Multimodal Imaging–Guided and Intraoperatively Verified Resection of Mediastinal Ectopic Parathyroid Adenomas: A Five-Case Series

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AIM: To present the diagnostic approach, surgical management, and early outcomes of patients with mediastinal ectopic parathyroid adenoma (MEPA) causing primary hyperparathyroidism.
CASE PRESENTATION: Between January 2015 and January 2025, patients with mediastinal ectopic parathyroid adenoma identified among 458 patients who underwent surgery for a solitary parathyroid adenoma were retrospectively reviewed, and five cases were identified (1%; n = 5). Diagnostic evaluation included cervical ultrasonography, technetium-99m sestamibi single-photon emission computed tomography/computed tomography (SPECT/CT), and CT. The surgical strategy was individualized according to lesion location and proximity to major vascular structures. Intraoperative confirmation was achieved using radioguided surgery, frozen section analysis, and intraoperative parathyroid hormone (ioPTH) monitoring. Patients were followed for one year with serial serum calcium and parathyroid hormone (PTH) measurements.
RESULTS: The median age was 62 years (range, 40–70 years), and three patients were female. Bone pain and fatigue were the most common presenting symptoms, whereas one patient was asymptomatic. Preoperative albumin-corrected serum calcium levels ranged from 11.24 to 13.43 mg/dL, and PTH levels ranged from 161 to 1493 pg/mL. Lesion size ranged from 8 × 8 mm to 35 × 22 mm, and four lesions were located in the anterior mediastinum. Four patients underwent J-shaped partial median sternotomy, and one underwent a transcervical approach. The 10-minute ioPTH decline ranged from 48.3% to 85.5%. No major surgical complications occurred. All patients remained normocalcemic and clinically stable at the 1-year follow-up.
CONCLUSIONS: In patients with MEPA, the combined use of functional and anatomical imaging, supported by multiple intraoperative confirmation modalities, may facilitate curative resection with low morbidity through an individualized surgical strategy.

Keywords: primary hyperparathyroidism; mediastinum; ectopic tissue; technetium-99m sestamibi; tomography; x-ray computed; parathyroidectomy

Introduction

Primary hyperparathyroidism (PHPT) is an endocrine disorder characterized by inappropriate overproduction of parathyroid hormone (PTH), most commonly accompanied by hypercalcemia [1]. The majority of PHPT cases are sporadic; the most frequent etiology is a solitary parathyroid adenoma (85–90%), followed by multiglandular hyperplasia (10–15%), while parathyroid carcinoma is rare (<1%) [2]. A parathyroid adenoma is a benign neoplasm arising from the parathyroid gland that, in most cases, leads to the clinical picture of PHPT through autonomous excessive PTH secretion [1,3].

Ectopic parathyroid adenomas result from abnormal embryological migration and are located outside the normal cervical position, with mediastinal localization posing particular challenges in terms of surgical access and the selection of an appropriate operative approach. The reported incidence of ectopic glands in parathyroid adenoma cases varies widely in the literature (4–22%); mediastinal localization is uncommon, accounting for approximately 2% of all ectopic adenomas [4,5]. In such cases, preoperative localization studies provide a critical roadmap for surgical planning, whereas intraoperative confirmation techniques help assess the adequacy of resection [6–8].

In this case series, we aimed to present the clinical and imaging characteristics, as well as the surgical management outcomes, of patients with mediastinal ectopic parathyroid adenoma (MEPA) who underwent surgery for PHPT.

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Case Presentation

This study was designed as a retrospective analysis of patients who underwent surgery for mediastinal ectopic parathyroid adenoma at Mersin University Faculty of Medicine between January 2015 and January 2025. This case has been reported in line with the case report guidelines: Case Report (CARE) Guidelines to ensure the accuracy and completeness of the report **(Supplementary Material)**.

Surgical indications were determined in accordance with the American Association of Endocrine Surgeons (AAES) guidelines for definitive management of primary hyperparathyroidism; only patients with histopathological confirmation after excision were included [9]. Patients with secondary or tertiary hyperparathyroidism, multiglandular disease, Multiple Endocrine Neoplasia type 1 (MEN1), or familial primary hyperparathyroidism were excluded.

Demographic, clinical, biochemical, imaging, and perioperative data were retrieved from electronic medical records. Surgical success was defined as postoperative normalization of albumin-corrected serum calcium during follow-up, while intraoperative biochemical response was evaluated by the percentage decline in intact PTH measured 10 minutes after excision compared with baseline. Persistent disease was defined as hypercalcemia persisting or recurring within the first 6 months after surgery, whereas recurrence was defined as the reappearance of hypercalcemia after at least 6 months of documented normocalcemia [9]. Postoperative complications were recorded; hypocalcemia was assessed by serum calcium levels and symptoms.

All patients underwent preoperative localization with cervical ultrasonography (USG) and technetium-99m sestamibi single-photon emission computed tomography/computed tomography (99mTc-sestamibi SPECT/CT). Cervicothoracic CT was performed in all patients to define lesion size, mediastinal relationships, and the surgical access route. Per institutional protocol, 5 mCi (185 MBq) of 99mTc-sestamibi was injected intravenously 2 hours before surgery.

All procedures were performed under general anesthesia in the supine position. Intraoperative neuromonitoring was used selectively for anticipated cervical dissection or re-exploration. The surgical approach was individualized according to lesion level, depth, vascular proximity, and prior cervical surgery. For lesions requiring anterior mediastinal exposure, a J-shaped partial median sternotomy was performed through a low cervical collar incision, continued with an upper partial median sternotomy extending vertically from the sternal notch to the level of the third intercostal space and then laterally toward the right side, providing access to the thoracic inlet and anterior mediastinum. Suprasternal or upper mediastinal lesions judged to be accessible from the neck were approached through a transcervical incision. Partial or en bloc thymectomy was added when intrathymic localization was suspected.

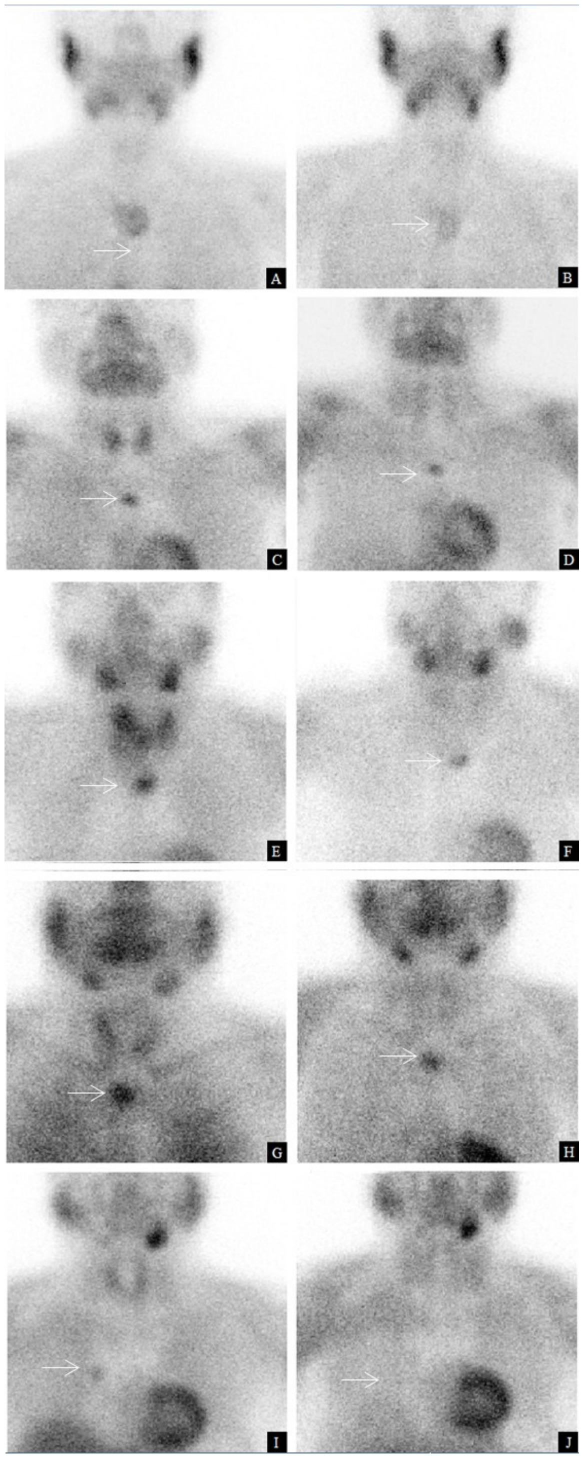

Fig. 1. Dual-phase 99mTc-sestamibi (MIBI) planar parathyroid scintigraphy (Cases 1–5). Early-phase images are shown in (A,C,E,G,I), and delayed-phase images in (B,D,F,H,J). Cases are arranged from bottom to top (Case 1 to Case 5). Arrows indicate the focal area of increased radiotracer uptake, with persistent uptake on delayed images, supporting hyperfunctioning parathyroid tissue in the appropriate clinical context.

For intraoperative confirmation, radioguided surgery was used in all cases. Background and target counts were recorded with a handheld gamma probe, and excised speci-

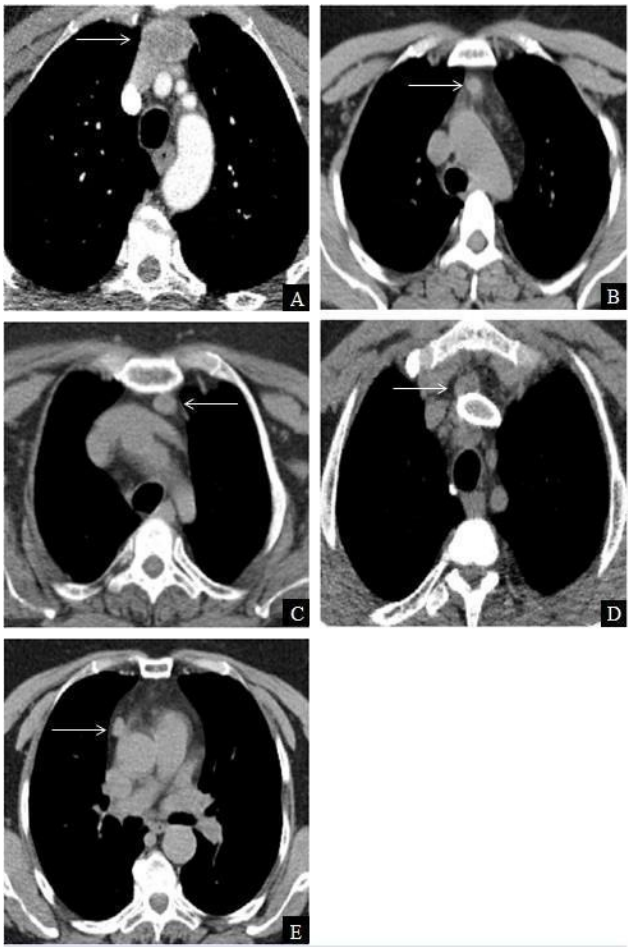

Fig. 2. Thoracic computed tomography (CT) findings in Cases 1–5. Axial CT images show well-circumscribed mediastinal soft-tissue lesions (arrows) consistent with ectopic parathyroid adenoma. Panels correspond to individual cases: (A) Case 1; (B) Case 2; (C) Case 3; (D) Case 4 (thoracic inlet/superior mediastinal lesion managed through a transcervical approach); (E) Case 5.

mens were verified *ex vivo*; an *ex vivo* count ≥20% of background and absence of residual activity in the resection bed supported complete excision [10]. Frozen section (FS) was performed to confirm parathyroid tissue.

Intraoperative parathyroid hormone (ioPTH) monitoring was used to confirm biochemical response; success was defined as >50% decline at 10–15 minutes after excision compared with baseline (institutional adaptation of the Miami criterion). The decision to conclude the operation required concordance among imaging, operative findings, gamma counts, FS, and ioPTH response.

Postoperatively, serum calcium and PTH were measured within 24 hours and before discharge. Patients were monitored for hypocalcemia, and calcium and/or calcitriol supplementation was administered when indicated. Outpatient follow-up was scheduled at 2 weeks and at 1, 6, and 12 months with clinical and biochemical assessment.

Given the small sample size, analyses were descriptive. Continuous variables are presented as median (minimum–maximum), and categorical variables as number and percentage.

Among 458 patients who underwent surgery for a solitary parathyroid adenoma, five cases of MEPA (1%; n = 5) were identified.

The median age was 62 years (40–70 years), and three patients were female, and two were male. One patient was asymptomatic at presentation, whereas the most common symptoms among the remaining patients were bone pain and fatigue. Associated clinical findings included nephrolithiasis, myalgia, palpitations, and osteoporosis.

Preoperative biochemical evaluation revealed albumin-corrected serum calcium levels ranging from 11.24 to 13.43 mg/dL and PTH levels between 161 and 1493 pg/mL. Preoperative localization was assessed by a combined imaging strategy in all patients. Cervical ultrasonography was negative in all cases. In contrast, 99mTc-sestamibi SPECT/CT demonstrated focal mediastinal uptake in all five patients (Fig. 1). Cervicothoracic CT further defined lesion size, depth, and relationships to adjacent mediastinal structures (Fig. 2). Four lesions were localized to the anterior mediastinum, whereas one lesion was situated at the thoracic inlet/superior mediastinum anterior to the left brachiocephalic vein. This lesion, shown in Fig. 2D, was relatively superficial on preoperative CT, without deep mediastinal extension or close adherence to major vascular structures; therefore, a transcervical approach was used.

Regarding surgical management, J-shaped partial median sternotomy was performed in four of five patients, whereas a transcervical approach was used in one patient. Operative time ranged from 56 to 150 minutes, and estimated blood loss ranged from 100 to 250 mL. In all cases, radioguided surgery enabled clear intraoperative localization of the mediastinal ectopic parathyroid adenoma. *Ex vivo* gamma probe measurements of the excised specimens exceeded the predefined threshold of ≥20% of background activity in all patients. Following excision, no residual radioactive signal was detected in the resection bed. All excised lesions were submitted for intraoperative FS analysis and were confirmed to be consistent with parathyroid tissue.

Based on the case-level biochemical follow-up data, serum calcium levels from postoperative day 1 through the 12-month follow-up period ranged between 8.60 and 11.76 mg/dL, while the overall temporal trend is illustrated in Fig. 3A. Based on the case-level intraoperative data summarized in Table 1, ioPTH monitoring demonstrated a marked decline after excision in all cases, with a 10-minute percentage decrease ranging from 48.3% to 85.5%; follow-up PTH levels showed a sustained postoperative decrease, as detailed in **Supplementary Table 1** and illustrated in Fig. 3B. No major surgery-related complications were observed. Only minor events corresponding to Clavien–Dindo grade I occurred. The length of hospital stay ranged from 3 to 5

Table 1. Summary of key diagnostic and therapeutic features of the five patients with mediastinal ectopic parathyroid adenoma.

Case	Age/sex	Presentation	Key localization findings	Lesion location	Surgical approach	Intraoperative confirmation	Outcome
1	66/M	Lethargy, fatigue, nephrolithiasis	Cervical USG negative; sestamibi positive; CT showed a 35 × 22 mm anterior mediastinal lesion	Anterior mediastinum (prevascular)	J-shaped partial median sternotomy	FS confirmed parathyroid tissue; ioPTH decline 48.3%	Normocalcemic and clinically stable at 1 year
2	40/F	Asymptomatic	Cervical USG negative; sestamibi positive; CT showed 8 × 8 mm midline anterior mediastinal lesion	Anterior mediastinum (midline)	J-shaped partial median sternotomy	FS confirmed parathyroid tissue; ioPTH decline 85.1%	Normocalcemic and clinically stable at 1 year
3	70/F	Bone pain, fatigue	Cervical USG negative; sestamibi positive; CT showed a 15 × 10 mm retrosternal lesion	Anterior mediastinum (retrosternal)	J-shaped partial median sternotomy	FS confirmed parathyroid tissue; ioPTH decline 85.5%	Normocalcemic and clinically stable at 1 year
4	49/M	Bone pain, fatigue, myalgia	Cervical USG negative; sestamibi positive; CT showed 18 × 10 mm thoracic inlet lesion	Superior mediastinum/thoracic inlet	Transcervical approach	FS confirmed parathyroid tissue; ioPTH decline 69.7%	Normocalcemic and clinically stable at 1 year
5	62/F	Bone pain, palpitations, osteoporosis	Cervical USG negative; sestamibi positive; CT showed a 12 × 8 mm lesion adjacent to the ascending aorta	Anterior mediastinum	J-shaped partial median sternotomy	FS confirmed parathyroid tissue; ioPTH decline 66.4%	Normocalcemic and clinically stable at 1 year

Abbreviations: USG, ultrasonography; CT, computed tomography; FS, frozen section; ioPTH, intraoperative parathyroid hormone.

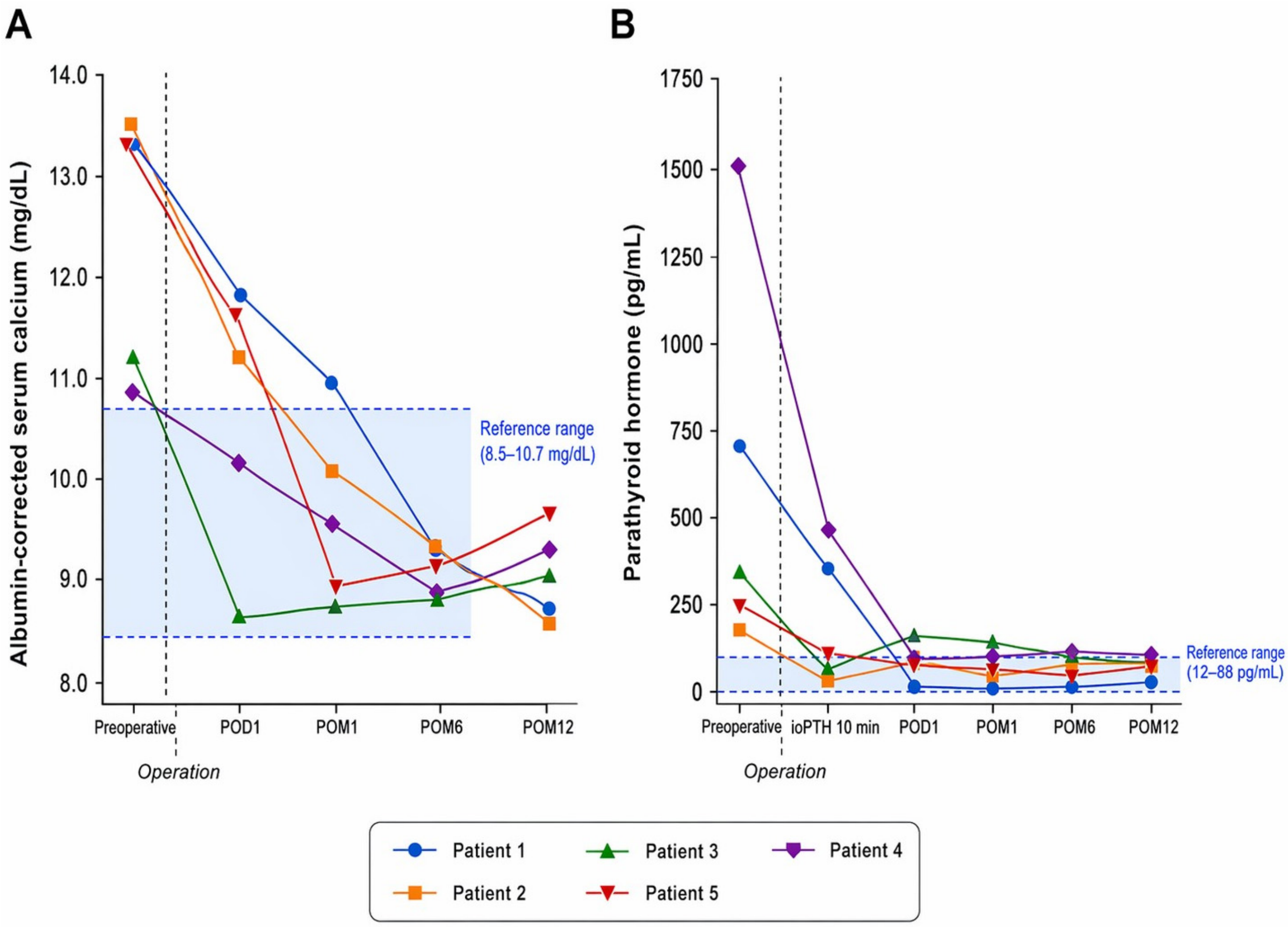

Fig. 3. Perioperative biochemical trends in the five patients with mediastinal ectopic parathyroid adenoma. (A) Perioperative trends in albumin-corrected serum calcium for Patients 1–5 from the preoperative period to postoperative month 12. (B) Perioperative trends in parathyroid hormone (PTH) for patients 1–5, including the 10-minute intraoperative PTH measurement after excision; the percentage decline in intraoperative parathyroid hormone (ioPTH) for each patient is shown in the figure. The dashed vertical line indicates the operation, and the shaded blue bands denote reference ranges (calcium 8.5–10.7 mg/dL; PTH 12–88 pg/mL). Time points: preoperative, 10-minute intraoperative ioPTH, postoperative day (POD) 1 and postoperative months (POM) 1, 6 and 12.

days. Final histopathological examination confirmed parathyroid adenoma in all cases. At follow-up visits conducted at 2 weeks and at 1, 6, and 12 months, all patients remained normocalcemic and clinically stable. The key demographic, diagnostic, surgical, and outcome characteristics of the cases are summarized in Table 1, while detailed clinical, imaging, biochemical, and follow-up data are provided in **Supplementary Table 1**.

Discussion

This case series underscores that curative treatment of MEPA relies on accurate preoperative localization, an access route tailored to lesion depth and mediastinal anatomy, and objective intraoperative confirmation of complete excision within the same operative session. In our cohort, despite negative cervical USG, the combined use of 99mTc-sestamibi SPECT/CT and cervicothoracic CT delineated the lesion and its relationships to adjacent structures and directly guided operative planning.

The concomitant use of intraoperative confirmation modalities—radioguided gamma probe assessment, FS analysis, and ioPTH monitoring—provided complementary verification of target tissue removal. Within this multimodal framework, all patients achieved biochemical normalization with an uneventful short-term clinical course.

Primary hyperparathyroidism may present across a broad spectrum, from the classic “stones, bones, groans, and psychic moans” to subtle or nonspecific symptoms. Musculoskeletal pain and fatigue are common, and target-organ involvement is often reflected by osteoporosis and nephrolithiasis [11]. In our series, bone pain and fatigue predominated, with osteoporosis and nephrolithiasis as frequent manifestations, while one patient was asymptomatic—consistent with increasingly detected “silent” PHPT [11].

Localization becomes more challenging in ectopic disease and is further amplified in mediastinal lesions. USG is operator dependent, has limited sensitivity for ectopic glands (approximately 11–59%), and many ectopic sites—including the mediastinum—are sonographically inaccessible [11,12]. Therefore, when clinical suspicion persists, functional imaging with 99mTc-sestamibi (SPECT/CT) combined with four-dimensional computed tomography (CT/4D-CT) is typically required. This multimodal, anatomy-oriented localization strategy is also supported by recent literature on ectopic parathyroid adenomas [11,13].

Dual-phase 99mTc-sestamibi scintigraphy is widely used for parathyroid localization and performs well in many patients with PHPT [4,5]. Adding SPECT/CT improves anatomic precision and increases detection of ectopic adenomas [14–16]. In reoperative settings, ectopic location may contribute to missed or persistent disease [17], and sensitivity may be lower, although specificity remains high [11,18]. When sestamibi findings are negative or equivocal, 18F-fluorocholine positron emission tomography/computed tomography (PET/CT) can provide additional value, particularly for small or occult lesions [19].

Cross-sectional imaging serves as a surgical "road map" by defining mediastinal relationships and guiding access selection. Cervicothoracic CT has been reported to localize ectopic adenomas with a sensitivity of approximately 75% [20]. Beyond conventional CT, 4D-CT offers high spatial resolution and dynamic enhancement, which can be helpful in mediastinal or thyrothymic localizations by clarifying the lesion's relationship to the inferior thyroid margin and the manubrium [21,22]. In our series, SPECT/CT enabled functional targeting, while cervicothoracic CT clarified lesion size and mediastinal anatomy to inform the operative approach.

Surgical excision remains the definitive treatment for PHPT caused by MEPA [3]. Deep mediastinal lesions may not be safely accessible via a transcervical approach; historically, sternotomy or thoracotomy provided reliable exposure and vascular control, but at the expense of higher morbidity and risk of major neurovascular injury [23–25].

Minimally invasive thoracic approaches are increasingly used for mediastinal ectopic parathyroid adenomas in selected patients. Compared with open surgery, video-assisted thoracic surgery (VATS) may offer reduced postoperative pain, shorter hospital stay, and faster recovery when the lesion is well localized and thoracoscopically accessible. Robot-assisted thoracic surgery (RATS) may provide additional technical advantages in the confined mediastinal space, particularly enhanced visualization and greater instrument dexterity, although cost and limited availability remain important constraints. Nevertheless, open approaches still provide the most direct exposure and the most secure vascular control in cases with deep anterior mediastinal location, retrosternal extension, large size, or close adjacency to major vessels. In our cohort, approach selection was driven by lesion depth and vascular proximity on preoperative imaging. Four lesions were located in the anterior mediastinum/prevascular-retrosternal region, including one adjacent to the ascending aorta, and were therefore managed through a limited J-shaped sternotomy to ensure controlled exposure while avoiding a full sternotomy. By contrast, the thoracic inlet lesion anterior to the left brachiocephalic vein was considered safely mobilizable through a transcervical approach [26–32].

A central determinant of success in mediastinal parathyroid surgery is confirming target tissue removal and adequacy of resection intraoperatively. A multilayered strategy integrating localization assessment, biochemical response, and tissue diagnosis helps minimize persistence and the need for reoperation.

Radioguided surgery facilitates real-time localization of hyperfunctioning tissue using a gamma probe after 99mTc-sestamibi administration and can strengthen confirmation through *ex vivo* counts and resection-bed assessment [9,33]. In selected cases, adjuncts such as near-infrared fluorescence/autofluorescence or dyes have been described, but their routine role for mediastinal lesions remains evolving [34,35].

ioPTH monitoring leverages the short half-life of PTH and the expected early kinetic decline after excision. A $\geq$50% reduction at 10 minutes compared with baseline (Miami criterion) is widely accepted as indicative of biochemical success [36–38]. When responses are near the cutoff, confirming the trend with an additional time point and interpreting results alongside intraoperative findings is recommended [37,39]. In our series, Case 1 showed a 48.3% decline in ioPTH at 10 minutes, which was slightly below the conventional $>$50% threshold. However, borderline responses around the cutoff may still be compatible with successful resection, particularly when interpreted together with the overall intraoperative and postoperative findings. In Case 1, radioguided localization was concordant with preoperative imaging, frozen section confirmed parathyroid tissue, no residual activity was detected in the resection bed, and the patient remained normocalcemic during follow-up. Therefore, this finding was considered more consistent with borderline early ioPTH kinetics than with persistent disease.

FS analysis provides rapid confirmation of parathyroid tissue, which is particularly useful in mediastinal dissections where thymic fat or lymph nodes may mimic the target lesion. Although high accuracy has been reported, FS may prolong operative time and is subject to sampling and interpretive limitations; therefore, routine use in all cases remains debated [40,41]. In our series, gamma probe measurements, FS, and ioPTH declines were jointly used to support intraoperative completeness of excision.

Postoperative care should focus on early verification of biochemical cure and timely recognition of hypocalcemia and hungry bone syndrome. Serum calcium (albumin-corrected and, when indicated, ionized), phosphate, magnesium, and PTH should be monitored in the first 24 hours with close clinical surveillance for paresthesia, cramps, or tetany. High-risk patients (very high preoperative PTH/calcium, significant bone disease, large adenomas, or vitamin D deficiency) may benefit from early oral calcium ± calcitriol and intensified laboratory follow-up; symptomatic or marked hypocalcemia warrants intravenous calcium and electrolyte replacement, including magnesium [42–44].

After sternotomy/thoracotomy, adequate analgesia, respiratory physiotherapy, and early mobilization are important to reduce pulmonary complications. Discharge should be based on clinical stability, pain control, and stable calcium levels; normocalcemia maintained for at least 6 months is generally considered confirmatory of cure [9,42].

In our cohort, serial calcium and PTH monitoring was routinely performed within the first 24 hours and prior to discharge, and follow-up was structured within a "cure–persistence–recurrence" framework. None of the patients developed clinical or biochemical hypocalcemia, and supplementation was not required.

The main practical insight from our series is that mediastinal ectopic parathyroid adenoma should be managed with an integrated stepwise strategy rather than reliance on a single localization modality or a uniform surgical approach. In our cohort, cervical ultrasonography was nonlocalizing, whereas 99mTc-sestamibi SPECT/CT provided functional localization, and cervicothoracic CT defined lesion depth, mediastinal relationships, and operative accessibility. This multimodal preoperative assessment helped determine whether a transcervical approach was feasible or whether sternotomy-based access was required. In addition, radioguided assessment, frozen-section confirmation, and intraoperative PTH monitoring provided complementary intraoperative assurance of complete excision. Taken together, these findings suggest that combining functional imaging, anatomical mapping, and multimodal intraoperative confirmation may improve surgical planning and support safe and effective treatment in anatomically challenging mediastinal cases.

This study is limited by its retrospective design, small sample size, and single-center nature. The predominance of sternotomy limits the comparative assessment of minimally invasive thoracic techniques.

Conclusions

In conclusion, surgical management of mediastinal parathyroid adenomas should be individualized according to lesion location, depth, and vascular relationships. While VATS or RATS may be preferred in selected patients, open approaches remain necessary in anatomically challenging cases; multimodal imaging and intraoperative confirmation are central to achieving safe and durable biochemical cure.

Availability of Data and Materials

The datasets generated and analyzed during the current study are not publicly available due to institutional data protection policies and patient confidentiality but are available from the corresponding author on reasonable request.

Author Contributions

MY, MBa, SB, and MBe made substantial contributions to the conception and design of the study. MY, MBa, MS, CZ, SB, and MBe contributed to the acquisition, analysis, and interpretation of the data. MY drafted the initial manuscript. All authors have been involved in revising the manuscript critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Formal ethics committee approval was not obtained for this retrospective case series. Written informed consent was obtained from the patients for publication of their anonymized clinical data. The study conformed to the provisions of the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62713/aic.4597.

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