Parathyroid Carcinoma:
Diagnosis and Clinical Implications

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ABSTRACT

Parathyroid carcinoma is a rare type of endocrine cancer, with significant morbidity and mortality associated with parathyroid hormone (PTH)-mediated hypercalcemia. Concerning clinical features for parathyroid cancer include severe hypercalcemia (albumin-corrected calcium >3 mmol/L), a palpable neck mass (>3 cm), 3rd/2nd generation PTH assay ratio (>1), and intraoperative suspicion of local invasion or regional metastasis. A definite diagnosis of malignancy is rendered when a parathyroid tumor presents one of the following clinicopathological features: (1) vascular invasion, (2) perineural invasion, (3) gross invasion into adjacent anatomical structures, and/or (4) metastasis. In difficult cases, the use of ancillary biomarkers is critical to establish an accurate diagnosis. Recent advances in molecular pathology have uncovered the important role of *CDC73/HRPT2*, a tumor suppressor gene deregulated in parathyroid carcinomas. Loss of nuclear and/or nucleolar expression of parafibromin (the gene product of *CDC73/HRPT2*) is now regarded as a diagnostic, prognostic and predictive biomarker for parathyroid carcinoma. Furthermore, over 15-20% of seemingly sporadic parathyroid carcinomas have underlying germline *CDC73/HRPT2* mutations. As a result, many centers have integrated the use of ancillary biomarkers, notably parafibromin staining, in their routine practise. Radical surgery with en bloc resection has emerged as a primary treatment modality in parathyroid cancer, achieving cure in some patients. However, in those with inoperable disease, there remains a dire need for new therapies, as current treatments are largely ineffective. This review provides an update on the current knowledge of parathyroid carcinoma and highlights its exciting changes in endocrine practice.

Key Words: Parathyroid neoplasms, Hyperparathyroidism, Atypical adenoma, HRPT2 protein, Parafibromin protein

INTRODUCTION

Parathyroid carcinoma is a highly aggressive endocrine tumor, with an annual incidence of less than 1 per million (1-8). Over 90% of patients present with excess parathyroid hormone (PTH), representing <1-5% of all patients with primary hyperparathyroidism (1,8-11). Despite recent developments in biochemical, radiological and molecular techniques, parathyroid carcinoma remains an elusive disease to recognize clinically and even pathologically in some cases (1,8,11-14). Accurate diagnosis is critical because parathyroid malignancies require more aggressive surgery to decrease the risk of disease recurrence (7,8,15-19). Furthermore, clinical acumen is paramount to ensure their early detection because untreated hyperparathyroidism can lead to severe hypercalcemia and end-organ damage, including renal failure, bone disease, cardiac arrhythmia and neurocognitive dysfunction (1,8,20). When the diagnosis is delayed, patients can present with inoperable or metastatic parathyroid carcinoma, which is often refractory to medical therapy and carries a fatal outcome (1,4,8).

In recent years, an oncologic surgical approach, comprising of at least "en bloc" resection of the parathyroid lesion with ipsilateral hemithyroidectomy, has emerged as the standard of care in parathyroid carcinoma (3,7,8,15,17,20-23). Given the lack of specific preoperative diagnostic tools, most parathyroid carcinomas are detected incidentally and postoperatively, during the routine examination of surgical specimens (1,2,8,11,12,15,17,24-26). Thus, all parathyroid gland(s) excised for hyperparathyroidism should be assessed carefully for malignancy. In patients with an unanticipated diagnosis of parathyroid carcinoma, re-operation may be warranted for disease control (1,2,8,11,12,15,17,24-26). While most cases occur sporadically, a significant portion (at least 15%) can present with germline *CDC73/HRPT2* mutations (2,4,8,27). Therefore, genetic testing should be offered to all patients with parathyroid cancer, given its important implications for affected patients and their family members (2,4,8,11,27,28). This review provides an update on the current knowledge of parathyroid carcinomas and highlights the clinicopathological correlates of this rare disease.

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CLINICAL AND BIOCHEMICAL FEATURES

Clinically, parathyroid carcinoma can occur at any age, with a peak in the fifth decade of life (1,8-10,29-31). It occurs with equal frequency in both sexes, in contrast to the female predominance reported in parathyroid adenomas (1,8-11,25,29,30,32). Although the distinction between benign and malignant parathyroid disease remains challenging at the clinical level, certain clinical features can raise a physician's suspicion for an underlying malignancy (Table I) (1,8-11,25,29,30,32). These findings will be highlighted here.

Most parathyroid carcinomas (>90%) secrete excess parathyroid hormone (PTH). Commonly reported symptoms relate to overt hyperparathyroidism, including renal (nephrolithiasis, nephrocalcinosis), skeletal (bone pain, osteopenia), and neurocognitive involvement (anxiety, depression) (1,4,8-10,19,29,33-35). In the past, both benign and malignant parathyroid disease would present symptomatically in affected patients (1,4,8-10,19,29,30,33-37). However, with the advance of routine serum calcium testing, the majority of patients with benign hyperparathyroidism are now diagnosed incidentally and asymtomatically (1,4,8-10,19,29,30,33-37). In other terms, the presence of the presence of overt renal and skeletal involvement is unusual in the modern presentation of benign parathyroid disease and should alert a clinician to exclude an underlying malignancy (1,4,8-10,19,29,30,33-38). Other clinical findings, which are worrisome but non-specific for parathyroid carcinoma, include a palpable neck mass, concomitant jaw tumor,

Table I: Risk factors for parathyroid carcinoma

Intraoperative suspicion of local invasion and/or regional metastasis*
Albumin-corrected calcium levels >3 mmol/L*
3rd/2nd generation PTH assay ratio >1*
Palpable neck mass (lesion > 3 cm)*
Infiltration and/or calcifications on neck ultrasound*
Suspicion of metastatic disease on sestamibi and/or CT scan*
PTH >3 times the upper limit of normal
Significant bone and/or kidney involvement
Positive personal or family history (HPT-JT)
Concomitant jaw tumor
Hoarseness and/or neck pain

* Indicates high-risk features that may warrant a referral to an endocrine surgeon. **PTH:** Parathyroid hormone, **HPT-JT:** Hyperparathyroidism-jaw tumor syndrome, **MEN:** Multiple endocrine neoplasia syndrome.

neck pain and hoarseness (1,8,10,11,39,40). A personal or family history of hypercalcemia and/or genetic syndromes (hyperparathyroidism-jaw tumor syndrome, multiple endocrine neoplasia syndrome and other familial parathyroid diseases) should also alert the physician (1,8-11,28,39-42). Rarely, patients with parathyroid carcinoma may present in a state of life-threatening hypercalcemia, with renal failure, cardiac arrhythmia, and/or neurological involvement (coma) (1,8-11,28,39-42).

Biochemically, parathyroid carcinomas tend to present with severe hypercalcemia (albumin-corrected calcium levels >3.0 mmol/L) as a result of overt hyperparathyroidism (PTH levels >3 times the upper limit of normal) (1,8,10,15,29,43). In contrast, benign parathyroid disease generally behave more indolently, with mild hypercalcemia (within 1 mg/dL of normal) and mild-moderate PTH levels, with the exception of large parathyroid adenomas and familial syndromes associated with more florid phenotype (8-10,30,38,42,44-49). Furthermore, secondary hyperparathyroidism can present with similar features and should be excluded, either clinically (history of lithium/thiazide intake, gastrointestinal disease/calcium malabsorption) or biochemically (presence of kidney disease, vitamin D deficiency, hypocalcemia) (9,10,50). Recently, some investigators described a promising method by which a 3rd-generation to 2nd-generation PTH ratio >1 can help predict whether a parathyroid tumor is more likely to be malignant in the preoperative setting (sensitivity: ~75-82%; specificity: ~97-98%) (1,8,24,51-54). Although this technique has not been widely adopted at this time, it has been proposed on the basis that parathyroid carcinoma tends to overproduce amino-PTH, which is recognized by 3rd-generation but not 2nd-generation PTH assays (1,8,24,51-55). Rarely, "non-functioning" parathyroid carcinomas have also been described in less than 10% of cases (8,11,26,35,56).

RADIOLOGICAL FINDINGS

In addition to clinical and biochemical information, certain radiological features can help distinguish benign from malignant parathyroid disease in the preoperative setting (1,8,21,33,57-60). However, in the absence of unequivocal metastatic disease, the decision to pursue more radical surgery on clinical suspicion alone remains controversial (1,8). Nonetheless, in all patients with primary hyperparathyroidism, radiological investigations is warranted to assess the extent of disease for treatment planning (9,10,21,30,61). In particular, extra-parathyroid imaging, comprising of renal ultrasonography and dual-energy X-ray absorptiometry, is used to assess for PTH-

related renal disease (nephrolithiasis, nephrocalcinosis) and bone disease (decreased bone density), as these findings may warrant surgical intervention even in the absence of clinical symptoms (9,10,21,30,38,61,62).

Neck ultrasonography is a non-invasive and relatively inexpensive tool that should be considered in all patients with overt hyperparathyroidism (1,8,33,57-60,63). Sonographic evidence of infiltration and/or calcification is strongly associated with parathyroid malignancy, whereas the absence of suspicious vascularity, presence of a thick capsule and heterogeneity within the parathyroid glands is more in keeping with benign parathyroid disease (1,8,33,57,59). The recent development and adoption of 99technetium-labelled sestamibi (99mTc-sestamibi) scintigraphy has enhanced our ability to distinguish between single-gland and multi-gland parathyroid disease (1,8,21,30,33,57-60,64-68). Increased and prolonged uptake of sestamibi is generally observed in abnormally "hyperfunctioning" parathyroid tissue (1,8,21,30,33,57-60,64-68). When compared to conventional imaging modalities, the sestamibi scan has the advantage of localizing ectopic hyperfunctioning parathyroid tissue; if present, this finding should prompt the physician to consider the possibility of a metastatic parathyroid carcinoma (1,8,10,15,21,30,33,57-60,64-68). Although not routine, CT scan of the neck and chest may also be indicated in some cases to assess for disseminated disease (1,8,39).

HISTOPATHOLOGICAL FEATURES

Given the current lack of specific preoperative diagnostic tools, parathyroid carcinomas are frequently diagnosed during the routine examination of parathyroidectomy specimens (1,7,15,17,33,69). Therefore, all parathyroid gland(s) resected for primary hyperparathyroidism should be carefully assessed for malignancy, which can occur in <1-5% of patients (1,8,11,14,15,25,31,33,39). Accurate recognition of parathyroid carcinoma is critical to guide treatment decision making (see section "Treatment and Prognosis") (1,7,8,15,33). Other pathological correlates in primary hyperparathyroidism include parathyroid adenoma (80-85%) and hyperplasia (10-15%) (11,14,25,32,44,70,71). Abnormal proliferation of parenchymal cells typically results in grossly enlarged cellular gland(s), characterized by increase in weight (> 40-60 mg) and size (> 6-8 mm) (11,13,14,26,32,44,70,72-74). Rapid intraoperative assay is extremely helpful in confirming the complete removal of abnormal "hyperfunctioning" parathyroid tissue (demonstrated by >50% decrease in circulating PTH level 10-15 min after surgical excision), and can help distinguish between single-gland and multi-gland

disease (10,11,21,22,75-77). Both parathyroid adenomas and carcinomas present as uniglandular parathyroid proliferations (11,13,14,26,32,44,70,72,73). Thus, at the time of intraoperative consultation, the distinction between parathyroid adenoma and carcinoma is often difficult or even impossible, if the tumor does not show grossly evident invasion into surrounding organs (1,8,11,14,17,19,73). Since the latter is generally identified by the surgeon, the role of intraoperative consultation is often limited.

In comparison to parathyroid adenomas, parathyroid carcinomas tend to be relatively large and bulky (mean diameter of 3.4 cm and weight of 19.15 g) (15), with variable degrees of fibrosis and irregular borders (1,11,13,14, 26,44,70,72,73,78,79). Common morphological findings include broad fibrous bands, necrosis and solid growth pattern (Figure 1). The presence of increased mitotic activity, atypical mitoses and nuclear atypia should raise the suspicion for an underlying malignancy (Table II) (11,13,14,26,44,70,72,73). However, it should be noted that not all parathyroid carcinomas present these features, and the identification of these findings also is not diagnostic for malignancy (11,13,14,26,44,70,72,73). For instance, a variety of conditions can be associated with broad band-forming fibrosis (11,26,70,72,73). Similar to artifacts occurring after fine-needle aspiration biopsy (FNAB) of the thyroid gland, patients with a previous manipulation of the parathyroid glands (FNAB for preoperative cytological assessment or PTH measurement) may show worrisome histological alterations including fibrous bands with or without hemosiderin deposits (Figure 2A) (80). Similar changes have also been described in individuals with primary hyperparathyroidism that underwent therapeutic ethanol injection (26,81). Moreover, band-forming fibrosis

Figure 1: Broad fibrous bands, solid growth and infiltrative growth are common morphologic features of parathyroid carcinomas. However, not all parathyroid carcinomas present these features.
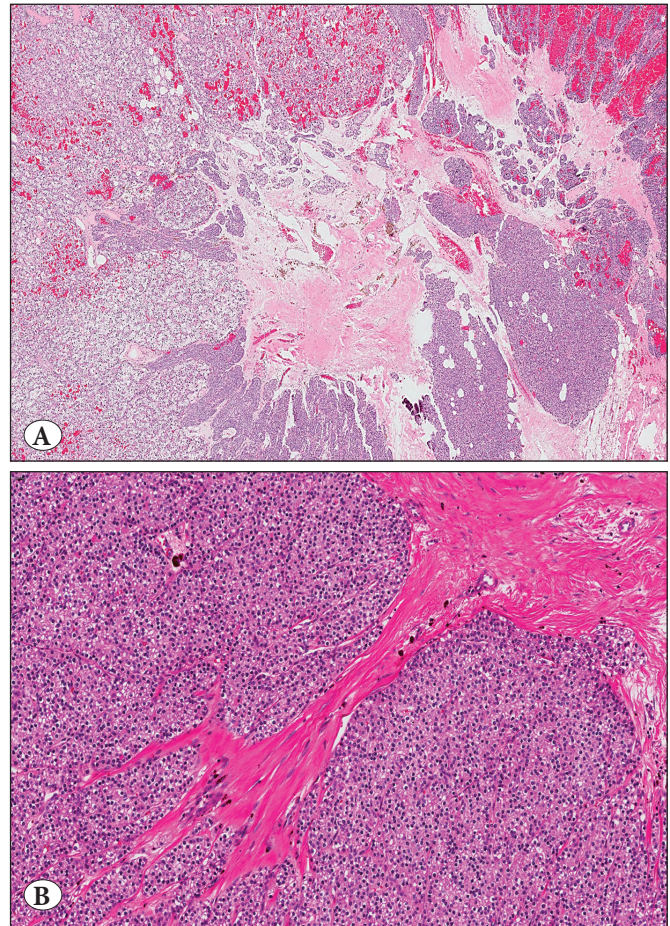
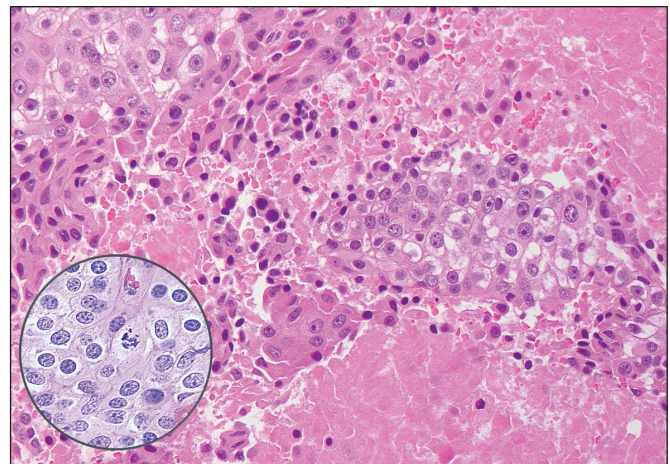**Table II:** Diagnostic features of parathyroid carcinoma

Diagnostic histopathological features (if ≥ 1 feature is present)	
Unequivocal vascular invasion	
Perineural invasion	
Gross invasion into adjacent anatomic structures	
Metastasis	
Worrisome histopathological features (non-diagnostic)	
Necrosis*	
Increased mitotic activity (>5/50 HPF)*	
Macronucleoli*	
Atypical mitoses	
Nuclear atypia	
Solid growth pattern	
Broad fibrous bands	
Ancillary biomarkers (to support a diagnosis of carcinoma in borderline cases)	
Parafibromin (-) **	PGP9.5 (+)
Rb (-)	Galectin-3 (+)
p27 (-)	p53 (+)
Bcl-2a (-)	MIB-1 (Ki67) >5%
APC (-)	
mdm2 (-)	

* Indicates triad of high-risk histopathological features. ** Complete loss of parafibromin expression is almost diagnostic for parathyroid carcinoma. (-) indicates loss of expression, (+) indicates overexpression.

Figure 2: A) Fibrous bands are not specific to parathyroid carcinoma and can be identified in benign parathyroid proliferations following previous FNA biopsy (either for cytological assessment or PTH measurements) and **B)** in patients with chronic renal failure-related parathyroid hyperplasia.

can occur in parathyroid proliferations from patients with MEN 1 or MEN 4 syndrome, lithium intake or chronic renal failure-related parathyroid hyperplasia (Figure 2B), parathyroiditis and large adenomas with spontaneous degeneration (11,26,44,70,72,73,82). Some experts have proposed a triad of high-risk histopathological features (foci of coagulative necrosis, macronucleoli and mitotic activity >5/50 high-power fields) to help select tumors which are more prone to malignant behavior (Figure 3) (11,74,83). However, increased mitotic activity, and lesional cells within a thickened fibrous capsule can also be identified in multiglandular parathyroid disease (11,26,70,72,73,79). Necrosis can also occur in a parathyroid proliferation with a previous biopsy or injection, especially in those with predominant oncocytic cytomorphology (11,26,70,72,73,83). It is unfortunate that despite the importance of clinicopathological correlation, many pathologists are still faced with diagnosing a parathyroid lesion in the absence of relevant clinical information (73,84).

Figure 3: Triad of high risk histopathological features: Foci of coagulative necrosis, prominent macronucleoli, and mitotic activity >5/50 high-power fields.

Practicing pathologists should recognize the significant overlap in the cytomorphological features of parathyroid carcinomas and some benign parathyroid proliferations (adenoma and hyperplasia) (11,12,26,70,72,73,83). Therefore, a histological diagnosis of parathyroid carcinoma should only be rendered when a parathyroid neoplasm shows any of the following features: a) vascular invasion (Figure 4A), b) perineural invasion, c) invasion into the adjacent anatomic structures (Figure 4B) and d) metastasis (Table II) (11,12,15,26,35,44,70,72,73,79,83,85,86). It is important to note that not all parathyroid carcinomas present with widely invasive growth and high grade proliferative changes (11,15,26,70,85) However, many of these parathyroid carcinomas simulating adenomas can be distinguished at the morphologic examination by the accurate identification of unequivocal angioinvasion, characterized by the presence of tumor cells invading through a vessel wall and intravascular tumor cells admixed with thrombus (Figure 4A) (11,12,15,70,73,85,86).

As a reflection of the diagnostic challenges associated with some borderline parathyroid proliferations, the 2004 WHO

Figure 4: The diagnosis of parathyroid carcinoma is rendered histologically when a parathyroid tumor shows unequivocal evidence of vascular invasion **(A)**, perineural invasion, invasion into the surrounding tissues **(B)**, and metastasis.

classification defined a category of "atypical parathyroid adenomas", representing parathyroid neoplasms without unequivocal signs of vascular or capsular invasion, but with some morphological features suspicious for parathyroid carcinomas, including broad fibrous bands with or without hemosiderin deposits, mitoses, and neoplastic cell groups in a thickened fibrous capsule (11,12,28,79,83,87-90). This controversial diagnostic category is almost non-existent in modern practices after clarifying relevant clinical information (e.g. underlying hyperplasia, MEN1 syndrome, medication history, etc..), applying the rigid criteria to identify vascular invasion, and using ancillary tools (8, 11,12,27,28,55,73,85,88,89,91). In this specific subgroup, recently discovered biomarkers through molecular pathology have enhanced our ability to differentiate parathyroid carcinomas from adenomas with atypical features (8,11,12,27,55,73,85,88,89,91). These tools with be discussed in the subsequent section. In summary, "atypical parathyroid adenomas" encompass both benign parathyroid proliferations with worrisome reactive changes, as well as some parathyroid carcinomas with insufficient diagnostic features at the morphologic level (11,12,73,85,87-89).

ANCILLARY BIOMARKERS

Many experts speculate that the concept of "atypical parathyroid adenoma" stems from the limitations of the histopathological examination (11,12,26,79,83). With the discovery of novel biomarkers and molecular biological techniques, surgical pathologists are increasingly able to better classify these lesions in their appropriate categories (either benign or malignant) to optimize patient care (2,8,11,12,27,28,55,85,88,89,91-98). Methylation profile of parathyroid tumors has been shown to distinguish parathyroid adenoma from parathyroid carcinoma (99-103). Moreover, over 70% of sporadic parathyroid carcinomas have been linked to sporadic mutations in the *CDC73/HRPT2* gene (2,28,92,95,104,105). While most laboratories are far away to adopt these molecular testing as a part of their routine patient care, the use of immunohistochemical biomarkers has been shown to be useful to reach a definite diagnosis in most cases to enhance patient care (2,8,11,12,27,28,55,85,88,89,91-98). Based on the current literature, an immunohistochemical signature comprising of loss-of-expression of parafibromin, retinoblastoma protein (Rb), p27, Bcl-2a, mdm-2, and APC, along with positivity for galectin-3, overexpression of p53, and increased MIB-1 (Ki67) proliferation index (>5%) has been suggested to confirm a diagnosis of malignancy in a parathyroid tumor with worrisome histopathological features (Figure 5A-F) (Table II) (2,8,11,12,27,28,55,73,85,88,89,91-98). It should
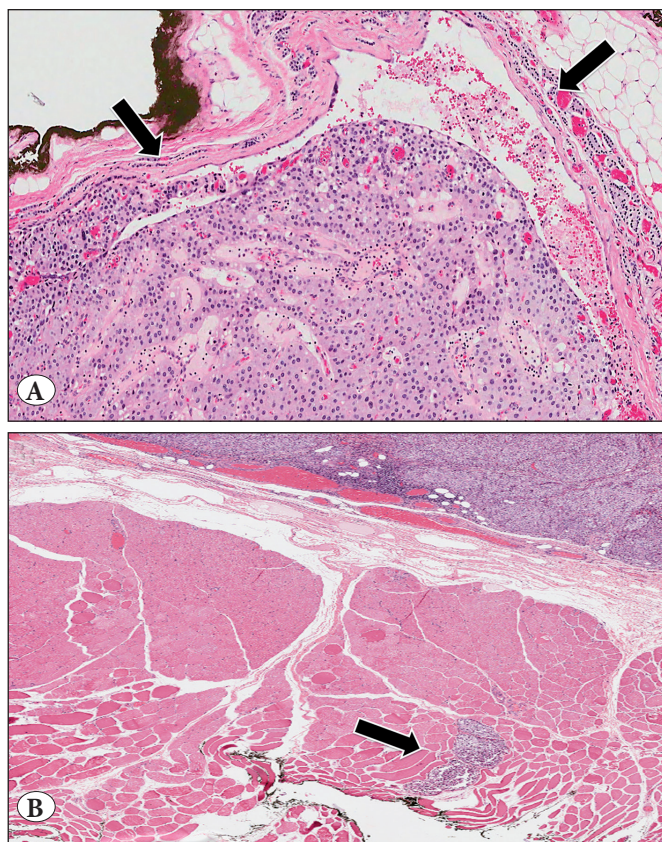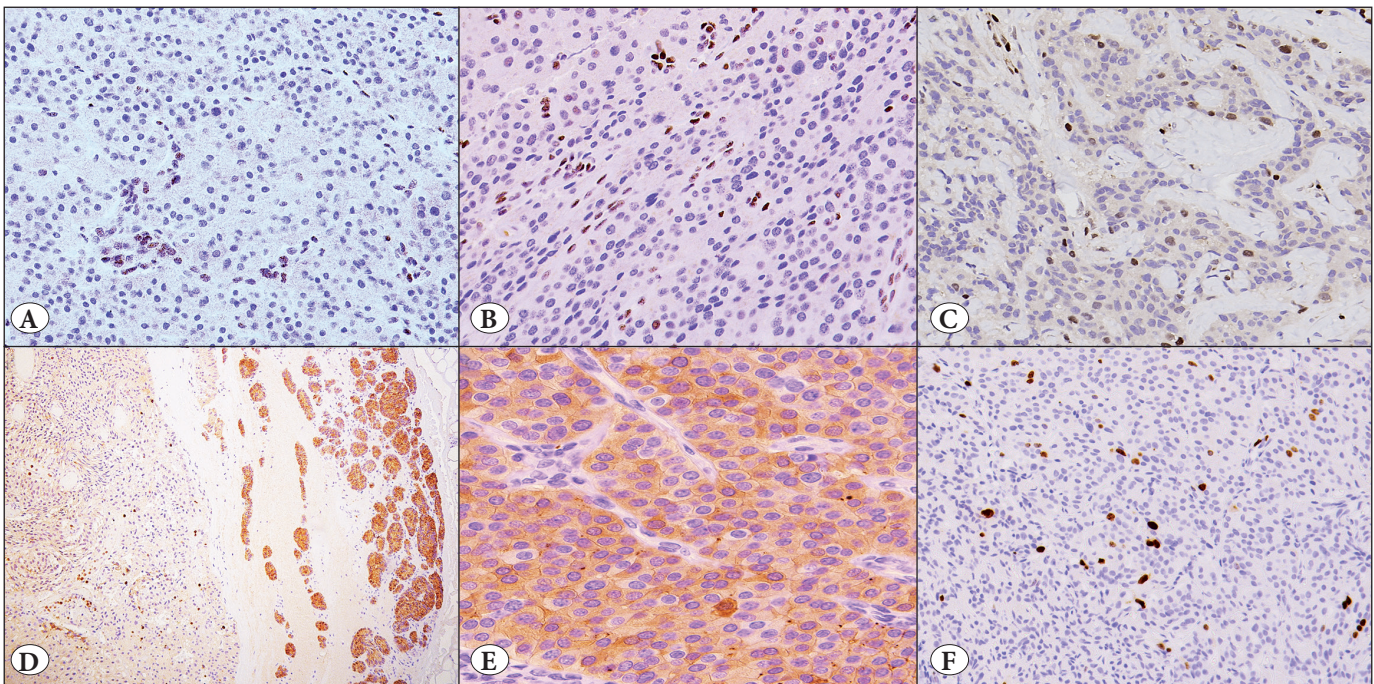
Figure 5: Biomarkers of parathyroid carcinoma. Global loss of nuclear and nucleolar parafibromin expression is regarded a reliable diagnostic marker of parathyroid carcinoma **(A)**. Parathyroid carcinomas can also show loss of Rb **(B)**, p27 **(C)**, and APC **(D)**. In solitary gland disease, the presence of galectin-3 expression **(E)** along with a MIB-1 labeling index >5% **(F)** can be identified in malignancy.

be noted that these new biomarkers were derived from recent genetic studies on the pathogenesis of parathyroid carcinoma, which will be discussed in the subsequent section ("Pathogenesis and molecular features"). In our experience, parafibromin, galectin-3, and bcl-2a are the most helpful ancillary biomarkers (73,85). In addition to serving a diagnostic role in tumors with complete loss of parafibromin (in the appropriate clinical and pathological setting), loss of parafibromin expression appears to be a prognostic biomarker for parathyroid carcinomas (1,27,28,73,85,88,91,92,94,96,106,107). Furthermore, it can help select high-risk patients for genetic testing of germline *CDC73/HRPT2* (1,28,89). Prognostically, when compared to those with intact parafibromin expression, parathyroid carcinomas with loss of parafibromin expression have a significantly higher risk of disease recurrence, a decreased 5-year survival of 59% and a decreased 10-year survival of 23% (28,89,106). In light of these findings, some groups suggest that it may be reasonable to perform routine parafibromin biomarker assessment in all cases of pathologically confirmed parathyroid carcinomas (1,28,73,85,94,106).

In addition to primary malignancies of the parathyroid (parathyroid carcinoma), secondary (metastatic or infiltrating) malignant neoplasms from various organs can also deposit in the parathyroid glands (35). Very recently, Shifrin et al. highlighted the importance of considering metastatic disease in the parathyroid glands as these are often overlooked and discovered incidentally at autopsy or during surgery for primary hyperparathyroidism (13,14,35,108-114). For instance, direct extension from thyroid carcinomainto the parathyroid glands may occur in up to 4% of patients with thyroid carcinoma (35,108,110). Most parathyroid glands are located within the thyroid pseudocapsule or within the thyroid gland, and intrathyroidal parathyroid carcinomas can mimic a variety of tumors including medullary thyroid carcinoma, thyroid paraganglioma, secondary (metastatic) neuroendocrine carcinoma and poorly differentiated thyroid carcinoma. In challenging cases, immunohistochemistry can confirm the origin of parathyroid (11,13,44,70,73). Positivity for PTH (strong cytoplasmic staining in chief cells), low molecular weight cytokeratins (CK8, CK18, CK19) and chromogranin-A are helpful in supporting the primary parathyroid origin of the tumor (26,32,79). One has to remember that PTH or PTH-related peptide can also be expressed in other neuroendocrine tumors (73,115-117). Therefore, application of transcription factors (e.g. GCM-2, GATA-3) expressed in parathyroid tissue can support parathyroid origin (Figure 6), along with a positive PTH expression (73,118-122).
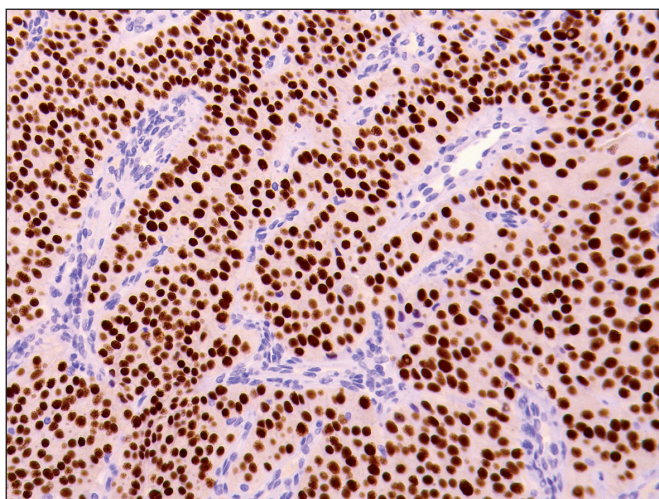
Figure 6: Confirmation of parathyroid origin. While most laboratories use PTH immunohistochemistry to distinguish a parathyroid origin, the demonstration of positivity for GATA-3 or GCM-2 also supports the origin of parathyroid when dealing with a PTH-producing neuroendocrine carcinoma.

PATHOGENESIS AND MOLECULAR BIOLOGY

While the etiology of parathyroid carcinoma remains large-ly unknown, it appears to be a complex interaction between environmental factors, causing sporadic alterations, and in-herited genetic predispositions (1,2,8,28,41,55,73,85,100). Contrary to other solid tumors, a definite hyperplasia-ade-noma-carcinoma progression sequence has not been estab-lished in parathyroid tissue (11,12,26,41,100,123-125). The lack of convincing data is largely attributed to the extreme rarity of parathyroid carcinomas (1,11,33,73,123). How-ever, if an adenoma-carcinoma progression truly prevailed, this would offer a valid explanation as to why parathyroid carcinomas are so uncommon, why parathyroid carcino-mas are so uncommon, because this would suggest that most parathyroid tumors are detected and resected prior to becoming malignant, at the benign "hyperfunctioning" adenoma stage. This hypothesis is further supported by the fact that most parathyroid carcinomas (>90%) produce ex-cess PTH, suggesting that hormonal oversecretion typically occurs simultaneous or prior to the development of malig-nancy (11,26,56). Nonetheless, a parathyroid hyperplasia-neoplasia progression sequence has been described in some patients with refractory secondary hyperparathyroidism (tertiary hyperparathyroidism) and/or familial disease (1, 2,8,11,12,25,26,28,31,33,73,86,100,106,126,127). The main pathways involved in parathyroid tumorigenesis, including aberrant CaSR, cyclin D1 and Wnt/β-catenin signalling, as well as their associated alterations will be highlighted here (55,100,128).

CaSR Signalling and PTH Oversecretion

Calcium sensing-receptor (CaSR) signalling plays a critical role in the regulation of parathyroid hormone (PTH) secretion by parathyroid chief cells (9,100,129-132,132). Aberrant inactivation of CaSR signalling has been linked to proliferative parathyroid disorders, including hyperplasia and neoplasia (50,55,100,127,132-145). For instance, patients with tertiary hyperparathyroidism tend to present with multifocal clonal proliferations (nodules/adenomas) in a background of polyclonal diffuse parathyroid hyperplasia (11,26,50,55,100,136,138,140,143,144). This neoplastic transformation has been linked to deregulated CaSR signalling, as demonstrated by loss-of-expression of calcium sensing-receptor (CaSR) and vitamin D receptor (VDR) (11,26,50,55,100,136,138,140,143,144). Deriving from studies of other organs, inactivation of CaSR is thought to induce cyclin D1 and possibly Wnt/β-catenin signalling (55,137,146-148). Furthermore, aberrant CaSR signalling has been reported in a large subset of parathyroid adenomas (50,55,100,127,132-145). Rare parathyroid carcinomas have also been reported with deregulated CaSR signalling from prolonged secondary/tertiary hyperparathyroidism (1,8,11,26,33,73,86,100,126,127,149). Although the exact mechanism underlying aberrant CaSR signalling remains unknown, genetic and epigenetic mechanisms underlying *CaSR* and *VDR* genes are infrequent in parathyroid tumors (55,100,133,137,146-148). These findings suggest that there are likely undiscovered mutations causing aberrant CaSR signalling, found in a large subset of parathyroid tumors (11,26,50,55,100,136-138,140,143,144).

Cyclin D1 Signalling and Parathyroid Tumorigenesis

In contrast to CaSR signalling, cyclin D1 signalling is involved in cell cycle progression (41,55,100,131,132,150-153). Aberrant activation of cyclin D1 signalling has been well described in a large subset of parathyroid tumors, implicating altered *CCND1/PRAD1*, *CDKIs*, and *ZFX* genes (2, 11, 28, 41, 55, 100, 131, 132, 150-155). *CCND1/PRAD1* (11q13) is a proto-oncogene encoding the cyclin D1 protein, a holoenzyme thought to inactivate the tumor-suppressor retinoblastoma protein (Rb) (41, 55, 100, 131, 132, 150-153, 156). Somatic activating mutations of *CCND1/PRAD1* with overexpression of cyclin D1 protein has been reported in up to 40% of parathyroid adenomas, and up to 90% of parathyroid carcinomas (11,32,41,55,100,131,132,145,150-153,157,158). In order to clarify the mechanisms underlying a putative progression from benign to malignant parathyroid tumors, Zhao et al. compared 7 parathyroid carcinomas to 14 adenomas; they reported a gain in copy number of the *CCND1* gene in carcinomas, and showed a

significant increase in CCND1 gene expression both at the mRNA level and immunohistochemically (153). While this study has While this study has limitations limitation, to our knowledge it is one of the first of its kind to explore copy number alterations in cyclin D1 signalling and its putative role in parathyroid adenoma-carcinoma progression.

Concurrent to the discovery of the parathyroid oncoprotein cyclin D1, its binding partners in cell cycle regulation, cyclin-dependent inhibitors (CDKIs), were also found to be altered in a subset of patients with hyperparathyroidism (11,32,41,55,85,100,131,132,159-161). Both germline and somatic inactivating mutations in CDKI-encoding genes (*CDKN1B* encoding p27kip1 protein, *CDKN1A* encoding p21Cip1, *CDKN2B* encoding p15Ink4b, *CDKN2C* encoding p18Ink4c, and *CDKN2D* encoding p19) were identified in parathyroid neoplasms (11,32,41,55,85,100,131,132,159-162). Of these, the tumor suppressor function of *CDKN1B* (12p13.1) and its gene product, p27kip1, have been well documented: germline inactivating mutations of *CDKN1B* gives rise to multiple endocrine neoplasia type 4 syndrome (MEN-4, also known as "MEN-X"), whereas somatic inactivating mutations in *CDKN1B* were reported in some parathyroid tumors, with loss of p27 protein expression (11,32,41,55,85,93,100,131,159,162). Moreover, immunohistochemical studies have reported a 3-to-4 fold decrease of p27 expression in parathyroid carcinomas in comparison to adenomas (11,85,93,159). Epigenetic alterations of CDKIs (*CDKN2A, CDKN2B*) have also been reported in parathyroid tumors (99,100,103,128,163). Recently, recurrent mutation of *ZFX*, a putative proto-oncogene thought to be a downstream target of cyclin D1, has also been found in a subset of parathyroid adenomas (~5%) (154,155). Activating mutations in *RET* proto-oncogene (10q11.2), a putative inducer of cyclin D1 signalling, is also described in some parathyroid tumors from patients with multiple endocrine neoplasia type 2A (MEN-2A) (11,100,124,145,164-166).

Wnt/β-Catenin Signalling and Parathyroid Tumorigenesis

Deregulation of Wnt/β-catenin signalling is an important tumorigenesis pathway in many organs, including the parathyroid glands, by inducing cyclin D1 overexpression (55,99,100,128,145,167-171). Several genetic and epigenetic alterations causing excess Wnt/β-catenin signalling have been uncovered in parathyroid neoplasms, implicating *MEN1, CTNNB1, SFRP1, SFRP2, SFRP4, GSK3B*, and *APC* genes (55,88,99,100,128,145,167-169,172-177). Of these, inactivation of *MEN1* (11q13) and its gene product, menin, is the most frequently described alteration, reported in 20-40% of parathyroid adenomas and rare carcinomas

(11,100,145,178-181). Menin protein is thought to play a tumor suppressor role by preventing nuclear translocation of β-catenin, thereby decreasing Wnt/β-catenin signalling (182,183). Mutation of *CTNNB1* has also been described in 2-5% of parathyroid adenomas, resulting in aberrant accumulation of β-catenin in tumor cells, although it remains unclear whether this step requires additional epigenetic alterations (55,100,172,176,176,177). Furthermore, hyper-methylation of secreted fizzled-related protein (SFRP)-encoding genes (*SFRP1, SFRP2, SFRP4*; thought to serve tumor suppressor functions in Wnt/β-catenin signalling) have been reported in a subset of parathyroid carcinomas (99,100,103,128). Loss-of-expression of glycogen synthase kinase 3-β (GSK3B), a putative tumor suppressor protein in Wnt/β-catenin signalling, has been reported in both adenomas and carcinomas, although the exact genetic mechanism remains unclear (169). Recently, the role of the tumor suppressor adenomatous polyposis coli (*APC*) gene, which is inactivated in the cancer predisposition familial adenomatous polyposis syndrome (FAP), was also explored in the parathyroid glands (88,99,100,103,128,169,184). Loss of its gene product, APC protein, was reported in parathyroid carcinomas (Figure 5D), whereas it is generally preserved in adenomas (88). While both adenomas and carcinomas often show hypermethylation of promoter 1A region of the *APC* gene; the preserved expression of APC protein and *APC* mRNA in adenomas could be partially explained by increased expression of promoter 1B region of the *APC* gene in parathyroid adenomas (88,100,168,184). These findings show the complex interaction between genetic and epigenetic alterations causing excess Wnt/β-catenin signalling in a putative adenoma-carcinoma progression sequence in the parathyroid glands (55,88,99,100,128,145,167-170,184).

Parafibromin and Parathyroid Carcinoma

In addition to the previously described alterations in CaSR, cyclin D1 and Wnt/β-catenin signalling, aberrant parafibromin expression is commonly described in parathyroid neoplasms, specifically parathyroid carcinomas (2,11,12,28,32,73,85,88,89,91,92,94-96,100,106). When used in the appropriate clinical and histopathological setting, parafibromin is currently the most specific biomarker for diagnosis and prognosis of parathyroid carcinoma, and helps stratify high-risk patients for genetic testing (11,12,28,32,73,88,89,91,92,94-96). Parafibromin protein, encoded by the *CDC73/HRPT2* gene (1q31.2), is thought to serve a critical tumor suppressor role in parathyroid tissue through several molecular mechanisms, by interacting with the polymerase associated factor 1 (PAF1) complex in histone

ubiquitination/methylation, mediating gene transcription, inducing apoptosis, inhibiting cyclin D1 signalling, regulating Wnt/β-catenin signalling and growth factor gene transcription (2,11,12,28,32,73,85,88,89,91,92,94-96,100,106). Given its central role in regulating cellular function, it is unsurprising that bi-allelic inactivation of *CDC73/HRPT2* gene and complete loss of parafibromin expression almost inevitably leads to parathyroid cancer (Figure 5A) (2,11,12,28,32,88,89,91,92,94-96,100,106). In particular, its role in a hyperplasia-neoplasia (adenoma-carcinoma) progression sequence has been well documented in patients with an inherited inactivated copy of *CDC73/HRPT2* (hyperparathyroidism-jaw tumor syndrome; HPT-JT or isolated familial hyperparathyroidism), who develop parathyroid carcinomas in the setting of pre-existing "cystic" adenomas/nodular hyperplasia in up to 20% of cases (2,11,12,28,32,88,89,91,92,94-96,100,106,185). Although bi-allelic inactivation of *CDC73/HRPT2* (either due to inherited/somatic, or somatic/somatic "hit") and complete loss of parafibromin expression is almost always seen in parathyroid carcinomas, partial loss of parafibromin expression (single allelic inactivation of *CDC73/HRPT2*) is less equivocal and may occur in both benign and malignant parathyroid tumors, (2,11,12,27,28,32,89,91,92,95,96,100,104,105,185-187) hence the critical role of confirming each diagnosis by integrating clinical and histopathological findings, as well as other biomarkers of parathyroid carcinoma (2,11,12,27,28,32,86,88,89,92,93,97,101,102,180-182).

DNA Hypermethylation, MicroRNA Deregulation and Other Molecular Alterations

Recently, DNA methylome and microRNAome uncovered additional mechanisms underlying parathyroid tumor formation (99,100,103,128). From these studies, substantial evidence emerged showing increased hypermethylation of specific CpG islands in malignant tumors when compared to benign ones, supporting a putative adenoma-carcinoma progression sequence in parathyroid tissue (99,100,103,128). In addition to previously described epigenetic silencing of *APC*, *SFRP* and *CDKI* genes, parathyroid tumors were shown to have aberrant hypermethylation of putative tumor suppressor genes *RASSF1A*, *HIC1*, *RIZ1*, and *WT1*, with down-regulation of their gene products (99,100,103,128,188). *RASSF1A* (Ras association domain protein family protein 1) gene (3p21) is thought to serve a tumor suppressor role by inhibiting cyclin D1 expression (184,189,190). *HIC1* (17p13.3) also serves a tumor suppressor role, by repressing transcription of histone deacetylase SIRT1 in p53 signalling to preserve genomic

stability (128,188). *WT1* (Wilms' tumor 1) gene encodes an important tumor suppressing transcription factor in cell growth and differentiation (99,100,103,128). Similarly, *RIZ1* (retinoblastoma-interacting zinc finger gene) serves a tumor suppressor function by regulating cell cycle in normal parathyroid tissue (99,100,103,128,185,191).

Aberrant expression of embryonic-related microRNAs was also reported in a series of parathyroid tumors, suggesting that reactivation of embryonic transcription factors may play a role in their pathogenesis (128,192). Recently, the use of whole-exome sequencing shed light on additional mutations in parathyroid carcinomas (100,164,180,193,194). In particular, a recent study of 22 parathyroid carcinomas and 40 parathyroid adenomas revealed recurrent mutations of *PRUNE2* in 4/22 (18%) parathyroid carcinomas and only a single adenoma was found to have rare missense polymorphism of this gene (193). Alterations involving *mTOR*, *MLL2*, *CDKN2C*, *THRAP3*, *PIK3CA*, and *EZH2* (mediating histone methyltransferase) were also reported in parathyroid carcinomas (100,164,180,193,194).

TREATMENT AND PROGNOSIS

In recent years, an oncologic surgical approach, comprising of en bloc resection with ipsilateral hemithyroidectomy, has emerged as the treatment of choice in localized parathyroid cancer (Table III) (1,8,15-17,19,22,39,195-197). Although controversial, central neck dissection has also been recommended on the basis that it does not impose significant risk to the patient, since lymph node metastasis at level VI can occur in ~15-30% of cases (1,8,15-17,22,39,197). Following this approach, the pathological confirmation of R0 resection margins (no cancer cells at margins and/or >1 mm from the edge) confers the highest chance of cure (1,8,15-18,22,39,197). The benefit of adjuvant therapy, including chemotherapy and radiotherapy, remains unclear (1,8,15,39). Some reports have proposed that postoperative radiotherapy may reduce the risk of local recurrence in patients with positive or close surgical margins, although this approach should not replace revision surgery in patients with inadequate resection margins (Table III) (1,4,8,15-18,22,39,197,198).

Although a formal AJCC/UICC TNM staging system for parathyroid cancer has not been established, a recent prognostic classification system has been proposed on the basis of a 2010 study by Schulte and colleagues (1,7,8,15,17,18,39). High-risk patients were defined as having one of the following clinicopathological criteria: vascular invasion, lymph node metastasis or invasion of the trachea, oesophagus or major cervical vessels

Table III: Prognostic and predictive factors in parathyroid carcinoma

Type of initial surgery	Clinical considerations
En bloc resection with ipsilateral hemithyroidectomy +/- central neck dissection is recommended	Consider revision surgery in unanticipated postoperative diagnosis of parathyroid carcinoma, to ensure an appropriate oncologic surgical resection
Histopathological features associated with worse prognosis	
Positive surgical margins	Consider revision surgery $\pm$ radiotherapy
Vascular invasion	Consider close surveillance for recurrence
Lymph node and/or distant metastasis	Consider surgical resection of metastases (if feasible)
Invasion of trachea, oesophagus and/or major cervical vessels	Consider close surveillance for recurrence
Gross capsular rupture	Consider close surveillance for recurrence
Prognostic markers associated with worse prognosis	
Complete loss of parafibromin expression	Genetic counselling and close surveillance for recurrence
Persistent PTH assay ratio >1 or PTH excess after surgery	Repeat imaging to localize residual disease $\pm$ revision surgery (if feasible)
Germline mutation of *HRPT2/CDC73**	Genetic counselling $\pm$ additional investigations for HPT-JT

* Genetic counselling should be offered to all patients with parathyroid carcinoma; if a germline inactivating mutation of *HRPT2/CDC73* is detected, genetic testing should also be offered to the affected patients' relatives; close surveillance and additional investigations (abdominal ultrasound, jaw radiography) may be warranted to exclude hyperparathyroidism-jaw tumor syndrome (HPT-JT).

(1,7,8,15,17,18,39). These patients had a significantly increased risk of disease recurrence and 50% disease-specific mortality at 5 years, compared with no deaths in the low-risk group (7,8,39). In particular, the presence of unequivocal vascular invasion is probably the single most important predictor of distant recurrence or metastasis, and has been proposed by some experts to warrant more aggressive postoperative surveillance and possible systemic therapy in future trials (1,7,8,18,39,85). Conversely, the absence of angioinvasion strongly predicts the absence of distant metastases (1,7,8,18,39,85). In terms of molecular testing, some experts advocate for routine parafibromin testing in all parathyroid carcinomas (1,11,27,28,92,94,95,106). In addition to being a valuable diagnostic marker, there is emerging evidence that complete loss of parafibromin is associated with a worst prognosis in definite parathyroid carcinomas (28,89,92,106). Those with loss of parafibromin expression should also be considered for genetic testing, as patients with germline *CDC73/HRPT2* mutations may require closer surveillance and screening for family members (Table III) (1,2,8,11,27,28,92,94,95,106).

In patients with inoperable disease, the prognosis remains poor, as current treatment modalities are largely ineffective (1,4,8). The most common approach pertains to symptom relief through control of PTH-mediated hypercalcemia, which is the main cause of morbidity and mortality in these patients (1,8). Biphosphonates offer short-term relief (up to several months), by inhibiting osteoclast-mediated bone resorption (1,8). Recently, denosumab, a monoclonal antibody against "receptor activator activator of nuclear factor κB ligand (RANKL)", has also been used with promising results (199-202). Calcimimetic agents (cinacalcet), allosteric modulators of calcium-sensing receptor (CaSR), have also been shown to reduce calcium levels on a short term basis in patients with inoperative parathyroid cancer (203-207). Rapid treatment with aggressive saline infusion and loop diuretics are required to counter the life-threatening effects of hypercalcemia in hypercalcemic crisis (1,8). Other interventions, including mithramycine, plicamicyn, calcitonin, glucocorticoids, and radiofrequency ablation offer variable benefits (1,8). More recently, immunotherapy has emerged as a promising treatment modality in parathyroid cancer, whereby induction of neutralizing autoantibodies against human PTH significantly improved PTH and calcium levels in some patients with metastatic parathyroid carcinoma (1,8,208-210).

CONCLUSION

Parathyroid carcinoma is a rare diagnosis with critical implications for affected patients (Table III). Clinical acumen is paramount to ensure early detection and timely treatment to prevent morbid complications of PTH-mediated hypercalcemia. In recent years, an oncologic surgical

approach has been shown to provide the best outcomes in parathyroid cancer. To this effect, new tools have been developed to enhance our ability to detect these aggressive lesions. Patients with high-risk features of parathyroid malignancy, including severe hypercalcemia (albumin-corrected calcium >3 mmol/L), a palpable neck mass (>3 cm), and/or 3rd/2nd generation PTH assay ratio (>1), should be referred to an endocrine surgeon for consideration of more radical surgery. Occasionally, an unanticipated postoperative diagnosis of parathyroid carcinoma may occur, prompting revision surgery to optimize disease control. While most parathyroid carcinomas are diagnosed morphologically by correlating with clinical information, a panel of biomarkers (parafibromin, Rb, p27, Bcl-2a, APC, p53, galectin-3, and MIB-1/Ki67 proliferation index) may be helpful in challenging cases. Genetic testing should be offered to all patients with parathyroid carcinomas, since germline *CDC73/HRPT2* mutation can occur in >15% of cases. In patients with inoperable disease, the prognosis remains poor and current treatments are largely ineffective. Recent advances in molecular pathology offer promising therapeutic targets implicating cyclin D1, Wnt/B-catenin and CaSR signalling, which have been found to be deregulated in a significant proportion of parathyroid carcinomas.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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