DOI: 10.4149/BLL_2014_125

Bratisl Lek Listy 2014; 115 (10)
649 – 652

CLINICAL STUDY

Primary hyperparathyreosis: Is concordant sonography and scintigraphy really so important?

Gergel M, Brychta I, Vician M, Olejnik J

1st Department of Surgery, Slovak Healthcare University and Bratislava University Hospital, Bratislava, Slovakia. **michal.gergel@3b2.sk**

Abstract: *Background:* In primary hyperparathyreosis, US and scintigraphy are the most usual preoperative localization methods for detection of parathyroid adenomas or hyperplasia.
Results: 88 (80 female) patients were detected. Unilateral neck exploration was performed in 43 patients (48.9 %) and bilateral exploration in 45 patients (51.1 %). The cure rate was 97.6 %. None case of parathyroid hyperplasia was detected, there were 2 cases of duplex adenoma. For left/right and quadrant localization, sensitivity of US was 71.05 % and 55.07 %, of scintigraphy 95.77 % and 88.71 %, and in concordant imaging 97.67 % and 96.77 %. Analogically, PPV was: US 91.53 % and 76.00 %, scintigraphy 87.18 % and 74.32 %, concordant imaging 93.33 % and 81.08 %. Only US sensitivity was significantly lower, all other differences showed no statistical significance.
Conclusion: Our data showed low sensitivity but a high positive predictive value of ultrasonography and a high diagnostic value of scintigraphy. Sensitivity and the positive predictive value of concordant localization showed no significant difference, compared to scintigraphy. The routine need for concordance for parathyroid adenoma localization appears dubious, however, its value for prediction of multiglandular disease remains important for protocols that do not apply peroperative localization *(Tab. 2, Ref. 35)*. Text in PDF *www.elis.sk.*
Key words: primary hyperparathyreosis, localization studies, ultrasonography, scintigraphy.

Primary hyperparathyreosis (pHPT) is a disorder of calcium metabolism caused by autonomous hypersecretion of parathyroid hormone (PTH) in abnormal parathyroid tissue. The most common pathology is the parathyroid adenoma of a single gland (75–90 %), followed by parathyroid hyperplasia (8–21 %) and duplex parathyroid adenoma (3–6 %). Parathyroid carcinoma is a rare cause of pHPT (< 1 %) (1, 2, 3, 4). Hyperplasia and duplex adenoma cases are described as *Multiglandular disease* (MGD), whereas solitary adenoma cases are described as *Uniglandular disease* (UGD).

The attitude towards surgery of spontaneous primary hyperparathyreosis (PHPT) has changed over the last 10 years, from the classical bilateral neck exploration (*BNE*) towards unilateral (*unilateral neck exploration, UNE*) and focused exploration of parathyroid glands (*Miniinvasive parathyroidectomy, MIP*). This change results from the introduction of routine preoperative localization and imaging, previously reserved mostly for reoperative parathyroid surgery. Endocrine surgeons have become encouraged by introducing intraoperative adjunct localization methods, such as intraoperative parathormone monitoring and radio-guided parathyroid surgery. In studies comparing bilateral and focused approach, the number of identified MGD cases was significantly lower in the focused group, showing no significant difference in the cure rates (5, 6). The authors suggested that focused parathyroidectomy may lead to long term recurrence, however 5 years follow up study showed no difference as well. (7) Possible explanation might be an overestimation of surgical finding during bilateral neck exploration. Many endocrine surgeons recently abandon routine perioperative localization and guide focused parathyroidectomies by preoperative localization (8, 9, 10, 11).

Preoperative localization is expected to provide 3 important information: 1) To verify cervical position or identify ectopic PHPT. 2) To locate the exact position with left/right and superior/inferior specificity in order to guide the unilateral or focused exploration. 3) To identify multiglandular disease.

Ultrasonography (US) is usually the first step in localization of parathyroid adenomas. It is a safe, non-invasive method, however the main disadvantage is its operator-dependence. Sensitivity varies between 51–85 %, specificity 90–95 %. In the metaanalysis of 19 studies, sensitivity and the positive predictive value was 76.1 % and 93.2 % respectively (12, 13). An important advantage is the capability to detect thyroid pathology, including thyroid cancer (14). In addition, US appears to be the most cost-effective method (15).

Scintigraphic imaging includes planar scintigraphy and single photon emission computed tomography (SPECT), both using SESTAMIBI (methoxy-isobutylisonitrile) as a carrier for ^{99m}Tc. Reported sensitivity of planar scintigraphy is 69–90 % (16, 17, 18, 19) with the positive predictive value 97.8 % in patients without thyroid pathology (10). SPECT is a more advanced method with

1st Department of Surgery, Slovak Healthcare University and Bratislava University Hospital, Bratislava, Slovakia

Address for correspondence: M. Gergel, MD, 1st Department of Surgery, Slovak Healthcare University and Bratislava University Hospital, Limbova 5, SK-833 05 Bratislava, Slovakia.
Phone: +421.903316458

Acknowledgments: This text is an original work based upon authors' experience and data. The text and none of its parts has never been published before.

sensitivity 78.9–96 % and the positive predictive value 90.7 % (12, 13, 20).

Other imaging methods, such as computed tomography, magnetic resonance imaging and positron emitting tomography are routinely used only if ectopic disease is suspected. A novel technique, 4d-CT parathyroid scan is a promising method with the reported sensitivity 93.9 % and positive predictive value for MGD 85.7 % (21). Invasive techniques such as selective angiography, selective venous blood sampling and fine needle biopsy are routinely used only if previous methods failed.

Most of recent protocols use both, US and scintigraphy, to determine the strategy of surgical intervention (bilateral or unilateral/focused), with particular stress on concordance of both methods. For example, concordant imaging adds automatically 3 points in CaPTHUS score, indicating safe focused parathyroidectomy without adjunct intraoperativé localization (8).

Exact quadrant localization is helpful for focused approaches, whereas left/right location is satisfactory for open unilateral exploration, if both ipsilateral glands are explored. Our aim was to compare sensitivity and the positive predictive value of US, scintigraphy and combination of both for left/right and quadrant-specific localization.

Patients and methods

We investigated retrospectively the records of all patients referred for parathyroid surgery for biochemically diagnosed spontaneous primary hyperparathyreosis during 5 years period (2008–2012). Data on preoperative localization (US and scintigraphy), surgical and histological findings and long term follow up data have been collected.

US was performed by outpatient endocrinologists who managed the patients and referred them for surgery. Scintigraphy was performed in various centres of nuclear medicine countrywide, both planar scintigraphy and SPECT data have been pooled.

Surgery was performed by one team, led by an experienced endocrine surgeon. Patients with concordant preoperative localisation were primarily indicated for unilateral neck exploration. In cases of non-satisfactory operative findings (e.g. small adenoma, atypical macroscopic features) and/or negative histological and intraoperative parathormone results, the procedure was converted to standard bilateral neck exploration. During the surveyed period, intraoperative histology was being abandoned in favour of intraoperative parathormone monitoring. Patients with discordant preoperative localization underwent bilateral neck exploration. If palpable nodular changes of the thyroid gland were found, adequate thyroid surgery was performed. All excised tissues were investigated histologically.

Patients were hospitalized at least 48 hours postoperatively and after discharge were followed up by the competent endocrinologists. Information on normocalcemia after 6 months follow up period as the main cure indicator was obtained in cooperation with these specialists.

Result of surgery verified by definitive histology as well as by long term follow up results was taken as golden standard to determine true/false values of imaging.

In data analysis, we concentrated on accuracy of preoperative localization results of ultrasonography, scintigraphy and their concordance separately for left/right and quadrant localization. The chi square test with Yates correction was used to compare sensitivities and positive predictive values. 95 % confidence test was used to determine probabilities and confidence intervals.

Results

We detected 88 patients, 80 female, 8 male, the median age was 58.5 years (33–80). The median initial calcium and ionised calcium levels were 2.77 mmol/l (1.93–3.61) and 1.45 mmol/l (1.16–2.83) respectively. The median preoperative parathormone level was 144,5 pg/ml (48.6–2042). Unilateral neck exploration was performed in 43 patients (48.9 %) and bilateral exploration in 45 patients (51.1 %), according to protocol mentioned above. Solitary adenoma (UGD) was detected in 81 patients (92.0 %) including 3 cases of intrathyroid adenoma, MGD was detected in 2 patients (2.3 %), both cases were duplex adenomas of both inferior glands. No case of hyperplasia was detected neither in surgical exploration, nor histologically. Of the two MGD cases, one was detected in primary operation, the other was detected in follow up and reoperated, we considered it as failure of UNE. No parathyroid pathology was found in the remaining 5 cases. Diagnosis of primary hyperparathyreosis was later reviewed in 4 (4.3 %) of them, in the remaining case total thyroidectomy was performed due to nodular goiter and persistent biochemical signs of primary hyperparathyreosis. Conservative cinacalcet therapy was recommended in this case due to poor general condition of the patient. Overall eucalcemia after 6 months follow up was 97.6 %.

78 patients were examined by both US and scintigraphy, 7 patients had US and 3 scintigraphic localization only, none of the patients was operated without any localization. US showed 26 (30.6 % of all US) negative results, scintigraphy only 3 (3.7 %). Concordance for left/right localization was present in 46 patients (59 %), 38 (48.7 %) of these were concordant for a specific quadrant. For the evaluation of left/right accuracy, we considered the positive result with the correct lateral positioning (compared to surgery) as true positive and the positive result with the incorrect side result as false positive. For the quadrant accuracy, all cases of the positive results with the incorrect quadrant position were considered false positive and vice versa. If the examination showed only left or right finding, without determining superior or inferior quadrant, the result was described as false negative in quadrant localization.

Of the two MGD cases, one was correctly concordantly detected by both US and scintigraphy, the other one was concordantly missed having diagnosed solitary adenoma of left inferior parathyroid. US showed the lowest sensitivity for left/right and quadrant localization 71.05 % and 55.07 % respectively, with positive predictive value 91.53 % and 76.00 %. Sensitivity and positive predictive value of scintigraphy was 95.77 % and 87.18 % respectively for left/right and 88.71 % and 74.32 % for quadrant localization. Analogically, concordant US/scintigraphy results parameters were 97.67 % and 93.33 % for left/side, 96.77 % and

Tab. 1. Sensitivity and specificity of US, scintigraphy and their concordance for left/right localization. P-value demonstrates difference between methods.

sensitivity:	US (n=85) 71.05% (CI: 59.51–80.88%)	Scintigraphy (n=81) 95.77% (CI: 88.13–99.07%)	Concordant (n=46) 97.67% (CI: 87.67–99.61%)
US	N/A	p<0.001	p<0.001
scintigraphy	p=0.60	N/A	p=0.36
US/scinti concordance	p=0.97	p=0.44	N/A
positive predictive value:	US (n=85) 91.53% (CI: 81.31–97.16%)	Scintigraphy (n=81) 87.18% (CI: 77.68–93.67%)	Concordant (n=46) 93.33% (CI: 81.71–98.53%)

Tab. 2. Sensitivity and specificity of US, scintigraphy and their concordance for quadrant localization. P-value demonstrates difference between methods.

sensitivity:	US (n=85) 55.07% (CI: 42.62–67.07%)	Scintigraphy (n=81) 88.71% (CI: 78.10–95.32%)	Concordant (n=46) 96.77% (CI: 83.24–99.46%)
US	N/A	p<0.001	p<0.001
scintigraphy	p=1	N/A	p=0.59
US/scinti concordance	p=0.76	p=0.58	N/A
positive predictive value:	US (n=85) 76.00% (CI: 61.83–86.93%)	Scintigraphy (n=81) 74.32% (CI: 62.84–83.77%)	Concordant (n=46) 81.08% (CI: 64.84–92.00%)

81.08 % for quadrant. Statistical analysis showed a significantly lower sensitivity of US, and non significant difference between sole scintigraphy and US/scinti concordance. Thepositive predictive values showed no significant differences in all aspects. Detailed results are in Tables 1 and 2.

Conclusion

The first result is an unusually low incidence of MGD among our patient group, as well as the complete absence of parathyroid hyperplasia. Due to very low incidence, we were not able to measure diagnostic reliability of MGD detection in our patients.

A small proportion of negative exploration followed by diagnosis revaluation is referred by several authors, varying around 3 % (1, 22). A small proportion of negative results is probably inevitable and it underlines surgery as an ultimate diagnostic method of primary hyperparathyreosis.

Although our results demonstrate a significantly lower sensitivity of US, it was overweighted by a high positive predictive value, which demonstrates the low diagnostic value of negative US. Despite the fact, that our scintigraphy data was pooled from planar scintigraphy and SPECT findings, it showed a high sensitivity, with a slightly lower positive predictive value due to a higher rate of false positive results. Lower diagnostic accuracy in recognizing superior/inferior position after having correctly identified the affected side supports the idea of routine exploration of both ipsilateral glands during unilateral parathyroidectomy (2).

Several authors refer concordant localization as the most accurate method to locate parathyroid adenomas, therefore most protocols accept it as the crucial information to guide focused parathyroidectomy (4, 18, 23). However, our data showed no significant diagnostic advantage compared to scintigraphy only. Therefore, we suggest, that demand for concordant results should not be the motivation for routine use of both localization techniques. Considering low cost, detection of thyroid pathology and a high positive predictive value, US is preferable as the first line method in diagnosing primary hyperparathyreosis. Several authors prefer US to scintigraphy (24, 25).

However, another important role of preoperative localization, apart from guiding focused exploration, is prediction of MGD. In protocols that do not routinely use perioperative localization (e.g. parathormone monitoring), application of both techniques appears to be essential. Unfortunately, due to unusually low MGD incidence, we were not able to verify this condition.

References

1. Nordenström E (Ed). Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery (SQRTPAS), Annual report 2012. www.thyroid-parathyroidsurgery.com

2. Cho NL, Gawande AA, Sheu EG, Moore FD Jr, Ruan DT. Critical role of identification of the second gland during unilateral parathyroid surgery: a prospective review of 119 patients with concordant localization. Arch Surg 2011; 146 (5): 512–516.

3. Moreno MA, Callender GG, Woodburn K, Edeiken-Monroe BS, Grubbs EG, Evans DB, Lee JE, Perrier ND. Common Locations of Parathyroid Adenomas. Ann Surg Oncol 2011; 18 (4): 1047–1051.

4. Mozzon M, Mortier PE, Jacob PM, Soudan B, Boersma AA, Proye CA. Surgical management of primary hyperparathyroidism: the case for giving up quick intraoperative PTH assay in favor of routine PTH measurement the morning after. Ann Surg 2004; 240 (6): 949–953.

5. Genc H, Morita E, Perrier ND, Miura D, Ituarte P, Duh QY, Clark OH. Differing histologic findings after bilateral and focused parathyroidectomy. J Am Coll Surg 2003; 196 (4): 535–540.

6. Lee NC, Norton JA. Multiple-gland disease in primary hyperparathyroidism: a function of operative approach? Arch Surg 2002; 137 (8): 896–899.

7. Westerdahl J, Bergenfelz A. Unilateral versus bilateral neck exploration for primary hyperparathyroidism: five-year follow-up of a randomized controlled trial. Ann Surg 2007; 246 (6): 976–980; discussion 980–981.

8. Kebebew E, Hwang J, Reiff E, Duh QY, Clark OH. Predictors of single--gland vs multigland parathyroid disease in primary hyperparathyroidism: a simple and accurate scoring model. Arch Surg 2006; 141 (8): 777–782.

9. Wong W, Foo FJ, Lau MI, Sarin A, Kiruparan P. Simplified minimally invasive parathyroidectomy: a series of 100 cases and review of the literature. Ann R Coll Surg Engl 2011; 93 (4): 290–293.

10. Moure D, Larrañaga E, Domínguez-Gadea L, Luque-Ramírez M, Nattero L, Gómez-Pan A, Marazuela M. 99MTc-sestamibi as sole technique in selection of primary hyperparathyroidism patients for unilateral neck exploration. Surgery 2008; 144 (3): 454–459.

11. Bachar G, Mizrachi A, Hadar T, Feinmesser R, Shpitzer T. Role of parathyroid hormone monitoring during parathyroidectomy. Head Neck 2011; 33 (12): 1754–1757.

12. Carlier T, Oudoux A, Mirallié E, Seret A, Daumy I, Leux C, Bodet-Milin C, Kraeber-Bodéré F, Ansquer C. 99mTc-MIBI pinhole SPECT in primary hyperparathyroidism: comparison with conventional SPECT, planar scintigraphy and ultrasonography. Eur J Nucl Med Mol Imaging 2008; 35 (3): 637–643.

13. Cheung K, Wang TS, Farrokhyar F, Roman SA, Sosa JA. A meta-analysis of preoperative localization techniques for patients with primary hyperparathyroidism. Ann Surg Oncol 2012; 19 (2): 577–583.

14. Adler JT, Chen H, Schaefer S, Sippel RS. Does routine use of ultrasound result in additional thyroid procedures in patients with primary hyperparathyroidism? J Am Coll Surg 2010; 211 (4): 536–539.

15. Lubitz CC, Stephen AE, Hodin RA, Pandharipande P. Preoperative localization strategies for primary hyperparathyroidism: an economic analysis. Ann Surg Oncol 2012; 19 (13): 4202–4209.

16. Glynn N, Lynn N, Donagh C, Crowley RK, Smith D, Thompson CJ, Hill AD, Keeling F, Agha A. The utility of (99m)Tc-sestamibi scintigraphy in the localisation of parathyroid adenomas in primary hyperparathyroidism. Ir J Med Sci 2011; 180 (1): 191–194.

17. Lavely WC, Goetze S, Friedman KP, Leal JP, Zhang Z, Garret--Mayer E, Dackiw AP, Tufano RP, Zeiger MA, Ziessman HA. Comparison of SPECT/CT, SPECT, and planar imaging with single- and dual--phase (99m)Tc-sestamibi parathyroid scintigraphy. J Nucl Med 2007; 48 (7): 1084–1089.

18. Patel CN, Salahudeen HM, Lansdown M, Scarsbrook AF. Clinical utility of ultrasound and 99mTc sestamibi SPECT/CT for preoperative localization of parathyroid adenoma in patients with primary hyperparathyroidism. Clin Radiol 2010; 65 (4): 278–287.

19. Akin M, Atasever T, Kurukahvecioglu O, Dogan M, Gokaslan D, Poyraz A, Koksal H, Taneri F. Preoperative detection of parathyroid adenomas with Tc-99m MIBI and Tc-99m pertechnetate scintigraphy: histopathological and biochemical correlation with Tc-99m MIBI uptake. Bratisl Lek Listy 2009; 110 (3): 166–169.

20. Balogova S, Cambal M, Simkova A, Kekenak L, Stecova A, Gregor P, Kinova S, Labas P. From preoperative to intraoperative detection of hyperfunctioning parathyroid glands using tetrofosmin (99mTc) in primary hyperparathyroidism. Bratisl Lek Listy 2011; 112 (12): 695–700.

21. Starker LF, Mahajan A, Björklund P, Sze G, Udelsman R, Carling T. 4D Parathyroid CT as the Initial Localization Study for Patients with De Novo Primary Hyperparathyroidism. Ann Surg Oncol 2010; 18 (6): 1723–1728.

22. Iannuzzi JC, Choi DX, Farkas RL, Ruan DT, Peacock JL, Moalem J. Surgeon beware: many patients referred for parathyroidectomy are misdiagnosed with primary hyperparathyroidism. Surgery 2012; 152 (4): 635–640; discussion 640–642.

23. Gawande AA, Monchik JM, Abbruzzese TA, Iannuccilli JD, Ibrahim SI, Moore FD Jr. Reassessment of parathyroid hormone monitoring during parathyroidectomy for primary hyperparathyroidism after 2 preoperative localization studies. Arch Surg 2006; 141 (4): 381–384; discussion 384.

24. Tublin ME, Pryma DA, Yim JH, Ogilvie JB, Mountz JM, Bencherif B, Carty SE. 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 2009; 28 (2): 183–190.

25. Tresoldi S, Pompili G, Maiolino R, Flor N, De Pasquale L, Bastagli A, Sardanelli F, Cornalba G. Primary hyperparathyroidism: can ultrasonography be the only preoperative diagnostic procedure? Radiol Med 2009; 114 (7): 1159–1172.

Received April 9, 2013.
Accepted March 23, 2014.