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Surgical Treatment of Secondary Hyperparathyroidism due to Chronic Kidney Disease

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It is a great honour for me to have this opportunity to present a review about surgical treatment of secondary hyperparathyroidism (2HPT) due to chronic kidney disease (CKD). Uppsala is a historical place concerning the parathyroid gland, because it was here that Ivar Sandström in 1877 initially discovered the small organs, Glandulae Parathyroideae, existing around the thyroid gland in human beings. This finding led to intensive studies of the parathyroid glands, focusing on their histopathology, pathophysiology, clinical diagnosis, and medical and surgical treatment (1) and investigations are still continuing in Uppsala today. I had the privilege to stay in Uppsala during 1989 to study the surgery and pathology of parathyroid glands and it was a pleasure to share clinical and basic research about these small and charming organs with my colleagues in Uppsala.

Background and frequency of parathyroidectomy in patients with chronic kidney disease

It is well known that chronic kidney disease (CKD) induces 2HPT, which is one of the serious complications that influence mortality and quality of life in patients with CKD. Parathyroidectomy (PTx) can most successfully decrease a high serum level of parathyroid hormone (PTH), and the role of endocrine surgery is very important. In this review I will present our strategy and outcomes of surgical treatment for 2HPT.

There are many haemodialysis patients in Japan and they have gradually increased in number, reaching approximately 250 thousand at the end of 2004, which corresponds to almost two thousand per million (2, 3). In our country we have only a small opportunity to perform kidney transplantation (about 900 cases/year) and CKD-patients have to continue on haemodialysis for a long time and almost 25% will have this treatment for more than 10 years (2).

The Japanese Society for Dialysis Therapy reported that among patients in whom the duration of haemodialysis was more than 10 years the frequency of PTx was about 10%, and after 20 years of dialysis it was about 30% (4). At the end of 2004 totally 10,216 cases, that is almost 6% of haemodialysis patients, had undergone PTx since this treatment was begun (2). Between June 1973 and December 2005 altogether 1932 patients underwent PTx for 2HPT in our department, and now we are performing about 20% of all PTxs for 2HPT in Japan.

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Table 1. Parathyroidectomy (PTx) by country at baseline and prospectively (reference 5)

Country	Baseline Prevalence (%)	Follow-up Incidence (/100 patients-year)
France (N=981)	14.3	1.8
Germany (N=908)	6.0	1.0
Italy (N=869)	5.0	0.9
Japan (N=2784)	4.1	0.6
Spain (N=936)	5.7	1.5
UK (N=897)	9.2	1.5
U.S. (N=9861)	4.0	0.5

Recently, the Dialysis Outcomes and Practice Pattern Study (DOPPS) evaluated the situation and quality of hemodialysis therapy in European countries, the United States of America (USA) and Japan. The study presented the frequency of PTx among haemodialysis patients in each country (Table 1). Compared with European countries, the frequency in Japan was lower (5).

Pathogenesis, histopathology, and pathophysiology of 2HPT

Pathogenetic factors of 2HPT resulting from CKD are presented in Table 2. The most important ones are hypocalcaemia, hyperphosphataemia, and deficiency of active vitamin D (6). Recently it has been confirmed that hyperphosphataemia, i.e. phosphate retention, acts directly on parathyroid cells and stimulates PTH secretion and synthesis as well as proliferation of the parathyroid cells (7). Moreover, it has been shown that in patients with CKD the expression of vitamin D receptor (VDR) and calcium sensing receptor (CaR) in parathyroid cells is diminished (8, 9), contributing to skeletal resistance to PTH due to diminished expression of PTH/PTHRP receptor in osteoblasts, overexpression of osteoprotegerin, and accumulation of 7–84 PTH fragments and some kinds of uraemic toxins (10). These factors form a very complicated system and the role of each factor has not been clarified.

The characteristic histopathological findings in 2HPT can be summarised as asymmetrical enlargement, nodularity and an increased number of oxyphilic and transitional oxyphilic cells (11). The pattern of parathyroid hyperplasia in 2HPT is classified into four categories, namely diffuse hyperplasia, early nodularity in diffuse hyperplasia, nodular hyperplasia and a single nodular gland (11). In our group we have evaluated the relationship between the glandular weight and hyperplastic pattern. When the glandular weight increases, the hyperplastic pattern is transformed from diffuse to nodular hyperplasia. If one gland exceeds 500 mg in weight, the gland almost always develops nodular hyperplasia (12). Based on these findings we hypothesised that in CKD patients polyclonal diffuse hyperplasia is transformed into nodular hyperplasia with several nodules, in which parathyroid cells proliferate monoclonally with a high growth potential (12–16). We have speculated

Table 2. Pathogenesis of secondary hyperparathyroidism due to chronic kidney disease

1. Hypocalcaemia
2. Hyperphosphataemia, phosphate retention
3. Deficiency of active vitamin D
4. Decreased expression of vitamin D receptor (VDR) in parathyroid cells
5. Diminished expression of calcium sensing receptor (CaR) on parathyroid cells
6. Skeletal resistance to PTH

that some kinds of genetic disorders occur in diffusely hyperplastic glands and the cells proliferate monoclonally, and the cells then constitute a nodule. We are very interested to know what kinds of genetic hits are involved in nodular hyperplasia in patients with CKD. In sporadic primary adenomas, some kinds of genetic disorders have been reported (16, 17). There are an overexpression of PRAD1/cyclin D1 induced by a DNA gene rearrangement of the PTH gene and a point mutation of the MEN 1 suppressor gene. Frequent loss of heterozygosity has also been observed on chromosomes 6q, 11q, 13q, 15q and X. However, in 2HPT deletion or point mutations of the MEN type 1 gene and overexpression of PRAD1/cyclic D 1 due to PTH gene rearrangement may not be the major genetic abnormality responsible for tumourigenesis (14, 17). We have found that different genetic hits seen in sporadic primary adenomas may occur in nodular glands in 2 HPT, but it is not yet clear what kinds of genetic disorders underlie these manifestations (14, 16, 17).

Moreover, it has been confirmed that expressions of VDR and CaR in parathyroid cells are diminished in cells constituting nodules (8, 9). This means that cells constituting nodules are resistant to calcitriol and hypercalcaemia. We therefore hypothesized that when at least one parathyroid gland progresses to nodular hyperplasia in patients with 2HPT, the patients may be refractory to medical treatment (12, 18).

To test our hypothesis, we performed two clinical studies. We evaluated the hyperplastic pattern in 179 patients with advanced 2HPT refractory to Maxacalcitol (OCT), a vitamin D analogue. The patients then underwent PTx at our department. We found that all patients had at least one nodular gland and the mean number of nodular glands per patient was 2.9. We also evaluated the relationship between the response to OCT treatment and the volume of the largest gland as estimated by ultrasonography (US). The conclusion drawn was that the volume of the largest gland as estimated by US could be a useful predictor of the response to OCT in patients with moderate or severe 2HPT. In patients whose glandular volume was less than 300 mm^3, the OCT was significantly more effective compared with that in patients whose volume was more than 300 mm^3 (19). These results indicated that when a patient has at least one nodular gland, 2HPT may be resistant to medical treatment, including OCT.

Volume of parathyroid gland estimated by ultrasonograpy

By US it is possible to detect swollen parathyroid glands and measure three dimensions, and to estimate the volume of glands by using the formula ($a*b*c*\pi/6$) (a,b,c: dimensions of the gland) (20). We have evaluated the relationship between the volume as estimated by US and the glandular weight measured at surgery, and found a significant correlation. Actually, the volume of the glands was underestimated by US and a volume of 330 mm^3 was equivalent to a weight of 500 mg as measured at surgery (21). Thus, when the gland has a volume of more than 300 mm^3 or a largest diameter of more than 1 cm, it is likely that the gland represents nodular hyperplasia. In these patients, 2HPT may be refractory to medical treatment, and PTx should be required (22–24).

Medical treatment of 2HPT

The aim of medical treatment of 2HPT is to prevent progression from diffuse to nodular hyperplasia. Thus to avoid progression of 2HPT, pathogenetic factors should be sought and eliminated (25). However, in some patients the parathyroid disorder advances in spite of adequate medical treatment. To control hypocalcaemia, dialysate containing a high calcium concentration is used and calcium-containing phosphate binders, i.e. calcium carbonate or calcium acetate, are administered. To control hyperphosphataemia, it is important to remove phosphorus by adequate haemodialysis, limitation of dietary phosphate intake, and administration of phosphate binders, e.g. calcium carbonate, calcium acetate or sevelamer hydrochloride, in which neither calcium nor aluminum is present (26). However, it is often difficult to control hyperphosphataemia by such medical treatment. Usually calcitriol or a calcitriol analogue, e.g. 1a-(OH)-D3, is given orally to prevent progression of 2HPT (25).

When 2HPT advances, usually calcitriol and a vitamin D analogue, e.g. maxacalcitol or falecalcitriol, which are available in Japan, and 1-alpha-OH-D2 and 19Nor-1,25(OH)2 D2 (Zemplar) can be used (27–32). However, hypercalcaemia and hyperphosphataemia are readily induced by these medicines and sometimes 2HPT is resistant to these drugs.

New medicines, (calcimimetics, Cinacalcet hydrochloride, Sensipar) have been tried in the USA and European countries. These drugs act on CaR of the parathyroid cells as calcium agonists and suppress PTH secretion remarkably without inducing hypercalcaemia or hyperphosphataemia (33). In Japan, clinical studies have been initiated to evaluate these new drugs.

Based on the clinical evidence obtained, the Kidney Foundation of the USA proposed that the Kidney Disease Outcomes Quality Initiative (K/DOQI) should issue clinical practice guidelines for bone metabolism and disease. The guidelines recommend that in haemodialysis patients the serum calcium level should be kept between 8.4 and 9.5 mg/dL and the serum phosphorus level between 3.5 and 5.5 mg/dL, the calcium- phosphorus product should be less than 55, and intact PTH

Table 3. Clinical symptoms of advanced renal hyperparathyroidism

1. High bone turnover, osteitis fibrosa bone pain, arthralgia, bone loss, skeletal deformity, fractures
2. Ectopic calcification vascular and valvular calcification, tumour calcinosis, calciphylaxis, calcification in the lung, intestine and stomach
3. Neuromuscular and psychiatric symptoms muscular weakness, gait disturbance, irritability, sleeplessness, loss of concentration, depression etc.
4. Anaemia resistant to erythropoietin, malnutrition, itching, cough
5. Heart failure (DCM- like heart)

level should be controlled between 150 and 300 pg/mL, mainly to avoid ectopic calcification and cardiovascular complications (34).

Clinical symptoms of 2HPT

In Table 3 the clinical symptoms of 2HPT are shown. Advanced 2HPT may induce bone disease, ectopic calcification, neuromuscular and psychiatric symptoms, anaemia, heart failure, and dilated cardiomyopathy-like heart (DCM-like heart) (35–38). Neuromuscular and psychiatric symptoms are usually more severe in 2HPT than in primary HPT. Patients frequently complain of muscular weakness, irritability, sleeplessness, itching, cough, etc. 2HPT not only disturbs the quality of life but also influences mortality. Ectopic calcification of vessels and heart valves leads to cardiovascular complications and contributes to a high mortality (39, 40). A high calcium-phosphate product, hyperphosphataemia and diminished Fetuin A have been proposed as pathogenetic factors of ectopic calcification of vessels in patients with CKD (41).

Surgical indications

The K/DOQI guidelines proposed that PTx should be recommended in patients with severe HPT (intact PTH level over 800 pg/mL) associated with hypercalcaemia and/or hyperphosphataemia (34). An additional indication for PTx is the presence of calciphylaxis with an elevated PTH level (>500 pg/mL), as calciphylaxis is a very serious complication in CKD patients (34). In patients who underwent PTx for advanced 2HPT in our department, calciphylaxis was very uncommon (42, 43). According to the algorithm published by the Association of European Dialysis Transplantation (EDTA), the size of the parathyroid gland is one of the main factors to consider among the indications for surgery (44).

Table 4 presents our surgical indications for advanced 2HPT (35–38). Fundamentally our indications are the same as these recommended by K/DOQI and EDTA.

1. A high PTH level (intact PTH level >500pg/mL)
2. Detection of an enlarged gland (volume of the largest gland more than 500 mm^3 or diameter larger than 1 cm)

Table 4. Our indications for parathyroidectomy

1. High level of intact PTH (>500 pg/mL)
2. Detection of enlarged parathyroid glands by ultrasonography (volume of the largest gland >500 mm^3 or diameter >1cm)
3. Hypercalcaemia (> 10.2mg/dL) and/or hyperphosphataemia (>6.0 mg/dL)
Absolute indications:
1. High bone turnover, osteitis fibrosa on X-ray
2. Severe symptoms
3. Progression of ectopic calcification
4. Calciphylaxis
5. Progression of bone loss
6. Anaemia resistant to erythropoietin
7. Dilated myocardiopathy (DCM) – like heart

3. Hypercalcaemia (s-Ca>10.2 mg/dL) and/ or hyperphosphataemia (s-Pi>6.0 mg/dL) .

Patients who have these three factors are recommended to undergo PTx. When patients have these three factors and also one of the symptoms listed in Table 4, PTx should absolutely be performed. We really emphasise that the volume or size of the largest gland is a very useful factor in deciding surgical indications.

Surgical procedures for 2HPT

There are many variations of surgical procedures in PTx for 2HPT. They include total PTx without autotransplantation, subtotal and total PTx with autotransplantation (45–47). We prefer total PTx with a forearm autograft, since in the event of recurrence parathyroid tissue can be removed from the forearm less invasively and be performed under local anaesthesia. Moreover, the function of grafted parathyroid tissue can be recognised by measuring PTH levels at grafted and non-grafted sites, and the parathyroid function can be easily controlled by changing the amount of parathyroid tissue used for the autograft (35–38, 45, 47).

In our series, the frequency of graft-dependent recurrent HPT gradually increased after PTx and reached 21.4% ten years after PTx. These patients required reoperation with removal of autografted tissue from the forearm (48). Recurrence cannot be neglected in 2HPT, especially in Japan, as the patients have to continue on haemodialysis for a long time after the initial PTx and we have to avoid adynamic bone disease induced by a low PTH level. We therefore believe that total PTx with a forearm autograft is a suitable operative procedure in 2HPT patients, at least for those who continue with haemodialysis for a long time (35–38, 45, 47). Indeed, more than 90% of the institutes in Japan have accepted this surgical procedure for 2HPT.

To avoid persistent and/or recurrent HPT, we need to concentrate on detecting

and removing all parathyroid glands at the initial operation. However, this is often difficult to accomplish, as the parathyroid glands are very small organs and often are located ectopically, moreover supernumerary glands are sometimes present.

Our operative strategy for 2HPT is as follows. At the initial and any subsequent PTx, we routinely perform preoperative image diagnosis, i.e. US, CT-scan, MRI, and 201TlCl or MIBI scintigraphy for localization of glands, especially to detect ectopic and supernumerary glands. To avoid missing supernumerary glands, we routinely excise the fat tissue surrounding the glands, remove as much of the thymic tongue as possible bilaterally, and open the carotid sheaths bilaterally to detect any glands around the carotid artery, trachea and oesophagus (35, 36).

Image diagnosis

Ectopic parathyroid glands may be pitfalls in attempts to detect all parathyroid glands. Therefore, special attention should be paid to seeking for ectopic glands, e.g. mediastinal, intrathyroidal, and undescended glands. Preoperative image diagnosis is effective in detecting these ectopic glands, and scintigrams can effectively identify parathyroid glands, especially those located in the mediastinum. US is very effective for detecting glands in the area surrounding the thyroid lobes and those located within the lobes. Glands weighing more than 200 mg can be recognised by US. Thus, we recommend a combination of US and scintigraphy preoperatively and if we cannot detect enlarged parathyroid glands by US or CT in the neck, we should look for mediastinal parathyroid glands by MIBI (Tc 99m sestamibi) scintigraphy before surgery (49, 50).

Supernumerary parathyroid glands in 2HPT

In 2HPT, the pathophysiological stimuli influence all parathyroid tissue and fundamentally all glands are hyperplastic. Thus, supernumerary glands are more important in 2HPT than in primary HPT. In our series, the frequency of supernumerary glands detected at the initial PTx was 14.4%. Adding the supernumerary glands that were removed at re-operation, the frequency was 16.1%. Moreover, when we added cases with supernumerary glands that were clinically suspicious, the frequency became 18.4% (51). Our findings are in agreement with those reported by other authors (52). Supernumerary glands can be classified into the rudimentary or split type and the proper type (53). In our series, the frequency of the rudimentary or split type was 24.8%. It was not so difficult to detect these types of glands at the operation, as they were usually located in the tissue surrounding the original glands. The frequency of the proper type was 76.0%. The most common location of these glands was in the thymus (46.2%). Thirty-two out of 48 glands were microscopically identified in thymic tissue and thus detected after operation (51). Sometimes parathyroid nests were identified microscopically in thymic tissue. In about 25% the inferior glands were located in the thymic tongue. Thus removal of thymic tissue from the neck incision is very essential to avoid missing glands. In

our experience the second frequent location of supernumerary glands was the left paratracheal – paraoesophageal area, and therefore a careful search for these glands by opening the carotid sheath is recommended (51). Other locations of proper type of supernumerary glands were in the mediastinum, intrathyroidal, in the tissue surrounding the carotid sheath, and in undescended glands (53). Glands of these types are often causes of persistent and recurrent HPT.

Pathological confirmation and intraoperative PTH assay

In cases of 2HPT, it is very important to remove all parathyroid glands and tissue at the initial operation. To ensure the removal of all parathyroid glands and/or tissue, histological confirmation during surgery and intraoperative PTH assay are useful (54). Our pathologists have a selected stamp method for the histopathological examination, and we can obtain the answer within 10 to 15 minutes. The accuracy of this method has been almost 100%. We have recently introduced intraoperative PTH assay by measuring 1–84 PTH. The half-life of 1–84 PTH is only some minutes and this method is less influenced by uraemia. Our preliminary results seem promising.

Autograft of parathyroid tissue

We found that graft-induced recurrent HPT was significantly more frequent when nodular hyperplastic tissue was autografted than when diffusely hyperplastic tissue was transplanted (15, 35). Thus to avoid recurrence, it is very important to choose diffusely hyperplastic tissue for autografting. Our autograft procedure is based on Well's report (55). Resected parathyroid glands are preserved in cold saline immediately after their removal. After pathological confirmation, we take 1x1x3 mm slices from diffusely hyperplastic tissue for autografting. We make pockets in the brachioradial muscle of the forearm without A-V fistula, put a piece of parathyroid tissue in each pocket, and tie the muscle using non-absorbable thread. The same procedure is carried out 30 times and totally about 90 mg parathyroid tissue is autografted (35).

Calcium replacement therapy after parathyroidectomy

After PTx the serum calcium level will drop rapidly, as autografted parathyroid tissue does not begin to function until 2 to 3 weeks after the operation. Usually patients have severe hungry bone syndrome, and calcium and phosphorus move to bone from the blood and pronounced bone formation becomes evident (47, 56). Calcium replacement therapy is initiated when the serum calcium level decreases to below 8.0 mg/dL. If the alkaline phosphatase (Al-p) level before PTx is more than 500 IU/L, this indicates that the patient has severe hungry bone syndrome, and calcium replacement is given both intravenously (1200 mg/day) and orally (alphacalcidol 3 ug/day and calcium carbonate 12 g/day). If the Al-p level is less

than 500 IU/L, calcium supplementation is only given orally. We adjust the dose of calcium and vitamin D to keep the serum calcium at a level of 8–9 mg/dL.

Medical treatment after PTx is important to prevent recurrent HPT and adynamic bone disease. The physicians have to check the serum calcium, phosphorus and PTH levels. When the intact-PTH level is less than 100 pg/mL, the serum calcium level should be kept within 8–9 mg/dL, and when the intact-PTH level exceeds 100 pg/mL the serum calcium should be kept between 9 and 10 mg/dL.

Functioning of autografted tissue

Functioning of grafted parathyroid tissue can be recognised by measuring PTH levels from both antecubital veins. If the PTH gradient between the grafted and non-grafted arm is over 1.5, this indicates that the autograft is functioning (47). The technique for grafting parathyroid tissue has improved and today we can assume that almost all patients will have a functioning graft with our procedure (48). Until a decade ago, we routinely cryopreserved parathyroid tissue for possible re-transplantation, but we have now abandoned this procedure as we have never needed to transplant cryopreserved tissue in recent years.

Clinical improvement by parathyroidectomy

The effect of PTx is dramatic. Symptoms such as bone and joint pain, irritability, sleeplessness, itching, and muscle weakness are quickly relieved by successful PTx (35, 36). The bone mineral content in trabecular bone measured by X-ray absorptiometry increases about 10% after PTx, but in cortical bone the increase is smaller (2–3%) (57). Biopsy has shown that bone resorption is immediately suppressed and bone formation is accelerated after PTx (58).

Recently it has been found that patients who have suffered from DCM-like heart, which is defined as a diffusely disturbed left ventricular function without ischaemic heart or valvular disease, are dramatically improved after successful PTx (59). Today PTx in these patients is performed under local anaesthesia because of the high risk associated with general anaesthesia. Unfortunately, vascular and valvular calcification can usually not be improved by even successful PTx. It is therefore important that PTx should be performed at an early stage before the calcification has become progressive (38, 59).

Mortality, survival rate and complications

In our series the mortality – defined as death within one month after PTx – was 3/1932 (0.15%). These three patients suffered from chronic heart failure. In a recent report from the USA the death rate within one month after PTx was started to be 3.1% (60). In the future we will certainly be facing more serious problems in connexion with surgery for 2HPT, as high-risk patients, i.e. patients with a high age

Table 5. Number of parathyroid glands removed at the initial PTx (n=1151)

Number of glands	Number of patients
7	1 (0.1%)
6	14 (1.2%)
5	135 (11.7%)
4	971 (84.4%)
3	28 (0.4%)
2	2 (0.2%)

and severe cardiovascular complications, are increasing. Hence it is important that cardiac disorders should be diagnosed before PTx.

We have evaluated the survival after PTx in patients followed up for more than 10 years after this operation. Although the mean duration of haemodialysis before PTx was about 11 years, more than 80% were alive 10 years after surgery (61). This means that patients can have not only a good quality of life but also good survival after PTx.

The frequency of husky voice due to palsy of the recurrent laryngeal nerve was less than 2%, and wound bleeding and re-operation occurred in less than 0.3% in our series. Incidentally about 25% of the cases were complicated by a thyroid tumour, and in 5.8% there was thyroid cancer (62). When a thyroid lesion is diagnosed before operation, we perform a thyroidectomy concomitantly.

Persistent and recurrent hyperparathyroidism

Table 5 shows the number of parathyroid glands resected at initial PTx in our series. We were able to remove more than three glands in 97.5% of the patients and in 13% the patients had supernumerary glands (48).

Intact PTH is measured routinely on day 1 after PTx. When the lowest PTH value exceeds the upper normal range (60 pg/mL), we consider that the patient has persistent HPT, which means that a gland or glands have possibly been left behind. When PTH decreases to a value under 60 pg/mL and then re-increases, we are dealing with a recurrent HPT and the patient requires re-operation (48, 63).

When fewer than four parathyroid glands were found at the initial operation, about 70% of these patients showed a decrease in their intact PTH level to below 60 pg/mL. These patients might have had only three glands, or more likely the fourth parathyroid gland was removed “accidentally” (64).

The incidence of persistent HPT in our series was 4.0%, and 1.6% required re-operation (48, 63). A mediastinal parathyroid gland was the most common cause of persistent HPT (65). Hence in patients with persistent HPT, MIBI scintigraphy is routinely carried out and if we find an abnormal uptake, CT or MRI, or both, are performed (66). The incidence of mediastinal glands was about 1.3% in our series and the most common location was at the aortico-pulmonary window (66).

Earlier the glands were removed after sternotomy, but recently we have excised mediastinal glands by an endoscopic technique.

In recurrent HPT, we need to consider several factors as possible origins of oversecretion of PTH after total PTx with a forearm autograft. These are the autograft itself, a residual gland in the neck or mediastinum, metastasis of parathyroid tissue in the lung, and implantation of parathyroid tissue in areas surrounding the thyroid gland (parathyromatosis) (35).

Before re-operation, detection of the origin by image diagnosis is essential. At first we have to determine whether the recurrence is graft-dependent or non-dependent on the basis of the PTH gradient or Casanova's test. Casanova's procedure is a useful examination for recognizing whether the recurrence is graft-dependent or not (67). When the PTH level does not drop significantly by blockade of the blood stream in the grafted arm, we can assume that the origin is not in the autografted tissue but it is more likely that we have a residual gland in the neck or mediastinum.

If the recurrence is graft-dependent, we look for an enlarged graft by MRI. It is often necessary to remove an autograft from the forearm several times. One patient required removal of grafted parathyroid tissue 8 times. Although grafted tissue is removed en bloc with surrounding muscle, small remnants of parathyroid tissue can be identified microscopically. In our series (totally 170 patients) we have never experienced severe hypoparathyroidism after this kind of operation. Nor have we ever experienced invasion of parathyroid tissue to surrounding muscle, or metastasis to distant organs (48).

If the recurrence is not graft-dependent, residual glands should be looked for, first with the help of US and then by scintigraphy. The incidence of recurrent HPT due to residual glands in the neck or mediastinum was only 1.4% in our series (48). In almost all cases we performed re-explorations at the neck (only in one of 21 cases was a mediastinal gland removed). Interestingly, several patients required removal of autografts simultaneously. The most common locations of residual glands in patients with recurrent HPT were the left paratracheal region, thymus, and intrathyroidal (48). The incidence of intrathyroidal parathyroid glands was about 2.5% in our series. The swollen glands could be detected by US and CT, and sometimes they were identified after thyroidectomy. An undescended parathyroid gland is a very uncommon cause of recurrence, and the incidence was about 1% (53). The undescended glands are located at the upper site of the upper pole of the thyroid lobe and they are one of the causes of recurrent and/or persistent HPT. In our series, the frequency of undescended parathyroid glands was 0.97%. At initial PTx undescended glands could be removed in nine cases. Usually an undescended thymus was a good landmark for detecting undescended glands. In all cases of recurrent HPT, undescended glands could be detected by image diagnosis, especially by US, CT and MRI. On the other hand MIBI scintigraphy was not useful for detecting an undescended gland, as salivary glands take up MIBI (68).

Re-operation in patients who underwent parathyroidectomy and/or percutaneous ethanol injection therapy (PEIT) at other hospitals

During the last few years PEIT has been used to treat advanced 2HPT in our country. However, advanced 2HPT is often not controlled by PEIT, especially when more than two parathyroid glands are considerably enlarged (69, 70). Moreover, palsy of the recurrent laryngeal nerve has not been a negligible complication of PEIT. PTx after PEIT is very difficult, as PEIT gives rise to adhesions of fibrous tissue and it is sometimes very difficult to identify parathyroid tissue and the recurrent laryngeal nerve (71). We strongly recommend that PEIT should be limited to patients in whom only one gland is substantially enlarged.

Among 55 patients who were referred to our department after the initial operation had been performed at other hospitals, we surgically removed residual glands from the neck or mediastinum on 52 occasions, removed an autograft on 17 occasions and removed lung metastatic nodules on 4 occasions. The remainig glands were frequently located at usual sites, including the thymic tongue. The re-explorations at the neck were not easy, as it was sometimes difficult to detect the recurrent laryngeal nerve (71). Undescended glands and glands located close to Berry's ligament were pitfalls.

Parathyromatosis and parathyroid carcinoma

Parathyromatosis is defined as multiple foci of benign hyperfunctioning parathyroid tissue in the neck or mediastinum. Parathyromatosis is usually induced by rupture of the capsule of parathyroid glands during surgical exploration or PEIT (72, 73). We have encountered ten cases of parathyromatosis, two of them after PEIT. Parathyromatosis is very problematic and contributes to a not inessential extent to recurrent renal HPT. To avoid iatrogenic parathyromatosis, the capsule of a gland should not be ruptured, fractured, or removed piecemeal. Subtotal PTx seems to imply some risk of parathyromatosis, as the hyperplastic gland is cut and parathyroid cells can easily become implanted in the surrounding tissues. We also consider that fine-needle aspiration entails a significant risk of developing parathyromatosis. We therefore do not recommend fine-needle aspiration for diagnosis and we would also warn against the use of PEIT in treatment of HPT. It is usually very difficult to diagnose parathyromatosis by an image technique but if such a complication is encountered during re-exploration for HPT, all gross disease should be removed along with the surrounding tissue. Although the operation seems radical, there is a high risk that the exploration will become incomplete.

We have encountered four haemodialysis patients with lung metastasis of parathyroid nodules. The histopathological findings in the original glands and lung metastatic nodules have been evaluated. In three cases we did not find any characteristic histopathological features of parathyroid carcinoma except for distant metastasis. Parathyroid carcinoma is very rare in patients with 2HPT (74–77) and we have only seen one patient who developed parathyroid carcinoma with lung metastasis during hemodialysis (74).

Parathyroidectomy after successful kidney transplantation

Successful renal transplantation generally ameliorates several derangements of renal HPT. In more than half of the patients with hypercalcaemia after kidney transplantation this disorder is self-limiting. It is sometimes difficult to decide whether the hypercalcaemia is reversible or not, and when diffuse hyperplasia progresses to nodular hyperplasia 2HPT cannot be relieved by successful kidney transplantation. It is therefore very valuable to assess the size of glands by US to judge whether HPT can be considered persistent or not after kidney transplantation. Surgically we prefer total PTx with forearm autograft in patients in whom renal HPT persists after kidney transplantation (78, 79).

Conclusions

Our conclusions about surgical treatment of 2HPT are as follows: (1) PTx is a most successful treatment for advanced renal HPT; (2) PTx should be performed at a relatively early stage before cardiovascular complications have progressed. The volume of the largest gland can be a useful factor to decide upon surgical indications; (3) To achieve a successful outcome, all parathyroid glands should be removed and to prevent parathyromatosis the capsule of the glands should not be damaged; (4) Surgeons should be familiar with the embryology and anatomy of the parathyroid gland and the pathophysiology of 2HPT.

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