



## Parathyroid carcinoma; facts and views

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### Abstract

Because of the rare nature of parathyroid carcinoma, few physicians and surgeons have had experience in management of this disease. Although parathyroid carcinoma is not a common cancer, however, in patients with early hyperparathyroidism is very important, especially due to its mortality. Parathyroid carcinoma could occur equally between two genders but the incidence of parathyroid carcinoma is increasing worldwide despite its rare occurrence, with youth and being female as two important related factors. There is no available lifestyle factor related to parathyroid carcinoma. In fact, the cause of parathyroid carcinoma is yet to be established and there is no data to confirm causal relationships between parathyroid carcinoma and any risk factor, although it may be some relations with familial and sporadic forms.

**Keywords:** Parathyroid carcinoma, Primary hyperparathyroidism, Hypercalcemia

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### Introduction

Behind of the thyroid gland, there are four glands named parathyroid which help the regulation of the calcium levels across the human body (1). Parathyroid carcinoma (PC) is the most rare cause of primary hyperparathyroidism which is one of the most common endocrine disease. It typically affects the elderly women and men and its clinical appearance is characterized by mild hypercalcemia, traditional classic bone, kidney manifestations and elevation of parathyroid hormone and often resulting in severe hypercalcemia (1,2). PC has also been reported rarely in patients with secondary hyperparathyroidism (2,3). The signs and symptoms of PC are renal stones, bone pains, osteoporosis, abdominal pain and weight loss. Physical examination may also reveal a cervical mass on population. The biochemical abnormalities are elevated serum calcium levels with concomitantly elevated parathyroid hormones levels (2-4). It has also been described in several patients with end-stage renal disease too (5). However, there is no agreed staging system for PC, thus there is not possible to provide patients with a solid prognosis (6). This disease occurs in patients of all ages, and there is no prediction for either sex. Histopathological criteria are key outcome predictors in PC (6). Physical examination may reveal a cervical mass on population.

### Epidemiology

Primary hyperparathyroidism is an important endocrine disease in general population (7). In fact, majority of the patients with primary hyperparathyroidism may show somehow benign or malignant tumors (6-8). The overall incidence of primary hyperparathyroidism is reported to be one in every 1000 persons and PC could account for 1% of all cases of primary hyperparathyroidism (4). In addition, familial primary hyperparathyroidism could also increase the risk of PC (9). On the other hand, the morbidity and mortality of PC is associated with the complications of hypercalcemia which is managed with surgical removing after proper identification (10), that is why PC should be taken into account in the differential diagnosis of hypercalcemia by clinicians (11). Moreover, PC is one of the rarest known cancer, even much rare among children under 16 years old (12), which might be occurred sporadically and could account for about 0.7-2.1% (13), 0.5%-5% (14) [on average 1% (15)] of patients with early primary hyperparathyroidism. Furthermore, although PC is rare, but it is an important cause of death in the group of patients with primary hyperparathyroidism and it accounts for 0.7%-2.1% of all cases of primary hyperparathyroidism, with an incidence of 0.4 to 0.6 per million based on surveillance, epidemiology and end result data (6).

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### ■ Implication for health policy/practice/research/medical education

The etiology of parathyroid carcinoma is unclear although some cases have been reported to develop within, or to coexist with, a parathyroid adenoma or a hyperplastic parathyroid gland.

Primary hyperparathyroidism emerged from 1970s to become the third most common endocrine disorder in more recent times (16). Heath and colleagues (17) have reported that the average annual incidence of early hyperparathyroidism has increased from 8 to 28 per 100 000 after the introduction of routine serum calcium measurements among hospital admissions. This dramatic change was brought about by the introduction of automated serum calcium measurements in mid-1974. As a result of this type of screening, the age-adjusted incidence rates of primary hyperparathyroidism increased from 15.8 (1970–1974) to 82.5 cases (1974–1982) per 100 000 person years for males and females (16). Since that time, the incidence rates have decreased. Moreover, research has shown that the incidence of PC has increased since 1974 (18). Numerous hypothesis have been advanced to explain the progressive decline, including the ‘sweeping’ effects of screening, the use of estrogen replacement in postmenopausal women, calcium and vitamin D dietary supplementation and the use of therapeutic head and neck irradiation in the 1930s and 1940s, which could have accounted for the ‘epidemic’ of hyperthyroidism observed in the late 1970s and 1980s (16). In fact, approximately 290 cases of PC were reported between 1930 and 1992 (5). Furthermore, there is a considerable variation in the incidence of this tumor in different parts of the world, with rates as high as 5% in some areas. Although this variability may represent true geographic differences in pathological criteria for the diagnosis of these tumors (5,16).

Moreover, PC is one of the rarest known malignancies that may occur sporadically or as a part of a genetic syndrome. For example, it accounts for approximately 1% of patients with primary hyperparathyroidism in USA but not in Japan and Italy (with about 5%) (16). The relatively higher incidence of PC in these countries may be related to true geographic differences or to varying criteria for its pathologic diagnosis. Most cases of PC are diagnosed between the ages of 44 and 54 years, which is approximately a decade earlier than the median age of patients with PC. It occurs rarely in children (3). In addition, the majority (90%) of PC tumors are hormonally functional and hypersecreting parathyroid hormone. Thus, most patients exhibit strong symptomatology of hypercalcemia at presentation (19). PC typically presents between 45–59 years and occurs equally in men and women, however, patients with benign parathyroid tumors are usually decade older than PC patients with a female to male gender ratio of 3:1 (19). The biochemical abnormalities are elevated serum calcium levels with

concomitantly elevated parathyroid hormones levels (4). Little is known about the etiology of PC. A history of prior radiation to the neck is a risk factor for the development of PC, but the role of radiation in the development of PC is less clear (3). There is little information on the etiology of PC, but prior radiation does not seem to be a significant factor. Rare cases of PC have been reported in patients with long-standing secondary hyperthyroidism (16). The etiology of PC is unclear although cases have reported to develop within, or to coexist with, a parathyroid adenoma or a hyperplastic parathyroid gland.

### Diagnosis

The diagnosis of early hyperparathyroidism is mainly clinical and biochemical. In fact, biopsy is not necessary before surgery. CT-scan would be the best method for detecting the early tumor, its local extent and metastasis (18). Most of the symptoms are related to hypercalcemia which should be treated immediately; in addition, early surgery is the only curative treatment (18). PC is usually resistant to radiotherapy; however, different chemotherapeutic methods are available (18). After operation, metastasis to other organs such as lungs, mediastinum and lymph nodes are common and difficult to control (20). Its clinical features are primarily attributable to the effects of hypercalcemia and excessive secretion of parathyroid hormone. Most of its symptoms—weakness, fatigue, anorexia, weight loss and nausea—are nonspecific (21). No single histologic feature is considered diagnostic for PC and a constellation of features can usually be used to support the diagnosis (21). Moreover, the excretion of urinary human chorionic gonadotropin in urine has the ability to distinguish between parathyroid adenomas and carcinomas and has the potential to become a marker of disease progression in malignant parathyroid disease (1). Furthermore, PC has been associated with a prior history of neck irradiation, with end stage renal disease and with familial hyperparathyroidism (2).

The clinical presentations of patients with PC are related primarily to the effects of markedly increased secretion of parathyroid hormone. Patients are more likely to present with secondary bone and renal diseases than those patients with hyperparathyroidism due to functioning adenomas. Renal involvement (nephrolithiasis, nephrocalcinosis and impaired renal function) has been demonstrated in up to 80% of patients with PC, whereas bone disease (osteitis fibrosa cystica) has been demonstrated in up to 90%. The combination of both renal and bone disease at presentation is a strong predictor of the presence of parathyroid malignancy (3). PC should be clinically suspected if a patient has a serum calcium level more than 14 mg/dl with a palpable nodule in the neck and intraoperative findings such as adhesion or local fibrotic reaction (22).

It should be noted that the diagnosis and treatment of PC would rise some challenges for clinicians due to its difficult identification during histological examination or operation (11). The diagnosis of PC is not too easy

to detect the patients only by using a historical exam. In fact, it needs more specific cytological or immunohistochemical markers and thus the combination of clinical and histological signs or symptoms is necessary (23).

### Treatment

The single most effective therapy for PC is complete resection of the primary lesion at the time of initial operation (5). PC is not a radiosensitive tumor (5). In addition, because of the rarity of PC, few researchers have sufficient numbers of patients to permit a large scale clinical trial. Attempts to control tumor with chemotherapy have been disappointing (5). In fact, complete surgical resection with microscopically negative margins is the recommended treatment and offers the best chance of cure. Persistent or recurrent disease occurs in more than 50% of patients with PC. Surgical resection is also the primary mode of therapy for recurrence since it can offer significant palliation for the metabolic derangement caused by hyperparathyroidism and allows hypercalcemia to become more medically manageable. However, reoperation is rarely curative and eventual relapse is likely. Chemotherapy and external beam radiation treatments have been generally ineffective in the treatment of PC. Typically, these patients require repeated operations that predispose them to accumulated surgical risks with each intervention (19).

The prognosis of PC is quite variable; in fact, no one characteristic correlates predictably with outcome. Early recognition and complete resection at the time of the initial surgery carry the best prognosis. The average time between surgery and the first recurrence is approximately three years, although intervals of up to 20 years have been reported. Once the tumor has recurred, complete cure is unlikely (5).

### Survival

PC patients typically have a long survival, which often includes multiple reoperations for recurrence and thus a high rate of surgical complications. Patients in whom there is high index of suspicion for PC should be referred to dedicated endocrine surgery center for their initial operation (24). Patients with PC typically live a life fraught with several recurrences, requiring reoperations. Death is usually due to uncontrollable hypercalcemia, causing complications such as renal failure, cardiac arrhythmias or pancreatitis (24). PC patients have a relatively long survival after the initial parathyroidectomy. However, their mortality influenced by several factors. These patients also often require multiple operations for recurrence. Because of this, they have a high rate of surgical complications, including a high proportion of recurrent laryngeal nerve injuries. There is a high suspicion of PC preoperatively because of profound hypercalcemia or a palpable parathyroid mass (24). The 5-year survival is about 50% and 10-year survival is varies from 13%-49% (18).

### Conclusion

Due to the rare nature of PC, few physicians and surgeons have had experience in management of these diseases (25). Although this disease is not a common cancer, however, in patients with early hyperparathyroidism is very important (15), especially due to its mortality (26). PC could occur equally between two genders (27) but the incidence of PC is increasing worldwide despite its rare occurrence, with youth and being female as two important related factors (13). There is no available lifestyle factor related to PC (28). In fact, the cause of PC is yet to be established and there is no data to confirm causal relationships between PC and any risk factor (20), although it may be some relations with familial and sporadic forms (29).

### Authors' contributions

All authors wrote the manuscript equally.

### Conflict of interests

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### Ethical considerations

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