A COMPARATIVE ANALYSIS OF THE INITIAL EAST EUROPEAN CENTER EXPERIENCE WITH A WESTERN HIGH-VOLUME CENTER FOR OPEN MINIMALLY INVASIVE PARATHYROIDECTOMY (OMIP) AS TREATMENT OF PRIMARY HYPERPARATHYROIDISM

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Abstract

Objective. To compare results of treatment of primary hyperparathyroidism (PHPT) in two teaching hospitals (eastern and western Europe) and to establish conclusions regarding quality of surgery for PHPT in Romania.

Methods. We reviewed two prospectively collected databases of patients submitted to open minimally invasive parathyroidectomy (OMIP) for symptomatic PHPT in two centers from Romania and the United Kingdom (UK). We included patients with biochemically proven PHPT and positive pre-operative localization studies. We excluded patients with negative localization studies, suspected multiglandular disease, concomitant thyroid disorders and chronic renal failure.

Results. 60 patients were included, 27 in group A (Romanian cohort) and 33 in group B (UK cohort). We noted significant differences between groups in pre-operative serum calcium and phosphorus levels ($p < 0.5$). There were no differences between groups regarding the presence of symptoms; in group A we had significantly more patients with renal calculi history ($p = 0.02$), digestive symptoms ($p = 0.006$) and osteitis fibrosa cystica ($p = 0.01$). Two patients from the UK group had lithium associated hyperparathyroidism and 2 patients had genetic disease. Intraoperative parathyroid hormone measurement (ioPTH) was available only for group B and frozen sections were selectively used in both groups. Both the adenoma size and weights were significantly higher in group A. The median operative time was significantly longer in Romanian group ($p = 0.001$); in this group we noted the single conversion to traditional cervicotomy (3.7%) from all studied patients. In group A we noted two patients (7.4%) with failed parathyroidectomy and persistent PHPT; the cure rate was 92.5% for Romanian group and 97% for the UK group.

Conclusions. OMIP can be performed safe with a high cure rate in "small" volume endocrine centres with results comparable to western experienced endocrine

centres. Romanian patients presented with more severe PHPT with more frequent end-organ damage, due probably to late diagnosis.

Key words: parathyroidectomy, minimally invasive, primary hyperparathyroidism, comparative analysis.

INTRODUCTION

Bilateral neck exploration (BNE) represented for almost one century the surgical approach of choice for treatment of primary hyperparathyroidism (PHPT). BNE has a cure rate of 95% and about 3% morbidity, being a safe operation if performed by an experienced parathyroid surgeon (1). Minimally invasive neck surgery was introduced to practice late 80' and early 90'. The fact that PHPT is due to single gland disease in about 85% of cases (2) and improvement of recent imaging techniques had made minimally invasive parathyroid surgery being the treatment of choice for PHPT nowadays (3, 4).

The term of minimally invasive parathyroid is somehow equivocal and includes all minimally invasive approaches remove enlarged parathyroids (open, endoscopic, video-assisted, with an incision less than 3 cm) (5). Advantages of this approach are: cost-effectiveness, lower complication rate, shorter operative time and hospital stay, better cosmetic results, reduced postoperative pain, all with the same cure rate as BNE (6, 7). Open minimally invasive parathyroidectomy (OMIP) is an "open" minimally invasive approach and the most used (if enlarged parathyroids localised by preoperative imaging), being easy to learn and combining all the anterior described advantages (4, 8,

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9). OMIP is feasible under local anesthetic or sedation (6) and in most hospitals done as a day case.

AIM

The aim of our study is to compare results of treatment of PHPT in two teaching hospitals (eastern and western Europe) and to establish conclusions regarding quality of surgery for PHPT in Romania.

MATERIAL AND METHODS

Study design

We retrospectively and comparatively reviewed two prospectively collected databases of patients submitted to OMIP for symptomatic PHPT in two university referral centers from Romania and United Kingdom (UK).

Patients and methods

From January 2013 to November 2015 data from all patients submitted to parathyroidectomy for PHPT at the Second Department of Surgery, University of Medicine and Pharmacy Targu Mures, Romania were prospectively collected in an electronic database. We have included in the present study patients with biochemically proven PHPT in whom pre-operative localization studies, i.e. sestamibi scan and/or ultrasonography (US) identified (suspected) a solitary parathyroid adenoma. These patients (group A, Romanian cohort) were submitted to a targeted parathyroid approach - OMIP; furthermore this group represents the initial experience of the main author (RMN) with the procedure. Romanian group was comparatively analyzed with another prospectively collected group of patients submitted to the same intervention in a Western academic high volume center (Leeds Teaching Hospital, United Kingdom, UK) between November 2014 and November 2015 (group B, UK cohort) all surgeries in this group being done by two experienced endocrine surgeons (ML,TC).

Exclusion criteria for OMIP and subsequently from the study were similar in both groups and included negative localization studies, suspected multi-glandular disease, concomitant thyroid pathology and chronic renal failure.

For both groups, subject characteristics including demographics, preoperative imaging and laboratory data, main symptoms were prospectively collected. Operative times, conversion rate to traditional BNE and postoperative outcome including histology

(gland weight, size and histology type), postoperative biochemical markers, i.e. serum calcium, phosphate and intact parathyroid hormone (iPTH), follow up to determine persistent or recurrent disease were analysed. Patients from both groups had biochemically (serum calcium, iPTH and phosphate) confirmed PHPT. OMIP was performed if at least one of the localizations preoperative studies were positive. For the Romanian group OMIP was done if sestamibi scan was positive preoperatively. For the UK group OMIP was performed if both studies were positive, single-photon emission computed tomography (SPECT-CT) positive (with or without positive ioPTH) and cervical ultrasonography (US) positive with ioPTH. All patients have signed an informed written consent form.

Surgical technique

OMIP was performed under general anesthesia combined with bilateral or unilateral superficial cervical blocks, using a lateral neck 2.5-3 cm skin incision over the sternocleidomastoid muscle, in the area of the preoperative localized parathyroid adenoma. For group A patients the enlarged parathyroid was marked on the skin US guided. US skin marking was used only for 2 cases in the UK group.

Our landmarks during operation were anterior border of sternocleidomastoid muscle, internal jugular vein, carotid artery, ipsilateral thyroid lobe as well as ipsilateral recurrent laryngeal nerve. Once identified the parathyroid adenoma was dissected carefully to avoid bleeding and rupture of the capsule. Hemostasis was achieved at end of operation and no drain was used.

Intraoperative parathyroid hormone assay (ioPTH) was considered only for few B-group patients using the modified Miami criteria (>50% drop and to the normal range within 10 min after excision); similarly, frozen section was selectively used for this group of patients. For Romanian group of patients ioPTH was not available but frozen section was used in few cases.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 20.0 (SPSS, Inc., Chicago, IL). Data are presented as the mean±SD if normally distributed and median (minimum, maximum) if non-parametrically distributed. Differences between groups were tested using two-tailed Student's t test or Mann Whitney U test as appropriate for two-group comparisons. Categorical variables were compared

Figure 1. A. OMIP - the adenoma resections; B. OMIP - the adenoma size; C. OMIP - the adenoma weight.

with the χ^2 -test. All p-values are two tailed, with $p < 0.05$ considered statistically significant.

RESULTS

Sixty patients were included in the present study, 27 in group A (Romanian cohort) and 33 in group B (UK cohort). Table 1 includes patients demographics and clinicopathological characteristics. Both groups were similar as regards age ($p = 0.09$) and gender ($p = 0.77$). Pre-operative total serum calcium levels (nv:8.5-10.5mg/dL) were significantly

higher in group A (11.71 vs. 11.34, $p = 0.04$); we also noted significant differences in pre-operative blood phosphorus (nv:2.7-4.5mg/dL), which was lower in the Romanian group (2.13 vs. 2.72, $p = 0.0001$). There were no differences between groups in pre-operative serum iPTH and vitamin D levels.

In Table 2 we have grouped the symptoms mainly according to the classical syntagma: “stones” (other than renal calculi history), “bones” (muscular and joint pains and weakness, bone pains), “groans” (anorexia, constipation, episodes of gastritis or pancreatitis), “moans” (mood changes); we separately

Table 1. Demographic, clinicopathological and therapeutic characteristics of patients

	Group A (Ro) 27 patients	Group B (UK) 33 patients	P value*
Age (years) mean $\pm$ SD	55.07 $\pm$ 13.6	61.64 $\pm$ 15.4	0.09**
Female/male (%)	24/3	29/4	0.77#
Preop serum Ca (mg/dl) mean $\pm$ SD	11.71 $\pm$ 0.67	11.34 $\pm$ 0.67	0.04**
Preop serum P (mg/dl) mean $\pm$ SD	2.13 $\pm$ 0.48	2.72 $\pm$ 0.46	0.0001**
Preop serum iPTH (pg/ml) median (min-max)	26.8 (9.22-95.05)	19.6 (5.8-81.9)	0.16*
Preop alkaline phosphatase (u/L) median (min-max)	274.0 (87.5-1181)	225.0 (100.0-653.0)	0.55*
Postop serum Ca (mg/dl) mean $\pm$ SD	8.82 $\pm$ 0.94	9.68 $\pm$ 0.65	0.0001**
Postop serum iPTH (pg/ml) median (min-max)	3.06 (0.37-26.08)	5.10 (0.8-44.3)	0.005*
US positive (%)	62.9	81.8	0.17#
Sestamibi scan /SPECT-CT positive (%)	100	93.9	0.55#
Concordant localization studies (%)	62.9	48.5	0.39#
Size (mm ³) median (min-max)	2125 (463.7-22060)	1305 (699.8-5400)	0.02*
Weight (gr) median (min-max)	2.55 (0.6-3.4)	1.0 (0.3-3.9)	0.03*
Operative time (min) median (min-max)	37 (19-72)	28 (13-68)	0.001*
ioPTH (%)	0 (0)	8 (24.2)	0.01#
Frozen section (%)	5 (18.51)	9 (27.27)	0.62#
Conversion to cervicotomy (%)	1 (3.7)	0 (0)	0.92#
Persistent PHPT(%)	2 (7.4)	1 (3)	0.85#
Follow-up (months) median (min-max)	20 (1-33)	6 (1-11)	0.0001*

* values expressed as median and range(min-max): Mann Whitney test. ** values expressed as mean $\pm$ SD: Student s test. #- chi square test.

Table 2. Patients symptoms, according to the “classical” syntagma; statistical significance assessed by chi square test*.

Symptoms	Group A (Ro) 27 patients	Group B (UK) 33 patients	P value*
asymptomatic	3 (11.1)	7 (21.2)	0.46
“stones”	9 (33.3)	5 (15.1)	0.17
nephrolithiasis	14 (51.8)	7 (21.2)	0.02
“bones”	19 (70.4)	16 (48.5)	0.14
osteitis fibrosa cystica	6 (22.2)	0 (0)	0.01
“moans”	6 (22.2)	3 (9.1)	0.29
“groans”	15 (55.5)	6 (18.2)	0.006
nonspecific	7 (25.9)	6 (18.2)	0.68

noted history or nephrolithiasis, osteitis fibrosa type lesions and nonspecific clinical complaints as part of “end-organ” damage.

Generally we did not find differences between groups when we statistically analyzed the presence or absence of symptoms; in group A we had significantly more patients with renal calculi history ($p=0.02$) and digestive symptoms ($p=0.006$). In Romanian group we also encountered 6 cases of “osteitis fibrosa cystica”, with patients having bone changes, pathological fractures and even 2 cases of tibial brown tumors; none of such cases were found in the English group ($p=0.01$). Despite of being non-statistically different other classical symptoms of hyperparathyroidism i.e. osteopenia or osteoporosis, muscular and joint pains, were more frequently encountered in Romanian group. Two patients from the UK group had lithium associated hyperparathyroidism and 2 patients had genetic disease, one patient with multiple endocrine neoplasia type 1 (MEN1) and one hyperparathyroid jaw tumour syndrome (HP-JT) syndrome.

Localization studies were performed in all subjects. In group A all patients had a positive sestamibi scan, which was, as we mentioned, an including criteria for OMIP in this group; concordant studies were demonstrated in 62.9% in group A and 48.5% in group B, respectively. Other localization studies were rarely used in both groups.

We encountered significant differences between groups as regards both the adenoma size and weights, which were higher in Romanian cohort ($p=0.02$ for size and $p=0.03$ for weight, respectively). We excluded from this analysis a giant adenoma excised in a female patient from Romanian group due to statistical reasons. ioPTH was used in 8 cases in group B (24.2%) and never in group A. Frozen section was used in 9 cases in group B (27.27%) and 5 cases in group A (18.51%). The median operative time was significantly longer in Romanian group ($p=0.001$); in this group we noted the single conversion to traditional cervicotomy (3.7%) from all studied patients.

There was no mortality in either group. Post-operative total serum calcium and iPTH levels (nv:15-68pg/mL) were significantly lower in group A which was consistent with the fact that in the Romanian group we encountered more patients with clinical manifested post-operative hypocalcemia and even “hungry-bone” syndrome. Five patients (15.15%) in group B had elevated postoperatively iPTH with normal calcium, most of this probably related to low vitamin D levels; all these 5 patients had normal serum calcium levels at 6 months after parathyroidectomy. In group A we noted two patients (7.4%) with failed parathyroidectomy and persistent PHPT, thus the cure rate for this group was 92.5%. These two cases underwent re-exploration through traditional cervicotomy with removal of the pathologic parathyroid gland. In group B there was one case of persistent PHPT, the patient being still on surveillance with raised serum iPTH levels and mild hypercalcemia; the cure rate for UK group was 97%. We did not encounter recurrences in either groups.

DISCUSSION

After Austrian surgeon Felix Mandl did the first parathyroidectomy in 1925, BNE (with identifying all four glands and excision of the enlarged ones) became standard of care for a long period (1). Tibblin *et al.* (10) describes in 1982 unilateral neck exploration and parathyroidectomy, but true minimally invasive techniques spread early 90’, concomitant with endoscopic parathyroidectomy and developing of imaging studies as well as ioPTH measuring (2, 8, 11).

Minimal invasive parathyroidectomy is the most used technique for treatment of PHPT and includes both OMIP as well as fully endoscopic or videoassisted. Even if endoscopic techniques as MIVAP (minimally invasive videoassisted parathyroidectomy) gained more use, OMIP remains the procedure of choice being easy to learn, cost-effective, with short learning curve (4, 8, 9). Randomized controlled trials from different endocrine surgical centers, comparing OMIP

with BNE, proved certain advantages of minimally invasive technique: shorter operative time, earlier discharge, reduced postoperative pain, better cosmetic results and at least same cure rates and morbidity as BNE (6, 7, 12, 13). Two prospective randomized trials which compare the most commonly utilized minimally invasive parathyroidectomies i.e., OMIP and MIVAP (14, 15), showing similar results (cure rate, morbidity, hospital stay, operative time), or some differences (multicentric study, different surgical experience) results being open for discussion.

We reviewed retrospectively our initial experience with OMIP in an academic centre from Romania with previous little experience in parathyroid surgery. Our aim was to correlate our results and compare outcome of treatment and complication rate with results from a tertiary referral centre in the UK. Indeed our database reviewed 27 patients in about three years as compared with 33 patients treated in one year in the UK centre.

Symptoms and signs in PHPT changed over the last decades, the classical “moans, stones, groans and boans” is rarely seen specially in western countries (16). Surprisingly we have not found any significant differences between the number of asymptomatic *versus* symptomatic patients in the two series. We identified differences when we analysed the types of symptoms: in the Romanian group patients presented with significant more renal and digestive symptoms. The Romanian series includes also few cases of osteitis fibrosa cystica, including two patients with brown tumours of tibia. The UK series surprisingly contains few asymptomatic patients with most of the patients presenting nonspecific symptoms like mood changes, polyuria, anorexia and nocturia. These symptoms are also in the Romanian case-series but shadowed by the major “end organ” complications.

Imaging studies are not diagnostic but are helping to localize the enlarged gland(s) and to facilitate a target approach. The most frequent localizing studies used are high resolution US, sestamibi scan and SPECT-CT scan with a positive predictive value between 60%-92% and 78-100% respectively (17). In concordant US parathyroids and sestamibi scan the accuracy of localization is above 95% (18) while in negative ones the likelihood of multiglandular disease is above 30% (19). In both study groups positive sestamibi scan was an inclusion criterion (especially in the Romanian group) but in the UK group SPECT-CT negative and US positive patients were offered OMIP with ioPTH. Barczynski *et al.* (20) suggested

that routinely ioPTH improves the cure rate up to 94-97%, but other studies showed that if localizing studies are positive and concordant then ioPTH is of little benefit (21). In the UK study group US parathyroids was used to localize associated thyroid pathology and for preoperative skin marking, SPECT-CT being the imaging method of choice. If SPECT-CT was negative we proceed with thin slice CT scan. Other centres (MD Anderson Texas, US) are using routine 4DCT scan when sestamibi/SPECT-CT is negative (22).

The operative technique was similar in both study groups. The Romanian group presented a conversion to open “traditional” neck exploration, operative time being significantly increased comparing to UK group all this related to learning curve. The weight of the resected parathyroid glands was significantly larger in the Romanian study group with a large 31.4 grams parathyroid resected in a female patient with severe PHPT and with brown tumour associated. Some authors advocated that adenomas weight is directly related with the functional status of the gland and severity of the symptoms (23), which appears to be true for the Romanian cohort.

In the same cohort we identified two “failed” parathyroidectomy with persistent disease, with both serum calcium and iPTH remaining elevated after operation. Histology revealed for one of the cases a thyroid nodule and for the other one a fibrohyaline involution of a papillary thyroid carcinoma metastasis in a lymph node in a female patient with previously RAI treated papillary thyroid carcinoma. In UK group we had few patients with persistent high serum iPTH levels after parathyroidectomy, but with normal serum calcium levels, interpreted as partially related to low serum vitamin D levels. All the serum iPTH levels came back to normal in time or after correction of vitamin deficiency and none of these patients had persistent disease. Some authors are suggesting that this could be related to an early recurrent primary hyperparathyroidism but data and studies are insufficient for now (24); we consider that these patients should have follow-up longer than one year after parathyroidectomy. In the same group we also noted patients with familial disease or lithium associated PHPT. It seems that in selected cases OMIP is also feasible for known familial hyperparathyroidism as well as for lithium induced PHPT, both associated classically with multigland disease and the need for BNE (25, 26).

The limits of this study are probably related to the different experiences of the operating surgeons

between the two groups and to the small number of patients included in the Romanian group. Being probably the first comparative analysis of OMIP performed in Romania, our study points to several particularities regarding diagnosis and treatment of primary hyperparathyroidism in Romania.

In conclusion, OMIP can be performed safe with a high cure rate in “small” volume endocrine centres with results comparable to western experienced endocrine centres. Differences are related to learning curve and lack of iPTH and SPECT-CT availability for the Romanian team. OMIP is feasible for all localized parathyroids in case of sporadic, familial and lithium associated hyperparathyroidism; iPTH is appropriate for lithium associated and familial hyperparathyroidism. Patients with persistent high iPTH and normal serum calcium levels should be offered a longer follow-up time. Romanian patients presented with more severe PHPT with more frequent end-organ damage, due probably to late diagnosis. There is need for specific guidelines for treatment of PHPT and the need of specialized referral centers for treatment of parathyroid diseases in Romania.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

References

1. Duh QY. Surgical approach to primary hyperparathyroidism (bilateral approach). In: Clark OH, Duh QY, editors. *Textbook of Endocrine Surgery*. Philadelphia: WB Saunders 1997:357-367.
2. Mazzeo S, Caramella D, Lencioni R, Molea N, De Liperi A, Marcocci C, Miccoli P, Iaconi P, Bossio GB, Viacava P, Lazzeri E, Bartolozzi C. Comparison among sonography, double tracer subtraction scintigraphy and double phase scintigraphy in the detection of parathyroid lesions. *AJR* 1996;166(6):1465-1470.
3. Bergenfelz AOJ, Hellman P, Harrison B, Sitges-Serra A, Dralle H. Positional statement of the European Society of Endocrine Surgeons (ESES) on modern techniques in pHPT surgery. *Langenbecks Arch Surg* 2009;394(5):761-764.
4. Udelsman R, Pasiacka JL, Sturgeon C, Young JE, Clark OH. Surgery for asymptomatic primary hyperparathyroidism : proceedings of the third international workshop. *J Clin Endocrinol Metab* 2009;94(2):366-372.
5. Brunaud L, Zarnegar R, Wada N, Ituarte P, Clark OH, Duh QY. Incision length for standard thyroidectomy and parathyroidectomy. When is it minimally invasive? *Arch Surg* 2003;138(10):1140-1143.
6. Bergenfelz A, Kanngiesser V, Zielke A, Nies C, Rothmund M. Conventional bilateral cervical exploration *versus* minimally invasive parathyroidectomy under local anesthesia for primary hyperparathyroidism. *Br J Surg* 2005;92(2):190-197.
7. Russel CF, Dolan SJ, Laird JD. Randomised clinical trial comparing scan-directing unilateral *versus* bilateral exploration for parathyroidectomy due to solitary adenoma. *Br J Surg* 2006;93(4):418-421.
8. Ursu H, Ioachim D, Muntianu L. About the guideline for diagnosis and treatment of primary hyperparathyroidism in a country with endemic goiter. *Acta Endocrinol (Buc)* 2010;6(1):129-138.
9. Sackett WR, Barraclough B, Reeve TS, Delbridge LW. Worldwide trends in the surgical treatment of primary hyperparathyroidism in the era of minimally invasive parathyroidectomy. *Arch Surg* 2002;137(9):1055-1059.
10. Tibblin S, Bondeson AG, Ljungberg O. Unilateral parathyroidectomy in hyperparathyroidism due to a single adenoma. *Ann Surg* 1982;195(3):245-252.
11. Irvin GL, Carneiro DM. Rapid parathyroid hormone assay guided exploration. *Op Tech Gen Surg* 1999;1:18-27.
12. Bergenfelz A, Lindblom P, Tibblin S, Westerdahl J. Unilateral *versus* bilateral neck exploration for primary hyperparathyroidism: a prospective randomized trial. *Ann Surg* 2002;236(5):543-551.
13. Westerdahl J, Bergenfelz A. Unilateral *versus* bilateral neck exploration for primary hyperparathyroidism: 5-year follow up of randomized controlled trial. *Ann Surg* 2007;249(6):976-980.
14. Barczynski M, Chicon S, Konturek A, Cichon W. Minimally invasive video-assisted parathyroidectomy for solitary parathyroid adenoma: a prospective, randomized, blinded trial. *World J Surg* 2006;30(5):721-731.
15. Hessman O, Westerdahl J, Al-Suliman N, Christiansen P, Hellman P, Bergenfelz A. Randomized clinical trial comparing open with video-assisted minimally invasive parathyroid surgery for primary hyperparathyroidism. *Br J Surg* 2010;97(2):177-184.
16. Power C, Kavanagh D, Hill AD, O'Higgins N, McDermott E. Unusual presentation of a giant parathyroid adenoma: report of a case. *Surg Today*, 2005;35(3):235-237.
17. Noureldine SI, Gooi Z, Tufano RP. Minimally invasive parathyroid surgery. *Gland Surg*. 2015;4(5):410-419.
18. Ruda JM, Hollenbeak CS, Stack BC Jr. A systematic review of diagnosis and treatment of primary hyperparathyroidism from 1995-2003. *Otolaryngol Head Neck Surg* 2005;132(3):359-372.
19. Sebag F, Hubbard JGH, Mawejia S, Misso C, Tardivet L, Henry JF. Negative preoperative localization studies are highly predictive of multiglandular disease in sporadic primary hyperparathyroidism. *Surgery* 2003;134(6):1038-1042.
20. Barczynski M, Konturek A, Chicon S, Hubalewska-Dydejczyk A, Golkowski F, Huszno B. Intraoperative parathyroid hormone assay improves outcomes of minimally invasive parathyroidectomy mainly in patients with a presumed solitary parathyroid adenoma and missing concordance of preoperative imaging. *Clinical Endocrinol* 2007;66(6):878-885.
21. 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.
22. Grubbs EG, Edeiken BS, Gule MK, Monroe BJ, Kim E, Vu T, Perrier ND. Preoperative Parathyroid Imaging for the Endocrine Surgeon. In: *Handbook of Parathyroid Diseases, A case- based practical guide*, Kahn AA, Clark OH, editors. Springer 2012:19-39.
23. Mózes G, Curlee KJ, Rowland CM, van Heerden JA, Thompson GB, Grant CS, Farley DR. The predictive value of laboratory findings in patients with primary hyperparathyroidism, *J Am Coll Surg*, 2002;194(2):126-130.
24. Stuart HC, Harvey A, Pasiacka JL. Normocalcemic hyperparathyroidism: preoperatively a disease, postoperatively cured. *Am J Surg*. 2014;207(5):673-680.
25. Wade TJ, Yen TW, Amin AL, Evans DB, Wilson SD, Wang TS. Focused parathyroidectomy with intraoperative parathyroid hormone monitoring in patients with lithium-associated primary hyperparathyroidism. *Surgery*. 2013;153(5):718-722.
26. Versnick M, Popadich A, Sidhu S, Sywak M, Robinson B, Delbridge L. Minimally invasive parathyroidectomy provides a conservative surgical option for multiple endocrine neoplasia type 1-primary hyperparathyroidism. *Surgery*. 2013;154(1):101-105.