Review Article

Parathyroid Carcinoma

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Parathyroid carcinoma is a very rare cancer, accounting for 0.5% to 5% of all causes of primary hyperparathyroidism. Parathyroid carcinoma has an equal frequency of occurrence in both genders, usually in the fifth decade of life. Preoperative diagnosis of parathyroid carcinoma is difficult due to a lack of clinical findings, laboratory results, or radiological characteristics specific to the disease. Though, parathyroid carcinoma patients usually present with severe hypercalcemia at the time of diagnosis. Complete en-bloc resection is the mainstay of the treatment. The adjuvant therapy such as radiotherapy or chemotherapy has not shown effective in the treatment of parathyroid carcinoma.

Keywords: Parathyroid; Carcinoma; Neoplasm; Parathyroid glands; Hyperparathyroidism

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Parathyroid glands were first discovered in 1852 by Sir Richard in Indian rhinoceros[1]. In 1880, A Swedish medical student named Ivar Sandstrom reported human parathyroid glands afterward[2]. Most people usually have four parathyroid glands. Supernumerary glands can be found in up to 12 glands (13% of random autopsies)[3]. The superior parathyroid glands are usually found at the posterior capsule of the superior thyroid pole, deep to the recurrent laryngeal nerve (RLN) in the coronal plane. The inferior parathyroid glands are located in more variable locations, typically found at the lower pole of the thyroid gland and superficial to RLN in the coronal plane. The chief cells of parathyroid glands secrete parathyroid hormone (PTH) to maintaining serum calcium levels. The target action of PTH is the kidneys, intestines, and bones by increasing renal tubular calcium reabsorption, acting on osteoclasts to stimulate bone resorption, and increasing calcium reabsorption from the intestine[2].

Abnormal hypersecretion of PTH can cause hyperparathyroidism, which can be classified as primary, secondary, and tertiary[4]. Primary hyperparathyroidism (PHPT) is caused by parathyroid adenoma, parathyroid hyperplasia, and parathyroid carcinoma (PC)[4].

PC is rare cancer, occurring in only 0.5% to 5% of PHPT[5-7]. Although rare, it poses a challenge in clinical care because the diagnosis of PC before surgery is difficult due to the lack of specific clinical, laboratory, and radiological characteristics of PC. There are often reveal more severe symptoms with high calcium levels[8,9]. PC is also extremely rare in children. A small number of case reports were published[10-13]. The objective of this article is to update the information on PC by reviewing the literature. The results of the studies reporting epidemiology, etiology, pathogenesis, pathology, stages of PC, clinical signs and symptoms, diagnosis, and treatment.

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Epidemiology

PHPT is found in about 1% of the world's population[6], with 80% to 85% of cases being single parathyroid adenoma, followed by parathyroid hyperplasia and PC[6].

PC is a very rare endocrine malignancy, only accounting for approximately 0.005% of all cancers. According to a US national cancer database survey from 1985 to 1995[14], it is less than 1% of all PHPT cases[5,15]. In a Japanese population, the incidence was reported as 5%[16]. According to the surveillance, epidemiology, and end results (SEER) program of the national cancer institute, the incidence of PC was 3.58 to 5.73 cases per 10,000,000 person-years from 2000 to 2012[17,18], and the incidence rate rarely changed in that period. The pediatric PHPT is uncommon in children and adolescents, the estimated incidence is 2 to 5 cases per 100,000[19]. The most common cause of PHPT is sporadic parathyroid adenomas (up to 80%)[12]. Pediatric PC is extremely rare (<1%)[10].

PC is most common in the middle ages, at a mean age of 50 years old, which is a lower average age than that of PHPT. The incidence rate of PC in males is nearby females, differ from the case of PHPT, which is often found in females, the racial factors do not affect disease occurrence[20].

Etiology and pathogenesis

The exact cause of PC is unknown. There are many factors involved, including both environmental factors and genetic factors. Environmental factors include having received radiation to the head and neck during childhood[20]; end-stage

renal disease[21]; and hereditary factors include familial PHPT, particularly the hyperparathyroidism jaw tumor syndrome (HPT-JT) and very rare MEN1, MEN2A, and familial isolated PHPT[6,22,23].

HPT-JT is a rare autosomal dominant disorder characterized by benign or malignant parathyroid tumors, cemento-ossifying fibrous tumors of the maxilla and/or mandible, and renal cysts or tumors and/or uterine tumors. The exact incidence is currently unknown, although 80% of cases are likely to be accompanied by symptoms of hyperparathyroidism in late adolescents. PC occurs in 10% to 15% of cases and compared with MEN1-related hyperparathyroidism, it was found to be more severe, manifesting as severe hypercalcemia and sometimes with symptoms of hypercalcemic crisis[24]. HPT-JT is caused by an abnormality of the CDC73 gene, also known as the hyperparathyroidism type 2 (HRPT2) gene, which is genetic encodes for a tumor suppressor protein that causes a loss of parafibromin expression. In HPT-JT, more than 50% of CDC73 genes were detected to have an abnormality[20], while 20% of sporadic PC are found as germline[20]. Therefore, testing for CDC73 mutations may be useful in predicting the development of PC.

The tumor suppressor genes MEN1, RET proto-oncogene in MEN2A, and GCM2 gene mutation in familial isolated hypoparathyroidism (FIH) is rarely associated with PC. The GCM2 gene mutation in FIH correlated the effect of parathyroid hyperproliferation and aggressive carcinoma phenotype[22,25]. The CCND1/PRAD1 oncogene has been found overexpressed in sporadic parathyroid adenomas and PC[25]. Several other mutations were reported that PRUNE2, MTOR, and PIK3CA genes were also found to be mutated in PC in these studies[26-28]. The recent study identified the genetic variations of 29 PC to candidate driver genes. The PIK3CA/AKT/mTOR pathway is identified as a potentially major oncogenic pathway in sporadic PC and metastatic PC[29].

Pathology

The pathological characteristics of parathyroid adenoma and PC are difficult to distinguish. Currently, the world health organization (WHO) classification shows that criteria for PC required evidence of invading the thyroid gland or adjacent tissues, vascular invasion or perineural invasion, or evidence of distant metastasis[30].

PC is usually large, mean diameter of approximately 3.0 cm, appearing as a grayish-white, lobulated, stony-hard mass, invading the surrounding structures with 21% possibility of finding cystic component characteristics[14,15]. The intraoperative frozen analysis is not useful for diagnosis of PC due to similar pathological features between PC and parathyroid adenoma, making it hard to distinguish them apart[31]. The key morphological features of PC are a fibrous band with a trabecular architecture (90%), capsular invasion (60%), vascular invasion (15%), and mitotic activity (80%)[14] (Figure 1).

Immunohistochemistry has a role in detecting PC. Positive immunostaining for PTH and chromogranin A and negative for thyroglobulin, calcitonin and thyroid transcription factor 1 (TTF-1) can use to confirm the parathyroid nature of the tissue and may help diagnose PC. However, PTH immunostaining may show less straining in some PC and other neuroendocrine tumors that express PTH can also detect the positive immunostaining of PTH[30]. GATA-3 is a sensitive immunohistochemical marker for parathyroid differentiation[32] that can assist in the differential diagnosis of parathyroid tumors. Expression of Ki-67 and parafibromin can indicate PC with an increase in the Ki-67 proliferation index (>5%) in parathyroid tumors, indicating a malignant condition[15,33,34].

Atypical parathyroid adenomas comprise a spectrum of parathyroid diseases with suspected histological features of PC (prominent fibrous bands, questionable capsular invasion, increased mitotic figures, marked nuclear atypia, adherence to surrounding tissues), without evidence of invasion or metastatic disease[35].

Absence of nuclear staining for parafibromin is conducive to diagnosis of PC. HPT-JT associated with PC may show a loss of parafibromin, while a complete loss of parafibromin is also detected in atypical parathyroid adenomas. However, a loss of parafibromin expression in atypical parathyroid adenomas may predict the likelihood of recurrence and aid diagnosis[35].

Stages of parathyroid carcinoma

As a disease with a low incidence, the International Union Against Cancer (UICC) has not included PC in the TNM staging system[35].

Consequently, in 2010, Talat and Schulte developed a TNM staging of PC[5] and developed a criterion as an alternative model (Schulte B). The model divides PC into two main groups: low risk (capsular invasion or invasion of surrounding soft tissues) and high risk (vascular invasion and/or lymph node metastases and/or invasion of vital organs and/or distant metastases)[5], as shown in Table 1. The model can be used to predict the recurrence of the disease[36].

Clinical signs and symptoms

PC is often more severe than parathyroid adenoma. In most cases, it is accompanied by symptoms resulting from hypercalcemia and hyperparathyroidism. The presence of a lump in the neck or hoarseness from RLN palsy together with hypercalcemia associated with hyperparathyroidism increases the suspicion of PC. Lymph node metastasis or distance metastasis at presentation is less than 10% of cases. The key symptoms that indicate hypercalcemia condition include polyuria, polydipsia, weakness, anorexia, vomiting, weight loss, and confusion. Other symptoms that might suggest PC include renal (nephrolithiasis, nephrocalcinosis, and impaired renal function) and skeletal involvement (osteitis fibrosa cystica, subperiosteal resorption, pathological fractures, "salt and pepper" skull)[35]. Clinical presentation of PHPT in the pediatric population show symptomatic more than in adults[19]. A current report of pediatric PC shows

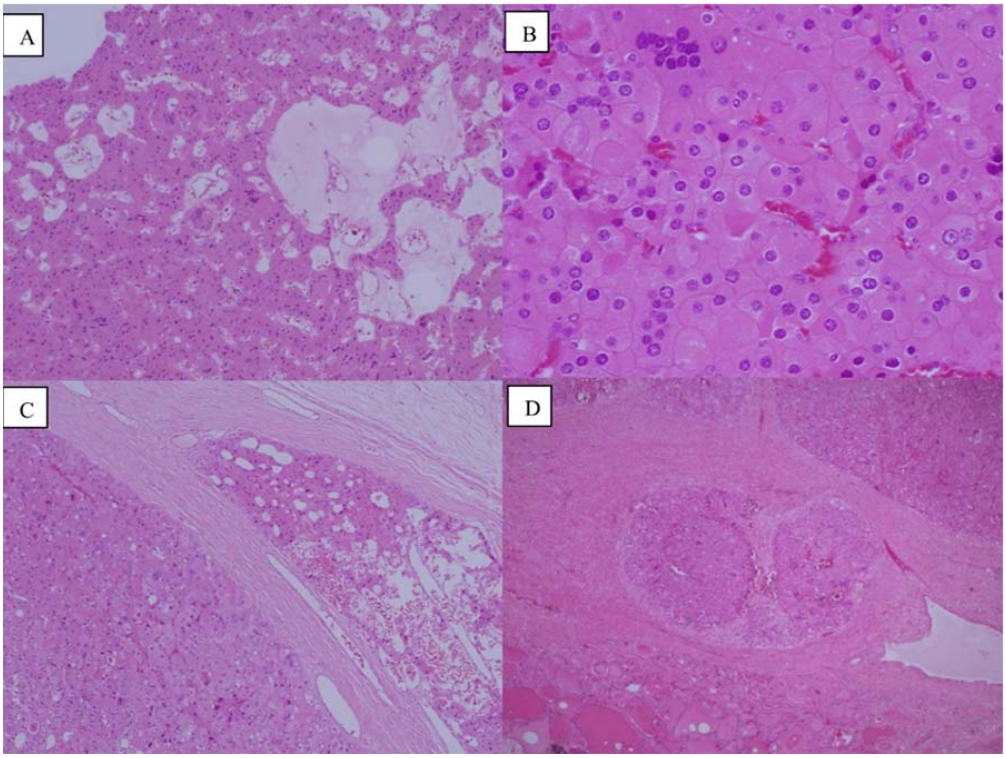

Figure 1. Histological features of parathyroid carcinoma: (A) Tumor cells (H&E staining, magnification x10); (B) Tumor cells (H&E staining, magnification x40); (C) Tumor with capsular invasion (H&E staining, magnification x10); (D) Tumor with capsular invasion, next to the thyroid gland (H&E staining, magnification x4).

Table 1. TNM staging systems for parathyroid carcinoma[5]

Schulte		Schulte B	
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	Low risk	Capsular invasion or invasion of surrounding soft tissues
N classification	Nx: Lymph node not assessed N0: No regional lymph node metastases N1: Regional lymph node metastases	High risk	Vascular invasion and/or lymph node metastases and/or invasion of vital organs and/or distant metastases
M classification	Mx: Distant metastases not assessed M0: No evidence of distant metastases M1: Evidence of distant metastases		
Stage	I: T1 or T2N0M0 II: T3N0M0 III: Any T, N1M0, or T4 IV: Any N, M1		

60% of palpable neck mass, 50% of skeletal involvement (including fracture and deformity), and 20% of metastasis (lungs and cervical lymph nodes)[10].

Acute PHPT (parathyroid crisis) is rare in PC. However, life-threatening hypercalcemia can occur with the involvement of the kidneys (renal failure), heart (cardiac arrhythmia), and/or brain (reduced consciousness till coma)[5].

PC without PTH production (i.e., nonfunctional) is found to be less than 10% of patients. These cases have no symptoms of hyperparathyroidism but usually have a poor prognosis, neck lumps may often be detected. These patients often experience hoarseness and difficulty in swallowing[8,9,15].

The symptom criteria for suspecting PC, as stated by Obara et al[16,37], include:

1) Age below 55/years

2) Marked hypercalcemia and hyperparathormonemia (more than 10 times over the limit)

3) Severe bone symptoms (fibrocystic osteitis in 40% to 70% of cases) and kidney symptoms (nephrocalcinosis, nephrolithiasis in 30% to 60% of cases)

4) RLN paralysis due to tumor invasion

5) Palpable cervical swelling, which is rare in benign disease (in 50% of patients with neck lumps, these are associated with the spread of the disease to other areas)[38].

Laboratory examination

The majority of patients with PC are found to have very high calcium levels (>13 to 15 mg/dl). Also, PTH levels are usually 3 to 10 times higher than normal[39]. Approximately 75% of people with the disease have calcium levels above 14 mg/dL, while only 10% have calcium levels less than 13 mg/dL.

Additionally, patients with PC often have higher levels of alkaline phosphatase (ALP) and a and b subunits of human chorionic gonadotrophin[40]. A study by Bae et al found that serum ALP levels and tumor size can predict the likelihood of developing PC, with serum ALP levels greater than 285 IU/L[41], or three-fold or more over baseline[42] and tumor sizes greater than 3 cm being predictor values for PC, while lower values are often found to be benign[41].

Radiological examination

Using ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and 99mTc-sestamibi (MIBI) scintigraphy, there is no known way to distinguish between parathyroid adenoma and PC[43,44] but the imaging techniques are mainly useful for localizing parathyroid lesions[45].

99mTc-MIBI dual-phase scintigraphy found delayed washout in parathyroid tumors more than normal thyroid glands and parathyroid glands[46,47]. MIBI dual-phase scintigraphy can help locate abnormal parathyroid glands and distinguish them from normal thyroid and parathyroid glands, but an early or delayed 99mTc uptake on imaging cannot be used to distinguish PC from the benign parathyroid lesion due to high mitochondrial number, metabolic activity, or blood flow might exist in both lesions[44,48]. A recent study found that PC has a significantly higher retention level of 99mTc-MIBI than benign parathyroid lesions, The cutoff value of the peak of retention index of the parathyroid lesion is more than -19% which related significantly to the suspicion of PC[48]. Metastatic lymph nodes can give false-negative results[49].

Ultrasonography is very useful for locating enlarged parathyroid glands. Ultrasound characteristics, such as a mass greater than 3 cm, marginal irregularity with local tissue invasion, heterogeneous echotexture, and the presence of calcifications are highly suggestive of PC, with a 100% sensitivity, 96.9% specificity, and 97.4% accuracy[50].

CT and MRI scans cannot be used to diagnose PC (Figure 2), but may help determine the location of the parathyroid mass, invasion of surrounding tissues, and identify any lymph node metastasis and distant metastasis[39]. PET/CT is useful in cases of suspected tumor recurrence or residual disease after treatment[51].

Using ^{18}F-Fluorocholine PET/CT (^{18}F-FCH PET/

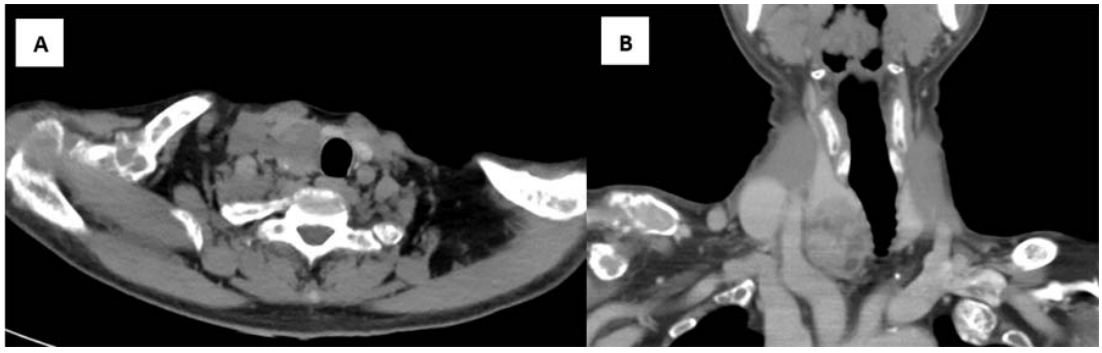

Figure 2. CT Neck with the contrast of parathyroid carcinoma; (A) Axial view. (B) Coronal view. Findings: well-defined heterogeneous hypervascularity lesion at the lower aspect of right thyroid gland size 2.9x3.2x3.7 cm, no cervical lymph node enlargement.

CT) is one of the newest ways to localize the parathyroid adenomas before surgery[52]. Many case reports show it is useful for recurrent PC which can detect local relapse, metastatic lymph nodes, and distance metastases when using complementary to ^{18}F-Fluorodeoxyglucose PET/CT (^{18}F-FDG PET/CT) due to the differences in FDG and choline uptake in tumor differentiation and proliferation[53]. So this may be used to help diagnose PC in the future. However, brown tumors are often found to be ^{18}F-FCH PET/CT positive as well, which can lead to confusion as it may be misinterpreted as metastasis[35].

Fine needle aspiration

Fine needle aspiration biopsy is not recommended in cases where PC is suspected. This is because parathyroid adenoma and PC cannot be distinguished. In addition, a puncture may cause the lesion capsule to rupture and allow the cancer cells to spread[54]. The role of the frozen section can be used to confirm parathyroid tissue but it is an unnecessary tool for parathyroid surgery[55]. The histopathological features of parathyroid adenoma and PC are similar and sometimes indistinguishable by frozen section analysis[56]. But sometimes it can identify histological features suggestion of malignancy in many reports[55,57].

Treatment

PC can cause severe hypercalcemia and need immediate treatment to reduce the calcium levels before the patient has surgery as well as in patients who cannot be operated on. Hydration with normal saline infusion in patients with hypercalcemia often reduces calcium levels due to dehydration[58] and also intravenous administration of bisphosphonates. Bisphosphonates inhibit osteoclastic activity which plays a major role in mediating hypercalcemia, although its mechanism of action is relatively slow[58,59]. Denosumab is a human monoclonal antibody that can be used to inhibit the RANK ligand by inhibiting RANK binding on the osteoclast. This result is a reduction in bone resorption[60]. While calcitonin acts to reduce blood calcium levels by inhibiting bone resorption and also decrease the resorption of calcium in the kidneys. This will have the effect of reducing calcium levels quickly that can be used in an initial with hydration[58]. In inoperable patients, cinacalcet, a second-generation calcimimetic drug, can be given, which increases the sensitivity of the calcium sensing receptor to circulating serum calcium, suppress PTH levels and the serum calcium will be reduced as well. This was found to lowering blood calcium levels in up to two-thirds of cases[60-62].

Surgery remains the gold standard treatment. The primary treatment is the complete en-bloc resection of the tumor with the ipsilateral thyroid lobe, and excision of any adjacent involved structures until clear gross margin and care to avoid rupture of the tumor[14,63]. The intra-operative PTH monitoring show (ioPTH) should be performed if possible[20]. The measurement of serum PTH was performed at a pre-incision sampling, at 5 min after the parathyroid tissue removal and at 10 to 15 min after excision. PTH level decreases >50% at 5 or 10 min post-excision compared to pre-incision level that can define a surgical success[64] because the half-life of PTH is approximately 5 min[65]. The ioPTH monitoring shows the superior drop in malignant parathyroid disease compared to benign disease due to a higher ioPTH baseline[64]. If the en-bloc resection was not performed in the primary surgery, the re-operation is not yet clear[36]. A study of 40 patients with PC found that underwent re-operative en-bloc resection had a better outcome if the first operation underwent local tumor excision. Although evidence of carcinoma tissue was not found in the surgical specimens in additional surgery[36].

The incidence of lymph node involvement at the first diagnosis is 6.5% to 32.1%. The neck dissection should be performed in the case with evidence of lymph node metastasis[66] and there is no conclusive evidence for prophylactic neck dissection[66]. Some authors reported routine en-bloc resection and central neck dissection in all patients with PC have found central lymph node metastasis up to 10% of cases[5]. A report shows lymph node metastases in PC were 7.5 times more frequent in patients with tumors ≥3 cm but not related to disease-specific survival (DSS)[67]. Prophylactic neck dissection would be useful in these cases[67].

Radiation therapy is controversial because PC is a radio-resistant tumor and is not recommended as a primary treatment[7]. Most studies have shown that radiation therapy does not improve loco-regional control or overall survival[68,69], but some studies have found it helpful for local control compared to those without radiation[70].

Chemotherapy showed no evidence of effectiveness for the treatment of PC. However, chemotherapy may be used in inoperable cases. Some studies reported partial responses to chemotherapy; however, no clear standardized protocols were available[71]. The chemotherapy regimens reported in these studies were monotherapy, dacarbazine, or combination therapy, consisting of fluorouracil, cyclophosphamide, and dacarbazine or methotrexate, doxorubicin, cyclophosphamide, and lomustin[14] administration.

Sorafenib is the targeted therapy approved for the treatment of different types of cancer that is successful in treatment in some PC cases[72]. Sorafenib is a multikinase inhibitor that inhibits Raf-1, B-Raf, VEGFR2, PDGFR and c-Kit receptors[73]. PC has increased angiogenesis and the study shows high expression of VEGFR, and PDGFR[72]. Then, sorafenib seems to act on these mechanisms. A reported in a 27-year-old female patient diagnosed with metastasis PC with CDC73 mutation showed successful use of sorafenib. A response to sorafenib was reported to significantly reduce pulmonary metastasis and reduce the progression of hyperparathyroidism. The overall follow-up period is 22 months[72].

Although treatment is more advanced nowadays, the recurrence rate of PC is high [74] (23% to 50% case)[35], and the average is 2 to 3 years after initial surgery[74]. Complete initial en-bloc resection shows a low recurrence rate. Most patients have a five-year survival rate of 90% and a 10-year survival rate of 67%[75].

Follow-up aims to check for a recurrence and other metastases, including by physical examination and checking calcium and PTH levels every six months during the first five years, and after that, follow-up appointments can be made every year for the rest of their lives with an ultrasound of the neck performed every year[39].

Conclusion

PC is a very rare cancer, an accurate diagnosis and correct treatment initially are of the utmost importance. However, these are quite difficult and there are challenges for the physician because no preoperative diagnosis can show a definitive diagnosis. High calcium and PTH levels can cause many different symptoms, so it is important to maintain the calcium balance in patients before surgery as well as in inoperable patients. The adjuvant therapy such as radiotherapy or chemotherapy has not shown effective in the treatment of PC. However, Complete en-bloc resection is the mainstay of the treatment.

What is already known on this topic?

PC is a rare endocrine malignancy and a rare cause of PHPT. Pre-operative diagnosis to differentiate malignant from benign hyperparathyroidism may be difficult because there are no specific clinical, laboratory, or radiological characteristics of PC. The "gold standard" treatment is en-bloc resection.

What this study adds?

This review literature has provided more information about the etiology, clinical presentation, investigation, and management of PC. Although, preoperative diagnosis remains challenging. Besides, medical treatment with calcimimetic drugs is the most effective treatment for the control of hypercalcemia in patients with inoperable PC. Sorafenib was successfully used in the patient with metastatic PC and germline CDC73 mutation. In the future, gene analysis may have benefits for metastatic PC.

Potential conflicts of interest

The authors declare no conflict of interest.

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