surgery remains debatable.

Introduction

Parathyroid carcinoma is a rare tumour reported to occur in 0.5–4 per cent of patients with primary hyperparathyroidism (HPT). It presents with a range of clinical and biochemical characteristics, but overall is considered to have an indolent evolution, characterized by slow growth and culminating in death from the metabolic complications of hypercalcaemia.

As the histological criteria for the diagnosis of parathyroid cancer have been poorly defined, there may have been a tendency to over-report this pathology. Atypical parathyroid adenoma (APA) shares some histological features with parathyroid cancer and at the time of initial surgery differentiation from parathyroid cancer can be difficult. Hence some equivocal lesions have in the past been reported as parathyroid cancer, but their clinical behaviour has not always been consistent with this diagnosis. Indeed, the presence of local recurrence or metastatic disease is the only reliable feature that differentiates benign from malignant parathyroid disease.

The ideal treatment strategy for parathyroid cancer has also been the source of controversy, although en bloc resection is associated with a longer relapse-free interval and overall survival.

The aim of this study was to determine whether parathyroid tumours classified as parathyroid cancer or APA have different clinical patterns and long-term outcomes, and to assess the results of various management strategies.

Methods

A retrospective review was undertaken of patients with parathyroid tumours initially diagnosed as parathyroid...
carcinoma or as suspicious for parathyroid carcinoma, and treated at La Timone University Hospital between 1974 and 2005. All the original histological slides were reviewed blindly by the same pathologist (DeM.C.), who was blinded to the clinical characteristics and outcomes. Adopting current histopathological criteria, a parathyroid tumour was defined as carcinoma only when it displayed unequivocal vascular, capsular and adjacent tissue invasion. The presence of metastasis was also considered diagnostic of malignancy. When the tumour capsule was absent, the presence of parathyroid tissue in the surrounding tissue with no evidence of infiltration was considered insufficient for diagnosis of parathyroid cancer. The presence of entrapped parathyroid cells within the capsule but without the typical sign of the tongue-like protrusion of tumour cells through the capsule was equally considered insufficient for diagnosis of parathyroid cancer. Neoplasms showing some features of malignancy but not unequivocal morphological findings of carcinoma, such as vascular, capsular or adjacent tissue invasion, were defined as APA in accordance with the revised histological criteria. Such features include the presence of fibrous bands, mitotic figures, trabecular growth pattern or atypical nuclear features (Table 1).

The surgical procedures performed included en bloc resection (total lobectomy/thyroidectomy and parathyroidectomy with central neck dissection) and simple open or endoscopic parathyroidectomy, and were documented along with the clinical follow-up data.

**Results**

Between 1974 and 2005, 2024 parathyroidectomies were performed, of which 27 (1.3 per cent) involved suspicious or malignant parathyroid tumours. After the histological review, specimens were divided into two groups: in group 1 a diagnosis of parathyroid cancer was confirmed and in group 2 the lesions were classified as APA.

**Table 1** Histological features

<table>
<thead>
<tr>
<th>Features</th>
<th>Atypical parathyroid adenoma (n = 16)</th>
<th>Parathyroid carcinoma (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trabecular growth</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Broad fibrous bands</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Nuclear atypia</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Mitosis</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Pseudo-capsular invasion</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Absence of capsule</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Capsular invasion</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Tissue invasion</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

There were 11 patients in group 1 (Table 2), giving a true frequency of parathyroid cancer of 0.5 per cent. The rate of parathyroid cancer decreased from 1.0 to 0.4 per cent after 1990, when calcium and parathyroid hormone (PTH) measurement became available routinely in the authors’ institution. There were seven women and four men in group 1, with a median age of 52 (range 25–69) years. No history of irradiation to the neck or familial HPT was reported. Severe hypercalcaemia (concentration greater than 3.50 mmol/l) was present in three patients. In four patients hyperparathyroidism was identified following routine calcium assay. A palpable lesion was present in five patients. Operative findings of a firm and adherent lesion were reported in seven patients, who underwent en bloc resection, with recurrent laryngeal nerve (RLN) sacrifice in one patient. The other four patients had tumour resection only, one by conventional open surgery and three by an endoscopic procedure; the histological diagnosis was parathyroid cancer with a clear margin of resection. Two of these four patients underwent a second-stage en bloc resection following a histological diagnosis of parathyroid cancer; histological examination confirmed that no parathyroid tissue had been left behind in either patient. Four of the seven patients who had en bloc resection at the initial operation had recurrences and died from hypercalcaemia after a total of 17 reoperations. The median disease-free interval was 31 (range 3–48) months, and their median survival was 117 (range 60–156) months. The other seven patients were alive with no evidence of disease at a median follow-up of 65 (range 36–96) months.

Group 2 included 16 patients (Table 2). At histological review the initial false-positive diagnoses of parathyroid cancer were due to entrapped parathyroid cells within the capsule, initially described as capsular invasion in

**Table 2** Clinical, treatment and follow-up details of 11 patients with parathyroid carcinoma (group 1) and 16 patients with atypical parathyroid adenoma (group 2)

<table>
<thead>
<tr>
<th>Means of discovery</th>
<th>Group 1 (n = 11)</th>
<th>Group 2 (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic HPT1</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Calcium assay</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Palpable lesion</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Suspicious operative findings</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Initial surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>En bloc resection</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Parathyroidectomy</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>No evidence of disease*</td>
<td>7 (65)</td>
<td>16 (91)</td>
</tr>
</tbody>
</table>

*Values in parentheses are median follow-up period (months).*
three patients, misdiagnosis of tissue invasion in an unencapsulated tumour in five patients, and the presence of trabecular growth and/or fibrosis and/or nuclear atypia and/or mitosis in the remaining eight. The median age at presentation of the 11 women and five men was 58 (range 32–81) years. No history of irradiation to the neck or familial HPT was reported. Three patients had severe hypercalcaemia. In six patients hyperparathyroidism was discovered by routine calcium assay. A palpable lesion was found in five patients. Operative findings of a firm and/or adherent lesion were reported in ten patients, of whom eight underwent en bloc resection based on operative findings, with RLN sacrifice in three; two patients had an open parathyroidectomy. Endoscopic parathyroidectomy was performed in the other six patients. Surveillance was carried out by yearly determination of calcium levels, with a median follow-up of 91 (range 24–360) months. No recurrence was found.

**Discussion**

Parathyroid cancer is a rare disease with a true incidence that is probably less than the widely quoted rate of 1 per cent of all patients with primary HPT. The introduction of routine calcium screening has led to an increasing incidence of diagnosed primary HPT but this has not resulted in a parallel increase in the number of cases of parathyroid cancer. Since the 1990s measurement of calcium levels has been undertaken routinely in the authors’ institution. In the present series the rate of parathyroid cancer was 1·0 and 0·4 per cent before and after 1990 respectively.

Most patients with parathyroid cancer have clinical manifestations that are virtually indistinguishable from those in patients with an APA or a parathyroid adenoma, although severe hypercalcaemia may be regarded as a risk factor for malignancy. However, hypercalcaemia above 3·50 mmol/l was not observed in the present patients with parathyroid cancer operated on since 1990, presumably due to earlier diagnosis. Indeed, previous series have suggested that only 2 per cent of parathyroid cancers are asymptomatic.

Four of the five patients with parathyroid cancer who underwent surgery in the authors’ institution after 1990 were diagnosed by biochemical screening. A palpable neck lesion has been reported in between 52 and 75 per cent of parathyroid cancers, although the tumour was palpable in only one of the five patients in the present series after 1990. This difference may be due to the introduction of routine calcium assay and access to PTH measurement, which leads to an earlier diagnosis of HPT and thus of parathyroid cancer.

Preoperative imaging before parathyroid surgery has been used increasingly since the introduction of minimal access approaches, and parathyroid cancer is usually associated with a positive finding on sestamibi scanning. However, the only feature that may permit the preoperative diagnosis of parathyroid cancer is clear evidence of invasion into adjacent tissue. Unsurprisingly, no cases of parathyroid cancer were diagnosed before surgery in the present series when imaging was performed.

At the initial operation for HPT, features of presumed malignancy, such as firm texture, grey colour and gross adherence to adjacent tissue, are not proven differentiators of APA from parathyroid cancer. Thus the risk for the surgeon is overtreatment of an APA or undertreatment of a true parathyroid cancer. Previously the authors’ practice was to perform an en bloc resection when malignancy was suspected during surgery.

In cases where the RLN was involved, en bloc resection involved sacrifice of the nerve despite normal preoperative function. It now appears that this approach may be unjustified, given that, of the four RLNs sacrificed at operation, only one patient was found to have parathyroid cancer on histological review, three being reclassified as APA. In all four cases the superior parathyroid gland was the source of disease and histological findings demonstrated gross adhesion of fibrotic tissue to the RLN but no evidence of cancer invasion of the nerve. It is clear that differentiation of gross adherence, which may exist in benign lesions, from macroscopic invasion to adjacent tissues is challenging even for an experienced surgeon. It therefore appears appropriate to perform a careful dissection of the RLN, and if possible to peel the tumour off this vital structure. The ability to do this may indeed be an intraoperative sign that no true perineural invasion is present, and thus of a benign lesion. Others authors have confirmed the rarity of perineural invasion.

With the increasing use of endoscopic and other minimal-access parathyroidectomy procedures, the issue of suspected parathyroid cancer presents new management problems. In the authors’ practice, when parathyroid cancer is suspected during an endoscopic procedure conversion to an open procedure has been considered mandatory and resection of the parathyroid with the attached thyroid lobe justified by the avoidance of capsular disruption. When parathyroid cancer is diagnosed histologically and clear margins of resection are confirmed, reoperation may not be justified as there is little evidence of benefit in such cases. Assuming that capsular integrity has not been breached—a principle that applies to surgery of benign or malignant

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parathyroid lesions—the value of radical surgery is unclear. Indeed, cervical recurrence of parathyroid cancer is related to the local implantation of malignant cells. Recurrence of parathyroid cancer within 2 years of initial appropriate surgery is a feature of aggressive biological behaviour; it may occur despite initial en bloc resection and is associated with a shorter survival and relapse-free interval. Lymph node metastases from parathyroid cancer are extremely rare. In the present series, central neck dissection, when performed, never demonstrated evidence of metastasis. A lymphadenectomy may therefore not be justified if no enlarged nodes are present. Distant metastases to the lung or bone are rarely the first presentation of parathyroid cancer but are a frequent cause of persistent hypercalcaemia after surgery. How en bloc resection might affect outcome is debatable, because no data are available to confirm or refute the presence of metastases at the time of first operation. When metastasis does occur, the treatment is primarily surgical for both attempted cure and palliation, as both chemotherapy and external-beam radiotherapy rarely achieve long-term cure.

This study has confirmed that histological features such as vascular, true capsular or tissue invasion and the presence of recurrence are essential for an unequivocal diagnosis of malignancy. A malignant evolution was found in four of the 11 patients who had these characteristics at a median disease-free interval of 31 months. In contrast, the presence of broad fibrous bands, mitotic figures, trabecular growth pattern and atypical nuclear features, more frequently found in parathyroid cancer, is not pathognomonic of malignancy, as these features may also be found in APA. Half of the patients with APA in the present study lacked a well-defined connective tissue capsule. The absence of a well-defined capsule was usually observed in larger adenomas displaying fibrosis, cystic degeneration or chronic inflammation, and explains why these tumours were initially considered potentially malignant. The tumour capsule may be absent or partially discontinuous, mimicking fat tissue invasion in a number of parathyroid adenomas, and entrapped tumour cells within the capsule may be mistakenly considered to be true capsular invasion. Several studies have demonstrated that, in individual patients, analysis of various markers (Ki-67, p53, bcl-2, cyclin D1) or DNA quantitation is also of limited diagnostic interest because there are no consistent differences in their expression between parathyroid cancer, APA and parathyroid adenoma. Thus, the final diagnosis of malignancy in parathyroid tumours still relies on histological findings demonstrating unequivocal evidence of vascular or tissue invasion.

New therapies, including immunotherapy and the use of calcimimetics, have been used effectively in some patients with metastatic parathyroid cancer. Immunotherapy achieves hormonal and biochemical normalization by immunizing against PTH in patients with parathyroid cancer. Calcimimetics are a new class of drugs with agonist action at the calcium-sensing receptor; they are licensed for the control of symptoms of severe hypercalcaemia in a palliative setting.

The aetiology of parathyroid cancer is obscure but the association with familial HPT and jaw tumour syndrome HPT suggests a possible genetic predisposition. Although a previous history of irradiation to the neck has been reported to be a risk factor, there were no such patients in the present series. Loss of heterozygosity of chromosome 1q, which contains the HRPT2 gene, also reported in familial and jaw tumour syndrome HPT, and patterns of chromosomal imbalance in parathyroid cancer may suggest the genetic pathway in parathyroid cancer tumorigenesis. This is relevant because it raises the possibility that parathyroid cancer may evolve from a previously benign lesion, and that APA may thus represent a precancerous or early-stage parathyroid cancer. This may be supported by the decreasing incidence of parathyroid cancer that has accompanied the earlier diagnosis and treatment of patients with primary HPT. As early diagnosis and intervention become more widely adopted, the risk of equivocal operative findings suggestive of parathyroid cancer or APA should decrease and the prognosis should improve.

References


