

Diagnostic, therapeutic and healthcare management protocols in parathyroid surgery: II Consensus Conference of the Italian Association of Endocrine Surgery Units (U.E.C. CLUB)

L. Rosato · M. Raffaelli · R. Bellantone · A. Pontecorvi · N. Avenia · M. Boniardi ·
M. L. Brandi · F. Cetani · M. G. Chiofalo · G. Conzo · M. De Palma · G. Gasparri ·
A. Giordano · N. Innaro · E. Leopaldi · G. Mariani · C. Marcocci · P. Marini ·
P. Miccoli · P. Nasi · F. Pacini · R. Paragliola · M. R. Pelizzo · M. Testini · G. De Toma

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Abstract

Aim To update the Diagnostic-Therapeutic-Healthcare Protocol (Protocollo Diagnostico-Terapeutico-Assistenziale, PDTA) created by the U.E.C. CLUB (Association of the Italian Endocrine Surgery Units) during the I Consensus Conference in 2008.

Methods In the preliminary phase, the II Consensus involved a selected group of experts; the elaboration phase was conducted via e-mail among all members; the conclusion phase took place during the X National

Congress of the U.E.C. CLUB. The following were examined: diagnostic pathway and clinical evaluation; mode of admission and waiting time; therapeutic pathway (patient preparation for surgery, surgical treatment, postoperative management, management of major complications); hospital discharge and patient information; outpatient care and follow-up.

Conclusions The PDTA for parathyroid surgery approved by the II Consensus Conference (June 2013) is the official PDTA of the U.E.C. CLUB.

L. Rosato (✉)
Department of Surgery, ASL TO/4 Ivrea Hospital (TO),
Piazza della Credenza, 2, 10015 IVREA, TO, Italy
e-mail: lodovico.rosato@unito.it

M. Raffaelli · R. Bellantone
Department of Surgery, Endocrine and Metabolic Surgery,
Catholic University, Rome, Italy

A. Pontecorvi · R. Paragliola
Department of Endocrinology, Catholic University, Rome, Italy

N. Avenia
Department of Surgery, “S. Maria” Terni Hospital,
Perugia University, Perugia, Italy

M. Boniardi
Department of Surgery, Niguarda Hospital, Milan, Italy

M. L. Brandi
Clinical Unit on Metabolic Bone Disorders, University Hospital
of Florence, Florence, Italy

F. Cetani · C. Marcocci
Endocrinology Unit, Pisa University, Pisa, Italy

M. G. Chiofalo
Department of Surgery, Thyroid Surgery,
I.N.T. “Pascale” of Naples, Naples, Italy

G. Conzo
Department of Surgery, Naples University, Naples, Italy

M. De Palma
Department of Surgery, A.O.R.N. “Cardarelli” Hospital,
Naples, Italy

G. Gasparri
Department of Surgery, Turin University, Turin, Italy

A. Giordano
Nuclear Medicine Institute, Catholic University, Rome, Italy

N. Innaro
Department of Surgery, “Mater Domini” Hospital, Catanzaro,
Italy

E. Leopaldi
Endocrine Surgical Unit, Department of Surgery, “Sacco”
Hospital, Milan, Italy

G. Mariani
Nuclear Medicine Institute, Pisa University, Pisa, Italy

P. Marini
Department of Surgery, Endocrine Surgery,
“S. Camillo-Forlanini” Hospital, Rome, Italy

Keywords Hyperparathyroidism · Parathyroid disease · Parathyroidectomy · Preoperative work up · Postoperative management

Abbreviations

Club delle U.E.C.	Italian Association of Endocrine Surgery Units
PDTA	Diagnostic-Therapeutic-Healthcare Protocol
HPT	Hyperparathyroidism
PTH	Parathyroid hormone
HPT I	Primary hyperparathyroidism
NIH	National Institute of health
SIN	Italian Society of nephrology
HPT II	Secondary HPT
AACE	American Association of clinical endocrinologists
AAES	American Association of endocrine surgeons
ESES	European Society of endocrine surgeons
AME	Association of clinical endocrinologists
JSDT	Japanese Society for dialysis therapy
MEN	Multiple endocrine neoplasia
SPECT	Single photon emission computed tomography
PET	Positron emission tomography
CBM	Computerized bone mineralometry
FNAB	Fine needle aspiration biopsy
PTx	Parathyroidectomy

P. Miccoli
Department of Surgery, Endocrine Surgery, Pisa University,
Pisa, Italy

P. Nasi
Thyroid Disease and Endocrine Surgery, “Sedes Sapientiae”
Private Hospital, Turin, Italy

F. Pacini
Department of Internal Medicine, Endocrinology and
Metabolism, University of Siena, Siena, Italy

M. R. Pelizzo
Department of Surgery, Endocrine Surgery, Padua University,
Padua, Italy

M. Testini
Unit of Endocrine, Digestive, and Emergency Surgery,
Department of Biomedical Sciences and Human Oncology,
Bari University, Bari, Italy

G. De Toma
Department of Surgery “P. Valdoni”-Endocrine Surgery,
“La Sapienza” University, Rome, Italy

OMIP	Open minimally invasive parathyroidectomy
MIRP	Minimally invasive radioguided parathyroidectomy
MIVAP	Minimally invasive video-assisted parathyroidectomy

Background

Advances in the diagnostic and surgical fields have allowed a more precise nosographic and therapeutic identification of parathyroid disease. The incidence of hyperparathyroidism (HPT), which appeared to be surprisingly high (3/1,000 of the general population) after the introduction of serum calcium measurement as a routine laboratory test in 1970, has become epidemiologically stable at about 20/100,000 [1] after the recognition of other important and common causes of increased calcium and parathyroid hormone (PTH) levels in the last decade, e.g. vitamin D deficiency.

In 1990 the *Consensus Conference* on primary hyperparathyroidism (HPT I) [2], promoted by the *National Institute of Health* (NIH), defined the indications for parathyroidectomy in asymptomatic patients. Subsequently, in 2002 an International Workshop also promoted by the NIH in collaboration with the *National Institute of Diabetes and Digestive and Kidney Diseases* sought to update and further define the criteria based on which either surgery or medical follow-up can be recommended in asymptomatic patients [3]. In 2003 the Italian Society of Nephrology (SIN) published a revision of the “Renal osteodystrophy guidelines” [4]. In the same year, the US *National Kidney Foundation* published its guidelines on the management of secondary HPT (HPT II) [5].

In 2000 the U.E.C. CLUB—The Association of the Italian Endocrine Surgery Units—published a volume on the surgical pathology of the thyroid and parathyroids [6] with the aim to initiate a systematic updating program for members. Furthermore, in 2003 the U.E.C. CLUB issued the first version of the Diagnostic-Therapeutic-Healthcare Protocol (Protocollo Diagnostico-Terapeutico-Assistenziale, PDTA) in parathyroid surgery [7], which was revised and updated during the I Consensus Conference in 2008 [8]. In 2005 the *American Association of Clinical Endocrinologists* (AACE) and the *American Association of Endocrine Surgeons* (AAES) published a *Position Statement* on diagnosis and management of HPT I [9]. In 2008, during the III International Workshop on the Management of Asymptomatic Primary Hyperthyroidism [10–14] held in Orlando, the results of previous Workshops were revised

and updated. Similarly, the *European Society of Endocrine Surgeons* (ESES) [15] in 2009, and the Association of Clinical Endocrinologists (AME) [16], in 2012, have issued their guidelines on HPT I. Furthermore, in 2008 the *Japanese Society for Dialysis Therapy* (JSDT) issued its guidelines for the management of HPT II [17].

In this context, the U.E.C. CLUB, being aware that the issuance of guidelines often causes reluctance among physicians due to fears of limited autonomy in clinical decision-making, organized the II Consensus conference for the revision of shared protocols. As in the case of the PDTA in thyroid surgery, issued by the III Consensus Conference in 2012 [18], a clear and concise style was chosen for motivating the rationales behind behaviours and to provide physicians and nurses with a guide as complete as possible on who, when, how and why to act. In the preliminary phase, the Consensus involved a selected panel of experts; all members were involved via e-mail in the elaboration phase; the conclusion phase took place during the X National Congress of the U.E.C. CLUB, held in Rome, Italy, on June 20–22, 2013. However, it is not within the scope of the authors nor of the U.E.C. CLUB to influence in any way the physician–patient relationship, which is based on trust and clinical judgement in each individual case. The following were examined:

- Diagnostic pathway and clinical evaluation;
- Mode of admission and waiting time;
- Therapeutic pathway:
 - patient preparation for surgery,
 - surgical treatment,
 - postoperative management,
 - Management of major complications;
- Hospital discharge and patient information;
- Outpatient care and follow-up.

Diagnostic pathway and clinical assessment

Diagnostic tests should be worthwhile and not only aimed at the nosographic definition of HPT (laboratory assessment), but also at localizing the affected parathyroid glands (instrumental investigations) and at defining a therapeutic indication.

Laboratory assessment

- First tier assessments
 - serum calcium (total or ionized calcium). Measurement of ionized calcium levels may be useful in case of altered plasma albumin levels [19];

- serum phosphorus;
- serum creatinine;
- intact PTH (1–84) (second- or third generation assay);
- 25-OH-Vitamin D [11, 19].

- Second tier assessments

- 24 h calciuria and phosphaturia;
- creatinine clearance (calculate the ratio of calcium clearance and creatinine clearance, for differential diagnosis with Familial Hypocalciuric Hypercalcemia).

In selected cases (patients aged <30 years at diagnosis, family history of hypercalcemia, neuroendocrine tumours), assessing the presence of a familial syndrome (Multiple Endocrine Neoplasia 1—MEN1, MEN2A, Hyperparathyroidism-jaw Tumour Syndrome, Familial Hyperparathyroidism), also by employing DNA sequencing for mutations of RET, CASR, MEN1, HRPT2 [11, 16, 19, 20], may be useful.

Localization studies

Imaging studies for preoperative localization have no role in the diagnosis of primary HPT, but they are necessary for planning the surgical strategy, especially in case of minimally invasive approaches and re-interventions:

- First tier studies

- Parathyroid ultrasound: not required for diagnosis, but useful for surgical planning:
 - in HPT I, preoperative localization of the affected gland facilitates minimally invasive surgical approach [9];
 - in HPT II, the finding of even a single parathyroid with a diameter of >10 mm is indicative of nodular hyperplasia, the reversibility of which should to be assessed [4]. Neck ultrasound must also provide information on:
 - thyroid structure and possible nodules;
 - presence or absence of lateral cervical lymph nodes.
- ^{99m}Tc-sestamibi scintigraphy: not required for diagnosis, but useful for surgical planning:
 - in HPT I, preoperative localization of the affected gland facilitates a minimally invasive surgical approach [9];

- in case of persistence and/or recurrence after parathyroidectomy;
- opposite to ultrasound, it allows visualization of ectopic mediastinal parathyroids;
- it is optimal in HPT II, where the finding of even a single parathyroid is indicative of nodular hyperplasia and therefore the surgeon will avoid leaving a remnant of that gland or reimplanting and cryopreserving it in sub-total (7/8) and total parathyroidectomy, respectively.

It should be considered that the sensitivity of ^{99m}Tc -sestamibi scintigraphy may decrease in the presence of multiglandular disease, small size adenomas (<5 mm) or lesions with a low proliferative index. The test may yield false-positive results in case of concomitant nodular thyroid disease (toxic adenoma or neoplasm). Furthermore, to perform the examination correctly, it may be useful to consider a wash-out period from potentially interfering medications or substances such as iodinated contrast medium, iodine-containing drugs, thyroxine, vitamin D, calcium mimetics and calcium antagonists (*Procedural Recommendations of the Italian Association of Nuclear Medicine and Molecular Imaging—Parathyroid Scintigraphy—V. 02/2012, p. 1/5*).

The recent development of SPECT (*Single Photon Emission Computed Tomography*) allows, after a scintigraphy and thanks to computerized analysis of images, a three-dimensional visualization of the diseased parathyroid gland in the anatomical region where it is located, providing functional and anatomical imaging at the same time. Precise localization, either in the anterior or posterior mediastinum, is of particular importance in the case of ectopic glands. In addition to scintigraphy with SPECT, further information for preoperative localization is provided by the SPECT/CT technique, which allows more accurate attenuation correction and provides anatomical landmarks that are very useful to the surgeon, independently of the use of an intraoperative gamma-probe.

- Second tier studies
 - CT–MRI: useful in case of ectopic glands, recurrent or persistent disease, or suspected cancer.

As compared to ultrasound, a CT scan may reveal ectopic mediastinal glands and provide more reliable information on possible spread of parathyroid carcinoma to the surrounding organs. MRI may provide more precise information, complementary to those from scintigraphy, in case of ectopic mediastinal glands or dislocation to other regions of the neck. This technique, however, has a limitation in the presence of thyroid nodules with an MR

appearance similar and indistinguishable from that of diseased parathyroids [21].

- Positron emission tomography (PET): PET, with or without simultaneous CT scan, may reveal diseased parathyroid glands in patients with persistent or recurrent HPT when results of other imaging techniques are negative or non-diagnostic [13]. However, the diagnostic accuracy of ^{18}F -FDG-PET is reduced in case of anatomic variants or benign uptake in the neck, which may yield false-positive results [16]. Studies with ^{11}C -Methionine and ^{18}F -DOPA appear to be more promising, although experience with these techniques is limited [16, 22].
- Computerized bone mineralometry (CBM) and renal ultrasound useful for completing diagnosis, but not required for surgical planning
- Fine needle aspiration biopsy (FNAB) with measurement of PTH: only when a diagnostic doubt cannot be resolved with other techniques. It should be avoided when a parathyroid carcinoma is suspected, to prevent the risk of local dissemination [13].
- Selective venous sampling for PTH: Selective venous sampling is an invasive procedure that can be used in patients with persistent or recurrent disease, when results of other imaging techniques are negative or non-diagnostic. It can allow localization in up to 80 % of cases, but in expert hands [13].
- Study of MEN associations, mainly with the aim of:
 - ruling out a concomitant pheochromocytoma; and
 - confirming a concomitant medullary thyroid carcinoma or C-cell hyperplasia.

Waiting time and mode of admission

- Priority for hospital admission:
 - *High*: within 1 month for malignancy or severe hypercalcemia (serum calcium ≥ 12 mg/dL) [16];
 - *Intermediate*: within 3 months for patients with chronic kidney disease, on transplant waiting list, with severe osteoporosis, requiring surgical treatment or lithotripsy for renal lithiasis; moderate/severe hypercalcemia, especially in advanced age and during summer (risk of dehydration and severe hypercalcemia);
 - *Low*: within 6 months or more for benign, non-invalidating disease, in the presence of clinical conditions for surgery, e.g. age <50 years.

- Preoperative work up (prior to or at admission):
 - Blood chemistry;
 - ECG;
 - Chest X-ray (when indicated, depending on patient's age and comorbidities);
 - Anaesthesiology consultation;
 - ENT consultation for the assessment of vocal cord mobility (preferably by means of fiberoptic laryngoscopy): advisable in all patients; strongly recommendable in case of re-interventions.
- Recommendations for patients:
 - follow a diet containing a moderate amount of calcium and drink much (≥ 2 L per day, water with low dry residue). A rigorously calcium-poor diet is not recommended, since it can lead to further bone demineralization and increased PTH levels;
 - beta-blockers should not be discontinued, if taken regularly; anaesthesiology consultation should be obtained if beta-blocker therapy has been started a few days earlier;
 - as in every surgical intervention, in patients with cardiovascular disease discontinuation of antiplatelet therapy—which may be substituted with low molecular weight heparins—at least 1 week prior to surgery needs to be balanced against the severity of the comorbidity.
- Admission:
 - on the same day of surgery, unless otherwise indicated or required.
- Blood units
 - as in thyroid surgery, autologous predeposit blood donation or preparation of blood units is not justified.
- Position on the operating table (joint responsibility of the surgeon and anaesthesiologist):
 - patient in the supine position with a small wedge beneath the shoulders, at the scapular level, to allow a mild hyperextension of the neck (not necessary during minimally invasive video-assisted procedures);
 - with the neck in hyperextension, although mild, arms should be secured next to the patient's body in order to avoid rare, but severe and sometimes irreversible, brachial plexus paralyses due to stretch injury [26];
 - elbows should be adequately padded to avoid ulnar nerve paralysis due to compression;
 - eye protection to avoid corneal ulceration and ocular trauma.
- Informed consent:
 - Patients should be adequately informed by the surgeon of the indications for surgery, possible alternative treatments, the expected advantages from surgery, general and specific complications and possible rehabilitation therapy, as well as of the clinical consequences of potential permanent postoperative injuries. The information provided should be clearly explained, complete and prompt. After providing the most complete information, the physician will seek the patient's consent to perform surgery, especially taking into full consideration any expression of dissent, even on individual aspects of the procedure or its potential consequences.

Therapeutic pathway

Patient preparation for surgery

- Antibiotics
 - as in thyroid surgery [23, 24], antibiotic therapy is not indicated, except for particular cases: severe diabetes, valvular disease, immune deficiency (hemodialysis or transplant patients).
- Antithrombotic prophylaxis
 - according to international guidelines [25], mechanical antithrombotic prophylaxis (with appropriate elastic compression stockings or intermittent pneumatic compression) and pharmacologic prophylaxis are indicated in surgeries lasting >45 min and in patients aged >40 years). There is no clinical evidence demonstrating an increased risk of intra- and postoperative bleeding in patients treated with low-dose low molecular weight heparin (2,000–4,000 IU/day) for antithrombotic prophylaxis.

Transmission of information and the informed consent should preliminarily take place at the initial outpatient visit and be renewed at admission (before surgery), especially if enough time has passed such that the initial conditions may have changed. In fact, the patient must be given the opportunity to discuss in depth with his/her physician (or other trusted person) the information received and, if desired, to get information on the health facility where he or she will be treated and/or on the team that will perform the surgery. Given the peculiarity of the therapeutic intervention (partial or total removal of parathyroid glands) and its potential consequences on the physical integrity of the subject [27], it is necessary that written documentation of the informed and conscious consent be retained, and that the informed consent process be documented in a specific chart note. To this end, the following consent form is accepted and should be personalized and signed off both by the patient and the physician each time:

Primary hyperparathyroidism

INFORMED CONSENT FORM

I, the undersigned, declare having been informed in a clear and understandable manner by Dr., both at initial visit and at admission, that the condition I was diagnosed with, i.e. Primary Hyperparathyroidism, requires surgical intervention.

The scope, benefits (also relative to alternative treatments), possible risks and/or foreseeable injuries have been clearly explained to me. It has been explained to me that, if ultrasound and/or scintigraphic findings will be confirmed intraoperatively, the scheduled surgery will consist of removal of the diseased gland or glands, or of sub-total or total removal of parathyroid glands in the event that all glands are affected.

I have been informed that this procedure may involve:

Persistent or recurrent hyperparathyroidism if intraoperative detection of the affected gland is not possible, or in case one or more supernumerary and/or ectopic diseased parathyroid glands remain undetected.

Temporary or permanent injury to the laryngeal nerves that innervate the vocal cords, with sometimes severe voice alterations. In case of bilateral laryngeal nerve injury, breathing difficulties may arise that may necessitate tracheostomy, which is nearly always temporary. Voice alterations may include hoarseness of the voice, breathy, diplophonic (double-toned), high-pitch voice, as well as changes in timbre, tone, extension, intensity and fatigue in vocal use, with singing difficulties. Difficulty swallowing liquids that is usually transient may accompany these alterations.

Temporary or permanent injury to the explored parathyroid glands or to the gland stump (sub-total parathyroidectomy), with subsequent alterations in calcium and phosphorus blood levels requiring calcium and vitamin D supplementation, possibly for life.

Need to remove one or both thyroid lobes if the surgeon suspects that a parathyroid gland is located within the thyroid, if malignant disease is suspected or in case of concomitant thyroid disease necessitating surgical removal of the gland. In the latter case, lifelong thyroid hormone replacement therapy will be needed.

Need to remove partially or completely the thymus gland.

Postoperative bleeding that could require reintervention for hemostasis.

Wound infection.

The surgeon has sufficiently informed me about the incidence of these complications (also referring to his/her own experience), and has explained to me that surgery, and parathyroid surgery in particular, cannot be considered as devoid of risks even when performed with rigorous technique, since the laryngeal nerves and parathyroid glands may be temporarily or permanently injured due to causes (nerve exposure, scarring, cold- or heat-induced nerve damage, vascular damage and other unknown causes) that are independent of a correct execution of the surgical procedure.

I have also been told that I will have a surgical scar on my neck.

In any case, I am aware that if the need to rescue me from an immediate, otherwise unavoidable danger arises that could cause serious injury to myself, or if difficulties are encountered with the planned technique during surgery, the surgical team will perform all the procedures they deem necessary in order to prevent or reduce the harm, and to conclude the surgical procedure in the safest conditions, varying the nature of the planned procedure if necessary.

Now, therefore, I hereby declare that I have been asked to read carefully the content of this two-page form, which actually corresponds to what I have been extensively told. I hereby declare that I understand the meaning of what has been explained to me and that I do not need further clarifications beyond those I asked for, which I have written with my own hand below:

Now, therefore, I consciously **consent / do not consent** to the proposed surgical procedure.

I am aware that I may withdraw this consent at any time, by telling the physicians in charge of my care.

Patient’s legible signature.

Physician’s legible signature.

P.S.: I hereby **authorize / do not authorize** the physicians in charge of my care to treat to the best of their knowledge and belief other conditions discovered during surgery and not previously diagnosed, but requiring non-deferrable treatment due to urgent or potentially life-threatening situations, being aware that the surgical plan originally proposed and agreed upon might have to be modified.

Patient’s legible signature.

Physician’s legible signature.

Date and time

Secondary hyperparathyroidism

INFORMED CONSENT FORM

I, the undersigned, declare having been informed in a clear and understandable manner by Dr., both at initial visit and at admission, that the condition I was diagnosed with, i.e. Secondary Hyperparathyroidism, requires surgical intervention. The scope, benefits (also relative to alternative treatments), possible risks and/or foreseeable injuries have been clearly explained to me. It has been explained to me that the scheduled surgery will consist of sub-total removal of parathyroid glands, leaving only a remnant of one gland, or of total removal of all parathyroid glands and possible reimplantation of a fragment.

I have been informed that this procedure may involve:

Persistent or recurrent hyperparathyroidism if intraoperative detection of the affected gland is not possible, or in case one or more supernumerary and/or ectopic diseased parathyroid glands remain undetected.

Temporary or permanent dysfunction of the parathyroid remnant left in place or reimplanted, with subsequent alterations in calcium and phosphorus blood levels requiring lifelong calcium and vitamin D supplementation

Need to remove one or both thyroid lobes if the surgeon suspects that a parathyroid gland is located within the thyroid, or in case of concomitant thyroid disease necessitating surgical removal of the gland. In the latter case, lifelong thyroid hormone replacement therapy will be needed.

Temporary or permanent injury to the laryngeal nerves that innervate the vocal cords, with sometimes severe voice alterations. In case of bilateral laryngeal nerve injury, breathing difficulties may arise that may necessitate tracheostomy, which is nearly always temporary. Voice alterations may include hoarseness of the voice, breathy, diplophonic (double-toned), high-pitch voice, as well as changes in timbre, tone, extension, intensity and fatigue in vocal use, with singing difficulties. Difficulty swallowing liquids that is usually transient may accompany these alterations.

Need to remove partially or completely the thymus gland.

Postoperative bleeding that could require reintervention for hemostasis.

Wound infection.

The surgeon has sufficiently informed me about the incidence of these complications (also referring to his/her own experience), and has explained to me that surgery, particularly parathyroid and thyroid surgery, cannot be considered as devoid of risks even when performed with rigorous technique, since the laryngeal nerves and parathyroid glands may be temporarily or permanently injured due to causes (nerve exposure, scarring, cold- or heat-induced nerve damage, vascular damage and other unknown causes) that are independent of a correct execution of the surgical procedure .

I have also been told that I will have a surgical scar on my neck.

In any case, I am aware that if the need to rescue me from an immediate, otherwise unavoidable danger arises that could cause serious injury to myself, or if difficulties are encountered with the planned technique during surgery, the surgical team will perform all the procedures they deem necessary in order to prevent or reduce the harm, and to conclude the surgical procedure in the safest conditions, varying the nature of the planned procedure if necessary.

Now, therefore, I hereby declare that I have been asked to read carefully the content of this two-page form, which actually corresponds to what I have been extensively told. I hereby declare that I understand the meaning of what has been explained to me and that I do not need further clarifications beyond those I asked for, which I have written with my own hand below:

Now, therefore, I consciously **consent / do not consent** to the proposed surgical procedure.

I am aware that I may withdraw this consent at any time, by telling the physicians in charge of my care.

Patient’s legible signature.

Physician’s legible signature.

P.S.: I hereby **authorize / do not authorize** the physicians in charge of my care to treat to the best of their knowledge and belief other conditions discovered during surgery and not previously diagnosed, but requiring non-deferrable treatment due to urgent or potentially life-threatening situations, being aware that the surgical plan originally proposed and agreed upon might have to be modified.

Patient’s legible signature.

Physician’s legible signature.

Date and time

Therapeutic pathway

Surgical treatment

- Indications for parathyroidectomy (PTx):
 - symptomatic primary hyperparathyroidism;
 - asymptomatic primary hyperparathyroidism [13, 19] with at least one of the following conditions:
 - serum calcium levels: 1.0 mg/dL above the upper limit of normal;
 - creatinine clearance <60 cc/min;
 - bone mineral density: *T* score < −2.5 at the 3 measurement sites (lumbar spine, femur, and 1/3 distal radius)/prior fragility fracture;
 - age <50 years.

In selected cases of asymptomatic HPT I (with difficult follow-up, when the patient appears to be willing to solve the problem even though the criteria are not met), PTx may be considered even in the absence of at least one of the aforementioned criteria, if only one parathyroid gland is suspected to be affected based on preoperative localization studies (ultrasound or scintigraphy) [16].

– Secondary hyperparathyroidism:

The indication for surgery is established by a nephrologist, in agreement with the surgeon, after the failure of medical therapy.

An absolute PTH value signifying the need for PTx has not been established. The decision should be based on [4]:

- laboratory values: PTH >500–1,000 pg/mL [4, 5, 17] and/or hypercalcemia (>10 mg/dL) or hyperphosphorremia (>6 mg/dl);
- ultrasound evidence of increased parathyroid volume (estimated volume >300–500 mm³ or maximum diameter >1 cm) [17];
- clinical signs (itch, bone pain, calciphylaxis: ischemic skin ulcers with extensive vascular calcifications);
- radiological signs (mainly subperiosteal bone resorption);
- histological signs (bone biopsy is not considered as a prerequisite for surgery in all cases).

Before surgery, patients should be assessed and treated for possible aluminium overload.

For a correct therapeutic approach aimed to exclude those forms in which functional autonomy of one or more glands has not been ascertained, treating patients with calcium-mimetic agents should always be considered and the individual response evaluated.

– Tertiary hyperparathyroidism [4, 28]:

Indications for PTx after renal transplantation have not been defined. However, PTx should be considered in case of:

- severe hypercalcemia (>11.5–12.0 mg/dL)
- persistently elevated serum calcium (>10.2 mg/dL) at 3 months–1 year after transplantation;
- severe osteoporosis;
- symptomatic hyperparathyroidism (fatigue, itch, bone pain and/or pathologic fractures; peptic ulcer, altered mental status, depression, irritability, nephrolithiasis);
- failure of the transplanted kidney secondary to hyperparathyroidism;
- persistently elevated PTH levels.

The best prevention of post-transplant HPT is the effective management of patients on transplant waiting list, even with pre-transplant PTx in advanced and resistant forms.

• Surgical treatment

- Primary hyperparathyroidism
Single gland disease suspected on preoperative localization studies

- Minimally invasive techniques (when imaging studies allow localization of the diseased gland, with concordance between ultrasound and scintigraphy):

- Open (*Open Minimally Invasive Parathyroidectomy*, OMIP) and intraoperative (I.O.) measurement of PTH [29];
- radioguided (*Minimally Invasive Radioguided Parathyroidectomy*, MIRP) [30];
- video-assisted (*Minimally Invasive Video-Assisted Parathyroidectomy*, MIVAP) and I.O. measurement of PTH [31];
- endoscopic, via median or lateral approach and I.O. measurement of PTH [32, 33].

Recent evidence suggests that, in case of minimally invasive “focused” parathyroidectomy, I.O. measurement of PTH may be omitted when there is a concordance between preoperative localization studies [15, 16].

- Traditional technique (four-gland exploration).
- Robotic-assisted parathyroidectomy

We briefly mention this technique that has been used in recent years, although to a minimum extent given the limited spread of robots and the high costs, with the transthoracic [34] (for ectopic mediastinal parathyroids) and transaxillary [35] approaches, even when parathyroidectomy is combined with thyroid surgery [36].

- Multiple gland disease suspected
 - Bilateral neck exploration with conventional or video-assisted technique in expert hands [37–39] (four-gland exploration: sub-total PTx, total PTx with autotransplantation and possibly, if a Tissue Bank is available, cryopreservation).
- Secondary and tertiary hyperparathyroidism
- Although there is no clear superiority of a technique over another [28], sub-total (7/8) PTx leaving a parathyroid remnant in situ [40] is advised [4].
Criteria for selecting the gland to represent the remnant gland left in situ:
 - Favourable location relative to the recurrent laryngeal (not close to the nerve);
- the smallest parathyroid gland, still surrounded by adipose tissue and well vascularized should be preferred, whereas glands with nodular hyperplasia and glands exhibiting sestaMIBI uptake should be excluded, if possible;
- a remnant corresponding to the size of two normal parathyroid glands should be left in situ [5];
- it is useful to secure two titanium clips to the gland stump using a Prolene 4–0, to create a landmark to use in case the stump needs to be removed.
- Total PTx with reimplantation [41, 42]
reimplantation in the forearm is advised since parathyroid graft function can be easily assessed by sampling blood from both forearms (do not use the arm with arteriovenous fistula in dialysis patients), preferably with cryopreservation of parathyroid tissue to reimplant in the event of severe and difficult to control postoperative hypocalcemia, if a Tissue Bank is available (which is essential as per the current Italian regulation).
- Total PTx is not advised [6] (there are justified doubts as to total PTx, since this procedure could favour the onset of adynamic bone disease, which predisposes to calcium deposition in extraskelatal tissues), although it can be offered to elderly patients not eligible for transplantation.

It is advisable to remove the thyreo-thymic ligament and the thymic horns [5, 28], even when routine I.O. PTH measurement (which has not been validated in HPT II) is performed and regardless of the technique used.

In patients with absolute contraindications to PTx, ultrasound-guided percutaneous ethanol injection of one or more hyperplastic glands [4, 5, 17, 43, 44] may be considered.

Medical therapy with calcium-mimetic agents should be considered for those patients in whom surgical treatment

for any form of hyperparathyroidism is contraindicated (due to relevant comorbidities, patient's refusal, persistent hyperparathyroidism after failure of surgery) [16, 45].

- Parathyroid carcinoma
Parathyroid carcinoma is a rare disease that should be suspected in the presence of substantially increased serum calcium and PTH levels. It must be treated surgically, with removal of the tumour and the surrounding structures: thyroid lobe, ipsilateral parathyroid gland, and ipsilateral central compartment lymph node dissection [46].
- Hyperparathyroidism associated with polyendocrine syndromes (MEN)
Primary HPT is common to both MEN1 [47], or Wermer's syndrome (with associated tumours of the pituitary gland, endocrine pancreas and digestive tract) and MEN2A [48], or Sipple's syndrome (with associated pheochromocytoma and medullary thyroid cancer).

In MEN1, hyperparathyroidism should be treated first, to remove the stimulant effect of hypercalcemia on gastrin secretion. Due to hyperplasia of all parathyroid glands, hyperparathyroidism should be preferably treated with sub-total parathyroidectomy or, as a second choice, with total parathyroidectomy with autotransplantation and cryopreservation. Regardless of the technique used, the thyreo-thymic ligament and the thymic horns must also be removed because of possible supernumerary parathyroid glands [49].

In MEN2A, adrenalectomy should precede thyroidectomy. During thyroidectomy, all parathyroid glands should be explored and, as in sporadic HPT I, removal should be limited to diseased glands (removal of enlarged glands, sub-total PTx, PTx with autotransplantation and possibly cryopreservation) [48].

- Intraoperative PTH
Intraoperative PTH measurement is a very useful adjunct to all minimally invasive techniques for the treatment of HPT I, with the exception of radioguided parathyroidectomy (where, however, I.O. PTH testing could confirm successful parathyroidectomy [50]). It may be omitted if there is any concordance between preoperative localization studies [15, 16]. Although a $\geq 50\%$ drop from baseline (blood sampling before induction) in serum PTH levels 10 min after removal of the adenoma is generally considered as adequate [51–53], this interpretative criterion of I.O. PTH is characterized by false-positive results in case of multiglandular disease [53]. More stringent criteria have been proposed [38, 55] that usually require a return of PTH

levels to the normal range to consider the procedure successful. The usefulness of I.O. PTH is controversial in secondary and tertiary HPT. When used, a drop in serum PTH levels by at least 75 % is considered satisfactory.

- Drainage
Not required after minimally invasive surgery, optional in other cases.
- Histological examination
On cryostat-prepared sections for tissue identification and, after processing, for definite diagnosis. If I.O. PTH measurement is performed, intraoperative histological examination is not required.

Therapeutic pathway

Postoperative management

Postoperative management should be provided by qualified medical and nursing staff who has been trained to recognize and treat possible complications, such as

- Dyspnea,
- bleeding,
- acute hypoparathyroidism.
- Nursing care:
 - check the wound for possible hematoma formation;
 - if present, check drains for patency and proper functioning;
 - immediately notify the on-call physician in case of:
 - abundant blood loss from drains,
 - swollen wound,
 - onset of agitation, dyspnea, feeling of tightness around neck,
 - signs of hypocalcemia (paresthesias, Chvostek's and Trousseau's signs);
 - in asymptomatic patients, measure calcium levels on the first and second postoperative day;
 - measurement of intact PTH levels 24 and 48 h after surgery is optional.
- Medical care:
 - in case of cervical hematoma with compressive symptoms, immediately remove dressing and sutures and reopen the wound at the bedside, if

required by the patient's conditions. In the meantime, on-site staff must quickly prepare the operating room and notify the surgeon for re-exploring the wound;

- wound dressing before discharge;
- drain removal (after removing suction) on the first or second postoperative day;
- in sub-total or total parathyroidectomy, calcium and vitamin D supplementation (intravenously, if necessary) should be started early after surgery (1–2 g of calcium carbonate t.i.d. and calcitriol up to 2 mcg/day [5]). In HPT II, further treatment adjustments should be guided by a consultant nephrologist;
- if PTx combined with thyroid lobectomy and isthmectomy, start thyroxine replacement therapy at adequate doses.

Therapeutic pathway

Management of major complications

- Hypocalcemia
Hypocalcemia may be more or less severe, with the onset of numbness, paresthesias, muscle cramps, tetany and, in some cases, even seizures. Besides being caused by the drop in PTH, hypocalcemia may be a consequence of the hungry bone syndrome secondary to osteodystrophy, in which the bone tends to “retrieve” calcium from the interstitial fluid after abrupt removal of the stimulus provided by HPT. After parathyroidectomy for HPT II, frequent measurements of serum calcium levels are required to adjust treatment with intravenous calcium gluconate. Measuring serum potassium levels in HPT II is essential to decide when dialysis should be done (untreated hyperkalemia may lead to irreversible cardiac arrest).
- Temporary or permanent injury to the recurrent laryngeal nerve
 - If respiratory diplegia is present at the time of tracheal extubation:
 - do not perform immediate tracheostomy and keep the patient intubated for 24 h. Then remove the endotracheal tube using a fiberoptic bronchoscope to verify that at least one vocal cord has functionally recovered;
 - if respiratory diplegia persists, keep the patient intubated for additional 24 h;
 - if respiratory diplegia persists after 48 h, perform tracheostomy.

- In case of phonatory diplegia with an adequate airway:
 - do not perform tracheostomy;
 - initiate speech therapy according to the timing established by the ENT surgeon/phoniatrist.
- In case of unilateral vocal cord paralysis:
 - initiate speech therapy according to the timing established by the ENT surgeon/phoniatrist, possibly after documentation (video recorded fiberoptic laryngoscopy).
- In case of severe dysphagia to liquids, administer oral thickened liquids (gels) to prevent dehydration.

In any case, clinical observations as well as proposed and/or performed treatments must be accurately noted in the patient's chart.

Hospital discharge and patient information

- Hospital discharge

- Patient information

- practical advice at discharge

It may be useful to provide the patient with a leaflet containing practical information on self-management of recovery and contact information for use in case of need for advice. The proposed form is as follows:

Practical advice after parathyroidectomy

An individual who has undergone parathyroid surgery will have to monitor serum calcium levels frequently, according to the indications provided by the physician who will follow his/her postoperative course, recovery and progresses over time (follow up). Background therapy with calcium and/or vitamin D, if prescribed, must be taken regularly in order to prevent hypocalcemia, which manifests as tingling in the arms, legs and lips, or as muscle spasms, particularly in the hands (tetanic spasms). Calcium tablets/sachets may be taken on an empty stomach or, if not well tolerated, with meals.

After surgery, a short recovery period is usually necessary. The patient is allowed to freely move the neck, and covering a dry wound is not necessary. After the recovery period, the patient will be able to engage in all work, family and social activities without limitations, even when parathyroidectomy is combined with thyroidectomy. Changes in voice tone are possible after surgery. The voice may either be clear or weak (early fatigability, difficulties in speaking loudly, yelling or singing). Most of these effects resolve completely within a few months. From an esthetic standpoint, a surgical wound is considered healed after about three months. During the weeks following surgery, the individual may experience difficulty swallowing (lump in the throat sensation, firm neck skin, sensation of tightness of the chest skin during swallowing). These disturbances are generally transient and caused by deep tissue scarring. Women of childbearing potential will be able to have normal pregnancies and breastfeed. Frequent monitoring of serum calcium levels will be necessary during pregnancy, as normal calcium levels are essential to normal bone formation in the fetus. In case partial or total thyroidectomy was performed, frequent monitoring of thyroid hormones will also be required.

For further clarification please contact the Endocrine Surgery outpatient service on between the hours of and, phone

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- Hospital discharge summary
 - Provide the patient with a complete clinical report, signed off by the attending physician who discharges the patient, to be given to his/her primary care physician and containing the following essential information:
 - date of admission and admit diagnosis;
 - main diagnostic investigations performed, with particular emphasis on those with altered results;
 - date, name and description of surgical procedure;
 - discharge diagnosis;

- description of the clinical course, with accurate highlighting of any complications (haemorrhage, dysphonia, dysphagia, hypocalcemia);
- medications on discharge, clearly indicating posology and method of administration;
- recommended clinical and/or diagnostic follow-up.

A copy of the discharge summary should be placed in the patient's chart.

Outpatient care and follow-up

The following take place at the Endocrine Surgery outpatient service:

- *Initial visits* of patients referred by their primary care physician or by a specialist.
 - Patients to whom surgery is proposed should be provided with the following information:
 - surgical treatment of hyperparathyroidism and concomitant thyroid surgery in case of co-existing thyroid disease or if during surgery the surgeon suspects that a parathyroid gland is located within the thyroid;
 - possible alternative therapies;
 - advantages that surgery may offer and possible risks associated with the surgical procedure to be performed;
 - clinical consequences of potential complications and possible treatments.
 - The patient is provided with a short clinical report that includes
 - medical history, with particular reference to health conditions that may require special consideration;
 - physical examination;
 - diagnosis;
 - proposed treatment;
 - ordered diagnostic testing/investigations;
 - agreement or disagreement with other consultants' reports brought by the patient for examination;
 - if surgery is proposed, the information provided should be clearly noted on the report, to obtain a preliminary consent to the recommended treatment;
 - application for hospital admission, including priority for admission.
- *Follow-up visits*, if surgical dressings are needed. Otherwise, the patient will be referred to the

appropriate outpatient department (Endocrinology, Nephrology and Dialysis, Urology) for follow-up.

- *ENT consultation* for follow-up, with fiberoptic laryngoscopy to assess vocal cords mobility in case of symptoms (hoarseness), and possible speech therapy, based on recommendations by the ENT surgeon and/or the phoniatrist.

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