REVIEW

Comparative Diagnostic Performance of Ultrasonography and 99mTc-Sestamibi Scintigraphy for Parathyroid Adenoma in Primary Hyperparathyroidism; Systematic Review and Meta-Analysis

Reza Nafisi Moghadam1, Amir Pasha Amlelshahbaz1, Nasim Namiranian2, Mohammad Sobhan-Ardekani1, Mahmood Emami-Meybodi3, Ali Dehghan4, Masoud Rahmanian2, Seid Kazem Razavi-Ratki1*

Abstract

Objective: Ultrasonography (US) and parathyroid scintigraphy (PS) with 99mTc-MIBI are common methods for preoperative localization of parathyroid adenomas but there discrepancies exist with regard to diagnostic accuracy. The aim of the study was to compare PS and US for localization of parathyroid adenoma with a systematic review and meta-analysis of the literature. Methods: Pub Med, Scopus (EMbase), Web of Science and the reference lists of all included studies were searched up to 1st January 2016. The search strategy was according PICO characteristics. Heterogeneity between the studies was accounted by P < 0.1. Point estimates were pooled estimate of sensitivity, specificity and positive predictive value of SPECT and ultrasonography with 99% confidence intervals (CIs) by pooling available data. Data analysis was performed using Meta-DiSc software (version 1.4). Results: Among 188 studies and after deletion of duplicated studies (75), a total of 113 titles and abstracts were studied. From these, 12 studies were selected. The meta-analysis determined a pooled sensitivity for scintigraphy of 83% [99% confidence interval (CI) 96.358 -97.412] and for ultrasound of 80% [99% confidence interval (CI) 76-83]. Similar results for specificity were also obtained for both approaches. Conclusion: According this meta-analysis, there were no significant differences between the two methods in terms of sensitivity and specificity. There were overlaps in 99% confidence intervals. Also features of the two methods are similar.

Keywords: Parathyroid neoplasms- ultrasonography- radionuclide imaging- sensitivity and specificity

Asian Pac J Cancer Prev, 18 (12), 3195-3200

Introduction

Primary hyperparathyroidism is 3rd most common neuroendocrine disorder (Johnston et al., 1996; Mazzeo et al., 1996; Tukagi et al., 1985; Ruda et al., 2006). Parathyroid adenoma is the most common pathology for hyperparathyroidism (Wong et al., 2015; Lumachi et al., 2000; Bahansali et al., 2006; Cakal et al., 2012; Perie et al., 2005 ). It is more prevalent in women. Hyperparathyroidism is characterized by parathyroid hormone (PTH) increase and hypercalcemia since PTH is the key calcium hemostasis regulator (Mahmoudi et al., 2015; Gupta et al., 2013). Bilateral neck exploration was the traditional surgical treatment (Shafieia et al., 2012). But recently, minimally invasive parathyroidectomy (MIP) is most important key treatment in parathyroid adenoma as a standard care for hyperparathyroidism. It needs locoregional anesthesia, minor cervical exploration and smaller incisions in comparison with conventional bilateral neck exploration (Shafieia et al., 2012).

Exact preoperative localization of parathyroid adenoma is very important for MIP (Gooding 1993). The radiological and nuclear imaging methods are suggested for preoperative planning. The 99mTc-MIBI parathyroid scintigraphy (PS) and ultrasonography (US) are acceptable imaging modalities to detect parathyroid adenoma prior to operation. But in literature there is a discrepancy between accuracy of these two methods. Clinicians should be aware of essential factors in choice of an appropriate plan such as diagnostic accuracy, radiation dose, cost benefit and availability (Patel et al., 2010; Frilling et al., 2000; Nabriski et al., 1992).

PS make available incremental diagnostic value in localization parathyroid adenoma and guide the surgeon. US is a simple, non-expensive and available imaging modality for parathyroid adenoma localization (Lumachi...
We designed a systematic review and meta-analysis to determine the diagnostic accuracy of parathyroid scintigraphy and ultrasonography for preoperative localization of parathyroid adenoma.

Materials and Methods

We conducted a systematic search of electronic database (MEDLINE, Scopus (EMbase), Web of Science) and MEDLINE non-indexed databases up to 1January 2016. The last updated search was done on 12 February 2017. The reference lists of all included studies were searched for further studies.

Search strategy

The search strategy was according PICO characteristics, Mesh term and key word are including: Patients/problem: Parathyroid Adenomas, Neoplasm, Parathyroid, Parathyroid Neoplasm, Neoplasms Parathyroid, Cancer of Parathyroid, Parathyroid Cancers, Cancer of the Parathyroid,Parathyroid Adenoma,Adenoma, Parathyroid,Adenomas, Parathyroid,’’ ‘‘primary hyperparathyroidism,’’ ‘‘parathyroid adenoma as population.

Index

Ultrasound Imaging, Imaging, Ultrasound Imagings, Ultrasound, Ultrasound Imagings, Sonography, Medical, Medical Sonography, Ultrasonic Imaging, Imaging, Ultrasonic, Diagnosis, Ultrasonic, Diagnoses, Ultrasonic, Ultrasonic Diagnoses, Ultrasonic Diagnosis

Comparison

Imaging, Radionuclide, Radioisotope Scanning, Scintigraphy, Gamma Camera Imaging, Gamma Camera, Scanning, Radioisotope, Scintiphotography, radionuclide imaging,’’ ‘‘SPECT,’’ ‘‘sestamibi,’’ ‘‘computed tomography.

Outcome

Specificity and Sensitivity, Sensitivity, Specificity, Diagnostic accuracy

The literature search was performed by two independent reviewers (NN and SKRR). After reviewed Titles study and abstracts relevant studies were selected. Selection criteria are included 1) studies of patients with suspected parathyroid adenoma 2) undergoing ultrasound, parathyroid scintigraphy and surgery as gold standard. 3) Tc-99m sestamibi with early and delayed images was considered as Sestamibi-scintigraphy techniques.

Letters to the editor, review articles, case reports, and paper with not enough information of sensitivity and predictive value were excluded. Studies quality was assessed using the modified QUADAS criteria (Quality Assessment of Diagnostic Accuracy Studies).

Results

All articles were reviewed by two reviewers. The 188 were included after 75 duplicate articles removal. 113 title and abstracts were reviewed and 40 non relevance articles were excluded. Then 73 full text studies were appraised. Finally 12 original articles with eligibility criteria were selected for meta-analysis (Figure 1). The quality assessment of included studies according modified QUADAS score 2 is presented in Figure 2. Table 1 shows the included studies characteristics. The pooled estimates of sensitivity, specificity and Receiver Operating Characteristics (ROC) are described in Table 2.

Discussion

Various diagnostic modalities are suggested to preoperative localization of parathyroid Adenoma (Lumachi et al., 2001; Arici et al., 2001; Berri et al.,...
US and 99mTc-Scintigraphy in Parathyroid Adenoma

Parathyroid adenoma localization (Carlson et al., 1990; Li et al., 2012; Carlier et al., 2008). Most key benefit of precise preoperative localization is minimally invasive parathyroid surgery. Accuracy of imaging methods is dissimilar (Li et al., 2012; Carlier et al., 2008; Maka et al., 1997; Haciyanli et al., 2003; Yip et al., 2008; Mihai et al., 2008). A wide range of sensitivity and specificity was informed in literature for PS and US. The operator dependence of US is known. Also several aspects may

Table 1. The Basic Study Characteristics

| First author | Publication year | Sample size | Female | Male | Type of study | Country | Mean age of participants |
|--------------|------------------|-------------|--------|------|---------------|---------|--------------------------|
| Arici        | 2001             | 338         | 242    | 96   | Retrospective | USA     | 60                       |
| Barcynski    | 2006             | 121         | 106    | 15   | Retrospective | Poland  | 56.1                     |
| Berczi       | 2002             | 63          | 50     | 13   | Prospective   | Hungary | 54                       |
| Bhansali     | 2006             | 46          | 33     | 13   | Prospective   | India   | 37.1                     |
| Cakal        | 2012             | 39          | 29     | 10   | Prospective   | Turkey  | 53.2                     |
| Freudenburg  | 2006             | 84          | 46     | 38   | Prospective   | Germany | 54                       |
| D.Hajioff    | 2004             | 48          | 36     | 12   | Prospective   | UK      | 60                       |
| Lo           | 2007             | 100         | 70     | 30   | Prospective   | China   | 55.5                     |
| Lumachi      | 2000             | 91          | 65     | 26   | Prospective   | Italy   | 59                       |
| Patel        | 2010             | 63          | 42     | 21   | Retrospective | UK      | 59                       |
| Tubline      | 2009             | 144         | 117    | 27   | Prospective   | USA     | 63.2                     |

Table 2. The Pooled Estimate of Sensitivity, Specificity and AUC of Tc-99m Sestamibi and Ultrasound Studies

|  | Pooled estimate | Ultrasound (99%CI) | Tc-99m sestamibi (99%CI) |
|---|-----------------|---------------------|-------------------------|
| sensitivity | 80%(77-83%) | 84%(80-87%) |
| specificity  | 77%(71-82%) | 87%(83-91%) |
| AUC(± standard error) | 0.87 (0.042) | 0.94 (0.033) |

Figure 2. The Quality Assessment of Included Studies According Modified QUADAS Score 2

2006; Kim et al., 2012; Tublin et al., 2009; Freudenburg et al., 2006). 99mTc-sestamibi parathyroid scintigraphy and ultrasonography are common diagnostic methods for parathyroid adenoma localization (Carlson et al., 1990; Li et al., 2012; Carlier et al., 2008). Most key benefit of precise preoperative localization is minimally invasive parathyroid surgery. Accuracy of imaging methods is dissimilar (Li et al., 2012; Carlier et al., 2008; Maka et al., 1997; Haciyanli et al., 2003; Yip et al., 2008; Mihai et al., 2008). A wide range of sensitivity and specificity was informed in literature for PS and US. The operator dependence of US is known. Also several aspects may
influence the accuracy of PS were identified (Shafieia et al., 2012; Gooding 1993).

Our study findings showed the pooled sensitivity of two methods are not statistically different but the pooled estimate of PS specificity is significantly higher than US specificity. Our research has directly compared PS and US, and we selected studies that PS and US were performed for each patient. According to individual studies, the findings are conflicting. As some studies, support these findings and some refer to the superiority of US.

Most of diagnostic studies report the positive predictive value (PPV) of test instead of specificity because of no true negative cases. PPV shows the number of true positive cases among total positive result. In real situation (not study) PPV is more affected by disease prevalence which is neglected in diagnostic studies. In this systematic review and meta-analysis we restricted the inclusion criteria to studies with adequate findings to calculate the specificity.

In a meta-analysis and systematic review study of nuclear imaging in the diagnosis of parathyroid adenoma, the results have mentioned using nuclear imaging as the most common parathyroid adenoma detection method. In this study only nuclear imaging method is studied. Cumulative sensitivity of nuclear imaging in diagnose of parathyroid glands in this meta-analysis obtained 86% with 81-90% confidence interval, which is quite consistent with the results of our recent study (Wong et al., 2015).

Another Meta-analysis and systematic review study on all type of diagnostic methods for preoperative localization techniques in primary hyperparathyroidism the sensitivity of two methods were not statistically different. Because of different inclusion criteria the specificity and positive predictive value of two studies were not comparable. The results of recent meta-analysis and systematic review study are provided acceptable sensitivity and specificity of this method.

In this systematic review only studies that have been done by SPECT imaging method has entered, because thallium studies did not earn enough score to enter the study. For this reason, in this study subgroup analyzes and comparison of the diagnostic accuracy of different methods of nuclear imaging was not possible.

One of the very significant limitations in diagnostic studies are performing diagnostic tests in patient groups, in this study all studies that clearly indicated this point were excluded. The many initial studies were case-reports with no gold standard comparison (surgical outcomes) were expressed, and these studies did not enter the data extraction process. Also a significant number of studies because of limitation entry criteria in terms of language study were published did not enter in meta-analysis and systematic review study.

The strengths of the study include the high quality of input studies, pointed out in a critical appraisal phase. All input studies obtained full score of key questions of critical appraisal check list.

Depending on the type of input studies that were diagnostic, accomplishment of famous tests and drawing funnel plot to explore the publication bias was not possible, So all studies were further investigated after
critical appraisal, that are listed in the Table.
As another limitation, the diagnosis of parathyroid
is affected by position, size, functional characteristics of
hyper-functioning, thyroid nodule and goiter. In our study
only the thyroid nodule and goiter were controlled. The
individual studies did not control this aspect of disease. It
should be noticed that gray literatures were not included.
In most studies, the time interval between diagnostic
tests and surgical procedures was not stated that could
affect results. As a conclusion, sensitivity in nuclear
imaging technique is similar to ultrasound, but the
specificity of nuclear imaging is higher than US. Also
features of two methods are close together.

Funding statements
There were no sources of funding for the article. This
research did not receive any specific grant from funding
agencies in the public, commercial, or not-for-profit
sectors.

References

Arici C, Cheah WK, Ituarte PH, et al (2001). Can localization
studies be used to direct focused parathyroid operation ?.
Surg J (N Y), 129, 720-9.
Barczyński M, Golkowski F, Konturek A, et al (2006).
Technetium-99m-sestamibi subtraction scintigraphy vs.
ultrasonography combined with a rapid parathyroid hormone
assay in parathyroid aspires in preoperative localization of
parathyroid adenomas and in directing surgical approach.
Clin Endocrinol, 65, 106-13.
Berczi C, Mazosi E, Galuska L, et al (2002). Technetium-
99m-sestamibi/pertechnetate subtraction scintigraphy vs
ultrasonography for preoperative localization in primary
hyperparathyroidism. Eur Radiol, 12, 605-9.
Berri RN, Lloyd LR (2006). Detection of parathyroid adenoma
in patients with primary hyperparathyroidism: the use of
office-based ultrasound in preoperative localization. Am J
Surg, 191, 311-4.
Bhansali A, Masoodi S, Bhadada S, et al (2006). Ultrasonography
in detection of single and multiple abnormal parathyroid
glands in primary hyperparathyroidism: comparison with
radionuclide scintigraphy and surgery. Clin Endocrinol,
65, 340-5.
Cakal E, Cakir E, Dilli A, et al (2012). Parathyroid adenoma
screening efficacies of different imaging tools and factors
affecting the success rates. Clin Imaging, 36, 688-94.
Carlier T, Oudoux A, Mirallié E, et al (2008). 99mTc-MIBI
pinhole SPECT in primary hyperparathyroidism: comparison
with conventional SPECT, planar scintigraphy and
ultrasonography. Eur J Nucl Med Mol Imaging, 35, 637-43.
Carlson GL, Farrndon JR, Clayton B, Rose PG (1990). Thallium
isotope scintigraphy and ultrasonography: comparative
studies of localization techniques in primary
hyperparathyroidism. Br J Surg, 77, 327-8.
Freudenberg LS, Frilling A, Sheu S-Y, Görges R
(2006). Optimizing preoperative imaging in primary
hyperparathyroidism. Langenbecks Arch Surg, 391, 551-6.
Frilling A, Görges R, Clauer U, Tecklenborg K, Broelsch CE
(2000). Minimally invasive parathyroidectomy under local
anaesthesia in connection with ultrasonography, sestamibi
scintigraphy and intra-operative parathormone measurement.
Chirurg, 71, 1474-9.
Gergel M, Brychta I, Vician M, Olejník J (2014). Primary
hyperparathyreosis: is concordant sonography and
scintigraphy really so important?. Bratisl Lek Listy, 115,
649-52.
Gooding G (1993). Sonography of the thyroid and parathyroid.
Radiol Clin North Am, 31, 967-89.
Grosso I, Sargiotti A, D’Amelio P, et al (2007). Preoperative
localization of parathyroid adenoma with sonography and
99mTc-sestamibi scintigraphy in primary hyperparathyroidism. J Clin Ultrasound, 35, 186-9.
Gupta S, Mittal A, Satthi B (2013). Significance of HCG to
distinguish parathyroid carcinoma from benign disease and
in adding prognostic information: A hospital based study from
Nepal. Asian Pac J Cancer Prev, 14, 325-7.
Hacıyanlı M, Lai G, Morita E, et al (2003). Accuracy of
preoperative localization studies and intraoperative
parathyroid hormone assay in patients with primary
hyperparathyroidism and double adenoma. J Am Coll Surg,
197, 739-46.
Hajioff D, Lyngkaran T, Panagamuwa C, Hill D, Stearns M
(2004). Preoperative localization of parathyroid adenomas:
ultrasonography, sestamibi scintigraphy, or both?. Clin Otolaryngol Allied Sci, 29, 549-52.
Johnston L, Carroll M, Britton K, et al (1996). The accuracy of
parathyroid gland localization in primary hyperparathyroidism using sestamibi radionuclide imaging.
J Clin Endocrinol Metab, 81, 346-5.
Kebapci M, Eniok E, Kebapci N, Adapinar B (2004).
Preoperative evaluation of parathyroid lesions in patients
with concomitant thyroid disease: role of high resolution
ultrasonography and dual phase technetium 99m sestamibi
scintigraphy. J Endocrinol Invest, 27, 24-3.
Kim YI, Jung YH, Hwang KT, Lee HY (2012). Efficacy of
(99)mTc-sestamibi SPECT/CT for minimally invasive
parathyroidectomy: comparative study with (99)mTc-
sestamibi scintigraphy, SPECT, US and CT. Ann Nucl Med,
26, 804-10.
Li CC, Yang C, Wang S, et al (2012). A 10-year retrospective
study of primary hyperparathyroidism in children. Exp Clin
Endocrinol Diabetes, 120, 229-33.
Lo C-Y, Lang BH, Chan W, Kung AW, Lam KS (2007). A
prospective evaluation of preoperative localization by
technetium-99m sestamibi scintigraphy and ultrasonography
in primary hyperparathyroidism. Am J Surg, 193, 155-9.
Lumachi F, Zacchetta P, Marzola M, et al (2000). Advantages
of combined technetium-99m-sestamibi scintigraphy and
high-resolution ultrasonography in parathyroid
localization: comparative study in 91 patients with primary
hyperparathyroidism. Eur J Endocrinol, 143, 755-60.
Lumachi F, Ermanni M, Basso S, et al (2001). Localization of
parathyroid tumours in the minimally invasive era: which
technique should be chosen? Population-based analysis of
253 patients undergoing parathyroidectomy and factors
affecting parathyroid gland detection. Endocr Relat Cancer,
8, 63-9.
Mahmoudi T, Karimi Kh, Arkani M, et al (2015). Parathyroid
gene hormone rs6256 and calcium sensing receptor gene
rs1801725 variants are not associated with susceptibility
to colorectal cancer in Iran. Asian Pac J Cancer Prev,
15, 6035-39.
Mazzeo S, Caramella D, Lencioni R, et al (1996). Comparison
among sonography, double-tracer subtraction scintigraphy,
and double-phase scintigraphy in the detection of parathyroid
lesions. AJR Am J Roentgenol, 166, 1465-70.
Mihai R, Weisters M, Stochman MJ, Glesson F, Sadler G (2008).
Cost-effectiveness of scan-directed parathyroidectomy.
Langenbecks Arch Surg, 393, 739-43.
Moka D, Voth E, Larena-Avellaned A, Schicha H (1997).
99mTc-MIBI-SPECT for the location of small parathyroid
lesions. J Clin Endocrinol Metab, 82, 340-5.
adenoma. *Nuklearmedizin*, 36, 240-4.

Nabriski D, Bendahan J, Shapiro MS, Freund U, Lidor C (1992). Sarcoidosis masquerading as a parathyroid adenoma. *Head Neck*, 14, 384-6.

Patel C, Salahudeen H, Lansdown M, Scarsbrook A (2010). Clinical utility of ultrasound and 99m Tc sestamibi SPECT/CT for preoperative localization of parathyroid adenoma in patients with primary hyperparathyroidism. *Clin Radiol*, 65, 278-87.

Perie S, Fessi H, Tassart M, et al (2005). Usefulness of combination of high-resolution ultrasonography and dual-phase dual-isotope iodine 123/technetium Tc 99m sestamibi scintigraphy for the preoperative localization of hyperplastic parathyroid glands in renal hyperparathyroidism. *Am J Kidney Dis*, 45, 344-52.

Ruda JM, Stack BC, Hollenbeak CS (2006). The cost-effectiveness of additional preoperative ultrasonography or sestamibi–SPECT in patients with primary hyperparathyroidism and negative findings on sestamibi scans. *Arch Otolaryngol Head Neck Surg*, 132, 46-53.

Shafei B, Hoseinzadeh S, Fotouhi F, et al (2012). Preoperative 99mTc-sestamibi scintigraphy in patients with primary hyperparathyroidism and concomitant nodular goiter: comparison of SPECT-CT, SPECT, and planar imaging. *Nucl Med Commun*, 33, 1070–6.

Takagi H, Tominaga Y, Uchida K, et al (1985). Comparison of imaging methods for diagnosing enlarged parathyroid glands in chronic renal failure. *J Comput Assist Tomogr*, 9, 733-7.

Tublin ME, Pryma DA, Yim JH, et al (2009). Localization of parathyroid adenomas by sonography and technetium tc 99m sestamibi single-photon emission computed tomography before minimally invasive parathyroidectomy: are both studies really needed?. *J Ultrasound Med*, 28, 183-90.

Wong KK, Fig LM, Gross MD, Dwamena BA (2015). Parathyroid adenoma localization with 99mTc-sestamibi SPECT/CT: a meta-analysis. *Nucl Med Commun*, 36, 363-75.

Yip L, Pryma DA, Yim JH, et al (2008). Can a lightbulb sestamibi SPECT accurately predict single-gland disease in sporadic primary hyperparathyroidism?. *World J Surg*, 32, 784-92.