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A single Institution experience and a review of the international literature

Ann Ital Chir, 2018 89, 4: 295-304
pii: S0003469X18028695
Epub Ahead of Print - June 11
free reading: www.annitalchir.com

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Parathyroid carcinoma. A single Institution experience and a review of the international literature

INTRODUCTION: *Parathyroid carcinoma (PC) is a slow-growing and very rare malignancy, representing less than 0.005% of all cancers. The rarity of PC makes it hard to create large-scale published series of patients affected by this condition.*
MATERIALS AND METHODS: *We present four cases of PC treated in our Institution and analyze the most salient aspects of this disease highlighted in recent international literature.*
DISCUSSION AND COMMENTS: *In our experience, in 3/4 cases, the clinical presentation of PC was not different compared to adenoma; therefore, the diagnosis was a post-operative histopathological surprise. We noticed a clear, preoperative laboratory evidence of higher values of PTH and calcemia in patients with PC compared to adenoma. In our experience, a surgical approach consisting in parathyroidectomy associated with ipsilateral loboisthmectomy and central neck lymph node dissection offers the best prognostic chance. Moreover, surgery should be performed only in referral centers where an interdisciplinary management is guaranteed. We are confident in suggesting the surgical approach also in patients with poor clinical status due to high calcemia. If performed by experienced surgeons, the surgical risk of parathyroidectomy is low and we assisted to a progressive restoration of neurological function and an improvement in the patient's quality of life. Finally, even if our experience is limited, we observed an association between PC and thyroid cancer that deserves a validation through more comprehensive further studies.*
CONCLUSION: *PC remains a complex disease in which a valid surgical approach represents the only curative treatment.*

KEY WORDS: Parathyroid, Parathyroid carcinoma, Parathyroidectomy, hormone, Surgical oncology

Introduction

Parathyroid carcinoma (PC) is a slow-growing and very rare malignancy, representing less than 0.005% of all cancers. Its reported incidence ranges from 0.5 to 5% due to some geographic variations (1% in USA and Europe and 5% in Japan) and represents less than 1% of all cases of primary hyperparathyroidism [1-9]. The first case of PC was described by the Swiss surgeon Fritz De Quervain in 1909 [10]. Data from the SEER (Surveillance, Epidemiology and End Results) cancer registry showed an increase in PC incidence up to 60% from 1988 to 2003 in the United States; this is probably due to the increased diagnosis of primary hyperparathyroidism (PHPT) in the same period. [6,11]
The etiology of PC remains largely unknown, but many Authors have proposed an association with radiation therapy to the neck, hyper-functioning parathyroid glands, thyroid cancers and chronic renal failure. [12-18] PC may occur sporadically or can be part of a genetic syndrome,

Pervenuto in Redazione Aprile 2018. Accettato per la pubblicazione Maggio 2018
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such as multiple endocrine neoplasia type 1 or 2A and isolated familial hyperparathyroidism. In addition, 15% of patients affected by hyperparathyroidism-jaw tumor syndrome (HPT-JT) develop PC. [19-24]. This autosomal dominant syndrome is characterized by the developing of primary HPT, ossifying fibromas of the mandible and maxilla and renal and/or uterine tumors. Inactivating germline mutations in the tumor suppressor gene HRPT2 (also known as CDC73) are responsible for the development of HPT-JT. HRPT2 encodes the nuclear protein parafibromin, whose function involves regulation of gene expression and inhibition of cell proliferation. [25-28]. Over 70% of sporadic PCs have been linked to sporadic mutations of HRPT2, suggesting a central role of this gene in the pathogenesis of PC. Sporadic PCs can also show abnormalities of other genes, such as retinoblastoma 1, tumor protein P53, adenomatous polyposis coli, and prune homolog 2; moreover, microRNAs and epigenetic abnormalities may also be involved. [29-34].

More than 90% of PCs are secreting tumors characterized by marked hypercalcemia and severe symptomatic disease either systemic or with bone and renal involvement. It is important to remember that two to seven percent of patients with PC have asymptomatic PHPT. [12,13,35,36]. On physical examination, from 30 to 70% of patients with PC present an extra-thyroid, hard, palpable laterocervical mass [12,37,38].

At the time of diagnosis, 15-30% of patients present lymph node metastases at level VI and nearly 30% have distant metastatic lesions. The most common site of distant metastases is the lung, followed by liver and bones [39-43].

Pathological diagnosis of PC is disputable since no firm morphological or molecular criteria are established. Therefore the diagnosis of PC relies on a combination of biochemical, clinical and morphological data.

Due to the rarity of PC, the published series of patients affected by this disease are rare and the number of cases described scanty. Therefore, etiology, natural course, management and prognosis are only partially understood. The purpose of this paper is to present four cases of PC treated in our Institution and to analyze the most salient aspects of this disease highlighted in recent international literature.

Materials and Methods

During the 8-year period (from January 2010 to December 2017), 70 patients underwent parathyroidectomy at Maria Vittoria Hospital for PHPT. Among these patients, four (5.71%) had a histological diagnosis of PC. Before surgery, the levels of calcium and PTH in peripheral blood were measured and we noted that the mean value of these two parameters is considerably higher in patients with PC. (adenoma: PTH 317.84 pg/mL, calcemia 2.665 mmol/L; carcinoma: PTH 1299.5 pg/mL, calcemia 3.073 mmol/L). Demographic, clinical and biochemical data of patients with PC are summarized in Table I.

Case N. 1

37yo male with a past medical history (PMH) positive for nephrolithiasis, erectile dysfunction, diarrhea (suspected Crohn's Disease, not confirmed with intestinal biopsies), and infertility. Diagnosis of PHPT was established on the basis of consensual increase in parathyroid hormone (PTH) and serum calcium (Table I). Neck ultrasonography (US) showed a pathologically enlarged (23 x 15 x 19 mm), hypoechoic, vascularized parathy-

Table I - *Demographic, clinical and biochemical data of patients with parathyroid carcinoma*

	Case 1	Case 2	Case 3	Case 4	Mean
Sex	M	F	F	F	
Age (years)	37	60	68	82	61.75
Basal ioPTH (pg/mL)	670	1193	1195	2140	1299.5
Preoperative calcemia (mmol/L)	3.35	3.02	3.22	2.7	3.073
Preoperative phosphoremia (mg/dL)	1.7	2.5	2.8	2.80	2.45
Lymph node MTS	No	No	No	No	
Distant MTS	No	No	No	No	
Surgical approach	Parathyroidectomy + R loboisthmectomy with LN VI level	Parathyroidectomy	1) Incomplete resection 2) Debulking	Parathyroidectomy + L loboisthmectomy with LN VI level	
Decrease in ioPTH > 50%	Yes	Yes	Not measured	Yes	
Tumor weight (g)	5.2	28	Not available	Not available	
Tumor dimension (cm)	2.5	5	3.4	2	
Post-operative normalization of PTH	Immediate	120 months	Immediate	Immediate	
Post-operative elevation of PTH	No	Yes	Yes, 2 years after surgery	No	
Post-operative hypercalcemia (4.3 years)	No	No	Yes, 2 years after surgery	No	
Recurrence	No	No	Yes, 2 years after surgery	No	

TABLE II - *Schulte Staging System*

T	Tx	No information available
	T1	Evidence of capsular invasion
	T2	Invasion of surrounding soft tissue excluding the vital organs trachea, larynx, and esophagus
	T3	Evidence of vascular invasion
	T4	Invasion of vital organs, i.e. hypopharynx, trachea, esophagus, larynx, recurrent laryngeal nerve, carotid artery
N	Nx	Lymph node not assessed
	N0	No regional lymph node metastases
	N1	Regional lymph node metastases
M	Mx	Distant metastases not assessed
	M0	No evidence of distant metastases
	M1	Evidence of distant metastases
Class		
	I	T1 or T2 N0 M0
	II	T3 N0 M0
	III	Any T, N1 M0, or T4
	IV	Any N, M1
Risk		
	Low risk	Capsular invasionInvasion of surrounding soft tissue
	High risk	Vascular invasion and/or lymph node metastases and/or invasion of vital organs and/or distant metastases

roid gland located below the right lobe of the thyroid gland. Dual-phase ^{99m}Tc-sestamibi scintigraphy showed an early tracer uptake by thyroid gland and a high uptake was revealed at the lower pole of the right thyroid lobe. Delayed imaging showed a decrease in radioactivity in the thyroid gland, while the uptake at the lower pole of the right thyroid lobe persisted. The co-registered CT images by a Hybrid SPECT/CT scan confirmed the presence of a right paratracheal mass in accordance with a right parathyroid adenoma. The patient underwent a right lower parathyroidectomy with a decrease in intraoperative PTH (ioPTH) from 670 pg/mL to 111.6 pg/mL. Histological examination revealed a 2.5-cm, well-differentiated parathyroid carcinoma with focal vascular and capsular invasion. Given the pathological result, the following week, a right loboisthmectomy with central neck lymph node dissection was performed. The post-operative course was uneventful. The histopathological report was negative for lymph node metastases or residual tumor. Patient was released home three days after the operation. At discharge, PTH was 67.6 pg/mL, blood calcium was 2.325 mmol/L, blood phosphate was 2.8 mg/dL and 24-hour urinary calcium was 137.6 mg. The patient did not have any adjuvant therapy. After surgery, the patient experienced a complete remission of the intestinal symptoms and regained a normal sexual function. The patient's follow-up consisted in checking levels of blood calcium, phosphate, PTH and 24-hour urinary calcium every 6 months. At the last follow-up, blood calcium was 2.35 mmol/L, blood phosphate was 2.1 mg/dL, PTH was 44 pg/mL and 24-hour urinary calcium was 180 mg. Currently, no signs of local or systemic recurrence are present.

CASE N. 2

60yo female with PMH of nephrolithiasis and an established diagnosis of PHPT. Preoperative laboratory exams highlighted severe hypercalcemia and a marked increase in PTH (Table I). Neck sonography showed a hypoechoic mass (5.7 x 4 cm) attached to the inferior pole of the left thyroid lobe. Dual-phase ^{99m}Tc-sestamibi scintigraphy showed a high uptake of the tracer at the lower pole of the left thyroid lobe, persisting in delayed imaging and after subtraction of thyroid images, compatible with hyperfunctioning parathyroid tissue. Patient underwent a left parathyroidectomy with a collapse of ioPTH greater than 80% (from 474.68 pg/mL to 78 pg/mL). Histopathological report revealed a 5-cm, encapsulated parathyroid carcinoma with no signs of vascular or capsular invasion. Patient was dismissed in 3rd post-operative day with normocalcemia (2 mmol/L). No adjuvant therapy were performed. Given the histopathological diagnosis, an ipsilateral loboisthmectomy with central neck lymph node dissection was proposed to the patient, who refused the operation. We then saw a progressive PTH elevation (324 pg/mL) associated with normocalcemia (2.30 mmol/L) and low phosphoremia (2.6 mg/dL). In the suspicion of a recurrence, a surgical revision was proposed, but the patient refused the operation. Therefore, a strict biochemical and imaging follow-up was started with controls every six months for 9 years. No clinical or biochemical recurrence of disease became apparent and the PTH gradually decreased. The last PTH value, measured 9 years after surgery, was 66 pg/dL.

Case N. 3

68yo female with family history of colon and parathyroid cancer and PMH positive for gastroesophageal reflux disease, depression and PHPT (Table I). Patient had a multinodular goiter confirmed with neck US for which she underwent a total thyroidectomy in another Institution in 2012, followed by ^{131}I therapy. At discharge, blood calcium level was 2.2 mmol/L and PTH was 55 pg/mL. Histological examination revealed 3 foci of thyroid papillary carcinoma and a 3.4-cm, encapsulated parathyroid carcinoma with focal vascular invasion and a Mib-1 proliferative index of 10%. Patient was referred to our Institution two years after the first surgery for an increase in PTH (255 pg/mL) and calcemia (3.2 mmol/L). A chest CT showed a 1-cm retrosternal mass and a neck US that revealed a 14-mm left paratracheal nodule. Fine-needle aspiration biopsy was performed twice on the paratracheal nodule, but the result was negative and PTH in the eluate was absent (4.4 pg/mL). A total body dual-phase ^{99m}Tc-sestamibi scintigraphy showed a high uptake of the tracer in two nodular areas behind the left clavicle. She then underwent a sestamibi radioimmunological guided surgical procedure with the removal of the retrosternal mass, the left paratracheal nodule, thymic remnant tissue and sestamibi-positive left paratracheal muscular tissue. No evidence of parathyroid tissue was found at pathological examination. After surgery, a partial decrease in PTH levels was observed (from 1000 pg/dL to 600 pg/dL), but PTH never reached values in accordance with resolution of PHPT. She experienced massive bone disease and hip fracture and then underwent therapy with high doses of cinacalcet (up to 270 mg/daily) together with high doses of clodronate followed by zolendronate and then denosumab (60 mg/monthly). During the course of this therapy, PTH levels remained high (4000-4500 pg/ml), while calcium levels declined to 2-2.5 mmol/L. In August 2017, she started temozolomide (200 mg/daily for 5 days, every 28 days). Therapy was followed by a reduction in PTH (1000 pg/ml) and calcium (2-2.25 mmol/L) levels and a decreased need of cinacalcet (90mg/daily). She is going on with cincalcet, denosumab 60 mg every 3 months and temozolomide.

Case N. 4

A 82yo female presented at the Emergency Department for recurrent pathological fractures and a progressive deterioration of the mental status with drowsiness and spatial-temporal disorientation, worsened in the previous 5 months. PMH positive for hypertension, atrial fibrillation, chronic obstructive pulmonary disease, osteoporosis, and uterine cancer. Laboratory exams showed PHPT (Table I). Neck US revealed a solid, round, non-homogeneous, hypovascularized mass (27 X 20 mm) inside the left thyroid lobe. Dual-phase ^{99m}Tc-sestamibi scintigraphy showed an early tracer uptake by thyroid gland with a higher uptake by the mass in the left thyroid lobe. Delayed imaging showed a decrease in radioactivity in the thyroid gland, except for the mass in the left lobe whose uptake persisted. Given the clinical, laboratory and radiological findings, a parathyroid carcinoma was suspected. Patient underwent left parathyroidectomy en bloc with left loboisthmectomy with a decrease in ioPTH from 312.9 pg/mL to 70 pg/mL. Histological examination revealed a 2-cm, mixed cell type, left parathyroid carcinoma with focal vascular invasion and capsular penetration. A 0.5-cm papillary thyroid carcinoma was also present (pTNM = pT1a). Post-operative was uneventful and patient was discharged 12 days after surgery. With the post-operative improvement of calcemia, we assisted to a progressive normalization of the neurologic and osteomuscular functions. At discharge, blood calcium level was 2.4 mmol/L. Patient did not have any adjuvant therapy. The patient's follow-up has always remained negative, with the last PTH 68 pg/mL, blood calcium level 2.175 mmol/L and alkaline phosphatase 92 U/I. At present, the patient has no signs of local or system recurrence.

Discussion and Comments

Parathyroid carcinoma is a slow-growing and very rare malignancy, accounting for an estimated 0.005% of all cancers. [1,3,6,9,44]. Differently from parathyroid adenoma, which is three times more common in women, in PC the ratio of men and women is 1:1 [3,45]. The median age at diagnosis is 56 years, with ranges from 45 to 59 years [2,3,6,46,47].

The etiology of PC remains unknown, but, among the most common risk factors and associated conditions, we observed that 2/4 of our patients had a concomitant thyroid cancer.

Clinical Findings

Most PCs (>90%) are secreting tumors associated with severe hypercalcemia and symptomatic disease such as polydipsia, myalgia, arthralgia, fatigue, anxiety, depression, peptic ulcer, abdominal pain, cardiac arrhythmias, hypertension, pancreatitis and weight loss. Bone involvement is important, leading in some cases to a manifest fibrous osteitis and pathological fractures. Renal involvement is massive with polyuria, nephrolithiasis, nephrocalcinosis, and renal insufficiency. A minority of patients (2-7%) could be asymptomatic [12,13,35,36]. In our experience, all patients were symptomatic with secreting tumors. 7-12% of patients with PC present in a state of life-threatening hypercalcemia (blood calcium > 4 mmol/L), also known as acute parathyroid toxicosis. This condition is characterized by azotemia, oliguria/anuria,

cardiac arrhythmia, and/or neurological involvement (profound weakness, somnolence and coma) and requires urgent medical attention [5,37,48]. Approximately 10% of PCs is hormonally inactive, showing only symptoms related to "mass effect" (i.e. palpable neck mass, hoarseness due to recurrent laryngeal nerve involvement, dysphagia or dyspnea) leading to a late diagnosis and a worse prognosis [49-51].

On physical examination, from 30 to 70% of patients with PC present an extra-thyroid, hard, palpable latero-cervical mass measuring from 3 to 6 cm in diameter. This is in contrast with benign parathyroid tumors, which are usually non-palpable [12,37,38]. Fifteen to thirty percent of patients with PC present lymph node metastases at level VI at presentation and nearly 30% have distant metastatic lesions. The most common site of distant metastases is the lung, followed by liver and bones [39-43]. From 65 to 75% of patients with PC present with severe hypercalcemia (blood calcium > 3.5 mmol/L); in addition, a plasma PTH concentration 3-10 times the normal upper limit is extremely suggestive of carcinoma (with a positive predictive value of 81%) [1,9,11,52]. All our patients presented with PTH values 8 times the normal upper limit, rising the suspicion for a PC. Recently, some Authors have demonstrated that PCs tend to overproduce amino-PTH, which is recognized by 3rd-generation but not 2nd-generation PTH assay. So, a 3rd-generation to 2nd-generation PTH ratio >1 could help predict whether a parathyroid mass is more likely to be malignant in the preoperative setting (sensitivity: 75-82%; specificity: 97-98%) [53-55]. Moreover, patients with PC present higher levels of alkaline phosphatase and – and – subunits of human chorionic gonadotropin compared to those with adenoma [15,35,56].

Imaging

Before surgery, it is fundamental to perform at least one imaging study; the most commonly used are neck US and 99mTc-sestamibi scintigraphy, followed by computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET). Neck US, thanks to its low cost and non-invasiveness, should be considered in all patients with HPT [57]. Echographically, PC appears as a lobulated, heterogeneous, hypoechoic mass with irregular borders. Specific criteria that predict malignancy are local infiltration and calcification, while the absence of suspicious intra-tumor vascularization and the presence of a thick capsule is more in keeping with benign parathyroid disease [2,9,58,59]. 99mTc-sestamibi scintigraphy has increased the possibility to distinguish between single-gland and multigland parathyroid disease and to localize ectopic hyperfunctioning parathyroid tissue. However, it does not supply information regarding the benign or malignant nature of the disease. [60-62] In addition to US and scintigraphy, CT and MRI may provide an exact anatomical description of the lesion, including the presence of local invasion into the surrounding structures. CT, MRI and PET are essential in the identification of metastases and recurrences [1,19]. When a PC is suspected, fine-needle aspiration (FNA) biopsy should be avoided because, besides being useless since the cytology is insufficient to differentiate between benign and malignant tumors, danger of possible tumor seeding in the biopsy tract has been reported. FNA may occasionally be utilized in cases of recurrence or metastatic disease in order to confirm the diagnosis. [35,40,63].

Surgical Approach

Since the only curative treatment for PC is surgery and most experts recommend en bloc resection, it becomes of paramount importance to identify preoperatively patients at risk of having a PC. The following are specific conditions associated with a higher risk of PC: young age, male gender, calcemia > 3.5 mmol/L, PTH 3-10 times the normal upper limit, palpable neck mass, large tumor size (>3 cm), concomitant renal and bone involvement, and a 3rd/2nd generation PTH assay ratio >1. The presence of cervical lymphadenopathy or hoarseness due to recurrent laryngeal nerve invasion are highly suggestive of malignancy [2,3,9,42]. All these characteristics, associated with imaging techniques, should support the suspicion of a PC and, therefore, the planned surgical technique should be that of complete en bloc resection. Most common sites of invasion are ipsilateral thyroid gland, strap muscles, ipsilateral recurrent laryngeal nerve, esophagus, and trachea. If tumor invasion is identified during the operation, it is recommended to remove the involved structure as well. [5,16]. In order to reduce the risk or recurrence, it is of great importance to achieve clear gross margins and to avoid the rupture of the capsule [40]. If lymph node involvement is suspected, a central neck lymph node dissection is indicated [44].

Several studies have shown that the monitoring of ioPTH is useful since a decrease in PTH > 50% ten minutes post-excision, compared to baseline, indicates complete excision with an accuracy of 97% (Miami criteria) [64-66]. With the exception of case 3, who was referred to our Institution for a surgical debulking in local recurrence, all our patients showed a decrease in ioPTH > 75%, indicating a complete resection. The use of ioPTH has decreased the need of intraoperative frozen sections because a significant drop in ioPTH is a better indicator of the removal of the affected gland. Frozen section can be helpful when the preoperative suspicion of PC is low, but characteristic signs of malignancy (i.e. adherence or infiltration of local structures) are found intraoperatively. In these cases, it is important to perform a frozen section. It is not essential to make a diagnosis of PC, but it is important to alert the surgeon to this possibility in order to support an en bloc resection of the gland [67].

Pathological Findings

Macroscopically, PCs are large, firm, grayish-white in color and spherical in shape. The weight ranges between 600 mg and 110 g, with the majority weighting between 2 and 10 g. The typical size of tumor is up to 3 cm. Microscopically, PCs show a monotonous solid growth pattern with sheets of chief cells, separated by dense fibrous trabeculae; necrosis and a thick fibrous capsule may also be present. Major histologic features diagnostic for malignancy include capsular and vascular invasion (present in 60% and 10-15% of PCs, respectively). Other helpful features more common in PCs include mitotic activity >5%, atypical mitoses, thick fibrous bands, necrosis, and prominent nucleoli [1,2,9,68,69]. Because the clinical and histopathological features of PC and adenoma may overlap, considerable efforts have been directed towards the development of other methods, such as immunohistochemistry and DNA analysis. In particular, the loss of staining for parafibromin has a sensitivity of ~70% and a specificity of 94.4% in the diagnosis of PC. [70] Moreover, a recent study by Cetani et al. showed that negative staining for parafibromin is associated to a higher risk of recurrence and a decreased 5- and 10-year survival rates [1,2,71]. Finally, all patients with PC should be tested for HRPT2 mutation because more than 20% of them have unrecognized HPT-JT syndrome even in the absence of family history [72,73].

Post-Operative Diagnosis and Staging Systems

When the diagnosis of PC is post-operative and the tumor was not suspected before surgery, a full workup to rule-out metastatic disease should be carried out, including whole body CT, MRI, and possibly FDG-PET/CT. A bone scan should be performed to rule out bone metastases [1]. Moreover, upon post-operative diagnosis of malignancy, many Authors recommend performing an ipsilateral loboisthmectomy with central neck lymph node dissection. Indications for re-exploration are the appearance of a histologically aggressive tumor with extensive vascular or capsular invasion and/or persistent hypercalcemia after the initial excision [2,8,41-43,74-76]. It is important to notice that the sole parathyroidectomy has a recurrence rate over 50%, while a complete en bloc resection followed by ipsilateral loboisthmectomy with lymphadenectomy has a recurrence rate of 33% [3,5,44].
To date, the American Joint Committee on Cancer has not yet developed a TNM staging for PC. The most commonly used staging system is the one proposed by Talat et al., known as Schulte Staging System, summarized in Table II [42]. Talat et al. also divided PCs into low risk and high risk. Low risk PCs presented capsular invasion or invasion of surrounding soft tissue, while high risk PCs had vascular invasion, invasion of vital organs, lymph node metastasis, and/or distant metastases. Schulte et al. [8] applied this classification to 82 patients, obtaining 4 classes of risk: class I (capsular invasion or invasion of surrounding soft tissues), class II (vascular invasion), class III (lymph node metastasis or vital organ invasion) and class IV (distant metastasis). The overall survival was statistically different in the 4 classes (98.6%, 79.2%, 71.4%, 40.0%, respectively), confirming the validity of the Schulte Staging System. The application of this System to our cases shows that all of them are part of class II due to the presence of vascular invasion, so we expect a survival rate near 80%.

Adjuvant Therapies

The use of adjuvant therapies is controversial. PC is considered a radio-resistant malignancy; however, several single institution case series reported decreased recurrence and increased disease free interval in patients who received adjuvant locoregional radiation therapy [37,77,78]. Chemotherapy is generally reserved for inoperable patients (extensive local or metastatic disease), and no standard protocol has been established. Some case reports present in the international literature show some benefit with regimens containing dacarbazine, either alone or in combination with other agents, such as cyclophosphamide or fluorouracil [35,79].

Follow-Up and Treatment of Recurrences

PC follow-up is performed by checking calcium and PTH levels at regular intervals. Recurrence is indicated by an increase in calcium and PTH levels, but requires a complete imaging work-up in order to localize the site of recurrence [4,37]. The risk of recurrence ranges from 49 to 60%, with most episodes occurring from 2 to 5 years after the initial surgery. The most common site of recurrence is locoregional, probably due to incomplete resection, and the best possible treatment is repeated surgical resection [1,38,39]. In presence of metastatic disease, metastatectomy is essential to reduce severe hypercalcemia and improve survival rate. This is due to the fact that mortality in advanced metastatic PC is most commonly secondary to the effects of chronic hypercalcemia, and not to the tumor bulk itself [1,15,37]. Therapeutic options for severe hypercalcemia include plicamycin, mithramycine, gallium nitrate, bisphosphonates, calcitonin and glucocorticoids. Calcimimetic agents (cinacalcet), allosteric modulators of calcium-sensing receptor (CaSR) and denosumab, a monoclonal antibody that inhibits osteoclast activity, have recently been shown to reduce refractory hypercalcemia [80-82]. Locoregional treatments such as ethanol ablation, radiofrequency ablation and transcatheter arterial embolization represent palliative treatment methods [82]. A new promising treatment modality is represented by immunotherapy, whereby

immunization and induction of neutralizing autoantibodies against human PTH significantly improved PTH and calcium levels in patients with metastatic PC [83-85].

Prognosis and Prognostic Factors

The prognosis of parathyroid cancer is variable, with a median overall survival of 14.3 years. In the National Cancer Database (NCDB) study, the overall 5 and 10-year survival rates were found to be 85.5% and 49.1%, respectively. In the SEER study, the 10-year survival rate was higher, 67.8% [1,3,6,16].
Several studies have identified numerous negative prognostic factors, such as: simple parathyroidectomy as the initial procedure, poor differentiation at histology, high mitotic activity, marked nuclear atypia, vascular invasion, weak parafibromin stain, nodal or distant metastatic disease at presentation, nonfunctioning parathyroid carcinoma, increased number of recurrences, higher calcium level at recurrence and a high number of calcium-lowering medications [8,16,42,86,87]. There is controversy on whether or not the presence of positive regional lymph nodes affects prognosis. The SEER study and the NCDB study 2,36 et al, the three most important negative prognostic factors appear to be: age > 65, preoperative serum calcium levels > 3.75 mmol/L and the presence of vascular invasion. Patients with these characteristics should be considered for adjuvant therapies and close follow-up [47].

Conclusion

Parathyroid carcinoma is a rare and complex disease, whose understanding is not fully complete.
In our experience, in 3/4 cases, the clinical presentation of PC was not different compared to adenoma; consequently, the diagnosis was a post-operative histopathological surprise. Only in one case (Case 4), the clinical presentation was so disruptive, with severe and progressive neurological deterioration, that we had a strong suspicion for a malignant disease. We also noticed a clear, preoperative laboratory evidence of higher values of PTH and calcemia in patients with PC compared to adenoma.
In our experience, a surgical approach consisting in parathyroidectomy associated with ipsilateral loboisthmectomy and central neck lymph node dissection offers the best prognostic chance. Moreover, in case 2, we saw that the simple parathyroidectomy was associated with an increase in post-operative PTH with normocalcemia that required almost 10 years to normalize, even if there was no recurrence of the tumor.
We recommend en bloc resection of the carcinoma with lymph node dissection, since the risk of local dissemination is real and has a bad prognosis. Moreover, surgery should be performed only in referral centers where an interdisciplinary management is guaranteed.
We are confident in suggesting the surgical approach also in patients with poor clinical status due to high calcemia. If performed by experienced surgeons, the surgical risk of parathyroidectomy is low and, in case 4, we assisted to a progressive restoration of neurological function and an improvement in the patient's quality of life.
Finally, even if our experience is limited, we observed an association between PC and thyroid cancer that deserves a validation through more comprehensive further studies.

Riassunto

Il carcinoma delle paratiroidi è una neoplasia rara e a lento accrescimento, la cui incidenza è aumentata di circa il 60% dal 1988 al 2003 negli Stati Uniti. Tale incremento sarebbe attribuibile ad un aumento delle diagnosi di iperparatiroidismo primario, di cui il carcinoma delle paratiroidi rappresenta l'agente eziologico nell'1% dei casi. L'eziologia rimane poco compresa, sebbene si sia osservata un'associazione con la radioterapia del collo, le neoplasie tiroidee e l'insufficienza renale cronica. Il carcinoma paratiroideo può manifestarsi in forma sporadica o può esser parte di sindromi genetiche, come le neoplasie endocrine multiple (MEN 1 o 2A), l'iperparatiroidismo familiare isolato o la sindrome iperparatiroidismo – tumore della mandibola. La rarità di questa neoplasia comporta la difficoltà nel creare ampi studi randomizzati.
In questo articolo vengono presentati 4 casi di tumore delle paratiroidi trattati presso il nostro Istituto e vengono analizzati gli aspetti più salienti di questa malattia evidenziati nella letteratura internazionale.
La nostra esperienza, associata ad una attenta revisione della letteratura, ci portano alla conclusione che la miglior chance prognostica sia quella offerta dalla paratiroidectomia in associazione a loboistmectomia omolaterale e dissezione linfonodale. Tale intervento andrebbe riservato ai Centri di Riferimento, dove sia anche garantito un approccio multidisciplinare. Siamo certi nel raccomandare l'intervento anche in pazienti con un quadro clinico compromesso a causa dell'ipercalcemia poiché, se effettuato da un chirurgo esperto, il rischio operatorio della paratiroidectomia è molto basso e i vantaggi clinici della correzione dell'ipercalcemia sono evidenti. In conclusione, il carcinoma delle paratiroidi rimane una neoplasia complessa e di difficile gestione, in cui però il ruolo della chirurgia risulta essere determinante.

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