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Current Knowledge on Atypical Parathyroid Tumors and Emerging Strategies for Risk Stratification

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Atypical parathyroid tumors (APTs) are an uncommon subset of parathyroid neoplasms that carry substantial clinical relevance because of their histological and clinical resemblance to parathyroid cancer. Despite this importance, the diagnosis of APTs remains persistently challenging, even for experienced pathologists. Their histopathological features overlap extensively with those of parathyroid cancer, and at present, no specific immunohistochemical markers are available that can reliably distinguish between these entities. Moreover, the clinical manifestations of APTs are indistinguishable from those of parathyroid adenomas or true parathyroid cancer. A major concern is the uncertain malignant potential of APTs, which contributes to difficulties in prognostic prediction and the absence of standardized surveillance guidelines. Although most published studies suggest a benign clinical course for the majority of APTs, these conclusions are frequently limited by relatively short follow-up durations. This limitation is underscored by several case reports describing recurrence or metastatic disease in patients initially diagnosed with APTs, subsequently prompting reclassification as parathyroid cancer. Recent advances in molecular technologies, particularly RNA sequencing and genomic profiling, have facilitated novel approaches to risk assessment and prognostic evaluation in APTs. This review aims to provide a comprehensive overview of the diagnosis, clinical manifestations, and current molecular strategies used to assess the malignant potential of APTs.

Keywords: Atypical parathyroid tumor; Parathyroid neoplasms; Parathyroid tumor; Risk stratification

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INTRODUCTION

Primary hyperparathyroidism (PHPT) is a common endocrine disorder, with the vast majority of cases arising from a single parathyroid adenoma (approximately 85%) or parathyroid hyperplasia (approximately 10%) [1,2]. Atypical parathyroid tumors (APTs) represent a rare but clinically important etiology, accounting for roughly 1% of PHPT cases [3]. These tumors are

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of particular concern because of their potential to behave similarly to parathyroid carcinoma, a malignancy associated with a poor prognosis. However, uncertainty surrounding the malignant potential of APTs complicates the development of optimal therapeutic approaches and appropriate long-term surveillance strategies.

The definitive diagnosis of APTs is based on histopathological evaluation, yet this process is fraught with significant challenges [4]. APTs occupy an intermediate position along the spectrum of parathyroid neoplasia, precluding clear classification as either benign adenoma or overt carcinoma. They commonly demonstrate concerning architectural and cytological features, including thick fibrous bands, increased mitotic activity, and capsular or vascular involvement, while lacking definitive criteria for malignancy such as broad capsular invasion or established metastatic disease. This diagnostic ambiguity is further compounded by the absence of distinctive clinical features that reliably differentiate APTs from other parathyroid disorders.

In response to this diagnostic uncertainty, major consensus organizations have taken steps to formally recognize tumors with uncertain malignant potential. In 2018, the American Joint Committee on Cancer introduced a 'Tis' category within the staging system for parathyroid carcinomas to designate tumors with indeterminate malignant behavior [5]. Similarly, the 2022 World Health Organization (WHO) classification formally replaced the historical term 'atypical parathyroid adenoma' with 'APT,' more accurately reflecting the intermediate and non-binary nature of these lesions [4].

Despite these formal acknowledgments, the optimal clinical management of APTs remains a subject of ongoing debate. While several studies suggest that APTs typically follow a benign and indolent course with a low risk of recurrence [6,7], other reports present conflicting evidence, describing cases initially diagnosed as APT that later recurred or metastasized and ultimately required reclassification as parathyroid carcinoma [8,9]. This uncertainty highlights a central clinical dilemma: although vigilant postoperative surveillance is crucial for patients at higher risk, excessively intensive follow-up for truly indolent lesions may contribute to patient anxiety and unnecessary interventions. Consequently, the development of reliable criteria for individualized risk stratification is essential; however, no universal consensus currently exists regarding the diagnosis, treatment, or long-term monitoring of APTs.

In this review, we summarize the current understanding of APTs, including diagnostic criteria, variability in clinical behavior, and emerging strategies for improved risk stratification, with particular emphasis on molecular and genomic approaches that may better define malignant potential in these diagnostically challenging tumors.

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

The incidence of APTs among patients undergoing surgery for PHPT has been reported to range from 0.5% to 4.4% [2,6,10-13]. Nevertheless, the true prevalence remains uncertain. This uncertainty arises from the rarity of these tumors and from historical variability in diagnostic definitions and classification criteria. Consequently, the available literature is dominated by small case series or single-center studies, most of which include only a limited number of patients [12,14,15].

APTs typically present in the setting of PHPT, with classic clinical manifestations that include hypercalcemia, reduced bone mass, and nephrolithiasis. Although the prevalence of low bone mass and nephrolithiasis does not appear to differ significantly between APTs and parathyroid adenomas, serum calcium and parathyroid hormone (PTH) levels in patients with APTs are generally higher than those observed in parathyroid adenomas but lower than those seen in parathyroid cancer [2,3,6,16]. In a study by Galani et al. [3] involving 107 patients with typical adenomas and 10 patients with APTs, symptomatic hypercalcemia was significantly more frequent in the APT group than in patients with benign parathyroid adenomas (60.0% vs. 12.1%, $P=0.001$). In contrast, other clinical manifestations, including nephrolithiasis, osteoporosis, neurocognitive symptoms, and impaired renal function, did not differ significantly between the two groups.

When compared with parathyroid cancer, APTs demonstrate significantly lower PTH levels, as shown in a study that included 31 carcinoma cases and 23 APT cases [16]. The proportions of patients presenting with renal stones, bone pain, and neuropsychiatric symptoms—including depression, memory loss, and decreased concentration—were not significantly different between the two groups. A large cohort study by McCoy et al. [6], which included 814 adenomas, 51 atypical parathyroid adenomas, and 41 carcinomas, reported that patients with atypical parathyroid adenomas were more likely to be male and had higher calcium and PTH levels than those with adenomas, whereas these values remained generally lower than those observed in carcinoma cases.

Data from Asian populations remain relatively limited. In a Chinese cohort study, Chen et al. [17] compared 79 cases of

atypical parathyroid adenomas with 79 cases of parathyroid cancer and 162 benign parathyroid lesions. Patients with atypical parathyroid adenomas were younger at presentation and exhibited higher serum calcium and PTH levels than those with benign lesions, findings that are consistent with previously reported trends. More recently, an Italian multicenter study including 57 patients with APTs and 74 patients with parathyroid carcinomas further demonstrated substantial overlap in clinical and biochemical profiles [18]. Notably, certain renal manifestations, including nephrolithiasis, nephrocalcinosis, and renal colic, were more frequently observed in carcinoma cases, independent of total serum calcium or urinary calcium levels.

In summary, the clinical and biochemical characteristics of APTs overlap substantially with those of both parathyroid adenomas and parathyroid carcinomas, particularly with respect to serum calcium and PTH levels. Demographic variables such as sex distribution and age at presentation, as well as clinical manifestations involving bone, renal, and neuropsychiatric systems, show considerable variability across studies. This heterogeneity is likely influenced, at least in part, by the small sample sizes inherent to most available studies.

HISTOPATHOLOGICAL FEATURES

The term 'APT' refers to parathyroid tumors that share selected histological features with parathyroid cancer but lack definitive evidence of lymphovascular or perineural invasion [4]. Histopathological features common to both APTs and parathyroid cancer include dense fibrous banding, trabecular growth patterns, entrapment of neoplastic cells, and adherence to adjacent structures. Fig. 1 illustrates representative histopathological features of APTs. According to Cetani et al. [2], thick fibrous bands

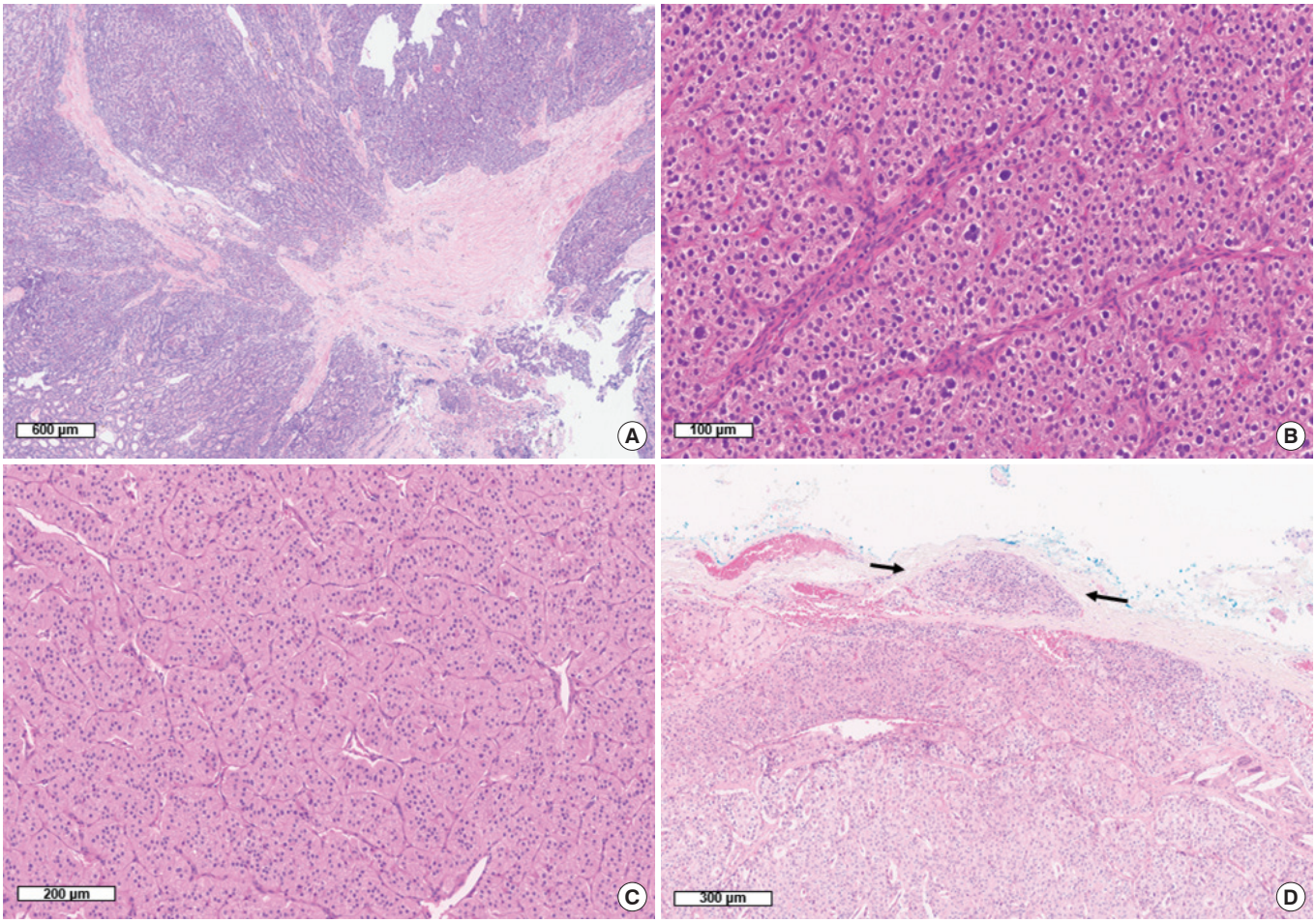

Fig. 1. Histopathological features of atypical parathyroid tumor. (A) Thick band-like fibrosis (scale bar: 600 μm). (B) Presence of enlarged hyperchromatic atypical cells (scale bar: 100 μm). (C) Tumor showing trabecular growth pattern (scale bar: 200 μm). (D) Tumor cell nests (arrows) in thick fibrous capsule (scale bar: 300 μm) (representative images from our institution).

are present in 76% of APT cases, followed by trabecular growth patterns (67%), increased mitotic activity (52%), pseudo-capsular invasion (42%), cellular pleomorphism (30%), and nuclear atypia (24%).

Although the atypical histological features outlined in the WHO classification are commonly used to support a diagnosis of APT [4], there is currently no consensus regarding the number or combination of features required to establish this diagnosis. For example, several studies require the presence of at least two features, including intraoperative adherence, fibrous bands, prominent trabecular architecture, increased mitotic activity, necrosis, diffuse sheet-like growth of monotonous small cells with a high nuclear-to-cytoplasmic ratio, cellular atypia, or nucleolomegaly, provided that unequivocal malignant features such as angioinvasion, lymphatic or perineural invasion, invasion of adjacent structures, or distant metastasis are absent [6,12,19,20]. In contrast, Kumari et al. [21] classified tumors as APTs when one to three of these features were present. Fernandez-Ranvier et al. [22] and Galani et al. [3] did not rely on a defined numerical threshold; instead, they classified APTs based on the presence of histological features suggestive of parathyroid cancer in the absence of unequivocal invasive behavior.

This marked lack of standardization, together with the inherent morphological overlap between APTs and parathyroid cancer, inevitably results in substantial interobserver variability among pathologists. These challenges emphasize the critical importance of comprehensive histopathological evaluation by experienced endocrine pathologists to ensure diagnostic accuracy and reproducibility.

IMMUNOHISTOCHEMICAL MARKERS

Immunohistochemistry (IHC) has become an essential adjunct in parathyroid pathology. In the initial diagnostic evaluation, neuroendocrine and hormone markers, including chromogranin A, synaptophysin, and PTH, can be used to confirm parathyroid origin and to distinguish parathyroid tissue from other entities [23,24]. For further assessment of malignant potential, a variety of IHC markers have been investigated to differentiate parathyroid cancer from adenoma (Table 1) [10,21,25-44].

Table 1. Suggested IHC Markers for Atypical Parathyroid Tumors

	Gene	Function	IHC results in parathyroid cancer	References
Parafibromin	*CDC73*	Critical role in cell regulation and tumor suppression. Mutations in this gene can cause hyperparathyroidism-jaw tumor syndrome and parathyroid cancer	Loss of parafibromin (33%–100%)	[21,25,26]
PGP9.5	*UCHL1*	Currently unclear. Abundantly expressed in neurons and might play a crucial role in the maintenance of axonal health and stability	Overexpression of PGP9.5 (45%–81%)	[32-34]
Galectin-3	*LGALS3*	Involved in regulatory functions including cell growth, apoptosis, differentiation, angiogenesis, inflammation, fibrosis and host defense	Overexpression of galectin-3 (4%–100%)	[27,35,36]
Ki-67	*MKI67*	Promotes cell proliferation and tumor growth; established as a pathological proliferation marker	High Ki-67 (>5%) expression (50%–86%)	[21,28,37]
P53	*TP53*	Tumor suppressor gene; controls cellular growth through growth arrest and apoptosis	Overexpression of p53	[38-40]
P27	*CDKN1B*	Tumor suppressor gene; exhibits ubiquitous expression,; integrates both mitogenic and growth inhibitory signals to regulate cell cycle.	Loss of p27 (82%–87%)	[41,42]
RB	*RB*	Tumor suppressor gene; controls cell cycle and apoptosis	Loss of RB (33%–88%)	[43]
CASR	*CASR*	Regulation of parathyroid hormone secretion and urinary calcium excretion; maintenance of mineral ion homeostasis	Loss of CASR (30%–50%)	[29,30,32,44]
APC	*APC*	Tumor suppressor gene; acts as an antagonist of the Wnt signaling pathway; uniformly expressed in normal parathyroid tissue and adenomas	Loss of APC (9%–100%)	[10,21]
WT1	*WT1*	Directly represses CDC73 and induces MYC and BCL-2 to promote cell proliferation and tumorigenesis	Overexpression of WT1 (85% in CDC73-mutant parathyroid cancer)	[31]

IHC, immunohistochemical; *CDC73*, cell division cycle 73; PGP9.5, protein gene product 9.5; *UCHL1*, ubiquitin C-terminal hydrolase L1; *LGALS3*, galectin 3; *MKI67*, marker of proliferation Ki-67; *TP53*, tumor protein p53; *CDKN1B*, cyclin dependent kinase inhibitor 1B; RB, retinoblastoma protein; CASR, calcium-sensing receptor; APC, adenomatous polyposis coli; WT1, Wilms tumor 1.

Parafibromin, encoded by the cell division cycle 73 (*CDC73*) gene, functions as a tumor suppressor protein and has been extensively studied as a valuable IHC marker in parathyroid cancer [45,46]. Loss of parafibromin expression has been reported in 33%–100% of parathyroid carcinomas [25,47,48] and has been associated with poor prognosis [26,49]. In APTs, loss of parafibromin expression has been reported at variable frequencies across studies [11,21,50,51]. Several investigations have shown that the proportion of parafibromin loss does not differ significantly between parathyroid cancer and APTs [11,15], suggesting that the use of parafibromin staining alone may be insufficient for reliably distinguishing between these entities. Nevertheless, parafibromin expression may still provide important prognostic insights regarding the malignant potential of APTs. In a study by Kruijff et al. [51], patients with APTs who retained parafibromin expression achieved cure, whereas those demonstrating loss of parafibromin staining exhibited a recurrence rate of 10%. This finding suggests that APTs with parafibromin loss may be more likely to display clinical behavior resembling that of parathyroid cancer. In alignment with this concept, the 2022 WHO guidelines have introduced a triaging scheme for parathyroid tumors utilizing parafibromin IHC staining [4]. Consistent with this framework, tumors initially classified as APTs based on routine histology are further stratified according to parafibromin IHC results, with parafibromin-negative APTs considered to carry a higher risk of recurrence than parafibromin-positive tumors. However, controversy persists regarding the routine use of parafibromin IHC, as staining can be technically challenging and difficult to standardize in routine clinical practice [52]. Therefore, standardized protocols for tissue fixation, antigen retrieval, staining procedures, and scoring systems are required before parafibromin IHC can be widely adopted as standard practice [53].

Protein gene product 9.5 (PGP9.5), encoded by the ubiquitin carboxyl-terminal esterase L1 gene, and galectin-3, a member of the lectin family involved in regulatory processes such as apoptosis, angiogenesis, metastasis, and inflammation, have been proposed as potential markers because of their overexpression in several malignancies [2,24]. In parathyroid cancer, both PGP9.5 and galectin-3 show increased expression, with significantly higher positivity rates than those observed in parathyroid adenomas. However, in APTs, reported overexpression rates vary widely across studies and generally fall between the levels seen in parathyroid cancer and parathyroid adenoma [21,27,51,54].

Ki-67, p53, p27, and retinoblastoma protein (RB) have also been investigated as potential IHC markers in parathyroid pathology because of their roles in cell-cycle regulation and apoptosis [24]. Among these, Ki-67 is expressed during the active phases of the cell cycle, and its assessment by IHC provides an estimate of cellular proliferative activity [55]. Reported mean Ki-67 labeling indices in parathyroid cancer range from 6.1% to 8.4%, with values as high as 70% in some cases [28,56,57], whereas lower levels, ranging from 1.9% to 4.3%, are typically observed in parathyroid adenomas [58,59]. A cut-off value greater than 5% has therefore been proposed to differentiate parathyroid cancer from parathyroid adenoma [2]. However, the utility of Ki-67 in distinguishing APTs from parathyroid adenomas remains limited. Reported rates of Ki-67 overexpression in APTs range widely, from 0% to 66.7%, across studies [12,27,57,60,61]. Accordingly, reliance on Ki-67 alone for differentiating APTs from parathyroid adenomas appears insufficient.

Other IHC markers, including the calcium-sensing receptor (CASR) and adenomatous polyposis coli (APC), have also been evaluated in parathyroid cancer and APTs. Downregulation of CASR expression has been identified as a prognostic factor in parathyroid cancer [29], with CASR loss reported in approximately 50% of parathyroid carcinomas and 7% of APTs, but not in benign parathyroid adenomas [30]. Similarly, frequent loss of APC expression has been observed in both APTs and parathyroid carcinomas, whereas APC expression is typically retained in parathyroid adenomas [10,62]. These observations suggest that CASR and APC may contribute to the IHC differentiation of parathyroid cancer, APTs, and benign parathyroid adenomas.

Despite these findings, the overall utility of individual IHC markers for distinguishing APTs remains limited. None of the currently available markers demonstrates clear superiority when used alone. Consequently, the use of combined marker panels has been proposed to improve diagnostic performance in APTs [54,63]. Truran et al. [63] reported that an IHC panel consisting of parafibromin, galectin-3, PGP9.5, and Ki-67 provided superior diagnostic performance for parathyroid cancer compared with any single marker. Based on existing evidence, loss of parafibromin expression, downregulation of APC, p27, and CASR, and upregulation of Ki-67 constitute the main features of an aberrant immunophenotype [55]. Nevertheless, validation of such IHC panels is limited by small sample sizes, and reported results remain inconsistent across studies.

The identification of specific transcriptomic signatures through RNA sequencing offers opportunities for the development of novel IHC markers. A recent study identified Wilms tumor 1 (*WT1*) as an upregulated differentially expressed gene in parathyroid cancer. Given that WT1 is known to suppress CDC73 and activate MYC proto-oncogene (MYC) and BCL2 apoptosis

regulator (BCL-2), thereby promoting cell proliferation and tumorigenesis [64], subsequent IHC analyses targeting WT1 were performed. This study demonstrated WT1 overexpression in five of six parathyroid cancer cases harboring CDC73 mutations, suggesting its potential utility as a marker for CDC73-mutant parathyroid cancer [31]. With ongoing advances in high-throughput sequencing technologies, further identification and validation of novel IHC markers for APTs are anticipated in future studies.

CLINICAL COURSE AFTER PARATHYROIDECTOMY

For parathyroid tumors, surgical resection of the hyperfunctioning lesion is the treatment of choice. The extent of surgery is determined by the presumed risk of malignancy, which is assessed based on clinical findings and intraoperative observations, such as adherence to adjacent tissues. Cetani et al. [2] performed a systematic analysis of APT cases and reported that 56% of patients underwent simple parathyroidectomy, 24% underwent *en bloc* resection, and 19% underwent bilateral cervical exploration. McCoy et al. [6] reported outcomes from a cohort of 51 patients with APTs, demonstrating no disease recurrence following parathyroidectomy over a mean follow-up period of 5 years. Based on these findings, the authors suggested that extended long-term surveillance may not be necessary for patients with APTs. Galani et al. [3] similarly reported an absence of disease recurrence among patients with APTs during a 5-year follow-up period, despite clear clinical and histological distinctions from typical parathyroid adenomas. In a Chinese cohort, recurrence rates among patients with atypical parathyroid adenomas were likewise comparable to those observed in benign adenomas and significantly lower than those reported for parathyroid cancer [17].

In contrast, cases of APTs with aggressive clinical behavior and recurrence have also been reported [65]. Russo et al. [66] described a 42-year-old woman who was initially diagnosed with an APT but developed recurrent disease with elevated serum calcium and PTH levels one year after surgery. Subsequent reoperation revealed parathyroid cancer with invasion into thyroidal and perithyroidal tissues [66]. Another case series examined recurrence rates in patients with parathyroid cancer and APTs [8]. In that study, the recurrence rate among patients with APTs was not significantly different from that observed in parathyroid cancer, although a trend toward higher recurrence was noted in parathyroid cancer compared with APTs (6 [25%] vs. 2 [13%], respectively). Additionally, recurrence-free survival did not differ significantly between the two groups. During follow-up, four patients—three with parathyroid cancer and one with APT—died, with no significant difference in overall survival between the groups. Although limited by a small sample size, these findings indicate that APTs should not be dismissed solely on the assumption of a benign clinical course.

More recently, an Italian multicenter study compared postoperative outcomes between 57 patients with APTs and 74 patients with parathyroid carcinomas [18]. Most patients with APTs underwent parathyroidectomy involving fewer than three glands, and isolated parathyroidectomy was performed significantly more often than in cases of parathyroid carcinoma. Complete tumor resection was achieved in more than 90% of APT cases, and postoperative normalization of serum calcium levels was reported in nearly all patients. Importantly, the rate of disease recurrence or persistence following surgery was relatively low in APTs (7.0%) and markedly lower than that observed in parathyroid carcinoma (23.0%). Nevertheless, despite the overall lower recurrence rate, disease recurrence did occur in a subset of patients with APTs, and when present, clinical outcomes were sometimes unfavorable. These observations suggest that overly optimistic assumptions regarding the benign nature of APTs may be unwarranted, and that careful long-term surveillance should remain a consideration, particularly in cases with equivocal histological or clinical findings.

It is also important to recognize a key limitation of many earlier studies reporting a benign course for APTs, namely that follow-up durations may have been insufficient. In a case report by Kotliarevskaia et al. [9], a patient initially diagnosed with an APT experienced disease recurrence 11 years after surgery, prompting reclassification as parathyroid cancer. A case series involving patients with parathyroid cancer further underscores the importance of prolonged follow-up [67]. In that series, eight patients were diagnosed with parathyroid cancer, five of whom experienced recurrence, with a mean time to first recurrence of 13.2 years. These findings suggest that even longer follow-up intervals may be necessary for patients with APTs. Accordingly, defining the true clinical course of APTs may require longitudinal data extending 10 years or longer.

In light of these considerations, it is essential to maintain awareness of APTs during the initial pathological evaluation of parathyroid tumors. Because of their rarity, APTs are often underrecognized, and accurate diagnosis is particularly challenging without careful and detailed histopathological assessment. If an APT with high malignant potential is misclassified as a be-

nign parathyroid adenoma at initial diagnosis, the consequences for patient outcomes can be substantial. Although reported prognoses for parathyroid cancer vary across studies, recurrence rates range from approximately 40% to 86%, and 10-year survival rates range from 57% to 77% in single-center series [68, 69]. Large nationwide datasets demonstrate similar variability; the 10-year survival rate was reported as 49.1% in the U.S. National Cancer Database (1985–1995) [70], whereas a more recent Korean nationwide study (2002–2017) reported a 10-year survival rate of 72.9% [71]. One case report described a 23-year-old woman whose parathyroid tumor was initially diagnosed as a parathyroid adenoma despite markedly elevated calcium and PTH levels (3.71 mmol/L [14.8 mg/dL] and 2,209.0 pg/mL, respectively) [72]. Disease recurrence occurred one year after the initial surgery, and re-exploration revealed parathyroid cancer. Despite medical therapy, hypercalcemia persisted, and the patient ultimately died. The authors suggested that an APT or minimally invasive parathyroid cancer may have been present at initial presentation. This case highlights the importance of considering APTs and parathyroid cancer in patients presenting with extremely elevated serum calcium and PTH levels.

STRATEGIES TO MOVE FORWARD: GENOMIC AND TRANSCRIPTOMIC ANALYSES

With the advent of the next-generation sequencing (NGS) era, researchers have sought to better understand genetic alterations underlying parathyroid disease. In particular, genomic and transcriptomic profiling comparing parathyroid cancer with parathyroid adenoma has revealed distinct patterns of genetic alterations between these disease entities. However, the molecular characteristics of APTs remain largely undefined. Mutations in *CDC73* represent a well-established driver of parathyroid cancer and have been identified in approximately 40%–100% of sporadic parathyroid cancer cases [73]. In APTs, *CDC73* mutations have been reported in approximately 38% of cases, although the reported frequency varies substantially across studies [2]. In a recent case series by Ullmann et al. [74], targeted NGS was performed on tumor samples from 18 patients with APTs. No mutations in *CDC73* were identified, and the most frequently mutated gene was multiple endocrine neoplasia type 1 (*MEN1*), showing alterations in four samples (22%). Additional mutated genes included phosphatidylinositol 3-kinase (*PI3KCA*), BCL6 corepressor like 1 (*BCORL1*), *CASR*, FA complementation group C (*FANCC*), mitochondrially encoded NADH dehydrogenase 5 (*MT-ND5*), TSC complex subunit 2 (*TSC2*), lysine methyltransferase 2C (*KMT2C*), enhancer of zeste 2 polycomb repressive complex 2 subunit (*EZH2*), and *RET*, with two cases for *PI3KCA* and one case for each of the others. The authors noted that the mutational profile observed in APTs closely resembled that previously reported for benign parathyroid adenomas. In contrast, a study involving 50 Chinese patients with APTs yielded different results. Targeted NGS analysis demonstrated *CDC73* mutations in 24% of cases, along with mutations in *EZH2* (8%), HIC ZBTB transcriptional repressor 1 (*HIC1*) (2%), and cyclin dependent kinase inhibitor 2A (*CDKN2A*) (2%) [75]. These discrepancies may reflect differences in patient ethnicity and in the gene panels used, as the latter study employed a more limited panel of 15 genes.

More recently, folliculin (*FLCN*) variants—typically associated with Birt-Hogg-Dubé syndrome—have been implicated in a subset of parathyroid cancers and APTs [76]. In a study analyzing both germline and somatic DNA from patients lacking *CDC73* or *MEN1* mutations, *FLCN* alterations were detected in cases of parathyroid cancer and APTs but were absent in parathyroid adenomas. These findings suggest that *FLCN* may represent a novel susceptibility gene and justify further investigation into its role in APT tumorigenesis and its potential therapeutic relevance.

Beyond targeted NGS approaches, whole-exome sequencing (WES) has also been applied to characterize the mutational landscape of APTs. In a study of 16 APT cases, WES of tumor tissue and matched peripheral blood samples identified a total of 192 nonsynonymous variants, with a median of nine protein-altering mutations per tumor [77]. Frequently mutated genes included BCL6 corepressor (*BCOR*), enhancer of zeste 1 polycomb repressive complex 2 subunit (*EZH1*), junctional adhesion molecule 2 (*JAM2*), mucin 16 (*MUC16*), and mechanistic target of rapamycin kinase (*MTOR*). Mutations in known cancer-related genes, such as *MEN1*, *CDC73*, *EZH2*, and *PI3KCA*, were also observed. Pathway analysis revealed involvement of phosphoinositide 3-kinase (PI3K)/AKT/mTOR and Wnt signaling pathways, as well as alterations affecting epigenetic regulators. Collectively, these findings indicate that APTs do not exhibit a clearly distinct mutational profile and instead share genomic features with both parathyroid adenomas and parathyroid carcinomas.

In a recent study by Jo et al. [31], transcriptomic profiling was used to define molecular characteristics of parathyroid cancer. The authors identified increased expression of E2F transcription factor (E2F) targets, KRAS signaling, tumor necrosis factor-α

(TNF-α) signaling, and epithelial–mesenchymal transition pathways in parathyroid carcinomas compared with adenomas and normal parathyroid tissue. Among *CDC73*-wildtype tumors, somatic tumor protein p53 (*TP53*) mutations were detected in two of four patients, along with truncating mutations in CCDC40 and additional alterations involving lysine methyltransferase 2D (*KMT2D*), *KRAS*, and FRAT regulator of Wnt signaling pathway 2 (*FRAT2*). Given that these genetic changes may also be relevant to APT biology, future studies of APTs should consider evaluating these alterations when exploring disease pathogenesis. The investigators further developed a molecular classification model based on carcinoma-specific gene expression signatures, which effectively distinguished parathyroid cancer from adenomas and normal tissues. The clinical relevance of this model was illustrated in two patients with APTs, who clustered separately, with one grouping with carcinomas and the other with adenomas. During postoperative follow-up, the patient classified within the cancer cluster experienced disease recurrence, whereas the patient classified within the adenoma cluster remained recurrence-free. The clustering model was subsequently applied to a larger cohort of 16 patients with APTs [61]. Using this approach, tumors were categorized as either cancer-type or adenoma-type APTs, and these classifications were compared with clinical characteristics. Although no significant differences were observed in histopathological or IHC features between the two groups, clustering analysis identified four tumors as cancer-type and 12 as adenoma-type. Notably, patients with cancer-type APTs exhibited more aggressive clinical features, including higher serum calcium and PTH levels and younger age at presentation, compared with those with adenoma-type tumors. These observations support the potential utility of transcriptomic clustering analyses as a tool for risk stratification in patients with APTs.

Single-cell analytical approaches have more recently emerged as powerful tools in cancer research. However, studies applying these techniques to parathyroid tumors remain scarce. In a study by Chen et al. [78], single-cell transcriptomic analysis was performed on two parathyroid cancer samples and five parathyroid adenoma samples. The analysis revealed substantial cellular heterogeneity within both parathyroid cancer and adenoma tissues. Dysregulation of cell-cycle regulators was identified, suggesting a potential role in parathyroid cancer tumorigenesis. Transcript-level expression of cyclin D1 (CCND1), cyclin dependent kinase inhibitor 2C (CDKN2C), PTH, and CASR was significantly higher in parathyroid cancer than in parathyroid adenoma. Although the observed upregulation of CASR transcripts appears counterintuitive in light of prior IHC studies reporting loss of CASR protein expression, this discrepancy highlights the potential importance of post-transcriptional regulatory mechanisms in parathyroid tumor biology. To date, no studies have applied single-cell transcriptomic techniques specifically to APTs. Emerging transcriptomic approaches, including single-cell RNA sequencing, are therefore anticipated to provide further insight into APT pathogenesis and to advance understanding of their underlying biology.

CONCLUSIONS

The histopathological and clinical characteristics of APTs demonstrate features that place them along a spectrum between parathyroid cancer and benign parathyroid adenoma, suggesting that this disease entity may represent a premalignant lesion [74]. APTs often do not receive sufficient clinical attention and may be overlooked without careful evaluation by experienced endocrine pathologists. However, given their uncertain malignant potential, APTs warrant heightened clinical awareness and consideration. At present, there is no definitive consensus regarding diagnostic criteria, treatment strategies, or postoperative monitoring guidelines for APTs. Accordingly, this article aims to summarize current knowledge and ongoing efforts to evaluate the malignant risk associated with APTs.

A thorough pathological review by experienced endocrine pathologists is essential for the accurate diagnosis of APTs. To support diagnostic assessment, IHC staining markers such as parafibromin, PGP9.5, and galectin-3 have been utilized. However, none of these markers individually demonstrates sufficient sensitivity and specificity, and ongoing efforts are directed toward identifying novel and more reliable markers. Genomic and transcriptomic analyses of APTs have been increasingly reported, with *CDC73* mutations representing the most frequently identified genetic alteration, a finding that parallels observations in parathyroid cancer. Further studies are needed to expand genetic profiling efforts and to deepen understanding of the molecular pathogenesis of APTs.

The existing literature generally suggests a favorable prognosis for most APTs. Nevertheless, this optimistic interpretation must be tempered by the important limitation that many studies are constrained by relatively short follow-up durations. Given the limitations of current diagnostic tools and the heterogeneity of clinical outcomes, a proposed management algorithm for APTs is presented (Fig. 2). To advance understanding of APT prognosis and optimize patient management, further investiga-

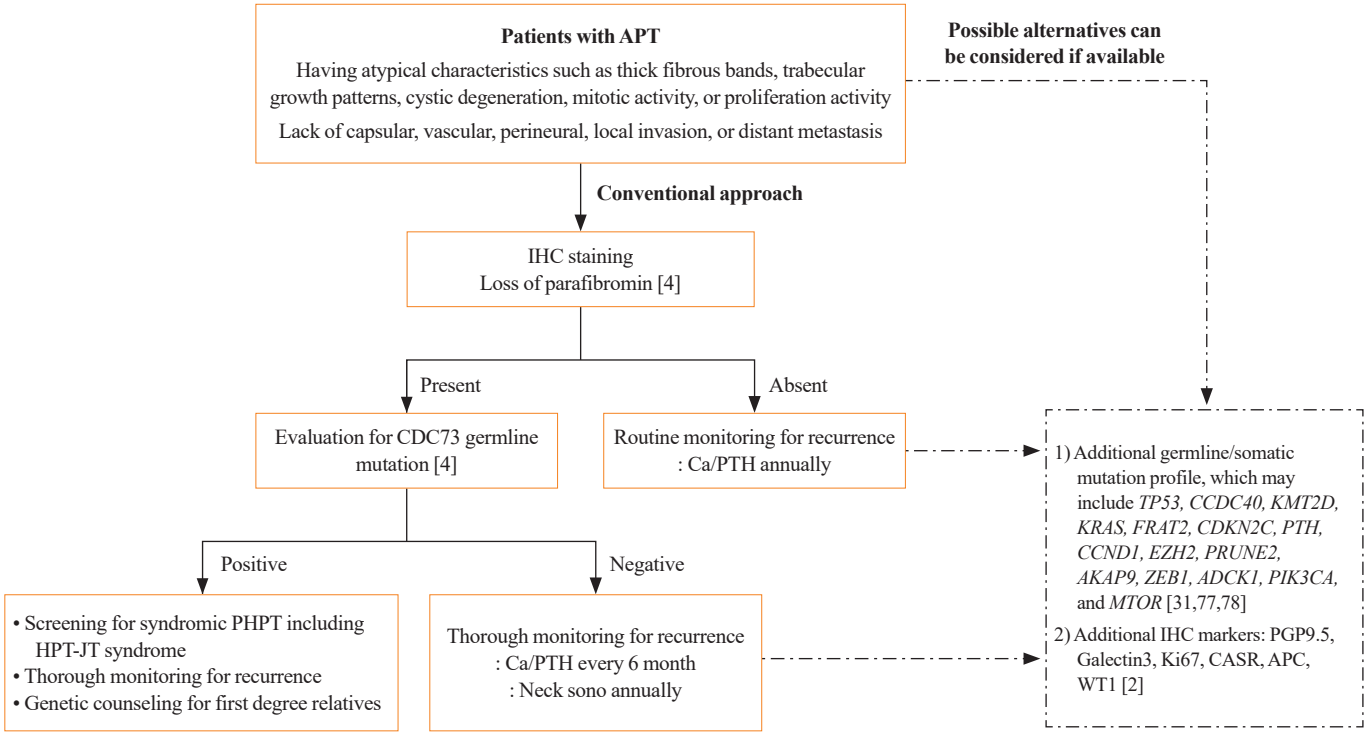

Fig. 2. Possible algorithm for management of patients with atypical parathyroid tumors (APTs). IHC, immunohistochemical; *CDC73*, cell division cycle 73; Ca, calcium; PTH, parathyroid hormone; PHPT, primary hyperparathyroidism; HPT-JT, hyperparathyroidism-jaw tumor.

tions involving larger cohorts with extended follow-up periods are required, along with continued validation and refinement of emerging molecular risk-stratification approaches.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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