Persistent or recurrent primary hyperparathyroidism



Ann. Ital. Chir., LXXIV, 4, 2003

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Approximately 100 000 new cases of primary hyperparathyroidism (PHPT) are diagnosed annually in the United States(1). Although parathyroid operations by experienced surgeons result in better than a 95% success rate, the success rate of surgeons doing fewer than 10 parathyroidectomy per year is about 70% (2). Incomplete resection of one or more abnormal parathyroid glands results in persistent or, some times, recurrent primary PHPT. Most of the patients with persistent PHPT can be treated via the same incision often indicating an inadequate initial exploration. In about 15% of patients with PHPT the parathyroid glands are located in atypical positions.

The upper parathyroid glands are less likely to be located in an ectopic position than the lower parathyroid glands because they migrate a shorter distance during their embryologic descent. Inability to recognize or locate abnormal parathyroid glands and inability to perform a bloodless, thorough dissection of the neck and upper superior mediastinum are common causes of failed initial explorations. The presence of a large nodular goiter, multiple lymph nodes, and brown fat can make identification of normal and abnormal parathyroid glands more difficult. Multiple abnormal parathyroid glands and supernumerary parathyroid glands are other common causes of failure. Patients with familial PHPT are more likely to develop persistent or recurrent disease. Reoperations are unfortunately associated with a lower success rate and a higher complication rate than occurs at initial operations.

Riassunto

IPERPARATIROIDISMO PRIMARIO PERSISTENTE O RECIDIVO

La percentuale di successo di una paratiroidectomia per iper paratirodismo primario è superiore al 95%, quando è pra ticata da un chirurgo esperto, ma è notevolmente inferiore quando è effettuata da operatori inesperti. L'approccio al paziente con iperparatiroidismo persistente o recidivo deve essere finalizzato a confermare la diagnosi ed a localizzare la possibile sede della ghiandola patologica. I reinterventi successivi ad una o più esplorazioni negative sono gravati sfortunatamente da una morbidità maggiore e da percen tuali di successo inferiori. L'affinamento delle tecniche dia gnostiche pre ed intraoperatorie hanno comportato un miglioramento dei risultati dei reinterventi e permettono la esecuzione di approcci più focalizzati. Preoperatoriamente, noi consigliamo la esecuzione di scintigrafia con sestamibi, associata ad ecografia e Risonanza Magnetica. Il dosaggio venoso ultraselettivo del PTH è indicato in quei casi in cui le indagini non invasive siano negative, incerte o discor danti. Molteplici fattori, quali età del paziente, severità dei sintomi, condizioni di comorbidità, assieme ai risultati del le indagini di localizzazione, dovrebbero essere considerati prima di porre l'indicazione al reintervento, sebbene noi riteniamo che un reintervento sia praticabile nella maggior parte dei casi. Attualmente infatti un reintervento può esse re eseguito con percentuali di successo superiori al 90% e tassi di morbilità relativamente bassi.

Parole chiave: Iperparatiroidismo persistente, iperparatiroidismo recidivo, reinterventi.

Abstract

More than 95% of patients with Primary Hyperparathyroidism (PHPT) are treated successfully at the initial operation when the operation is done by an experienced surgeon, but the success rate is considerably lower when done by an unexperienced surgeon. The approach to patients with persistent and recurrent PHPT is to confirm the diagnosis and to use precise localization procedures done by expert radiologists. Reexploration after one or more previously failed parathyroid operations is unfortunately associated with a higher morbidity and a lower success rate. Improved pre- and intraoperative testing during the last decade has improved the results of reoperation and allowed more focused approaches. Preoperatively, we recommend a combination of sestamibi scanning, ultrasound, and MRI scanning. Highly selective venous sampling for iPTH is recommended for patients with recurrent or persistent PHPT when the non-invasive studies are negative, equivocal, or discordant. Several factors such as age of the patient, severity of symptoms, comorbidity, and the results of localization studies, should all be considered in the management of these patients although we believe that reoperation is indicated for most of these patients. Today successful reoperations can be done in more than 90% of patients with a relatively low morbidity rate.

Key words: Persistent hyperparathyroidism, recurrent hyperparathyroidism, reoperation.

Persistent versus recurrent primary hyperparathyroidism

Causes of persistent or recurrent PHPT are summarized in Table I (3-12). Patients with hypercalcemia following initial operations for PHPT can be classified as having either persistent or recurrent disease.

Persistent disease is defined as hypercalcemia occurring immediately postoperatively or within 6 months of the initial operation. Persistent hypercalcemia is the most common indication for reoperation, and is usually due to a missed parathyroid tumor. Causes of persistent PHPT include:

• Failure to locate and remove a parathyroid adenoma or double adenomas.

• Inadequate resection of parathyroid hyperplasia (all parathyroid glands are hyperplastic).

- Subtotal resection of a parathyroid tumor.
- Parathyroid carcinoma (residual or metastatic disease).

• Parathyromatosis from embryologic development of multiple parathyroid glands or from rupture of a parathyroid gland at an initial operation, with subsequent implantation of adenomatous or hyperplastic cells.

Recurrent disease is defined as the development of hypercalcemia in a patient who has been hypocalcemic or normocalcemic for at least 6 months after the initial neck exploration. Recurrent PHPT is usually caused by inadequate surgery for parathyroid hyperplasia and occurs most often in patients with familial PHPT. In patients

Tab. I – CAUSES OF FAILURE IN THE INITIAL OPERA-TION FOR PRIMARY HYPERPARATHYROIDISM

• Inadequate resection of hyperplastic parathyroid glands in the initial exploration. In up to 15 %, there is more than four parathyroid glands

- Failure to recognize, localize, or adequately resect parathyroid adenoma
- Presence of more than one adenoma in 5 % (double adenomas).
- Subtotal resection of an abnormal parathyroid gland.
- Parathyroid carcinoma
- Parathyromatosis.
- Error in diagnosis.
- Surgical inexperience

with sporadic PHPT, recurrent PHPT occurs in about 1% of patients whereas in patients with familial HPT recurrence occurs in about one third of the patients. Causes of recurrent PHPT include:

- Regrowth of hyperplastic parathyroid tissue.
- · Regrowth of autotransplanted parathyroid tissue.
- Metachronous second adenoma.
- Parathyroid carcinoma.
- Parathyromatosis.

Pathology

1. Parathyroid adenoma

The most common cause of persistent PHPT is a missed parathyroid adenoma (13). Recurrent or persistent PHPT may be caused by incomplete resection of an adenoma or by failure to remove a metachronous second adenoma (double adenoma) (14). The incidence of double adenomas is 2% in patients under 60 years of age but up to 10% in patients who are older than 60 years (15). Undescended adenomas and intrathyroidal adenomas occur in about 1% and 7% of patients respectively, and may be overlooked during parathyroid reoperation. When an experienced surgeon fails to remove an abnormal parathyroid gland, the possibility of an ectopic parathyroid tumor, or undecended parathyroid tumor becomes more likely (16). Localization studies such as sestamibi scanning are particularly useful for detecting ectopically situated parathyroid adenomas. A focal approach can then be successfully used to remove the elusive parathyroid tumor.

2. Parathyroid hyperplasia

About 37% of patients who develop persistent or recurrent PHPT have multiglandular disease as opposed to only about 15 % of patients having multiglandular disease at their initial operations (10, 11, 17). Parathyroid hyperplasia or multiple parathyroid tumors are the second most common causes of both recurrent and persistent PHPT. Parathyroid hyperplasia occurs both sporadically, and more commonly in patients with familial PHPT (18). About 85% of patients with multiple endocrine neoplasia type 1 (MEN-1) syndrome and other patients with familial PHPT have multiple abnormal parathyroid glands. Patients with familial PHPT without MEN-1 or MEN-2, not only have multiple parathyroid glands as mentioned, but are more likely to present with profound hypercalcemia or hypercalcemic crisis, in contrast to all other patients (19).

Interestingly, localization studies in patients with multiglandular disease are often inaccurate (about 35% correct), and no localization test or combination of localization tests are as accurate at identifying all abnormal parathyroid glands as is an experienced surgeon. However, neither an experienced surgeon nor a pathologist can distinguish between a solitary hyperplastic gland and a parathyroid adenoma, either grossly or by histological examination.

However, lobular glands and softer parathyroid tumors and those without a compressed rim of normal parathyroid tissue are more likely to be due to hyperplasia. Parathyroid gland firmness, color and, size helps determine whether it is a normal or an abnormal parathyroid. Parathyroid tumors are firmer, darker and larger than normal parathyroid glands.

3. Parathyroid carcinoma

About 1% of patients with PHPT have parathyroid cancer (20-23). A palpable neck mass and hoarseness of voice in a patient with profound hypercalcemia (>13mg/dl) suggests parathyroid carcinoma. A firm, whitish, pale, large, and locally invasive parathyroid tumor at operation is likely to be a parathyroid cancer. The distinction between parathyroid adenoma and carcinoma is sometimes difficult (4). The rate of persistence or recurrence of parathyroid carcinoma is as high as 75%(24). Reoperation for persistent or recurrent hyperparathyroidism is indicated whenever feasible, potentially to cure the patient, but also to debulk the tumor and control local disease as well as the profound hypercalcemia. Reoperation for persistent or recurrent parathyroid cancer can be difficult.

Preoperative localization studies are helpful for documenting the site and the extent of the tumor and occasionally reveal distant metastases (Figure 1). Selective venous sampling of intact parathyroid hormone is helpful in selected patients. Early detection of recurrent disease makes reoperation easier and decreases the detrimental clinical and metabolic effects of PHPT and hypercalcemia (14, 24, 25).



Figure 1: A CT scan showing multiple pulmonary metastasis from parathyroid carcinoma.

4. Parathyromatosis

Parathyromatosis is characterized by finding multiple parathyroid nodules often throughout the neck and mediastinum. The two common causes of parathyromatosis include rupture of a parathyroid tumor with seeding of parathyroid cells and embryologic variants of parathyroid tissues. Since parathyroid tissue can be found within muscle, in some of these patients one might consider that parathyromatosis is a form of low-grade parathyroid cancer.

This conclusion is supported by the fact that parathyromatosis is a rare condition despite the number of patients having parathyroid tumors biopsied or subtotally resected. Thus one must suspect that the initial tumor was a low grade parathyroid carcinoma. Parathyromatosis is most often seen in patients with MEN syndrome and in patients with secondary hyperparathyroidism (26, 27). To decease the rate of parathyromatosis care should always be taken during parathyroid operations to avoid fracturing the parathyroid gland.

One should avoid sheading of cells when biopsying or subtotally resecting an adenomatous or hyperplastic parathyroid gland.

Approach to the reoperative patient

Prior to reoperation for PHPT, the diagnosis must be reconfirmed.

The previous operative note or notes and pathology reports must be carefully reviewed. When there is a question about the histology, the actual slides should be examined. Localization tests such as sestamibi scanning, ultrasound, and MRI scanning can help identify the tumor prior to reoperation. The best results are obtained when the radiologist is experienced in parathyroid localization procedures. Highly selective venous catheterization for PTH sampling is helpful for patients with equivocal or negative non invasive localization tests. Evaluation of patients with persistent or recurrent PHPT should include:

• A thorough *history* and family history to diagnose Benign Familial Hypocalciuric Hypercalcemia (BFHH), familial endocrinopathies, previous radiation and taking lithium should be obtained. Multiple gland hyperplasia is suggested from the findings of the previous operation, or by a family history of PHPT, or MEN syndrome, and by a personal history of pituitary, thyroid, adrenal tumors or endocrine tumors of the pancreas.

• A careful *physical examination* is necessary to asses surgical risk and possible coexistent thyroid disease or pheochromocytoma. Direct or indirect laryngoscopy should be done in all patients prior to reoperation to asses vocal cord function.

• Biochemical confirmation and differential diagnosis:

The diagnosis is usually confirmed by documenting concomitant elevation in serum calcium and intact PTH levels. Documentation of increased calcium and PTH levels in a patient without hypocalciuria (to rule out BFHH) establishes the diagnosis of PHPT. The only very rare exception occurs in patients with a malignant tumor that secrets pure PTH (28). These patients usually have clinically evident and large tumors. Selective venous catheterization of the veins draining the tumor for PTH or aspiration of the tumor and PTH analysis can diagnose these rare tumors. Intact PTH assays are not appreciably influenced by renal insufficiency whereas C-terminal and mid regional PTH assays are altered so that intact or two sites PTH assays are recommended for diagnosis. Diagnosing patients who are normocalcemic with kidney stones or osteoporosis who have a high PTH level is more difficult. If these patients have hypercalciuria, they should be treated with thiazide diuretics (25 mg by mouth twice daily for 10 days). Treatment with thiazide diuretics decreases the urinary calcium loss in patients with renal leak hypercalciuria. The increased serum iPTH level in response to the renal leak of calcium with consequent elevated urinary calcium level return to normal in patients with renal leak hypercalciuria but not in patients with normocalcemic PHPT. Some patients with PHPT have serum calcium levels at the upper limit of normal with inappropriately high PTH; determining the ionized calcium level helps diagnose these patients. Finally, a persistent elevation of the PTH level occurs in up to 10% of patients with PHPT following curative parathyroidectomy using intact PTH assay and up to 40% using mid or C-terminal assay (29). An increased PTH level postoperatively is present most frequently in patients with more profound hyperparathyroidism preoperatively and in patients with "bone hunger" or renal dysfunction. In some of these patients, the PTH level returns to normal several months following parathyroidectomy probably due to bone remineralization (30). Patients with BFHH often have a family history of hypercalcemia and some family member may have had a failed parathyroid operation. The serum calcium and PTH levels are only minimally increased in patients with BFHH and their 24-hour urinary calcium clearance is less than 100mg/24 hours. In patients with BFHH, the ratio of urinary calcium clearance to creatinine is below 0.01 and these patients may also have a high serum magnesium level. Documenting a normal serum calcium level at any time prior to the development of hypercalcemia essentially rules out BFHH.

• *Review* of the original biochemical tests, localization studies, and the pathological slides is important as previously mentioned. The preoperative and postoperative serum calcium levels before and after the previous

parathyroid operation should be reviewed to determine whether the patient has persistent or recurrent PHPT. Transient hypocalcemia is common after a successful parathyroid operation. Careful review of the previous operative reports is essential both for documenting whether one or more parathyroid glands are abnormal, the extent of the resection, and the position of the recurrent laryngeal nerve (RLN) and the number and position of the parathyroid glands. Particular attention should be paid to the location of histologically confirmed parathyroid glands identified at the initial operation. By reviewing the previous operative notes and pathology reports, one can often predict where the missing parathyroid gland will be situated. Although this is most important only parathyroid glands confirmed by biopsy should be considered as definitive information because a surgeon may confuse a lymph node, ectopic thymus or thyroid tissue as a parathyroid gland. After reviewing the previous operative reports and pathology reports, one should already have a reasonably good idea about whether the patient has a solitary parathyroid tumor, hyperplasia, double adenomas, or other pathology. This information is helpful for interpreting the subsequent localization studies. For example: when four normal parathyroid glands have been documented, the parathyroid tumor is usually in the mediasinum and, likely to be solitary parathyroid adenoma. In most of these patients it is still possible to remove this adenoma via the previous cervical incision. When one or more abnormal parathyroid glands have been biopsied or were removed at the initial operation(s) and confirmed histologically, the diagnosis is most likely parathyroid hyperplasia or double adenomas. Patients with double adenomas tend to be older, and often have more symptoms than patients with hyperplasia (31). The distinction between parathyroid hyperplasia and double adenomas is clinically difficult, however this information is crucial to plan surgery (18, 32). Localization studies and intraoperative iPTH assay help to discriminate between these two conditions.

• Localization studies

Failed parathyroid operations usually result from an ectopically situated solitary parathyroid adenoma or from multiple abnormal parathyroid glands, and from a surgeon's inexperience. Subtotal resection of an adenomatous or hyperplastic parathyroid gland, leaving too large remnant, failure to remove metastatic or locally invasive parathyroid carcinomas and parathyromatosis are other causes of failure. Other factors that contribute to failure include difficult body habitus such as obesity with short neck, large coexistent goiter, Hashimoto's thyroiditis, numerous lymph nodes, brown fat and bleeding. Brown fat makes it difficult to recognize normal parathyroid glands, as they are similar in color.

Reoperation for persistent or recurrent PHPT is often dif-

Test	Sensitivity (%)	Comments
Non-invasive studies: (10, 11, 33, 46, 47, 99, 100).		
Sestamibi scan	50-85	 Single most sensitive test. Can identify ectopic parathyroid glands False positive with thyroid nodules and other tumors.
Ultrasound	17-57	 Good for perithyroidal and intrathyroidal parathyroid glands. Documents specific site and relation to thyroid gland. Can guide FNA for PTH assay.
MRI	29-88	 Good for mediastinal and paraesophageal tumors but not as good for small tumors. Expensive
CT scan	16-42	 Good for mediastinum imaging Involves the use of radiation Sparkler artifacts and shoulder distortions are potential problems
Invasive studies:		
Selective venous sampling for iPTH (54, 55)	50-83	 Help to localize abnormal parathyroid glands where other tests fail.
Selective Angiography(56-60).	60 (mediastinal adenoma)	May helps localize and ablate mediastinal parathyroid ade nomas but rarely indicated today. – Associated with neurovascular complications.
Combined studies:		
 Ultrasound + sestamibi + MRI (10, 11) #1 + Selective venous sampling for iPTH (10) MRI + Sestamibi (101) # 3 + Selective venous sampling for iPTH (34) 	87 95 94 94	 Improved accuracy with combined tests. Combined morphological and functional tests should be employed first. If the results are negative or discordant, selective venous sampling of PTH is particularly useful.

Tab. II – LOCALIZATION STUDIES FOR ABNORMAL PARATHYROID GLANDS IN PATIENTS WITH PERSISTENT RECURRENT HYPERPARATHYROIDISM.

ficult, and technically challenging because of the extensive scarring near the RLN. The abnormal parathyroid gland is also more likely to be situated in an ectopic position. The complication rates of parathyroid reoperations have been reported to be as high as 40 % by experienced surgeons but should be appreciably lower (17).

The accuracy of different localization studies for patients with persistent or recurrent hyperparathyroidism is shown in Table II (8-11, 33-35). Precise localization studies and surgeons experience are essential for the best results of reoperation. Numerous reports documented that more than 90 % of patients with persistent or recurrent PHPT have a parathyroid tumor or tumors that can be removed via the initial cervical incision (36). A combination of a functional (such as sestamibi scanning) as well as a morphological studies (ultrasound or MRI scan) are recommended prior to reoperation. Localization studies in combination with information about the previous operative operations and histologic findings, usually direct the surgeon to the abnormal gland, thus minimizing complications and shortening the operative time. One prefers not to do bilateral reoperation when possible because unilateral neck exploration avoids putting both RLNs at risk. Intraoperative PTH testing appears to be helpful for confirming when all abnormal parathyroid tissue has been removed.

1 - Radionuclide scanning: Sestamibi scanning is the most accurate parathyroid imaging study. Both thyroid and parathyroid tissues take up labeled sestamibi, but this isotope remains in parathyroid tissues for a longer period of time. It can identify about 80% of abnormal cervical and mediastinal parathyroid glands prior to an initial operation and about 65% of patients prior to reoperation (10). False negative results may be related to the small size of the gland or by the obscuration caused by the heart, whereas false positive studies may be due to coexisting thyroid nodules. Single photon emission computed tomography (SPECT) helps to determine whether an adenoma is in the anterior or posterior mediastinum with a sensitivity of more than 85% in patients requiring reoperation (37-39). This is especially helpful to localize adenomas in the middle mediastinum such as in the aortopulmonary window or in the thymus since those in the thymus and anterior mediastinum can almost always be removed via a cervical incision, whereas other tumors warrant a median sternotomy or thoracoscopic removal (40, 41, 42). Confirmation of the sestamibi scan results with an MRI or a CT scan is helpful. Sestamibi scanning is unfortunately not as helpful as mentioned previously in patients with multiglandular disease (about 35% accurate). Sestamibi scanning however, can help to locate some abnormal parathyroid glands situated in ectopic locations. Sestamibi scanning is more accurate in patients with hyperplasia who have already had several hyperplastic parathyroid glands removed.

Sestamibi scanning has replaced thaelium-technetium scanning in most medical centers. Some nuclear medical physicians have found Technetium-99m tetrofosmine to be as useful as (99m)Tc-MIBI for the detection of abnormal parathyroid glands(43, 44). Positron emission tomography has been reported to accurately identify about 75% of parathyroid adenomas and 30% of hyperplastic glands (45). We have used it in a few patients with persistent or recurrent PHPT but see no advantage over sestamibi scanning.

2 – Ultrasonography

Neck ultrasound is noninvasive and is the least expensive imaging study. It is especially useful to detect missed parathyroid tumors immediately adjacent to thyroid gland and intrathyroidal parathyroid adenomas. Ultrasound, however, cannot image mediastinal parathyroids, or parathyroid tumors behind the trachea or clavicle. It also requires an experienced radiologist for the best results. The sensitivity of the ultrasound to detect parathyroid glands ranges between 17 % and 80% depending on the series, with false positive rates of 15-20%(10, 11, 33, 46, 47). This wide range of results emphasizes that expertise and proper equipment is required. Fine needle aspiration biopsy (FNA) for cytology and PTH testing can be done with ultrasound guidance (48, 49). When ultrasonography is combined with sestamibi scanning, and both tests independently suggest the same site, they are 90% accurate with few falsepositives (50, 51). Thus, in virtually all patients with persistent or recurrent PHPT, we obtain both ultrasound and sestamibi scans. If the studies still failed to localize a parathyroid gland or the results are discordant, we proceed to further localizing studies.

3 – MRI and CT scans

Both are useful for imaging parathyroid tumors situated in the mediastinum or within the tracheoesophageal groove. MRI scanning is preferable to CT scanning because it is not adversely affected by a shoulder artifact or by multiple clips that are frequently left at the previous procedures. CT scans and ultrasound scanning can be used to guide FNA for PTH determination and cytology examination. The sensitivity of MRI scanning about is about 60% and MRI scanning does not require the administration of contrast (52, 53). MRI combined with sestamibi scanning localizes many of the ectopic parathyroid tumors situated in the mediastinum. About two thirds of parathyroid tumors enhance on T2 images or after gadolinium administration.

4 – Highly selective venous sampling for PTH assay

This procedure is primarily used when the noninvasive localization tests are negative or equivocal (54). In general, venous sampling of serum PTH levels lateralizes rather than localizes, but when combined with a questionably positive noninvasive localizing test, it changes it into a positive study. We have found a 75% true positive rate and a 16 % false positive rate (55).

5 – Selective Angiograhy

When the above imaging studies are negative, selective injection of the superior and inferior thyroid arteries, and internal mammary arteries may be helpful for localizing parathyroid tumors. Some parathyroid tumors have increased vascularity, and a blush is observed at the site of the tumor. Occasionally one can use angiographic ablation of mediastinal parathyroid tumors, with longterm control of PHPT in about 60% of patients. The procedure is, however, invasive, the sensitivity is about 60%, and cerebrovascular catastrophes including cortical blindness has occurred (56-60). We have only rarely used selective angiography in the past 10 years.

6 – Combined localization studies

Two issues should be addressed when one advocates using multiple localization studies. First, multiple imaging studies done together localize abnormal parathyroid gland more efficiently than any single localizing study (Table II). Second, multiple localizing studies, although more costly, often help the surgeon to do a focused dissection with a shorter operative time (61, 62). It also eliminates any need to do intraoperative sestamibi scanning with the probe and helps to identify patients with more than one remaining abnormal parathyroid gland.

Indications for reoperation

The indications for reoperation in patients with PHPT are basically the same as for an initial exploration. There is a general agreement that surgery is indicated for all patients with symptomatic PHPT and for asymptomatic patients with serum calcium level above 11.5 mg/dl or

who are younger than 50 years (1). Parathyroidectomy improves symptoms in approximately 85 % of patients with PHPT including patients who are considered "asymptomatic" by NIH consensus (1, 63). The most marked improvement is observed in patients with severe complications, such as osteitis fibrosa cystica, renal stones and pancreatitis. Considerable disagreement continues among experts about the treatment of patients with asymptomatic PHPT. Numerous recent publications, however, suggest that few patients are asymptomatic or without associated conditions, and that many of these nonspecific symptoms, as well as quality of life and metabolic complications improve after parathyroidectomy (64-66). In patients with mild or asymptomatic PHPT, renal function and bone density deteriorate in about one third of patients, and often improve or stabilize after parathyroidectomy (64, 67). Older patients also appear to receive the same clinical and metabolic benefits from parathyroidectomy as younger patients so that recommending a nonoperative approach in "asymptomatic" patients over 50 is questioned (68). The cost of follow up of nonoperative management is also higher than operative management after 5 years (69). Numerous

Tab. III – A SUGGESTED APPROACH FOR MANAGEMENT OF PATIENTS WITH PHPT, WHO FAILED THEIR NECK EXPLORATION.



investigations have also suggested that patients with PHPT have an increased mortality rate related to cardiovascular disease and cancer (65, 70-77).

One investigation by Wermers et al found no increase in overall mortality in a relatively small group of patients with PHPT, but patients with the highest calcium level (>12 mg /dl) in this group had a worse outcome (78). Overall the current evidence strongly supports a liberal approach regarding surgical managment in patients with PHPT. The authors believe that nonoperative therapy should be limited for a number of older or poor risk patients with multiple comorbid conditions (79). A suggested algorithm for management of patients with primary HPT, who failed initial neck exploration, is shown in Table III.

Reoperative neck exploration

Reoperation for most patients with persistent PHPT should be within the first week after a failed operation or 3 months or more to decrease the problems of loss of tissue planes and scarring (39). The procedure is best done under general anesthesia although for well-localized tumors in the neck, local or regional anesthesia could be used.

Reoperation for persistent or recurrent PHPT is best when a focused procedure can be done based on the review of the previous operative and histologic findings and positive consistent localization tests. A focused reoperation decreases the risk of the hypoparathyroidism and nerve injury although these risks are rare during a bilateral operation when done by an experienced surgeon. As previously mentioned even at reoperation for PHPT, the majority of abnormal glands can be removed through the previously made cervical incision. Most missed solitary abnormal parathyroid glands are situated along the tracheoesophageal groove, or in the thymus or perithymic fat in the anterior superior mediastinum. Other common sites include intrathyroidal (8%), in carotid sheath (2%), retropharangeal (1%) and undecended in 0.5%.

Parathyroid adenoma

• A missed parathyroid adenoma is suggested when no abnormal parathyroid gland and at least one normal parathyroid gland has been removed at the initial operation. The focused reoperation should be guided by the previous operative findings and more importantly by preoperative localization studies, and terminated if an abnormal gland is found. PTH testing is helpful in these situations.

• When *a superior parathyroid gland* can not be identified and three other normal parathyroid glands were observed and or biopsied, the superior parathyroid gland is most likely situated low in the neck or in the upper posterior mediastinum in a paraesophageal position. If not found here, it may be within the carotid sheath. A lateral cervical approach is preferable for most parathyroid reoperations especially for identifying deeply seated upper parathyroid glands. The lateral approach also makes it easier to identify the RLN. During a lateral approach the dissection plane is lateral to the sternohyoid and sternothyroid muscles and medial to the sternocleidomastoid muscle.

The carotid artery, jugular vein, and the vagus nerve are retracted laterally and the thyroid and strap muscles are retracted anteriorly and medially. The dissection plane is often deep to the previous dissection plane, so that there is less scar tissue.

• *Inferior parathyroid gland* is best approached through either a lateral or an anterior approach. The anterior approach is preferred for tumors localized preoperatively in the thymus or anterior superior mediastinum as they are situated anterior to the RLN.

• Most *mediastinal adenomas* (about 80%) are found within or closely associated with the thymic tissue. Since intrathymic mediastinal adenomas are supplied by the inferior thyroid artery, they can usually be removed via a cervical incision.

Median sternotomy is occasionally indicated for middle mediastinum tumors. Median sternotomy or thoracoscopic removal is performed when localization studies identify a mediastinal tumor that is unlikely to be accessible though a cervical approach, such as a parathyroid tumor located in the aortopulmonary window (41, 80).

Parathyroid hyperplasia

Primary parathyroid hyperplasia is present when all parathyroid glands are hypercellular. Hyperplasia is common in patients with familial disease but also occurs in about 12% of patients with sporadic PHPT. Patients with hyperplasia should be treated by subtotal or total parathyroidectomy with parathyroid autotransplantation. We prefer the former because there is a lower incidence of permanent hypoparathyroidism, which is rare after subtotal parathyroidectomy but occurs in about 5% after autotransplantation.

At reoperation, if three or four hyperplastic parathyroids have already been removed, autotransplantation is recommended into the brachioradialis muscle in the nondominant forearm. We usually transplant about 12, 1 mm pieces of parathyroid tissue into separate muscle pockets. Parathyroid tissue is also cryopreserved, and can be used in case the transplant fails to function appropriately. Unfortunately, cryopreserved parathyroid tissues only function normally in about 60% of patients (81, 82).

Adjunct to surgery

1 – Intraoperative ultrasound using a 10-MHz transducer helps to image abnormal glands during reoperation. It is especially helpful for identifying parathyroid adenomas within the thyroid gland; however, if an ultrasound was done preoperatively, intraoperative ultrasound is not necessary. Ultrasound reduces the need for blind thyroid lobectomy (83). FNA with iPTH assay under ultrasound guidance can document whether a mass in the neck is a parathyroid gland. This is especially helpful for intrathyroidal masses.

2 – Handheld gamma-detecting camera probe: Norman et al recommended minimally invasive radioguided parathyroidectomy and found it helpful in 21 pateints who previously had a failed initial operation (84). A unilateral neck exploration is guided by handheld gamma probe. We believe that preoperative sestamibi scanning is as accurate as the gamma probe and we do not recommend this procedure.

3 – Intraoperative PTH monitoring: Intraoperative iPTH assay may lateralize the side of parathyroid tumor. The PTH level usually increases after massaging the area containing the parathyroid tissue. Intraoperative iPTH testing is primarily used to determine whether all hyperfunctioning parathyroid tissue has been removed. A decrease of the PTH level greater than 50% at 10 minutes (from the baseline value or from immediate pre-removal value) after resection of a parathyroid adenoma usually indicates that operation is successful. When the PTH does not drop by 50%, the test should be repeated and there are probably more abnormal parathyroid glands that need to be removed (85-89).

Intraoperative PTH monitoring has replace frozen section analysis in some medical centers (86, 90). In patients with familial PHPT it is useful to do an intraoperative PTH testing even when three or four glands have been removed, because there might be a fifth, sixth or even seventh parathyroid gland. However, reliance on intraoperative iPTH assay results without using good surgical judgment can unnecessarily prolong an operation. For example, it may encourage the surgeon to continue to explore when all of the abnormal parathyroid glands have already been identified as PTH level falls more slowly in some patients after parathyroidectomy.

4 – Cryopreservation and autotransplantation: A portion of the removed parathyroid tissue is immediately placed in sterile iced physiological saline for subsequent autotransplantation during the operation or may be cryopreserved for future delayed autotransplantation, if needed. As previously mentioned when the tumor is found and four glands have already been resected, immediate autotransplantation of a portion of the tumor is indicated. In addition, if the intraoperative PTH falls to less than 0.2 or undetectable within 30 minutes, or if it appears that the patient has a significant chance of becoming hypoparathyoid, immediate autotransplantation rather than cryopreservation is indicated, whereas, when 2 or fewer parathyroid glands have been removed autotransplantation is not indicated and cryopreservation should be done (91). Using the above recommendation we have only had to use cryopreserved tissue in about 2% of our patients to correct permanent hypoparathyroidism.

Postoperative Complications

1. Vocal cord paralysis occurs in about 4 % (0-10%) of patients having parathyroid reoperations (7, 8, 10, 11, 17, 92, 93). We believe that this complication should be less than 2%.

2. Postoperative hypocalcemia 2-16% (at least 2% required autotransplantation of cryopreserved parathyroid tissue). We believe that permanent hypoparathyroidism should be present in fewer than 2% of pateints having parathyroid reoperations.

3. Failure of reoperation to resolve hypercalcemia occurs in approximately 5% to 10% of patients with persistent or recurrent PHPT. Patients with familial PHPT, parathyromatosis, parathyroid cancer and those with no tumor identified on localization studies are more likely to have failed reoperations.

Alternatives

Palliative treatment may be achieved with any the following modalities of treatment:

• *Medical therapy* including hydration, estrogens for postmenopausal women, and bisphosphonates, are helpful. The newly described calcimimetic agents appear to be effective and directly block secretion of parathyroid hormone from parathyroid tumor (94). Such therapy may be of value in patients with parathyroid cancer, parathyromatosis, and for patients with mild persistent or recurrent PHPT when all localization tests are negative.

• Alcohol ablation of the gland under ulterasound or CT guidance: FNA confirmation of parathyroid tissue either by cytology or by detecting PTH is essential to maximize the results of alcohol ablation and to reduce the complications. Patients who have parathyroid tumors that have been localized, however, are the easiest to treat surgically. Alcohol ablation can be effective but it is associated with an unacceptable high rate of temporary and permanent vocal cord paralysis (95,96, 97, 98). There is also a high recurrence rate if all parathyroid cells are not destroyed and parathyroid tissue is not available for cryo-

preservation or autotransplantation. We recommend that most patients with comorbid conditions have a focused reoperation under local anesthesia with intraoperative PTH monitoring rather than alcohol injection.

• Angiographic ablation may be indicated in selected high risk patients, who have middle mediastinum parathyroid tumors. The procedure is done by injecting contrast material into the supplying artery to cause necrosis of the adenoma (58). Rare but potential complications include vocal paralysis, cortical or spinal cord damage, parathyromatosis, and permanent hypoparathyroidism since no tissue is available for autotransplantation or cryopreservation.

Conclusion

More than 95% of patients with PHPT are treated successfully at the initial operation when the operation is done by an experienced surgeon, but the success rate is considerably lower when done by an inexperienced surgeon. Successful parathyroid explorations require knowledge of both anatomy and embryology. The approach to patients with persistent and recurrent PHPT is to confirm the diagnosis and, to use precise localization procedures done by expert radiologists. Reexploration after one or more previously failed parathyroid operations is unfortunately associated with a higher morbidity and a lower success rate. Improved pre- and intraoperative testing during the last decade has improved the results of reoperation and allowed more focused approaches. Preoperatively, we recommend a combination of sestamibi scanning, ultrasound, and MRI scanning. Highly selective venous sampling for iPTH is recommended for patients with recurrent or persistent PHPT when the non-invasive studies are negative, equivocal, or discordant. Several factors such as age of the patient, severity of symptoms, comorbid conditions, and the results of localization studies, should all be considered in the management of these patients although we believe reoperation is indicated for most of these patients. Today successful reoperations can be done in more than 90% of patients with a relatively low morbidity rate.

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