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Preoperative Location of Parathyroid Adenomas in Primary Hyperparathyroidism: The Role of Cervical Doppler Ultrasound

Localização Pré-operatória de Adenomas da Paratiroide no Hiperparatiroidismo Primário: O Papel da Ecografia Cervical com Doppler

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ABSTRACT

Introduction: Parathyroid adenoma is the most frequent cause of primary hyperparathyroidism. In recent years, the preoperative location of parathyroid adenomas allowed minimally invasive surgical techniques that have become preferred over the traditional bilateral neck exploration. The more recent guidelines on this subject highlight the role of nuclear medicine imaging tests. The aim of this study was to review the current role of Doppler ultrasound (US) in assessing the preoperative location of parathyroid adenomas in patients with primary hyperparathyroidism.

Material and Methods: Retrospective study based on data from patients with primary hyperparathyroidism that underwent parathyroidectomy between January 2013 and January 2022 at the Centro Hospitalar Universitário Lisboa Central. Statistical analysis was performed with IBM SPSS Statistics, version 26.0.0.0®.

Results: Parathyroidectomy was performed in 171 patients (77.8% females) with primary hyperparathyroidism. Cervical Doppler ultrasound was the most performed test (64.3%, n = 110) for preoperative location and detected a suspicious lesion in 98 patients (89.1%). The preoperative location of the parathyroid adenomas was assessed through the Doppler ultrasound and was compared with the surgical reports and histological findings; a correct identification was made in 76 patients (77.6%). Doppler ultrasound slightly underestimated the mean adenoma size (18.1 ± 7.7 mm preoperative *versus* 22 ± 8.4 mm postoperative). Calcium, parathyroid hormone levels, adenoma size and concomitant presence of thyroid nodules did not affect the accuracy of Doppler ultrasound.

Conclusion: Doppler ultrasound showed high diagnostic accuracy even in patients with nodular thyroid disease regardless of calcium and parathyroid hormone levels and adenoma size. Furthermore, its safety, affordability and availability should favor its use as first line test in primary hyperparathyroidism to assess the preoperative location of parathyroid adenomas.

Keywords: Hyperparathyroidism, Primary; Parathyroid Neoplasms/diagnostic imaging; Ultrasonography, Doppler

RESUMO

Introdução: O adenoma da paratiroide é a causa mais frequente de hiperparatiroidismo primário. Nos últimos anos, a localização pré-operatória de adenomas da paratiroide tem permitido técnicas cirúrgicas minimamente invasivas que se tornaram preferíveis à exploração cervical bilateral tradicional. As recomendações internacionais mais recentes relativamente a este tópico têm dado ênfase aos exames de imagem de medicina nuclear. Neste estudo, os autores revêem o papel atual da ecografia cervical com Doppler na localização pré-operatória de adenomas da paratiroide em doentes com hiperparatiroidismo primário.

Material e Métodos: Estudo retrospetivo de doentes com hiperparatiroidismo primário submetidos a paratiroidectomia entre janeiro de 2013 e 2022 no Centro Hospitalar Universitário Lisboa Central. Análise estatística realizada com IBM SPSS Statistics, versão 26.0.0.0®.

Resultados: Foram identificados 171 doentes com hiperparatiroidismo primário submetidos a paratiroidectomia (77,8% sexo feminino). A ecografia cervical com Doppler foi o exame mais solicitado para localização pré-operatória de adenomas da paratiroide (64,3%, n = 110) e detetou a lesão em 98 doentes (89,1%). A análise comparativa da localização pré-operatória do adenoma da paratiroide baseada na ecografia cervical com Doppler com os achados cirúrgicos e histológicos demonstrou identificação correta do adenoma em 76 doentes (77,6%). A ecografia cervical com Doppler subestimou ligeiramente a dimensão dos adenomas (18,1 ± 7,7 mm pré-operatório *versus* 22 ± 8,4 mm pós-operatório). Os níveis de cálcio, paratormona, a dimensão do adenoma e a presença concomitante de nódulos tiroideus não afetou a eficácia diagnóstica da ecografia cervical com Doppler.

Conclusão: A ecografia cervical com Doppler demonstrou elevada precisão diagnóstica independentemente da presença concomitante de nódulos tiroideus, dos níveis de cálcio e paratormona e da dimensão dos adenomas da paratiroide. A sua disponibilidade, segurança e custo aliado à capacidade diagnóstica demonstrada devem favorecer o seu uso como primeira linha na localização pré-operatória de adenomas da paratiroide no hiperparatiroidismo primário.

Palavras-chave: Neoplasias da Paratiroide/diagnóstico por imagem; Hiperparatiroidismo Primário; Ultrassonografia Doppler

INTRODUCTION

Primary hyperparathyroidism (PHPT) is one of the most common endocrine disorders. More asymptomatic patients are being diagnosed due to a greater use of routine screening tests. Incidence estimates for PHPT vary from 0.4 to 82 cases per 100 000.[1] Solitary parathyroid adenoma is the cause of PHPT in about 80% of patients. The remaining

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causes are multiple adenomas, hyperplasia and, rarely, carcinoma.[2] In recent years, minimally invasive surgical techniques have challenged the traditional bilateral neck exploration. They are believed to offer distinct advantages such as shorter operative time and reduced complication rate (early postoperative hypocalcemia and injury to the adjacent tissues).[3] There are different imaging techniques for preoperative location of parathyroid adenomas. Ultrasonography (US) and ^{99m}TC-sestamibi scintigraphy are the dominant imaging techniques, followed by contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI). The most recent guidelines on this subject highlight the use of nuclear medicine imaging techniques to get the best sensitivity and specificity.[4]

Ultrasonography is an available non-invasive and cost-effective imaging method. The advances in equipment such as enhanced contrast resolution, increased dynamic range and color power Doppler have increased its accuracy.[5] Parathyroid adenomas are usually oval or bean-shaped and, in the large majority, homogeneously hypoechoic on gray-scale imaging because of its marked and compact cellularity. Color and power Doppler imaging is a very helpful tool to confirm a suspicious parathyroid adenoma. Different parenchymal flow patterns of parathyroid adenomas have been reported, including no flow, central vascularity, peripheral vascularity (ring) with a large polar feeding vessel and combined central and peripheral vascularity.[6,7]

The aim of this retrospective study was to review the current role of Doppler US in assessing the preoperative location of parathyroid adenomas in patients with PHPT.

MATERIAL AND METHODS

Study population

The authors reviewed data from patients with PHPT that underwent parathyroidectomy between January 2013 and January 2022 at the Centro Hospitalar Universitário Lisboa Central and had a histological result of adenoma. Surgical criteria were based on the 2014 Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism.[8] At least one of the following criteria should be present: serum calcium > 1.0 mg/dL upper limit of normal; bone mineral density by dual-energy X-ray absorptiometry (DEXA) with a T-score < -2.5 at lumbar spine, total hip, femoral neck, or distal one-third radius; vertebral fracture; creatinine clearance < 60 mL/min; 24-h urine for calcium > 400 mg; presence of nephrolithiasis or nephrocalcinosis or age < 50 years-old. Patients with parathyroid carcinoma and hereditary PHPT including multiple endocrine neoplasia type 1 and 2A, familial isolated hyperparathyroidism and hyperparathyroidism-jaw tumor syndrome were not included. Patients with history of a previous neck surgery and/or chronic kidney disease stage 3 or higher were also excluded. A study cohort of 171 patients was obtained. Parathyroidectomy was performed by high-volume surgeons in all cases. Doppler US was performed by the same radiologist in 108 patients (98.1%). No patient underwent parathyroid hormone (PTH) washout on the lesions detected by Doppler US.

Study variables

Data on the following parameters were collected: age, gender, preoperative serum calcium, phosphate, intact parathyroid hormone and 25-hydroxyvitamin D. The performed tests and preoperative location findings, surgical findings and histopathological results were also collected. The results of the imaging studies were compared with the intraoperative and histological findings.

Statistical analysis

Measurement data on normal distribution were expressed as mean ± standard deviation. The correlations between continuous variables were evaluated using the Spearman test. The χ^2 test was used to compare the nominal variables between the groups. The analyses were completed using IBM SPSS Statistics, version 26.0.0.0® (IBM Corporation, Armonk, NY, USA). All *p*-values were two-tailed, and statistical significance was set at $p < 0.05$.

The study was approved by the local Ethics Committee and informed consent was waived.

RESULTS

From January 2013 to January 2022, 171 patients (133 female and 38 male) with PHPT underwent parathyroidectomy. The baseline characteristics of the patients are reported in Table 1. Most patients required one or two tests to detect the enlarged parathyroid(s). The frequency of each performed test is reported in Fig. 1.

The Doppler US found a suspicious lesion in 98 patients (89.1%): left superior (n = 11), right superior (n = 9), left inferior (n = 32), right inferior (n = 43), and multiple locations (n = 3). The preoperative location of the parathyroid adenomas was assessed through both the Doppler US and the surgical reports and histological findings (Fig. 1). Doppler US was able to correctly locate parathyroid lesion in all cases of left superior parathyroid adenomas (11/11), 88.9% (8/9) of right superior adenomas, 81.3% (26/32) of left inferior adenomas, 65.1% (28/43) of right inferior adenomas and 100% (3/3) of multiple adenomas. Overall, a correct identification was made in 77.6% of cases (76/98). Considering the laterality, Doppler US correctly located 86.5% (n = 45) of lesions on the right side and 100% (n = 43) on the left side.

No correlation was found between the accuracy of cervical Doppler US and calcium levels ($p = 0.339$) or PTH levels ($p = 0.804$) at diagnosis. Adenoma size did not interfere with

Table 1 – Baseline characteristics

		Range	Reference range
Patients	n = 171		
Female	n = 133 (77.8%)		
Male	n = 38 (22.2%)		
Mean age at HPTP diagnosis (years-old)	64.4 ± 13	22 – 89	
Dual energy X-ray absorptiometry (DEXA)	n = 131 (76.6%)		
Renal Ultrasound	n = 121 (70.8%)		
Mean serum calcium at HPTP diagnosis (mg/dL)	11.5 ± 1	9.9 – 18	8.6 – 10.3
Mean serum phosphorus at HPTP diagnosis (mg/dL)	2.5 ± 0.6	0.6 – 4.3	0.6 – 4.3
Mean serum intact PTH (pg/mL)	286.1 ± 400.3	50.3 – 4738	10 – 52
Mean 25-hydroxivitamin D level (ng/mL)	18.1 ± 10.5	4.2 – 59.6	25 – 80
Concomitant nodular thyroid disease	n = 116 (67.8%)		
Number of performed tests preoperatively:			
1 test	n = 59 (34.5%)		
2 tests	n = 61 (35.7%)		
3 tests	n = 45 (26.3%)		
4 tests	n = 6 (3.5%)		

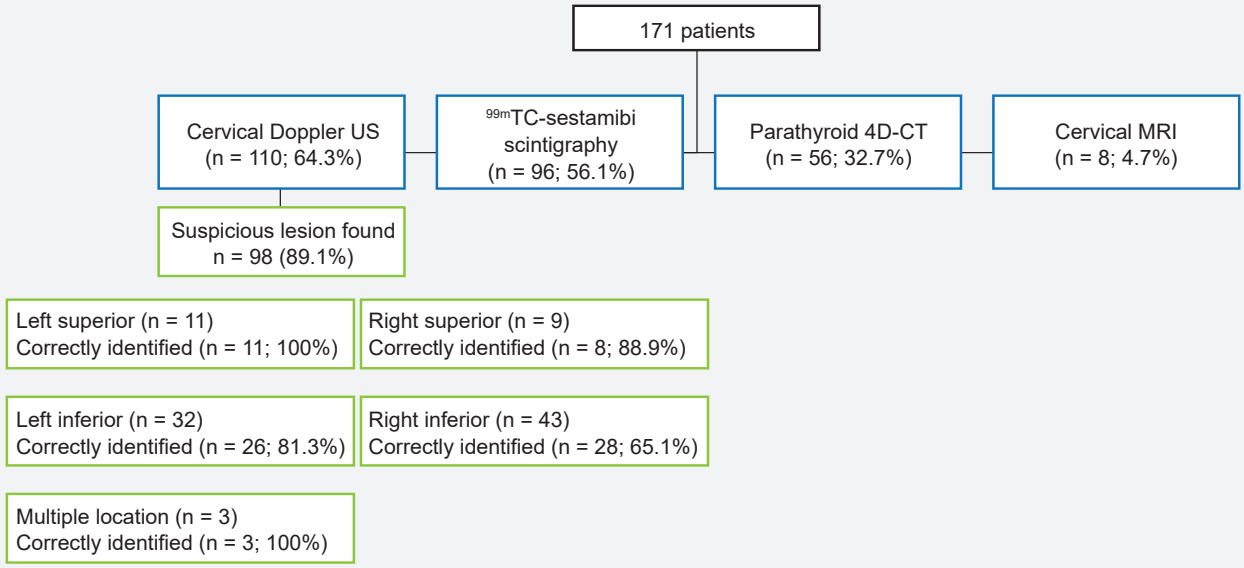

Figure 1 – Tests performed for preoperative location in the cohort of patients with primary hyperparathyroidism. Findings of cervical doppler ultrasound (compared with surgical and histological reports).

Doppler US accuracy (p = 0.832).

The impact of simultaneous nodular thyroid disease with the accuracy of Doppler US was also evaluated. Multinodular goiter was present in 116 patients (67.8%). Doppler US was performed in 60 patients with simultaneous nodular thyroid disease. Diagnostic accuracy was not affected by the presence of thyroid nodules (p = 0.419).

Doppler US was performed by the same radiologist in almost all cases (108/110; 98.1%). The mean adenoma size with this technique was 18.1 ± 7.7 mm (ranged 5 to 37 mm). Postoperative mean adenoma size was 22 ± 8.4 mm (ranged 7 to 48 mm).

In 12 patients, Doppler US did not find any parathyroid lesion. In those cases, ^{99m}TC-sestamibi scintigraphy was

performed in nine patients and correctly located the lesion in eight of them (88.9%) finding an ectopic location (mediastinal) in three (33.3%). Parathyroid 4D-CT was also performed in nine patients and detected the lesion in six (66.7%). Cervical MRI was performed in one patient with correct identification of parathyroid lesion. Bilateral neck exploration was needed in four patients. Those four patients had negative results with Doppler US, ^{99m}TC-sestamibi scintigraphy and parathyroid 4D-CT.

The median follow-up time after surgery was 5.4 ± 2.1 years. Cure was achieved in 108 of 110 patients (98.1%) that performed Doppler US for preoperative location of enlarged parathyroids and was sustained during the follow-up time. Two patients had persistent hypercalcemia after surgery, defined by hypercalcemia within six months following surgery.

DISCUSSION

Although an experienced surgeon remains the best option to detect parathyroid lesions, it is widely accepted that preoperative location reduces the operative time and complication rate.[9]

A variety of imaging techniques have been employed with different accuracy rates. No universally accepted algorithm exists to assess the preoperative location of parathyroid lesions and different tests have various advantages and disadvantages depending on the clinical scenario.[10]

Ultrasonography has improved in recent years. The enhanced gray-scale contrast resolution and color power Doppler increased the sensitivity for the detection of parathyroid adenomas.[5,11,12] It allows the investigation of the vascularization pattern of tumors and the distinction between parathyroid lesion and fibrotic areas, lymph nodes or other parts of the thyroid gland. A meta-analysis performed by Ruda *et al* encompassing 54 studies done between 1995 and 2003 using ultrasonography to assess the preoperative location in primary hyperparathyroidism estimated the ultrasonographic sensitivity for the detection of adenoma at 79%.[13]

^{99m}TC-sestamibi scintigraphy has been extensively used in the setting of PHPT and studies report a sensitivity range of 44% - 88%.[14] The advantages include relative operator-independent effectiveness and improved detection of ectopic or far posterior lesions that US is prone to miss. However, and according to the literature, approximately 20% of sestamibi scans are false negative or inconclusive despite biochemical evidence of PHPT.[15-18] Recently, the use of SPECT/CT allowed better identification of parathyroid lesions providing anatomical and functional information that led to a high sensitivity and specificity.[19]

4D-CT is more commonly used as a problem-solving tool for inconclusive or discordant first line imaging outcomes which introduces potential bias in most studies that assess its performance. The reported sensitivity when used as the initial imaging study ranges from 62% to 92%.[10,20] An advantage of 4D-CT is the ability to identify parathyroid lesion that were avascular on color Doppler but that will still enhance after contrast injection. The main advantage of MRI is its potential performance that is comparable to 4D-CT without radiation exposure. However, in comparison with 4D-CT, it is less available, more expensive and time consuming. The reported sensitivity ranges from 64% to 93%.[10,21]

Our study with 110 patients that performed Doppler US confirms the validity of this imaging technique to assess the preoperative location of parathyroid adenomas in PHPT. Almost all patients (98.1%) underwent Doppler US by the same radiologist which reduces inter-operator variability. Overall Doppler US recognized the correct side of parathyroid adenomas in the neck (100% for left adenomas and 86.5% for right adenomas). The reliability for predicting superior or inferior location was lower (52.8%). This could be explained mainly by the fact that adenomas have a longitudinal expansion which makes it difficult for the radiologist to classify as a superior or inferior lesion. Our study demonstrates that the main mistake occurs when the radiologist locates the lesion on the inferior pole. As shown in Table 2,

Table 2 – Comparative results of parathyroid lesion location with Doppler US *versus* surgical/histological findings

Suspected location (Doppler US)	**Histologically confirmed location of the lesion**				
	Superior right (n = 17)	**Superior left** (n = 19)	**Inferior right** (n = 28)	**Inferior left** (n = 31)	**Multiple** (n = 3)
Superior right (n = 9)	8	1	0	0	0
Superior left (n = 11)	0	11	0	0	0
Inferior right (n = 43)	9	1	28	5	0
Inferior left (n = 32)	0	6	0	26	0
Multiple (n = 3)	0	0	0	0	3

six of the 32 adenomas located in the inferior left pole were actually in the upper pole and the same happened to nine of the 43 adenomas initially identified in the inferior right pole. Nevertheless, cervical Doppler US was effective in correctly identifying laterality which still allows minimally invasive surgical techniques and a unilateral neck exploration in nearly all patients.

A brief note should be done to the patient that presented with a high PTH (4738 pg/mL) due to a suspicious parathyroid carcinoma – the histology slides of this patient were reviewed, and the diagnosis of a massive 4.5 cm parathyroid adenoma was confirmed (Bcl2+; Ki67 < 1%).

Multiglandular disease is responsible for 10% to 15% of primary hyperparathyroidism. In this study there were three patients with multiglandular disease. These patients had preoperative cervical Doppler US suggesting two parathyroid adenomas. Despite this preoperative location the surgeon performed a conventional bilateral neck exploration in all these cases. The surgery and histological report confirmed the ultrasound findings, and all patients are cured. The few patients with multiglandular disease in this sample does not allow conclusions to be drawn. In patients with suspicious multiglandular disease all parathyroid glands should be exposed and examined with an intraoperative determination of the extent of parathyroidectomy.

Contrary to expectations, the adenoma size did not interfere with Doppler US accuracy. This is probably explained by the fact that most adenomas were large enough to be detected by Doppler US (18.1 ± 7.7mm). The experienced radiologist that performed almost all the tests could also explain the good rate of detection.

In our study we calculated an overall sensitivity of 89.1% and an accuracy of 77.6% for Doppler US which is slight lower than what is described in the literature.[5,6,22] This could be explained by the fact that some superior lesions were identified by the radiologist as being inferior and vice versa. When considering only the ability to locate the right side of the neck, we calculated an overall sensitivity of 92.6%. Furthermore, we did not find any statistically significant differences in the accuracy of Doppler US between patients with and without nodular thyroid disease. Calcium levels, PTH levels at diagnosis and adenoma size also did not affect the cervical Doppler US accuracy. Doppler US slightly underestimated the mean adenoma size (18.1 ± 7.7 mm preoperative *vs* 22 ± 8.4 mm postoperative), but a moderate to strong correlation was observed between preoperative and postoperative adenoma size (r_s = 0.558, p < 0.001).

Parathyroid tissue generally consists of chief cells, but it may contain oncocytic cells, transitional cells, and clear cells. Previous studies have reported some associations between the ultrasound pattern and the histological subtype of the parathyroid adenoma. The typical parathyroid adenoma is usually hypoechoic and well-defined with homogenous echotexture as a result of a uniform arrangement of

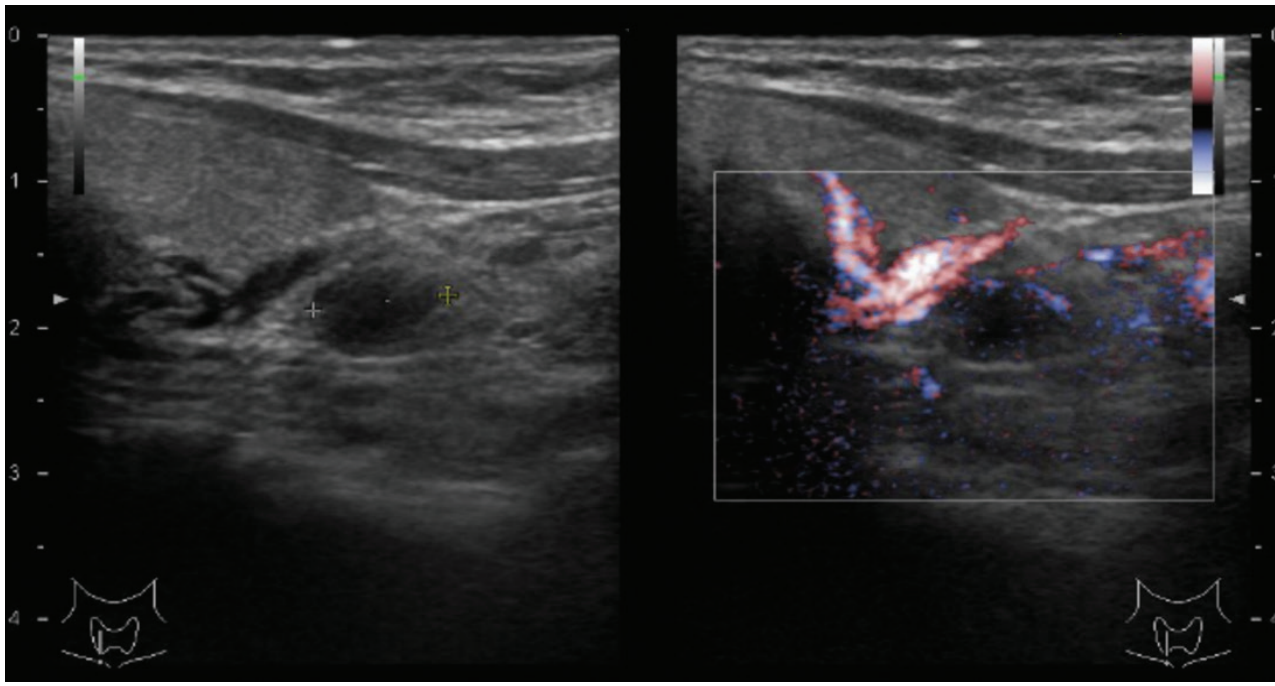

Figure 2 – A parathyroid adenoma was identified adjacent to the lower pole of the right thyroid lobe. The left image shows a solid lesion with 8.9 mm, rounded and well-circumscribed, hypoechoic with respect to the thyroid tissue. On the right image with Doppler technique a feeding artery is identified that enters the adenoma through one of its poles and is distributed towards the periphery (vascular arch pattern).

the parathormone-producing chief cells (Fig. 2). Connective and fat tissue usually have an hyperechogenic pattern. Due to the presence of fibrous bands and cellular atypia in atypical parathyroid adenomas, the finding of a parathyroid adenoma with greater hyperechogenic area may indicate an atypical lesion and therefore clinical follow-up can be performed more closely.[22] In our study, the histological composition of parathyroid adenomas lacks in histological reports. However, in the future, it would be interesting to compare the ultrasound pattern and the histological subtype of the parathyroid adenoma in a prospective study.

In 12 patients of this study, no lesion was found with Doppler US. ^{99m}TC-sestamibi scintigraphy and 4D-CT was performed in nine of them, being diagnosed in 88.9% (n = 8) and 66.7% (n = 6), respectively. In four patients, no parathyroid lesion was found with these imaging modalities.

While it is relatively consensual that Doppler ultrasound should be used as a first line test for parathyroid imaging due to its safety, availability, accuracy and ability to assess for concomitant thyroid disease,[23] there is no consensus on which should be the second line test.

The 2016 Guidelines for Definitive Management of Primary Hyperparathyroidism of The American Association of Endocrine Surgeons recommend that patients who are candidates for parathyroidectomy should be referred to an expert clinician to decide which imaging studies should be performed based on their knowledge of regional imaging capabilities. They recommend cervical ultrasonography performed by an experienced radiologist as the first line test and suggest adding ^{99m}TC-sestamibi or 4D-CT to get the most cost-effective strategy.[25] The advantage of radionuclide parathyroid imaging over US lies in the identification of ectopic glands, as well as in easier recognition of posteriorly located upper glands.[4]

However, more recent practice guidelines for parathyroid imaging of the European Association of Nuclear Medicine recommend combining ^{99m}TC-sestamibi SPECT/CT with cervical ultrasound performed by an experienced sonographer as a first-line strategy. PET/CT with ^{18}F-labeled choline analogues has shown better results but data from large cohorts and on cost-effectiveness are not currently available.[25] It may be considered a potential alternative first-line method whenever possible as it appears to be an effective technique even in patients with negative/equivocal standard imaging findings. 4D-CT may be useful in case other imaging studies are negative or inconclusive, in patients with distorted neck anatomy, or after futile surgery. It has similar diagnostic accuracy compared with ^{99m}TC-sestamibi SPECT but a higher radiation exposure. ^{18}F-labeled choline analogue PET may be combined with 4D-CT in complicated cases (e.g., re-operated patients) to enhance the sensitivity and predictive positive value compared with either technique alone. MRI may be also used after negative/inconclusive first-line imaging or in pregnant patients. Invasive diagnostic procedures remain as last resort.[4]

A similar recommendation was made by the last consensus of the European Society of Endocrinology Education Program of Parathyroid Disorders (PARAT 2021). To detect multiglandular disease and/or small lesions, the preoperative localization procedures that are more sensitive are 18F-fluorocholine PET/CT, with or without enhanced arterial imaging, and 4D-CT.[27]

In our study, there were only few patients with no detected parathyroid lesion on Doppler ultrasound. Based on our results and on its safety, availability, and low cost, we still agree that color Doppler ultrasound should be the first line test to assess the preoperative location of parathyroid adenomas.

Among the strengths of this study are the homogeneity of the cohort and the reduced inter-operator variability. To the best of our knowledge, this is the first study on preoperative location of parathyroid adenomas from a nationally representative cohort of patients.

The limitations of the study include the relatively small sample size compared with other similar studies. The ultrasound detection of parathyroid hyperparathyroidism is largely dependent on radiologist experience. The strength we focused on having one experienced radiologist performing almost all tests, could also be considered a limitation to apply this technique in other centers and highlights the need to have an experienced radiologist dedicated to performing parathyroid US. Another limitation is related to the retrospective nature of the study. The clinic's preoperative location approach to primary hyperparathyroidism was not the same in all patients. Even though most patients performed Doppler US as a first line test, the second-line test was different among the ones that had no suspicious lesion identified on Doppler US. This fact limits our conclusion about which test should be performed next in the cases where Doppler US does not find any lesion. Given this limitation, future research to focus on the best clinical approach would be interesting. In our center, Doppler US is now being performed as the first-line test in all patients and 4D-CT as the second line test. The present findings should be further confirmed in a prospective study.

CONCLUSION

Doppler US showed an overall sensitivity of 89.1%. When regarding the location on the correct side of the neck we found a sensitivity of 92.6%. It was also valuable to evaluate the thyroid preoperatively and even in patients with nodular thyroid disease, the accuracy of Doppler US was not affected. Its widespread availability, low cost, lack of radiation exposure and high sensitivity may justify its use

as a first line test in most situations for preoperative location of parathyroid adenomas in PHPT.

AUTHOR CONTRIBUTIONS

SA: Conception of the study; Data collection, analysis, and interpretation; Drafting of the manuscript.

TR: Conception of the study; Data collection, analysis, and interpretation; Revision of the results and approval of the final version of the manuscript.

AP: Data analysis and interpretation; Revision of the results and approval of the final version of the manuscript.

NC, JMC, PT, JSN: Revision of the results and approval of the final version of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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