A comparative analysis of three types of parathyroidectomies in renal hyperparathyroidism

Single centre prospective cohort of 77 patients

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BACKGROUND: *There is no consensus regarding optimal timing or best surgical procedure for refractory renal hyperparathyroidism patients. We aim to compare the results after three types of parathyroidectomies performed for sHPT in a single referral centre.*
METHODS: *This study included patients on chronic hemodialysis submitted to three types of parathyroidectomy between 2010 and 2017. The primary outcome measure was relief of the symptoms and normalization of the main biochemical parameters.*
RESULTS: *All symptoms improved significantly after surgery, especially osteoatricular pains. iPth dropped significantly immediately and during the follow up in all 3 groups; on short term, iPth values for group C(tPtx) were significantly lower compared to the other 2 subgroups (p=0.009). Furthermore, 5 patients from group C presented iPth values <12 pg/ml one year post-surgery, though this values tend to improve after. Patients from group B and C developed most often acute postoperative hypocalcemia, and persistent hyperparathyroidism was encountered especially after sPtx(10.3%).*
CONCLUSION: *Significant improvement of both symptoms and biochemical parameters was noted in the majority of cases, regardless the parathyroidectomy type. tPtx is frequently followed by chronic hypoparathyroidism and subtotal parathyroidectomy is followed by a higher number of persistent and recurrent sHPT.*

KEY WORDS: Secondary hyperparathyroidism, Parathyroidectomy, Parathyroid autotransplant

Introduction

Medical treatment is the preferred option for the management of renal origin secondary hyperparathyroidism (sHPT). Indications for parathyroidectomy for this subgroup of patients are expanding, probably due to prolonged time spent on dialysis [1,2]. There is no consensus regarding the optimal timing or the best surgical procedure for patients with refractory renal hyperparathyroidism; majority of authors accept that progressive symptoms despite optimal medical treatment, persistent elevated intact parathyroid hormone levels (iPTH), elevated calcium and phosphate serum levels, calciphilaxis, osteitis fibrosa cystica are certain indications for parathyroidectomy [2-4]. Several techniques are described in literature with no definitive superiority. Subtotal or

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total parathyroidectomy with autotransplantation (at the level of the neck or other anatomical regions), occasionally grouped as remnant-conserving techniques, are the most frequently used, despite being criticized for having high potential risk of recurrence [3,4]. In recent years, an initially abandoned technique (due to severe hypoparathyroidism and adynamic bone), emerged as acceptable for those patients with severe sHPT and not eligible for renal transplant [3-5].

This study conducted a comparative prospective analysis on hemodialysis patients who underwent either remnant-conserving parathyroidectomy techniques i.e. subtotal parathyroidectomy (sPtx) and total parathyroidectomy with cervical autotransplant (tPtx+AT), or total parathyroidectomy without autotranplantation of autologous parathyroid tissue (tPtx), performed in a single referral centre. Our aim was to review postoperative short, medium and long term results, in view of clinical and biochemical parameters and to find the most suitable technique for our daily practice.

Material and Methods

Study Population

In this prospective study, we analysed and followed up patients on chronic hemodialysis and different types of parathyroidectomies i.e. sPtx, tPtx+AT and tPtx, performed between February 2010 and December 2017 in the Second Surgical Department affiliated to the University of Medicine and Pharmacy Tirgu Mures. All interventions have been performed by a single surgeon (RMN) and the initial experience has been previously reported [6,7]. The main indication was refractory sHPT associated with: very high levels of intact parathyroid hormone (iPth>800 pg/ml) unresponsive to available medical therapy, severe clinical symptoms such as osteoarticular pain, pruritus, muscle weakness, radiological findings indicating severe osteoporosis, bone changes or osteitis fibrosa cystica, high serum levels of calcium or phosphorus (serum calcium-phosphate production over 70 mg/dl). Patients with less than 3 months follow up were excluded from this study; two patients (with an initial intervention in another surgical department and referred for persistent disease) have also been excluded.

Preoperatively, we performed routine biochemical workup and localization studies; parathyroids ultrasound (US) was constantly performed, while Tc-99m sestamibi parathyroid scans was not used in all cases. All patients were loaded with vitamin D preoperatively and were dialysed the day before and after surgery. They were informed about the aim of the study and underwent written consent.

The study was undertaken with the approval of the Hospital Ethics Committee.

Surgical Procedures

In our study we performed subtotal parathyroidectomy (sPtx), total parathyroidectomy with cervical autotransplant (tPtx+AT) and total parathyroidectomy without autotranplantation (tPtx) under general anaesthesia. During sPtx, we have preserved a small portion of the least "affected" inferior parathyroid gland, which has been placed above the straps preserving a small vascular pedicle of a thymic or mediastinal vessels; when tPtx+AT was performed, the remnant was minced and implanted in sternocleidomastoid muscle in 3-4 pockets. We constantly marked the remnants with metal clips, for better localization in case of reintervention. Total parathyroidectomies without autotransplantation have been performed initially in selected cases with refractory sHPT and for patients non-eligible for a kidney transplant; during the last part of our study, we also performed tPtx for patients on long term dialysis, as well as for patients with no perspective for a renal transplant. All the excised specimens have been measured, weighed and sent for a macroscopic and microscopic analysis.

Routinely, transcervical thymectomy was not used if 4 parathyroid glands were identified. In few cases, where we could not identify all 4 parathyroid glands, we performed ipsilateral central compartment dissection on the site of the non identified parathyroid gland. Simultaneously lobectomies or total thyroidectomies for associated thyroid diseases were performed where necessary.

Postoperative follow up

All patients have been closely monitored after surgery. Symptomatic hypocalcaemia was treated with iv calcium gluconate and oral alphacalcidiol; as soon as patients had their biochemistry stabilized, iv calcium was discontinued and oral calcium was started. The first postoperative dialysis was usually performed on postoperative day 1 and serum calcium, iPth and phosphate were checked within the first 48 hours. Patients had a 3 months initial follow-up; improvement of symptoms, iPth, total calcium, phosphate and alkaline phosphatase (AlkPhos) serum levels were noted. We considered as a short follow-up the first six postoperative months, 6-18 months were considered medium, while long-term follow-up was considered afterwards. Five patients from our group were lost during follow-up.

Hypoparathyroidism was defined as iPth levels constantly low (under 12 pg/mL) on long term after parathyroidectomy, with normal or low serum calcium levels with appropriate supplementation. We defined persistent or recurrent HPT according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K-DOQI) [8].

Statistical Analysis

All statistical calculations were performed using Graph Pad Software, San Diego, California, USA. We tested the normal distribution for continuous variable using Kolmogorov-Smirnov test. We characterised them as mean and standard deviation of the mean (SD) for variables with normal distribution, or as median and 25-75 percentiles for variables with abnormal distribution. We chose adequate statistical tests according to data distribution. The frequencies of nominal variables were compared with the chi-square test. Differences between mean age values were determined by Student t-test. Differences in values between compared postoperative variables were determined by Kruskal-Wallis test (associated with the Dunns multiple comparison test) and ANOVA test (associated with the Bonferroni multiple comparison test). All the tests were interpreted relative to the significance threshold p = 0.05, and statistical significance was considered for p-values below the significance threshold value.

Results

During the studied period, we operated on 77 patients, on whom we performed 80 parathyroidectomies. The general cohort was divided in three groups: we had a first group of 29 patients with a mean age 51.4±10.5 year and 31 sPtx performed (group A), a second group with 33 patients and a mean age of 51.3±10.9 years, with 34 tPtx+AT (group B) while the study group comprises of 15 patients with a mean age of 56.5±7.14 for which we performed tPtx (group C). There were no statistically significant differences between groups as far as demographics, causes of end stage renal disease (ESRD) and preoperative clinical data are concerned (Table I).
Our patients presented with severe symptoms as bone, joint and muscle pains, pruritus and muscle weakness. There were cases with rare symptoms encountered in recent years: brown tumors with different localization, severe deformity of the spine, osteitis fibrosa cystica, calcification of the soft tissue. Regarding biochemistry, we identified constantly high elevated preoperative iPth levels (mean value > 1500 pg/ml). We found often cases with high phosphate levels, while hypercalcemia was not found regularly amongst our patients. In order to localize enlarged parathyroids, preoperatively we performed high resolution cervical ultrasound. 99m Tc Sestamibi parathyroid scans was used more frequently at the beginning of our experience, while for the last period this method was preferred for reinterventions, in case of recurrent or persistent disease. For the majority of cases, these preoperative localisation studies have not identified all enlarged parathyroids.
Cases with associated thyroid pathology: in the group with sPtx we performed 4 unilateral or total thyroidectomies, in group B we performed 8 associated thyroid surgeries, while in group C only one thyroid operation was performed. Papillary micro- or carcinoma was associated in some cases with sHPT (n=2); in group tPtx+AT we performed a total thyroidectomy and ipsilateral central compartment lymph node dissection (CCLD) for a patient with severe sHPT and associated metastatic papillary thyroid carcinoma. Central compartment neck dissection was done for 2 cases in group B, for which we have not identified the inferior parathyroid gland after ipsilateral neck exploration and thymectomy. Cervical thymectomy has not been performed routinely and was done when we have not found 4 enlarged parathyroid glands after careful bilateral neck exploration.
There was no postoperative mortality in our general cohort; we had two postoperative bleedings, one in group A and one in group C, for which reexploration and hemostasis within the first 24-48 hours was undertaken.

Table I - *Demographic and clinical data of the studied patients.*

	sPtx (group A)(n=29)	tPtx+AI (group B)(n=33)	tPtx (group C)(n=15)	p value
Sex (males/females), no (%)#	10 (34.5)/19 (65.5)	14 (42.4)/19 (57.5)	7 (46.7)/8 (53.3)	>0.5
Age (years), mean±SD*	51.45±10.5	51.3±10.9	56.5±7.14	0.21
Dialytic age (years), mean±SD*	9.14±2.77	8.19±2.71	8.90±2.37	0.41
Preoperative iPth, (pg/ml), median (min-max)**	2100 (450-10000)	1987 (357-6115)	1654 (718.5-4042)	0.14
Preoperative total serum calcium, (mg/dl), mean±SD*	9.25±0.95	9.56±0.55	9.45±0.67	0.25
Preoperative serum phosphorus,(mg/dl), mean±SD*	5.76±1.32	6.02±0.83	6.03±1.28	0.63
Preoperative AlkPhos, (U/I)median (min-max)**	482.2 (59-2636)	436 (84-987)	404.5 (66-889)	0.52
Associated thyroid pathology, n (%)#	4 (13.8)	8 (24.2)	1 (6.6)	0.27
In hospital stay, (days), median (min-max)**	4 (2-9)	3 (2-6)	3 (2-7)	0.59
Persistent hyperparathyroidism	3 (10.34)	1 (3)	0 (0)	0.25
Follow-up (months)median (min-max)**	27 (1-84)	21 (1-60)	12 (1-36)	0.34
Recurrent sHPT, n (%)#	4 (13.8)	3 (9)	0 (0)	0.32
Deaths during follow-up, n (%)#	6 (20.6)	3 (9)	0 (0)	0.10

*Data expressed as mean±SD, Student test; **Data expressed as median (min-max), Mann Whitney test; #-chi square test

TABLE II - *Sequential values for of iPth, serum calcium, phosphorus and AlkPhos during follow-up for all groups; values are calculated for short (under 6 months), medium (6-18 months) and long-term follow-up (over 18 months).*

Variables	sPtx(n=29)	tPtx+AI (n=33)	Ptx(n=15)	P value
Ca (1 month), mg/dl*mean±SD	8.24±1.20	7.74±1.22	7.57±1.09	0.14
Ca (short), mg/dl*mean±SD	8.17±1.09	7.83±1.00	7.67±0.88	0.23
Ca (medium), mg/dl*mean±SD		8.59±0.90	8.33±0.53	8,17±0.80
0.21				
Ca (long), mg/dl*mean±SD	8.83±0.74	8.73±0.60	8.35±0.30	0.23
P (1 month), mg/dl*mean±SD	3.77±1.54	3.53±1.00	2.87±0.90	0.07
P (short), mg/dl*mean±SD	4.42±1.46	3.95±1.08	3.60±1.22	0.11
P (medium), mg/dl*mean±SD	5.17±0.87	4.56±1.27	4.26±1.22	0.03
P (long), mg/dl*mean±SD	5.55±0.80	4.90±0.97	4.86±0.31	0.01
iPTH (1 month), pg/ml**median (min-max)	24.53 (3-611)	26.7 (5.7-1074)	15.40 (3-27.6)	0.06
iPTH (short), pg/ml**median (min-max)	30.25 (0.8-76.8)	34.06 (6.29-1385)	14 (7.6-33.75)	0.009
iPTH (medium), pg/ml**median (min-max)	25.10 (3-210.9)	42.15 (5-163.3)	16.05 (7.4-58.4)	0.007
iPTH (long), pg/ml**median (min-max)	43.4 (4.33-356)	50.72 (4.2-201.3)	19.83 (9.63-67.8)	0.10
AlkPhos (1 month), U/I**median (min-max)	464 (123-2236)	356 (78-767)	371.2 (36-425.5)	0.45
AlkPhos (short), U/I**median (min-max)	216.8 (39.6-416.5)	186.3 (61-321.0)	206.8 (115-322.0)	0.55
AlkPhos (medium), U/I**median (min-max)	121.6 (68.5-390.7)	110.4 (81.5-165.0)	127.8 (62.8-345)	0.74
AlkPhos (long), U/I **median (min-max)	123.7 (58.5-291.2)	117.6 (81.5-315.0)	145.3 (45.5-336.0)	0.09

*Data expressed as mean±SD Student test; ** Data expressed as median (min-max), Mann Whitney test; short=follow-up under 6 months; medium=follow-up 6-18 months; long=follow-up above 18 months

Voice changes and "hungry bone" syndrome was not statistically significant between the analysed groups; all postoperative hypocalcemias were treated initially with iv calcium supplements. Persistent hyperparathyroidism was found in 3 cases within the group with sPtx and one in group B and was due to ectopic glands. We performed a thoracic approach (mini sternotomy) and a mediastinal hyperfunctioning parathyroid was removed for one persistent disease patient. There were no differences between subgroups regarding length of hospital stay. The follow-up period was significantly longer for the sPtx group (the first group operated on at the beginning of the study period). During follow-up we lost 5 cases (3 patients from group A and 2 from group B); all other patients have been reviewed at 3 months regarding symptoms and biochemistry. Sequential values of iPth, serum calcium, phosphorus and AlkPhos during follow-up for all groups are presented in Table II.

Joint and bone pain improved significantly after surgery. iPth dropped significantly immediately and during the follow up in all 3 groups. On short term iPth values for group C (tPtx) were significantly lower compared to the other 2 subgroups, while on medium term, there were differences only between tPtx+AT and tPtx groups; on long term there were no statistical differences between subgroups. Even so patients from group B and C developed most often acute postoperative hypocalcemia; furthermore, 5 patients from group C presented iPth values under 12 pg/ml one year after surgery, though this values tend to improve after. Definitive hypoparathyroidism was encountered in two patients in the sPtx group (6.8%) and one from group B (3%); in tPtx group we have 2 patients with iPth values under 12 pg/ml at 18 months follow up (the number of patients with a long term follow up in this group is too small for adequate conclusions).

We encountered 4 cases of recurrent sHPT in sPtx group (13.8%) and 3 recurrences in the tPtx+AT group (3%); 2 patients from the sPtx group underwent further surgery and the suprasternal parathyroid implant was excised. Two cases from the tPtx+AT group had recurrent graft excised from the sternocleidomastoid muscle (Fig. 1 a,b).

Mortality during follow up for the whole group was significant: 6 patients from the sPtx (20.6%) and 3 from the group B (9%); in the majority of cases, death was caused by complications from renal failure.

TABLE III - *Type of parathyroid hyperplasia in the resected parathyroids from all groups.*

Type of parathyroid hyperplasis	sPtx (29 cases)	tPtx+AT (33 cases)	Ptx (15 cases)	p
nodular, *n* (%)#	16 (55.17)	16 (48.48)	7 (46.6)	0.82
diffuse, *n* (%)#	9 (31)	10 (30.3)	4 (26.6)	0.95
mixed, *n* (%)#	4 (13.8)	7 (21.2)	4 (26.6)	0.56

#-chi square test

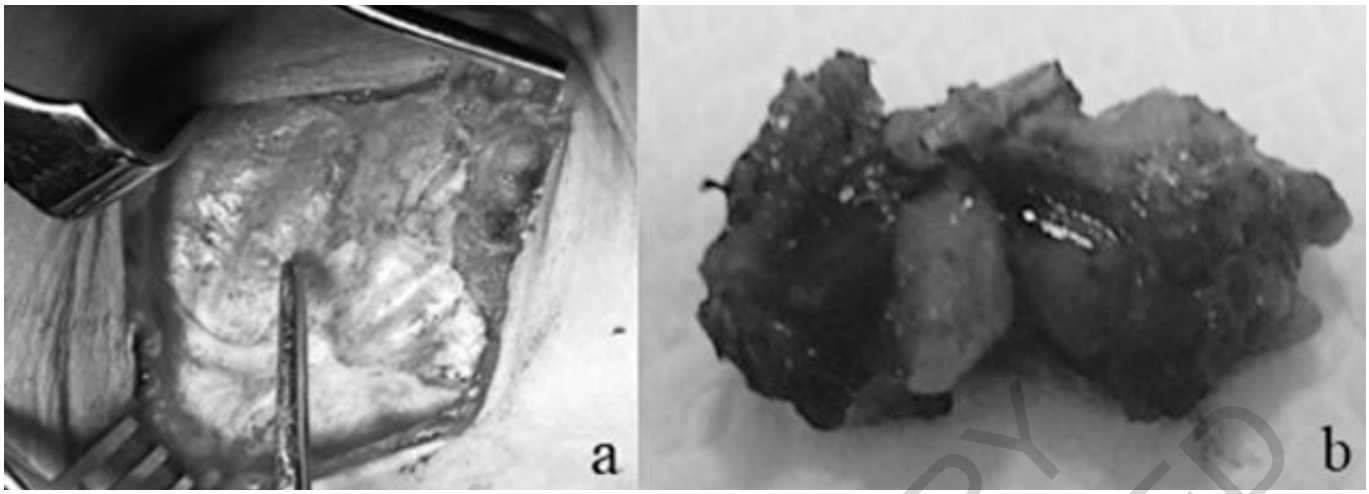

Fig. 1: (a) Redo surgery for recurrent hyperparathyroidism - the place of implant (metallic clip in place); (b) the specimen – the hyperplasic graft excised.

Histopathology showed nodular parathyroid hyperplasia (diffuse or mixt) without certain differences between subgroups (Table III).

Discussion

During the recent years improvement of the haemodialysis regimen and the outcomes of medical treatment of sHPT have reduced significantly the incidence of complications. About 1-2% of patients with chronic dialysis will be referred annually for parathyroidectomy due to refractory sHPT [9], at least as a "bridge therapy" before renal transplant - which remain the optimal therapeutic option. Parathyroidectomy is an old and accepted concept for treatment of sHPT; there are still controversies regarding the timing and extent of the surgical approaches [10]. In Romania, the access to renal transplant is limited compared to other EU countries [7,11], the majority of our patients being therefore on long term dialysis; it seems that the number of interventions performed for sHPT is less than expected [7].

This study presents the experience of one centre and a single surgeon in Romania, in treating patients with sHPT. We performed a comparative analysis of three groups of patients who underwent surgical treatment for sHPT i.e. sPTX, tPtx+AT respective tPtx. The first two techniques (remnant-conserving procedures) are keeping a small portion of the parathyroid gland (least affected by nodular hyperplasia) in the neck or autotransplanted in a muscle [neck or another anatomical region] in order to have a residual low iPth secretion [3]. The aim of the third technique i.e tPtx is to obtain low-normal iPth levels or completely suppress the iPth secretion (if associated with bilateral thymectomy); majority of authors showed that even after total parathyroidectomy there is a secretion of parathyroid hormone (due to small islands of parathyroid tissue in the neck or mediastinum); therefore there are very few cases where we see a "real" severe postoperative hypoparathyroidism [12,13].

The main indication for parathyroidectomy is sHPT refractory (persistent hypercalcemia and severe serum hyperphosphatemia, iPth >800pg/ml despite correct medical treatment); surgery is also indicated for patients with severe symptoms of hyperparathyroidism: severe itching, bone and joints pain and deformities, severe osteoporosis, calciphilaxis [2,3]. Although these indications for surgery have a vague description even in accepted therapeutical guidelines [8,14], it seems that for these cases with refractory sHPT after medical treatment, only parathyroidectomy will reduce mortality due to cardiovascular events or ectopic calcifications and will bring biochemical parameters within the acceptable range: normal range for serum calcium and phosphate, iPth between 150-300 pg/ml [8,10]. Majority of our cases presented with severe symptoms, bone deformities, pathologic fractures or osteitis fibrosa cystica; these severe symptoms corroborated with high elevated iPth levels betrayed a prolonged sHPT, "tertialisation" of the disease and even a significant delay of parathyroidectomy [6,7].

Along with biochemical workup, we also performed preoperative localizations studies; during our learning curve we have constantly performed cervical ultrasound and scintigraphy [99mTc Sestamibi] to have more information about the enlarged parathyroid(s) [6]. Similar to other authors, we noticed that both localizations studies and scintigraphy in particular, could not localize all parathyroid glands; these studies have a lower sensibility when compared with the intraoperative experience of the surgeon [15,16]. After the initial period, we used 99Tc sestamibi-scintigraphy with or without single-photon emission computed tomography (SPECT), CT, MRI neck for redo surgeries due to persistent or recurrent disease.

Our patients had three types of surgeries; at the beginning we performed sPtx (a technique which we found to be simple and facile) [6]. In order to reduce the difficulty of dissection during reintervention, we slightly modified our technique: we tried to position the parathyroid remnant of the inferior parathyroid in a suprasternal position above the straps, based on vascular pedicle from the thymic vessels. Recent recommendation suggests association of cervical thymectomy for sPtx in order to reduce the rate of recurrence [10]; similar with others [17], we performed thymectomy only in cases where we could not identify 4 parathyroids at the level of the neck. In this group, we found the highest rate of persistent hyperparathyrodism which is probably due to our learning curve; 2 cases had further surgery and the "missed" parathyroid was identified in an ectopic position - superior in the mediastinum or behind the cervical oesophagus.

For the tPtx+AT group we have not used the classic technique described by Wells [18]; we did the autotransplantation in the sternocleidomastoid muscle and marked the area with metal clips to facilitate future surgery. We noticed persistent hyperparathyroidism in one patient within this subgroup; an enlarged lymph node was mistakenly confused with an enlarged parathyroid. As far as we know, there is only one prospective randomised trial which compares the remnant conserving technique i.e. sPtx vs tPtx+AT and which noticed significantly better outcomes after tPtx+AT [19]; this study is criticized for the small number of patients and is not a strong argument to standardize this surgical approach. Other retrospective studies or meta-analysis could not demonstrate the superiority of one of the two techniques [2,4,10]. We found the same conclusion in a previous study [7].

In a smaller group, which underwent surgery more recently and therefore had a short follow-up, we performed tPtx without autotransplantation. Similar to previous publications [20], we tried to avoid this procedure at the beginning of our experience due to risks i.e. refractory postoperative hypoparathyroidism and adynamic bone; therefore tPtx was considered only for patients with advanced dyalitic age and non-eligible for renal transplant. Recent data from literature, showing similar results on short and medium follow up of tPtx with remnant-conserving techniques [21,22], convinced us to "extend" the indications for this technique. A statistical significance was found only when we compared postoperative iPth, patients from the tPtx group presenting lower iPth levels after surgery at short term follow up. Indeed, in this group we had more cases of acute postoperative hypocalcemia, much more difficult to managed that those encountered after primary hyperparathyroidism or thyroid surgeries [23,24]. On the long term, serum iPth values gradually normalize, thus no statistical difference between groups was observed. Similar results after tPtx were noted by others [5] and a possible explanation might be the absence of bilateral thymectomy which (theoretically) completely suppresses the iPth secretion. In this group of patients we associated unilateral thymectomy only when we could not identify 2 parathyroids on the side of the neck. Recent results of a randomized trial which compares tPtx+AT and thymectomy versus tPtx without thymectomy (TOPAR) found no significant differences between the two techniques, reporting only a small advantage of tPtx in regards of iPth drop and rate of recurrence at 3 years after surgery [22]. Some authors support the idea of concomitant central compartment neck dissection to remove all secreting parathyroid tissue [4]; we used this only for 2 cases when we could not find 2 parathyroids on the same side, even after ipsilateral thymectomy. We did not have the opportunity to use intraoperative parathyroid hormone (IOPTH) assessment in monitoring the surgery results, a procedure otherwise described in literature to be less sensitive.

Data from literature shows significant higher rates of recurrence for sHPT after remnant-conserving techniques, especially sPtx [2,16]; same results were found in our study where the most recurrences were noted within the first 2 subgroups (A and B). For recurrent disease we performed reoperations for few cases; in case of initial sPtx we identified the hyperplasic graft in the suprasternal region, removed it and thus, obtained a total parathyroidectomy without autotransplantation. For initial tPtx+AT cases we tried to excise only the hyperplastic graft and to keep 2-3 normofunctioning transplant sites in situ. In a meta-analysis including 7 studies and 931 patients and comparing results of tPtx+AT and tPtx on long term, Jia X et al [25] showed that tPtx techniques have a smaller incidence of reinterventions for recurrent or persistent sHPT; similarly, in this particular subgroup we found no cases of persistent or recurrent disease, but our follow up period was too short. As far as we know, there is only one retrospective study including a signficant number of patients and comparing the same three techniques from our study; this study shows better outcomes of tPtx+AT and tPtx when comparing with sPtx regarding incidence of persistence or recurrence [15]; this data is comparable with the results of our study, even if we did not obtain statistical significance [probably due to smaller number of subgroups]. Mortality in our general cohort was high, unrelated with parathyroidectomy and probably reflecting particularities of our patients.

This study has certain limitations – it is non-randomized, with small sample size per arm and several group selection biases – but it reflects the reality regarding several aspects of sHPT in our geographical area: patients on long-term dialysis, with advanced disease and with low perspective of renal transplantation; indeed as a curiosity only 9 patients [11.6%] were submitted to renal transplant during the analysed period. A significant and enduring improvement of both the symptoms of sHPT

and main biochemical parameters was noted in the majority of cases, regardless the type of parathyroidectomy; tPtx is frequently followed by a chronic hypoparathyroidism but on long term iPth values tend to normalize. Subtotal parathyroidectomy is followed by a higher number of recurrent sHPT cases when compared to tPtx+AT and even more obvious when compared to tPtx. Further randomized control trials and meta-analysis are needed to confirm these results.

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