

## How to deal with parathyroid carcinoma: case report, histological difficulties and literature review

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### Summary

The histological diagnosis of parathyroid carcinoma is often difficult due to the existence of many potentially misleading similarities, between this malignant entity and its main differential diagnosis: parathyroid adenoma.

Several histological criteria of malignancy have been proposed in order to solve this diagnosis problem: the presence of fibrous bands emerging from a thick capsule dividing the tumor proliferation into lobules, tumor cells arranged in clusters and trabeculae, moderate to clear cytonuclear atypia and low mitotic activity. Unfortunately, these criteria are not exclusive to carcinomas and can also be seen in cases of adenomas.

The more relevant histological criteria of malignancy are proposed, such as atypical mitosis, capsular invasion, vascular invasion or the exceptional perineural invasion. But these criteria are rarely found. Infiltration of the thyroid gland, adjacent soft tissue and the occurrence of metastases remain the only indisputable signs of malignancy.

Immunohistochemistry can contribute to the differential diagnosis, especially with the loss of expression of Parafibromin, commonly found in carcinomas unlike adenomas, or the expression of parathormone, allowing the elimination of a thyroid tumor.

**Keywords:** Parathyroid carcinoma; Parathyroid adenoma; Histological difficulties; Comparative table

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### Introduction

Parathyroid carcinoma (PC) is a rare endocrine malignancy that remains enigmatic. Commonly a sporadic disease, it may occur in familial PHPT, namely the hyperparathyroidism-jaw tumor syndrome (HPT-JT), and very rarely, in the multiple endocrine neoplasia type1 (MEN1) [1]. Usual clinical features are mainly due to the excessive secretion of Parathormone (PTH) causing hypercalcemia, hypophosphatemia, and hypercalciuria. Thus, the clinical phenotype is characterized by symptoms of hypercalcemia and end-organ damage, including renal failure, bone disease, cardiac arrhythmia and neurocognitive dysfunction [2].

The disease commonly has an indolent and slow progressive course, and most patients ultimately succumb to complications of relentless hypercalcaemia rather than tumour invasion or metastatic spread. None of these, however, are strict rules. Indeed, the very first documented case of parathyroid carcinoma

was a non-functioning carcinoma reported by Fritz De Quervain, in 1904 [3]. It wasn't until 1933 that Sainton and Millot were first to report a patient with a functioning parathyroid carcinoma [4]. The main differential diagnosis is the parathyroid adenoma, which shares with parathyroid carcinoma a lot of clinical, biological and histological features that can make the diagnosis challenging.

Given the lack of specific clinical and biological features, the distinction between benign and malignant parathyroid tumor is often difficult preoperatively and very often it is diagnosed postoperatively at histological examination. However, even histology of PC can be equivocal or frankly misleading. Thus, it is common that the diagnosis of PC is made a posteriori, when local recurrence or distant metastases occur [5]. Although no breakthrough have been made regarding curative options, the greater expansion of the parathyroid carcinoma's molecular pathogenesis knowledge, has led to the development of diagnostic markers that can be helpful in making the diagnosis

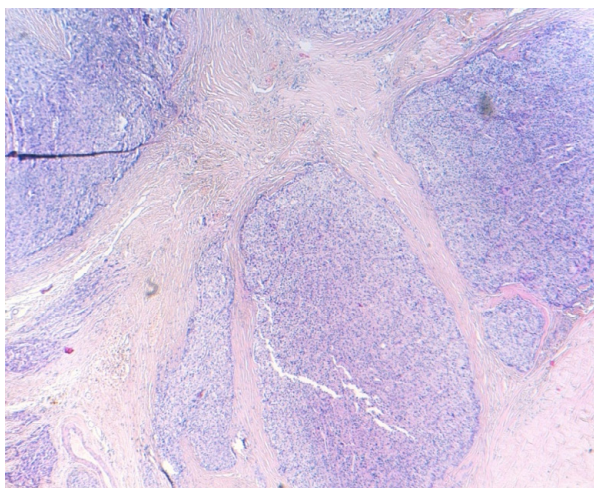
more certain, particularly when the histological presentation is ambiguous.

Surgical resection is the accepted 'gold standard'. There is now a growing consensus on the use of adjuvant radiotherapy as it has been shown to provide a survival benefit [6]. The understanding of the natural history and prognostic factors of the parathyroid carcinoma was for a long time restrained by the rarity of this kind of neoplasia on the one hand, and on the another hand by the paucity of series and case reports in the literature, preventing a clear consensus about its surgical and adjuvant treatment. The aim of this article is to discuss histological criteria's of this tumor, and to make a review of the literature in order to clarify its pathogenesis, clinical features, or pathology diagnosis, and on the basis of this, to shed the light on the management of this condition, for practitioners generally, and for pathologists specifically.

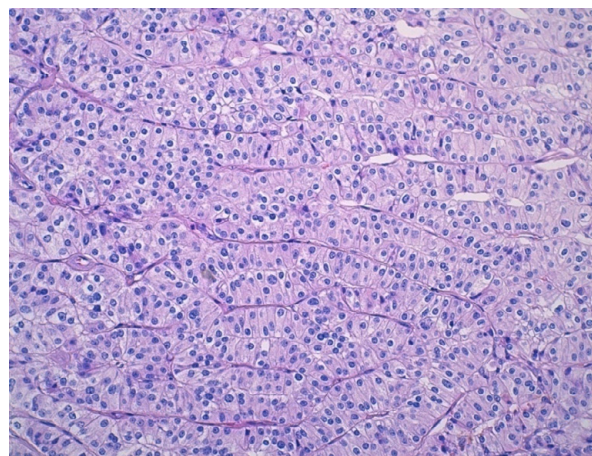
## Case Report

We report the case of a 54-year-old man, who consulted in January 2019 and for whom the laboratory work-up revealed hypercalcemia and elevated serum parathormone. CT scan revealed a mass of the right inferior parathyroid gland, with images of liver metastasis. Right parathyroidectomy was performed. Macroscopically, the parathyroid mass was badly limited, of firm consistency, measuring 3 x 2 x 1.5 cm with a weight of 6.9 grams. On section, it comprised multiple whitish color nodules, of variable sizes, with fibrous and hemorrhagic features. Histological examination revealed a badly limited tumor proliferation, made of uniform cells arranged in lobules, trabeculae and clusters that are separated by dense fibrous bands. A vast network of fine-walled vessels was insinuated between the tumoral trabeculae. (Figure 1 and 2)

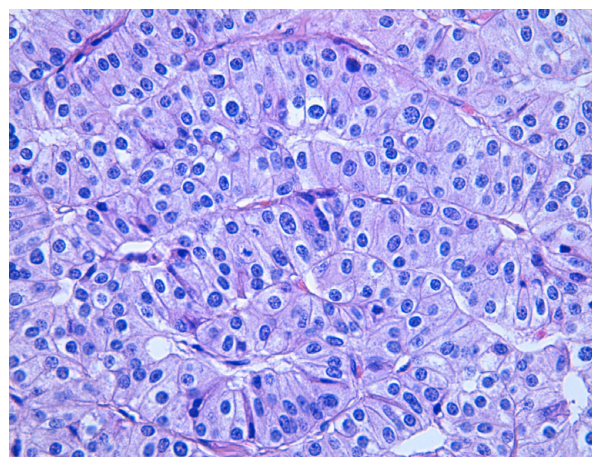
Neoplastic cells were roughly polygonal. Numerous cytonuclear atypias were observed, with irregular, nucleated nuclei and an abundant eosinophilic, sometimes clear cytoplasm. Mitotic activity was estimated at 7 Mitosis per 10 high magnification fields (Figure 3).



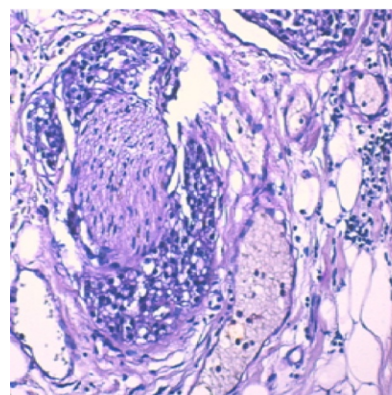
**Figure 1** Tumor proliferation made of uniform cells arranged in lobules, trabeculae and clusters that are separated by dense fibrous bands.



**Figure 2** A vast network of Fine-walled vessels was insinuated between the tumoral trabecular.



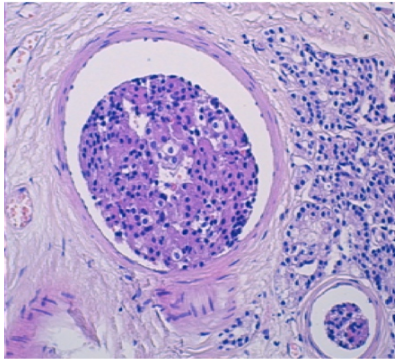
**Figure 3** Neoplastic cells are roughly polygonal, with an atypical nucleus, a prominent nucleoli and an abundant cytoplasm. Mitotic figures are frequent



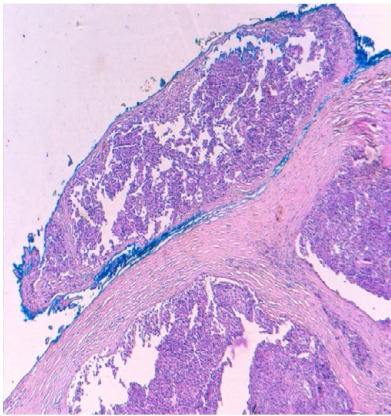
**Figure 4** Vascular and capsular invasions were observed inside the tumor and in the surrounding tissues. The tumors also displays evidence of capsular invasion.

Vascular and capsular invasions were observed inside the tumor and in the surrounding tissues.

The tumors also displayed evidence of capsular invasion (Figure 4, 5 and 6).



**Figure 5** Vascular and capsular invasions were observed inside the tumor and in the surrounding tissues. The tumors also displays evidence of capsular invasion.



**Figure 6** Vascular and capsular invasions were observed inside the tumor and in the surrounding tissues. The tumors also displays evidence of capsular invasion.

However, some tumor cells that exceeded the peripheral celluloadipose tissue were observed, without true invasion of adjacent thyroid tissue. The diagnosis of (PC) was based on the criteria of invasion and local aggressiveness, and the presence of hepatic metastasis.

## Discussion

### Epidemiology

Parathyroid cancer is a rare entity, with an incidence of 0.005% of all registered cases in the The National Cancer Registry Database in the USA [7]. It accounts for 1% of all cases of primary hyperparathyroidism in the United States and most Western European countries [5]. Most cases of parathyroid carcinoma are diagnosed between the ages of 44 and 54 years, which is approximately a decade earlier than the median age of patients with parathyroid adenomas [5,8,9]. It occurs rarely in children, although patients as young as 8 years of age have been reported [10]. In contrast to parathyroid adenomas where women predominate over man by a ratio of 3-4:1, the sex distribution is equal for parathyroid carcinomas [11].

### Etiology

The etiology of parathyroid carcinoma remains unknown.

No predisposing dietary factors have been identified [12]. Inadequate sunlight exposure has been observed to be a risk factor for benign hyperparathyroidism but not for carcinomas, and the potential role for prior neck irradiation is less clear than in PA [1]. Rare cases of PC have been reported in patients with end-stage renal disease [13]. Commonly a sporadic disease, PC has also been reported in familial isolated hyperparathyroidism (FIHP) and, rarely in multiple endocrine neoplasia type 1, MEN1 and MEN2A syndrome [14-17].

### Pathogenesis

Even though the cause of PC remains unclear, a few revealing associations exists between some chromosomal aberrations and the pathogenesis of PC. Kytola *et al.* reported that losses of 1p, 4q and 13q, and gains of 1q, 9q, 16p, 19p and Xq, were more commonly observed in parathyroid carcinoma than in adenomas, whereas the main chromosomal aberration observed in parathyroid adenoma, which is the loss of 11q13 region, is absent in carcinoma. [18]. Several different mutations have also been implicated in the ontogenesis process of parathyroid carcinoma, including the retinoblastoma (Rb), p53, breast carcinoma susceptibility (BRCA2) and cyclin D1/parathyroid adenomatosis gene 1 (PRAD1) genes. But none of these have been assigned a primary role in pathogenesis [19-24].

The hyperparathyroidism jaw tumor (HPT-JT) has provided the best evidence for a defined gene in parathyroid cancer. The responsible gene is known now as *HRPT2* [25]. It codes for a nuclear protein named "Parafibromin" [26,28], which acts as a regulator of transcription. Over expression of this protein causes inhibition of cell proliferation and G1 phase arrest [29,30]. Non-functional isoforms, such as mutations in hereditary hyperparathyroidism jaw tumor syndrome, have anti-apoptotic effects.

Mutation of *HRPT2* was found to be much more commonly present, in cases of sporadic parathyroid carcinoma than in adenomas (up to 76% of carcinomas vs 0.8e1.8% of adenomas) [31,32]. This evidence suggest the significant role, the *HRPT2*'s mutation have in the pathogenesis of parathyroid carcinoma. Furthermore, in order to facilitate early diagnosis and eventual cure for the disease, monitoring on a regular basis, with serum calcium estimation, for individuals with *HRPT2* mutation has been proposed. [33]. However, more studies and a further apprehension of PC oncogenesis will certainly be helpful to promote the early diagnosis and provide new biological targets for more efficient therapy.

### Diagnosis

#### A) Clinical Features

Usual clinical features of patients with functioning parathyroid carcinoma are mainly due to the excessive secretion of Parathormone (PTH). Thus, the clinical presentation is characterized by symptoms of moderate to severe hypercalcemia, associated with renal and bone disease, cardiac arrhythmia and neurocognitive dysfunction [34]. Physical examination is commonly unrevealing, but the finding of palpable cervical mass and laryngeal nerve palsy may predict the presence of PC [2]. Suspicion of PC on a clinical level is determining, for it may guide

the extent of the initial surgery which is crucial for definitive cure. Rarely parathyroid carcinomas may be non-functional [35].

### B) Biochemical Features

As might be expected, parathormone levels are markedly elevated in patients with carcinoma<sup>2</sup>s (3-10 times above the upper normal limit) contrary to those with adenomas in whom parathormone levels are typically more modest [2]. Most patients with adenomas have serum calcium levels within 1 mg/dL above the normal limit, whereas the levels in patients with parathyroid carcinoma are usually in excess of 14 mg/dL [5]. Hypophosphatemia, and hypercalciuria could also be found. PC should be suspected in patients with acute hyperparathyroidism [2]. The combined finding of markedly elevated serum calcium (>12 mg/dl (>3 mmol/l)) and a large parathyroid lesion (>3 cm) (the so-called >3 + >3 rule should raise the suspicion of PC) [36].

### C) Imaging Features

Various imaging modalities such as ultrasonography, Tc99m-labeled sestamibi scintigraphy (MIBI), computed tomography (CT), and magnetic resonance imaging (MRI) can be used to investigate parathyroid carcinoma. These investigations are not diagnostic but are effective in determining the size and location of the abnormal parathyroid gland, which is of value in planning curative resection. The choice of imaging should be guided by the clinical presentation. Neck ultrasound and MIBI help to localize the abnormal parathyroid tissue prior to surgery [37]. At neck ultrasound, a size >3 cm, a lobulated non-homogeneous pattern, marked hypoechogenicity, degenerative changes, calcifications, and irregular halo sign may raise the suspicion of PC [38]. MIBI allows identifying eutopic and ectopic parathyroid tissue as well as recurrent disease, but there are no specific features to distinguish benign and malignant tumors. Both CT and MRI can accurately localize the primary tumor or its recurrence, their relationship with adjacent structures and lymph node metastases [2].

### D) Intraoperative suspicion

The treatment of parathyroid carcinoma is essentially surgical. Given the lack of specific preoperative diagnostic tools,

most parathyroid carcinomas are detected incidentally and postoperatively, during the routine examination of surgical specimens [39]. In some cases, patients initially undergo operation for presumed benign primary hyperparathyroidism, which turned out to be malignant in the postoperative assessment.

Thus, for patient with an unanticipated diagnosis of parathyroid carcinoma, re-operation may be warranted for disease control [39]. In fact, it is reported that 25% of cases of Parathyroid carcinoma are not recognized by the surgeon at the time of initial parathyroidectomy [40]. During surgery the presence of a firm to hard, greyish-white, lobulated mass surrounded by a dense fibrous capsule, with large size (> 3 cm if solid), should raise the suspicion that the lesion is malignant. In addition, infiltration into adjacent structures and the presence of enlarged lymph nodes is highly suggestive of parathyroid carcinoma. Frozen-section analysis is of little value, as the distinction between adenoma and well differentiated carcinoma is very difficult [41].

### E) Histopathology

#### 1) Macroscopic Features

The diagnosis of Parathyroid carcinoma is often challenging, given the fact that a lot of similarities exists between this malignant entity and the benign parathyroid adenoma. However, some differences in the macroscopic evaluation of the specimen received for histological examination, may suggest the malignancy (**Table 1**). Parathyroid carcinomas are usually solitary and arise from a single gland. However, there have been reports of multiglandular involvement [42]. Adenomas are also solitary tumors, although some cases of multiple sites have been reported.

Both right and left inferior glands have been counted as the most common location. Ectopic tumors usually arise from glands in the mediastinum, but ectopic location does not increase the chance of malignant transformation of a gland [9, 43, 44]. In the series of Koea and Shaw, within 155 cases, seventy four cases (48%) occurred in the left inferior gland, although other series have noted a right inferior preponderance. The remaining carcinomas were evenly distributed between the left upper position (20 cases), right lower position (38 cases), and the right upper

**Table 1:** Comparative table between the macroscopic features of parathyroid carcinoma and adenoma.

	Parathyroid carcinoma	Parathyroid adenoma
<b>Number</b>	Solitary, rarely multiple	Solitary, rarely multiple
<b>Size</b>	Average of 3cm diameter	Variable sizes
<b>Weight</b>	Average of 6.7g	Variable, 0.1g to 100g
<b>Form</b>	Irregular	Round to oval, ellipsoid
<b>Encapsulation</b>	May be encapsulated, which makes it indistinguishable from adenomas	Well encapsulated
<b>Cross section</b>	Irregular, poorly limited, lobulated Fibrous and hemorrhagic features possible Areas of necrosis may be apparent as soft yellow foci	Homogeneous, well circumscribed Cystic and hemorrhagic rearrangements possible
<b>Color</b>	grayish-to-white	reddish brown
<b>Consistency</b>	Firm- hard	Soft
<b>Infiltration</b>	May infiltrate the thyroid, adjacent muscles, recurrent laryngeal nerve, trachea or oesophagus	Absent

position (18 cases). Five carcinomas occurred in the mediastinum [45].

Parathyroid carcinoma most often appears as a poorly circumscribed mass, quite large with an average diameter over 3 cm, that may be palpable at presentation [31], and can weigh between 2 and 10 g. (overview rose). In the series of Wang and Gaz, 40 carcinomas ranged in size from 1.5 to 6.0 cm (average of 3 cm) with weights ranging from 1.5 to 27 g (average of 6.7 g) [9]. Adenomas on the other hand, are usually well limited, with variable sizes and their weight can reach up to 100 g. Occasional carcinomas may be grossly encapsulated and may resemble parathyroid adenomas.

On cross-section, parathyroid carcinomas are irregular, lobulated, with firm to hard consistency, and have a grayish-to-white color [45]. Occasional areas of necrosis may be apparent as soft yellow foci (over view noir 2005). While adenomas have a round-oval, or ellipsoid form, homogenous with a soft consistency and a reddish brown to tan in appearance [46]. Cystic and hemorrhagic features may be found.

Carcinomas are densely adherent to the adjacent soft tissues of the neck or the thyroid gland. It can infiltrate the ipsilateral lobe of the thyroid, the strap muscles and even the recurrent laryngeal nerve, trachea or esophagus [9]. Cases of synchronous parathyroid carcinoma and adenoma have been reported [47]. In our patient, parathyroid carcinoma was suspected macroscopically because of the badly limited character of the mass, with 3 cm diameter and a weight of 6.9 grams, and the finding of variable sizes, whitish color nodules on the cross section, associated with fibrous and hemorrhagic features.

## 2) Microscopic Features

Histopathological diagnosis of parathyroid carcinoma can be obvious in some cases, but others can be extremely difficult for the reason that plenty of features overlap with those of parathyroid adenoma. Indeed, in a large series of patients with metastases, up to 50% of them were initially classified as beginning tumors. [48]. several criteria's should be considered.

### Growth pattern

The growth pattern varies. Typically, a parathyroid carcinoma shows a thick fibrous capsule from which, thick acellular fibrous bands appear to extend into the central regions of the tumor and tend to divide it into sharply outlined, irregular shaped and sized compartments, creating a lobular appearance [49]. Most carcinomas display a solid growth pattern with tumor cells arranged in diffuse masses, small nests, or trabecular [50]. Sometimes, palisading or rosette-like growth may be present [49]. Other tumors may demonstrate follicular or spindle cell patterns, with rare tumors having a predominantly papillary growth pattern. Exceptionally, tumors may have a carcinosarcomatous pattern [50].

### Tumor cells

Chief cells are almost always the predominant cell type. Sparse oxyphil and transitional oxyphil cells may be found and, very rarely, they may predominate [46]. Many carcinomas show mild to

moderate variation in nuclear size and shape; however, occasional tumors show marked degrees of pleomorphism with coarsely granular chromatin and macronucleoli. The cytoplasm may vary from clear to faintly eosinophilic, and occasional tumors may be composed of oncocyctic cells exclusively. Tumors composed of an Admixture of chief cells and oncocytes are relatively common [49]. Some tumors may show necrosis, a feature that should alert the pathologist to the possibility of carcinoma. [49]. This feature should be distinguished from the atypia encountered in parathyroid adenomas and other benign endocrine tumors.

### Mitosis

The mitotic activity in carcinoma is generally low and common; however, it is also detected in PA [2]. A higher mitotic activity has been observed in poorly differentiated tumors and is associated with a poor prognosis [51]. Atypical mitosis usually indicates malignancy

### Capsular invasion, vascular invasion and perineural invasion

The most specific features are capsular invasion vascular invasion, perineural invasion, or direct extension into adjacent soft tissues, but these can still be subjective to assess [52]. Invasion of the capsule is rather common. Less frequently vascular invasion also occurs in 10–15% of cases [53]. Whereas perineural invasion is exceptional.

### 3) Histological Difficulties Usually Encountered

In 1973, Schantz and Castleman [54] were the first to set criteria of malignancy, which can help to differentiate parathyroid carcinoma from adenoma, including:

- Lobular architectures separated with thick fibrous bands.
- Mitotic figures
- Capsular invasion
- Vascular invasion.

However, these findings are inconstantly observed in cases of PC and may also be observed in parathyroid adenomas [55]. Therefore, the lack of specific criterion of malignancy can be source of challenging histological difficulties, encountered in many levels of the histological examination. According to the World Health Organization, no specific has yet been identified.

### Growth pattern

Fibrous bands were present in 90% of the case studied by Schantz and Castleman. Such fibrosis is not specific though, and may also be seen in large adenomas that have undergone degenerative changes [52]. Bondeson *et al.* [55] have noted that as many as 1/5 of carcinomas do not show the typical fibrosis and lobular growth pattern; these features can also be seen in parathyroid hyperplasia and adenomas.

### Tumor cells atypia

The epithelial cells of a carcinoma are larger than normal chief cells, with round to oval nuclei; the cytoplasm may be clear or oncocyctic. The nuclei are usually quite monotonous with

pleomorphic nuclei being more typical of an adenoma [49, 54]. McKeown *et al.* [56] have pointed out that cellular pleomorphism and atypia are not reliable indicators of malignancy in endocrine tumors. Sometimes, however, a carcinoma may show marked nuclear pleomorphism with coarsely clumped chromatin and prominent nucleoli, distributed diffusely in contrast to the patchy pleomorphism of adenoma nuclei [57].

## Mitosis

Although mitotic activity is present in approximately 80% of parathyroid carcinomas, mitotic figures are also relatively common in adenomas and hyperplasia. Snover and Foucar [58] identified mitoses in 70% of adenomas, and similar findings have been reported by San Juan *et al.* [59]. And so, care must be taken by the pathologist in assessing mitotic activity in parenchymal cells, which have to be distinguished from mitoses in endothelial cells and other stromal elements. Atypical mitosis however, correlates more strongly with carcinoma [49, 52].

## Capsular invasion

The capsules of carcinomas are generally thicker than those of adenomas of similar size [34]. True capsular invasion is highly predictive of malignancy and is said to be seen in 60% of cases. It is characterized by irregularly shaped and pointed tongue-like protrusions of parathyroid parenchyma through the capsule. This may be mimicked by entrapment of parenchymal cells within the capsule in adenomas [49, 52]. When assessing for capsular invasion, the pathologist should be wary of over-interpreting “pseudo invasion” of entrapped tumor cells, present within the capsule of adenomas, or by a multilobulated or multinodular growth pattern.

## Vascular and perineural invasion

Vascular invasion is present in 10–15% of carcinomas [54]. The diagnosis of vascular invasion should be made only when tumor is present within capsular vessels or in vessels in the soft tissue surrounding the gland. To qualify as true invasion, tumor must be present within a vascular channel and must also be at least partially attached to its wall. This can easily be mimicked by artefactual separation of parathyroid epithelial cell groups from stroma when fresh specimens are handled for intraoperative frozen sections [60].

An endothelial covering may or may not be present. Perineural invasion is more objective to interpret but is relatively uncommon finding. In front of all histological difficulties that can stand in the way of parathyroid carcinoma diagnosis, Invasion of the thyroid and/or adjacent soft tissues, and metastases remains the only unequivocal features of parathyroid malignancy [61].

In our case, the neoplastic proliferation was poorly limited, arranged in lobules, trabeculae and clusters separated by dense fibrous bands. Numerous cytonuclear atypias were observed, with irregular, nucleolated nuclei and an abundant eosinophilic, sometimes clear cytoplasm. Mitotic activity was estimated at 7 Mitosis per 10 high magnification fields. Vascular and capsular invasions were observed inside the tumor and in the surrounding tissues, with evidence of capsular invasion. The diagnosis of (PC)

was based on the criteria of invasion and local aggressiveness, and the presence of hepatic metastasis.

## 4) Immunohistochemistry

Immunohistochemistry may improve the diagnostic accuracy of parathyroid carcinoma. Parathyroid adenomas and carcinomas are generally positive for broad-spectrum cytokeratin's. Additionally, they are positive for parathyroid hormone, chromogranin, and synaptophysin but are negative for thyroglobulin, calcitonin, and thyroid transcription factor-1 [62].

This immunohistochemical profile is of value in the distinction of parathyroid carcinomas from thyroid malignancies and other tumor types that may be present in this anatomic site. However, the distinction of benign and malignant parathyroid tumors is fraught with difficulty, and to date, limited data are available in equivocal cases. Increased labeling of cell cycle-associated proteins (Ki-67, cyclin D1) has been shown in parathyroid carcinoma as compared to adenoma, but overlap among these tumors has limited the utility of this approach [28,63].

Evaluation of *HRPT2* gene abnormalities seems to be a more promising diagnostic tool [64]. Loss of heterozygosity or mutation at the *HRPT2* gene and loss (total or focal) of parafibromin staining have been reported in the large majority of parathyroid carcinomas but very rarely in adenomas [28,64–68]. The retinoblastoma (RB) protein has been analyzed extensively in parathyroid tumors by immunohistochemistry. Cryns *et al* reported that parathyroid adenomas were consistently positive for the RB protein, whereas carcinomas were negative. Other studies, however, have been unable to demonstrate consistent differences between carcinomas and adenomas with respect to RB expression. [69, 70]

## F) Differential Diagnosis

The main differential diagnosis is parathyroid adenoma, but parathyroid hyperplasia, thyroid cancer or, more rarely, metastasis of renal cell carcinoma, must also be excluded.

## A) Parathyroid adenoma

This benign entity is much more common in women, whereas carcinoma occurs with equal sex ratio. Historically, the criteria for adenoma have generally included a pushing border with an absence of intralesional fibro adipose tissue, complete circumscription with a rim of “normal” parathyroid at the periphery, and an absence of lobular growth. The current definition is no longer purely histologic, but rather includes the effect of gland removal, with intraoperative PTH decrease and subsequent return to normocalcemia and long-term cure [71].

While most adenomas are composed of chief cells, a small percentage may be oxyphilic and rare “water-clear” adenomas have also been described. Lipoadenoma are another exceedingly uncommon entity, with fewer than 50 reported cases [71]. The **Tables 1 and 2** sums up the main differences between PC and PA

## 2) Atypical Adenoma

The term “atypical adenoma” has been used to describe a subset of parathyroid tumors that share some of the features of carcinomas (fibrosis, mitoses, questionable capsular invasion) but

**Table 2:** Comparative table between histological features of parathyroid carcinoma and adenoma.

	Parathyroid carcinoma	Parathyroid adenoma
<b>Growth pattern</b>	<ul style="list-style-type: none"> <li>Thick fibrous capsule with fibrous bands dividing it into irregular compartments.</li> <li>Mostly diffuse masses, lobules, nests, or trabeculae</li> <li>Follicular, spindle cell patterns, papillary, palisading or rosette-like growth patterns may be present.</li> </ul>	<ul style="list-style-type: none"> <li>A single nodule, which is usually oval or bean-shaped and surrounded by a very thin fibrous capsule.</li> <li>Nest, trabeculae</li> <li>Papillary and follicular pattern possible</li> <li>rim of residual parathyroid tissue outside the capsule</li> <li>Fibrous band may be present (degenerative changes)</li> </ul>
<b>Tumor cells Atypia</b>	<ul style="list-style-type: none"> <li>Mostly chief cells, rarely oxyphil cells</li> <li>Mild to moderate atypia</li> <li>Sometimes marked pleomorphism diffusely distributed</li> </ul>	<ul style="list-style-type: none"> <li>Predominantly either chief cells or oxyphil cells, sometimes both. Rarely water clear cells</li> <li>Sometimes abundant fat cells: Lipoadenoma (rare variant)</li> <li>Often patchy nuclear pleomorphism</li> </ul>
<b>Mitosis</b>	<ul style="list-style-type: none"> <li>Low mitotic activity common</li> <li>Higher mitotic activity observed in poorly differentiated tumors and is associated with a poor prognosis</li> <li>Atypical mitosis</li> </ul>	<ul style="list-style-type: none"> <li>May be present, should be of normal form.</li> </ul>
<b>Capsular invasion</b>	<ul style="list-style-type: none"> <li>Common</li> </ul>	<ul style="list-style-type: none"> <li>“pseudo invasion” of entrapped tumor cells within the capsule may mimic a true capsular invasion</li> </ul>
<b>Vascular invasion</b>	<ul style="list-style-type: none"> <li>Present in 10-15% cases</li> <li>Tumor present within a vascular channel, partially attached to its wall</li> </ul>	<ul style="list-style-type: none"> <li>Absent</li> </ul>
<b>Perineural invasion</b>	<ul style="list-style-type: none"> <li>Rarely</li> </ul>	<ul style="list-style-type: none"> <li>Absent</li> </ul>
<b>Infiltration</b>	<ul style="list-style-type: none"> <li>Thyroid, and adjacent tissue, distant metastases muscles,</li> </ul>	<ul style="list-style-type: none"> <li>Absent</li> </ul>

that lack unequivocal evidence of invasive growth [72]. According to Seethala et al [4], the presence of 2 or more of the following attributes will lead to this diagnosis: incomplete invasion of the capsule, fibrous bands, pronounced trabecular growth, mitotic activity greater than 1 per 10 high-power fields, and tumor necrosis [71].

There is apparently debate as to whether abnormal mitoses should be acceptable in the diagnosis of atypical adenoma; their presence should certainly lead to further investigation toward the elimination of malignancy [52]. Guiter and DeLellis [73] studied a series of 24 tumors that were classified as atypical adenomas based on the presence of peritumoral and intratumoral fibrosis, mitotic activity, questionable capsular invasion, and cytologic atypia. In this series, the mean tumor size was 2.2 cm with a mean weight of 6.5 g. The most common features in this group were entrapment of tumor within the capsule (87%), intratumoral fibrosis (75%), hemosiderin deposition (58%), cyst formation (50%), mitoses (29%), and peritumoral fibrosis (25%). Capsular invasion (without extension beyond the capsule) and intratumoral vascular invasion were each present in single cases, but none of the cases had evidence of necrosis. The average follow-up in this group was 4 years, and none of the patients has developed evidence of recurrent or metastatic disease. These findings suggest that the behavior of atypical adenomas, as defined in this study, does not differ from that of adenomas of usual type.

## Treatment

### Surgery

Surgery is the only curative treatment for parathyroid carcinoma

and consists of complete resection of the primary lesion at the time of initial operation. For this reason, both preoperative suspicion and intraoperative recognition are of great importance [5]. The finding of a parathyroid tumor with gross features suggestive of malignancy should lead to “en bloc” resection. Generally, an open biopsy of such a lesion during surgery is contraindicated because of the risk of capsular rupture with seeding of the operative site [34].

As it often happens, the diagnosis of parathyroid carcinoma is made after initial parathyroid surgery on the basis of pathology, then, the management plan may become more problematic. When telling histologic features are absent, the patient is normocalcemic and the diagnosis is only based on equivocal pathology, immediate reoperation is not indicated, because the simple complete resection of the tumor may turn out to be curative. However, such patients should be monitored closely with regular measurement of serum calcium and PTH levels [48].

### Chemotherapy

Several chemotherapy protocols have been attempted (vincristine, cyclophosphamide, and actinomycin D, and Adriamycin alone or in combination with cyclophosphamide and 5-fluorouracil), but none of them has proved to be effective [45,74]. Chemotherapy remains disappointing and has no role in the management of patients with parathyroid carcinoma.

### Radiotherapy

In selected patients, adjuvant radiotherapy appears to decrease the rate of local recurrence [75] and may improve the disease-free survival, particularly in high-risk patients. Radiofrequency ablation alone or in combination with arterial embolization has

successfully been used in the treatment of hepatic and lung metastases in two patients with PC [76,77].

## Prognosis

The prognosis of PC is variable. Patients with complete resection of the tumor at initial surgery carry the best prognosis. The mean time to recurrence is usually 3 years. Once the tumor recurs, a complete cure is unlikely, although prolonged survival is still common with palliative surgery. A 5- and 10-year survival rate of 78.3 and 49%, respectively, has been reported [2]. Negative prognostic factors for survival were higher calcium level at recurrence, numbers of neck recurrences, the use of several calcium-lowering medications, and simple parathyroidectomy as initial surgery, presence of lymph nodes or distant metastases, and nonfunctioning PC. In addition, patients whose tumor carries a CDC73 mutation, and/or loss of parafibromin or CASR expression have a worse survival rate [2].

## Conclusion

Parathyroid carcinoma is a rare disease, considered as the least common cause of primary hyperparathyroidism.

Because of the rarity of this tumor type, its biology, natural history, and prognosis are poorly understood

The disease is indolent but progressive. The most common presentation is complications of hypercalcaemia, but other ways of presentations are possible.

The main differential diagnosis is the parathyroid adenoma, and the differentiation between the two entities can be very difficult in some cases. Recent attempts to distinguish between benign and malignant disease both by genetic and immunohistochemical analyses are promising.

Given the lack of specific features, the diagnosis of parathyroid carcinoma continues to be a difficult challenge at the time of presentation. Thus, a multidisciplinary approach, considering all clinical, biochemical and histopathological aspects of the disease, offers the best chance for accurate diagnosis, before the appearance of metastases.

Invasion of the thyroid and/or adjacent soft tissues, and metastases remains the only unequivocal pathological features of parathyroid malignancy.

Surgery is the only curative option. The best opportunity to cure parathyroid carcinoma is to diagnose it before or at the time of parathyroid surgery and for the tumor to be completely removed at the time of the initial operation.

Other treatments such as chemotherapy, has not been reported to be effective, whereas radiotherapy may reduce the risk of recurrence.

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