

## ORIGINAL RESEARCH

# A multi-institutional study evaluating and describing atypical parathyroid tumors discovered after parathyroidectomy

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**Abstract**

**Objective:** To describe common intraoperative and pathologic findings of atypical parathyroid tumors (APTs) and evaluate clinical outcomes in patients undergoing parathyroidectomy.

**Methods:** In this multi-institutional retrospective case series, data were collected from patients who underwent parathyroidectomy from 2000 to 2018 from three tertiary care institutions. APTs were defined according to the AJCC eighth edition guidelines and retrospective chart review was performed to evaluate the incidence of recurrent laryngeal nerve injury, recurrence of disease, and disease-specific mortality.

**Results:** Twenty-eight patients were identified with a histopathologic diagnosis of atypical tumor. Mean age was 56 years (range, 23–83) and 68% (19/28) were female. All patients had an initial diagnosis of primary hyperparathyroidism with 21% (6/28) exhibiting clinical loss of bone density and 32% (9/28) presenting with nephrolithiasis or renal dysfunction. Intraoperatively, 29% (8/28) required thyroid lobectomy, 29% (8/28) had gross adherence to adjacent structures and 46% (13/28) had RLN adherence. The most common pathologic finding was fibrosis 46% (13/28). Postoperative complications include RLN paresis/paralysis in 14% (4/28) and hungry bone syndrome in 7% (2/28). No patients with a diagnosis of atypical tumor developed recurrent disease, however there was one patient that had persistent disease and hypercalcemia that is being observed. There were 96% (27/28) patients alive at last follow-up, with one death unrelated to disease.

**Conclusion:** Despite the new AJCC categorization of atypical tumors staged as Tis, we observed no recurrence of disease after resection and no disease-specific mortality. However, patients with atypical tumors may be at increased risk for recurrent laryngeal nerve injury and incomplete resection.

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## KEYWORDS

atypical, parathyroid tumors, recurrent laryngeal nerve

## 1 | INTRODUCTION

Parathyroid tumors are a relatively homogeneous group of neoplasms affecting between 0.1% and 0.3% of the population, most commonly associated with unregulated production of parathyroid hormone (PTH), resulting in primary hyperparathyroidism (PHPT).<sup>1</sup> The majority of these tumors are solitary adenomas (85%), followed by multiple gland hyperplasia (10%–15%) and rarely, carcinomas or atypical parathyroid tumors (APTs) (<1%).<sup>2,3</sup>

Classification of the latter group, specifically APTs, has historically been controversial, due to their ambiguous characteristics both clinically and histopathologically. However, in 2018, the American Joint Committee on Cancer (AJCC) released its eighth edition and added a “Tis” category to the staging of parathyroid carcinomas, specifically describing “Tis” as an atypical parathyroid neoplasm with uncertain malignant potential.<sup>4</sup>

APTs were defined as not meeting criteria of carcinoma (i.e., invasion, metastasis), but nonetheless contain some worrisome features that place them in between the benign and malignant categories. Such features include fibrous bands, mitotic figures, necrosis, trabecular growth, or adherence to surrounding tissues intraoperatively, but these APTs are usually smaller and less likely to have coagulative tumor necrosis than a true carcinoma.<sup>4</sup>

Given the recent clarification from the AJCC staging guidelines, this study aims to evaluate immediate and long-term clinical outcomes—specifically, recurrent laryngeal nerve injury and recurrence of disease—in patients undergoing parathyroidectomy for PHPT who were then discovered to have APT. Anecdotally, these APTs have been observed clinically for years, yet few studies have examined the clinical presentation and behavior of these tumors. There is a paucity of information regarding the clinical outcomes (e.g., morbidity and mortality) and surveillance management of these patients. Increasing awareness among endocrine surgeons and pathologists of these

tumors can help support accurate diagnoses and management in light of the most recent AJCC staging guidelines.

## 2 | MATERIALS AND METHODS

In this multi-institutional retrospective case series, data were collected from patients who underwent parathyroidectomy from 2000 to 2018 as identified through billing codes (CPT 60500) and searching pathology records from three tertiary care institutions. From this set of patients, all subjects with a histopathologic diagnosis of APT were selected for inclusion. Demographic criteria (age, sex), date of surgery, medical history, comorbid illnesses, laboratory values (i.e., calcium, PTH, comprehensive renal panel), complications, and outcomes (recurrence of disease and disease-specific mortality) were collected.

Diagnosis of APT was defined by presence of >2 of the following gross or pathologic criteria according to Seethala et al.: intratumoral fibrotic bands, trabecular growth, increased mitotic activity (>1 mitosis/10 high power field), cytologic atypia, necrosis, or adherence to surrounding tissues intraoperatively, but not reaching the threshold for carcinoma (invasive growth into surrounding tissues, atypical mitotic figures, lymphovascular invasion) (Figure 1).<sup>5</sup> Retrospective chart review was performed to evaluate the incidence of recurrent laryngeal nerve injury, recurrence of disease, and disease-specific mortality. Recurrent laryngeal nerve injury was defined as known injury during surgery as described by the operative report and/or evidence of hypomobility or immobility on postoperative clinical laryngoscopy. Disease recurrence was defined as recurrent hypercalcemia with high serum PTH levels, after a disease-free period (normocalcemia) of at least 6 months. Descriptive statistics were used for demographic information. This study complied with institutional review board protocols regarding privacy of patient data at each respective institution.

### Atypical Parathyroid Adenoma Pathologic Criteria (Adapted from Seethala et al.<sup>5</sup>)

Presence of >2 of the following features:

Intratumoral fibrotic bands

Trabecular growth

Increased mitotic activity (>1 mitosis/10 HPF)

Necrosis

Cytologic atypia

Gross adherence to surrounding tissues intraoperatively

Does not reach threshold for carcinoma (regional invasive growth, atypical mitotic figures, lymph-vascular invasion)

**FIGURE 1** Adapted from Seethala et al.<sup>5</sup>: pathologic criteria for atypical parathyroid adenoma.

### 3 | RESULTS

#### 3.1 | Demographics and preoperative findings

This retrospective case series identified 29 patients with an initial histopathologic diagnosis of APT. One patient was identified with a histopathologic diagnosis of parathyroid carcinoma in a separate gland 14 years after initial surgery and was excluded from analysis of APTs. Mean age was 55.7 years (range, 23–83) and 68% ( $n = 19$ ) were female. All patients had an initial diagnosis of PHPT with 21% (6/28) exhibiting clinical loss of bone density and 32% (9/28) presenting with nephrolithiasis or renal dysfunction (Table 1). Preoperative imaging (ultrasound, computed tomography, and/or nuclear medicine sestamibi localization) was obtained for patients per standard of care prior to surgery. Representative imaging from selected patients with proven pathologic atypical tumors are shown in Figure 2.

#### 3.2 | Intraoperative findings

Intraoperatively, 29% (8/28) of patients also underwent a thyroid lobectomy, 29% (8/28) had evidence of APT gross adherence to adjacent

structures, and 46% (13/28) had RLN adherence. The most common pathologic finding was fibrosis, 46% (13/28) (Table 2 and Figure 3).

#### 3.3 | Follow-up

After parathyroidectomy, postoperative complications included RLN paresis/paralysis 14% (4/28) and hungry bone syndrome 7% (2/28), but no patients with a diagnosis of atypical tumor developed recurrent tumor at the same site after a follow-up time of mean 26.3 months (SD 30.7) (Table 3). There was one patient that had persistent disease and hypercalcemia that is being observed, believed to have had multi-gland hyperplasia. The patient diagnosed with parathyroid carcinoma in a separate gland on subsequent surgery did not experience any RLN injury or postoperative complications. There were 27 of 28 patients alive at last follow-up, with one death unrelated to disease.

### 4 | DISCUSSION

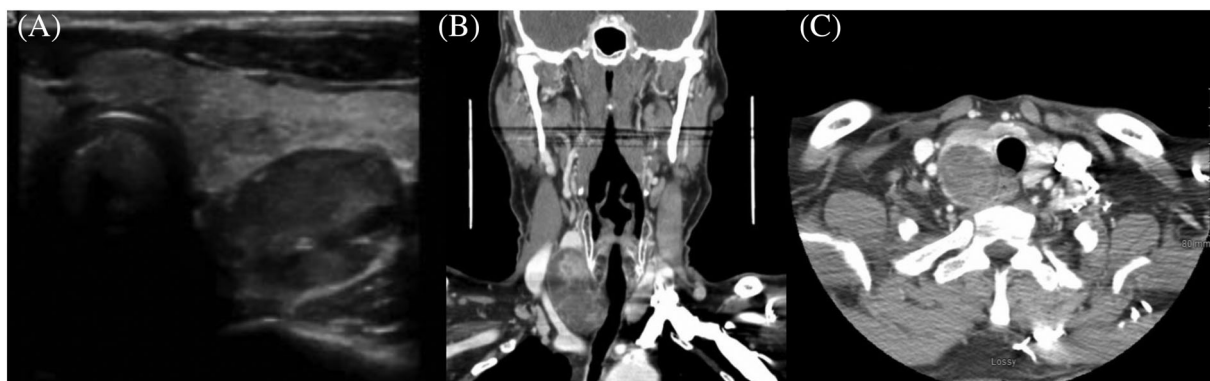
Given the most recent AJCC categorization of APTs as “Tis,” this study aimed to evaluate the frequency of RLN injury and tumor recurrence in patients undergoing parathyroidectomy later determined to have an APT. In this study, we observed no recurrence of tumor after resection and no disease-specific mortality. However, we did observe

**TABLE 1** Demographics and preoperative clinical findings.

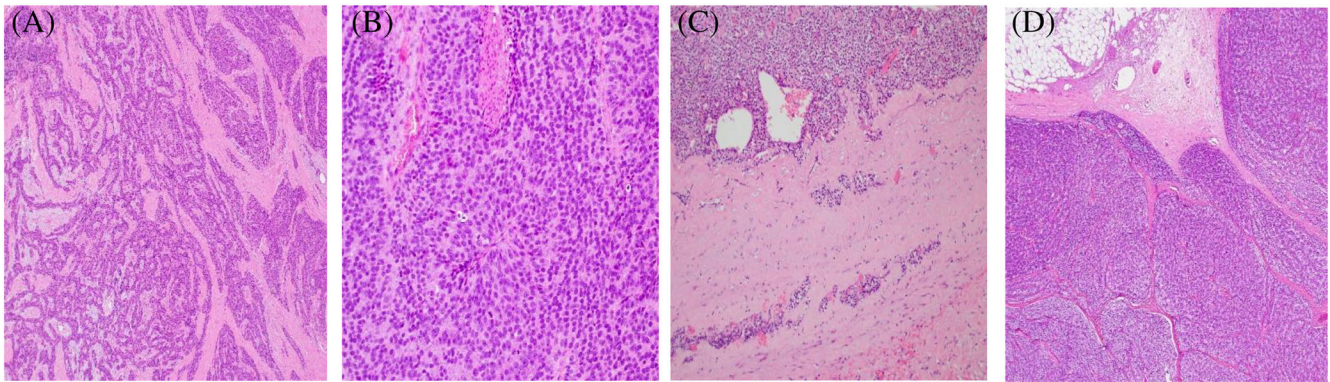
	<i>n</i>	%
Sex		
Male	9	32
Female	19	68
Diagnosis of primary hyperparathyroidism	28	100
Clinical loss of bone density	6	21
Nephrolithiasis or renal dysfunction	9	32
Mean age at date of operation [years (range)]	55.7 (23–83)	
Mean follow-up [months; SD]	26.3; 30.7	

**TABLE 2** Postoperative histopathologic findings.

	<i>n</i>	%
Thyroid lobectomy	8	29
Gross adherence	8	29
Recurrent laryngeal nerve adherence	13	46
Fibrosis on histopathology	13	46



**FIGURE 2** Representative imaging findings of atypical parathyroid adenoma. (A) Ultrasound of an atypical parathyroid adenoma demonstrating a hypoechoic lesion with hyperechoic and cystic foci inferior to the left lobe of the thyroid. (B and C) Coronal and axial CT of an atypical parathyroid adenoma demonstrating an isodense lesion with hyperdense foci posterior to the right lobe of the thyroid.



**FIGURE 3** Representative slides of hematoxylin and eosin stains of pathologic features of atypical parathyroid adenomas. (A) Pattern revealing prominent fibrous bands and trabecular pattern of growth ( $\times 40$ ). (B) Cytologic atypia, focal necrosis, and mitotic activity ( $\times 200$ ). (C) Intracapsular growth of atypical parathyroid adenoma ( $\times 100$ ). (D) Prominent intralesional fibrotic bands, as well as a trabecular growth pattern ( $\times 40$ ).

**TABLE 3** Postoperative clinical findings.

	n	%
Recurrent laryngeal nerve paresis/ paralysis	4	14
Hungry bone syndrome	2	7
Recurrent disease	0 <sup>a</sup>	0

<sup>a</sup>One patient with persistent hypercalcemia is currently under observation. One death occurred unrelated to disease.

a high incidence of recurrent laryngeal nerve injury from parathyroidectomy surgery.

Patients with APTs may be at increased risk for RLN injury due to the fibrotic nature of the disease. Gross adherence to nearby structures was noted during many cases in this series, with specific RLN adherence in 46% of the cases. Routine parathyroidectomy for PHPT due to parathyroid adenoma typically experience clean planes during surgical dissection with relative ease of removal using simple blunt dissection in the majority of cases.<sup>6</sup> However, because APTs have increased fibrosis and inflammation, we observed that the rate of RLN adherence intraoperatively and injury postoperatively in this study (46% and 14%, respectively) to be much higher than published injury rates of benign adenomas (<1%).<sup>7</sup> Yet it still lower than that of parathyroid carcinoma, which has been reported to be as high as 38%.<sup>8</sup>

Preoperatively, laboratory values and imaging can play an important role in anticipating a more difficult surgery from an APT. On laboratory evaluation, APTs are characterized by elevated calcium and PTH to levels similar to that of parathyroid carcinoma.<sup>3</sup> Unfortunately, this study was limited by inability to access the preoperative PTH and calcium data for all subjects. Compared to typical parathyroid adenomas, which appear hypochoic on ultrasound, APTs more frequently have isochoic or cystic components, similar to parathyroid carcinoma.<sup>9,10</sup> In reviewing our preoperative imaging, the APTs exhibited a variable appearance, with hypochoic, cystic, and isodense features in different patients, similar to the findings of previous studies (Figure 2).

The mean age of diagnosis in this study is similar to that previously reported for sporadic APT.<sup>2,3</sup> Similarly, the APT female: male ratio has been reported to be between 1:1 and 2:1, where parathyroid carcinoma is typically 1:1 and benign adenomas are typically 4:1.<sup>3,8,11</sup>

Interestingly, there was no recurrence and only one case of persistent hypercalcemia on follow-up. This is distinct from parathyroid carcinoma, in which the prevalence of persistent or recurrent disease is up to 49%–60%, and more in line with single adenoma or multiple gland hyperplasia, in which the recurrence rate is <1%.<sup>8,12</sup> This is surprising considering the fibrotic nature of APTs relative to their benign adenoma counterparts, it would be expected that incomplete resection intraoperatively (and ensuing persistent disease) would be more common, but it falls in line with Christakis et al., who reported a recurrence rate of <5% in APT resection.<sup>2,13</sup> Only 7% of patients in this study experienced hungry bone disease post-parathyroidectomy. This is in line with the prevalence of hungry bone disease after parathyroidectomy for adenomas causing PHPT in a case series from the 1980s (13%); however, more recent data suggested a larger range from 4% to 82%.<sup>14</sup>

This study continues to demonstrate the ambiguous nature of APTs. Some features were more similar to benign adenomas (recurrence rate), others to carcinoma (intraoperative fibrosis and adherence), and others fell in between (female: male ratio, RLN injury). In 2013, Kruiff et al. reported that negative parafibromin staining predicted malignant behavior in APTs.<sup>15</sup> Given the spectrum of APT behavior noted in this study, future studies should characterize how various APT qualities (such as parafibromin staining) can help predict postoperative outcomes. As expected, the main limitations of this study include retrospective nature and small sample size, due to the rarity of APTs.

## 5 | CONCLUSION

Despite the new AJCC categorization of atypical tumors staged as “Tis,” we observed no recurrence of disease after resection and no

disease-specific mortality. However, patients with atypical tumors may be at increased risk for RLN injury and incomplete resection intraoperatively given the fibrotic nature of the tumor. Additional studies will be needed to explore the factors that may predispose APTs to fibrosis and adherence to surrounding structures to allow surgeons to anticipate potential complications prior to surgery.

### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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