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REVIEW ARTICLE

Surgical management of secondary hyperparathyroidism in chronic kidney disease—a consensus report of the European Society of Endocrine Surgeons

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Abstract
Background Despite advances in the medical management of secondary hyperparathyroidism due to chronic renal failure and dialysis (renal hyperparathyroidism), parathyroid surgery remains an important treatment option in the spectrum of the disease. Patients with severe and complicated renal hyperparathyroidism (HPT), refractory or intolerant to medical therapy and patients with specific requirements in prospect of or excluded from renal transplantation may require parathyroidectomy for renal hyperparathyroidism.
Methods Present standard and actual controversial issues regarding surgical treatment of patients with hyperparathyroidism due to chronic renal failure were identified, and pertinent literature was searched and reviewed. Whenever applicable, evaluation of the level of evidence concerning diagnosis and management of renal hyperparathyroidism according to standard criteria and recommendation grading were employed. Results were discussed at the 6th Workshop of the European Society of Endocrine Surgeons entitled *Hyperparathyroidism due to multiple gland disease: An evidence-based perspective.*
Results Presently, literature reveals scant data, especially, no prospective randomized studies to provide sufficient levels of evidence to substantiate recommendations for surgery in renal hyperparathyroidism. Appropriate surgical management of renal hyperparathyroidism involves standard bilateral exploration with bilateral cervical thymectomy and a spectrum of four standardized types of parathyroid resection that reveal comparable outcome results with regard to levels of evidence and recommendation. Specific patient requirements may favour one over the other procedure according to individualized demands.
Conclusions Surgery for patients with renal hyperparathyroidism in the era of calcimimetics continues to play an important role in selected patients and achieves efficient control of hyperparathyroidism. The overall success rate and long-term control of renal hyperparathyroidism and optimal handling of postoperative metabolic effects also depend on the timely indication, individually suitable type of parathyroid resection and specialized endocrine surgery.

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Introduction

Considerate synchronous improvement of medical treatment and haemodialysis regimen in patients with chronic kidney disease (CKD) resulted in decreasing severity of renal hyperparathyroidism (HPT) requiring parathyroid surgery. Awareness of the metabolic problems increased, and earlier medical treatment may obviate parathyroid surgery in some patients developing renal HPT. Nevertheless, medical treatment does not achieve satisfactory adjustment of renal HPT and correlated complications in all renal HPT patients. For these, parathyroid surgery represents a valuable option for an efficient definitive treatment or may bridge the time from overt renal HPT until renal transplantation may be performed.

While parathyroidectomy (PTX) is a long-established and accepted concept in the treatment for renal HPT, timing, extent and the best type of surgery remain a constant matter of debate. This debate is refreshed with the advent of innovative medical treatment utilizing calcium receptor antagonists, calcimimetics (further referred to as cinacalcet). Very recent nephrologists' published data represent markedly the central issues of debate and contradictory perspectives regarding optimal management of renal HPT and the potential benefit from parathyroid surgery. In a longitudinal international cohort observation study of therapeutic approach and outcome among renal HPT patients on haemodialysis, data were split into four phases from 1996 to 2011, and samples were analysed for specific questions. Median parathyroid hormone (PTH) levels increased significantly from the start in 1996 to the actual phase 5, from 153 pg/ml in Europe, Australia and New Zealand to 252 pg/ml (p trend <0.001), and likewise in North America from 160 to 318 pg/ml (p trend<0.001) [1]. With the increasing use of intravenous vitamin D analogues and cinacalcet in the treatment of renal HPT starting 2005, the rate of PTX declined significantly (p<0.001). Greater elevation of PTH at 300–450 pg/ml was associated with increased all-cause mortality (hazard ratio (HR)=1.09; 95 % CI 1.01–1.18). PTH>600 pg/ml (HR 1.23; 95 % CI 1.12–1.34) and was also associated with increased cardiovascular and all-cause mortality and cardiovascular hospitalization. In a no-treatment study subgroup, very low PTH levels of <50 pg/ml were associated with increased mortality (HR 1.25; 95 % CI 1.04–1.51) [1]. While the association of significantly increased mortality and hospitalization support surgery as valuable treatment option to acquire immediate and durable adjustment of PTH level when medication is unsuccessful, the similar association of morbidity with very low PTH levels raises concerns regarding patients in the post-PTX follow-up.

By contrast, a North American renal data analysis identified 4435 renal HPT patients who underwent PTX in the years 2007–2009, comparing medical data in the year before and after PTX, and showed that PTX was associated with 2 % postoperative 30-day mortality. Rehospitalization within 30 days was 29.3 %, and 39 % required intensive care. In the 12 months postoperatively, negative increases compared to the year before PTX included higher hospitalization rate by 39 %, hospital days in 58 %, and 69 % intensive care admissions. Emergency room and observation visits were increased 20-fold. Cause-specific hospitalizations for acute myocardial infarction (HR 1.4; 95 % CI 1.60–2.46) and dysrhythmia (HR 1.3; 95 % CI 1.16–1.78) were increased, while fracture risk remained unaffected (HR 0.82; 95 % CI 0.6–1.1) [2]. The overall 2 % postoperative mortality rate after PTX was divided into 0.9 % in-hospital, and 1.1 % within 30 days. Mortality in the year following PTX was 9.8 %. Cause-specific analysis of increased hospitalization after PTX identified cerebrovascular events (relative risk (RR) 1.83; 95 % CI 1.38–2.34), acute myocardial infarction (RR 1.98; 95 % CI 1.60–2.46), and dysrhythmia (RR 1.44; 95% CI 0.80–1.02). Cause-specific morbidity after PTX identified observation/emergency room visits (RR 20.4; 95 % CI 16.8–24.9) and ambulatory treatment for hypocalcaemia treatment (RR 17.9; 95 % CI 11.8–24.5) [2]. This alarmingly negative result of post-PTX course specifically regarding mortality and hypocalcaemia raises several questions and concerns. The main challenging questions are whether patients in this data system were operated too late and/or by surgeons and/or in institutions with insufficient experience, respectively. Moreover, postsurgical follow-up proved to be insufficient and post-PTX metabolic adjustment was poorly managed.

Both studies represent conflicting appraisal of the role PTX should take in the management of renal HPT. Noteworthy, both publications do not include any cooperating surgeon in their data analyses and interpretation. Moreover, both studies were supported by a pharmaceutical company manufacturing the most frequently administered drug cinacalcet, an allosteric calcium receptor modulator.

Against this background it appears appropriate to address the current issues of debate regarding management and treatment of renal HPT according to evidence from published data and recommendations from the endocrine surgeon perspective in a consensus conference approach.

Methods

A literature review was performed including publications in English language from recent years concerning medical and surgical treatment of renal HPT identified by Pubmed search. Whenever applicable, effort was made to state the level of evidence in order to arrive at substantiated account of current

knowledge and open clinical questions. The grading level of incidence was adapted from the criteria according to Sackett and recommendations according to Heinrich et al. [3, 4]. Following electronic provision of the draft version and oral presentation, audience feedback and discussion were considered and the statements revised accordingly. Consensus statements were finalized after further electronic provision and ESES member's consent.

Results

Definition, medical treatment, diagnostics and indication for surgery in renal hyperparathyroidism

Renal HPT is characterized by derangement of calcium homeostasis and reactively increased PTH level mainly due to progressive CKD. Tertiary HPT refers to the spontaneous autonomous development of hypercalcemia in pre-existent renal HPT following successful renal transplantation [5] according to surgical definition, but may infrequently develop previously. Other forms of secondary HPT with similar metabolic disorder may be due to long-term lithium therapy, gastrointestinal absorption dysfunction like coeliac disease, vitamin D deficiency, liver diseases, and pseudohyperparathyroidism and were excluded from the present review.

The majority of patients is managed medically according to recently proposed international practice guidelines (Kidney Disease Improving Global Outcome (KDIGO) for management of CKD related to mineral and bone disease (CKD-MBD)) [6], aiming to lower phosphate level into the normal range and keep PTH levels between two and nine times of the upper normal range of intact PTH in dialysis patients [6]. The National Kidney Foundation of the USA proposed for renal HPT patients on dialysis in the Kidney Disease Outcomes Quality Initiative (K/DOQI) a serum calcium level between 8.4 and 9.5 mg/dl, serum phosphate level of 3.5–5.5 mg/dl, calcium/phosphorus product of <55 mg^2/dl^2, and intact PTH (iPTH) of 150–300 pg/ml [7]. While there are no specific indications for PTX listed in the KDIGO guidelines, it is considered in severe renal HPT refractory to medical treatment as it proficiently and quickly lowers calcium, PTH and phosphorus levels and also aims to prevent cardiovascular complications and ectopic calcifications. With adequate vitamin D treatment in renal HPT, surgical indication shifted from severe symptoms and bone disease to correct metabolic parameters (e.g., iPTH >800 pg/ml; hypercalcemia; hyperphosphataemia) when medical treatment fails because evidence of increased mortality in CKD patients is associated with mortality due to cardiovascular complications and ectopic calcifications [7–9]. Thus, PTX rates in CKD are clearly affected by trends in the medical treatment (4A) [6, 10, 11].

Prevalent basic PTX rates and PTX incidence at follow-up/100 patients/year between 1996 and 2001 were approximated per country in the Dialysis Outcome and Practice Pattern study (DOPPS) as follows: France 14.3 %, 1.8; Germany 6 %, 1; Italy 5 %, 0.9; Japan 4.1 %, 0.6; Spain 5.7 %, 1.5; UK 9.2 %, 1.5; USA 4 %, 0.5 [12].

Preoperative routine evaluation in renal HPT planned for PTX includes neck ultrasound and laryngoscopic evaluation of vocal cord function. Ultrasonography aims to assess localization of parathyroids, evaluate for concomitant thyroid disease as well as to identify possible intrathyroidal parathyroids. Moreover, assessed parathyroid mass may be used to predict response to medical treatment [13]. ^{99}Tc sestamibi-scintigraphy with/without single-photon emission computed tomography (SPECT) is appreciated by some surgeons to exclude ectopic parathyroid localization despite convincing evidence in defined multiglandular disease. Therefore, enhanced localization measures including ^{99}Tc sestamibi-scintigraphy with/without SPECT and CT, MRI, $^{(11)}$C-methionine PET-CT or ^{18}F-FDG-PET-CT as well as selective venous catheterization with PTH assessment presently appear to be reserved for special indications and possibly rare reoperative situations, since standard conventional bilateral exploration in renal HPT does not rely on preoperative localization [14–16].

Adherence and conflicts of practiced endocrine surgery with present nephrologist recommendations

Indication for parathyroidectomy in patients with renal hyperparathyroidism

All patients with CKD within the group of metabolic abnormalities termed mineral and bone disorder (CKD-MBD) suffer from some degree of renal HPT, as early as glomerular filtration rate (GFR) <60 and preceding dialysis (K/DOQ, AJKD 2003). Generally, PTX is a valuable option in any patient diagnosed with renal HPT; however, the majority of patients may be controlled medically. Successful medical treatment can be achieved with phosphate binders, calcium supplements, active vitamin D analogues and cinacalcet which alter calcium receptor sensitivity of parathyroid glands and kidneys, thus reducing PTH secretion and restoring calcium-phosphorus homeostasis [17–20] (evidence level (EL); recommendation grade (RG) EL 1a; RG A) [21]. Cinacalcet is stated to reduce mortality in renal HPT patients, while contradictory reports acclaim a lack of patient-relevant outcomes improvement and relevant side-effects in patients on dialysis [22]. Initial randomized controlled studies (RCT) with placebo arm recognized that cinacalcet could cause severe hypocalcaemia (<7.5 mg/dl) in up to 5 % of patients requiring oral calcium and/or vitamin D substitution [17]. Even more patients (35–45 %) experience digestive intolerance, in 8–15 %, requiring to terminate treatment [19, 20, 23]

(EL 2b; RG B). The benefit of cinacalcet to improve bone mineral density is described; however, data are scarce and further studies with long-term follow-up are needed to substantiate this effect [24] (EL 3a). Although very rare, cinacalcet may also be the first choice for patients in whom surgical HPT management appears challenging, e.g., patients at risk for general anaesthesia, when mediastinal approach becomes necessary; reoperative surgery when parathyroid glands remain completely unlocalized; or percutaneous ethanol injection therapy (PEIT) was previously performed.

Surgery may further be indicated for patients with uncontrollable renal HPT while on cinacalcet, expected long-term survival with severe symptomatic renal HPT including pruritus, intractable bone pain, advanced osteopaenia/osteoporosis, calcinosis and calciphylaxis (EL 2b). All over, approximately 1–2 % of patients with renal HPT require PTX each year [5], acknowledging that the specific indications for PTX in a CKD patient today remain essentially the same as in the pre-cinacalcet era. Therefore, PTX is indicated in patients with uncontrollable renal HPT while on cinacalcet or intolerance thereof [25, 26].

Non-surgical guidelines and role of parathyroid surgery

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative [7] and Kidney Disease: Improving Global Outcomes (KDIGO) [6] established guidelines for the treatment of renal HPT. The KDOQI guidelines suggest maintaining iPTH levels between two and nine times the upper normal limit for patients in dialysis [6]; however, this is not based on strong evidence or validated by prospective clinical trials (EL 2c; RG C). Subsequent reports showed that the majority of patients failed to reach recommended iPTH values with medical treatment. For these patients, parathyroid surgery can be regarded as the preferable therapeutic tool for targeting the recommended ranges for serum calcium, phosphate and PTH levels. Therefore, PTX remains a valuable tool to attain the NKF-K/DOQI recommendations for serum calcium, phosphorus and calcium phosphate product in dialysis patients with renal HPT not responding to medical treatment with effective decrease of these parameters not only from a surgical perspective [27, 28].

Surgical concepts in renal hyperparathyroidism

Goals of surgery for renal hyperparathyroidism The surgical strategy in renal HPT should be focussed on an adequate balance between extent of parathyroid resection, prevention of persistent/recurrent disease and avoidance of postoperative permanent hypoparathyroidism. Irrespective of the strategy, the primary goal of surgery for renal HPT is elimination of the PTH excess. The selection of specific operative approach will be mainly directed by the patient's chances to receive a kidney transplant, since the optimal treatment of renal HPT is successful renal transplantation. Thus, the prospective time on dialysis and realistic prospect of kidney transplantation, as well as the target range of iPTH between 150 and 300 pg/ml for patients on permanent dialysis according the KDOQI guidelines, should guide the surgical strategy [7]. This is especially important in patients with severe renal HPT and for patients on permanent dialysis with otherwise uncontrollable renal HPT.

Development of surgery for renal HPT and types of procedure Following the first PTX for renal HPT in 1960 [29], four different approaches were reported for the surgical treatment of renal HPT: (1) subtotal PTX with bilateral cervical thymectomy (3.5 parathyroid gland resection; subtotal PTX), (2) total PTX (TPTX) with autotransplantation of parathyroid tissue and bilateral cervical thymectomy (TPTX+AT), (3) TPTX without autotransplantation and without thymectomy, and (4) TPTX without autotransplantation and with bilateral cervical thymectomy (TPTX+BCT), respectively [30, 31] (Table 1). The first three procedures aim to maintain a long-standing residual production of PTH, whereas the goal of TPTX+BCT is complete elimination of PTH production. Since no large randomized controlled trials comparing one surgical approach to another exist, the level of evidence is low (EL 1b-3) regarding identification of the most effective procedure. However, the KDOQI guideline initiative (2003) as well as most experts recommend subtotal PTX and TPTX+AT as standard procedures [31] (EL 3; RG B). Resection of less than 3.5 parathyroid glands in renal HPT patients with asymmetric parathyroid hyperplasia may not be considered an adequate option due to the high risk of persistence/recurrence [32–34] (EL 3, RG B).

Table 1 Surgical procedures for renal hyperparathyroidism

Procedure	Percentage of patients treated[a]	Proposed indications	EL
Subtotal PTX with BCT	19.8	Renal HPT, especially in prospect of kidney transplant, tertiary HPT	1b, 3
Total PTX with BCT and AT	68.1	Renal HPT, no prospect of kidney transplant	1b, 3
Total PTX without BCT and AT	10.3	Renal HPT, prospect of kidney transplant	3, 4
Total PTX with BCT without AT	1.6	Renal HPT, prospect of kidney transplant	3, 4

AT parathyroid autotransplantation, *BCT* bilateral cervical thymectomy, *EL* evidence level according to Sackett, *HPT* hyperparathyroidism, *PTX* parathyroidectomy

[a] Calculated according to studies listed in tables SPTX, TPTX+AT and TPTX

Subtotal versus total parathyroidectomy

Subtotal parathyroidectomy Subtotal parathyroidectomy (subtotal PTX) is the resection of approximately 3.5 parathyroid glands, leaving between 40 and 80 mg of the most normal-appearing parathyroid gland well-vascularized in situ after marking it with a non-resorbable suture or a metallic clip. It appears preferable to save an inferior gland as they are usually located more anteriorly in the neck, making the remnant more accessible to reoperation if necessary. Bilateral cervical thymectomy is considered an essential part of this procedure in an effort to remove any supernumerary glands or parathyroid nests, defined as histologically identifiable parathyroid tissue distinct from the parathyroid glands within the thymus (see role of thymectomy below) (EL 1a+3; rec A/B; Table 2).

Total parathyroidectomy with synchronous autotransplantation TPTX+AT includes careful identification and resection of all four parathyroid glands with bilateral cervical thymectomy to remove any supernumerary glands and parathyroid nests. For autotransplantation, the most normal-appearing gland should be minced into 10–20 $1mm^3$ pieces for reimplantation [35, 36]. The sternocleidomastoid muscle, the brachioradial muscle of the non-dominant forearm as well as the subcutaneous fat of the abdomen are potential sites for reimplantation. In all cases the site of reimplantation should be marked with metallic clips or non-absorbable sutures so that it can be identified in case of necessary re-intervention. Reimplantation into the forearm may obviate the need for surgical reexploration of the neck in the event of recurrent HPT due to graft hyperplasia. Another advantage is that the site of recurrence can be assessed by a Casanova autograftectomy test [37] or its simplified modification [38].

The only prospective randomized trial comparing the outcome of 40 patients with either subtotal PTX or TPTX+AT showed significantly decreased rates of recurrence, significantly more often normalization of serum calcium and alkaline phosphatase as well as significant improvement of clinical signs like pruritus and muscle weakness after TPTX+AT compared to subtotal PTX [39] (EL IB). However, this RCT was underpowered to lead to standardization of this operative approach. According to several retrospective case series and cohort studies, the rates of persistent/recurrent HPT and postoperative permanent hypoparathyroidism ranged between 0 to 12 % and 2 to 17 % for subtotal PTX (EL 1b-3, Table 3). For TPTX+AT these rates varied between 0 to 10 % and 0 and 85 %, respectively (EL 1b-3, Table 3). However, the retrospective design of these studies and the wide variation of the respective study populations regarding definitions of recurrence/persistence and hypoparathyroidism as well as the length of follow-up make a comparative analysis difficult. The interpretation of these data remains difficult as outcomes also rely on the quality of the initial operation, independent of the approach being PTX or TPTX+AT. A recent systematic review of 53 publications on reoperations for recurrent or persistent renal HPT identified 501 patients who had either subtotal PTX (36 %) or TPTX+AT (64 %) as initial operation [40] (EL 2). Reoperation determined that inadequate cervical explorations occurred in 42 % of patients who had undergone subtotal PTX and in 34 % of patients who had undergone TPTX+AT. Some experts consider subtotal PTX as the most favourable approach for patients with a realistic chance of short-term kidney transplantation and mild to moderate renal HPT [41, 42]. An unresolved controversy addresses the possible deterioration of renal function due to PTX, especially in renal transplant patients. Some authors claim that in contrast to older studies [43, 44], recent investigations generally show an increase in blood creatinine levels after PTX [45–48]. The reason for the discrepancy might be that formerly only patients with severe hypercalcemia were referred for PTX. As severe hypercalcemia impairs GFR as a result of inducing renal vasoconstriction and nephrocalcinosis when hypercalcemia in these patients is

Table 2 Results of subtotal parathyroidectomy for renal hyperparathyroidism (RCT or >50 patients)

Author	Year	Study design/evidence level	Number	Recurrence (%)	Hypoparathyroidism (%)	Follow-up (months)
Johnson	1988c	RS/3	61	9.8	0	28
Henry	1990	RS/3	79	2.5	0	48
Rothmund	1991	RCT/1b	20	20	0	43
Koonsmann	1994	RS/3	53	7	7	36
Willeke	1996	RS/3	54	0	2	nd
Gasparri	2001	CRS/3	229	8.2	4.8	58
Dotzenrath	2003	CRS/3	190	3.7	10.9	51
Low	2009	CRS/3	68	13.2	2	46
Schneider	2012	CRS/3	21	9.5	0	57
Total		1B-3	775	8.2 (0–20)	2 (0–10.9)	47 (28–58)

RCT randomized controlled trial, *RS* retrospective study, *CRS* comparative retrospective study, *nd* no data

Table 3 Results of total parathyroidectomy and autotransplantation for renal hyperparathyroidism (RCT or >50 patients)

Author	Year	Study design/evidence level	Number	Recurrence (%)	Hypoparathyroidism (%)	Follow-up (months)
Wells	1979	RS/3	100	3	0	32
Rothmund	1983	RS/3	56	2.2	2.2	26
Alexander	1988	RS/3	110	11	0	nd
Henry	1990	RS/3	152	4	0	30
Rothmund	1991	RCT/1b	20	0	0	43
Walgenbach	1997	RS/3	79	4.5	1.5	18
Kinnaert	2000	RS/3	59	12	nd	38
Tominaga	2001	RS/3	1053	8	15	42
Gasparri	2001	CRS/3	41	4.8	2.4	58
Chou	2002	RS/3	185	8.1	1.4	54
Dotzenrath	2003	CRS/3	304	nd	6	51
Schneider	2012	CRS/3	504	5.4	1.2	58
Total		1b-3	2663	4.8 (0–12)	2.2 (0–15)	43 (18–58)

RCT randomized controlled trial, *RS* retrospective study, *CRS* comparative retrospective study, *nd* no data

corrected, graft function may improve. Renal function deterioration in the early postoperative period may be related to the hemodynamic effects of PTH. Indeed, PTH has a vasodilator effect on preglomerular vessels at the same time as efferent arterioles are constricted, presumably secondary to renin release [49]. When these effects are reversed, renal function may deteriorate acutely. In the long term, however, these hemodynamic changes may attenuate progression of renal failure as was shown in an animal model [50]. Overall, there appears to be no difference in the overall graft survival between patients who underwent PTX between 1966 and 1997 [51] and those who did so later [47, 52]. Only one study reported decreased graft survival after PTX, and since only a 10 % graft survival was reported at 6 years, it is hard to believe that these poor results can be explained by PTX alone [46]. However, one recent study suggests that the renal function might be better preserved, if patients at risk for tertiary HPT undergo PTX before renal transplantation, with GFR being significantly lower in patients who underwent PTX after transplantation as compared to patients who underwent PTX before renal transplantation [53].

Contrary, others claim that in predialytic patients subtotal PTX might also be the preferable approach, since it was shown that subtotal PTX deteriorates kidney function less than TPTX+AT [52, 54] (EL 3) due to the postoperatively less pronounced transient hypoparathyroidism, which may provoke reduced graft perfusion, as one possible cause of kidney graft deterioration associated with PTX (Table 4).

Total parathyroidectomy without synchronous autotransplantation without routine cervical thymectomy

TPTX without autotransplantation and without routine cervical thymectomy, first described in 1967 [55], may provide an alternative strategy to the currently preferred procedures subtotal PTX and TPTX+AT. During this procedure at least four parathyroid glands will be resected. Unilateral thymectomy

Table 4 Total parathyroidectomy with autotransplantation versus subtotal parathyroidectomy (only RCT and CRS)

Author	Year	Study design/evidence level	Type of surgery	Number	Recurrence (%)	Hypoparathyroidism (%)	Follow-up (months)
Rothmund	1991	RCT/1b	SPTX	20	20	0	43
			TPTX+AT	20	0	0	
Gasparri	2001	CRS/3	SPTX	229	8.2	4.8	58
			TPTX+AT	41	4.8	2.4	
Dotzenrath	2003	CRS/3	SPTX	190	3.7	10.9	51
			TPTX+AT	304	6	6	
Schneider	2012	CRS/3	SPTX	21	9.5	0	57
			TPTX+AT	504	5.4	1.9	
Total		1b-3	SPTX	528	6 (3.7–20)	2.4 (0–10.9)	54 (43–58)
			TPTX+AT	869	5.2 (0–6)	1.6 (0–6)	

RCT randomized controlled trial, *RS* retrospective study, *CRS* comparative retrospective study, *SPTX* subtotal parathyroidectomy, *TPTX+AT* total parathyroidectomy with autotransplantation

will be only performed if fewer than two glands are detected at regular positions at the respective side. In retrospective case series with 11–150 patients (EL 3; Table 3), the rates of recurrent/persistent renal HPT of 0–4 % after TPTX during long-term follow-up were lower than after subtotal PTX or TPTX+AT [54]. Of note, patients after TPTX did not develop hypoparathyroidism and particularly adynamic bone disease as initially expected. Moreover, patients lacking a parathyroid remnant maintained a noncritical calcium/phosphate product during the ongoing follow-up compared to individuals with persisting PTH secretion after PTX. One explanation for the absence of serious adverse events may be that thymectomy was not performed on a regular basis. Even in case of resection of all four parathyroid glands (TPTX), residual microscopic parathyroid tissue or supernumerary glands located in the thymus may prevent the patients to develop hypoparathyroidism and its sequelae. However, the observed superiority of TPTX is flawed due to different definitions of outcomes, varying follow-up periods and different surgical treatment strategies (with or without routine thymectomy). The results of a prospective randomized controlled multicentre trial (TOPAR-PILOT) [56], performed between 2007 and 2013 to compare TPTX and TPTX+AT, are thus anticipated with interest to potentially provide better evidence for future recommendations. Preliminary results showed that there is no statistical significant difference regarding recurrence or persistence of disease as well as postoperative hypoparathyroidism (Schlosser et al., oral communication at the Congress of the German Surgical Society, Munich, April 29, 2015). There is only one retrospective study on 606 patients with renal HPT comparing subtotal PTX, TPTX+AT and TPTX [57] (EL 3). Persistent renal HPT occurred in 2/504 patients with TPTX+AT (0.4 %), 0/32 (0 %) patients with TPTX and 1/21 (4.8 %) patients with subtotal PTX, respectively. After a mean follow-up of 57 months, recurrent renal HPT occurred in 27/504 (5.4 %) patients with TPTX+AT, in 0/32 (0 %) of patients with TPTX and in 2/21 (9.5 %) of patients with subtotal PTX. The authors concluded that TPTX with and without autotransplantation are the preferable surgical procedures for patients on permanent dialysis with otherwise uncontrollable renal HPT.

Total parathyroidectomy without synchronous autotransplantation with routine cervical thymectomy

The fourth approach to severe renal HPT on permanent dialysis is TPTX with routine bilateral cervical thymectomy and without autotransplantation (TPTX+BCT). This aims to completely eliminate PTH production. The concept of TPTX+BCT offers the advantage of a highly standardized procedure without uncertainty regarding adequate size and function of parathyroid remnants. One small-scale retrospective study on 23 patients TPTX+BCT achieved a better biochemical cure than subtotal PTX (74 % vs. 63 %) after a median follow-up of 27 months [58] (EL 3; Table 3). Contrary to the arguments regarding imminent development of adynamic bone disease and difficult medical management after TPTX, follow-up after 2 years showed no clinical evidence thereof in this group. The possible higher risk of developing adynamic bone disease and secondary calciphylaxis must be carefully determined during long-term follow-up in patients devoid of PTH excretion. However, presently, data is too scarce to evaluate merits and risks of this procedure to recommend it outside of controlled studies.

Determining the role of cervical thymectomy in renal hyperparathyroidism surgery

The frequency of intrathymic parathyroid glands or parathyroid cell rests in patients undergoing PTX for renal HPT varies considerably between 14.8 and 45.3 % [59, 60]. However, parathyroid cell nests are not restricted to the thymus and, owing to their embryological origin and subsequent migration, can occur almost anywhere in the neck [61]. In a study of 60 patients undergoing PTX, extraglandular parathyroid rest was found in 37 % of patients including the cervical fat, the thymus and thyroid [61] (EL 3). Parathyroid tissue was also found in the pharyngeal submucosa, along the vagus nerve, within the carotid sheath, within mediastinal soft tissue and at the level of the angle of the mandible [62, 63] (EL 3). The clinical significance of supernumerary glands and parathyroid cell rests detached from parathyroid glands is underscored by the fact that the majority of patients after TPTX and even after TPTX+BCT have measurable PTH levels after surgery [57, 64, 65] (EL 3). Thus, routine bilateral cervical thymectomy (BCT) is a continuous matter of debate in patients undergoing surgery for renal HPT.

One large retrospective study on 461 patients [60] (EL 3) undergoing TPTX+AT with routine BCT intrathymic parathyroid glands (IPGs) were identified in 205 (44.5 %) patients, which were supernumerary in 30 patients (6.5 %). The frequency of supernumerary IPGs in patients on permanent hemodialysis was 7.4 % (29/392), 3.9 % (1/26) in predialysis patients, and 0 % (0/43) in patients after successful kidney transplantation. These differences reached no statistical significance. Another retrospective study [42] (EL 3) evaluated how often reoperation might be avoidable, if adequate cervical thymectomy was performed during initial surgery. Of 161 patients who underwent reoperative PTX for recurrent/persistent renal HPT, 95 had neck re-explorations. Among them were 29 patients with total PTX+AT, 7 with subtotal PTX (3.5 glands resected), and 59 with incomplete PTX at initial surgery. Complete BCT during initial PTX was performed in only 12 of 95 patients (12.6 %). Reoperative PTX revealed intrathymic parathyroid glands in 27 of 95 patients (28.4 %). Both ectopic and supernumerary IPGs were found in two patients (7.4 %). Based on this very recent study and a

previous systematic review [40], it may be postulated that routine complete BCT is essential during subtotal PTX and TPTX+AT, especially if fewer than four glands were identified in typical position to avoid recurrence/persistence of renal HPT (EL 3; rec B). Because of the low frequency of supernumerary IPGs and a suspected low-proliferation stimulus, the relevance of BCT after resection of four glands in predialytic patients and those after successful kidney transplantation has to be questioned [41, 42] (Table 5). There is presently no sufficient data to give a definitive statement about the value of routine BCT during TPTX without autotransplantation.

Surgical approach for persistent and recurrent renal hyperparathyroidism

Reoperations for persistent or recurrent renal HPT in the neck are challenging due to scar formation aggravating identification of parathyroid glands and meticulous preparation and since they are related to a higher rate of recurrent laryngeal nerve palsy (RLNP, 2 to 10 %) [40, 60]. Thus, there are several important aspects to consider. The cause of persistence or recurrence must be defined, since it is crucial for the surgical strategy. It is mandatory to review all operative notes and pathology reports from the previous operation(s) as well as previous localization studies to clarify (1) which glands were identified and removed, (2) the borders of dissection where scar tissue can be expected, (3) whether BCT was performed, (4) whether an autograft might be the source of persistence/recurrence, (5) whether parathyromatosis might be the PTH source due to capsule rupture, and (6) to learn about the experience of the surgeon who performed the procedure. The potential location of a missing parathyroid gland or the source of PTH secretion can often be predicted based on this information. Once the diagnosis of recurrent or persistent renal HPT is established, one must decide whether reoperation is indicated. There is a general agreement that reoperative surgery is indicated, if a targeted approach to either the neck or autograft site is possible as it harbours the lowest complication rate [31]. Also, targeted approach to the mediastinum by thoracoscopy or open in accordance to unequivocal localization study may be justified. Therefore, in contrast to primary surgery, imaging studies to localize the enlarged parathyroid gland(s) are mandatory. In case of previous autograft into the forearm, an autograft-related PTH excess can be determined by the Casanova test [37] or its modification [38]. In case of a neck recurrence, imaging modalities should at minimum include neck ultrasound and ^{99}Tc sestamibi-SPECT scintigraphy, possibly supplemented by magnetic resonance imaging (MRI) of the neck and mediastinum, methionine-positron emission tomography (PET) CT or selective venous sampling (SVS), depending on the outcome of the respective studies [31]. In patients with a high perioperative risk or persistent or recurrent disease with no localized source of parathyroid hormone producing source on imaging, medical treatment appears preferable (EL 4, RG C).

Surgical treatment of patients with renal hyperparathyroidism and calciphylaxis

Between 1 and 4 % of patients on chronic haemo- or peritoneal dialysis develop calciphylaxis, characterized by advancing cutaneous gangrene with extremely painful skin ulceration involving mainly the extremities and/or the trunk and, rarely, the face. Obesity, systemic corticosteroid as well as vitamin K antagonists use besides severe renal HPT were identified as

Table 5 Results of total parathyroidectomy with/without bilateral cervical thymectomy for renal hyperparathyroidism

Author	Year	Study design/ evidence level	Number	Routine BCT	Recurrence/ Persistence (%)	Hypoparathyroidism (%)	Follow-up (months)
Ljutic	1994	RS/3	43	No	2.3	33	104
Nicholson	1996	RS/3	24	No	0	0	24
Hampl	1999	RS/4	11	No	0	nd	26
Ockert	2002	RS/4	11	No	0	0	22
Saunders	2005	RS/3	55	No	13	76	29
Lorenz	2006	RS/3	23	Yes	0	48	27
Low	2009	CRS	43	Yes	2.3	nd	46
Stracke	2009	RS/3	46	No	26	11	63
Coulston	2010	RS/3	115	No	12.2	28.7	31
Schneider	2012	CRS/3	32	No	0	0	58
Conzo	2012	RS/3	25	No	8	0	36
Iwamoto	2012	RS/3	88	No	nd	nd	52
Sharma	2013	RS/3	150	No	nd	nd	42
Total		3/4	403	2 yes; 11 no	0% (0–26)	11% (0–76)	36 (22–104)

BCT bilateral cervical thymectomy, *RCT* randomized controlled trial, *RS* retrospective study, *CRS* comparative retrospective study, *nd* no data

predisposing factors in the development of calciphylaxis [66, 67]. The treatment encompasses local wound care with judicious local debridement and/or excision when severe soft tissue infection ensues. Medical treatment should always be promptly initiated and is directed to control renal HPT based on a low phosphorus diet, phosphate binders (sodium thiosulphate) and cinacalcet, although a variety of calcium metabolism drugs have been used [67].

Available studies investigating the effect of PTX to treat calciphylaxis were only of retrospective design and reveal considerate bias in this particular condition. While some authors claim a clear survival advantage [68, 69], other studies report that PTX did not offer any survival advantage [67]. Although there were no therapeutic clinical trials conducted, PTX was contemplated only in patients with PTH levels >20 pmol/l sustaining a calcium-phosphorus product consistently above 70 refractory to medical treatment (EL 2c) [70]. The estimated disease-specific survival rate for calciphylaxis 1 year after the diagnosis is 45.8 %, and patients infrequently survive longer than 2 years [66, 67, 70].

In conclusion, the decision of medical versus surgical treatment of renal HPT requires interdisciplinary discussion between nephrologists and endocrine surgeons. Patients with a severe renal HPT, including PTH levels of more than 800 pg/ml and hypercalcaemia or hyperphosphataemia despite medical treatment, will benefit from surgical treatment [7]. Controversy remains concerning the optimal surgical technique due to the lack of large prospective studies or randomized controlled trials comparing the aforementioned different surgical techniques. Based on the available data, TPTX with or without autotransplantation can be considered as safe standard techniques for patients on permanent dialysis and otherwise uncontrollable renal HPT. Subtotal PTX may be the preferable procedure in predialytic patients, and patients with moderate renal HPT awaiting a renal transplantation in the near future (EL 3; RG B). However, this interpretation of prevalent data awaits confirmation by multicentre RCTs.

Evidence for and against cryopreservation of parathyroid tissue in surgery of renal and tertiary hyperparathyroidism

Patients with renal HPT undergoing any type of parathyroid tissue removal (subtotal PTX, TPTX+/−AT) are at risk for developing permanent hypoparathyroidism. Parathyroid cryopreservation and delayed heterotopic parathyroid tissue autotransplantation was advocated and practiced as a protection against permanent postoperative hypoparathyroidism. Numerous experimental and clinical reports verify the viability and safety of this procedure. However, the most recent reports on results of this strategy show a very low utilization ratio of cryopreserved material (typically 1–2 %) in sharp contrast with the series published in the last decade of last century contesting rationale of the procedure [71–73]. A comprehensive review of the literature suggests that less than 200 autotransplants from cryopreserved parathyroid tissue have been reported [74]. In a recent extensive survey comprising 86 centres encompassing high- and low-volume parathyroid surgery, 27 % carried out cryopreservation in selected cases, and a total of 54 patients received grafts (32). The Japanese unit with the largest published series of patients treated TPTX+AT (n=>2000) abandoned cryopreservation more than a decade ago because in no case demand for the frozen tissue developed [75] (EL 3).

Furthermore, the reported success rates of cryopreserved autografts are highly variable (25–100 %) but usually lie below immediately autotransplanted glands (Table 6). In a representative study of long-term functionality of cryopreserved parathyroid autotransplants into the forearm musculature, about 60 % of the grafts were partially functional but less than 50 % of the patients could be completely weaned from calcium and/or vitamin D supplementation [76] (EL 3).

The cryopreservation process, independent of diligence of procedural quality, appears to decrease total cell viability, and further decrement of cell viability is associated with increased storage time. Therefore, the duration of cryopreservation

Table 6 Cryopreservation of parathyroid tissue and metachronous autotransplantation

Author	Year	Study period (years)	Aetiology	Patients with cryopreserved tissue	Patients transplanted (%)	Delay AT (months)	Successful (%)
Shepet	2013	10	Mixed	442 (21 %)	4 (1.0)	nd[a]	1 (25)
Agarwal	2013	10	Mixed	630 (≈30 %)	9 (1.5)[b]	3–22	4 (44)
Schneider	2012	24	Only renal HPT	883 (100 %)	15 (1.6)	1–86	15 (100)
Borot	2010	8-29	Mixed	1376[c]	22 (1.6)		
Cohen	2005	13	Mixed	436 (NR[a])	26 (6)[d]	1–22	12 (46)[e]

[a] *nd* no data

[b] 1 patient with renal hyperparathyroidism, 2 patients with tertiary hyperparathyroidism and 6 with primary hyperparathyroidism

[c] Multicentre French Study (n=9)

[d] Only 13 patients with renal/tertiary hyperparathyroidism

[e] Additionally, 6 patients (23 %) reported to have "partially functioning grafts"

predicts graft failure, and in two series no functioning autografts could be verified after 2 years of cryopreservation [73, 77, 78] (EL 3). Most authors believe that maintaining a cryopreservation program is unlikely to be successful except in selected institutions with extensive experience in parathyroid surgery. In specialized high-volume centres with higher incidence of reoperative procedures, the demand for cryopreservation may be virtual and cryopreservation effectively maintained with standard quality. However, in the majority of PTX performed for renal HPT, the demand for autotransplantation is extraordinarily small and diminishes over time. Besides relevant expenditure, costs and logistic challenges, cryopreservation maintenance is, in some countries, further complicated by extensive procedural, ethical and legal licensing terms. Nevertheless, in rare occasions when cryopreserved parathyroid tissue is successfully reimplanted, permanent hypoparathyroidism may be prevented [79]. Thus, cryopreservation is not necessary for the standard PTX procedures performed for renal HPT, despite distinct situations such as conceivable problems with access or intolerance to substitution, while it appears recommendable to inform the patient whether provision of cryopreservation is available (EL 3; RG C) (Table 7).

Surgery with and without utilization of intraoperative parathormone assay

When is it useful to perform parathyroidectomy with IOPTH for renal hyperparathyroidism? The role of intraoperative parathormone assay (IOPTH) monitoring for renal HPT remains undefined and is certainly not as clear in its potential for use in surgery as it is for primary hyperparathyroidism. Several studies report that a significant reduction in IOPTH levels compared to preoperative levels is highly predictive of postoperative success. Additionally, IOPTH is regarded by some as a valuable tool in intraoperative decision-making and to discern patients with both supernumerary, ectopic and fewer than four parathyroid glands removed [25, 80–83] (EL 1b-3).

In sharp contrast, other authors consider IOPTH of no or limited practical utility. Pitt et al. concluded that in 33 consecutive patients with refractory renal HPT, IOPTH levels did predict outcome but did not alter surgical management in any patient [84] (EL 3). Roshani et al. reported that IOPTH predicted biochemical resolution of hyperparathyroidism but failed to predict persistent hypoparathyroidism [85] (EL 4). Moore et al. found that although IOPTH levels predicted early outcomes, it did not predict long-term outcomes or likelihood of recurrence [86] (EL 3a). A common finding among IOPTH detractors is that predicting surgical failures with renal HPT persistence as well as permanent postoperative hypoparathyroidism was considerably more difficult than predicting surgical success regarding correction of renal HPT based on IOPTH levels.

An interesting purpose of IOPTH in renal HPT would be to detect, if a presumed total PTX is complete and, therefore, guide the decision to autotransplant or not. Unfortunately, the decision for simultaneous autotransplantation after TPTX cannot be based on IOPTH monitoring because the reliability in the prediction of early postoperative PTH status is insufficient [87] (EL 3).

In conclusion, IOPTH monitoring demonstrates high positive predictive values between 67 and 84 % of cure but poor negative predictive values between 25 and 47 % and, therefore, is of limited utility to guide PTX in renal HPT. It does not replace meticulous exploration of all potential sites of glandular hyperplasia, and its true cost-effectiveness remains to be seen (EL 3c; RG C).

Does the type of IOPTH assay influence accuracy of IOPTH results? The accuracy of IOPTH monitoring during surgery for renal HPT depends on the renal function and on the assay specificity. Patients with CKD have an excess of PTH fragments (as 7–84 PTH) that may cross-react with the iPTH assay [88] (EL 4). It was claimed that whole PTH assays would eliminate this cross-reactivity and therefore would be more accurate in predicting surgical outcome [89] (EL 4) (Table 8).

However, while some groups observed a more pronounced decline of IOPTH when using the whole PTH assay compared to the iPTH assay [90] (EL 4), other groups found that

Table 7 Recommendations regarding cryopreservation of parathyroid tissue after total parathyroidectomy for renal hyperparathyroidism

Statements Cryopreservation of parathyroid tissue after parathyroidectomy for renal hyperparathyroidism…	Level of evidence	Recommendation grade
…is routinely used by less than half of the units reporting results	4	C
…will be used for a delayed autotransplantation in only 1–5 % of patients	4	C
…will be useful to totally correct hypoparathyroidism in 25–75 % of patients	4	C
…should not be expected to function after 2 years of storage	3b	B
…should be abandoned when not performed in very large and experienced centres	5	D

Table 8 Studies analysing the performance of different IOPTH assays

Author	Year	Setting	Assay	Patients	Results
Haustein	2005	3HPT	1-84 iPTH[1a]	32	16 % change in operative management
Bieglmayer	2006	Renal HPT 3HPT	1-84 iPTH[1a] PTH[2]	35	PTH(1–84)[3] monitoring will avoid the need for unnecessarily prolonged surgical explorations
		Rec renal HPT	whole PTH (1-84)[3]		
Freriks	2010	Renal HPT 3HPT	1-84 iPTH[1b]	42	Sensitivity 95 % Specificity 8 %

IOPTH intraoperative parathormone assay, *HPT* hyperparathyroidism, *3HPT* tertiary HPT, *rec* recurrent, *1a* Roche Diagnostics on the Elecsys® 1010 (iPTH-R). Binds to amino acids 26–32 and 55–64, *1b* immunoluminometric STAT-intraoperative-intact PTH assay kit (Future Diagnostics, Wijchen, The Netherlands), *2* Nichols Institute Diagnostics on the Nichols Advantage® system (iPTH-N). Binds to amino acids 12–34 and 39–84, *3* Nichols Institute Diagnostics Bio-Intact PTH(1-84) assay (Bio-iPTH). Binds to amino acids 1–6

changing the type of PTH assay to whole PTH measurements did not significantly improve the sensitivity and specificity ratio of intraoperative PTH measurements [88] .

Criteria of IOPTH decline determining successful parathyroid surgery in patients with renal hyperparathyroidism The customary criteria of IOPTH decline determining success of PTX in renal HPT range from 50 to 90 % of preoperative levels (Table 9). The majority of studies are retrospective and emphasise the fact that applying the criteria used for primary hyperparathyroidism yields unacceptable low specificity. In a detailed Dutch report, the sensitivity at both 10 and 20 min was 100 % when using a 50 % intraoperative IOPTH decline as a criterion for cure but the specificity was extremely low (15 and 9 %, respectively), and therefore a 70 % decline from baseline was recommended to declare biochemical cure in surgery of renal HPT [88].

Postoperative metabolic complications following a successful parathyroidectomy for renal hyperparathyroidism

Concerns regarding mortality associated with parathyroidectomy in patients with renal hyperparathyroidism

The postoperative mortality (30 days) after PTX for renal HPT is reported to range between 1 and 3 % [2, 91, 92]. In a retrospective large cohort study, long-term relative risks of death among patients undergoing PTX for renal HPT were estimated to be 10 to 15 % lower than those of matched control patients not undergoing surgery. Median survival was 53.4 months in the PTX group and 46.8 months in the control group [92] (EL 2b). The North American renal data analysis mentioned earlier showed that PTX was associated with 2 % of postoperative 30-day mortality [2] (EL 3). The single most preventable cause of postoperative death is hyperkalaemia.

Table 9 Recent series assessing IOPTH to guide parathyroidectomy for renal hyperparathyroidism

Author	Year	Number[a]	Results	Criteria
Kim	2012	80	Cure predicted with sensitivity=86 % and specificity=60 %	>85 % decline at 40 min
More	2011	57	Is of no use in predicting long-term cure	"Standard criteria"
Pitt	2010	33	Did not alter the surgical approach in any renal HPT patient	
Kara	2010	42	Accurately predicts the completeness of resection	>90 % decline
Freriks	2010	42	Sensitivity=95 % and specificity=8 % Specificity could be improved to 50 % using a 70 % decrease criterion	50 % decrease at 10 min (Miami)
Gasparri	2009	211	IOPTH helpful but not essential except in reoperations	
Müller-Stich	2007	34	PPV 62.5 % and sensitivity=90.9 %	50 % decrease
			PPV 68.8 % and sensitivity=50.0 %	90 % decrease
			PPV 81.8 % and sensitivity=81.8 %	final value <100 pg/ml
Barczyński	2005	102	Impact on surgical decision-making in 15 % Overall accuracy of 100 %	2 samples Decrease >60 % of the baseline at 10 min

IOPTH intraoperative parathormone assay, *PPV* positive predictive value

[a] Number of patients assessed

Cardiac complications, acute hypocalcaemia, infection, pancreatitis and respiratory complications are other miscellaneous causes of mortality.

Concerns regarding cardiac morbidity associated with parathyroidectomy in patients with renal hyperparathyroidism

Conzo et al. compared TPTX (with or without autotransplantation) to medical treatment in a non-controlled trial. Postoperative cardiovascular events were observed in 18/30 (54 %) surgical patients and in 4/20 (20 %) medical patients, with a mortality rate of respectively 23.3 % in the surgical group versus 15 % in the control group. PTX was not associated with a reduced risk of cardiovascular morbidity, and survival rate was unaffected by surgical treatment [93] (EL 3).

Costa-Hong et al. concluded that PTX confers protection against future major cardiovascular events and death in selected patients with severe refractory renal HPT on haemodialysis. PTX was associated with a reduced incidence of major cardiovascular events and overall mortality in a cohort of 50 patients compared to 68 patients who continued medical treatment and maintenance haemodialysis without PTX. Multivariate analysis showed that variables no-PTX and age were associated independently with cardiovascular events [94] (2b).

Concerns regarding immediate postoperative hypocalcaemia following parathyroidectomy in patients with renal hyperparathyroidism

Protracted hypocalcaemia is the most common postoperative complication after PTX for renal HPT. Immediately after PTX, serum PTH and calcium concentrations decline abruptly and hypocalcaemia develops in 20 to 85 % of patients if it is not adequately prevented. However, severe or permanent hypocalcaemia requiring admission for longer than 1 week or readmission is uncommon [95] (EL 3).

Post-PTX hypocalcaemia is precipitated by several factors: increased deposition of calcium in bone (hungry bone syndrome), uncoupling of bone formation and resorption [96], failure of the parathyroid remnant (if any), and sometimes coexistent hypomagnesaemia [97, 98]. Young age (<36 years), low preoperative calcium levels (<10 md/dl), elevated alkaline phosphatase (>1.92 mmol/l) and elevated presurgery PTH (>150 pmol/l), and subperiosteal bone resorption were recognized as preoperative risk factors [95, 99, 100] (EL 3–4).

Postoperative hypocalcaemia is likely when preoperative calcium-phosphorus product is higher than 53 mg^2/dl^2 and/or when preoperative alkaline phosphatase concentrations are higher than 200 IU/l [101, 102]. Prophylactic calcium and calcitriol administration can be started before or immediately after surgery. Calcitriol (up to 2 μg) given during dialysis has been used for 5 days before the operation to prevent postoperative hypocalcaemia [30, 97] (EL 4). Some authors use preoperative bisphosphonates, if alkaline phosphatises is >500 UI/l to prevent postoperative hypocalcaemia [102] (EL 2b). Patients on peritoneal dialysis can be given intraperitoneal calcium therapy to control hypocalcaemia. Supplementation with 1 meq/kg/day of elemental magnesium should be started if serum magnesium concentration drops below 1.5 mg/dl [97] (EL 3).

The National Kidney Foundation of the USA published precise recommendations on how to monitor and treat immediate postoperative hypocalcaemia: The blood level of ionized calcium should be measured every 4 to 6 h for the first 48 to 72 h after surgery and then twice daily until stable. If the blood levels of ionized or corrected total calcium fall below normal (<0.9 mmol/l or <3.6 mg/dl corresponding to corrected total calcium of 7.2 mg/dl), a calcium gluconate infusion should be initiated at a rate of 1–2 mg elemental calcium per kilogram body weight per hour and adjusted to maintain an ionized calcium in the normal range (1.15–1.36 mmol/l or 4.6–5.4 mg/dl). The calcium infusion should be gradually reduced when the level of ionized calcium attains the normal range and remains stable. When oral intake is possible, the patient should receive calcium carbonate 1–2 g three times a day, as well as calcitriol of up to 2 mcg/day, and these therapies should be adjusted as necessary to maintain the level of ionized calcium in the normal range [7] (EL 5). Phosphate binders should be adjusted to maintain serum phosphate concentration between 3.5 and 5.0 mg/dl.

Concerns regarding permanent postoperative hypoparathyroidism after parathyroidectomy for renal hyperparathyroidism

Owing to the reporting heterogeneity of and varying definitions used in most surgical renal HPT series, the exact percentage of hypoparathyroidism is difficult to assess. In early series, its prevalence varied from 0 to 73 % but most commonly between 4 and 25 % [103]. Parathyroid autotransplant can fail and cause hypocalcaemia up to 2 years after surgery [104]. After successful kidney transplantation, reverses of the acidosis symptoms of hypocalcaemia can be exaggerated. The follow-up of patients with hypoparathyroidism should focus on maintaining serum calcium in the low-normal range and a calcium phosphate product of less than 55 mg^2/dl^2.

Concerns regarding persistence and recurrence of renal hyperparathyroidism after parathyroidectomy

Persistent or recurrent hyperparathyroidism occurs between 2 % and up to 30 % even in the hands of experienced surgeons when performing either subtotal PTX or TPTX+AT. Persistence is extremely rare, and recurrence is lower after TPTX

without autotransplantation. A detailed meta-analysis comprising the pre-cinacalcet era (1983–2004) scrutinized 53 publications with 501 patients reoperated for recurrent or persistent renal HPT. Inadequate prior exploration was the main cause of operative failures for both procedures, subtotal PTX (42.5 %) and total PTX+AT (34 %) [40] (EL 2) (Table 1).

Timing of parathyroid surgery prior to renal transplantation

For patients suffering from CKD, prevention of renal HPT is a high-priority therapeutic aim [105], and close follow-up with optimal active vitamin D supplementation, calcium and phosphorus normalization is desirable (EL 2). The ideal therapy remains normalization of the kidney function by transplantation (EL 1; RG A), but only a selection of patients will have access to transplantation, and many patients will only have access to transplantation after a long waiting time. During this time, renal HPT may worsen and become severe. Presently, no criteria define the optimal timing of PTX to complement medical therapy or to select those patients who benefit most from PTX. Moreover, whether patients who will never receive a renal transplant will benefit most from surgery remains a matter of debate [106].

Renal HPT in CKD can be responsible for several symptoms or organs failures [107], leading to a significant decrease of the life expectancy [105, 108]. Three categories of patients with renal HPT can be distinguished: dialysis patients without perspective of renal transplantation; dialysis patients with perspective of renal transplantation and patients with renal transplant. There is some clinical overlap in these three situations because most of the renal transplantation recipients will experience decreasing renal function over time, and some patients on the transplantation waiting list will never receive a renal graft.

Many dialysis patients suffer from hypertensive renal failure with potential deleterious effects on a renal graft. Most studies reported a decrease in blood pressure after PTX [48] (EL 3), suggesting the importance of an early treatment of persistent HPT, best prior to transplantation.

Life expectancy of transplanted patients is less than in general population, and cardiovascular disease is the leading cause of death following renal transplantation particularly from ischemic heart disease which is up to five times higher than in the normal population. Successful PTX is also associated with improvement of lipid profile. This reinforces the interest of early surgical treatment of HPT.

Despite better understanding of the pathophysiologic mechanisms of renal HPT and efforts to standardize management of patients with renal HPT [40], controversial opinions regarding different treatment options and their effectiveness prevail [107]. The two main problems are the variations of follow-up[5] of patients suffering from renal HPT either before or after renal transplantation and the management of the treatment with medical and surgical strategies.

Surgery in renal hyperparathyroidism with and without continuation of calcimimetics (cinacalcet)

Many published studies do not report the level of vitamin D [109] and use different thresholds to define hypercalcaemia, sometimes using ionized calcium, total calcium levels or corrected calcium levels [107]. Dialysis patients require intensive medical therapy [7] to compensate for hypocalcaemia, hyperphosphoraemia and lack of vitamin D; and nephrologists often hesitate to discuss surgery before a long-standing medical treatment history evolves refractory. The reasons are linked to a lack of standardized surgical management in some countries, the increased operative risk in this population with severe comorbidities [110, 111], and the increasing interest for cinacalcet [112]. Surgery in patients for renal HPT without cinacalcet was described in numerous studies and is in its performance not influenced by the specific medical treatment.

However, data regarding potential influence of cinacalcet relevant to the surgical procedure are scarce. Oral reports of increased fragility and capsule softness of the parathyroids when operated on cinacalcet cannot be found in published series. In a very recent 2-year follow-up study of cinacalcet treatment in renal HPT patients, a maximal and total decrease of parathyroid gland volume by 30 % was found alongside significant decrease of serum PTH levels, calcium, and phosphate. However, 10 out of 60 patients revealed a 30 % increase of maximal parathyroid volume after 2 years [113] (EL 3). From these changes no essential effect on surgical procedure may be expected, except possible challenge in preoperative parathyroid gland localization in ultrasonography and intraoperative parathyroid gland identification.

Another study in patients with tertiary HPT investigating effect of cinacalcet on intraoperative findings found that patients on the drug showed a steeper IOPTH decrease but without the need to modify IOPTH protocol. Cinacalcet treatment was also associated with increased weight of resected parathyroid glands, increased hungry bone rate and higher preoperative IOPTH levels, all of which represent more severe disease compared to patients operated on without cinacalcet. Continuation of cinacalcet did not adversely affect surgical cure rate [114] (EL 3).

Early versus late parathyroidectomy in tertiary (post-renal transplantation) hyperparathyroidism

After renal transplantation, poor follow-up of parathyroid function is not uncommon because systematic normalization of parathyroid function is predominantly expected after successful renal transplantation and other medical management problems appear to be of superior importance than monitoring

parathyroid function. However, progressive renal dysfunction potentially due to consequences of persistent hyperparathyroidism was described in tertiary HPT patients [115] (EL 2). Moreover, medical treatment with cinacalcet [112] is often used after renal transplantation, despite lack of approval for this indication in many countries [116]. Only 0.6–5.6 % of patients with successful renal transplantation will eventually require PTX [116].

Almost all parathyroid glands weighing more than 500 mg contain hyperplastic nodules [117, 118] (EL 4). Unlike diffuse hyperplasia, these adenomatous nodules involute rarely after restored renal function and may cause persistent HPT even if only one gland appears morphologically enlarged (EL 4). Parathyroid volume can be reliably evaluated by ultrasound, and nodular hyperplasia is likely in diameter >1 cm or volume >500 mm^3 [119] (EL 4).

After successful renal transplantation, PTH level decreases with a two-phase decline, first with a rapid drop until to 3 to 6 months [106, 109, 120, 121] and second with a low decline up to 1 year [109] (EL 1). Approximately 25 % of patients presented with persistent renal HPT after this time [97, 122, 123], and hypocalcaemia episodes were observed in 30 % of patients at 1 year and in about 10 % at 5 years according to a study on 1165 patients [109].

Many studies tried to define criteria [106, 109, 124, 125] for predicting the occurrence of persistent hyperparathyroidism despite successful renal transplantation, probably reflecting the severity of nodular parathyroid hyperplasia. The most commonly recognized criteria were prolonged renal failure before and after dialysis (EL 3), highly elevated levels of PTH (EL 3), serum calcium and phosphorus levels, and large parathyroid glands observed on ultrasonography (EL 4). Parathyroid glands are stimulated by renal failure at any level of impaired kidney function, prevailing as long as renal function stays compromised. Thus, patients with long-standing renal insufficiency carry a greater risk to develop severe renal HPT during dialysis, as well as persistent HPT after renal transplantation (EL 3). Likewise, longer waiting time on transplantation list is associated with increased the risk for requiring PTX after transplantation [121] (EL 3). Published series of patients transplanted with living donors [69] show a resolution of HPT for almost all patients (EL 2) due to the short duration of dialysis and reduction of severe HPT in this situation.

Post-transplant bone loss is very important during the first 6 months (about 1.5 % per month at lumbar spine) [126] (EL 3), mainly because of high PTH level, renal phosphorus wasting and vitamin D deficiency. In patients with successful renal transplantation, underlying persistent HPT may induce hypercalcaemia and hypophosphataemia impeding conventional medical therapy (phosphate binders, calcium supplements, vitamin D) and PTX is required (EL 3). Many studies showed an increase of bone mineral density after PTX, suggesting a benefit for PTX early after transplantation when parathyroid function does not normalize rapidly and prior to transplantation when renal HPT is severe with poor chances of spontaneous restoration after transplantation (EL 3).

Generally, PTX in renal HPT should be performed by specialized surgical teams with a standardized perioperative management [40, 110, 127] to avoid persistent or recurrent HPT (EL 2), with minimal morbidity and with a postoperative uneventful course (EL 3) by means of careful surveillance, prevention and management of the expected postoperative hypocalcaemia following PTX.

It was demonstrated that patients who underwent PTX after successful renal transplantation suffered from more severe HPT before transplantation than non-PTX patients [106]. Pre-transplantation PTH levels of ≥500 pg/ml during 1 year before transplantation [22, 125] predicted persistent HPT necessitating PTX (odds ratio=28 for undergoing PTX in case of PTH >500 pg/ml 1 year before transplantation [106]), contrary to patients with PTH levels <500 pg/ml (EL 3). Serum calcium level of >9.5 mg/dl [106, 125] was also a significant risk factor for necessary PTX after transplantation (EL 4) but was less specific than PTH levels (OR=6 for undergoing PTX in case of Ca >9.5 mg/dl 1 year before transplantation [106]). Some authors claim PTH of >800 pg/ml and serum calcium of >10.4 mg/dl despite medical therapy represent an absolute indication for PTX before transplantation due to the high rates of persistent HPT after transplantation in these patients [107] (EL 4).

Also, post-transplantation PTX exposes to a risk of declining renal function due to immediate haemodynamic effect of PTH level drop [128–130] (EL 2) and to hypercalciuria secondary to medical treatments of hypocalcaemia. Patients should be operated after efficient vitamin D supplementation in order to avoid severe postoperative hypocalcaemia [115] (EL 3). However, hypercalcemia before PTX may prevent vitamin D supplementation in some. Patients with higher pre-PTX PTH levels will experience the greatest PTH decline any may experience greater decrease of renal function [128–130] (EL 3). Severe persistent renal HPT is associated with hypercalciuria. Nephrocalcinosis is an independent risk for chronic allograft nephropathy knowing that nephrocalcinosis decreases 12-year allograft survival from 75 to 48 % [131] (EL 3).

Cinacalcet is an alternative to PTX in post-renal transplantation HPT as well, but its effects are not evidenced. Its introduction decreases renal function, which is reversible after cessation, suggesting the same haemodynamic effect like PTX. Some studies observed a regression of parathyroid gland volume on ultrasonography with cinacalcet [132, 133] (EL 3), but its effect on urinary calcium excretion is not known and studies reported contradictory results (unchanged, increased or reduced calcium excretion) [107]. Above all, cinacalcet is only approved for treatment of renal HPT and is very expensive

[134] (EL 2), rendering PTX as primary effective and long-term option for transplanted patients. Cinacalcet in these patients should be reserved for very few patients with hypercalcemia and no possibility of PTX (previous parathyroidectomy, increased operative risk) (EL 3).

During 1 year after kidney transplantation, maximal regression of hyperplastic parathyroid glands develops (EL 3), but earlier PTX may lessen the detrimental metabolic effects in case of persistent HPT. Therefore, a delay of 3 months should be considered in case of severe HPT and 1 year in the case of persistent HPT [106, 109, 116, 135] (RG C). A serum calcium level greater than 11.5 mg/dl, unexplained renal function deterioration or a progressive bone mineral density loss underscore arguments for PTX (RG C). Even if moderately persistent HPT may spontaneously resolve in some patients, the time allowing involution of the parathyroid glands risks increased cardiac, bone and graft complications. Because of potential cardiovascular, bone and graft deterioration, PTX should be discussed not later than 1 year after transplantation (RG C), although several studies demonstrated a longer latency before PTX [106, 129, 135, 136] (EL 2).

The fundamental negative consequence of well-managed PTX remains a rapid and partially reversible decline of renal function. Significant increase of serum creatinine from 7 to 35 % following PTX in patients with tertiary HPT occurs mainly in the early postoperative phase, while long-term follow-up revealed stabilization of renal function within 12 months post-PTX without significant differences compared to post-renal transplantation patients not submitted to PTX [128–130] (EL 2). The degree of early postoperative renal impairment represented by increase of GFR was in tendency prone to be higher in TPTX+AT compared to subtotal PTX [129], and a more pronounced decrease of GFR post-PTX was associated with higher preoperative PTH [130] (EL 2b). In conclusion, patients with underlying renal HPT should be evaluated for severity and perspective of successful medical treatment of renal HPT prior to PTX.

Whenever conservative treatment of renal HPT is critical and future PTX conceivable, PTX should ideally be performed prior to renal transplantation with stable metabolic condition. In patients who manifested tertiary HPT, the extent of PTX should be conservative and subtotal PTX appears preferable. Close surveillance, immediate correction of metabolic or renal function derangement during the first 2–3 postoperative months, and long-term follow-up of renal function and parathyroid function is mandatory (EL 2b, RG C).

Extent of surgery in persistent HPT after renal transplantation

Until very recently, the recommended surgical procedure for patients with HPT after renal transplantation was similar to that for patients with renal HPT under dialysis, a form of subtotal resection of all parathyroid tissue (usually subtotal PTX or total PTX+AT), because of the increased risk of recurrence if more parathyroid tissue is left in place [34, 116] However, despite recent reports suggesting that hypoparathyroidism, even if definitive, is manageable in patients with a good renal function [66, 137–139], it seems that the current trend is to be less aggressive for three main reasons:

1. After PTX, there is a constant decline in renal function, probably due to haemodynamic effects of PTH on the preglomerular and efferent arterioles [49]. It should be noted, however, that current studies suggest that the graft survival is not decreased by PTX [47, 132, 135, 140]. It seems that the risk and intensity of the decrease of renal function are highly dependent on the severity of HPT (high level of PTH) and probably on the slope of decline, and therefore avoiding/reducing post-PTX hypoparathyroidism and hypocalcaemia could reduce the risk of significant decline of the renal function [129] It is therefore expected that a less aggressive parathyroid resection should lead to a less important decline in PTH and therefore to a decreased risk of decline of renal function.
2. In the presence of a good renal function, the hyperplastic parathyroid glands will continue to undergo apoptotic changes leading to a reduced parathyroid cell mass [109, 120, 125], and therefore it does not seem absolutely necessary to obtain a "very" low PTH level immediately after PTX because one can expect a spontaneous decrease of PTH levels if the autonomous nodules have been removed. This suggests that resecting the more abnormal parathyroid glands could be sufficient to obtain the main clinical benefits of normalizing the calcium level.
3. There are current reports of different groups suggesting that a "less than subtotal" PTX could lead to similar rate of cure in a significant proportion of patients (around 30 %) when this rate of cure is indicated by the normalization of the calcium level [51, 131, 141].

In conclusion, a less than subtotal PTX could be an acceptable option in a subset of patients with persistent HPT after renal transplantation. It should be noted that most surgeons suggesting this approach (in particular, the Wisconsin team that reports the largest series of patients [141]) still report performing a systematic bilateral cervical exploration, and it is therefore not known whether a limited approach directed by preoperative imaging studies and/or IOPTH could lead to similar good results.

Summary

Despite considerate improvement of medical treatment and dialysis regimen in patients with CKD, renal hyperparathyroidism develops frequently. Increase of CKD may be

expected with an increasingly older population and critical illness survivors due to continuous medical advances. The disparity of available and demand for donor organs is expected to spread. Opportunity to preclude manifest and retrievable renal HPT in CKD is probably narrow because any degree of renal insufficiency functions as parathyroid stimulus; and only full restoration of renal function, mainly renal transplantation, will provide cure. Therefore, parathyroid surgery for renal HPT will continue to be required.

The primary treatment of CKD and developing renal HPT is medical. Administration of active vitamin D analogues, calcium, phosphate binders and cinacalcet aims to control metabolic homeostasis; however, only timely renal transplantation is expected to cure renal HPT. The majority of patients with renal HPT require sustained control of PTH, and earlier decrease of PTX rates with the advent of cinacalcet remained temporary, today about 1–2 % will undergo PTX [5].

The review of the actual literature revealed contradictory evaluation regarding benefit of PTX from surgical and nephrology perspectives. Restraints to refer patients for surgery from nephrology perspective may be explained by the low-level evidence of surgical data. Actual larger multicentre RCT data with long-term follow-up from surgical perspective are lacking. Presently, accepted criteria to refer renal HPT patients to surgery are severe HPT, hypercalcaemia, hyperphosphataemia, intractable calcium-phosphorus product and calciphylaxis as well as medically refractory and progressive renal HPT. The role of parathyroid surgery in determining the best clinical practice for renal HPT remains presently unresolved at low-level evidence.

Within the surgical literature assessing outcomes of PTX for renal HPT, determination of the optimal extent of resection is futile. While evidence for standard bilateral exploration and identification of all four parathyroids appears convincing (EL 1–2, RG A), evidence levels of present studies available to compare the four standard procedures of subtotal PTX, TPTX with and without AT, as well as standard bilateral cervical thymectomy in all patients, show only exceptional EL 1, few EL 2 and the majority EL 3 and 4 making general recommendations impossible. Present data show best evidence for subtotal PTX and TPTX+AT and standard cervical thymectomy in regard to provide good postoperative success with satisfactory avoidance of permanent hypoparathyroidism (Table 1). Long-term superiority of TPTX+BCT without AT in regard to prevent recurrence remains at EL 3–4.

The role of IOPTH during surgery for renal HPT remains inconclusive in regard to costs and benefit evaluation. No published data of good evidence level identify IOPTH success criteria to pertain prognostication of postoperative PTH levels. However, evidence for reliable exclusion of persistent HPT with IOPTH is good. Recommendations to use IOPTH in surgery for renal HPT are presently RG D.

The indication to surgery and the optimal timing and surgical procedure performed for tertiary HPT is also debated. Pertinent literature provides data EL 2–3 for subtotal PTX in tertiary HPT once renal HPT persists or worsens and hypercalcaemia occurs or renal function appears affected.

The review of the literature on management of renal HPT with reference to the role surgery identified several limitations to emerge with reliable recommendations today. Mainly, the majority of studies available are of lower evidence levels and include patients with considerate heterogeneity. This applies also to the spectrum of indication to PTX and the procedures performed. Frequently in the surgical series, specific data or surgical details are missed, and long-term follow-up data are rarely provided. Studies evaluating cost-effectiveness and benefit or disadvantages from surgical intervention for renal and tertiary HPT are additionally hampered by low numbers, undetermined medical influence and internationally divergent health system with respective guidelines.

Nevertheless, specialized endocrine surgery offers efficient metabolic correction of renal HPT with very low surgical morbidity. The summarized data in this review reveals that infrequently surgical treatment remains the last choice, a negative selection of severely comorbid patients with advanced intractable cardiovascular manifestation and calciphylaxis are offered surgery too late to benefit. From the surgical perspective, earlier cooperation between nephrologists and endocrine surgeon in the management of renal HPT is desirable and cooperative studies without industrial influence are needed to establish interdisciplinary consented guidelines for the role of surgery in renal HPT.

Recommendations for clinical practice

- Level 5 evidence defines criteria for PTX in renal HPT at PTH levels exceeding nine times the upper normal range or >880 pg/ml, sustained hypercalcaemia, hyperphosphataemia and elevation of calcium-phosphorus product (RG D).
- Level 3 evidence suggests PTX in renal HPT with severe symptomatic bone affection or calciphylaxis (RG C).
- Level 2b evidence suggests very high and very low levels of PTH to be associated with increased cardiovascular events in medically treated renal HPT patients; however, implication of these findings to postsurgical PTH levels and outcome are lacking (RG B).
- Level 3 evidence data imply increased mortality rate and hospitalization for hypocalcaemia within 30 days postoperative to PTX. Strict preoperative selection of patients with specific reference to cardiovascular risk factors and intensified postoperative surveillance emerge necessary (RG B).
- Level 3 evidence supports preoperative localization of parathyroid glands in primary PTX restricted to cervical ultrasound and level 2 evidence for enhanced localization

utilizing sestamibi-SPECT scintigraphy or other modalities in reoperative renal HPT (RG B).
- Levels 1–3 equally favour TPTX+AT and subtotal PTX as standard surgical procedure in regard to outcome of successful elimination of renal HPT and median recurrence rates at 7 % and hypoparathyroidism at 2 %, respectively (RG B).
- Level 3 evidence supports benefit of routine cervical thymectomy with PTX in regard to decreasing persistence and recurrence rates of renal HPT (RG B).
- Level 3 evidence does not support the need for cryopreservation in standard PTX for renal HPT (RG C).
- Level 1b-3 evidence suggests effective prediction of operative success utilizing IOPTH (RG B). Contrarily, levels 3–4 evidence demonstrates no influence of IOPTH on surgical strategy and prediction of postoperative PTH levels (RG D). Levels 3–4 evidence support IOPTH success criteria of 70 % decrease of preoperative PTH level and/or normal range (RG C).
- Levels 3–4 evidence supports routine and intensified postoperative supplementation of calcium and vitamin D following PTX (RG C).
- Level 4 evidence favours PTX prior to renal transplantation in with persistent or high probability of developing renal HPT (RG C).
- Level 3 evidence supports subtotal PTX (or a more conservative approach in a subset of patients) in tertiary HPT with intensified surveillance of renal function and calcium levels postoperatively, especially during the first 2 months (RG C).
- Level 4 data do not demonstrate disadvantages performing PTX under the influence of cinacalcet (RG C).

Compliance with ethical standards This article does not contain any studies with human participants or animals performed by any of the authors.

Conflicts of interest None

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