

Total Parathyroidectomy without Autotransplantation Effective Treatment in Renal “Refractory” Chronic Kidney Disease - Metabolic Bone Disease

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Abstract: *Introduction:* Aim of our study attempts to demonstrate the superiority and benefits of total parathyroidectomy without autotransplantation (TPtx) versus subtotal parathyroidectomy (STPtx) or total parathyroidectomy with autotransplantation (TPtx+At) in cases of refractory, adenomised “renal” hyperparathyroidism, actually renamed Chronic Kidney Disease – Metabolic Bone Disease (CKD – BMD).

Patients Study Design: Sixtytwo cases with CKD – MBD underwent surgery between 1994-2013. There were 25 SPTx and 9 TPtx+At both procedures determining 7 (18,4%) recurrences so in the last decade we performed preponderantly TPtx in 28 selected patients (12 males and 16 females, with median age of 43,6 (range) 22 – 66 years and median hemodialysis before surgery of 8,5 (range 3-12) years. Demography, clinical and biological data, imaging procedures, surgical protocols and pathology reports together with immediate and long-term results were recorded.

Results and Discussions: Main indications for TPtx were severe bone disease, soft tissue calcifications, neuromuscular features, grossly elevated iPTH and sometimes hypercalcemia. TPtx were done in 27 subjects in the 28th one suffering a completion PTx one year after outward exeresis of only two gland. One patient required a re-exploration for a cervical hematoma but none presen-ted permanent hypocalcemia or recurrent hyperparathyroidism. Pathology revealed nodular hyperplasia in all cases but a parathyroid carcinoma of the fourth gland and an incidentally papi-llary thyroid microcarcinoma were found in each one case. Follow-up at 6-60 months showed in 24 cases (87,7%) an effective clinical and biological improvement stable over time, continuing their hemodialysis regimen.

Conclusions: TPtx alone proved to be an an equally safe and successful as another techniques currently used in management of CKD – MBD eliminating the hyperparathyroid status but being superior in regard to apparition of recurrences. The procedure is indicated especially in patients with aggressive, refractory forms of this condition without the prospect of renal transplant.

Keywords: Renal hyperparathyroidism, CKD – MBD, total parathyroidectomy, kidney transplant.

INTRODUCTION

Renal hyperparathyroidism (secondary/renal) condition wich virtually affect tota-lity of uremic patients on hemodialysis is redefined actually in an integrative concept under the acronym CKD-MBD (Chronic Kidney Disease – Metabolic Bone Disease), characterized by isolated or combined presence of three components:

- anomalies of calcium, phosphorus, PTH and D vitamin metabolism due to parathyroid hyperactivity;
- anomalies of the turnover, mineralization, growth and bone resistance (“old renal osteodistrophy”);
- vascular, cardiac and soft tissues calcifications, calciphylaxia, all of these realsing an increment of morbidity and mortality [1-3].

Steady increase in patients with chronic kidney failure and therefore of those with CKD-MBD re-sulted

in efficient development of hemodialysis programs, completed by administration of active D vitamin products, biophosphonates and calcimimetics products which, in absence of ideal the-rapy - i.e kidney transplant - ensure effective and long standing control of the clinical and biolo-gical evolution of most of these patients [4, 5].

However in a percentage of 15% of these cases with so called “refractory” renal hyperparathyroi-dism (who after 20 years of hemodialysis can reach even 38%) in which the irreversible transfor-mation of diffuse in nodular parathyroid hyperplasia, together with severe, invalidant evolution of the clinical syndrome alongside biologic data can no be longer be influenced by medical treatment and a surgical solution is necessary [6, 7].

Reduction operative techniques initiated half a century ago successively resorted either subtotal parathyroidectomy (PTxSt) or total parathyroidectomy with glandular autotransplantation in the different anatomic areas (PTxT+AT). Main objective of the first procedure is approximate lesse-ning of the hypersecretory glandular parenchyma removing three parathyroids conserving ”half of the smallest, most

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Table 1: Frequency of Main Clinical Manifestations in CKD – MBD

Osteoarticular pains, osteoporosis, fractures	28	100%
Rebel itching	24	85.7%
Insomnia, neurasthenia, behavioral troubles	21	75.0%
(mi)asthenia, anemia, hypoproteinemia, malnutrition	19	67.8%
HTA, coronary cardiac disease, myocardosclerosis	16	57.1%
calciophylaxia, ectopic calcifications, "uremic red eyes"	11	39.2%
dyspepsia	8	28.5%
urolithiasis, renal colics	6	21.4%

normal and well vascularised gland" while in the second one after pulling out all four glands, 25-30 pieces sliced 1x1x3 mm of parathyroid tissue are implanted into prepa-red muscular pockets in the forearm excluding thereby possibility of cervical reinterventions. Over time both traditional procedures become disappointing due to their high percentage of recurrences ranging from 5 to 80% [8-17].

Proposed by Ogg in 1967, total parathyroidectomy (PTxT) was rapidly abandoned of the risk of adynamic osteopathy and hypoparathyroidism but reconsidered by numerous specialists in the last two decades due to inconsistency of this risk but especially favorable results in the immediate and medium term, comparable to the other two methods [16, 18-24].

In our experience totalizing 62 cases of CKD-MBD operated on in the last two decades (1994-2013) we practiced all three techniques. Initially we performed only PTxSt (n=26) and PTxT+AT (n=9), recording 17,1% (n=6) recurrences thus in the last 7 years we focused mainly towards PTxT performing 28 surgeries of this type.

Patients Study Design

Our series includes 28 cases of "refractory" CKD-MBD, 12 males and 16 fe-males, aged 22 – 66 (mean 43,6) years, undergoing hemodialysis from 3 – 12 (mean 8,5) years. In 27 cases it was the first intervention but only in a 22 year young subject it was a completion parathyroidectomy after an initially "targeted" extra muros exeresis of only two identified glands. In the etiology of our patients we noted chronic glomerulo(pyelo)nephritis (n=18) urolithiasis (n=6), polikystic kidney (n=3), nephroangiosclerosis (one case). In their anamnesis three patients presented a failed kidney transplant.

Criteria for inclusion in the "refractory" variety CKD-MBD were the prolonged evolution of disease as well as hemodialysis, particular severity of clinical features and their complications, significant disturbances of laboratory data but especially the lack of response (more than absence of compliance) to the medical treatment and of the perspective of a renal transplant. Clinical syndrome (Table 1) was an implicit component of the surgical indication containing:

Table 2: Medium Values of Main Laboratory Tests in CKD – MBD

Preoperative		postoperative
iPTH	1620 +- 320 ng/L	65 +- 50 ng/L
Serum calcium	8,70 +- 1,00 mg/dL	7,90 +- 0,50 mg/dL
Ionized calcium	4,45 +- 0,38 mg/dL	4,50 +- 0,20 mg/dL
Serum phosphorus	4,80 +- 0,55 mg/dL	3,40 +- 0,20 mg/dL
Calcium/phosphorus product	55,0 +- 3,1 mg ² /dL ²	45,5 +- 1,5 mg ² /dL ²
Alkaline phosphatase	230 +- 38 ui/L	128 +- 12 ui/L
Hemoglobin	11,3 +- 2,3 mg/dL	12,1 +- 1,1 mg/dL
Proteins	49,5 +- 0,9 g/dL	51,1 +- 1,5 g/dL
Urea	140 +- 40 mg/dL	90,0 +- 25,0 mg/dL
Creatinine	1,8 +- 0,3 mg/dL	9,80 +- 2,0 mg/dL

The values of main biological constants and of the Ca/P product were also modified Table 2.

Ultrasound practiced routinely and sestamibi or tetrofosmin scan accessible only sporadically were not relevant for the diagnostic of our observations, obtaining the identification of just 1 – 3 parathyroids “larger” than 5 -10 mm in diameter and especially of the concomitant thyroid lesions.

The presence of at least one parathyroid with these dimensions together with anamnesis, severe clinical syndrome and excessive amounts of iPTH, attesting the failure of medical therapy, all of them adding the social considerations and the absence of perspective of a kidney transplantation, contribute to the indication of surgical treatment in these cases. However intraoperative findings were decisive element for the option of this radical technique. Two to four gland appeared glo- bular, pseudoadenomatous and especially much enlarged, far exceeding usual size, being easily identified intraoperatively thus frozen section assumed a formal character. There were a total of 111 excised glands, having between 0,8 – 2,8 cm (three parathyroids from which one supernumerary, located retrosternally were founded in the patient with reintervention). Total mass of glandular parenchyma removed exceeding sometimes ten times normal weight, reaching right 1,500 mg in certain cases. In all these situations the the size and macroscopic aspect practically forced removal of all four glands, the entirely pathological character of glandular tissue providing no even after section any apparently normal fragments to be conserved or transplanted (Figure 1).

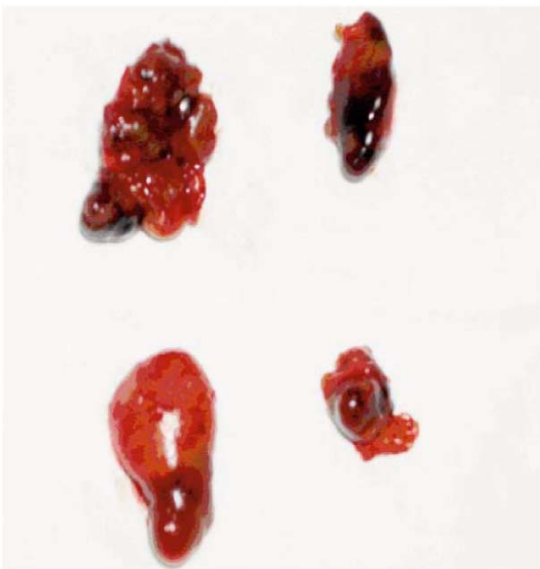


Figure 1: Nodular hyperplasia of all four parathyroids: surgical specimen.

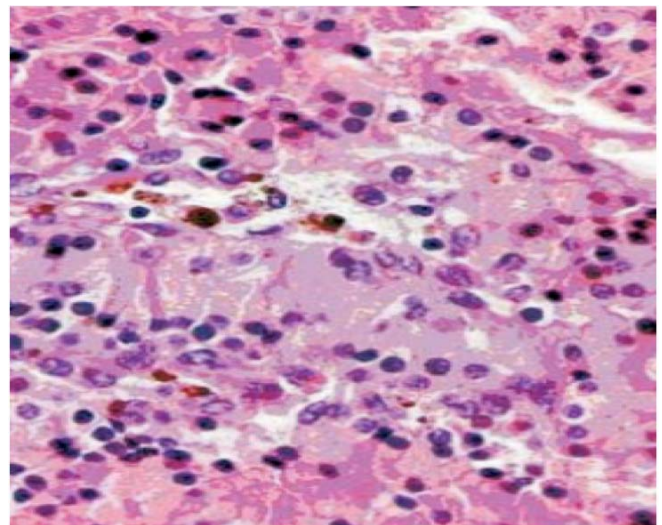


Figure 2: Nodular hyperplasia; microscopic aspect (col HE x 200).

Beside microscopic examination in all specimens nodular hyperplasia was identified composed of main cells and less of clear and oxyphil cells arranged in acinar or trabecular architectural patterns which together with degenerative aspects, sclerosis, necrosis, cystic or hemosiderin loaded areas virtually interested all the gland, without any nest of normal parenchyma (Figure 2).

In one of typically cases of refractory CKD – BMD presenting severe clinical and biological syn- drome also present an “ordinary” thyroid nodule 3 cm in diameter (Figure 3). Intraoperatively have been identified relatively easy the “nodule” (Figure 3), three parathyroids but not the fourth one. Since nodule frozen section outcome was uncertain a total left lobectomy was performed. Paraffine section precised the diagnosis of main cell parathyroid carcinoma, thus glandular exeresis becoming total (Figure 4). Our patient, which is the 26th case of

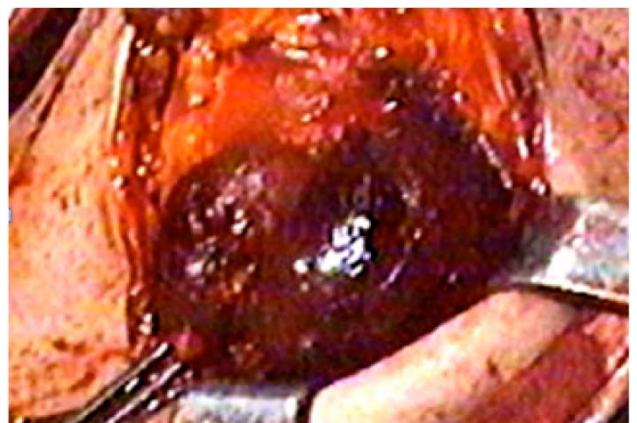


Figure 3: Ordinary “thyroid nodule”.

coexistence between CKD – BMD on hemodialysis with a parathyroid cancer reported in literature, had a favorable postoperative immediate evolution with clinical and biological improvement but also at 5 years follow-up continuing his hemodialysis without recurrence or metastasis [25].

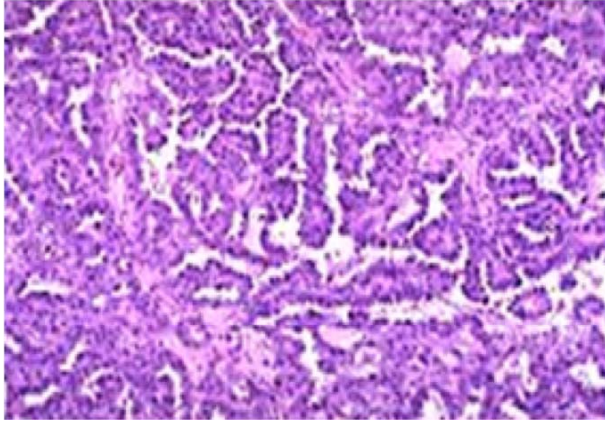


Figure 4: Parathyroid main cell carcinoma (Hex100).

In five cases some thyroid exeresis (one nodulectomy, three lobectomies and one near total thyroidectomy) for four benign lesions and one papillary microcarcinoma were done (Figure 5).

Ablation for retromanubrial fibrofatty tissue was not practiced systematically. In the subjects when it was still performed a supranumerary parathyroid (unique in our experience), a benign thymoma and thymic rests in another three cases has been identified (Figure 6).

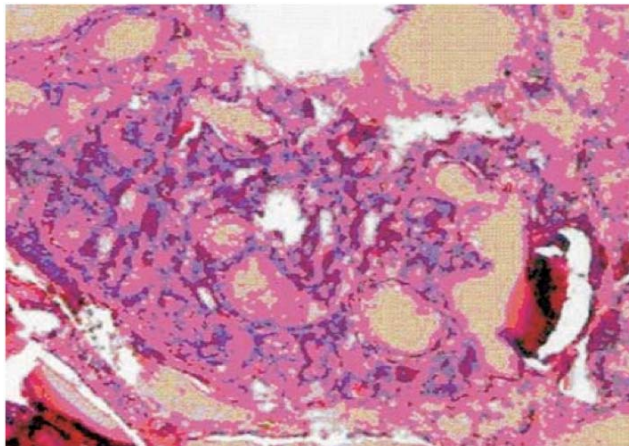


Figure 5: Papillary thyroid microcarcinoma (HEX20).

The immediate and long-term postoperative course (6 – 60 months) has been generally favorable. We recorded a postsurgical hematoma which required reoperation and drainage and four cases presented transient hypocalcemia (5,2 – 8,4 mg/dl) two of them being symptomatic. All operated patients subsequently

recommended calcium-containing solutions and vitamin D products.

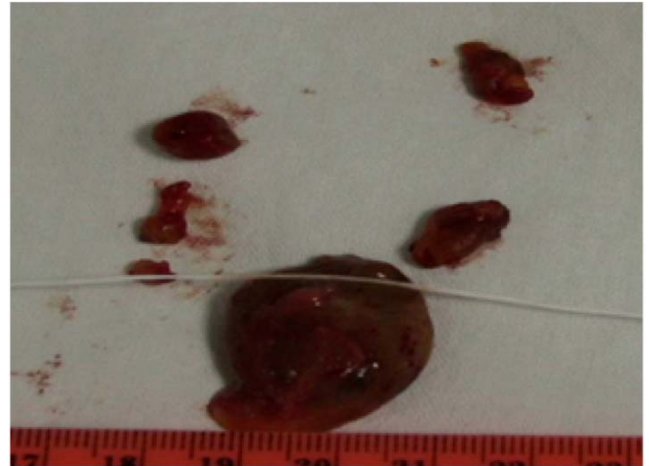


Figure 6: Benign thymoma associated with CKD-MBD.

Over time the outcome was spectacular with rapid disappearing of pruritus and pain mitigation but but general condition, asthenia and psychoneurotic manifestations were slowly and incompletely relieved by parathyroidectomy. Serum calcium, phosphorus and alkaline phosphatase were normalized or significantly reduced as compared with preoperative levels. Monitored of iPTH showed normalized hormone level in all patients investigated.

The most important element in our modest experience is that any patient showed no clinical or biological relapse, permanent hypoparathyroidism or adynamic bone disease all of them continuing their hemodialysis program benefiting from an improved quality of life.

DISCUSSIONS AND CONCLUSIONS

Currently recommended surgical techniques in the treatment of secondary and tertiary hyperparathyroidism redefined as Chronic Kidney Disease – Metabolic Bone Disorder are ongoing debated, many specialists and teams striving to argue the advantages and superiority of results of each of them.

Traditionally subtotal parathyroidectomy appreciated by its apparent expeditiousness, and total parathyroidectomy with autotransplantation strongly recommended by Japanese school, are both the most preferred alternatives [6, 8, 10-13, 14-17].

Often inadequate quality and quantity of glandular tissue preserved or transplanted in these both surgical

options lead to the appearance of persistence or recurrence of suffering difficult to assess and especially treat surgically. This fact has stimulated in the last two decades the reap-praisal of total parathyroid extirpation [18-24, 26-34].

The experience is limited to several studies totaling a few hundreds of cases in which encouraging and stable over the time results were obtained without adynamic bone disease or permanent symptomatic hypocalcemia, entirely comparable if not superior to other methods.

From some authors the total elimination of parathyroid tissue defined by an iPTH level of 0-1 ng/l appears impossible because the embryological development of these glands along the tract of migration in the cervical region and mediastinum persist some nests of functional glandular tissue. They are subjected to the same hormonal factors as those stimulating the eutopic or ectopic parathyroid properly called tissues. In terms of total elimination of pathological glands these remnant may provide an enough endocrine secretion (which does not happen after inadvertently excision of all four parathyroids sometimes seen in surgery of this territory [35].

From the technical point of view, the impressive, sometime asymmetric enlarged glands, exceeding 1-2 cm in diameter facilitates their highlighting and dissection, actually observed in some of our cases. However the difficulties related to the length of evolution, size, anatomical relations and eventually topographic abnormalities are incomparably lower than of those of reinterventions.

Finally CKD – MBD enter into the so called social pathology defined by one of main indications of total parathyroidectomy in this disease, namely the lack of opportunities and/or perspectives to perform a kidney transplant (sometimes also in its failure as in two of our cases). This criterion together with anamnestic, clinical and lesional data constitute arguments for the rigorous selection of patients to which this technique is recommended, the only ones that can provide immediate and subsequent positive results.

Of course in order to certify total parathyroidectomy as a reasonable method among other surgical techniques used in this pathology a prolonged clinical and biological pursuit in all these patients with prompt calcium and vitamin medication is mandatory.

CONCLUSIONS

Together with medical treatment the three current techniques of parathyroidectomy dispute their indications, advantages and successes in the management of CKD – MBD. Reconsidering total parathyroidectomy alone in well-selected cases of severe disease refractory to any medication which do not have a practical perspective of a kidney transplant, offers in terms of lower morbidity, especially cancellation risk of relapse, evident symptomatic effects and surprising absence of postoperative hypocalcemia all this stable in time.

CONFLICTS OF INTEREST

The authors had no conflicts of interest to declare in relation to this article.

AUTHOR'S CONTRIBUTIONS

DMR conceived of the study, has been involved in drafting the manuscript and revised for intellectual content; GI and CI were mainly involved in the analysis and interpretation of data; all of them constituted the operative team; DS made substantial contribution to conception and design, gave final approval of study to be published.

REFERENCES

- [1] Moe S, Drucce T, Cunningham J, *et al.* Definition, evaluation, classification of renal osteodystrophy: a position statement for Kidney Disease Improvement Global Outcome (KDIGO). *Kidney Int* 2006; 69(11): 1945-53. <http://dx.doi.org/10.1038/sj.ki.5000414>
- [2] Levey AS. A decade after the KDOQI CKD guideline. *Am J Kidney Dis* 2012; 60(5): 683-5. <http://dx.doi.org/10.1053/j.ajkd.2012.08.019>
- [3] Kidney Disease. Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; 7(1): 1-150.
- [4] Cepoi V, Onofriescu M, Segall L, Covic A. The prevalence of chronic kidney disease in the general population in Romania: a study of 60000 persons. *Int Urol Nephrol* 2012; 44(1): 213-20. <http://dx.doi.org/10.1007/s11255-011-9923-z>
- [5] Mircescu G, Stefan G, Garneata L, Mititiuc I, Siropol D, Covic A. Outcome of dialytic modalities in a large registry cohort from Eastern Europe: The Romanian Renal Registry. *Int Urol Nephrol* 2014; 46(2): 443-51. <http://dx.doi.org/10.1007/s11255-013-0571-3>
- [6] McHenry CR, Wilhelm SM, Ricanati E. Refractory renal hyperparathyroidism: clinical features and outcome of surgical therapy. *Am Surg* 2001; 67(4): 310-6.
- [7] Tominaga Y, Matsuoka S, Sato T, *et al.* Clinical features and hyperplastic patterns of parathyroid glands in hemodialytic patients with advanced secondary hyperparathyroidism refractory to maxacalcitol treatment and requiring parathyroidectomy. *Ther Apher Dial* 2007; 11(4): 266-73. <http://dx.doi.org/10.1111/j.1744-9987.2007.00489.x>

- [8] Drueke TB, Zingraff J. The dilemma of parathyroidectomy in chronic renal failure. *Curr Opin Nephrol* 1994; 3(4): 386-95. <http://dx.doi.org/10.1097/00041552-199407000-00004>
- [9] Malberti F, Marcelli D, Conte E, Limido A, Spotti D, Locatelli F. Parathyroidectomy in patients on renal replacement therapy: an epidemiological study. *J Am Soc Nephrol* 2001; 12(6): 1242-8.
- [10] Stanbury SW, Lumb GA, Nicholson WF. Elective subtotal parathyroidectomy for renal hyperparathyroidism. *Lancet* 1960; 1(7128): 793-9. [http://dx.doi.org/10.1016/S0140-6736\(60\)90678-4](http://dx.doi.org/10.1016/S0140-6736(60)90678-4)
- [11] Anderson WW, Mann JB, Kenyon N, Farrell JJ, Hills GG. Subtotal parathyroidectomy in azotemic renal osteodystrophy. *N Engl J Med* 1963; 288: 575-80. <http://dx.doi.org/10.1056/NEJM196303142681103>
- [12] Decker PA, Cohen PE, Doffek KM, *et al.* Subtotal parathyroidectomy in renal failure: still needed after all these years. *World J Surg*, 2001; 25(6): 708-12. <http://dx.doi.org/10.1007/s00268-001-0019-2>
- [13] Tsai WC, Peng YS, Yang JY, *et al.* Short-and long-term impact of subtotal parathyroidectomy of bone and mineral parameters recommended by clinical practice guidelines in dialysis patients: a 12-year single-center experience. *Blood Purif* 2013; 36(2): 116-21. <http://dx.doi.org/10.1159/000353415>
- [14] Wells SA Jr, Gunnells JC, Shelburne JD, Schneider AB, Sherwood LM. Transplantation of parathyroid glands in man: clinical indications and results. *Surgery* 1975; 78(1): 34-44.
- [15] Rothmund M, Kohler D, Dieker P, Kummerle F. Total parathyroidectomy and autotransplantation of parathyroid tissue for renal hyperparathyroidism. A one- to six-year follow-up. *Ann Surg* 1983; 197(1): 7-16.
- [16] Tominaga Y, Uchida K, Haba T, *et al.* More than 1000 cases of total parathyroidectomy with forearm autograft for renal hyperparathyroidism. *Am J Kidney Dis* 2001; (4 Suppl 1): S168-71. <http://dx.doi.org/10.1053/ajkd.2001.27432>
- [17] Naranda J, Eckart R, Pecovnik-Balon B. Total Parathyroidectomy with Forearm Autotransplant as the Treatment of Choice for Secondary Hyperparathyroidism. *J Int Med Res* 2011; 39(3): 978-87. <http://dx.doi.org/10.1177/147323001103900333>
- [18] Ogg CS. Total parathyroidectomy in treatment of secondary (renal) hyperparathyroidism. *Br Med J* 1967; 4(5575): 331-4. <http://dx.doi.org/10.1136/bmj.4.5575.331>
- [19] Kaye M, D'Amour P, Henderson J. Elective total parathyroidectomy without auto-transplant in end-stage disease. *Kidney Int* 1989; 35(6): 1390-9. <http://dx.doi.org/10.1038/ki.1989.138>
- [20] Skinner KA, Zuckerbraun L. Recurrent secondary hyperparathyroidism. An argument for total parathyroidectomy. *Arch Surg* 1996; 131(7): 724-7. <http://dx.doi.org/10.1001/archsurg.1996.01430190046012>
- [21] Ockert S, Willeke S, Richter A, *et al.* Total parathyroidectomy without autotransplantation as a standard procedure in the treatment of secondary hyperparathyroidism. *Langenbeck's Arch Surg* 2002; 387(5-6): 204-9. <http://dx.doi.org/10.1007/s00423-002-0307-9>
- [22] Saunders RN, Karoo MR, Metcalfe MS, Nicholson ML. Four gland parathyroidectomy without reimplantation in patients with chronic renal failure. *Postgrad Med J* 2005; 81(954): 255-8. <http://dx.doi.org/10.1136/pgmj.2004.026450>
- [23] Lorenz K, Ukkat J, Skulla C, Gumm O, Brauckhoff M, Dralle H. Total parathyroidectomy without autotransplantation for renal hyperparathyroidism: experience with a qPTH-controlled protocol. *World J Surg* 2006; 30(5): 743-51. <http://dx.doi.org/10.1007/s00268-005-0379-0>
- [24] Schlosser K, Veit JA, Witte S, *et al.* Comparison of total parathyroidectomy without autotransplantation and with thymectomy versus total parathyroidectomy with autotransplantation and without thymectomy for secondary hyperparathyroidism TOPAR PILOT-Trial. *Trials* 2007; 8: 22. <http://dx.doi.org/10.1186/1745-6215-8-22>
- [25] Diaconescu MR, Glod M, Costea I, Grigorovici M, Covic A. Parathyroid carcinoma in a patient on hemodialysis for renal failure. *Rev Med Chir Soc Med Nat Iasi* 2006; 110(1): 152-6.
- [26] Nicholson ML, Veitch PS, Feehally J. Parathyroidectomy in chronic renal failure: comparison of three operative strategies. *J R Coll Surg Edinb* 1996; 41(6): 382-7.
- [27] Schneider R, Slater EP, Karakas E, Bartsch DK, Schlosser K. Initial parathyroid surgery in 606 patients with renal hyperparathyroidism. *World J Surg* 2012; 36(2): 318-26. <http://dx.doi.org/10.1007/s00268-011-1392-0>
- [28] Riss P, Asari R, Scheuba C, Niederle B. Current trends in surgery of renal hyperparathyroidism (RHPT) – an international survey. *Langenbecks Arch Surg* 2013; 398(1): 121-30. <http://dx.doi.org/10.1007/s00423-012-1025-6>
- [29] Rayes N, Seehofer D, Schlinder R, *et al.* Long-term results of subtotal vs total parathyroidectomy without autotransplantation in kidney transplant recipients. *Arch Surg* 2008; 43(8): 756-61. <http://dx.doi.org/10.1001/archsurg.143.8.756>
- [30] Drakopoulos Koukoulaki M, Apostolou T, Pistolas D, *et al.* Total parathyroidectomy without autotransplantation in dialysis patients and renal recipients, a long follow-up evaluation. *Am J Surg* 2009; 98(3): 78-83.
- [31] Shih ML, Du Qy, Hsieh CB, *et al.* Total parathyroidectomy without autotransplantation for secondary hyperparathyroidism. *World J Surg* 2009; 33(2): 248-54. <http://dx.doi.org/10.1007/s00268-008-9765-8>
- [32] Coulston JE, Egan R, Willis E, Morgan JD. Total parathyroidectomy without auto-transplantation for renal hyperparathyroidism. *Br J Surg* 2010; 97(11): 1674-9. <http://dx.doi.org/10.1002/bjs.7192>
- [33] Puccini M, Carpi A, Cupisti, *et al.* Total parathyroidectomy without autotransplantation for the treatment of secondary hyperparathyroidism associated with chronic kidney disease: clinical and laboratory long-term follow-up. *Biomed Pharmacother* 2010; 64(5): 359-62. <http://dx.doi.org/10.1016/j.biopha.2009.06.006>
- [34] Conzo G, Perna AF, Sinisi AA, *et al.* Total parathyroidectomy without autotransplantation in the surgical treatment of secondary hyperparathyroidism of chronic kidney disease. *J Endocrinol Invest* 2012; 14(1): 8-13.
- [35] Aly A, Douglas M. Embryonic parathyroid rests recur commonly and have implications in the management of secondary hyperparathyroidism. *ANZ J Surg* 2003; 73(3): 284-8. <http://dx.doi.org/10.1046/j.1445-2197.2003.t01-1-02620.x>