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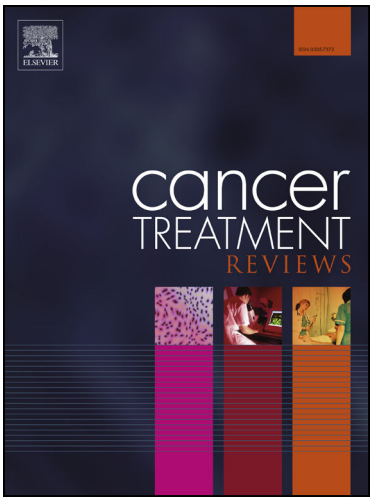

Tumour Review

Parathyroid cancer: an update

Juan P. Rodrigo, Juan C. Hernandez-Prera, Gregory W. Randolph, Mark E. Zafereo, Dana M. Hartl, Carl E Silver, Carlos Suárez, Randall P. Owen, Carol R. Bradford, Antti A. Mäkitie, Ashok R. Shaha, Justin A. Bishop, Alessandra Rinaldo, Alfio Ferlito

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PARATHYROID CANCER: AN UPDATE

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PARATHYROID CANCER: AN UPDATE

ABSTRACT

Parathyroid cancer (PC) is a rare malignant tumor which comprises 0.5-5% of patients with primary hyperparathyroidism (PHPT). Most of these cancers are sporadic, although it may also occur as a feature of various genetic syndromes including hyperparathyroidism-jaw tumor syndrome (HPT-JT) and multiple endocrine neoplasia (MEN) types 1 and 2A. Although PC is characterized by high levels of serum ionized calcium (Ca) and parathyroid hormone (PTH), the challenge to the clinician is to distinguish PC from the far more common entities of parathyroid adenoma (PA) or hyperplasia, as there are no specific clinical, biochemical, or radiological characteristic of PC. Complete surgical resection is the only known curative treatment for PC with the surgical approach during initial surgery strongly influencing the outcome. In order to avoid local recurrence, the lesion must be removed en-bloc with clear margins. PC has high recurrence rates of up to 50% but with favorable long-term survival rates (10-year overall survival of 60-70%) due to its slow-growing nature. Most patients die not from tumor burden directly but from uncontrolled severe hypercalcemia. In this article we have updated the information on PC by reviewing the literature over the past 10 years and summarizing the findings of the largest series published in this period.

KEY WORDS: Hyperparathyroidism; Hypercalcemia; parathyroid cancer; *CDC73* gene; treatment; prognosis.

INTRODUCTION

Parathyroid cancer (PC) is a rare malignant tumor which comprises 0.5-5% of patients with primary hyperparathyroidism (PHPT) [1-3]. As opposed to the female predominance in benign causes of PHPT, parathyroid cancer has an equal frequency of occurrence in both sexes and is usually diagnosed in the fifth decade of life [4,5]. The challenge to the clinician is to distinguish PC from the far more common parathyroid adenoma (PA) or hyperplasia, as there are no specific clinical, biochemical, or radiological characteristic of PC. Indeed, the diagnosis of malignancy is often made after surgery, and sometimes after recurrence [2,3].

Complete surgical resection is the only known curative treatment for PC. In order to avoid local recurrence, the lesion must be removed en-bloc with clear margins [1,5-7]. Although patients with PC have a long survival, they often develop local recurrence and/or distant metastases. Most patients die not from tumor burden directly but from uncontrolled severe hypercalcemia [1, 5-9].

The objective of this article is to update the information on PC by reviewing the literature over the past 10 years (2010-2019). The results of the studies reporting more than 20 patients with PC published in this period are summarized (Table 1 [1,4-8,10-14]).

EPIDEMIOLOGY

Parathyroid cancer usually represents less than 1% of PHPT cases [1,4-6] although a higher proportion (up to 8,1%) has been reported in Asian populations [7].

The Surveillance of Rare Cancer in Europe (RARECARE) project reported the incidence of PC in the European Union in 2008 as 2 new cases per 10,000,000 person-years [15]. Using the National Cancer Institute's (NCIs) Surveillance, Epidemiology and End Result (SEER) database to analyze incidence rates from 2000 to 2012, James et al. [16] found an incidence rate for PC of 3.6 per 10,000,000 person-years, and a 19.5 % decrease in incidence over the study period. In contrast, other reports have shown an increase in the incidence of PC in the USA and other Western countries. According to another 16-year analysis from the SEER database, the incidence of PC increased by 60% from 3.58 per 10,000,000 individuals in the 1988–1991 period to 5.73 per 10,000,000 individuals in the 2000–2003 period [17]. In Finland, in the years 1955 to 2000, the mean incidence was 1.42 cases/10,000,000/person-years, whereas during 2000 to 2013 the mean incidence was 7.14 cases/10,000,000/person-years [4]. These variations in the reported incidences could be explained by the rarity of the disease (which translates in a large variation by itself) and the differences in diagnostic accuracy among centers.

ETIOLOGY AND PATHOGENESIS

The etiology of PC is incompletely understood. PC is commonly a sporadic disease, but it may occur as a part of specific syndromes in familial PHPT, particularly, the hyperparathyroidism-jaw tumor syndrome (HPT-JT), and, very rarely, the multiple endocrine neoplasia types 1 (MEN1) and 2A (MEN2A)[18,19].

HPT-JT is a rare autosomal dominant disease, characterized by multiple parathyroid tumors (usually metachronous) with an increased risk of PC (15 %), ossifying fibromas of the maxilla/mandible (15 %), renal abnormalities (25–50 %) and uterine neoplasms (in up to 75 % of female patients) [2]. Germline mutations of the *CDC73* gene (located in 1q32.1 and initially named *HRPT2* for 'Hyperparathyroidism 2') have been identified in HPT-JT [2,19]. 15 to 70 % of sporadic PC carry a somatic mutation of the *CDC73* gene. In one-third of apparent sporadic PC such mutations are found as germline [20].

The *CDC73* gene encodes for a tumor suppressor protein called parafibromin [21]. Most of the mutations are nonsense and result in a loss of parafibromin expression [20]. In fact, most tumors harboring *CDC73* mutations display loss of parafibromin expression, and loss of nuclear parafibromin expression has been found in the majority of PC [4,22].

Other genetic alterations of PC have been elucidated by whole exome sequencing (WES) analysis of sporadic PCs [23,24]. These studies show that 42% of the tumors harbored mutations of *CDC73*, and that genes encoding the PI3K/AKT/mTOR pathway are altered in 21% of the 24 cases, via activating mutations in *PIK3CA* and *MTOR,* identifying this as a putative major signaling pathway involved in parathyroid carcinogenesis [23]. *CCND1* amplification, whose protein is overexpressed in 90% of PCs [25], was observed in 29% of the tumors. Other frequent mutations occur in the *PRUNE2* gene as well as *ADCK1, FAT3, AKAP9*, and *ZEB1* [23,24].

Epigenetic mechanisms, which may involve histone methylation modifications and DNA methylation, and dysregulation of micro RNAs (miRNAs) expression have been also reported to occur in PCs [26].

PATHOLOGY

Macroscopically, PC is more often a large (mean diameter 3.0 cm, Table 1) grayish-white, lobulated, stony-hard mass, often with adherence to and invasion of the surrounding neck structures. PC occurs frequently in the context of multiglandular disease, as up to 35% have an additional, usually benign, parathyroid tumor [4,8].

Traditionally, the microscopic criteria for malignancy of a parathyroid neoplasm were defined in 1973 by Schantz and Castleman, and included the presence of thick fibrous bands,

trabecular growth pattern, mitotic figures, and capsular and blood vessel invasion [27]. However, except for invasion, the other histological features are also present in benign parathyroid disease. Consequently, the criteria of PC have been redefined and the current WHO classification restricts its diagnosis to tumors with unequivocal evidence of invasive or to those tumors with documented metastases [28].

The key morphological feature of PC is invasion (Figure 1). Complete transgression of the capsule may be seen in some cases; however more often tumors lose their encapsulation and show multiple fronts of infiltration into adjacent anatomic structures, such as the thyroid and surrounding soft tissues. For vascular invasion, the affected vessel should be identified within or outside the capsule of the lesion. The presence of endothelial cells surrounding the tumor embolus is traditionally accepted and the identification of a fibrin thrombus in association with the tumor cells has been regarded as unequivocal evidence of angioinvasion. Perineural invasion is diagnostic for malignancy [28].

Other histopathological features described in PC include (Figure 2) solid/sheet-like growth, trabecular growth, broad fibrous septa including a thick capsule, cytologic atypia, tumor necrosis, prominent nucleoli, and high mitotic activity, usually above five mitoses per 50 high-power fields [28,29]. The latter three features have been associated with more aggressive behavior [30] but are not themselves diagnostic for PC.

The term atypical parathyroid adenoma (APA) has been utilized to describe tumors with histological features suspicious for PC (i.e., prominent fibrous bands, questionable capsular invasion, increased mitotic figures, marked nuclear atypia and adherence to surrounding tissues) but lacking evidence of invasion and/or metastatic disease. From a clinic-pathological perspective APA could be referred as borderline parathyroid tumors [28]. However, some authorities believe that by applying strict diagnostic criteria and using recently discovered biomarkers a definitive diagnosis of parathyroid carcinoma can be rendered [31,32].

Immunohistochemistry (IHC) may improve the diagnostic accuracy of PC [22]. First, a positive immunostaining for PTH and chromogranin A, but not for thyroglobulin, calcitonin and thyroid transcription factor 1 (TTF-1), may allow for the confirmation of the parathyroid nature of the tissue in most cases. However, PTH immunostaining may be weak in some PC and other neuroendocrine tumors may express PTH [28,33]. GATA-3 has emerged as a reliable marker for parathyroid differentiation [34]. To confirm malignancy, the most studied markers have been Ki-67 and parafibromin. An increased Ki67 proliferation index (>5%) in a parathyroid tumor is suggestive of malignancy [4,35-37].

Nuclear loss of parafibromin is most helpful in supporting a diagnosis of parathyroid carcinoma when interpreted within the correct clinical and pathologic context [22]. However, loss of

parafibromin is variably defined in the different studies, and several groups have reported that parafibromin IHC can be a technically demanding or difficult antibody to deploy in the routine clinical setting [19]. In addition, HPT-JT associated PA also may also show loss of parafibromin, and complete loss of parafibromin has also been described in APA [4,19,22]. Moreover, the loss of parafibromin expression in APAs might predict the likelihood of recurrence and supports the use of this biomarker as part of their diagnostic assessment [38]. Although one must keep these caveats in mind, complete loss of parafibromin seems to be helpful in identifying PC [4,22,39].

Recently, Gill et al. [39] defined the characteristics of the parafibromin-deficient (*CDC73* mutated) parathyroid tumors and propose that they be considered a distinct subtype. These neoplasms were more common in younger patients who had larger tumors and more marked hypercalcemia and are characterized by a sheet-like growth of neoplastic cells. Other particularly distinctive features were their eosinophilic cytoplasm, nuclear enlargement and distinctive perinuclear cytoplasmic clearing imparting a koilocytotic appearance [39]. Moreover, total loss of parafibromin staining and mutation in the *CDC73* gene might have prognostic implications, as PC with these alterations appear to have a higher risk of local recurrence and/or distant metastasis [40].

In addition to its use as diagnostic and prognostic biomarker, loss of parafibromin expression helps in the identification of high-risk patients that would benefit from genetic testing. Confirmation of germline *CDC73* mutation in such patients also allows for genetic analysis of family members [2,19,39].

Because of the low incidence, the International Union Against Cancer (UICC) has not yet developed a TNM staging system for PC. Two different TNM staging systems have been proposed by Shaha and Schulte in 1999 and 2010, respectively (Table 2) [1,41]. The main differences between these two TNM systems relate to T1-T3 classification; the Shaha system uses the diameter (3 cm) to separate T1 and T2 tumors, whereas with the Schulte system the division is based on histopathological features. T3 tumors are defined by invasion of surrounding soft tissues in the Shaha system and by vascular invasion in the Schulte system. Talat and Schulte also developed an alternative model (Schulte b) that classifies the PCs in a binary fashion as low risk (capsular invasion or invasion of surrounding soft tissues) or high risk (vascular invasion and/or lymph node metastases and/or invasion of vital organs and/or distant metastases)[1].

CLINICAL FEATURES

The characteristics of the patients included in the reviewed studies are shown in Table 1. Preoperative suspicion of PC is of paramount importance, as it may guide the extent of the initial surgical procedure. Some clinical and biochemical features may raise the suspicion of a PC. First, most PC are functioning, and the signs and symptoms are primarily because of hypercalcemia and high levels of PTH and not to the tumor mass/volume. In some patients the finding of a palpable cervical mass and/or laryngeal nerve palsy in a hypercalcemic patient may suggest the presence of PC. Nodal or distant metastases at presentation are rare (<10%). Most patients with PC show markedly elevated levels of calcium (>13–15 mg/dl) associated with symptoms of hypercalcemia (often with polyuria, polydipsia, weakness, anorexia, vomiting, weight loss, confusion). PTH levels are also higher than twice and often 3-10 times above the normal upper limit (Table 1). The combined finding of a large parathyroid lesion (>3 cm) and severe hypercalcemia [>3 mmol/l (>12 mg/dl)], the so-called >3 + >3 rule, should raise the suspicion of PC [42]. Less frequently, the patients present with acute PHPT (parathyroid crisis), with life-threatening hypercalcemia with involvement of kidney (renal failure), heart (cardiac arrhythmia) and/or brain (reduced consciousness till coma) [1,2]. Concomitant renal (nephrolithiasis, nephrocalcinosis, and impaired renal function) and skeletal involvement (osteitis fibrosa cystica, subperiosteal resorption, pathological fractures, “salt and pepper” skull) also raise the suspicion of PC.

Sometimes (fewer than 10% of cases), the PC is nonfunctioning, being characterized by the involvement of surrounding structures by the tumor mass and in these cases, it presents as a palpable solid neck mass associated with hoarseness and dysphagia [4,6,7,43].

DIAGNOSIS

Laboratory testing

The main clinical indicators of malignancy have been reported in many studies and, as stated above, are severe hypercalcemia and high levels of PTH, as well as a large lesion [4,7,42,44]. Bae et al. found that alkaline phosphatase levels, in combination with tumor size, can also predict the benignity or malignancy of a suspicious parathyroid lesion. The cut-off level with highest discriminatory power was a serum alkaline phosphatase level of 285 IU/L and a tumor size greater than 3.0 cm. Below these levels, the suspicious enlarged gland is more likely to be benign [44].

Imaging studies

Ultrasonography (US) and MIBI (^{99m}Tc-sestamibi scintigraphy) imaging are the most used imaging studies for detecting parathyroid abnormalities in patients with PHPT. MIBI dual-phase scintigraphy is widely used in clinical practice for localizing enlarged parathyroid glands due to its longer retention level in parathyroid adenomas than healthy thyroid and parathyroid tissue [42]. Until now it was believed that MIBI intensity uptake cannot differentiate between malignant and benign parathyroid lesions. However, one recent study demonstrated that PCs have a higher retention level of MIBI than benign parathyroid lesions, and that the peak of retention index (RIpeak) may contribute to a preoperative differential diagnosis of PC [45]. US plays a major role in the preoperative localization of enlarged parathyroid glands but has shown low specificity for differentiating PC from adenoma or hyperplasia [46]. Some US characteristics could allow for a preoperative differentiation of PC and PA [47,48]: lesions of large size (>3.0 cm) and marginal irregularity with local tissue invasion, heterogeneous echotexture, calcifications, and palpability had a high probability of being a PC. Using these features, the diagnostic performance values of US for the differentiation of PC and PA were a sensitivity of 100%, specificity of 96.9%, and accuracy of 97.4% [48]. The ratio between the depth and width of the lesions (D/W ratio) was correlated with the probability of malignancy in one study, with a D/W ratio >1 suggestive of malignancy [49].

CT and MRI scans are useful for detecting the parathyroid mass and invasion of surrounding tissues and for distant metastases. The CT features suggestive of malignancy are a high short-to-long axis ratio, irregular shape, the presence of peritumoral infiltration and calcification, and low contrast enhancement [50]. On MRI, all parathyroid lesions are very bright on fat saturated T2W images. Parathyroid hyperplasia and adenoma are usually small in size, homogenous, well-defined and low on T1W, high on T2W and avidly enhancing. In contrast, PC is large, ill-defined and very heterogeneous on MRI including DWI [51]. Four dimensional CT (4D-CT), which adds multiphase dimension to CT imaging, has primarily been studied in benign parathyroid disease, but can also be utilized for parathyroid carcinoma [52].

PET/CT with 18F-FDG could provide additional information related to the location and extent of parathyroid carcinoma, compared to CT, MRI and 99mTc-sestamibi. The impact of PET/CT in staging was mainly addressed to evaluate loco-regional and distant spread of disease, adding data on lesion metabolism. PET/CT may also be useful in the identification of suspected tumor recurrence, and evaluation of potential residual disease after primary treatment [53].

18-fluorocholine-PET (18F-Choline-PET) is a promising novel method for preoperative localization of parathyroid masses [54], and isolated case reports have shown that PC are 18F-Choline-PET positive, suggesting that this agent should be considered in the future for

parathyroid carcinoma work-up [55,56]. However, brown tumors also are 18F-Choline-PET positive, which must be considered, and should not be confused with metastasis [57]

Fine needle aspiration biopsy

Fine needle aspiration biopsy (FNAB) is not recommended when PC is suspected because cytology is poor at distinguishing malignancy in a parathyroid tumor [8]; moreover, the rupture of the lesions capsule and the spreading of neoplastic cells has been reported [58].
In contrast, FNAB could be performed for the confirmation of metastatic lesions by the identification of parathyroid tissue in an aberrant location, usually with a PTH aspirate-hormone test that confirms PTH-secreting tissue. The fear of seeding tumor cells during the procedure is less than that for primary lesions because the patient already has a metastatic tumor [8].

Differential diagnosis

In the usual presentation of a hyperfunctioning tumor, the differential diagnosis is established between benign and malignant causes of hyperparathyroidism, as discussed above. But in the rare cases of a non-functioning tumor the differential diagnosis must include other masses of thyroid origin (especially medullary thyroid carcinomas) or metastases to parathyroid glands. Metastasis to the parathyroid glands are very rare and only 127 cases have been reported (reviewed in reference #59). Metastatic malignancies to the parathyroid gland usually occur in patients with widely disseminated disease, with breast carcinomas the most frequent primary tumor (66.9%), followed by melanomas (11.8%). The single case reports of isolated metastatic disease to the parathyroid glands alone are exceptional with only four cases described [59].

TREATMENT

Medical treatment

Medical management for lowering serum calcium and correcting metabolic abnormalities is the main treatment of patients awaiting surgery and in those with inoperable PC. The first step is hydration with normal saline infusion as hypercalcemic patients are often dehydrated [60]. The next step in management usually includes intravenous administration of bisphosphonates (pamidronate and zoledronic acid). Bisphosphonates inhibit osteoclastic activity, which is the major mechanism responsible for severe hypercalcemia, and are the treatment of choice, but onset of action is slow [60,61]. Denosumab is a human monoclonal antibody against the RANK ligand and prevents its binding to RANK on osteoclasts, decreasing osteoclastic resorption of bone [62]. It has shown to lower serum calcium in bisphosphonate-refractory patients with

persistent hypercalcemia secondary to malignancy [62]. Calcitonin mainly inhibits bone resorption but also decreases renal tubular reabsorption of calcium. It has a rapid hypocalcemic effect that can be useful as an initial adjunct to hydration while waiting for other treatment modalities to take effect [60].

In patients with inoperable PC, calcimimetics have emerged as the most effective treatment for control of hypercalcemia [63]. They are allosteric modulators of the calcium sensing receptor (CASR), which increase the receptor's affinity for calcium and reduces PTH secretion. Cinacalcet, a second-generation calcimimetic, has been used in patients with inoperable PC, reducing hypercalcemia in approximately two thirds of cases [63,64].

Surgical treatment

The only curative treatment of PC is surgery and the best chance of cure can be achieved by complete excision at the first operation. The "gold standard" treatment is en-bloc resection of the tumor with the ipsilateral thyroid lobe, and adjacent involved structures as necessary with gross clear margins, with care to avoid spillage of tumor cells into the surgical field [42,65,66]. An adequate surgical approach depends upon the pre-operative suspicion of PC. But, as mentioned above, the diagnosis of a PC often occurs after surgery, which is reflected in the fact that in most series (Table 1) the most frequently performed procedure is a simple local excision [5,7,10,12,14]. If the PC was not diagnosed preoperatively but malignant features as described above are identified during surgery, the surgeon should elect to perform en-bloc resection of any involved tissues without compromising the tumor capsule [7,65,66]. However, up to one third of PC do not show adhesions and adhesions can be found in APA and even PA; therefore the distinction between PC, APA and PA cannot rely solely on intraoperative observations, and PC cannot be excluded simply by normal macroscopic morphological characteristics [7]. For those PC patients who do not undergo en-bloc resection during their first operation, timely additional surgery may offer a second chance for a cure. Xue et al. showed that the recurrence rate was reduced by reoperation increasing the extent of the resection by removing the ipsilateral thyroid lobe and central compartment lymph nodes within one month [7]. However, the benefit of this additional surgery is unclear for patients with complete initial resection, and other authors suggest close follow-up for these patients [3,8,14]

Regarding the management of the lymph nodes, if there is evidence of lymph node involvement the affected nodes must be removed, but there is no consensus about the role of prophylactic neck dissection. The incidence of regional lymph node involvement at initial diagnosis varies widely, ranging between 6.5% and 32.1% [12]. Some authors support routine

dissection of the ipsilateral central (level VI) compartment as current standard for surgical treatment of PC [2,6,7,42,66], but there is no evidence that prophylactic neck dissection improves the survival rate. Other authors suggest that neck dissection should be performed only if there is evidence of lymph node involvement, to avoid unnecessary morbidity [3,8,10,65,67]. To specifically address this question, Hsu et al. reviewed 405 patients with PC from the SEER cancer registry treated between 1988 and 2010 [11]. Regional lymph nodes were examined in 114 patients, 12 of whom (10.5%) were found to have nodal metastasis. Nodal metastasis were 7.5 times more frequent in patients with tumors >3 cm (21% vs 2.8%). Their results showed that lymph node status did not influence disease specific survival except for tumors larger than 3 cm, suggesting that prophylactic neck dissection could be indicated only in these cases [11].

Radiotherapy

The role of radiation therapy (RT) in the management of PC is controversial. PC is a radio-resistant tumor and there is no indication for the use of RT as a primary treatment [3]. There have been some series published in which radiation therapy was used after surgery to prevent disease progression. However, in most of these series the administration of RT was not associated with better loco-regional control or overall survival [8,10]. An analysis of 733 patients from the NCDB showed that RT did not improve overall survival in the 51 patients who received RT compared with the remaining 674 patients who did not receive it [12]. And in the largest series of patients published, patients who received RT had a lower 5-year overall survival, although this may reflect patients with more aggressive disease being referred for RT [5]. Only a few studies suggest a role for postoperative RT. The MD Anderson Cancer Center experience suggests a potential benefit of adjuvant radiation after surgery in high-risk cases, achieving long-term disease control with surgery (often revision surgery) and postoperative RT, despite factors that would typically make them otherwise very high risk for local recurrence [68].

Chemotherapy

Cytotoxic chemotherapy has not been shown to be effective in the treatment of PC, except for partial responses in a few case reports and there are no standardized protocols for its use [2,3,13,69]. The chemotherapy regimens reported in these cases include monotherapy using dacarbazine or combination therapy consisting of fluorouracil, cyclophosphamide, and dacarbazine or a combination of methotrexate, doxorubicin, cyclophosphamide, and lomustine [65].

The only targeted therapy that has shown efficacy against PC in case reports is sorafenib. Sorafenib was successfully used in a young female patient with metastatic PC, carrying a germline *CDC73* mutation [70]. A response to sorafenib was also observed in another recent report [32], showing promise for this treatment in recurrent/metastatic disease. Recently, the MD Anderson Cancer Center published a small experience of next generation sequencing of 11 recurrent/metastatic PC patients undergoing systemic therapy, demonstrating actionable mutations in some of these patients [71]. In the future, gene analysis will likely direct targeted therapies for advanced PC patients.

Recurrent disease

The management of recurrent disease is mainly surgical. Often multiple surgical interventions are performed over time [7,8,10,11,13]. Finding a recurrent tumor in a previously operated neck can be challenging. It is recommended that two preoperative localization studies be performed prior to reoperation [65]. FNAB of equivocal lesions with measurement of PTH could be of use, especially in metastatic disease. As relapsed PC has an indolent course with prolonged survival despite recurrences, the aim of the surgery is not only to remove the tumor, but also to control the PTH-driven hypercalcemia that represents the primary cause of morbidity and mortality [3,4,8,42,65]. Indeed, surgical debulking of functioning tumor induces reduction, and sometimes normalization, of serum PTH and calcium levels that could be long lasting (months to years) making the control of hypercalcemia more amenable to medical therapies and providing effective relief of symptoms [1,6,8,65].

The role of radiotherapy in the palliative setting is also unclear as reported experience is scarce. However, adjuvant RT after salvage surgery has produced a temporary drop in calcium and PTH levels for a period of up to 12 months [68].

As mentioned above, cytotoxic chemotherapy has a limited efficacy, and sorafenib emerges as a potential targeted therapy [32,65,70], while future hope lies in genetic molecular testing, with the possibility of targeting actionable mutations [71].

Radiofrequency or ethanol ablation have both demonstrated promise as options for palliation in patients with recurrent/metastatic unresectable disease [72,73].

Finally, in case of intractable disease, the primary aim is to control PTH driven hypercalcemia, the main cause of morbidity and mortality in these patients. The calcimimetic cinacalcet is probably the most effective agent in this setting [60,64].

Follow-up

Given the usual high preoperative levels of calcium and PTH, in the early postoperative period patients should be monitored because of the risk of symptomatic hypocalcemia due to the "hungry bone syndrome".

After surgical treatment, the aim of follow-up is early detection of loco-regional recurrence and/or metastases [3,42,65]. Patients with PC should be followed up for their lifetime with serum calcium and PTH closely monitored (i.e., biannually for 5 years and then yearly), as well as performing neck ultrasounds annually.

The follow-up of the patients with nonfunctioning PC can only rely on imaging studies.

PROGNOSIS

Because of the rarity of PC, survival and prognostic factors should be extrapolated from studies of cancer registries and the small number of retrospective studies from single institutions with enough experience.

Recurrences are frequent (23-51% cases; Table 1), but due to the indolent course of the disease long-term survival is favorable: 78-91% and 60-72% overall survival at five and ten years, respectively (Table 1). When the disease progresses, patients complain mostly because of the clinical manifestations of hypercalcemia and its complications, rather than because of symptoms related to the spread of the tumor [1-3]. Distant metastasis usually involves lungs and/or bones and are most frequently associated with loco-regional recurrence (Table 1).

To date, there is no consensus on the prognostic factors which influence outcome in PC. In the review of the literature no variable was identified by all ten analyses (Table 1). The variables most frequently associated with poor prognosis in these studies were inadequate surgery (six studies), the presence of lymph node metastasis (five studies), and high-risk Schulte classification (five studies).

In some studies, surgery was an important outcome predictor with more radical surgery protecting against recurrence and death. Limited excision of the parathyroid alone carries a significant adverse prognostic effect when compared with more extensive oncological resections [1,6,7]. However, a lack of significant association between radical resection and improved survival was observed in other studies [8,14], which could be explained by a selection bias, since en-bloc surgery could have been more frequently performed in patients with aggressive tumors [3]. Another explanation is that surgical information in cancer registries could not adequately address the extent of the resection [5,11,12].

Regarding the predictive value of lymph node metastases on mortality, data from the literature are conflicting. Some studies showed that lymph node status was significantly

associated with poor prognosis [1,4,5,8,10], but others failed to find this association [6,7,11,12,14]. These discrepancies could be due to the small proportion of patients that received a neck dissection (less than 1/3; Table 1), with no information about the lymph node status in most patients. Thus, it is highly likely that a significant proportion of patients were under-staged regarding lymphatic disease [1].

A Schulte high-risk classification and vascular invasion (a feature of this classification) were associated with poor prognosis in five studies (Table 1). The tumors classified as high-risk showed a significantly higher risk of recurrence and death in these studies [1,5-7].

Other prognostic factors that have been reported in varying degrees to negatively impact survival include older age [5,12,14], male gender [1,12], tumor size [11], presence of distant metastases [8,10,11], higher serum calcium level at diagnosis [1,14], and loss of parafibromin expression [4,40,74].

Combining age (>65 years), preoperative calcium levels (>15 mg/dL), and vascular invasion, Silva-Figueroa et al. [14] developed a prognostic scoring system for recurrence-free survival rates in PC patients. These three objectively measured adverse characteristics can be used to adequately stratify PC patients and identify those at high risk for recurrence and might justify aggressive surveillance or adjuvant therapeutic care.

Parafibromin loss has a higher prognostic significance than *CDC73* mutations, but the added value of *CDC73* mutation analysis is the identification of germline mutations, which prompts screening of family members [74].

CONCLUSIONS

Parathyroid cancer is a rare disease with high recurrence rates of up to 50% but with favorable long-term survival rates (10-year overall survival of 60-70%) due to its slow-growing nature. The main cause of morbidity and mortality is related to complications of hypercalcemia rather than to tumor burden or infiltration. Given its rarity and nonspecific symptoms it is still too frequently understaged and undertreated. Surgery is the primary mode of treatment for PC. The best chance for cure is realized with complete en-bloc primary surgical resection with attainment of microscopically negative margins. However, there is no consensus about the benefit of elective neck dissection of the central compartment. Patients with suspected PC should be referred to specialized centers because a surgical approach that meets oncological criteria is likely to improve outcome in these patients. PC patients require long-term follow-up for the early identification of recurrences and/or metastases. Since recurrences are frequent, multiple surgical procedures may be required during the disease course, even if they represent a palliative option, to reduce serum calcium and PTH levels. The efficacy of adjuvant therapies,

such as radiotherapy and chemotherapy, in the management of persistent, recurrent, or metastatic PC has been disappointing, while studies demonstrating potentially actionable targets for targeted systemic therapy provide some hope for the future. When the tumor is no longer resectable, medical treatment of the hypercalcemia is the main goal. PC has many prognostic unknowns, and methods used to stratify patient's risk that can help physicians predict the clinical progression of this disease, reliably aid immediate postoperative treatment decisions, and guide clinical monitoring for progression, are lacking.

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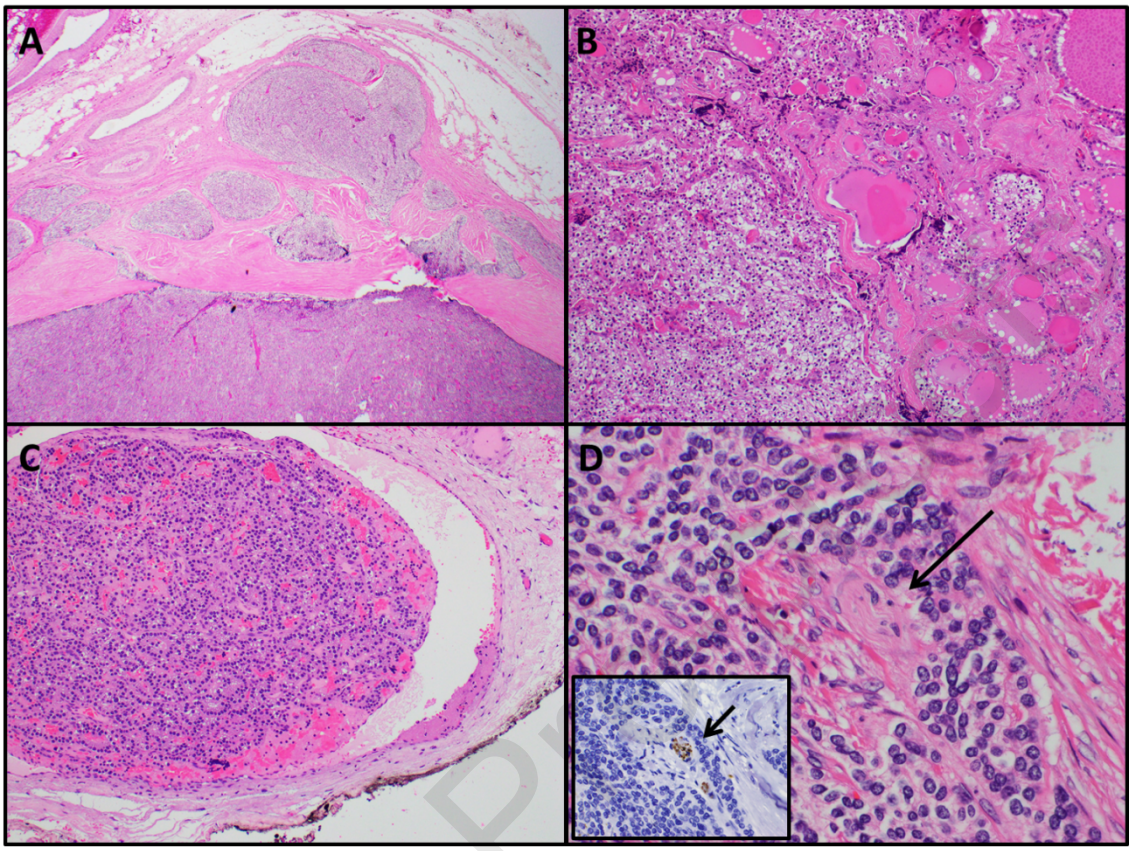
FIGURE LEGENDS

Figure 1. The diagnosis of PTC is established by the presence of invasion: A) Tumor showing invasion through its thickened capsule into surrounding soft tissue. B) Tumor cells invading into adjacent thyroid parenchyma. C) Tumor embolus adherent to vessel wall and associated with fibrin thrombus. D) Perineural invasion by PTC (arrows mark involved nerve and insert show S100 IHC highlighting involved nerve)

Figure 2. Other non-specific histological features seen in PTC: A) Solid growth and B) trabecular growth patterns. C) Increased mitotic activity and tumor cells with prominent nucleoli (arrow marks atypical mitosis). D) Confluent areas of tumor necrosis. E. Fibrous bands dividing the tumor into irregular nodules. F) Diffuse nuclear staining GATA-3 supports parathyroid tissue differentiation.



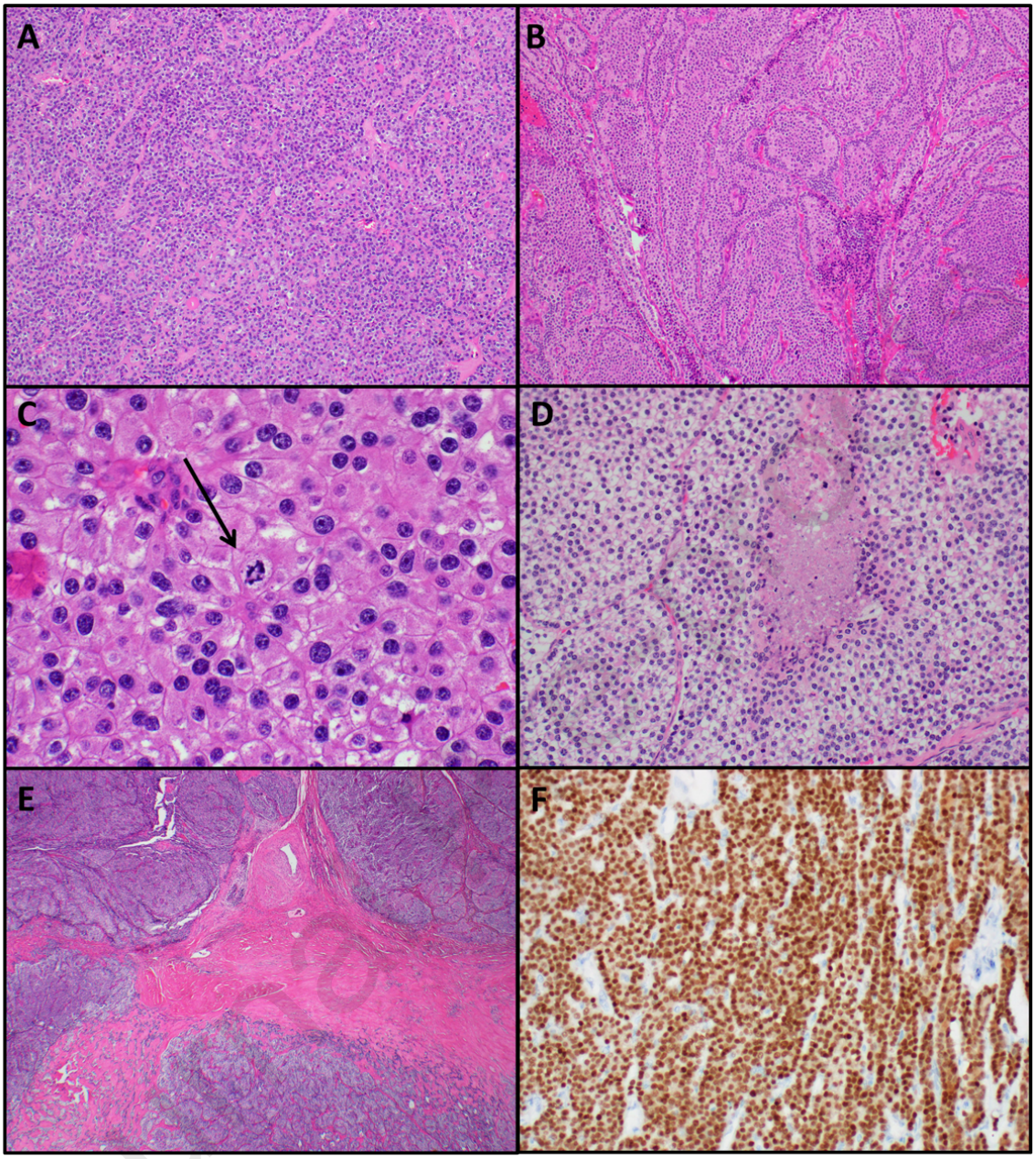


Table 1: Summary of the largest series (>20 patients) of parathyroid cancer published in the last 10 years.

Study	Talat et al. 2010 (1)	Harari et al. 2011 (8)	Schaapveld et al. 2011 (10)	Hsu et al., 2014 (11)	Sadler et al., 2014 (5)	Villar del Moral et al., 2014 (6)	Asare et al., 2015 (12)	Xue et al., 2016 (7)	Ryhänen et al., 2017 (4)	Silva-Figueroa et al., 2017(14)
Number of patients	330	37	41	405	1022	62	733	40	32	68
Source	Reports in the literature (1961-2009)	Single institution (1966-2009)	Population-based (Netherlands Cancer Registry; 1989-2003)	Population-based (SEER cancer registry; 1988-2010)	Population-based (NCDB; 1998-2011)	Multicenter study (1980-2013)	Population-based (NCDB; 1985-2006)	Single institution (2000-2015)	Population-based (Finnish Cancer Registry; 2000-2011)	Single institution (1980-2016)
Gender										
Male	152 (46%)	23(62%)	21 (51%)	212 (52%)	505 (49.6%)	38 (61%)	327 (45%)	17 (42%)	14 (44%)	32 (47%)
Female	169 (51%)	14 (38%)	20 (49%)	193 (48%)	519 (50.4%)	24 (39%)	406 (55%)	23 (58%)	18 (56%)	36 (53%)
Age (years)										
Median	48	-	62	56	57	59	57	NR	NR	53
Mean	49	53	-	-	56.9	NR	56.1	49.1	61	NR
Range	18-83	23-75	-	-	10-89	NR	15-89	NR	17-83	13-82
Tumor size										
Mean (cm)	2.9	3.1	NR	2.8	NR	2.8	2.9	3.25	2.95	2.5 cm
Lymph nodes										
Unknown	287	37	0	291	701	42	553	31	0	48
N0	27 (64%)		40 (97.5%)	102 (90%)	298 (93%)	12 (60%)	157 (87%)	8 (89%)	30 (94%)	18 (90%)
N1	15 (36%)		1 (2.5%)	12 (10%)	23 (7%)	8 (40%)	23 (13%)	1 (11%)	2 (6%)	2 (10%)
Treatment		NR	NR							
Local excision	164 (49%)			329 (81%)	917 (90%)	18 (29%)	132 (19%)	14 (35%)	14 (44%)	30 (44%)
En-bloc surgery	166 (51%)			42 (10%)	53 (5%)	44 (71%)	72 (11%)	26 (65%)	15 (47%)	38 (66%)
Debulking	0			7 (2%)	12 (1%)	0	444 (66%)	0	3 (9%)	0
Unknown	0			27 (7%)	40 (4%)	0	28 (4%)	0	0	0
Neck dissection		NR	NR						NR	
No	290 (88%)			291 (72%)	539 (65%)	42 (68%)	553 (75%)	31 (77.5%)		48 (70.5%)
Yes	43 (12%)			114 (28%)	295 (35%)	20 (22%)	180 (25%)	9 (22.5%)		20 (29.5%)
Radiotherapy										
No	283 (86%)	31 (84%)	36 (88%)	368 (91%)	880 (87%)	62 (100%)	674 (93%)	40 (100%)	28 (87.5%)	60 (88%)
Yes	47 (14%)	6 (16%)	5 (12%)	37 (9%)	127 (13%)	0	51 (7%)	0	4 (12.5%)	8 (12%)
Margins		NR		NR			NR	NR	NR	NR
RX	NR		6 (15%)		128 (24%)	0				
R0	NR		20 (49%)		601 (59%)	55 (89%)				
R1	NR		14 (36%)		183 (18%)	7 (11%)				
Recurrence				NR	NR		NR			
No	164 (49%)	19 (51%)	29 (71%)			48 (77%)		38 (70%)	23 (72%)	42 (62%)
Overall	166 (51%)	18 (49%)	12 (29%)			14 (23%)		12 (30%)	6 (28%)	26 (38%)
Loco-regional	66 (20%)	NR	10 (24%)			11 (19%)		9 (22.5%)	1 (12.5%)	12 (18%)
DM	69 (21%)	NR	2 (5%)			1 (1.5%)		3 (7.5%)	0	3 (4%)
Loco-regional+DM	31 (9%)	NR	-			2 (3%)		0	5 (15.5%)	11 (16%)
Survival										
5-y OS	NR	78.3%	80.4%	82.5%	81.1%	NR	82.3%	78.9%	91%	80%
10-y OS	NR	66.7%	68%	65.4%	NR	NR	66%	60.7%	72%	68%
5-y DSS	NR	NR	82.5%	94%	NR	92.2%	NR	NR	NR	NR
10-y DSS	NR	NR	78.9%	89.9%	NR	69.1%	NR	NR	NR	NR
Poor prognosis factors	Male gender; Younger age: High calcium levels; High-risk Schulte; LNM; Local excision alone	LNM; DM	Positive surgical margins; LNM; DM	Tumor >3 cm; DM	Older age; Positive surgical margins; LNM; High-risk Schulte	Tumor rupture during surgery; High-risk Schulte	Older age; Male gender; Increased tumor size; Incomplete resection	Local excision alone; High-risk Schulte	LNM; High mitotic activity; Loss of parafibromin	Vascular invasion; Age >65 y; Calcium >15 mg/dL

NR: Not reported; OS: Overall survival; DSS: Disease-specific survival; LNM: Lymph node metastasis; DM: Distant metastasis; Y: years

Table 2: Proposed TNM staging systems for parathyroid cancer

Shaha [41]	**Schulte [1]**
T classification - (Tx) Not defined by authors - T1: Primary tumor <3 cm - T2: Primary tumor >3 cm - T3: Primary tumor of any size with invasion of the surrounding soft tissues, i.e., thyroid gland, strap muscles, etc. - T4: Massive central compartment disease invading trachea and esophagus or recurrence parathyroid cancer	**T classification** - Tx: No information available - T1: Evidence of capsular invasion - T2: Invasion of surrounding soft tissues 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 classification - (Nx) Not defined by authors - N0: No regional lymph node metastases - N1: Regional lymph node metastases	**N classification** - Nx: Lymph node not assessed - N0 No regional lymph node metastases - N1 Regional lymph node metastases
M classification - (Mx) Not defined by author - M0: No evidence of distant metastases - M1 Evidence of distant metastases	**M classification** - Mx: Distant metastases not assessed - M0: No evidence of distant metastases - M1: Evidence of distant metastases
Stage - I: T1N0M0 - II: T2N0M0 - IIIa: T3N0M0 IIIb: T4N0M0 IIIc: Any T, N1M0 - IV: Any T, Any N, M1 IV Any N, M1	**Stage** - I: T1 or T2N0M0 - II: T3N0M0 - III: Any T, N1M0, or T4 - IV: Any N, M1

PARATHYROID CANCER: AN UPDATE

HIGHLIGHTS

- Parathyroid cancer comprises 0.5-5% of patients with primary hyperparathyroidism.
- 15 to 70 % of sporadic parathyroid carcinomas carry a somatic mutation of the *CDC73* gene.
- Complete surgical resection is the only known curative treatment.
- Recurrence is frequent (20-50%) but long-term survival is favorable due to its slow-growing nature.

CONFLICT OF INTEREST STATEMENT

ARTICLE: PARATHYROID CANCER: AN UPDATE

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The authors declare that there are not conflict of interests regarding this submission