A Retrospective Cohort Study of the Utility of Ultrasound, 99mTc-Sestamibi Scintigraphy, and Four-Dimensional Computed Tomography for Pre-Operative Localization of Parathyroid Disease To Facilitate Minimally Invasive Parathyroidectomy

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Abstract
Background
This study investigated the utility of ultrasound (US), 99mTc-Sestamibi scintigraphy (Sestamibi), and four-dimensional computed tomography (4DCT) for pre-operative localization of a single abnormal parathyroid gland prior to minimally invasive parathyroidectomy (MIP) to determine the optimum pre-operative scans to facilitate a MIP.

Methods
Patients with primary hyperparathyroidism who underwent curative parathyroidectomy at Broomfield Hospital, Mid and South Essex NHS Foundation Trust between 2009 and 2018 were included. Diagnostic performance parameters and the agreement between US, Sestamibi, and 4DCT were evaluated. Cohen’s \( \kappa \) was used to assess the strength of agreement between imaging modalities.

Results
At localizing pathology to the correct side of the neck, Sestamibi had the highest sensitivity (87%), followed by US (76%) and 4DCT (64%). 4DCT had a positive predictive value (PPV) of 95%, similar to Sestamibi (96%), but higher than US (92%). Amongst patients who underwent both US and Sestamibi, the abnormal parathyroid gland was localized to the same area by both imaging modalities in 77% of patients (Cohen’s \( \kappa \): 0.383). Following an inconclusive US or Sestamibi scan, or discordance between the two modalities, 4DCT was correct at localization in 63% of patients.

Conclusion
Sestamibi has the highest sensitivity and PPV for accurately localizing parathyroid pathology. The addition of US to a positive Sestamibi scan adds little additional value. 4DCT is the preferred imaging modality following an inconclusive Sestamibi or US.

Categories: Endocrinology/Diabetes/Metabolism, Radiology, General Surgery
Keywords: parathyroid disease, localisation, primary hyperparathyroidism, four-dimensional computed tomography, 99m-tc sestamibi scintigraphy, ultrasound (u/s), minimally invasive parathyroidectomy

Introduction
Primary hyperparathyroidism (PHPT) is an endocrine disorder characterized by increased release of calcium from skeletal hydroxyapatite, leading to hypercalcemia due to an inappropriately normal or elevated plasma parathyroid hormone (PTH) level. In the 1970s, with the advent of multichannel biochemical screening, the incidence of PHPT rose sharply [1]. Since then, there has been a steady worldwide rise in its prevalence [2].

PHPT is predominantly caused by a solitary benign adenoma [3-6]. Although most patients with PHPT are largely asymptomatic, and diagnosis may be made incidentally on routine blood tests, epidemiological studies have demonstrated that if untreated, PHPT inevitably results in gastrointestinal dysfunction,
impaired renal function and nephrolithiasis, reduced bone mineral density and fragility fractures, and/or psychiatric disturbances [7,8]. The American Association of Endocrine Surgeons guidelines recommends that parathyroidectomy be offered to all symptomatic patients with PHPT. For asymptomatic PHPT patients, parathyroidectomy may also be considered a therapeutic option [9].

Historically, a bilateral neck exploration and excision of a macroscopically abnormal parathyroid gland or glands were considered the gold standard operation [10]. In the 21st century, however, there has been a move towards more focused approaches, with several randomized controlled trials investigating the merits and pitfalls of a unilateral neck exploration [11-13]. In 2002, Bergenfelz et al. conducted the first unselected randomized controlled trial of unilateral neck exploration for PHPT. This study identified a higher incidence of early severe symptomatic hypocalcemia following a bilateral neck exploration than patients who received unilateral neck exploration [11]. Since then, further randomized trials have added to the body of evidence supporting a unilateral neck exploration by demonstrating shorter operative times and reduced morbidity as some of the key benefits [12,13]. Alternative approaches have also been reported, with Miccoli et al. describing their experience with a video-assisted parathyroidectomy [14] and Henry et al. publishing their results from an endoscopic approach [15].

More commonly, however, surgeons adopt open, minimally invasive parathyroidectomy (MIP) in patients with a radiologically proven single enlarged parathyroid adenoma. In Kunstman et al., this approach was associated with numerous secondary benefits, including decreased hospital cost, improved patient satisfaction, decreased operative time, and same-day discharge [3]. According to Kluijfhout et al., the key to undertaking MIP is the pre-operative localization of the pathological parathyroid gland, ideally to a specific quadrant in the neck [16]. There are many scans available to facilitate localization, including ultrasound (US), 99mTc-sestamibi scintigraphy (Sestamibi), four-dimensional computed tomography (4DCT), and magnetic resonance imaging (MRI). These imaging modalities can be utilized alone or in combination, each with advantages and disadvantages. Neck US is often a first-line imaging modality utilized in most centers as it is inexpensive, non-invasive, and often reproducible on the operating table. In addition, the US allows for thyroid nodules to be biopsied at the time of the scan if required. However, the US is operator-dependent and limited by a high body mass index (BMI) and reduced neck extension.

In the United Kingdom (UK), there are currently no standardized investigations or referral criteria to guide decision-making regarding PHPT identified in primary care. There is variability in the utilization of different diagnostic tests and imaging modes in secondary care. The UK National Institute of Health and Care Excellent (NICE) recommends using one imaging modality prior to surgery and the second form of imaging only if this is thought to add value [17].

The main objective of this study was to identify the optimal pre-operative scan, or combination of scans, to accurately localize a single pathologically abnormal parathyroid gland to a specified side or quadrant in the neck, thereby facilitating a MIP approach. This objective was met by evaluating the diagnostic performance and interobserver agreement between US, Sestamibi, and 4DCT imaging. A comparison was made between the location of the abnormal parathyroid gland as per the diagnostic imaging reports and the location of the abnormal gland as identified during surgery. This article was previously presented as a meeting abstract at the 2020 European Society of Radiology on July 15th-19th, 2020.

Materials And Methods

Patient population and data collection

A retrospective analysis of electronic patient records (EPR) was undertaken at a single secondary care unit at Broomfield Hospital, Mid and South Essex NHS Foundation Trust, UK. All patients treated surgically with a parathyroidectomy over 10 years (January 1st, 2009 to December 31st, 2018) were eligible for consideration for inclusion in this study. This included individuals who met the UK NICE guidelines for PHPT requiring surgical intervention [17]. Specifically, these were patients with symptoms of hypercalcemia, such as thirst, frequent or excessive urination, or constipation, end-organ disease (renal stones, fragility fractures, or osteoporosis), or an albumin-adjusted serum calcium level of ≥2.85 mmol/L. Prior to surgery, all patients underwent an assessment of their vitamin D levels. Familial hypocalciuric hypercalcemia was assessed and excluded on a case by cases basis.

The final cohort of included patients included those with a successful, curative, surgical excision of a single pathologically abnormal parathyroid gland and pre-operative elevated serum calcium above normal levels as defined by NICE guidelines, followed by a sustained return to normocalcaemia in the post-operative period. All included patients also had a post-operative histologically proven single gland disease, defined as identifying a macroscopically abnormal parathyroid gland at the time of surgery with a subsequent diagnosis of a single parathyroid adenoma, hyperplasia, oxyphil, or carcinoma on final histology. Patients with histological multi-gland pathology or recurrent PHPT requiring further surgery were excluded. Patients with incomplete or missing surgical, histological or radiological data were also excluded.

Data extracted from EPR included diagnostic, operative, histological, and outcomes data. Radiology reports for each patient were obtained from the Picture and Archiving Communication Systems (PACS).
Operative approach

The location of the pathological parathyroid intra-operatively (as described in the operation note) to a side or a quadrant in the neck was considered the gold standard for comparison with imaging. The parathyroid operations employed either a midline collar incision, where some doubt remained as to the exact side of the pathological gland or a MIP with a lateral approach, where the parathyroid was presumed well-localized pre-operative imaging. Intraoperative calcium and biochemical analysis of parathyroid hormone levels were used case-by-case for any diagnostic uncertainty.

Imaging

Ultrasound

A group of radiologists performed ultrasound and specialist ultra-sonographers trained in parathyroid adenoma detection. Imaging was performed in neck extended position with a high-frequency linear transducer (8 to 15MHz) depending on neck size and patient habitus.

Sestamibi

A dual-phase 99mTc-sestamibi washout study was performed as early phase 20-minute and late phase 120-minute planar images. Planar images were obtained on a 256 x 256 matrix at 140keV 15% to 20% window. Two cameras were used. Single-photon emission computer tomograms (SPECT) were performed at 150 minutes in most patients, particularly when the planar images did not demonstrate an apparent nodule or washout was suboptimal on the 120-minute images. SPECT was obtained on a 128 x 128 matrix, zoom 1.46, at 140keV 15% or 20% window, with 64 projections with a total scan time of 5 minutes.

Four-Dimensional Computed Tomography

4DCT studies were performed on a Toshiba Aquillion CX 64 detector scanner with a rotation time of 500ms, the pitch of 64x, tube voltage of 120kVP, and smart mA acquisition (nQ mA algorithm, Toshiba), as a multiphasic technique with coverage from internal auditory meatus down to the mid-sternum. After a precontrast acquisition, images were obtained at 25 and 80 seconds following contrast as a “triple phase study.” The weight-based volume of ioversol (Optiray 350) was used as contrast media and given at a rate of 3ml/s through a pump injector.

Statistical Analysis

The diagnostic performance and interobserver agreement between imaging modalities were assessed. Where histological analysis concluded the presence of a single pathological parathyroid gland, the operative site was considered the gold standard for comparison to an imaging location. The sensitivity/true positive rate (TPR), false-negative rate (FNR), positive predictive value (PPV), and false detection rate (FDR) of each imaging modality at correctly localizing parathyroid disease to the correct side or quadrant of the neck, was calculated. Cohen’s $\kappa$ was used to determine concordance between imaging modalities. To assess the concordance between imaging modalities, the anatomical location identified for each test was categorized into one of either left, left upper, left lower, right, right upper, right lower, ectopic, or not localized (inconclusive). Calculations were based on true positive scans that localized the pathological parathyroid gland to the correct side/quadrant in the neck as found at surgery. A false positive scan identified a pathological gland but localized it to the incorrect side/quadrant in the neck. Inconclusive scans, where no abnormal parathyroid gland was seen on imaging, were treated as false negatives. There were no true negative scans as all patients included in this study had a single pathological parathyroid gland excised at the surgery. Table 1 summarises the test positive and test negative test cases. Data handling was conducted using Microsoft Excel 2013. Statistical analysis was performed with GraphPad Prism 9.2.0.

| Scan location | Correct | Incorrect |
|---------------|---------|-----------|
| location at surgery | True positive | False-positive |
| location at surgery | Inconclusive |
| No pathological parathyroid gland was seen on imaging, but an abnormal gland was found at surgery | |

**TABLE 1: Summary of test positive and test negative cases for the purposes of statistical analysis**

Results
Patient characteristics

This study reviewed 203 consecutive patients treated for PHPT. Forty-seven patients did not meet the inclusion criteria, 156 patients were included in the final analysis. These patients had a mean age of 62 years and 11 months (SD 12 years and one month) at the time of surgery.

On final histology, a diagnosis of parathyroid adenoma was obtained in 87% of patients (n=136). The operation note specified the side of the neck-bearing disease for all 156 included patients, of which 76 had disease located on the left and 80 on the right side of the neck. Localization of parathyroid disease to a quadrant of the neck was specified in the operation note of 140/156 patients. Table 2 summarises these patient characteristics.

| n          | 156 patients                                      |
|------------|--------------------------------------------------|
| Age, mean (SD) | 62 years 11 months (12 years 1 month)               |
| Histology, n (%) |                                                  |
| Parathyroid adenoma | 136 (87%)                                          |
| Parathyroid hyperplasia | 19 (12%)                                           |
| Parathyroid carcinoma | 1 (0.006%)                                        |
| Location at surgery, n (%) |                                               |
| Side | Specified in n=156                              |
| Right | 80 (51%)                                        |
| Left | 76 (49%)                                        |
| Quadrant | Specified in n=140                            |
| Right upper | 29 (21%)                                       |
| Right lower | 40 (29%)                                        |
| Left upper | 34 (24%)                                        |
| Left lower | 37 (26%)                                        |

TABLE 2: Patient characteristics

SD, standard deviation

Imaging

In total, 152 US, 155 Sestamibi, and 29 4DCT scans were performed. Most patients were investigated pre-operatively using two different imaging modalities (n=125). Only four patients had a pre-operative scan, and 29 received all three scans. Figure 1 summarises the utilization of pre-operative imaging in our patient cohort.
The US correctly identified the presence of a pathological parathyroid gland in the neck in 118/152 patients (78%). The US was inconclusive (i.e., failed to visualize an abnormal parathyroid gland anywhere in the neck) in 34 patients (22%). All patients with the inconclusive US had a Sestamibi scan, which correctly identified the presence of a pathological gland in 23/34 patients (68%) and remained inconclusive for 11/34 patients (32%). Twenty-two patients with an inconclusive US scan also underwent a subsequent 4DCT scan which correctly identified the presence of a pathological parathyroid gland in the neck for 14/22 patients (64%) but remained inconclusive for 8/22 patients (36%).

Sestamibi

Sestamibi correctly identified the presence of a pathological parathyroid gland in the neck in 129/155 patients (83%). It failed to identify any abnormal parathyroid gland in the neck of 20/155 patients scanned (13%). Of these 20 patients, 4DCT and the US correctly identified the presence of a pathological gland in the neck in 10 (50%) and nine (45%) patients, respectively. For the remaining patient, both scans remained inconclusive.

Four-Dimensional Computed Tomography

4DCT correctly identified the presence of a pathological parathyroid gland in the neck in 19/29 patients (66%). The remaining scans were inconclusive and failed to report abnormal parathyroid glands in the neck. Of the 29 4DCT scans, 19 were performed in patients in whom the Sestamibi and US findings were discordant. A subsequent 4DCT scan correctly located the pathological gland in the neck in 12/19 (63%) patients.
patients.

Four patients had no parathyroid pathology identified by all three imaging modalities. Of these four patients, three (75%) had a parathyroid adenoma, and one (25%) had parathyroid hyperplasia affecting a single gland identified at surgery.

**Localization of parathyroid disease to the correct side of the neck**

Regarding localization of parathyroid disease to the correct side of the neck, Sestamibi had the highest TPR (87%), followed by US (76%). The TPR of 4DCT was the poorest of the three imaging modalities (64%). The FNR of Sestamibi was the lowest (13%), followed by the US (24%). The FNR of 4DCT was the poorest of the three imaging modalities (36%). The PPV - that is, where a pathological gland was identified, its location was attributed to the correct side of the neck - was similar for all three imaging modalities. The PPV for Sestamibi, 4DCT, and US was 96%, 95%, and 92%, respectively. The FDR was also similar for all three imaging modalities, with Sestamibi, 4DCT, and US having an FDR of 4%, 5%, and 8%, respectively (Figure 2).

**FIGURE 2: True positive rate, false-negative rate, positive predictive value, and false discovery rate for US, Sestamibi, and 4DCT at localizing parathyroid disease to the correct side of the neck**

Diagnostic performance parameters are shown for each scan type. TPR, true positive rate; FNR, false-negative rate; PPV, positive predictive value; FDR, false discovery rate; 4DCT, Four-Dimensional Computed Tomography.

Cohen’s κ analysis was utilized to assess the strength of agreement between imaging modalities in terms of their ability to localize parathyroid disease to the side of the neck. For Sestamibi, Cohen’s κ indicated the addition of US in the same patient was likely to identify the pathological gland in the exact location or remain inconclusive due to a location agreement seen between Sestamibi and US in 77% of patients (Cohen’s κ: 0.38). The addition of 4DCT to Sestamibi yielded the same result in 66% of patients (Cohen’s κ: 0.58). By contrast, the scan agreement between US and 4DCT was only 47% (Cohen’s κ: 0.01) (Figure 3).
Localization of parathyroid disease to the correct quadrant in the neck

A sub-analysis, which included 140 patients, was performed to assess the ability of US, Sestamibi, and 4DCT’s ability to localize parathyroid disease to the correct quadrant in the neck. These patients had a mean age of 62 years and 11 months (SD 12 years and five months) at the time of surgery. After exclusion of imaging reports which did not specify a quadrant in the neck, a total of 133 US, 135 Sestamibi, and 25 4DCT scans were included in the sub-analysis.

In terms of localizing parathyroid disease to the correct quadrant in the neck, Sestamibi had the highest TPR (80%), followed by US (70%). The sensitivity of 4DCT was the poorest of the three imaging modalities (44%). The FNR of Sestamibi and the US were similar (20% and 21%, respectively), but the FNR of 4DCT was much poorer (56%). The PPV of Sestamibi and the US were also similar (62% and 64%, respectively), while 4DCT was much poorer (44%). Finally, the FDR was also similar for US and Sestamibi (37% and 39%, respectively), but 4DCT had a much poorer FDR (56%) (Figure 4).

FIGURE 3: Percentage agreement, and Cohen’s kappa between the US, Sestamibi, and 4DCT at localizing parathyroid disease to the correct side of the neck

Scan report agreement (percentage of patients) and Cohen’s κ for each combination of two scan types; US, ultrasound scan; Sestamibi, 99mTc-sestamibi scintigraphy; 4DCT, four-dimensional computed tomography scan.
Cohen’s κ was also utilized to assess the strength of the agreement between imaging modalities in terms of the ability to localize parathyroid disease to the correct quadrant in the neck. For Sestamibi, Cohen’s κ indicated that the addition of US in the same patient was likely to yield a similar result, with quadrant location agreement between Sestamibi and US scans of 72% (Cohen’s κ: 0.54). The addition of the 4DCT scan to the Sestamibi scan was 71% likely to yield a similar result (Cohen’s κ: 0.56). By contrast, the agreement between US and 4DCT was only 42% (Cohen’s κ: 0.08) (Figure 5).
FIGURE 5: Percentage agreement and Cohen’s kappa between US, Sestamibi, and 4DCT at localizing parathyroid disease to the correct quadrant of the neck

Scan report agreement (percentage of patients) and Cohen’s κ for each combination of two scan types; US, ultrasound scan; Sestamibi, 99mTc-sestamibi scintigraphy; 4DCT, four-dimensional computed tomography scan

Discussion

Although there are no clear UK guidelines regarding which patients with PHPT should be operated upon, the American Association of Endocrine Surgeons Guidelines stipulates that surgery should be offered to symptomatic patients with PHPT [9]. Asymptomatic patients also benefit from surgery to prevent the known sequelae of PHPT [18]. In addition, it is argued that no patient is truly asymptomatic and may indeed be suffering from vague neuro-cognitive symptoms, which are seen to improve significantly after treatment [18]. However, taking a well, asymptomatic patient and exposing them to the risks of a parathyroidectomy needs to be carefully weighed. This is where the MIP approach is most relevant.

Randomized trials comparing the focused MIP with the traditional bilateral approach have shown similar cure and recurrence rates [4,11,15,19]. A recent systematic review and meta-analysis have shown that MIP has a shorter mean operative time (105 versus 64 minutes) and lower overall complication rates (17% versus 4%) compared with the traditional bilateral approach [19]. Other studies have shown similar advantages to adopting a MIP approach with patients reporting lower post-operative pain, lower analgesic requirements, shorter scar length, and improved patient satisfaction [3,13]. For these reasons, we advocate for a MIP approach where possible, and underpinning a successful MIP is the accurate pre-operative localization of the pathological parathyroid gland [5].

In the absence of UK guidelines, this study aimed to determine the optimum scan, or combination of scans,
The results of this study suggest that Sestamibi, in comparison to US or 4DCT, has higher sensitivity at scans might adjust outcomes by accounting for these confounding factors.

Conclusions
The results of this study suggest that Sestamibi, in comparison to US or 4DCT, has higher sensitivity at
correctly localizing pathological parathyroid disease to the correct side and quadrant in the neck. When a Sestamibi scan can correctly localize parathyroid disease to a side of the neck, it has a PPV of 96%. Adding the US to a positive Sestamibi scan adds little additional value in the localization of a pathological parathyroid gland in the neck because it is highly likely to yield the same result. Following an inconclusive Sestamibi or US, 4DCT adds the most value for the localization of a pathological parathyroid gland to facilitate a MIP.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Research Ethics Committee at Broomfield Hospital issued approval NA. Local approval for data collection, analysis, and publication was sought and granted for this study. National level approval was not applicable as the study was limited to secondary use of information previously collected in the course of normal care and was anonymized for analysis and publication. The obtaining of written consent from patients included in this work was not required because this is a retrospective study based on patient data collected as part of their routine care. No additional or novel interventions were undertaken as part of this work and the data were anonymized for analysis and publication. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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References

1. Wermers RA, Khosla S, Atkinson EJ, Achenbach SJ, Oberg AL, Grant CS, Melton LJ 3rd: Incidence of primary hyperparathyroidism in Rochester, Minnesota, 1995-2001: an update on the changing epidemiology of the disease. J Bone Miner Res. 2006, 21:171-7. 10.1359/JBMR.050910
2. Abood A, Vestergaard P: Increasing incidence of primary hyperparathyroidism in Denmark. Dan Med J. 2013, 60:A4567.
3. Kunstman JW, Udelman R: Superiority of minimally invasive parathyroidectomy. Adv Surg. 2012, 46:171-89. 10.1016/j.asu.2012.04.004
4. Ruda JM, Hollenbeck CA, Stack BC Jr: A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. Otolaryngol Head Neck Surg. 2005, 132:559-72. 10.1016/j.ototms.2004.10.005
5. Fraser S: Surgical management of parathyroid disease. Surg (United Kingdom). 2017, 35:582-588. 10.1016/j.ansur.2017.06.018
6. Wong KK, Fig LM, Gross MD, Dwamena BA: Parathyroid adenoma localization with ⁹⁹mTc-sestamibi SPECT/CT: a meta-analysis. Nucl Med Commun. 2015, 36:565-75. 10.1097/NMN.0000000000000262
7. Rubin MR, Bilezikian JP, McMahon DJ, et al.: The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. J Clin Endocrinol Metab. 2008, 93:3462-70. 10.1210/jc.2007-1215
8. Yu N, Leese GP, Smith D, Donnan PT: The natural history of treated and untreated primary hyperparathyroidism: the parathyroid epidemiology and audit research study. QJM. 2011, 104:515-21. 10.1093/qjmed/hcq261
9. Wilhelm SM, Wang TS, Ruan DT, et al.: The American association of endocrine surgeons guidelines for definitive management of primary hyperparathyroidism. JAMA Surg. 2016, 151:959-68. 10.1001/jamasurg.2016.2510
10. Shaferi B, Hoseinzadeh S, Fotouhi F, et al.: Preoperative ⁹⁹mTc-sestamibi scintigraphy in patients with primary hyperparathyroidism and concomitant nodular goiter: comparison of SPECT-CT, SPECT, and planar imaging. Nucl Med Commun. 2012, 33:1070-6. 10.1097/NMN.0b013e32835710b6
11. Bergenzela A, Lindblom P, Tibblin S, Westerdahl J: Unilateral versus bilateral neck exploration for primary hyperparathyroidism: a prospective randomized controlled trial. Ann Surg. 2002, 236:543-51. 10.1097/00000658-200211000-00001
12. Russell CP, Dolan SJ, Laird JD: Randomized clinical trial comparing scan-directed unilateral versus bilateral cervical exploration for primary hyperparathyroidism due to solitary adenoma. Br J Surg. 2006, 93:418-21. 10.1002/bjs.5250
13. Slepavicius A, Beisa V, Janusonis V, Strupas K: Focused versus conventional parathyroidectomy for primary hyperparathyroidism: a prospective, randomized, blinded trial. Langenbecks Arch Surg. 2008, 393:659-66. 10.1007/s00423-007-0408-1
14. Miccoli P, Bertt P, Materazzi G, Massi M, Picone A, Minuto MN: Results of video-assisted parathyroidectomy: single institution’s six-year experience. World J Surg. 2004, 28:1216-8. 10.1007/s00268-004-7635-3
15. Henry JF, Sebag F, Tamagnini P, Forman C, Silaghi H: Endoscopic parathyroid surgery: results of 365 consecutive procedures. World J Surg. 2004, 28:1219-25. 10.1007/s00268-004-7601-3
16. Kluijfhout WP, Vorselaars WM, Vriens MR, Borel Rinkes IJH, Valk GD, de Keizer B: Enabling minimal
invasive parathyroidectomy for patients with primary hyperparathyroidism using Tc-99m-sestamibi SPECT-CT, ultrasound and first results of (18)F-fluorocholine PET-CT. Eur J Radiol. 2015, 84:1745-51. 10.1016/j.ejrad.2015.05.024

17. Hyperparathyroidism (primary): diagnosis, assessment and initial management NICE guideline [NG132]. (2019). Accessed: November 11, 2021: https://www.nice.org.uk/guidance/ng132.

18. Udelsman R, Pasieka JL, Sturgeon C, Young JE, Clark OH: Surgery for asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. J Clin Endocrinol Metab. 2009, 94:566-72. 10.1210/jc.2008-1671.

19. Jinih M, O Connell E, O Leary DP, Liew A, Redmond HP: Focused versus bilateral parathyroid exploration for primary hyperparathyroidism: a systematic review and meta-analysis. Ann Surg Oncol. 2017, 24:1924-34. 10.1245/s10434-016-5094-1.

20. Campbell MJ: The definitive management of primary hyperparathyroidism: who needs an operation? JAMA. 2017, 317:1167-8. 10.1001/jama.2017.1620.

21. Nafisi Moghadam R, Amelshahbaz AP, Namiranian N, et al.: Comparative diagnostic performance of ultrasonography and 99mTc-Sestamibi scintigraphy for parathyroid adenoma in primary hyperparathyroidism; systematic review and meta-analysis. Asian Pac J Cancer Prev. 2017, 18:5195-200. 10.22034/APJCP.2017.18.12.1995.

22. Greene AB, Butler RS, McIntyre S, et al.: Focused versus bilateral parathyroid exploration for primary hyperparathyroidism: a systematic review and meta-analysis. Ann Surg Oncol. 2017, 24:1924-34. 10.1245/s10434-016-5094-1.

23. Smith RB, Evasovich M, Girod DA, Jorgensen JB, Lydiatt WM, Pagedar NA, Spanos WC: Ultrasound for localization in primary hyperparathyroidism. Otolaryngol Head Neck Surg. 2013, 149:566-71. 10.1016/j.otears.2013.07.031.

24. Aarum S, Nordenstrom J, Reihnæ E, et al.: Operation for primary hyperparathyroidism: the new versus the old order, a randomized controlled trial of preoperative localisation. Scand J Surg. 2007, 96:26-30. 10.1111/j.1457-4969.2006.00105.

25. Vitetta GM, Neri P, Chiechicho A, Carriero A, Cirillo S, Mussetto AB, Codegone A: Role of ultrasonography in the management of patients with primary hyperparathyroidism: retrospective comparison with technetium-99m sestamibi scintigraphy. J Ultrasound. 2014, 17:1-12. 10.1007/s40477-014-0067-8.

26. Carral F, Ayala MD, Jiménez AI, García G, Robles MI, Vega V: High capacity of ultrasound for locating parathyroid adenomas in endocrinology (the ETIEN 4 study) [Spanish]. Endocrinol Diabetes Nutr (Engl Ed). 2020, 67:272-8. 10.1016/j.endinu.2019.04.011.

27. Treglia G, Trimboli P, Huellner M, Giovannella L: Imaging in primary hyperparathyroidism: focus on the evidence-based diagnostic performance of different methods. Minerva Endocrinol. 2018, 43:133-43. 10.23736/S0391-9177.17.02685-2.

28. Rodgers SE, Hunter GJ, Hamberg BM, et al.: Improved preoperative planning for directed parathyroidectomy with 4-dimensional computed tomography. JAMA. 2006, 140:932-41. 10.1001/jama.2006.07.028.

29. Hoang JK, Sung WK, Bahl M, Phillips CD: How to perform parathyroid 4D CT: tips and traps for technique and interpretation. Radiology. 2014, 270:15-24. 10.1148/radiol.13122661.