Primary hyperparathyroidism with surgical indication and negative or equivocal scintigraphy: safety and reliability of PTH washout. A systematic review and meta-analysis

Marco Castellana¹, Camilla Virili², Andrea Palermo³, Francesco Giorgino¹, Luca Giovanella⁴ and Pierpaolo Trimboli⁴

¹Section of Internal Medicine, Endocrinology, Andrology and Metabolic Diseases, Department of Emergency and Organ Transplantation, University of Bari Aldo Moro, Bari, Italy, ²Science and Medico-Surgical Biotechnologies, Sapienza University of Rome, Roma, Italy, ³Unit of Endocrinology and Diabetes, Campus Bio-Medico University, Roma, Italy, and ⁴Department of Nuclear Medicine and Thyroid Centre, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland

Correspondence
should be addressed
to M Castellana
Email
marco.castellana@uniba.it

Abstract

Objective: Despite the improvements in ultrasound (US) and scintigraphy, 10–20% of patients with primary hyperparathyroidism (PHPT) still have discordant findings. We performed a systematic review and meta-analysis to assess the safety and the diagnostic performance of US-guided PTH washout (FNA-PTH) in patients with PHPT, a suspected parathyroid lesion on US but negative or equivocal scintigraphy.

Methods: The review was registered on PROSPERO (CRD42019124249). PubMed, Scopus, CENTRAL and Web of Science were searched until February 2019. Original articles reporting complications and diagnostic performance of FNA-PTH in biochemically and histopathologically diagnosed PHPT were selected. The risk of bias of included studies was assessed through QUADAS-2. Summary operating points were estimated using a random-effects model.

Results: Out of 2573 retrieved papers, nine cohort studies were included in the review. No major procedure-related complications were found. Pooled sensitivity was 95% (95% CI: 91–98; I^2 : = 14%) and positive predictive value was 97% (95% CI: 93–100; I^2 : = 39%). There were not enough data for specificity and negative predictive value to perform a meta-analysis. However, pooling results of all lesions, they were estimated to be 83 and 73%, respectively.

Conclusions: In patients with biochemically proven PHPT and discordant imaging, FNA-PTH was a safe and accurate procedure. In this specific setting of patients, FNA-PTH could be used as a rule-in test for minimally invasive parathyroidectomy.

European Journal of
Endocrinology
(2019) **181**, 245–253

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by an autonomous secretion of parathyroid hormone (PTH). In North America and Europe, it is usually diagnosed as an asymptomatic

disease, following the widespread laboratory testing. Specific clinical manifestations are related to acute hypercalcemia and/or involvement of target organs, including bone (osteitis fibrosa cystica, osteoporosis,

fractures), kidney (chronic kidney disease, stones, nephrocalcinosis) and neuromuscular system (muscular weakness). Peptic ulcer, pancreatitis, hypertension or cognitive decline have also been described (1, 2, 3, 4).

Surgery is the only definitive treatment for PHPT and is thus strongly recommended in all symptomatic patients as well as in asymptomatic patients aged less than 50 years meeting specific criteria (5, 6). The traditional procedure is represented by bilateral neck exploration with identification of all four parathyroids, followed by removal of the adenoma or subtotal resection in patients with parathyroid hyperplasia. In the rare cases of parathyroid carcinoma, a specific surgical approach possibly including *en bloc* resection of adherent tissues is suggested. Since approximately 80% of cases of PHPT are caused by a single adenoma, current guidelines recommend preoperative localization of disease followed by minimally invasive parathyroidectomy with intraoperative PTH monitoring to achieve the same cure rates while reducing complications (6).

The two most widely used imaging techniques are US and scintigraphy. US is widely available and accurate, with reported sensitivity and positive predictive value (PPV) of 76 and 93%, respectively. The typical aspect of parathyroid adenoma on US is an ovoid, solid, hypoechoic mass with well-defined margins and a polar feeding artery, located posteriorly or inferiorly to the thyroid gland (7, 8). Scintigraphy is usually performed with ^{99m}Tc-MIBI, with pathologic parathyroid showing a selective uptake. Compared to conventional planar scintigraphy, a higher diagnostic performance has been reported for hybrid single-photon emission computed tomography/computed tomography (SPECT/CT); this technique allows both 3D localization of disease and detailed definition of anatomy, reaching sensitivity and PPV of 84 and 95%, respectively (8). Importantly, in patients with concordant results between US and scintigraphy, a PPV for localization of 97% was reported (9).

Despite the improvements in imaging, 10–20% of patients have still discordant findings (8). Several factors can reduce accuracy: concomitant thyroid disease (nodules, goiter, autonomous thyroid adenomas); small size of parathyroid lesions; histology, with predominantly chief cells lesions showing lower detection rates than predominantly oxyphil cells (10). In these patients, additional imaging can be considered, including 4D-CT, MRI, 18F-choline PET/CT, 18F-choline PET/4D-CT and selective venous sampling. The high cost, general lack of availability, radiation exposure, requirement for a dedicated expert to interpret results and invasiveness limit

the impact of the modalities above (6, 8, 11, 12). Fine-needle aspiration (FNA) cytology has also been proposed. However, this technique can accurately differentiate neither parathyroid and thyroid lesions, nor parathyroid adenoma, hyperplasia and carcinoma (13, 14, 15).

US-guided PTH washout (FNA-PTH) has been proposed as first-line option in the preoperative localization of disease in patients with PHPT and a suspected lesion on US, in substitution for scintigraphy (16). However, according to the American Association of Endocrine Surgeons, FNA-PTH should be considered only in patients meeting both of the following criteria. First, the patients should be eligible to surgery. Second, the preoperative localization through imaging should not be conclusive. In patients not eligible for or refusing surgery, a conservative management based on nutritional and pharmacological approach is advised and thus no preoperative localization, including FNA-PTH, is needed (5, 6).

The present systematic review and meta-analysis aimed to reach more robust evidence on the safety and diagnostic performance of FNA-PTH when performed in the specific setting of cases of biochemically and histopathologically diagnosed PHPT with a suspected parathyroid lesion on US but negative or equivocal localization at scintigraphy. As the primary end points, the rate of complications with performing FNA in these lesions and both sensitivity and PPV of FNA-PTH were considered.

Methods

The systematic review was registered on PROSPERO (registration number CRD42019124249) and performed in accordance with the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) statement (Supplementary Tables 1 and 2, see section on [supplementary data](#) given at the end of this article) (17).

Search strategy

A six-step search strategy was planned. First, we searched sentinel studies in PubMed. Secondly, keywords and MeSH terms were identified in PubMed. Thirdly, in order to test the strategy, the terms ‘parathyroid hormone’, ‘parathormone’, ‘PTH’ and ‘washout’ or ‘aspirate’ were searched in PubMed. Fourthly, PubMed, CENTRAL, Scopus and Web of Science were searched. Fifthly, studies reporting FNA-PTH in patients biochemically and histopathologically diagnosed with PHPT, with a suspected

parathyroid lesion on US but with negative or equivocal scintigraphy were included. Scintigraphy was classified as equivocal if the original report described a presumed lesion with doubt, a double focus of uptake, a single focus of uptake projected on a nodule not corresponding to US or on a neck area with more than one US lesion. Finally, references of included studies were screened for additional papers. The last search was performed on February 1, 2019. No language neither time restriction was adopted. Two investigators (MC, PT) independently and in duplicate searched papers, screened titles and abstracts of the retrieved articles, reviewed the full-texts and selected articles for their inclusion.

Data extraction

The following information was extracted independently and in duplicate by two investigators (MC, PT) in a piloted form: (1) general information on the study (author, year of publication, country, study type, number of patients, number of evaluated lesions, histopathological diagnosis, age, sex); (2) FNA-PTH technique; (3) procedure-related complications; (4) criteria for the interpretation of FNA-PTH; (5) classification of lesions according to FNA-PTH and final diagnosis. For example, in a patient diagnosed with PHPT we classified a lesion histopathologically proven to be of parathyroid origin and FNA-PTH higher than reported cut-off as true positive. The main paper and the supplementary data were searched; if data were missing, authors were contacted via email. Data were cross-checked and any discrepancy was discussed.

Study quality assessment

The risk of bias of included studies was assessed independently by two reviewers (MC, PT) through the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool for the following aspects: patient selection; index test; reference standard; flow and timing. Risk of bias and concerns about applicability were rated as low, high or unclear risk (18). Data presentation was arranged using RevMan 5.3 (the Cochrane Collaboration, 2014).

Statistical analysis

The overall number of procedure-related complications was evaluated. The sensitivity, specificity, PPV and negative predictive value (NPV) of FNA-PTH was calculated from each article on a per lesion-based analysis;

the only exception was Ozderya, 2017 in which data were reported on a per-patient basis (19). Pooled data were presented with 95% confidence interval (95% CI). Heterogeneity between studies was assessed using I^2 , with 50% or higher regarded as high. Funnel plot asymmetry was assessed with Egger's test. All analyses were carried out using StatsDirect (StatsDirect) with a random-effect model; $P < 0.05$ was regarded as significant.

Results

Study characteristics

A total of 2573 papers were found, of which 1077 on PubMed, 836 on Scopus, 499 on Web of Science and 161 on CENTRAL. After removal of 698 duplicates, 1875 articles were analyzed for title and abstract; 1834 records were excluded (reviews, intraoperative FNA-PTH, case reports, not within the field of the review, studies not in humans). The remaining 41 papers were retrieved in full-text and 9 articles were finally included in the systematic review (Fig. 1). No additional studies were retrieved after screening the references of these papers.

Study quality assessment

The risk of bias of the included studies is shown in the Supplementary Figures 1 and 2. Overall, a low risk of bias was found: all consecutive eligible patients in a specific period were included. FNA-PTH was conducted before the reference test and interpreted according to prespecified criteria.

Figure 1

Flow chart of the systematic review.

Reference standard bias was rated as high since histology is commonly performed in knowledge of the results of the index test. Flow and timing bias was rated as low since PHPT is a chronic condition. The only exceptions to the statements above include Li *et al.* 2017 in which the study design was not clearly stated; Aydin *et al.* 2019, Ince *et al.* 2018, Ozderya *et al.* 2017, in which a consecutive enrollment of patients was not reported; Boi *et al.* 2013, in which FNA-PTH cut-off was defined after histology (19, 20, 21, 22).

Qualitative analysis (systematic review)

The characteristics of the included articles are summarized in Table 1 (19, 20, 21, 22, 23, 24, 25, 26, 27). The papers were published between 1998 and 2018, had sample sizes ranging from 6 to 44 patients. Six studies were retrospective, two prospective cohort; the design was not clearly stated in one paper. Five studies were carried in Turkey, two in Italy, one in China and one in USA. Participants were adult outpatients diagnosed with PHPT, with a suspected parathyroid lesion on US and negative or equivocal scintigraphy. FNA-PTH was performed with a 21- to 27-gauge needle, washed out with 0.5–1 mL of 0.9% saline or PTH-free serum. The result was considered as positive if higher than patient's serum PTH level at the time of sampling in four studies (19, 21, 24, 25), two times this level in one (22); the remaining papers reported a cut-off ranging from 40 to 103 pg/mL (Table 2) (20, 23, 26, 27). Overall, 222 lesions in 182 patients were evaluated. The histopathological diagnosis consisted in parathyroid adenoma in 178 patients, parathyroid hyperplasias in 2 and parathyroid carcinoma in 2. The largest diameter of the parathyroid lesions ranged from 6 to 50 mm.

Quantitative analysis (meta-analysis)

No major procedure-related complications were reported. One minor infection among 182 patients (0.5%) was recorded (27). Fibrosis, difficulties in operating setting, histopathological changes due to FNA-PTH, doubt in distinguishing benign from malignant parathyroid lesion, peri- or post-operative complications in the up to 3-year follow-up were not described.

The absolute number of true positive, true negative, false positive and false negative is reported in Table 3. Pooled sensitivity was 95% (95% CI: 91–98; $I^2=14\%$) (Fig. 2) and PPV 97% (95% CI 93–100; $I^2=39\%$) (Fig. 3). For specificity and NPV, there were not enough data to perform a meta-analysis. Out of 29 lesions with a final diagnosis

other than of parathyroid origin, 24 were negative at FNA-PTH. Out of 33 lesions with negative FNA-PTH, 24 were not of parathyroid origin. This corresponded to a specificity and NPV of 83 and 73%, respectively.

No funnel plot asymmetry was found for sensitivity ($P=0.22$) or PPV ($P=0.25$).

Discussion

The aim of this systematic review and meta-analysis was to identify the best available evidence on the safety and the diagnostic performance of FNA-PTH in patients biochemically and histopathologically diagnosed with PHPT, with a suspected parathyroid lesion on US but negative or equivocal scintigraphy. Nine cohort studies were found, evaluating 222 lesions in 182 patients. No major procedure-related complication was reported. The overall results showed a high sensitivity and PPV, a moderate specificity and NPV. Then, if the FNA-PTH is positive, we can confirm that the evaluated lesion is of parathyroid origin, but, if the FNA-PTH is negative, we cannot exclude it.

To our knowledge, this is the first systematic review and meta-analysis evaluating FNA-PTH as a tool for preoperative localization in patients eligible to surgery and with discordant imaging. Papers were searched without time restrictions, inclusion criteria were defined prior to the database search and data were searched on original articles and supplementary data.

The main limitation of FNA-PTH is represented by the possible undesirable results. Parathyroid tissue is characterized by the ability to grow in various settings, explaining successful autotransplantation, and FNA-PTH may result in dissemination, either malignant or benign (parathyromatosis) (28). Worrisome histologic alteration following FNA have also been reported. These include hemorrhage, abscess and inflammation, which may result in difficult surgery, as well as fibrosis and pseudoinvasion which may alter the final diagnosis (29, 30). It is worth noting that the overall rate of complications in literature is low and often limited to hemorrhage or infection (31). In a retrospective study on 41 patients, no case of FNA-induced parathyromatosis was identified after a mean follow-up of 5.8 years (32). Accordingly, in the present systematic review, no procedure-related complication was reported, except for a minor infection (27). As demonstrated for thyroid FNA, the complication rate strictly depends on needle caliber, number of passes, operator technique and experience (33). The use of

Clinical Study	M Castellana and others	US-guided PTH washout in primary hyperparathyroidism	181:3	249
----------------	-------------------------	--	-------	-----

Table 1 Characteristics of studies included in the meta-analysis.

Ref.	Country	Type of study	Number of patients with PHPT	Number of evaluated lesions	Population	FNA-PTH preparation			
						US guidance	Needle gauge	Number of passes	Dilution buffer
(21)	Turkey	RCS	20	28	PHPT with a suspected lesion on US and negative or equivocal ^{99m} Tc-MIBI	Yes	25	–	0.5 mL of 0.9% saline
(23)	Italy	RCS	27	47	PHPT with a suspected lesion on US and negative or equivocal ^{99m} Tc-MIBI	Yes	22–25	1 or 2	0.5 mL of PTH-free serum
(24)	Turkey	RCS	29	29	PHPT with a suspected lesion on US and negative ^{99m} Tc-MIBI	Yes	25	–	1 mL of 0.9% saline
(22)	Turkey	RCS	21	21	PHPT with a suspected lesion on US and negative or equivocal ^{99m} Tc-MIBI or SPECT/TC	Yes	22	–	1 mL of 0.9% saline
(25)	Turkey	RCS	12	12	PHPT with a suspected lesion on US and negative or equivocal ^{99m} Tc-MIBI	Yes	22	–	1 mL of 0.9% saline
(20)	China	–	11	11	PHPT with a suspected lesion on US and negative ^{99m} Tc-MIBI	Yes	21	–	–
(26)	Italy	PCS	12	12	PHPT with a suspected lesion on US and negative ²⁰¹ Tl- ^{99m} Tc or ^{99m} Tc-MIBI	Yes	22	2	0.5 mL of PTH-free serum
(27)	USA	PCS	6	8	PHPT with a suspected lesion on US and negative or equivocal ^{99m} Tc-MIBI	Yes	25	2 to 7	1 mL of 0.9% saline
(19)	Turkey	RCS	44	54	PHPT with a suspected lesion on US and negative or equivocal ^{99m} Tc-MIBI	Yes	27	1 or 2	1 mL of 0.9% saline

–, not reported; PCS, prospective cohort study; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; RCS, retrospective cohort study; US, ultrasound.

small needle gauge under US guidance with no more than one or two passes seems to be the best technique in order to minimize the risk of possible complications. Further studies are needed to reach a robust evidence on this aspect. A delicate issue is represented by parathyroid carcinoma, accounting for less than 1% of PHPT cases. It is well known that FNA-PTH should not be performed if parathyroid carcinoma is suspected preoperatively (6). Characteristics associated with parathyroid carcinoma include moderate-to-severe signs and symptoms of hyperparathyroidism; a palpable firm cervical mass; laryngeal nerve palsy; markedly elevated levels of serum total calcium (>14–15 mg/dL) or PTH (3–10 times above the upper normal limit); a nodule larger than 3 cm in size, with lobulated non-homogeneous pattern, marked hypoechogenicity, degenerative changes, calcifications, irregular halo sign or local infiltration at US; lymph nodes/distant metastases (1, 34). Any of these elements should dissuade from considering FNA-PTH. Unfortunately, the clinical presentation is often indistinguishable from other causes of PHPT and the final diagnosis will only be reached after surgery in most cases. At present, the most common surgical procedure is a simple parathyroidectomy in

79% of patients, while only 13% undergo *en bloc* resection, indeed. In the former cases, re-exploration of the neck with resection of contiguous tissues is recommended. Moreover, the intraoperative histological examination of all parathyroidal tissue has also been proposed in order to increase the number of cases undergoing the latter approach (35). All in all, the preoperative diagnosis of parathyroid carcinoma is still challenging, and it can be missed in a number of cases. However, given its limited prevalence, the American Association of Endocrine Surgeons guidelines support minimally invasive parathyroidectomy in the management of PHPT caused by single gland disease, except in those cases suspected of being parathyroid carcinoma (6). For the same reasons, FNA-PTH can be considered as an additional preoperative localization strategy.

Approximately 15–20% of cases of PHPT are caused by multiglandular disease. Four-gland parathyroid hyperplasia as well as multiple parathyroid adenomas have been described (2). In the present review, only two (1%) patients were finally diagnosed as having parathyroid hyperplasia. One patient had two neck nodules at US and a negative scintigraphy. One patient had a first neck

Clinical Study	M Castellana and others	US-guided PTH washout in primary hyperparathyroidism	181:3	250
----------------	-------------------------	--	-------	-----

Table 2 Assays and cut-offs.

Ref.	Assay	Fixed cut-off proposed		Patient's specific cut-off proposed	
		Absolute value, pg/mL	Comment	Patient's serum PTH level at the time of sampling	Serum PTH (pg/mL; median (range))
(21)	Elecsys, Roche diagnostics (ECLIA)	-	-	1×	114 (55–371)
(23)	Immulate 2000, Diagnostic Products Corporation (CLIA)	103	More than three times the maximal concentration found in histologically proven not-parathyroid lesions	-	-
(24)	Access Intact PTH, Beckman Coulter (CLIA)	-	-	1×	142 (113–197)
(22)	-	-	-	2×	170 (82–997)
(25)	-	-	-	1×	190 (78–1709)
(20)	Immulate 1000 Intact PTH, Siemens Medical Solutions Diagnostics (CLIA)	57	Cut-off reported in the literature	-	-
(26)	Nichols (IRMA)	100	Arbitrary	-	-
(27)	Quick-IntraOperative Intact PTH assay, Nichols Institute Diagnostics (ICMA)	40	Higher than normal range for serum PTH	-	-
(19)	Abbott Diagnostics (ICMA)	-	-	1×	147 (114–255)

–, not reported; CLIA, chemiluminescence assay; ECLIA, electrochemiluminescence assay; ICMA, immunochemiluminescence assay; IRMA, immunoradiometric assay.

nodule with unsuspected presentation at US but positive scintigraphy and a second neck nodule with suspicious presentation at US but negative scintigraphy. The FNA-PTH allowed the identification of the parathyroid lesions in both cases and their differentiation from a hyperplastic thyroid nodule and a toxic adenoma, respectively (23). Although data are limited, the performance of FNA-PTH should not be impaired in this setting of patients. FNA-PTH has to be regarded as a short-sighted technique, since allowing the characterization only of those lesions found at US and that underwent FNA. If a lesion is found, patients are candidates for minimally invasive parathyroidectomy. Intraoperative PTH monitoring should be used in these cases and, if residual hypersecreting tissue is suspected, conversion to bilateral neck exploration is warranted according to current guidelines (6).

Several cut-offs have been proposed for the interpretation of FNA-PTH. In a study performed in

170 patients of which 50 with thyroid disease, 100 with PHPT and 20 with secondary hyperparathyroidism, a FNA-PTH higher than 1000 pg/mL was associated with a sensitivity of 87%, a specificity of 75%, a NPV of 88% and a PPV of 74%; a lower cut-off of 100 pg/mL with 96%, 86%, 97% and 81%, respectively (36). No specific cut-off is reported in the American Association of Endocrine Surgeons guidelines (6). In the present systematic review, FNA-PTH was considered positive by some authors if higher than 40 up to 103 pg/mL. In studies using patient's serum PTH at the time of sampling as cut-off, the absolute value ranged from 55 to 1709 pg/mL. In order to incorporate differences in sample size, FNA-PTH preparation technique, assays and cut-offs into the calculation of the common effect among the studies, we chose a random-effect model for pooling data. Despite the differences above, high sensitivity with no heterogeneity and moderate specificity were found, with out-of-scale results in histology-proven parathyroid lesions frequently reported (20, 23, 26). The limited number of false-negative results could be due to insufficient aspiration, aspiration of adjacent tissues instead of parathyroid lesion in the cases of very small lesions or unusual locations, PTH truncated fragments; false positive could be attributed to blood contamination or hook effect (21, 26, 37). Finally, a possible reason for misclassification is represented by the circadian and seasonal rhythms of serum PTH, as well as the influence of physical exercise. Given the above considerations, the proposal of a cut-off for FNA-PTH of PTH washout/serum PTH ratio ≥ 2 seems to be reasonable (37).

Table 3 Classification of lesions according to FNA-PTH and final diagnosis.

Ref.	True positive	True negative	False positive	False negative
(21)	18	2	5	3
(23)	28	19	0	0
(24)	25	1	0	3
(22)	21	0	0	0
(25)	12	0	0	0
(20)	11	0	0	0
(26)	11	0	0	1
(27)	6	2	0	0
(19)	42	0	0	2

Figure 2

Forest plot of meta-analysis for sensitivity of FNA-PTH.

Our results are partially in line with the American Association of Endocrine Surgeons guidelines, describing FNA-PTH as highly specific (6). We found only two studies reporting an adequate number of lesions other than parathyroid: in Aydin *et al.* 2019 there were five false positive out of seven evaluated masses, while in Boi *et al.* 2013 all the 19 lesions were correctly classified as true negative with US-guided FNA. No reason for the low specificity in the former paper was reported (21, 23).

This review has several limitations. Firstly, the majority of studies were small sized. It is not unusual the early report of positive findings not replicated in subsequent larger studies; however, studies were published in a 20-year interval and no heterogeneity was found for sensitivity and PPV. The limited number of evaluated patients may thus potentially be related to the epidemiology of the disease and the diffusion of the technique. Secondly, we were not able to perform a meta-analysis for specificity and NPV, so caution should be taken in considering FNA-PTH as a rule-out exam. Thirdly, only two cases of parathyroid

carcinoma were found. Lastly, FNA-PTH cannot obviously be performed in 5% of patients with PHPT because of ectopic disease; therefore, other preoperative localization approaches should be considered in these patients (38).

Conclusions

The presentation of a parathyroid adenoma on US is characteristic and the performance of US as single preoperative localization modality of disease high. However, in some situations the accuracy of US is impaired. It is well known that the detection of a parathyroid adenoma can be difficult in patients with concomitant thyroiditis, thyroid nodules or goiter. Also, lymph nodes can be mistaken for parathyroid lesions, given the similar US presentation. Furthermore, the typical presentation of a parathyroid adenoma, being an ovoid, solid, homogeneously hypoechoic with well-defined margins and a polar feeding artery located posteriorly or inferiorly to the thyroid gland, can be missed, missing or lesions be intrathyroidal. Then, the support of a second imaging modality is needed for the patient to be candidate for minimally invasive parathyroidectomy. Unfortunately, scintigraphy performance may be also impaired in the scenarios above. In patients with biochemically proven PHPT and discordant imaging, FNA-PTH proved to be a safe procedure. Also, it was demonstrated to be accurate for preoperative assessment of parathyroid gland with excellent sensitivity and PPV. In this specific setting of patients, FNA-PTH improves a tailored surgery and can be used as a rule-in test for minimally invasive parathyroidectomy.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-19-0160>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Figure 3

Forest plot of meta-analysis for positive predictive value of FNA-PTH.

Acknowledgements

The authors thank Prof. Sule Temizkan (Istanbul, Turkey), Dr Asena Gökçay Canpolat (Ankara, Turkey), Dr Semra Ince (Ankara, Turkey), Dr Sefika Burcak Polat (Ankara, Turkey) and Dr Edda Vignali (Pisa, Italy) for providing the requested data.

References

- Goswamy J, Lei M & Simo R. Parathyroid carcinoma. *Current Opinion in Otolaryngology and Head and Neck Surgery* 2016 **24** 155–162. (<https://doi.org/10.1097/MOO.0000000000000234>)
- Bilezikian JP, Bandeira L, Khan A & Cusano NE. Hyperparathyroidism. *Lancet* 2018 **391** 168–178. ([https://doi.org/10.1016/S0140-6736\(17\)31430-7](https://doi.org/10.1016/S0140-6736(17)31430-7))
- Silva BC, Cusano NE & Bilezikian JP. Primary hyperparathyroidism. *Best Practice and Research: Clinical Endocrinology and Metabolism* 2018 **32** 593–607. (<https://doi.org/10.1016/j.beem.2018.09.004>)
- Walker MD & Silverberg SJ. Primary hyperparathyroidism. *Nature Reviews: Endocrinology* 2018 **14** 115–125. (<https://doi.org/10.1038/nrendo.2017.104>)
- Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelman R, Marcocci C & Potts JT Jr. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the fourth International Workshop. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 3561–3569. (<https://doi.org/10.1210/jc.2014-1413>)
- Wilhelm SM, Wang TS, Ruan DT, Lee JA, Asa SL, Duh QY, Doherty GM, Herrera MF, Pasieka JL, Perrier ND *et al.* The American Association of endocrine surgeons guidelines for definitive management of primary hyperparathyroidism. *JAMA Surgery* 2016 **151** 959–968. (<https://doi.org/10.1001/jamasurg.2016.2310>)
- Andrioli M & Valcavi R. Sonography of normal and abnormal thyroid and parathyroid glands. *Frontiers of Hormone Research* 2016 **45** 1–15. (<https://doi.org/10.1159/000442273>)
- Treglia G, Trimboli P, Huellner M & Giovanella L. Imaging in primary hyperparathyroidism: focus on the evidence-based diagnostic performance of different methods. *Minerva Endocrinologica* 2018 **43** 133–143. (<https://doi.org/10.23736/S0391-1977.17.02685-2>)
- Khan AA, Hanley DA, Rizzoli R, Bollerslev J, Young JE, Rejnmark L, Thakker R, D'Amour P, Paul T, Van Uum S *et al.* Primary hyperparathyroidism: review and recommendations on evaluation, diagnosis, and management. A Canadian and international consensus. *Osteoporosis International* 2017 **28** 1–19. (<https://doi.org/10.1007/s00198-016-3716-2>)
- Mihai R, Gleeson F, Buley ID, Roskell DE & Sadler GP. Negative imaging studies for primary hyperparathyroidism are unavoidable: correlation of sestamibi and high-resolution ultrasound scanning with histological analysis in 150 patients. *World Journal of Surgery* 2006 **30** 697–704. (<https://doi.org/10.1007/s00268-005-0338-9>)
- Piccardo A, Trimboli P, Rutigliani M, Puntoni M, Foppiani L, Bacigalupo L, Crescenzi A, Bottoni G, Treglia G, Paparo F *et al.* Additional value of integrated 18F-choline PET/4D contrast-enhanced CT in the localization of hyperfunctioning parathyroid glands and correlation with molecular profile. *European Journal of Nuclear Medicine and Molecular Imaging* 2019 **46** 766–775. (<https://doi.org/10.1007/s00259-018-4147-4>)
- Ibraheem K, Toraih EA, Haddad AB, Farag M, Randolph GW & Kandil E. Selective parathyroid venous sampling in primary hyperparathyroidism: a systematic review and meta-analysis. *Laryngoscope* 2018 **128** 2662–2667. (<https://doi.org/10.1002/lary.27213>)
- Agarwal AM, Bentz JS, Hungerford R & Abraham D. Parathyroid fine-needle aspiration cytology in the evaluation of parathyroid adenoma: cytologic findings from 53 patients. *Diagnostic Cytopathology* 2009 **37** 407–410. (<https://doi.org/10.1002/dc.21020>)
- Heo I, Park S, Jung CW, Koh JS, Lee SS, Seol H, Choi HS & Cho SY. Fine needle aspiration cytology of parathyroid lesions. *Korean Journal of Pathology* 2013 **47** 466–471. (<https://doi.org/10.4132/KoreanJPathol.2013.47.5.466>)
- Dimashkieh H & Krishnamurthy S. Ultrasound guided fine needle aspiration biopsy of parathyroid gland and lesions. *Cytojournal* 2006 **3** 6. (<https://doi.org/10.1186/1742-6413-3-6>)
- Erbil Y, Salmassioğlu A, Kabul E, İşsever H, Tunaci M, Adalet I, Bozbor A & Ozarmağan S. Use of preoperative parathyroid fine-needle aspiration and parathormone assay in the primary hyperparathyroidism with concomitant thyroid nodules. *American Journal of Surgery* 2007 **193** 665–671. (<https://doi.org/10.1016/j.amjsurg.2006.09.038>)
- McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, the PRISMA-DTA Group, Clifford T, Cohen JF, Deeks JJ, Gatsonis C *et al.* Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the PRISMA-DTA statement. *JAMA* 2018 **319** 388–396. (<https://doi.org/10.1001/jama.2017.19163>)
- Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM & QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of Internal Medicine* 2011 **155** 529–536. (<https://doi.org/10.7326/0003-4819-155-8-201110180-00009>)
- Ozderya A, Temizkan S, Cetin K, Ozugur S, Gul AE & Aydin K. The results of parathyroid hormone assay in parathyroid aspirates in pre-operative localization of parathyroid adenomas for focused parathyroidectomy in patients with negative or suspicious technetium-99m-sestamibi scans. *Endocrine Practice* 2017 **23** 1101–1106. (<https://doi.org/10.4158/EP171921.OR>)
- Li W, Zhu Q, Lai X, Sun J, Jiang Y, Ren X, Zhang Q, Meng Z, Li J & Dai Q. Value of preoperative ultrasound-guided fine-needle aspiration for localization in Tc-99m MIBI-negative primary hyperparathyroidism patients. *Medicine* 2017 **96** e9051. (<https://doi.org/10.1097/MD.00000000000009051>)
- Aydin C, Polat SB, Dellal FD, Kaya C, Dogan HT, Turkolmez S, Kılıç M, Ersoy R & Çakır B. The diagnostic value of parathyroid hormone washout in primary hyperparathyroidism patients with negative or equivocal 99 m Tc-MIBI results. *Diagnostic Cytopathology* 2019 **47** 94–99. (<https://doi.org/10.1002/dc.24065>)
- Ince S, Emer O, Deveci S, Okuyucu K, Alagoz E, San H, Ayan A, Karacalioglu O, Haymana C, Gunalp B *et al.* Complementary role of parathormone washout test to 99mTc-MIBI parathyroid scintigraphy and histopathologic analysis of cell types in parathyroid adenomas. *Revista Española de Medicina Nuclear e Imagen Molecular* 2018 **37** 205–210. (<https://doi.org/10.1016/j.rem.2017.12.006>)
- Boi F, Lombardo C, Cocco MC, Piga M, Serra A, Lai ML, Calò PG, Nicolosi A & Mariotti S. Thyroid diseases cause mismatch between MIBI scan and neck ultrasound in the diagnosis of hyperfunctioning parathyroids: usefulness of FNA-PTH assay. *European Journal of Endocrinology* 2013 **168** 49–58. (<https://doi.org/10.1530/EJE-12-0742>)
- Gökçay Canpolat A, Şahin M, Ediboğlu E, Erdoğan MF, Güllü S, Demir Ö, Emral R & Çorapçıoğlu D. Diagnostic accuracy of parathyroid hormone levels in washout samples of suspicious parathyroid adenomas: a single-centre retrospective cohort study. *Clinical Endocrinology* 2018 **89** 489–495. (<https://doi.org/10.1111/cen.13812>)
- Kuzu F, Arpacı D, Cakmak GK, Emre AU, Elri T, Ilikhan SU, Bahadır B & Bayraktoglu T. Focused parathyroidectomy without intra-operative parathormone monitoring: the value of PTH assay in preoperative ultrasound guided fine needle aspiration washout. *Annals of Medicine and Surgery* 2016 **6** 64–67. (<https://doi.org/10.1016/j.amsu.2015.12.065>)
- Marcocci C, Mazzeo S, Bruno-Bossio G, Picone A, Vignali E, Ciampi M, Viacava P, Naccarato AG, Miccoli P, Iacconi P *et al.*

- Preoperative localization of suspicious parathyroid adenomas by assay of parathyroid hormone in needle aspirates. *European Journal of Endocrinology* 1998 **139** 72–77.
- 27 Maser C, Donovan P, Santos F, Donabedian R, Rinder C, Scoutt L & Udelsman R. Sonographically guided fine needle aspiration with rapid parathyroid hormone assay. *Annals of Surgical Oncology* 2006 **13** 1690–1695. (<https://doi.org/10.1245/s10434-006-9180-z>)
 - 28 Kim J, Horowitz G, Hong M, Orsini M, Asa SL & Higgins K. The dangers of parathyroid biopsy. *Journal of Otolaryngology: Head and Neck Surgery* 2017 **46** 4. (<https://doi.org/10.1186/s40463-016-0178-7>)
 - 29 Alwaheeb S, Rambaldini G, Boerner S, Coiré C, Fiser J & Asa SL. Worrisome histologic alterations following fine-needle aspiration of the parathyroid. *Journal of Clinical Pathology* 2006 **59** 1094–1096. (<https://doi.org/10.1136/jcp.2005.029017>)
 - 30 Norman J, Politz D & Browarsky I. Diagnostic aspiration of parathyroid adenomas causes severe fibrosis complicating surgery and final histologic diagnosis. *Thyroid* 2007 **17** 1251–1255. (<https://doi.org/10.1089/thy.2007.0081>)
 - 31 Bancos I, Grant CS, Nadeem S, Stan MN, Reading CC, Sebo TJ, Algeciras-Schimnich A, Singh RJ & Dean DS. Risks and benefits of parathyroid fine-needle aspiration with parathyroid hormone washout. *Endocrine Practice* 2012 **18** 441–449. (<https://doi.org/10.4158/EP11148.OR>)
 - 32 Kendrick ML, Charboneau JW, Curlee KJ, van Heerden JA & Farley DR. Risk of parathyromatosis after fine-needle aspiration. *American Surgeon* 2001 **67** 290–293; discussion 293.
 - 33 Abraham D, Duick DS & Baskin HJ. Appropriate administration of fine-needle aspiration (FNA) biopsy on selective parathyroid adenomas is safe. *Thyroid* 2008 **18** 581–582; author reply 583. (<https://doi.org/10.1089/thy.2007.0341>)
 - 34 Cetani F, Pardi E & Marcocci C. Update on parathyroid carcinoma. *Journal of Endocrinological Investigation* 2016 **39** 595–606. (<https://doi.org/10.1007/s40618-016-0447-3>)
 - 35 Kirigin Biloš LS, Pavlović D & Kellar F. Parathyroid carcinoma: a diagnostic and treatment challenge. *Endocrine Oncology and Metabolism* 2016 **2** 194–205. (<https://doi.org/10.21040/eom/2016.2.3.4>)
 - 36 Kiblut NK, Cussac JF, Soudan B, Farrell SG, Armstrong JA, Arnalsteen L, Biechlin A, Delattre AA & Proye CA. Fine needle aspiration and intrapathyroid intact parathyroid hormone measurement for reoperative parathyroid surgery. *World Journal of Surgery* 2004 **28** 1143–1147. (<https://doi.org/10.1007/s00268-004-7563-5>)
 - 37 Trimboli P, D'Aurizio F, Tozzoli R & Giovannella L. Measurement of thyroglobulin, calcitonin, and PTH in FNA washout fluids. *Clinical Chemistry and Laboratory Medicine* 2017 **55** 914–925. (<https://doi.org/10.1515/cclm-2016-0543>)
 - 38 Tattera D, Wong LM, Vikse J, Sanna B, Pękala P, Walocha J, Ciocchi R, Tomaszewski K & Henry BM. The prevalence and anatomy of parathyroid glands: a meta-analysis with implications for parathyroid surgery. *Langenbeck's Archives of Surgery* 2019 **404** 63–70. (<https://doi.org/10.1007/s00423-019-01751-8>)

Received 4 March 2019

Revised version received 1 June 2019

Accepted 26 June 2019