An updated mini-review on parathyroid cancer

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Abstract
Parathyroid cancer is a rare malignancy originating from the parathyroid glands, which regulate calcium levels in the body. This review article aims to provide a comprehensive overview of parathyroid cancer, including its epidemiology, etiology, clinical presentation, diagnostic methods, treatment options, and prognosis. The article also highlights recent advancements in research and potential future directions for improving the management of this challenging disease.

Keywords: Parathyroid cancer, Parathyroid glands, Malignancy, Primary hyperparathyroidism, Multiple endocrine neoplasia type 1, Metastasis

Introduction
Parathyroid cancer is a rare malignancy that arises from the parathyroid glands, which regulate calcium levels in the body (1,2). Parathyroid cancer's rarity presents unique diagnostic and therapeutic challenges (3). This mini-review aims to provide a comprehensive overview of parathyroid cancer, including its epidemiology, etiology, clinical presentation, diagnostic modalities, treatment options, and prognosis. Additionally, we will discuss the ongoing research efforts and future directions in managing this rare malignancy.

Search strategy
For this review, we extensively searched various databases including PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ), and Embase. We used a wide range of keywords to ensure comprehensive results, such as parathyroid cancer, parathyroid glands, malignancy, primary hyperparathyroidism, multiple endocrine neoplasia type 1, hypercalcemia, kidney stones, bone pain, neck masses, hoarseness, dysphagia, and metastasis

Epidemiology
Parathyroid cancer is an extremely rare malignancy, accounting for less than 1% of all cases of primary hyperparathyroidism. It predominantly affects middle-aged adults, with a slight female predominance (2,3). Parathyroid cancer's exact incidence and prevalence are difficult to determine due to its rarity and the lack of population-based studies (4).

Etiology of parathyroid cancer
The etiology of parathyroid cancer remains largely unknown. However, specific genetic syndromes, such as multiple endocrine neoplasia type 1 (MEN1) and hyperparathyroidism-jaw tumor syndrome (HPT-JT), have been associated with an increased risk of developing parathyroid cancer. Somatic mutations in genes such as CDC73 and HRPT2 have also been implicated in the pathogenesis of sporadic parathyroid cancer (2,5).

Clinical presentation
Parathyroid cancer often presents symptoms similar to primary hyperparathyroidism, including hypercalcemia, kidney stones, bone pain, and fatigue. However, patients with parathyroid cancer may also experience more severe manifestations, such as palpable neck masses, hoarseness, dysphagia, and respiratory distress (2,6).

Diagnosis of parathyroid cancer
The diagnosis of parathyroid cancer is challenging and relies on a combination of clinical, biochemical, radiological, and histological findings. Serum calcium and parathyroid hormone levels are typically elevated in patients with parathyroid cancer. Imaging modalities such as ultrasound, computed tomography, magnetic resonance imaging, and technetium-99m sestamibi scintigraphy can
Managing parathyroid cancer necessitates a collaborative effort from a multidisciplinary team consisting of endocrinologists, surgeons, pathologists, radiologists, and oncologists. This collaboration is crucial for ensuring an accurate diagnosis, optimizing surgical intervention, and developing personalized treatment plans tailored to each patient’s circumstances (1,19).

**Prognosis of parathyroid cancer**

Parathyroid cancer is associated with a poor prognosis with a high risk of recurrence and metastasis. The 5-year survival rate ranges from 50% to 80%, depending on the stage of the disease. Prognostic factors include tumor size, extent of invasion, lymph node involvement, and distant metastasis (17,20).

**Conclusion**

Parathyroid cancer is a rare, aggressive malignancy with significant diagnostic and therapeutic challenges. Further research is needed to improve our understanding of the underlying molecular mechanisms, develop effective targeted therapies, and identify reliable prognostic markers. Multidisciplinary collaboration and international registries are crucial for advancing the management and outcomes of patients with parathyroid cancer.

**Authors’ contribution**

Conceptualization: MAEP, AK.
Validation: MAEP, AK.
Investigation: MAEP, AK.
Resources: MAEP, AK.
Data Curation: MAEP, AK.
Visualization: MAEP, AK.
Supervision: MAEP, AK.
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The authors declare that they have no competing interests.

**Ethical issues**

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**Molecular Pathways and prognostic factors**

The molecular pathways involved in parathyroid cancer are still being elucidated. Common genetic alterations, such as cyclin D1 (CCND1) and retinoblastoma 1 (RB1) gene mutations, have been identified, along with alterations in the Wnt signaling pathway (13,14). These insights into the molecular basis of parathyroid cancer may aid in the development of targeted therapies in the future. Additionally, several prognostic factors, including tumor size, presence of lymph node or distant metastases, and histological characteristics, have been identified to guide treatment decisions and predict patient outcomes (15,16).

**Clinical features and diagnosis**

Parathyroid cancer usually affects adults, with a slight female predominance. Patients often present with symptoms related to hypercalcemia, such as fatigue, kidney stones, bone pain, and neuropsychiatric manifestations (2,8). However, these symptoms can overlap with those of benign parathyroid disease, making diagnosis challenging. Radiological imaging, including neck ultrasound, computed tomography, and technetium sestamibi scan, are helpful in localization. Still, a definitive diagnosis typically needs histological examination through fine-needle aspiration or surgical biopsy (11,12).

**Treatment**

Surgical resection is the mainstay of treatment for parathyroid cancer. However, due to the rarity and aggressiveness of the disease, complete resection is often challenging, and local recurrence and distant metastasis are common. Adjuvant therapies, including radiation therapy and chemotherapy, have shown limited efficacy in improving outcomes. Targeted therapies, such as tyrosine kinase inhibitors and mammalian target of rapamycin (mTOR) inhibitors, are currently being investigated in clinical trials (17,18).

**Multidisciplinary approach**

Managing parathyroid cancer necessitates a collaborative effort in localizing the tumor (7,8). Definitive diagnosis requires histopathological examination of the resected tissue, which may reveal characteristic features such as capsular invasion, vascular invasion, and mitotic activity (9,10).


