International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

ARTICLE TITLE	PARATHYROID CARCINOMA: CURRENT STATE OF KNOWLEDGE AND LITERATURE REVIEW
DOI	https://doi.org/10.31435/ijitss.4(48).2025.4241
RECEIVED	15 October 2025
ACCEPTED	14 December 2025
PUBLISHED	22 December 2025
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

PARATHYROID CARCINOMA: CURRENT STATE OF KNOWLEDGE AND LITERATURE REVIEW

Anna Barbara Tuleja *[ABT] (Corresponding Author, Email: abtuleja@gmail.com)*
University Hospital in Wroclaw (USK), Wroclaw, Poland
ORCID ID: 0009-0003-9185-9493

Julia Kosmulska *[JK]*
University Hospital in Wroclaw (USK), Wroclaw, Poland
ORCID ID: 0009-0000-8770-3793

Jakub Nowak *[JN]*
Independent Public Healthcare Institution of the Ministry of the Interior and Administration, Kraków, Poland
ORCID ID: 0009-0003-7097-0635

Michał Drabik *[MD]*
5th Military Clinical Hospital with Polyclinic SPZOZ, Kraków, Poland
ORCID ID: 0009-0004-0198-4926

Mateusz Kęska *[MK]*
5th Military Clinical Hospital with Polyclinic SPZOZ, Kraków, Poland
ORCID ID: 0000-0003-0712-7613

Michael Platschek *[MP]*
Blessed Marta Wiecka Hospital in Bochnia, Bochnia, Poland
ORCID ID: 0009-0008-9085-4531

Klaudia Dybalska *[KD]*
Brzeziny Specialist Hospital, Brzeziny, Poland
ORCID ID: 0009-0006-9900-0167

Maksym Sikora *[MS]*
Hospital of the Brothers of St. John of God, Kraków, Poland
ORCID ID: 0009-0008-4495-7732

Karol Józef Szkarłat *[KJS]*
Medical University of Silesia in Katowice, Faculty of Medical Sciences, Katowice, Poland
ORCID ID: 0009-0004-2889-8382

Sylwia Wiktoria Kolano *[SWK]*
Independent Public Healthcare Institution of the Ministry of the Interior and Administration, Kraków, Poland
ORCID ID: 0009-0000-1180-1135

ABSTRACT

Parathyroid carcinoma (PC) is a rare malignancy of the parathyroid glands, accounting for only a minute fraction of all cancers worldwide. Although uncommon, it poses significant diagnostic and therapeutic challenges because its clinical features often resemble those of benign primary hyperparathyroidism (PHPT). This review summarizes current understanding of PC, integrating recent advances in epidemiology, genetics, diagnostics approaches and management. The global incidence is estimated at 3–6 new cases per 10 million people annually, affecting men and women equally and typically presenting around the fifth decade of life. Genetic alterations play a central role in pathogenesis. Mutations in CDC73 with consequent loss of parafibromin function are the most characteristic finding, especially in the hereditary hyperparathyroidism–jaw tumor (HPT-JT) syndrome. Other hereditary conditions such as multiple endocrine neoplasia types 1 and 2 (MEN1 and MEN2) or isolated familial hyperparathyroidism may also involve the parathyroid glands, though carcinoma remains rare in these syndromes. Additional molecular abnormalities, such as alterations in RB1, TP53, BRCA2, and CCND1, and activation of PI3K/AKT-/mTOR and MAPK pathways - have been linked to tumor progression.
The cornerstone of treatment is early, complete en bloc resection, offering the best chance of cure. For recurrent or metastatic disease, therapy focuses on controlling hypercalcemia using cinacalcet, denosumab, and, in selected cases, adjuvant radiotherapy. Early recognition, genetic testing, and multidisciplinary care are crucial for improving long-term outcomes in this rare but challenging endocrine malignancy.

KEYWORDS

Parathyroid Carcinoma, Primary Hyperparathyroidism, Hypercalcemia, Hyperparathyroidism–Jaw Tumour (HPT-JT) Syndrome, Parafibromin

CITATION

Anna Barbara Tuleja, Julia Kosmulska, Jakub Nowak, Michał Drabik, Mateusz Kęska, Michael Platschek, Klaudia Dybalska, Maksym Sikora, Karol Józef Szkarłat, Sylwia Wiktoria Kolano. (2025) Parathyroid Carcinoma: Current State of Knowledge and Literature Review. *International Journal of Innovative Technologies in Social Science*. 4(48). doi: 10.31435/ijitss.4(48).2025.4241

1. Introduction

Parathyroid carcinoma (PC) is a rare malignant tumour of the parathyroid glands, representing only about 0.005% of all cancers diagnosed each year [1,2]. According to population registries such as SEER and NCDB, its estimated incidence is 3–6 new cases per 10 million people annually. The apparent rise in reported cases in recent decades is believed to reflect earlier detection and improved diagnostic accuracy rather than a true increase in disease occurrence [2–4]. Unlike benign forms of primary hyperparathyroidism (PHPT), PC affects men and women equally, with a median age at diagnosis of about 50 years [3–5].

Clinically, PC is characterized by severe hypercalcemia and markedly elevated parathyroid hormone (PTH) levels. Most tumors are hormonally active, and morbidity as well as mortality result primarily from metabolic complications rather than the tumour mass itself [1–3].

Non-functional tumors are uncommon, typically diagnosed at an advanced stage and carrying a less favourable prognosis [3,4]. Despite progress in imaging and histopathology, establishing a preoperative diagnosis remains challenging, as cytological and radiological findings may overlap with adenomas or atypical parathyroid lesions. The 2022 WHO Classification of Parathyroid Tumors highlights that the diagnosis of carcinoma requires unequivocal evidence of invasive growth - vascular or perineural invasion, infiltration of adjacent structures, or distant metastasis, because cytologic atypia alone is insufficient [2,43,53]. Genetic alterations play a central role in the pathogenesis of PC. The best-documented are CDC73 (formerly HRPT2) mutations leading to loss of parafibromin protein function, observed in both sporadic cases and in the hereditary hyperparathyroidism–jaw tumour (HPT-JT) syndrome, which carries the strongest predisposition to malignancy [3,4,14,49]. Additional genetic and epigenetic aberrations have been described, including mutations in RB1, TP53, BRCA2, and CCND1, as well as alterations in DNA methylation, histone modification, and microRNA or circular RNA (circRNA) regulation. Recent genomic studies further implicate activation of the PI3K/AKT/mTOR and MAPK pathways through mutations in PTEN, NF1, KDR, PIK3CA,

and TSC2 [7–10,18]. These findings have opened new perspectives for the development of targeted therapies, although clinical evidence for their efficacy remains limited [10–13,30]. Surgical resection remains the cornerstone and only potentially curative treatment for PC. Early, complete en bloc excision with tumour-free margins provides the best prognosis, whereas delayed or incomplete surgery markedly increases the risk of recurrence and disease-specific mortality. Intraoperative tumour manipulation should be minimized to prevent dissemination [6–9,11]. Perioperative management includes intraoperative PTH monitoring - as a supportive tool rather than a determinant of surgical extent and careful prevention or treatment of hungry bone syndrome following successful surgery [8,10–12]. In patients with recurrent or metastatic disease, management is primarily palliative and aimed at controlling hypercalcemia. Supportive measures include hydration, bisphosphonates, cinacalcet and denosumab; radiotherapy may be considered in selected high-risk cases, while ablation techniques can provide temporary relief. Chemotherapy plays only a marginal role in treatment [2,4–7,12–13,37]. Prognosis remains variable. Five-year survival rates range from 77% to 85%, but recurrence occurs in 40–65% of patients, typically within two to five years after initial surgery. Refractory hypercalcemia remains the leading cause of death [1–6]. The 8th edition of the AJCC/UICC Cancer Staging Manual introduced a TNM-based classification for PC for the first time, although validated prognostic stage groupings are still lacking. Consequently, clinical decision-making continues to rely mainly on the degree of invasiveness, margin status, and recurrence risk [27]. The aim of this review is to provide a comprehensive and up-to-date overview of parathyroid carcinoma—from its epidemiology, etiology, and molecular biology to its clinical features, diagnostic evaluation, surgical management, and palliative treatment. Special attention is given to the recent updates in classification systems (WHO 2022, AJCC 8th edition) and to emerging therapeutic strategies. Emphasis is also placed on prognostic factors, methods to reduce recurrence risk, and practical aspects of hypercalcemia control in this rare but clinically challenging disease [2,6–7].

2. Epidemiology

Parathyroid carcinoma (PC) is an exceptionally rare endocrine malignancy, accounting for less than 1% of all primary hyperparathyroidism (PHPT) cases and roughly 0.005% of all cancers diagnosed annually [1,2]. According to population-based studies, including recent updates from the SEER and NCDB registries, the estimated global incidence is approximately 3–6 new cases per 10 million people per year [2,3]. Earlier epidemiologic analyses suggested a gradual rise in recorded cases, which is now believed to result mainly from earlier detection and improved diagnostic methods rather than a genuine increase in disease frequency [2,4].

PC occurs equally often in women and men, unlike PHPT, which is more common in women [3,5]. The median age at diagnosis is typically around 50 years (slightly younger patients than in benign PHPT) [4,5].

3. Etiology and Pathogenesis

Genetic predisposition in PC is uncommon and environmental risk factors remain uncertain. Most PC cases are sporadic and familial syndromes are rare [1]. Exposure to ionizing radiation in childhood, especially to the head and neck region, and the presence of thyroid disease have been described as potential risk factors but a direct causal link remains uncertain [1,2].

Among hereditary syndromes, hyperparathyroidism jaw tumor (HPT-JT) syndrome shows the strongest association with PC. It is a rare autosomal dominant condition caused by germline mutations in the CDC73 gene (formerly HRPT2), which encodes the tumor suppressor protein - parafibromin [3,4]. Patients with HPT-JT are prone to develop parathyroid tumors - both benign and malignant, as well as ossifying fibromas of the jaw, renal cysts, and uterine tumors [3,5]. Parafibromin normally regulates gene transcription and inhibits uncontrolled cell proliferation; loss of its function due to CDC73 mutation promotes malignant transformation [4]. Germline CDC73 mutations occur in over 50% of HPT-JT families and in approximately 20% of apparently sporadic PC cases [3,6]. Other hereditary forms of primary hyperparathyroidism, such as isolated familial hyperparathyroidism (IFH) and multiple endocrine neoplasia (MEN) types 1 and 2, may also involve the parathyroid glands. However, in these syndromes, carcinoma is rare, disease limited to hyperplasia or adenoma is more common. [1,6]. In addition to CDC73, several somatic gene alterations have been linked to the pathogenesis of PC, including mutations in RB1, TP53, BRCA2, and CCND1 (PRAD1) [2,7]. Epigenetic mechanisms such as DNA methylation, histone modification, and microRNA or circRNA (circular RNA) dysregulation may further contribute to tumor progression [8]. Recent genomic studies have also identified mutations in PTEN, NF1, KDR, PIK3CA, and TSC2, suggesting potential involvement of the PI3K/AKT/mTOR and MAPK signaling pathways [9,10]. Genetic testing for CDC73 mutations is recommended in all patients with confirmed parathyroid carcinoma and should be considered in those with atypical parathyroid tumors, early-onset disease (<45 years), tumor size >3 cm, loss of parafibromin staining, or a family history consistent with HPT-JT [6,11].

4. Clinical features

Parathyroid carcinoma (PC) is usually symptomatic, and symptoms most often result from severe hypercalcemia, in contrast to benign causes of primary hyperparathyroidism (PHPT), such as adenoma or hyperplasia, where hypercalcemia is milder and frequently asymptomatic. The clinical course of PC is typically more aggressive, and complications related to calcium excess contribute to increased mortality [1,2]. Most cases of PC are hormonally active, with the tumor causing increased production of PTH, while non-functional tumors represent only about 1–2% and are usually diagnosed at an advanced stage due to mass effect or metastases [3,4]. Clinical manifestations are mainly the consequence of sustained hypercalcemia, which affects multiple organ systems. The most common symptoms include fatigue, generalized weakness, anorexia, nausea, vomiting, constipation, polyuria, and weight loss. Neuropsychiatric symptoms such as anxiety, depression, irritability, or confusion may occur in advanced disease. In severe cases, a parathyroid crisis may develop, characterized by calcium concentrations above 3.5 mmol/L, dehydration, altered mental status, and cardiac arrhythmias, which constitute a medical emergency [1,5,6]. Renal and skeletal complications are also frequent and represent hallmark features of PC. Nephrolithiasis, nephrocalcinosis, and chronic renal insufficiency occur in approximately 40–60% of patients, while bone pain, pathological fractures, and osteitis fibrosa cystica are observed in nearly half of all cases.

Radiologic findings often reveal subperiosteal bone resorption also known as “brown tumors.”

The coexistence of renal and skeletal symptoms should always raise suspicion for malignancy rather than benign PHPT [2,5,7]. Gastrointestinal complaints such as abdominal pain, nausea, constipation, and pancreatitis are also common, particularly when hypercalcemia is severe. Cardiovascular abnormalities, including hypertension, arrhythmias, and QT interval shortening may accompany chronic hypercalcemia or acute parathyroid crisis [8]. Local symptoms are another distinguishing feature of PC. A palpable firm neck mass is reported in 30–70% of patients and may adhere to surrounding tissues. Hoarseness or vocal changes may indicate invasion of the recurrent laryngeal nerve, whereas dysphagia or dyspnea can result from infiltration of the trachea, esophagus, or strap muscles. Local lymph node metastases occur in about one-quarter of cases, and distant metastases most frequently involve the lungs, bones, and liver [1,2,6,9]. Several features help differentiate PC from benign PHPT at presentation. These include serum calcium concentrations exceeding ≥3.5 mmol/L, PTH levels at least three to ten times above the upper reference limit, concurrent skeletal and renal manifestations, a palpable neck mass or hoarseness, tumor diameter greater than 3 cm, evidence of local invasion, and rapid recurrence following parathyroidectomy [2,5,7]. Although most PCs are functional, non-functional or normocalcemic variants exist and usually present with compressive symptoms or metastatic spread. These atypical cases are associated with poor prognosis because the absence of biochemical abnormalities delays diagnosis [9,10].

Recent analyses confirm that hypercalcemia remains the principal determinant of clinical severity. In a large retrospective study by Wang and colleagues (2022), 85% of patients presented with symptomatic hypercalcemia, 41% had bone involvement, and 37% showed renal manifestations. The mean serum calcium level was 3.47 ± 0.52 mmol/L, and the mean PTH level was more than ten times the upper normal limit. Non-functional cases were significantly larger and demonstrated higher rates of invasion and recurrence [5]. Similar findings were observed in subsequent reviews by Roser et al. (2023) and Viswanatha et al. (2024), confirming that severe hypercalcemia, rather than tumor size alone, s the main factor contributing to morbidity and mortality in PC. [1,2].

5. Diagnosis

5.1 Biochemical and Histopathological Markers

Differentiating PC from benign causes of primary hyperparathyroidism (PHPT) before surgery remains a significant clinical challenge. The 2022 WHO Classification of Parathyroid Tumors redefined diagnostic categories, emphasizing evidence of invasive growth—such as vascular or perineural invasion, infiltration of adjacent structures, or distant metastasis—as essential criteria for carcinoma [2]. This approach underscores that cytologic atypia alone is insufficient for diagnosis and highlights the importance of correlating histopathological findings with biochemical and clinical features [2,3]. Among biochemical parameters, markedly elevated serum calcium, PTH, and alkaline phosphatase (ALP) have been repeatedly associated with malignancy [3–5]. In a retrospective analysis of 194 patients with pathologically confirmed PHPT conducted at Seoul National University (Bae et al., 2000–2011), 11 cases were diagnosed as carcinoma, 171 as adenoma, and 12 as hyperplasia [1]. Patients with PC demonstrated significantly higher serum calcium ($P < 0.001$), ioPTH ($P = 0.003$), and ALP ($P < 0.001$) levels compared with benign disease. In multivariate analysis, only

ALP remained an independent biochemical predictor of carcinoma ($P < 0.001$), while tumor size also showed a significant association ($P = 0.03$). Receiver operating characteristic (ROC) analysis identified practical diagnostic thresholds: a tumor size of ≥3.0 cm (sensitivity 90.9%, specificity 92.1%) and a serum ALP level ≥285 IU/L (sensitivity 83.3%, specificity 97.0%) were strongly predictive of PC in patients with PHPT [1]. Elevated ALP reflects increased bone turnover secondary to excessive PTH secretion and serves as an indirect marker of tumor aggressiveness [3,4]. Clinically, an unusually large parathyroid mass and disproportionately high ALP levels should therefore raise suspicion for carcinoma. Although histopathological confirmation remains the gold standard, integration of these biochemical indicators with imaging and intraoperative findings can substantially improve preoperative diagnostic accuracy and guide the extent of surgical intervention [3,5].

5.2 Imaging and Preoperative Evaluation

Ultrasonography (US) is the first-line imaging tool for evaluating parathyroid carcinoma. Typical findings include a lesion larger than 3 cm, irregular margins, heterogeneous echotexture, hypoechogenicity, and a depth-to-width ratio ≥ 1, often indicating local tissue invasion. Additional features such as calcifications, cystic components, and increased vascularity further suggest malignancy [1,2]. Recent developments, such as Detective Flow Imaging (DFI), have improved the detection of low-velocity blood flow, enhancing the differentiation between benign and malignant parathyroid lesions [3].

Technetium-99m sestamibi (^{99}mTc-MIBI) scintigraphy remains the main radionuclide imaging method and, when combined with US, increases lesion localization sensitivity to approximately 81–95%. However, sestamibi uptake cannot reliably differentiate carcinoma from adenoma, and false-positive results may occur due to thyroid nodules or inflammation [1,4].

Cross-sectional imaging with contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) is valuable for assessing local invasion and tumor extension. CT features suggestive of PC include irregular shape, peritumoral infiltration, calcification, and minimal contrast enhancement. Four dimensional CT (4D-CT) provides additional perfusion data, achieving specificity up to 90% when combined with other modalities [2,5].

Positron emission tomography/computed tomography (PET/CT), particularly using ^{18}F-fluorocholine (^{18}F-FCH), improves detection of small or ectopic lesions compared to sestamibi scans. A dual-tracer approach combining ^{18}F-FDGand ^{18}F-FCH may help assess metastatic spread in advanced disease [3,5]. Fine-needle aspiration cytology (FNAC) or core biopsy should generally be avoided in potentially resectable PC, as capsule disruption can lead to tumor seeding. Biopsy may be reserved for confirming distant metastases or recurrence [2].

In summary, no single imaging technique can definitively diagnose PC preoperatively, but combining high-resolution US, ^{99}mTc-MIBI scintigraphy, and 4D-CT or PET/CT provides the highest accuracy and improves surgical planning.

6. Staging

Due to the rarity of parathyroid cancer (PC) and the limited availability of prognostic data, there has long been a lack of a widely accepted classification system for staging PC [1,2].

While previous attempts at PC classification, such as the clinical system proposed by Talat and Schulte in 2010, provided useful prognostic information, they have not been prospectively verified and are no longer used in clinical practice [1]. In the 8th edition of the Cancer Staging Manual, the American Joint Committee on Cancer (AJCC) introduced the first formal TNM-based framework for PC, developed in collaboration with the International Union Against Cancer (UICC) [3, 4]. This system classifies the stage of the disease according to the degree of tumor invasion (T), lymph node involvement (N), and distant metastases (M), as summarized in Table 1. However, due to limited data on treatment outcomes, no prognostic groups (I–IV) have been approved yet. Consequently, clinical decisions continue to be based primarily on pathological invasion, margin status, and risk of recurrence rather than solely on the TNM category [2, 5].

Table 1. TNM Classification for Parathyroid Carcinoma (AJCC/UICC 8th Edition)

Category	Definition	Description / Criteria
T – Primary Tumor		
T1	Tumor ≤2 cm in greatest dimension	Confined to the parathyroid gland, no invasion of adjacent tissues
T2	Tumor >2 cm but ≤4 cm	Confined to the parathyroid gland, no extraglandular extension
T3	Tumor >4 cm **or**minimal invasion	Tumor shows microscopic invasion into surrounding soft tissue without involvement of vital structures
T4a	Moderately advanced local disease	Tumor invades thyroid gland, strap muscles, or recurrent laryngeal nerve
T4b	Very advanced local disease	Tumor invades trachea, esophagus, carotid artery, prevertebral fascia, or mediastinal structures
N – Regional Lymph Nodes		
N0	No regional lymph node metastasis	—
N1	Regional lymph node metastasis present	May involve central (Level VI/VII) or lateral cervical nodes
M – Distant Metastasis		
M0	No distant metastasis	—
M1	Distant metastasis present	Most commonly lungs, bones or liver

7. Treatment

7.1 Surgical Management

Surgery remains the gold standard and only potentially curative treatment for parathyroid carcinoma (PC). Early and complete surgical excision offers the best long-term outcomes, while incomplete or delayed resection significantly increases the risk of recurrence and death. Preoperative recognition of malignancy is crucial because the success of treatment depends on performing an adequate en bloc resection at the initial operation. When PC is suspected based on biochemical, radiological, or clinical features, referral to an experienced endocrine or head and neck surgeon is strongly recommended [1–3].

Before the surgery, patients should undergo tests including biochemical and functional assessment. Severe hypercalcemia must be corrected with intravenous hydration, bisphosphonates, calcitonin, or denosumab to reduce peroperative complications. Laryngoscopic evaluation of vocal cord mobility is essential to assess potential recurrent laryngeal nerve involvement, which can influence the extent of resection. High-resolution ultrasonography, 4D-CT, or MRI is used to evaluate tumor localization, possible invasion of surrounding structures, and regional lymph node status. Fine needle aspiration biopsy is contraindicated due to the risk of spreading the cancer [4–6]. The recommended surgical approach for localized disease is en bloc resection of the tumor with the ipsilateral thyroid lobe and adjacent soft tissue to ensure complete removal with negative margins. All suspicious or invaded structures, including the strap muscles, trachea, esophagus, or recurrent laryngeal nerve, should be resected in continuity when necessary. Tumor manipulation must be minimal to prevent capsular rupture and dissemination. Intraoperative exploration of all parathyroid glands is advised to rule out synchronous adenomas or hyperplasia. The tumor is typically firm, gray-white, and fibrotic, often adherent to adjacent tissues, which differentiates it from the soft and well-circumscribed adenoma [3,7]. Lymph node management is selective. Therapeutic central neck dissection (levels VI–VII) should be performed when nodal metastases are suspected preoperatively or confirmed intraoperatively. In contrast, prophylactic lateral neck dissection is not routinely recommended, as it does not improve survival and increases morbidity. The recurrent laryngeal nerve should be preserved whenever possible, but if directly infiltrated, en bloc resection including the nerve may be necessary to achieve complete tumor clearance [8,9]. Intraoperative parathyroid hormone (ioPTH) monitoring is increasingly applied as an adjunct during surgery for parathyroid carcinoma. A decrease of more than 50% from baseline within 10 minutes after tumor excision indicates an adequate removal of hormonally active tissue. However, persistently elevated ioPTH values do not necessarily imply incomplete cervical resection and may reflect the presence of microscopic residual disease or distant metastases. Therefore, extended exploration based solely on ioPTH results is not recommended [10,11]. Postoperative management requires vigilant biochemical monitoring. A rapid fall in serum calcium levels within 24 hours after successful tumor removal is expected, whereas persistent hypercalcemia suggests residual or metastatic disease. A major postoperative concern is hungry bone

syndrome (HBS) - condition characterized by profound and prolonged hypocalcemia caused by rapid remineralization of bone following abrupt withdrawal of PTH excess. It typically occurs in patients with high preoperative PTH, markedly elevated alkaline phosphatase, or extensive skeletal involvement [12]. HBS manifests with symptomatic hypocalcemia, low phosphate and magnesium levels, and high bone turnover markers. Treatment involves intravenous calcium gluconate followed by high-dose oral calcium and active vitamin D (calcitriol) supplementation, along with frequent laboratory monitoring. Severe cases may require prolonged hospitalization with continuous calcium infusion until stabilization. Following discharge, patients should have their serum calcium and PTH levels monitored every three months for at least the first year, then less frequently if stable. Persistent or recurrent disease can appear months or even years after initial resection, so lifelong surveillance is essential. Complete en bloc resection at the primary operation provides the best chance of cure, with reported five-year survival rates exceeding 80%, whereas limited excision or delayed reoperation is associated with significantly higher recurrence and poorer prognosis [1–3,9,11].

7.2 Palliative and Adjuvant Therapies

Although complete surgical excision remains the only potentially curative treatment for parathyroid carcinoma (PC), adjuvant and palliative therapies play an important role in patients with residual, recurrent, or metastatic disease. Their main goals are to reduce tumor burden, control hypercalcemia, and improve quality of life rather than to achieve cure [1–3].

Adjuvant radiotherapy may be considered in high-risk cases, although PC has historically been described as radioresistant. Recent retrospective studies have reported improved local control and longer disease-free survival with postoperative external beam radiotherapy (EBRT), particularly in patients with capsular invasion or positive margins [4–6]. In a study from the Princess Margaret Hospital, five- and ten-year disease-specific survival rates were 100% and 69% in patients receiving surgery plus adjuvant radiotherapy compared with 80% and 43% in those treated with surgery alone [6]. Typical adjuvant doses range from 50 to 60 Gy delivered in 25–30 fractions. EBRT may also be used palliatively to alleviate symptoms related to unresectable local recurrences or bone metastases [2,7].

Chemotherapy has a very limited role in PC due to its low mitotic activity and resistance to cytotoxic agents. Only isolated case reports have shown partial or transient responses with dacarbazine, 5-fluorouracil, or cyclophosphamide, either as monotherapy or in combination [8,9]. Systemic chemotherapy is therefore reserved for patients with progressive metastatic disease unresponsive to surgical or radiotherapeutic measures [3]. Targeted therapies and immunotherapy are new areas of interest in the treatment of advanced PC. Molecular studies have identified potential therapeutic targets, including mutations in VEGF, PDGFR, BRAF, PIK3CA, PTEN, and NF1 [10,11]. Small-molecule inhibitors such as sorafenib and sunitinib have produced biochemical improvement and partial tumor regression in individual cases with metastatic disease [12,13]. Experimental immunologic therapies include anti-parathyroid hormone antibodies, telomerase inhibitors (azidothymidine), and peptide receptor radionuclide therapy directed at somatostatin receptor subtypes (SSTR2 and SSTR5), which are variably expressed in malignant parathyroid tissue [5,14]. Although data are still limited, these targeted approaches may offer potential future treatment options [1,10].

Control of hypercalcemia remains the cornerstone of palliative management, as this is the main cause of morbidity and mortality in advanced disease. Initial measures include intravenous hydration, loop diuretics, and intravenous bisphosphonates (pamidronate or zoledronic acid). For refractory cases, cinacalcet, a calcimimetic that suppresses parathyroid hormone secretion, is highly effective and well tolerated [15]. The monoclonal antibody denosumab, which inhibits RANKL-mediated osteoclastic bone resorption, has also been successfully used in patients with renal impairment or bisphosphonate resistance, achieving sustained normalization of calcium levels [16,17]. Its adverse effects include musculoskeletal pain, gastrointestinal disturbances, and, rarely, osteonecrosis of the jaw [18]. In patients with severe or refractory hypercalcemia unresponsive to medical therapy, hemodialysis should be considered [19].

For unresectable local recurrences or metastatic lesions not amenable to systemic therapy, minimally invasive ablative techniques such as ultrasound-guided ethanol injection or radiofrequency ablation may provide transient biochemical improvement and symptom relief [20]. These image-guided procedures should be performed in experienced centers as part of a multidisciplinary approach.

In summary, although surgical excision remains the definitive treatment, adjuvant and palliative modalities including: radiotherapy, targeted agents, and calcium-lowering therapies are essential components of long-term management in advanced parathyroid carcinoma.

8. Survival and Outcomes

8.1 Overall Survival and Recurrence Rates

Parathyroid carcinoma (PC) typically follows an indolent yet persistent clinical course, characterized by a high rate of local recurrence and potential for distant metastases even many years after the initial diagnosis. Reported five-year overall survival ranges between 77–85%, while ten-year survival varies from 50–70% [1–4]. Disease-specific mortality is usually related to uncontrolled hypercalcemia rather than tumor burden itself. Recurrence rates remain high - approximately 40–65% of patients experience local or regional recurrence, often within two to five years following surgery, though late recurrences have also been described [2,5].

Median overall survival is typically 6–12 years, with substantially worse outcomes in patients with metastatic disease at presentation. Distant metastases most frequently involve the lungs, bones, and liver, though soft tissue and brain metastases have also been reported in isolated cases [3,6].

8.2 Prognostic Factors

Several clinicopathologic parameters have been identified as key determinants of long-term outcomes in PC. Complete en bloc surgical resection with negative margins is the most significant predictor of positive prognostic outlook [5,7]. In contrast, positive or uncertain resection margins are strongly associated with higher recurrence rates and shorter disease-free intervals.

The presence of distant metastasis at diagnosis is an independent adverse prognostic factor, markedly reducing five-year survival [3]. Persistent or recurrent hypercalcemia after surgery also indicates residual disease and correlates with decreased survival [8].

According to Talat and Schulte, lymph node metastases confer a 6.2-fold higher risk of disease-specific mortality, emphasizing the importance of early detection and radical initial surgery [9]. Other features associated with poor outcome include large tumor size (>3 cm), vascular invasion, high mitotic index, and elevated postoperative PTH and calcium levels [1,6,10].

8.3 Biochemical and Clinical Correlates of Outcome

Biochemical markers play a critical role in postoperative monitoring and prognostication. Persistently elevated serum calcium or PTH levels after surgery often signal incomplete resection or metastatic spread [8]. Conversely, normalization of both parameters within 24–48 hours postoperatively typically predicts favorable outcome and long-term remission.

The main cause of death in PC remains refractory hypercalcemia, which can lead to renal failure, cardiac arrhythmias, or neurocognitive complications [3,6]. Control of serum calcium—through surgery, bisphosphonates, calcimimetics, or denosumab—has been shown to improve both quality of life and survival [11,12].

Functional tumors tend to have more severe hypercalcemia and higher biochemical activity, correlating with more aggressive disease course compared to nonfunctional carcinomas, which often present at advanced stages [13].

8.4 Clinical Implications

Long-term treatment of parathyroid carcinoma requires lifelong biochemical and radiological follow up due to the high risk of late recurrence. Postoperative surveillance should include periodic assessment of serum calcium and PTH every three months during the first year and at increasing intervals thereafter. Patients with residual disease or biochemical relapse should undergo re-imaging for localization and potential re-operation in specialized endocrine centers. Given the rarity and heterogeneity of PC, multidisciplinary management—integrating endocrinologists, endocrine surgeons, oncologists, and radiologists—remains crucial. Early recognition, radical primary resection, and vigilant postoperative monitoring are the cornerstones of achieving durable remission and improving survival outcomes.

REFERENCES

1. Alharbi, N., Asa, S. L., Szybowska, M., Kim, R. H., & Ezzat, S. (2018). Intrathyroidal parathyroid carcinoma: An atypical thyroid lesion. *Frontiers in Endocrinology, 9*, 641. https://doi.org/10.3389/fendo.2018.00641
2. Bae, J. H., Choi, H. J., Lee, Y. J., Kim, J. H., Kim, J. S., Kim, S. W., et al. (2014). Preoperative predictive factors for parathyroid carcinoma in patients with primary hyperparathyroidism. *Endocrine Journal, 61*(12), 1211–1218. https://doi.org/10.1507/endocrj.EJ14-0280
3. Cardoso, L., Stevenson, M., & Thakker, R. V. (2017). Molecular genetics of syndromic and non-syndromic forms of parathyroid carcinoma. *Human Mutation, 38*(12), 1621–1648. https://doi.org/10.1002/humu.23323
4. Cetani, F., Pardi, E., & Marcocci, C. (2018). Parathyroid carcinoma: A clinical and genetic perspective. *Minerva Endocrinologica, 43*(2), 144–155. https://doi.org/10.23736/S0391-1977.18.02789-2
5. Chakrabarty, N., et al. (2024). Imaging recommendations for diagnosis and management of primary parathyroid pathologies. *Cancers, 16*(14), 2589. https://doi.org/10.3390/cancers16142589
6. Christakis, I., et al. (2016). Long-term outcomes after surgery for parathyroid carcinoma. *European Journal of Endocrinology, 174*(3), 315–323. https://doi.org/10.1530/EJE-15-0910
7. Clarke, C. N., Katsonis, P., Hsu, T.-K., et al. (2019). Comprehensive genomic characterization of parathyroid cancer identifies novel candidate driver mutations and core pathways. *Journal of the Endocrine Society, 3*(3), 544–559. https://doi.org/10.1210/js.2018-00043
8. Dobrinja, C., Santandrea, G., Giacca, M., Stenner, E., Ruscio, M., & de Manzini, N. (2023). Effectiveness of intraoperative parathyroid hormone monitoring in predicting malignant parathyroid disease. *International Journal of Surgery, 109*, 26–33. https://doi.org/10.1016/j.ijsu.2023.04.030
9. Dudney, W. C., Bodenner, D., & Stack, B. C. Jr. (2024). Parathyroid carcinoma. *Otolaryngologic Clinics of North America, 57*(2), 341–355. https://doi.org/10.1016/j.otc.2023.10.005
10. Endocrine Society. (2023). Clinical practice update on rare parathyroid tumors. *Journal of Clinical Endocrinology & Metabolism, 108*(9), e546–e556. https://doi.org/10.1210/clinem/dgad222
11. Erovic, B. M., Goldstein, D. P., Kim, D., Mete, O., Brierley, J., Tsang, R., et al. (2013). Parathyroid cancer: Outcome analysis of 16 patients treated at the Princess Margaret Hospital. *Head & Neck, 35*(1), 35–39. https://doi.org/10.1002/hed.22908
12. Fingeret, A. L. (2021). Contemporary evaluation and management of parathyroid carcinoma. *JCO Oncology Practice, 17*(2), e282–e290. https://doi.org/10.1200/OP.19.00540
13. Fountas, A., Andrikoula, M., Giotaki, Z., et al. (2015). The emerging role of denosumab in the long-term management of parathyroid carcinoma-related refractory hypercalcemia. *Endocrine Practice, 21*(4), 468–473. https://doi.org/10.4158/EP14267.CR
14. Gheorghe, A. M., et al. (2024). Insights into hyperparathyroidism–jaw tumour syndrome. *International Journal of Molecular Sciences, 25*(4), 2301. https://doi.org/10.3390/ijms25042301
15. Grabill, N., et al. (2024). Parathyroid carcinoma: Diagnostic challenges and outcomes—A case series and review. *Cancers, 16*(12), 3145. https://doi.org/10.3390/cancers16123145
16. Harari, A., et al. (2011). Parathyroid carcinoma: A 43-year outcome and survival analysis. *Journal of Clinical Endocrinology & Metabolism, 96*(12), 3679–3686. https://doi.org/10.1210/jc.2011-1571
17. Hsu, K.-T., Sippel, R. S., Chen, H., & Schneider, D. F. (2014). Is central lymph node dissection necessary for parathyroid carcinoma? *Surgery, 156*(6), 1336–1341. https://doi.org/10.1016/j.surg.2014.07.009
18. Hu, Y., Zhang, X., Cui, M., et al. (2019). Circular RNA profile of parathyroid neoplasms: Analysis of co-expression networks of circular RNAs and mRNAs. *RNA Biology, 16*(9), 1228–1236. https://doi.org/10.1080/15476286.2019.1620052
19. Hundahl, S. A., et al. (1999). Parathyroid carcinoma: A population-based study of 286 cases treated in the U.S. between 1985 and 1995. *Cancer, 86*(3), 538–544. https://doi.org/10.1002/(SICI)1097-0142(19990801)86:3<538::AID-CNCR6>3.0.CO;2-M
20. Iacovitti, C. M., et al. (2024). Dual-tracer PET/CT in metastatic parathyroid carcinoma. *Diagnostics, 14*(14), 1532. https://doi.org/10.3390/diagnostics14141532
21. Ippolito, G., Palazzo, F. F., Sebag, F., De Micco, C., & Henry, J. F. (2023). Intraoperative diagnosis and treatment of parathyroid cancer and atypical parathyroid adenoma. *British Journal of Surgery, 110*(5), 566–574. https://doi.org/10.1093/bjs/znad022
22. Jentus, M. M., et al. (2025). The molecular landscape and clinical profile of non-functional parathyroid carcinoma. *Virchows Archiv*. https://doi.org/10.1007/s00428-025-04193-4
23. Kang, H., Pettinga, D., Schubert, A. D., et al. (2019). Genomic profiling of parathyroid carcinoma reveals genomic alterations suggesting benefit from therapy. *The Oncologist, 24*(6), 791–797. https://doi.org/10.1634/theoncologist.2018-0334
24. Karuppiah, D., Thanabalasingham, G., Shine, B., Wang, L. M., Sadler, G. P., Karavitaki, N., & Grossman, A. (2014). Refractory hypercalcaemia secondary to parathyroid carcinoma: Response to high-dose denosumab. *European Journal of Endocrinology, 171*, K1–K5. https://doi.org/10.1530/EJE-14-0110

25. Kubal, M. (2024). Advances in the management of parathyroid carcinoma. *Best Practice & Research Clinical Endocrinology & Metabolism, 38*(5), 101777. https://doi.org/10.1016/j.beem.2024.101777
26. Laforgia, R., et al. (2023). Management and surgical treatment of parathyroid carcinoma. *Frontiers in Endocrinology, 14*, 1278178. https://doi.org/10.3389/fendo.2023.1278178
27. Landry, C. S., Wang, T. S., & Asare, E. A. (2017). Parathyroid. In M. B. Amin (Ed.), *AJCC Cancer Staging Manual*(8th ed., pp. 903–910). Springer. https://doi.org/10.1007/978-3-319-40618-3_98
28. Lazzaro, A., Zhao, G., & Kulke, M. (2024). Diagnosis and management of parathyroid carcinoma. *Clinical Pharmacology & Therapeutics, 116*(5), 780–792. https://doi.org/10.1002/cpt.3432
29. Limberg, J., et al. (2020). Use and benefit of adjuvant radiotherapy in parathyroid carcinoma. *Annals of Surgical Oncology, 27*(10), 3648–3656. https://doi.org/10.1245/s10434-020-08391-3
30. Long, K. L., & Sippel, R. S. (2018). Current and future treatments for parathyroid carcinoma. *International Journal of Endocrine Oncology, 5*(1), IJE06. https://doi.org/10.2217/ije-2018-0006
31. Longo, F., et al. (2024). Two-step surgical strategy for parathyroid carcinoma. *Medicina, 60*(12), 2054. https://doi.org/10.3390/medicina6012054
32. Machado, N. N., & Wilhelm, S. M. (2019). Parathyroid cancer: A review. *Cancers, 11*(11), 1676. https://doi.org/10.3390/cancers11111676
33. Marini, F., Giusti, F., Palmini, G., et al. (2023). Parathyroid carcinoma: Update on pathogenesis and therapy. *Endocrines, 4*(1), 18. https://doi.org/10.3390/endocrines4010018
34. Matsui, M., et al. (2023). Usefulness of ultrasonographic detective flow imaging for detecting parathyroid tumors. *Journal of Nippon Medical School, 90*(6), 460–464. https://doi.org/10.1272/jnms.JNMS.2023_90-605
35. McInerney, N. J., et al. (2024). Parathyroid carcinoma: Two unique cases detailing multifocal disease and review of recent literature. *Journal of Endocrine Oncology, 11*(3), e2311. https://doi.org/10.1080/23772484.2024.2327322
36. Minisola, S., et al. (2023). Hungry bone syndrome: Still a challenge in parathyroid disorders. *European Journal of Endocrinology, 168*(3), R45–R53. https://doi.org/10.1530/EJE-22-0921
37. National Cancer Institute. (2024). *Parathyroid cancer treatment (PDQ®)*. https://www.cancer.gov/types/parathyroid/hp/parathyroid-treatment-pdq
38. Owen, R. P., Silver, C. E., Pellitteri, P. K., et al. (2010). Parathyroid carcinoma: A review. *Head & Neck, 33*(3), 429–436. https://doi.org/10.1002/hed.21473
39. Roser, P., Leca, B. M., Bittner, M. I., et al. (2023). Diagnosis and management of parathyroid carcinoma: A state-of-the-art review. *Endocrine-Related Cancer, 30*(4), e220287. https://doi.org/10.1530/ERC-22-0287
40. Roser, P., Niederle, B., & Riss, P. (2023). Diagnosis and management of parathyroid carcinoma: A state-of-the-art review. *European Journal of Endocrinology, 188*(2), R29–R42. https://doi.org/10.1530/EJE-22-0786
41. Rozhinskaya, L., et al. (2017). Diagnosis and treatment challenges of parathyroid carcinoma in a 27-year-old woman with multiple lung metastases. *Endocrinology, Diabetes & Metabolism Case Reports, 2017*, 17-0016. https://doi.org/10.1530/EDM-17-0016
42. Saad, F., Brown, J. E., Van Poznak, C., et al. (2012). Incidence, risk factors, and outcomes of osteonecrosis of the jaw: Integrated analysis from three phase III trials in cancer patients with bone metastases. *Annals of Oncology, 23*(5), 1341–1347. https://doi.org/10.1093/annonc/mdr435
43. Schalin-Jäntti, C., Ryhänen, E. M., Heiskanen, I., et al. (2020). Parathyroid carcinoma: Current understanding and evolving diagnostic and therapeutic strategies. *Endocrine Reviews, 41*(3), 231–255. https://doi.org/10.1210/endrev/bnz011
44. Schulte, K. M., et al. (2012). Parathyroid cancer: Diagnosis and management. *Current Opinion in Oncology, 24*(1), 31–36. https://doi.org/10.1097/CCO.0b013e32834d8b1b
45. Shane, E. (2001). Parathyroid carcinoma. *Journal of Clinical Endocrinology & Metabolism, 86*(2), 485–493. https://doi.org/10.1210/jcem.86.2.7182
46. Silverberg, S. J., Rubin, M. R., Faiman, C., et al. (2007). Cinacalcet hydrochloride reduces the serum calcium concentration in inoperable parathyroid carcinoma. *Journal of Clinical Endocrinology & Metabolism, 92*(10), 3803–3808. https://doi.org/10.1210/jc.2007-0601
47. Storvall, S., Leijon, H., Rähnän, E., et al. (2019). Somatostatin receptor expression in parathyroid neoplasms. *Endocrine Connections, 8*(9), 1213–1223. https://doi.org/10.1530/EC-19-0321
48. Talat, N., & Schulte, K. M. (2010). Clinical presentation, staging and long-term evolution of parathyroid cancer. *Annals of Surgical Oncology, 17*(8), 2156–2174. https://doi.org/10.1245/s10434-010-1003-6
49. van der Tuin, K., et al. (2017). CDC73-related disorders: Clinical manifestations and case series. *Journal of Clinical Endocrinology & Metabolism, 102*(12), 4534–4542. https://doi.org/10.1210/jc.2017-01674
50. Viswanatha, A., Drakou, E. E., Lajeunesse-Trempe, F., et al. (2024). Parathyroid carcinoma: New insights. *Endocrine Oncology, 4*(1), e00012. https://doi.org/10.1530/EO-23-0024
51. Wang, C., Wen, K., Dai, L., Wen, S., & Zhang, Y. (2022). The clinical features and treatment strategy of parathyroid cancer: A retrospective analysis. *BioMed Research International, 2022*, 1913900. https://doi.org/10.1155/2022/1913900
52. Warrell, R. P., Jr., et al. (2006). Randomized, double-blind, phase II trial of gallium nitrate compared with pamidronate for acute control of cancer-related hypercalcemia. *Cancer Journal, 12*(1), 47–53. https://doi.org/10.1097/00130404-200601000-00009
53. WHO Classification of Tumours Editorial Board. (2022). *Endocrine and neuroendocrine tumours* (5th ed., Vol. 10). IARC.