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Clinicopathological Phenotype of Parathyroid Carcinoma. Therapeutic and Prognostic Aftermaths

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Rezumat

Fenotipul morfoclinic al cancerului paratiroidian. Consecințe terapeutice și prognostice

Cancerele paratiroidiene (CP) sunt cauze rare dar "devastatoare" ale hiperparatiroidismului primar (HP), diagnosticate cel mai adesea fortuit și cu o confirmare histologică uneori îndoelnică având chiar după un tratament chirurgical bine condus, o evoluție și un prognostic capricios. Sunt prezentate patru neoplasme paratiroidiene din care trei cancere autentice și un adenom paratiroidian atipic (APA). Am înregistrat trei femei și un bărbat cu vârste cuprinse între 32-49 (medie 44) ani. În trei cazuri CP a fost asociat cu HP primar și într-un caz a apărut în cadrul HP renal. Toți pacienții au prezentat fenomenele clinice și biochimice severe produse de hipercalcemie cu o intensitate crescută a simptomatologiei renale, osteoarticulare, musculare sau nervoase, iar într-un caz s-au adăugat manifestările uremice. În două cazuri (unul fiind APA) diagnosticul a fost suspectat pre sau intraoperator, în celelalte două fiind stabilit prin stigmatele de malignitate relevate de examenul la parafină. În toate observațiile s-a practicat exereza în bloc a tumorii cu lobul tiroidian adiacent. Două cazuri (între care și adenomul atipic) au prezentat o vindecare stabilă în timp, în celelalte două înregistrându-se decese la circa 14 luni de la operație. Observațiile noastre, puține la număr, subliniază diversitatea clinică, evolutivă și prognostică a CP care se adaugă dificultăților de diagnostic al acestor leziuni care trebuie evocate în orice condiții suspecte pentru efectuarea unei exereze cu intenție radicală, singura care poate asigura vindecarea.

Cuvinte cheie: cancer paratiroidian, hipeparatiroidism, chirurgie radicală

Abstract

Parathyroid carcinomas (PC) are rare and "devastating" causes of hyperparathyroidism (HP), frequently discovered fortuitously, with not always doubtless pathological confirmation, and dissociate post-therapeutic outcomes and prognosis even after well-performed surgery. We herein report four PT neoplasms, three of them proving to be authentic PCs, and one an atypical parathyroid adenoma. There were three females and one male, aged 32-49 (mean 44) years. In three circumstances PC was associated with primary HP and in one case the tumor had developed on a CKD-BMD (renal HP) background. All patients presented marked clinical and biochemical phenomena related to hypercalcemia with greater intensity of renal, bone, neuromuscular and psychological signs and symptoms to which in one observation specific uremic manifestations were added. Preoperative and intraoperative diagnosis was suspected only in two cases (one of them being in fact an atypical PT adenoma), but in the other two it was established by paraffin section on histological evidence of peremptory stigma of malignancy. Our little experience underlines the wide and protean range of the origins, clinical aspects, course and prognosis of PC, which adds to the difficulties of pre- and intraoperative diagnosis. Awareness of this lesion must be permanent to detect its presence in any unusual eventuality, imposing a radical en bloc resection at the initial operation, assuring the best chance of cure.

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Key words: parathyroid carcinoma, hyperparathyroidism, radical surgery

Background

Even if the first description of parathyroid carcinoma (PC) was attributed to De Quervain (1904), his observation was not accredited so that the first mentions of this tumour remained those of Rankin and Priestley (1928), Wilder (1929), Sainton (1933), Hall and Chaffin (1934). PC is a rare lesion accounting for 0.17 to 5.2 % of patients with PHP, the entity having a higher prevalence in Japan and Italy. (1-8)

Nevertheless the few case reports, retrospective series and several meta-analyses published in the literature totalized about one thousand cases. (9) PCs tend to occur a decade earlier than benign lesions, the sex ratio approaching unity in contrast with female predominance of adenomas. Although the clinical picture is somehow suggestive, most patients having severe hypercalcemia with its corollary features, more than 50% of cases showing bone and kidney disease associated with a multitude of general complaints, many of them exhibiting also a palpable neck tumor, the diagnosis of PC is rarely claimed before surgery. (10,11)

Sure malignancy can be affirmed only by paraffin section showing tumoral invasion of capsule, blood vessels, perineural spaces, soft tissues, thyroid gland and other contiguous structures, or in presence of documented lymph nodes or distant metastases. However, due to its reputed aggressiveness and prognosis dependence of the earliness of diagnosis and radical therapy approach, it is paramount that the clinical suspicion be made before surgery. (12,13,14)

Our own cases discussed below are characterized by large differences in etiology and clinical or pathological expression, which determined the surgical tactics and postoperative results.

Case reports

Case report 1. *ME, a 45 year-old female is hospitalized in our unit with a clinical and biological PHP recurrence after the excision of a huge (15 g) right sided parathyroid adenoma performed 3½ years ago in another unit resulting in disappearance or at least diminution of the majority of her complaints. However, for about 6 months she accused the reinstallation of bone pains and urinary signs with growing level of serum Ca^{2+} (3.30 mmol/L), iPTH (190 ng/L), FA (340 ui/L). Ultrasound noticed a round, regular hypoechogenic lesion of 1.5 cm ϕ (Fig. 1) situated approximately in the same location. Reintervention, hampered by adhesions, identified a 1.5 cm ϕ well-constituted, irregular, firm mass, which was en bloc resected with the ipsilateral thyroid lobe and isthmus.*

Paraffin section objectifies the presence of a thick capsule, invasion of neighbouring tissues, trabecular growth pattern enabling the diagnosis of typical chief cell PC (Fig. 2). Postoperatively, after about one year of clinical and biological improvement, the hypercalcemic features reappeared and despite radiotherapy, the patient died 14 months after the second intervention. (15,16)

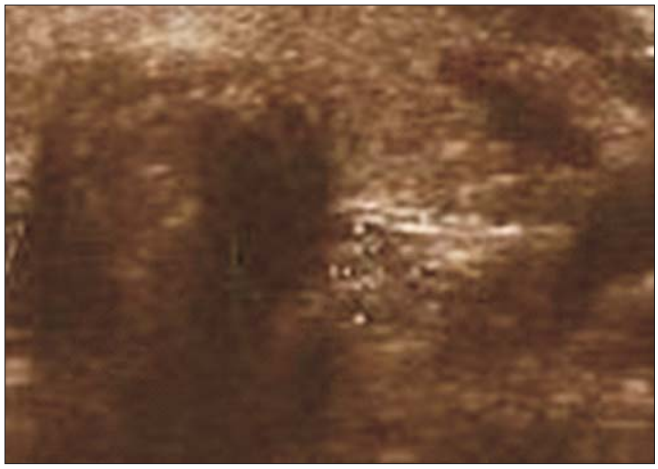

Figure 1. *US: inferior left hypoechogenic mass*

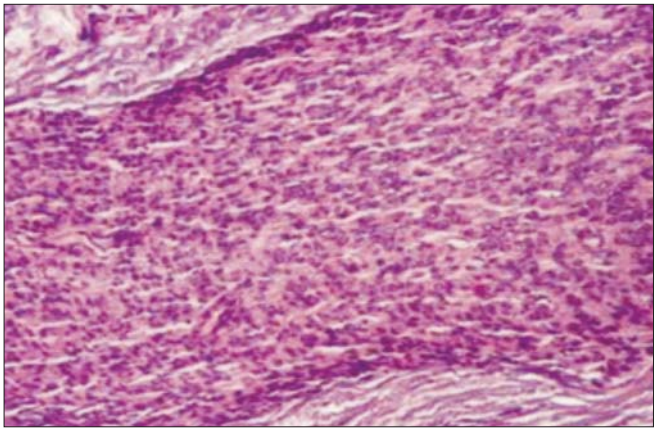

Figure 2. *Chief cell parathyroid carcinoma HE x 200*

Case report 2. *CM, a 32 year-old female addressed our clinic with cachexia (40 kg !), influenced general condition, secondary anemia (Hct=27%), generalized osteodistrophy, recent fracture sequelae (right humerus and femur bilaterally) and renal lithiasis treated by ESWL. Clinical examination revealed a 3 cm ϕ firm formation situated at the right thyroid lobe level without limphadenopathy.*

Laboratory findings were suggestive for PHP: calcemia 3.1 mmol/L, iPTH 390 mmol/L, FA 340 Ui/L. Ultrasound revealed normal thyroid gland but at the level of the inferior pole of the right lobe identified a large 3 cm ϕ, hypoechoic, homogeneous tumor which we thought to be a parathyroid carcinoma due to its severe clinical and laboratory features. Intraoperative findings confirmed the clinical assumption: a firm, bulky tumor adhering closely to the thyroid, was discovered and widely removed together with the thyroid lobe and isthmus (operative piece 35 g).(Fig. 3) Pathology

confirmed the diagnosis of PT carcinoma showing increased and disorderly chief cell proliferation, necrosis, capsular and vascular invasion. (Fig. 4) After nearly 9 months of favourable outcome with reduction of serum Ca^{2+} and iPTH, their levels begin to rise again and clinical and metabolic complaints reoccurred together with multiple metastases, complementary therapy being ineffective. The patient died 14 months after surgery.

Case report 3. *CV, a 49 year-old male on a hemodialysis regimen for three years for chronic renal failure consecutive to a chronic glomerulonephritis dating back 13 years. He accused general and especially muscular asthenia, adynamia, generalized, intense pruritus and progressive osteoarticular pain. Bioumoral data indicated iPTH 710 nmol/L, serum Ca 2.6 mmol/L, ionized Ca 1.3 mmol/L. Clinical examination and cervical ultrasound highlighted a painless left hypoechoic "thyroid" nodule of 44x37 mm ϕ, with firm elastic consistency (Fig. 5).*

With a diagnosis of chronic kidney disease-metabolic bone disorder (i.e. "renal" hyperparathyroidism) our patient underwent surgical exploration, three parathyroids (both right and the left superior), all of them rounded, with increased volume being successively identified in their usual locations and excised (total weight 3 g). The fourth (left inferior) gland could not be found so we proceeded to extirpation of the adherent "thyroid" nodule together with the adjacent tissue. The frozen section asserted the presence of thyroid tissue, but to our surprise paraffin section specified a clear cell carcinoma (Fig. 6). In defiance of total elimination of parathyroid tissue, hypocalcemic features did not appear and postoperative course was favourable, the patient presenting normal values of iPTH, continuing hemodialysis and being alive at 5-year follow-up. (17,18)

Last case report: *IA, a 49 year-old female, presented for a 2 cm ϕ, firm, rather immobile nodule without regional lymph node swelling, situated in the left paramedian cervical region. She also accused weakness, weight loss, bone pains and neurotic complaints. Laboratory results showed normal thyroid tests, but hypercalcemia (13.1 mg dL) and elevated iPTH level (380 pg/nL). Rx examination showed osteoporosis and cervical ultrasound detected a 20 x 18 mm ϕ round, well-defined, homogenous, hypoechoic mass situated posterior and inferior to*

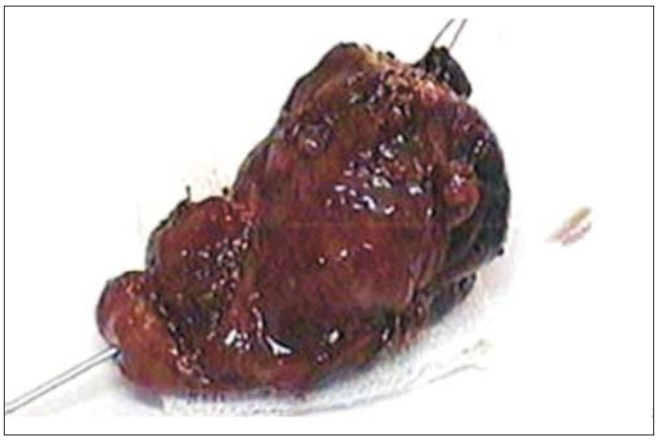

Figure 3. *Operative specimen*

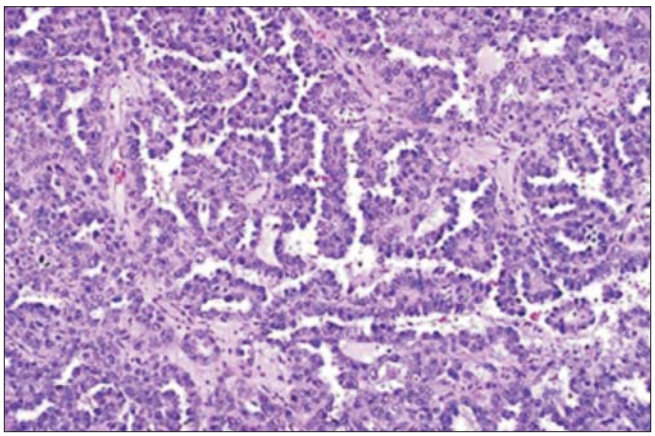

Figure 4. *Chief cell parathyroid carcinoma HE x 100.*

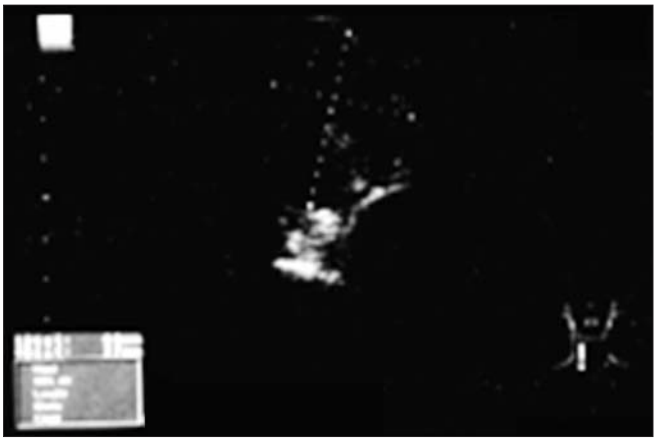

Figure 5. *US:left inferior "thyroid" nodule*

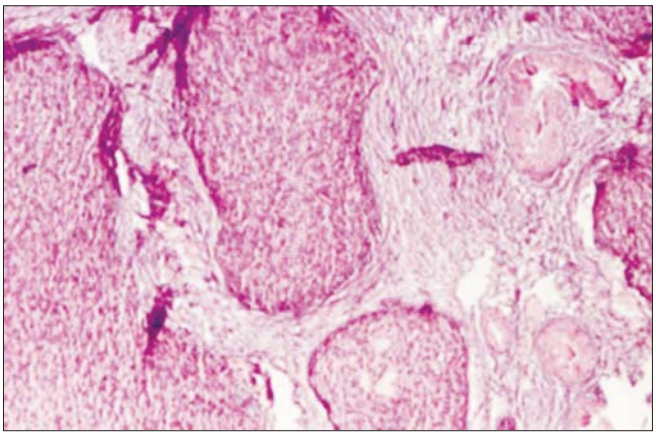

Figure 6. *Parathyroid clear cell carcinoma HEx40*

the left thyroid lobe.

Establishing the diagnosis of hyperfunctioning parathyroid adenoma she underwent surgical exploration and a large, firm, yellowish brown tumor making common body with the thyroid lobe was discovered. The size, consistency, adhesions and biochemical dates suggesting the possibility of a malignant lesion led us to practice an en bloc exeresis of the lesion with the intimated adhered thyroid lobe (Fig. 7). The other parathyroids were normal. Postoperatively, moderate hungry bone syndrome effects occurred. Histology showed an encapsulated lesion composed of islands and nests of mainly chief cells with trabecular growth pattern, nuclear pleomorphism, rare mitotic activity and broad fibrous bands traversing the tumor, but no local, vascular and perineural invasion certifying the diagnosis of atypical adenoma (Fig. 8). (20)

Long term follow up certified the complete and stable cure of our patient.

Discussions

Our little case series illustrates the large clinical and morphological variability of PC, confirming fully the outstanding diagnostic difficulties of these rare endocrine entities.

Our first case underlines the uncertainty of the histologic examination, the initially affirmed diagnosis of adenoma becoming doubtful after clinical and lesion recurrence, imposing parathyroidectomy after a three year interval. We evoked either possibility of an erroneous first microscopic evaluation in a indiscernible or with low malignant potential lesion, with possible capsular effraction and "parathyromatosis effect" in the surgical bed, explaining the long free disease interval, or the metachronous development of a "true" new tumor from the other ipsilateral gland. This case highlights the compulsoriness of prolonged surveillance in tumors with unusual volume and appearance with excessive amounts of serum Ca^{2+} and iPTH.

The second case is the "robot portrait" of a PC with florid malignancy, both by appearance in an young person, dimensions of the lesion and severity of multiorgan clinical and bioumoral syndrome of hypercalcemia and hormonal excess. Although even in this patient there were some doubts about regarding the pathologic verdict, the unfavourable evolution and precipitated death confirmed the diagnosis.

The third case represents a type which is extremely rare in the literature, there being less than thirty observations published. The possibility of lesion sequence should be mentioned: hyperplasia, adenoma, carcinoma after a prolonged period of hemodialysis. In this case we should also mention the pitfalls of intraoperative diagnosis, since after relatively " comfortable" removal of three hyperplastic parathyroids, the fourth one was not be found anywhere, and frozen section was not helpful, indicating a false-positive diagnosis of thyroid tissue! Also worth noting is that it is our only case with immediate and long-term favourable evolution, probably due to the "protective role" ensured by chronic kidney insufficiency. (18,19)

Finally, the last lesion was definition ambiguous, whose final diagnosis and unpredictable prognostic, both the amount of clinical and mostly histological elements, imposed an adapted surgical strategy. We were unfortunately unable however to anticipate neither a definite cure nor an aggressive clinical behaviour that overtime may acquire the active features of malignancy. (20,21)

The presented cases encompass the etiopathogenical, clinical, pathological and evolutive extreme variability of malignant parathyroid tumors due to which diagnostic hesitations and surgical inadequacies arise.

So sporadic or familial, isolated or associated with another pathology (MEN, HPT-Jaw Tumor), functional or nonfunctional, eutopic or ectopic, PC is characterized by hypercalcemic bone and urinary syndrome magnitude, "massive" levels of calcemia and PTH (true biologic marker of the disease), frequent but inconstant presence of a neck tumor and malignant potential with preferential locoregional dissemination, but frequent recurrences and late metastasis. Severe complications such as hypercalcemic crisis, acute pancreatitis, perforated or recurrent bleeding peptic ulcer disease and multiple fractures are also noted. In 30-76% of cases a cervical

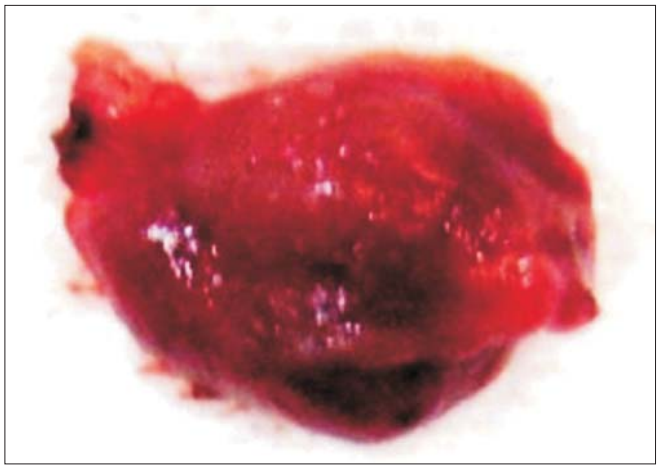

Figure 7. *Operative specimen*

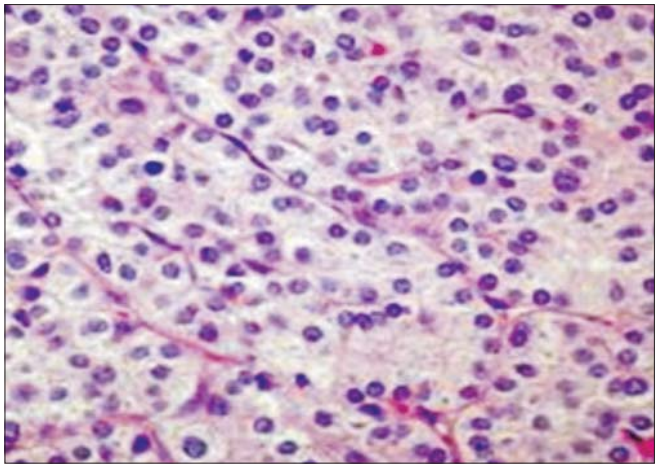

Figure 8. *Atypical parathyroid adenoma HE x 400*

tumor with variable volume, firm consistency and tendency to invasion of contiguous anatomic structures (i.e. thyroid gland, laryngeal recurrent nerve, trachea, oesophagus, musculature, regional lymph nodes), and also to determine late hematogeneous distant metastasis (lung, liver). (12,22,23,24,25,26)

Standard diagnostic approaches in PHP include sonography and sestamibi scan which confirm the presence, volume and location of the lesion, however being unable to specify its benign or malignant nature, but objectifying the presence of adenopathy or associated thyroid lesions. CT scanning, MRI and 99Tc sestamibi scanning combined with sestamibi single photon computer tomography (SPECT) present the highest predictive value of the available imaging techniques, without having a role in the diagnosis of these lesions, but can be ordered when a decision has been made to operate. (25,26, 27,28,29,30)

Diagnostic difficulties are mainly related to pathological examination. Paraffin section is the only exam specifying the exact nature of the lesion, FNAB and frozen section being formally contraindicated because of the risk of tumoral seeding.

Pathology is very similar to that of adenomas, creating confusions even for trained specialists. The tumor is composed mainly by chief cells and rare oxiphylic cells, with trabecular, acinous or compact disposal. Stated by Schantz and Castleman the traditional criteria of malignancy includes presence of glandular fibrous septs, nuclear pleomorphism and atypias, high mitotic activity and capsular, vascular or perineural infiltration and nodal and distant metastases or recurrences. Because many lesions diagnosed as carcinomas subsequently do not recur, some authors believe that only the last three features certify the diagnosis and Kameyama proposed a classification of PCs with limited infiltration as low grade and those with widespread infiltration as "high grade" tumors. (10,12,19,30,31)

Electron microscopy attests nuclear and mitochondrial changes significant for increased secretory activity, nuclear higher diameter and atypias and DNA aneuploid pattern. These elements, without stating a clear difference from adenoma, may be predictive for any eventual aggressive potential of the tumor. Immunohistochemistry objectifying complete loss of HRTP2 (parafibromin) gene and retinoblastoma protein expression, and overexpression of galectin-3 and Ki-67 antigen, help to distinguish PC from over parathyroid lesions. (32,33) Surgery is the only effective method of therapy for PC and must be adapted to the oncologic principles, the standard operation achieving an en bloc tumor exeresis (respecting the capsule integrity) along with a whole territory of security, including the ipsilateral thyroid lobe, isthmus paratraheal areolar tissue and fat, retrosternal cellular atmosphere, including also the thymus with eventual node dissection. The purpose of thyroid lobectomy, more than removal of the invaded tissue, is to obtain clear margins of the excision specimen.(13,14,24,25,26,34,35). Adenopathy is present in 4-20% of cases and nodal dissection interested laterocervical, central and mediastinal lymphatic metastasis. Prophylactic lymphadenectomy is not recommended.

A more aggressive surgical approach including excision of strap muscles, tracheal "cleaning" or recurrent nerve sacrifice is adopted by few practitioners. Complete tumor removal is sometimes impossible due to important invasion of contiguous structures. (36)

Oncologic exeresis of PC is potentially curative, with a 5 year survival rate situated between 40-85% of cases. Evolution is characterized by the repeated occurrence of relapses at different times, many of which can be surgically removed.

Recurrences appearing in approximatively 40% - 60% of operated PCs in the range of 2 and 5 years after the initial resection are due to an initial erroneous histologic diagnosis, effractions of capsule or incomplete tumoral removal, as well as its aggressive behaviour. They are confronted with their own avatars and risks of iterative cervical surgery: presence of scar tissues and disruption of normal anatomical planes consecutive to previous intervention(s), which may result in greater nervous, vascular or other vital structure deficits. Add to this the volume, the anatomical characters and reports of tumoral recurrences, as well as the difficulties related to topographic distribution and number of these glands. (37,38) Reoperation is mandatory preceded by review of previous surgery procedures and pathology reports, and also imaging studies appropriate for localization of the disease.

From a tactical point of view, after isolation of the jugular vein and internal carotid axis, a symmetrical cervical dissection and a systematic exploration of normal and ectopic locations of these glands, including also the one already operated, are carried out. Operability and ampleness of re-exploration should be objectively assessed before engaging in mutilating or generating complication gestures.

A large resection of tumoral recurrence together with the ipsilateral thyroid lobe and isthmus is done (if it is no practiced in the preceding surgery). Muscular strap structures can be sacrificed, but exeresis may be extended within reasonable limits to muscular layer of the esophagus and even the traheea. (37,38,39)

The attitude toward eventual lymphadenopathy is similar to that recommended during the primary intervention.

Together with precise preoperative location, the intraoperative iPTH assay are important for the successful ablation of these lesions. (39)

Although reoperations, even burdened by important morbidity, represent the main method of therapy for recurrent PC, providing significant symptomatic relief and a transient biochemical remission, a complete cure of the disease is unlikely. Repeated glandular exeresis and also resection of distant metastases have also a palliative character. (38,39,40)

Medical therapy with cinacalcet and bisphosphonates can ameliorate the hypercalcemia but radiotherapy and chemotherapy have been disappointing in recurrent, metastatic or inoperable cases.(41,42)

In conclusion, PC is a rare cause of hyperparathyroidism presenting with a large and misleading clinical and morphological "mask" which continues to pose diagnostic and management challenges for clinicians. The firm preoperative diagnosis is rarely certified at the time of surgery but, if suspected, operation should include an en bloc removal of the

tumor mass together with the ipsilateral thyroid lobectomy, offering the best opportunity for a stable cure of the disease and assuring a long survival. Surgery of recurrences and adjuvant therapies have only palliative effects.

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