Revista de Osteoporosis y Metabolismo Mineral

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10.20960/RevOsteoporosMetabMiner.00114

06/16/2026

00114

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Revisión narrativa de la literatura sobre adenoma paratiroideo ectópico en la región submandibular a raíz de un caso detectado mediante PET/TC con ^{18}F-FCH

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Received: 21/05/2026
Accepted: 11/06/2026

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Ethical approval statement: This study was conducted in accordance with the principles of the Declaration of Helsinki, and ethical approval was obtained from the institutional ethics committee of our center.

Artificial intelligence: The authors declare not to have used artificial intelligence (AI) or any AI-assisted technologies in the elaboration of the article.

Conflict of interest and funding statement: The authors declare that they have no conflicts of interest related to this work.

ABSTRACT

The ectopic location of the parathyroid glands poses a significant challenge in the diagnosis and management of primary hyperparathyroidism, particularly when planning minimally invasive parathyroidectomy, whose success relies heavily on accurate preoperative localization. Ectopic parathyroid adenomas in the submandibular region are exceptionally rare, and their surgical management may require conversion to a bilateral open exploratory approach or a subsequent reoperation due to persistent disease. Motivated by a complex clinical case, this narrative review examines the current literature on ectopic submandibular parathyroid adenomas, highlighting diagnostic strategies, imaging modalities, and surgical considerations. The findings underscore the critical importance of precise preoperative localization to achieve successful targeted resection, even in challenging ectopic presentations.

Keywords: Primary hyperparathyroidism. Submandibular ectopic parathyroid adenoma. Ultrasound. Scintigraphy with Tc99m-sestamibi. SPECT-TC; PET CT with ^{18}F-Choline.

RESUMEN

La ubicación ectópica de las glándulas paratiroides plantea un desafío importante en el diagnóstico y tratamiento del hiperparatiroidismo primario, particularmente cuando se planifica una paratiroidectomía mínimamente invasiva, cuyo éxito depende en gran medida de una localización preoperatoria precisa. Los adenomas paratiroideos ectópicos en la región submandibular son excepcionalmente raros y su tratamiento quirúrgico puede requerir conversión a un abordaje exploratorio abierto bilateral o una reintervención posterior debido a la persistencia de la enfermedad. Motivada por un caso clínico complejo, esta revisión narrativa examina la literatura actual sobre adenomas paratiroideos submandibulares ectópicos, y destaca estrategias de diagnóstico, modalidades de imágenes y consideraciones quirúrgicas. Los hallazgos subrayan la importancia crítica de una localización preoperatoria precisa para

lograr una resección dirigida exitosa, incluso en presentaciones ectópicas desafiantes.

Palabras clave: Hiperparatiroidismo primario. Adenoma paratiroideo ectópico submandibular. Ecografía. Gammagrafía con Tc99m-sestamibi. SPECT-TC. PET CT con ^{18}F-colina.

INTRODUCTION

Primary hyperparathyroidism (PHPT) is caused by increased activity of the parathyroid glands, resulting from excessive secretion of parathyroid hormone (PTH). The majority of cases are due to a single adenoma (85 %), of which 5-20 % are ectopic (1-4), and, to a lesser extent, by hyperplasia of all four glands (10-15 %) (2,5-7). It has an approximate prevalence of 1 % in the general population, with a female predominance of 3-4:1, typically affecting middle-aged women between 40 and 60 years of age (3,6-8). It is the third most common endocrine disorder, after diabetes mellitus and thyroid disease (2,3,5,7).

The diagnosis of PHPT is biochemical, often made incidentally through the detection of hypercalcemia in repeated laboratory tests, regardless of the presence of clinical symptoms suggestive of the disease. Simultaneous elevation of serum calcium and PTH levels is required for the diagnosis of PHPT. The curative treatment for PHPT is the surgical removal of the affected parathyroid glands. Once diagnosed, surgery is considered only if the patient meets the criteria established by both European and American guidelines (9-11). Preoperative imaging for the localization of hyperfunctioning parathyroid glands is indicated only when the patient meets the surgical criteria.

Traditionally, a wide-open surgery with standard bilateral cervical exploration (BCE) was performed, aiming to identify all four parathyroid glands. Currently, surgery has evolved toward a more targeted approach, minimally invasive parathyroidectomy (MIP), in which precise preoperative imaging plays a fundamental role. MIP reduces pain and the number of complications, shortens operative time and hospital stay, and, of course, lowers healthcare costs while achieving better aesthetic outcomes (2,6).

Currently, the combination of ^{99m}Tc-sestamibi scintigraphy and ultrasonography is considered the gold standard technique for the localization of parathyroid

adenomas (6). However, in negative, uncertain, or discordant cases, guidelines recommend performing additional imaging techniques depending on availability at each center, including single-photon emission computed tomography (SPECT/CT) and four-dimensional computed tomography (4D-CT) or magnetic resonance imaging (4D-MRI) (9,10). More recently, PET/CT with ^{18}F-fluorocholine (^{18}F-FCH PET/CT) has been increasingly used for the localization of parathyroid adenomas.

The ectopic location of a parathyroid adenoma in the submandibular triangle is an uncommon presentation (2-7 %) that represents a diagnostic and surgical challenge (12). Despite its complexity, with adequate preoperative radiological localization and intraoperative tools such as intraoperative PTH (ioPTH) monitoring, effective MIP can be performed even in these atypical ectopic cases. We present the case of a patient with persistent PHPT despite a previous bilateral cervical exploration (BCE), without postoperative normalization of calcium or PTH levels, in whom a hidden ectopic adenoma was suspected.

MATERIAL AND METHODS

Study design

A narrative literature review was conducted with the aim of analyzing the available scientific evidence on ectopic parathyroid adenomas in the submandibular region.

Information sources

The literature search was performed in the PubMed (Medline) database. Articles published up to July 2025 were included.

Selection criteria

Included: Original articles, reviews, meta-analyses, and case studies.

Excluded: Articles with no full-text available and studies irrelevant to the topic.

Search strategy

The following MeSH terms and keywords were used: Primary hyperparathyroidism; submandibular ectopic parathyroid adenoma; ultrasound; Tc99m-sestamibi scintigraphy; SPECT/CT; ^{18}F-Choline PET/CT. Boolean operators AND and OR were applied to combine terms.

Data extraction

The following data were collected from each article:

- Article title, first author, city, year of publication, and reference.
- Study type and sample size.
- Main results relevant to the topic: number of surgeries, preoperative imaging, surgical technique, time to case resolution, complications, and conclusions.

Data synthesis

The extracted data were organized descriptively in tabular form to summarize and compare the findings of the different studies (Table I).

CASE REPORT

A 42-year-old Caucasian woman presented to her primary care physician with dizziness and generalized weakness of three days' duration. Her medical history included hypertension treated with hydrochlorothiazide. Physical examination and vital signs were unremarkable. Blood analysis revealed hypercalcemia with a protein-corrected calcium of 10.3 mg/dl.

Further evaluation revealed phosphorus = 2.5 mg/dl, PTH = 156 pg/ml, vitamin D = 43 ng/ml, and TSH = 1.6 µIU/ml. A 24-hour urine collection showed hypercalciuria (486 mg/24 h). She was referred to the Endocrinology department.

Directed anamnesis confirmed typical PHPT symptoms, including joint pain, asthenia, and dizziness. The patient had no pathological fractures but reported two episodes of nephrolithiasis two years earlier. Abdominal ultrasound and X-rays ruled out current lithiasis. Bone densitometry revealed lumbar and femoral z-scores within normal range for her age and sex.

INVESTIGATIONS AND DIFFERENTIAL DIAGNOSIS

The patient's evaluation began with the incidental finding of hypercalcemia. Differential diagnosis includes PHPT, malignancy-related hypercalcemia, vitamin D intoxication, chronic kidney disease, medications (e.g., thiazides,

lithium), familial hypocalciuric hypercalcemia, and granulomatous diseases such as sarcoidosis or tuberculosis (11).

Following correction of a concurrent vitamin D deficiency with monthly hydroferol and replacement of hydrochlorothiazide, repeated labs showed persistent abnormalities: calcium = 10.4 mg/dl, PTH = 128 pg/ml, and calciuria = 594 mg/24 h. These findings confirmed PHPT after ruling out secondary causes.

The patient met both European and American surgical criteria due to her age and persistent hypercalcemia (9-11). Surgical intervention was proposed and accepted. Initial imaging with cervical ultrasound and Tc^{99m}-sestamibi SPECT/CT was negative. Endoscopic ultrasound identified a potential 4 mm left inferior parathyroid adenoma near the vascular bundle.

The patient underwent bilateral neck exploration. The left side was explored first without lesion identification; exploration proceeded to the right side, where a 2 cm nodule was excised and sent for pathology. Intraoperative PTH monitoring showed no decrease (baseline PTH = 135 pg/ml; ioPTH = 165 pg/ml; percent drop = -1.85 %), prompting extended exploration to retroesophageal, thymic, thyroid capsule, and vascular compartments without further findings. Suspecting a mediastinal ectopic adenoma, surgery was concluded. Postoperative calcium remained elevated (10.7 mg/dl). Pathology identified the excised tissue as a reactive lymph node.

The patient was followed over 4 years. Labs remained abnormal: calcium = 11.2 mg/dL; PTH = 197 pg/ml; calciuria = 172 mg/24 h. Repeated imaging remained negative. During this period, the patient experienced a new, more severe episode of renal colic. Abdominal ultrasonography confirmed a 2 mm calculus in the lower calyceal group of the left kidney.

Given the need for a curative solution, it was decided to perform a new preoperative imaging modality that had just been introduced in the field of parathyroid surgery: ^{18}F-FCH PET/CT. This study identified a hypermetabolic lesion measuring 6 × 6 × 14 mm in the left submandibular cervical level IIA, adjacent to the submandibular gland (Fig. 1).

The visualization of a hypermetabolic focus in the submandibular region, in the clinical context of this patient, suggested an ectopic parathyroid adenoma, which had to be differentiated from reactive lymphadenopathy, salivary gland tumors, or superior thyroid lesions. These alternatives were promptly excluded

through histological analysis with fine-needle aspiration, which confirmed elevated PTH levels and supporting ectopic adenoma diagnosis.

TREATMENT

A second revision surgery was performed. Intraoperatively, a brownish nodule posterior and caudal to the left submandibular gland, corresponding to the imaging findings, was excised. ioPTH monitoring showed a > 50 % drop (baseline PTH = 225 pg/mL; ioPTH = 87.6 pg/mL). Pathology confirmed a 17 mm, 0.7 g parathyroid adenoma.

OUTCOME AND FOLLOW-UP

Two years postoperatively, the patient remains under follow-up. Clinical symptoms have improved, with no further nephrolithiasis episodes. Calcium and calciuria levels are within normal range (8.5 mg/dl and 138 mg/24 h, respectively).

DISCUSSION

The parathyroid glands are usually four small oval structures located on the posterior surface of the thyroid gland. However, their position may vary, making localization difficult in some patients, as in the present case. In fact, up to 20 % of cases involve ectopic localization (2-4). The most frequent ectopic locations are retroesophageal, thymic, carotid, mediastinal, and intrathyroidal, with the submandibular region being the rarest (2,4,7,8).

Such an atypical submandibular location (< 1 %) can be explained by embryological migration defects of the parathyroid glands. For this reason, they are referred to as “high cervical or undescended parathyroid adenomas”, often resembling lymph nodes or salivary lesions (2,4,12). Lee et al. reported 16 high cervical adenomas among 5,241 patients (0.3 %), only one in the submandibular region. 14 were primary parathyroidectomies, while 2 cases were reoperated. In this group of patients, scintigraphy showed a sensitivity of 67 %, with a total of 9 patients requiring BCE (2).

The treatment of PHPT is surgical, and resection of the hyperfunctioning parathyroid glands is curative. Reoperation is common in ectopic cases following failed initial surgery (2,13). Axelrod et al. reported three submandibular ectopic adenomas discovered only during revision surgery (6).

Calcutt et al. described a case that required three surgeries before finding the submandibular adenoma (14). Preoperative localization is thus crucial to minimize unnecessary surgical exploration. Aboisheva et al. even reported the case of an 84-year-old woman who underwent years of conservative medical management without normalization of calcium levels due to failure to identify the pathological focus (7).

Conventional imaging modalities (scintigraphy and ultrasound) have high sensitivity and specificity in the detection of adenomas (70-80 %) (3-5,15-18). For the 20-30 % of patients with negative results, more advanced techniques are necessary. ^{18}F-FCH PET/CT combines functional and anatomical imaging, offers higher spatial resolution in less time and radiation exposure, despite their higher cost and limited availability, it has shown promising results. A 2019 meta-analysis reported 95 % sensitivity, 97 % positive predictive value, and 91 % detection rate for ^{18}F-FCH PET/CT (19), potentially avoiding unnecessary bilateral exploration in 75-87 % of cases (20).

This case illustrates a rare submandibular ectopic adenoma diagnosed after years of persistent PHPT and failed surgery. While conventional imaging was non-diagnostic, ^{18}F-FCH PET/CT provided accurate localization, enabling curative surgery.

There are few published cases of parathyroid adenoma in the submandibular region. To be exact, we have done a bibliographic review finding a total of 14 articles in Pubmed, the oldest being from 1997 (Table I). In most cases, conventional images have been able to detect them or SPECT-TC (1,4,21-26). There are only two published cases that have found submandibular adenoma thanks to the PET-CT modality: one with the 11C-choline tracer (18) and another with the ^{18}F-choline (26). We report one more case of parathyroid adenoma in the submandibular region located by ^{18}F-FCH PET/CT, when neither scintigraphy + SPECT/CT - Tc^{99m}-sestamibi nor cervical ultrasound have been able to detect it.

The identification of an ectopic submandibular adenoma constitutes a very unusual location, which can be a real challenge for the head and neck surgeon. The majority of these patients have already undergone a first bilateral exploratory open surgery without resolution with persistent hyperparathyroidism, requiring a reintervention in a second stage, increasing the rate of postoperative complications. More precise imaging modalities are

necessary for preoperative localization of the adenoma, to achieve its removal with targeted surgery, even in atypical ectopic cases like our patient.

The use of ^{18}F-FCH PET/CT as a preoperative localization tool in the surgical treatment of PHPT represents a significant advancement in terms of patient safety and clinical benefit. With its higher sensitivity and accuracy, it enables more targeted and less invasive surgical planning. This leads to shorter operative times, a reduced risk of complications such as recurrent laryngeal nerve injury or hypocalcemia, and a faster recovery. Moreover, by increasing the success rate of the initial surgery, the need for reoperations is reduced, which improves clinical outcomes and the patient's quality of life.

CONCLUSION

The case presented emphasizes the need for surgical management of PHPT to reduce its morbidity and mortality. A rigorous clinical, biochemical and radiological correlation is important, as well as the surgeon's skill in knowing the existence of various migratory patterns of the parathyroid glands and their possible anatomical variants. Furthermore, it highlights the value of advanced preoperative imaging techniques in optimizing surgical results, especially in the context of minimally invasive approaches. ^{18}F-FCH PET/CT is a promising modality in the preoperative localization of ectopic adenomas, in our case it represents the possibility of cure and resolution of the disease with surgery, which was not possible to achieve with conventional tools.

Finally, it is necessary to highlight the importance of multidisciplinary clinical committees that bring together different specialist physicians from different areas (endocrinology, otorhinolaryngology, radiology, nuclear medicine, etc.) to discuss different clinical cases.

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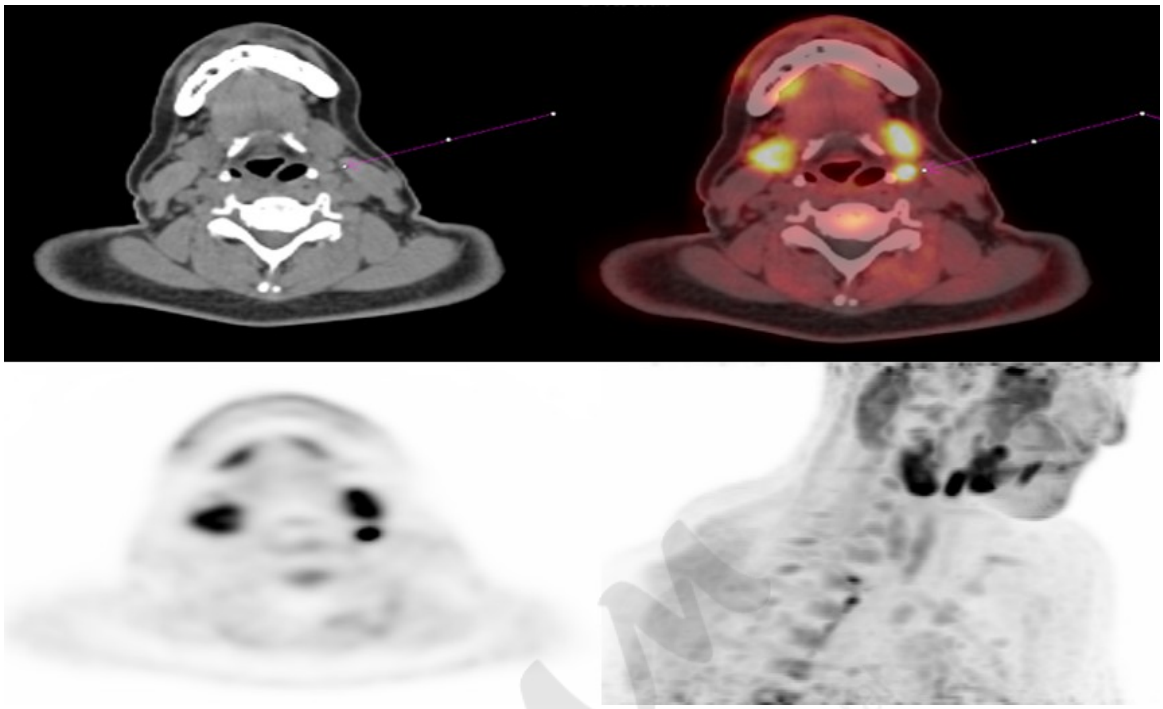

Figure 1. A nodular lesion with an elongated morphology measuring approximately 6 × 6 × 14 mm (AP × T × CC) is identified in the left submandibular region at level IIA. It is located posterior and inferior to the left submandibular gland, anterior to the vascular bundle, and medial to the sternocleidomastoid muscle. The lesion appears hyperintense in the arterial phase, with intense ^{18}F-Choline uptake, suggestive of an ectopic parathyroid adenoma. No other lesions with radiotracer uptake are observed. Physiological tracer uptake is seen in the bone marrow, salivary glands, and thyroid. SUVmax: post-injection: 20.9; at 20 min: 15.8; at 60 min: 15.9.

Table I. Table literature review on ectopic adenoma in the submandibular region

Title	Author year city	*n*	Design	Image	Number of surgeries technique	Location	Complication	Time of resolution	Conclusion
SPECT and subtraction imaging of an ectopic parathyroid adenoma (23)	LS Serchuk, 1997 USA	1 (1 submandibular)	Case report	CT-99m sestamibi + SPECT and subtraction imaging	2 (BCE)	In relation to the right submandibular salivary gland	-	-	SPECT localized the ectopic parathyroid adenoma in relation to the right submandibular salivary gland, while subtraction imaging confirmed that the focus was indeed a parathyroid lesion and not simply an anatomical variant of a normal salivary gland
Localization of abnormal parathyroid tissue with use of technetium-99m-sestamibi (14)	VG Calcutt, 1997 USA	24 (1 submandibular)	Case series	CT-99m sestamibi	3 (BCE)	Medial to the right carotid artery below the angle of the mandible	No	-	Precise localization of an adenoma simplifies surgical exploration. CT-99msestamibi has become the preferred method for noninvasive localization of ectopic parathyroid glands
Appearance of ectopic undescended inferior parathyroid adenomas on technetium CT 99m sestamibi scintigraphy: a lesson from reoperative parathyroidectomy (6)	D Axelrod, 2003 USA	3 (3 submandibulars)	Case series	CT-99m sestamibi	3 (BCE + thymectomy + subtotal thyroidectomy)	In the left carotid sheath inferior to the jaw angle	-	-	Pay attention to the contour of radioactivity in the region of the submandibular salivary gland that can alert surgeons to the presence of an inferior undescended adenoma. This can facilitate selective operation
65-year-old female patient with persistent hypercalcemia (21)	Wiedmann, 2007 Germany	1 (1 submandibular)	Case report	CT-99m sestamibi + SPECT + CT + US	2 (BCE + thyroidectomy)	left submandibular region	Transient hypocalcemia	-	If adenoma is not identified during exploratory surgery, consider ectopic location; it is recommended to suspend and complete a localization study with subsequent

									reintervention
Para-hyoid ectopic parathyroid adenoma localized by CT-99m MIBI SPECT (22)	Rajagopalan, 2008 USA	1 (1 subman dibular)	Case report	CT-99m sestamibi + SPECT + CT + US	2 (BCE)	Posteroinferior parahyoid adenoma of the right submandibular gland	-	2 years	Pay attention to the focus of uptake in the “submandibular tail” suspected of ectopic parathyroid adenoma in the submandibular region
Adenomas of cervical maldescended parathyroid glands: pearls and pitfalls (2)	James C Lee, 2012 Australia	5241 (1 subman dibular)	Case series	CT-99m sestamibi + US	1 (MIP)	Triangle submandibular	-	-	High surgical success rates can be achieved with PMI if knowledge of embryology and reliable preoperative localization are available
Ectopic Undescended Parathyroid Adenoma-SPECT/CT Avoids False-Negative Interpretation on 99mCT-MIBI Dual-Phase Scintigraphy (4)	S Mahajan 2018 USA	1 (1 subman dibular)	Case report	CT-99m sestamibi + SPECT	-	Ectopic adenoma inferior to the left submandibular gland	-	-	Ectopic adenomas close to the submandibular gland may go unnoticed on scintigraphy due to overlapping gland activity. Our case demonstrates the potential advantage of SPECT/CT over sestamibi
Ectopic parathyroid adenoma in the submandibular region: a case report (24)	Y Kong 2019 China	1 (1 subman dibular)	Case report	CT-99m sestamibi + SPECT	1 (MIP)	Posteromedial to the left submandibular gland	No	-	Ectopic parathyroid adenomas should be considered part of the differential diagnosis of tumors of the submandibular region
Acute hyperparathyroid crisis: ectopic submandibular parathyroid gland the culprit (13)	M Unais, 2020 India	1 (1 subman dibular)	Case report	US + CT	2 (MIP)	Right submandibular region	No	1 week	The adenoma requires precise localization, complicated in life-threatening situations such as a hyperparathyroid crisis. The images have limitations and further surgical re-exploration may be necessary
Ectopic Submandibular Parathyroid Adenoma by CT-	Fung Him Ng 2020 China	1 (1 subman dibular)	Case report	CT-99m sestamibi + SPECT	-	Inferior to the right submandibular gland	-	-	Ectopic adenomas require a multimodal approach in operative planning. SPECT-CT provides good information on

99m Sestamibi SPECT/CT Localization (1)									anatomical details
99CTm-MIBI SPECT/CT negative ectopic parathyroid adenoma in submandibular region: a case report (18)	Y Lai 2023 China	1 (1 submandibular)	Case report	CT-99m sestamibi + SPECT + US + PET/CT 11C-colina	2 (BCE + right hemithyroidectomy)	Submandibular region posterior to the right submandibular gland	No	6 years	Ectopic adenoma in the submandibular region is exceptional. When conventional tests are negative, suspicion should be raised and 11C-choline PET/CT can accurately localize and achieve surgical success
Submandibular Ectopic Parathyroid Adenoma: A Case Report (26)	JA H Tawil 2023 Colombia	1 (1 submandibular)	Case report	CT-99m sestamibi + SPECT + US + 18F-FCH PET/CT	1 (MIP)	Right submandibular region	No	6 months	Surgical management of PHPT reduces morbidity and mortality. It is important to consider ectopic locations of adenomas. 18F-FCH PET/CT locates the adenoma precisely and facilitates successful surgery
Multimodality Evaluation of Persistent Hyperparathyroidism in a Rare Case of Ectopic Submandibular Parathyroid Adenoma (25)	Edamadaka 2024 India	1 (1 submandibular)	Case report	CT-99m sestamibi + SPECT + US + CT-4D	1 (MIP)	Submandibular region	-	-	99mCT MIBI-SPECT/CT and 4D-CT improve preoperative detection of parathyroid adenoma in rare ectopic sites, such as in this case of persistent hyperparathyroidism
Management of primary hyperparathyroidism with rare localization of ectopic adenoma parathyroid gland (7)	Aboisheva, 2024 Russia	1 (1 submandibular)	Case report	CT-99m sestamibi + SPECT + US + CT	Conservative treatment (high surgical risk)	Posterior to the internal jugular vein next to the right submandibular gland	No	10 years	Ectopic adenomas make topographic diagnosis difficult and require advanced imaging methods. Management should be individualized based on location and comorbidities

US: ultrasound; CT: computed tomography; SPECT: single photon emission computed tomography; ^{18}F-FCH: ^{18}F-fluorocholine; PET: positron emission tomography; BCE: bilateral cervical examination; MIP: minimally invasive parathyroidectomy.