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Review

Focus on parathyroid carcinoma

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ABSTRACT

Parathyroid carcinoma is a malignant neoplasm affecting 05–2 per cent of all patients with primary hyperparathyroidism that was first described by de Quevain in 1904. To day it continues to defy diagnosis and treatment. It is difficult to diagnose in part because of its rarity, lack of definitive diagnostic markers and overlapping clinical features of benign primary hyperparathyroidism. As a result initial surgical treatment is inadequate essentially leading to disease recurrence where complete cure is unlikely. En bloc surgical resection remains the only curative treatment, and high priorities are improving diagnostic methods, and clinical staging for resection once the disease is suspected. Margin status at resection is related to prognosis. Thus, a trend towards aggressive surgical management has improved outcomes. The recurrence rate of parathyroid carcinoma is as high as 80% with survival rates <50% at 10 years. Results of chemotherapy are disappointing. However, recent trials using radiation therapy are promising, but require further study.

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1. Introduction

Parathyroid carcinoma is an uncommon malignancy mostly seen in patients treated for primary Hyperparathyroidism (PHPT) and is the least common endocrine malignancy accounting for only 0.005% of reported cases.[1] This disease was first described in 1904 by de Quevain[2] in a patient who presented with a non-functioning lesion. Subsequently, in 1933, Sainton and Millot[3] described the first functioning parathyroid carcinoma. It is a slow-growing tumor of low malignant potential but frustrating and difficult clinical problem. The majority of patients are diagnosed between ages 45 and 60 years, but the tumor arises over a wide age range.[4] In most series, parathyroid carcinoma accounts for less than 1% of patients with PHPT.[5–7] However, it can also occur as a non-functioning lesion in patients with normal parathyroid function,[8] Table 1. The exact cause of parathyroid carcinoma is unknown, and most cases occur sporadically, but there are several clinical situations that may predispose to the development of this cancer. The most common of these are a history of neck irradiation,[9,10] Parathyroid adenoma or a hyperplastic parathyroid gland,[11,12] and prolonged secondary hyperparathyroidism.[13,14] Parathyroid carcinoma may also occur in association with familial HPT or multiple endocrine neoplasia (MEN) type I syndrome.[15]

The reported incidence of parathyroid carcinoma is may be somewhat more common in Japan and Italy than in the rest of the west, accounting for 5%–5.2% of patients with PHPT.[16–18] Previous studies indicate that this wide variation may be due to genetic or environmental influences, local referral practice or may even represent underdiagnosis or overdiagnosis.[19] No other disproportionate clustering such as by gender, age and ethnicity/race was observed.[1] Patients with this entity typically present at advanced stage with symptomatic hypercalcemia, osteolytic bone changes, and renal impairment, and cure rates are low, even with aggressive therapy.[5,20,21] Morbidity and Mortality are always related to metabolic complications due to severe hypercalcemia. Making a definitive diagnosis of parathyroied carcinoma when the macroscopic and microscopic findings are ambiguous is difficult. It is difficult to diagnose in part because of its rarity, the limited knowledge regarding its natural history, and its clinical course, which is that of benign primary hyperparathyroidism. As a result initial surgical treatment is inadequate essentially leading to disease recurrence where complete cure is unlikely.[22] Whether functional or non-functional, this tumor can often be difficult to differentiate from benign parathyroid adenoma and diagnosis has been always based on both clinical and histological criteria.[4] In this review we discuss etiologic factors, molecular pathogenesis, clinical features, diagnosis and contemporary management of parathyroid carcinoma.

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Table 1
Published collective series of parathyroid carcinoma.

Author	Year	N
Wilkins et al.[4]	1920–2009	19*
Holmes et al.[71]	1933–1968	41
Shane et al.[5]	1969–1981	62
Obara et al.[30]	1981–1989	163
Koea et al.[29]	1990–1999	94
Hundahl et al.[1]	1985–1995	286**

* Non-functioning parathyroid carcinomas.
** Parathyroid carcinomas in the USA.

Table 2
Factors that may predispose to the development of parathyroid carcinoma.

History of irradiation of the head and neck[9,10,13]
Familial isolated primary hyperparathyroidism (PHPT)[15,24]
Hereditary hyperparathyroid-jaw tumor syndrome (HPT-JT)[4,24]
Multiple endocrine neoplasia syndromes (MEN-1 and MEN-2A)[25–27]
Parathyroid adenoma or hyperplastic parathyroid gland[11,12,31]
Prolonged secondary hyperparathyroidism[14]
End-stage renal disease[32]

1.1. Etiologic factors

Several etiologic factors are associated with parathyroid carcinoma (Table 2), although most cases occur in the absence of any of them. A strong association exists between parathyroid carcinoma and hyperparathyroidism-jaw tumor (HPT-JT) syndrome. HPT-JT is an autosomal dominant disease characterized by the occurrence of parathyroid and fibro-osseous tumors of the jaw bones.[23] The prevalence of parathyroid carcinoma has been estimated as high as 15% in patients with HPT-JT.[4,24]

Other clinical conditions that are etiological factors for parathyroid carcinoma include familial hyperparathyroidism, a rare autosomal dominant disorder,[25–27] and multiple endocrine neoplasia (MEN) type-1. MEN type-1 is a separate entity from that of familial hyperparathyroidism and also carries an increased risk for parathyroid carcinoma.[28] Previous radiation to the neck is known to be a risk factor for head and neck cancer and this may also holds for parathyroid carcinoma and this association has been reported in several cases of parathyroid cancer.[9,10,13,29,30] Furthermore, parathyroid cancer has been reported in association with Hyperplastic parathyroid gland,[11,12,31] secondary hyperparathyroidism,[14] and end-stage renal disease.[32]

1.2. Tumor biology

The majority of all human malignancies including parathyroid carcinoma is sporadic and arises from the acquisition of somatic, genetic and epigenetic alterations leading to changes in gene sequences, structure, copy number and expression. A number of different molecular defects have been reported in parathyroid carcinoma. These mutations primarily involve oncogenes and tumor suppressor genes, suggesting that these cancers likely develop due to a series of cellular injuries. Significant evidence exists for the presence of genes whose acquired activation or inactivation contributes to the development of parathyroid carcinoma. In one study, losses of 1p, 4q and 13q, and gains of 1q, 9q, 16p and Xq, were more commonly observed in parathyroid carcinoma than in benign adenomas.[33] Others have demonstrated mutations in genes that are involved in the regulation of cell cycle activity such as parathyroid adenoma 1 gene (PRAD1), p53 and retinoblastoma (RB) tumor suppressor genes that may contribute towards malignant transformation.[24,34]

PRAD1 or cyclin D1 is an oncogene located at chromosome band 11q13. Its protein product is a cell cycle regulator.[35] Many reports have implicated Overexpression of cyclin D1 in parathyroid carcinoma.[34,36] Cyclin D1 has been identified in up to 91% of such tumors.[34] Furthermore, the presence of a gene on chromosome 13 whose acquired inactivation contributes to the development of parathyroid cancer has also been demonstrated.[37,38] This deletion contains the coding regions for the retinoblastoma (RB) and hereditary breast carcinoma susceptibility gene (BRCA2) tumor suppressor genes. Together with cyclin D1, Retinoblastoma, the classic tumor suppressor gene, is important in cell cycle control.

A more recently described tumor suppressor gen is the HRPT2 gene. This gene encodes the parafibromin protein, and is associated with the HPT-JT syndrome.[39] Inactivating germ-line Mutations in this gene were recently identified in sporadic parathyroid carcinomas.[40]

P53 tumor suppressor gene is another cell cycle regulator and a well-established frequent participant in human carcinomas.[41] The role of p53 tumor suppressor gene in parathyroid carcinoma has been examined and no coding region mutations were identified.[37,42] This implies no major contributions of this gene to the pathogenesis of Parathyroid carcinoma.

Taken together, although there is much speculation regarding the factors that induce the various mutations, little or nothing is known about how these factors actually cause parathyroid cancer.

2. Diagnosis

2.1. Clinical presentation

The typical age of presentation of parathyroid carcinoma is the fifth decade of life, about as much as two decades earlier compared

Table 3
Functioning and Non-functioning parathyroid carcinoma and benign PHPT: comparison of clinical features[4,8,17,24,29,35].

	PCA (functioning)	PCA (non-functioning)	PHPT
Average Age	45	49	55
FMR	1	1.3	3.5
Serum calcium	markedly elevated (>14 g/dl)	normal	above upper limit of normal
PTH	markedly elevated (3–10x an)	normal	mildly elevated
Symptoms of hypercalcemia	yes (>98%)	no	rare (<20%)
Palpable neck mass	common (30–76%)	common (>80%)	rare
Renal involvement	common (32–80%)	not known	rare
Skeletal involvement	common (34–91%)	not known	rare
Local recurrence after SPTX	common (>50%)	common (>50%)	na
Overall survival rate after SPTX	<53%	<53%	na
Local recurrence after EBR	rare (<8%)	rare (<8%)	na
Overall survival rate EBR	>89%	>89%	na
Distant Metastases	yes (LN, lung, bone, liver)	yes (LN, lung, bone, liver)	na

PCA, parathyroid carcinoma; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; SPTX, simple parathyroidectomy (excision of the involved gland alone); EBR, En bloc resection (resection of the involved gland and a surrounding margin of normal tissue); an, above normal; na, not applicable; LN, Lymph node.

to patients with benign parathyroid adenomas (Table 3). Half of all cases present between the ages 45 and 60 years.[4]

However, these tumors may arise over a wide age range. Apparently parathyroid carcinoma has a considerably lower female to male ratio than that generally observed in benign HPT (Table 3). Hyperparathyroidism occurs in more than 90% of Patients. As a result the most common presenting symptoms of parathyroid carcinoma are caused by severe hypercalcemia and include renal colic, painful joints, bone or low back pain, thirst, nocturia, polydipsia, anorexia, abdominal Pain, constipation and fatigue.[4,22,43] Clinically, a patient with primary hyperparathyroidism is most likely to have a parathyroid adenoma. The Overlap in symptoms between functioning parathyroid carcinoma and benign HPT makes it difficult to differentiate between both entities. As a result, parathyroid carcinoma is most often misdiagnosed and mismanaged as benign primary hyperparathyroidism.[44] Given the rarity of this malignancy, and the surgeon's expectation of parathyroid adenoma for which simple gland removal is appropriate, this situation is not surprising. Clues that the patient may have parathyroid carcinoma include, severe hypercalcemia (>14 mg/dl) or extremely high serum PTH levels (>5× the upper limit of normal),[45] and a palpable neck mass with hoarseness due to unilateral vocal cord paralysis indicating involvement of the recurrent laryngeal nerve in a patient without a previous neck surgery.[30,43] The diagnosis of non-functioning parathyroid carcinoma is even more difficult than for functioning parathyroid carcinoma, primarily due to lack of symptoms until late in the disease course. This extremely rare subtype of parathyroid carcinoma has been reported to present with locally advanced neck masses.[8,46]

2.2. Laboratory tests

Biochemical tests, such as the intact PTH and serum calcium levels, though most common indicator of Hyperparathyroidism, are of little Help in accurately differentiating parathyroid carcinoma from benign PHPT, since they all can be associated with both conditions.[20] However, Hypercalcemia in parathyroid carcinoma is usually profound, with serum calcium concentrations 3–4 mg/dl above the upper limit of normal and PTH levels as high as 75 fold.[35,47] This is in contrast to the values of PTH and Calcium found in benign PHPT, which are mildly elevated or near the upper limit of normal in the majority of cases. These patients may or may not have symptoms and are often discovered while being investigated for an unrelated condition.[24] In addition, some patients with parathyroid carcinoma have elevated alkaline phosphatase, Hypophsphatemia, and hyperchloremic metabolic acidosis.[16,48] No potential specific tumor marker of parathyroid carcinoma that may show some utility as an aid in the diagnosis of carcinoma has been jet identified.

2.3. Imaging

Although the presence of functioning parathyroid carcinoma or residual disease can be suspected by measuring the intact serum PTH level, the localization of all tumor sites remains a clinical challenge. The initial diagnostic imaging procedure to evaluate a patient with suspected parathyroid carcinoma or residual disease is neck ultrasound. This imaging modality is fast and inexpensive, and may help to differentiate benign parathyroid adenoma from parathyroid carcinoma. The normal parathyroid gland is typically not visualized because of its deep location and small size. Parathyroid adenoma and parathyroid carcinoma may be detected as mass lesions. While large size, inhomogeneous appearance, and irregular borders may point toward parathyroid carcinoma, ovoid, well-marginated solid lesions indicate parathyroid adenoma.[49] Study results indicate a sensitivity ranging from 27% to 97% for detecting adenomas and 50%–90% for carcinomas.[50,51] In a recent meta-analysis this figure increases to 79% and 100% respectively.[52] The wide range of sensitivities is reflective of the difficulties inherent to this examination indicating the limited utility of ultrasound to distinguish parathyroid carcinoma from parathyroid adenoma. Generally, the sensitivity and specificity of ultrasound vary with the location of parathyroid carcinoma,[53] the quality of the equipment, the presence of concomitant thyroid disease,[54] and the experience of the operator. In a report from Ruda et al.[52] about 62% of undetected lesions were greater than 2 cm in diameter, where as 75% of detected lesions were less than 2 cm in diameter. The results of this study imply that size is not necessarily a limiting factor.

^{99m}Tc sestamibi scanning is like ultrasound among the primary means of assessing parathyroid lesions. This method relies on different radiotracer uptake patterns and kinetics between the thyroid gland, the normal parathyroid gland, and the abnormal parathyroid gland. It is effective in localizing abnormal parathyroid lesion, and has a sensitivity and specificity as high as 85% and 96% respectively.[55,56] Because it allow for whole-body scanning, it has been used successfully for preoperative localization of parathyroid carcinoma and particularly to detect metastatic disease.[57] However, this nuclear medicine imaging method is not 100% parathyroid specific, so that detection of abnormal parathyroid glands requires in addition to altered tracer kinetics in the abnormal gland, unaltered kinetics in the surrounding structures. Unfortunately, such a finding das not always exist. For example, thyroid nodules including adenomas and carcinomas can have very prominent ^{99m}Tc sestamibi with marked tracer retention on delayed imaging, mimicking a parathyroid adenoma.[58] Single photon emission computed tomography (SPECT), SPECT-CT, when available, can be quite useful in simplifying the localization of a parathyroid lesion, improving the sensitivity of ^{99m}Tc sestamibi scintigraphy.[59]

Contrasted computed tomography (CT) is may be useful in identifying ectopic lesions in the neck and recurrent parathyroid carcinoma, although this test also lacks sensitivity in diagnosing parathyroid carcinoma. In one series of 8 patients, the sensitivity of contrast-enhanced CT in identifying recurrent parathyroid carcinoma was only 53%.[60] When interpreting CT of parathyroid disease, it is almost mandatory to have additional imaging in the form of ultrasonography or ^{99m}Tc sestamibi scanning in order to find out the most likely location of the abnormal glands and differentiate the parathyroid gland from non pathologic lymph nodes and other unrelated findings.[61] Therefore, CT is used as an additional diagnostic tool in the management of de novo or, more commonly, recurrent parathyroid carcinoma. However, visualization of pulmonary, tracheoesophageal groove and superior mediastinal metastases is best achieved by contrasted CT.[62]

Ultrasound, sestamibi scanning and CT are useful diagnostic tools for detecting cervical parathyroid recurrences. However, magnetic resonance imaging (MRI) with fat suppression is superior and permits excellent visualization of recurrent lesions.[63] It can raise the diagnostic sensitivity to as high as 93%; is non invasive, does not involve exposure to radiation and avoids the artifacts produced by surgical clips that make interpretation of CT difficult.[22] Therefore, MRI is optimally suited in helping to navigate the complex anatomy of the neck, delineate the full extent of disease, and aid in planning curative surgery. Drawbacks of MR include, inability to accurately differentiate between concomitant Thyroid disease and parathyroid pathology, and extremely high sensitivity to patient motion, including respiration, swallowing and normal patient movement, which may give rise to several confusing artifacts.[62]

Selective venous catheterization with PTH measurement plays a specific role in localizing a functioning parathyroid lesion. Study results found selective venous sampling to have the highest

Table 4
Pathologic appearance of Parathyroid carcinoma[24,68].

Macro
Mostly larger than 3 cm
Irrgegular
Gerayish-white
Hard
Adherent to adjacent tissue
May invade the ipsilateral thyroid gland, strup musles, RLN, oesophagus and trachea
Micro
Trabecular pattern
Mitotic figures
Thick fibrous bands
Capsular and blood vessel invasion

RLN, recurrent laryngeal nerve.

sensitivity for localization.[64–66] However, it is invasive, not widely available, and localizes tumors only to a region. Therefore, selective venous sampling is recommended only when noninvasive imaging studies do not identify a tumor site or results are equivocal.[22]

2.4. Biopsy

Cytologic and/or histologic analysis is traditionally the gold standard of cancer diagnosis. However, due to procedure-related complications such as bleeding, tumor seeding along the needle tract following disruption of the tumor capsule and problems in interpretation such as false negative diagnosis, biopsy of parathyroid carcinoma including fine-needle aspiration cytology (FNAC) should be avoided.[67] Because there are no specific and valid criteria to distinguish parathyroid carcinomas from their benign counterparts, making a definitive tissue diagnosis of parathyroid carcinoma is difficult. Thus, like all parathyroid lesions the diagnosis of parathyroid carcinoma is a clinical one and based on appearance at operation. Intraoperatively, whereas parathyroid adenomas tend to be soft, oval, and brownish-red in appearance, carcinomas tend to be larger in size (>3 cm), grey-white, lobulated and have a dense, fibrous capsule. Adherence to, or invasion of, adjacent structures is suggestive of malignancy. Histologic features of parathyroid carcinoma have been described by Shanz and Castelman[68] (Table 4). They include: sheets or lobules of tumor cells separated by dense fibrous bands, mitotic figures, necrosis, capsular and vascular invasion. Unfortunately, these classic pathologic features are not always present in parathyroid carcinoma.[69] Furthermore, some of these features, particularly, mitotic figures and trabecular architecture also may be observed in parathyroid adenomas.[70] Therefore, much like other endocrine malignancies, histological confirmation of parathyroid carcinoma is based on clinical information of the surgeon and an ultimate diagnosis of carcinoma can be made with confidence only after recurrence or distant metastasis occurs.[4]

3. Treatment

3.1. Surgery

Surgery remains the only intervention offering the possibility of a cure for parathyroid carcinoma (both functional and non-functional) and the most effective treatment for recurrence as well. The main treatment goal should be complete removal of the parathyroid cancer with negative margins. This includes, en bloc resection of the primary lesion, ipsilateral thyroid lobectomy, isthmectomy, tracheal skeletonization, and excision of any adherent muscle.[43,71] In case of recurrent parathyroid carcinoma, the aim of surgery is to reduce the tumor load and normalize serum calcium.[24] Because parathyroid carcinoma is slow-growing, and distant metastases occur late in the course of the disease, initial aggressive surgical approach is recommended when the diagnosis is suspected at the time of parathyroidectomy to avoid local recurrence.[21] Simple parathyroidectomy in case of suspected parathyroid carcinoma is inadequate and not recommended. En bloc resection results in up to 50% a cure rate and has a survival advantage over simple parathyroidectomy.[29] More recent studies have demonstrated simple parathyroidectomy to be inadequate, with recurrence rates as high as 100%, and most recurrences occurring within 1–6 years of initial treatment.[72,73] Unfortunately, a greater number of patients undergo simple parathyroidectomy as their initial procedure for presumed primary hyperparathyroidism. Data in the literature shows that only about 12% of parathyroid carcinomas underwent primarily en bloc resection, as opposed to 80% who underwent parathyroidectomy alone.[74,75] This trend is a clear reflection of the diagnostic challenges prior to surgical treatment. Patients who have an aggressive surgical resection with clean margins at initial diagnosis have a longer disease-free and overall survival than those who have a lesser procedure.[21,29] Overall survival directly correlates with the margin status of the initial resection.[76] For this reason, both preoperative suspicion and intraoperative carful evaluation and recognition of parathyroid carcinoma are of great importance. Along with en bloc resection, bilateral neck exploration and identification of all four parathyroid glands is indicated for suspected parathyroid carcinoma, as it can coexist with adenomas and hyperplasia.[77] Sacrifice of the recurrent laryngeal nerve can almost always be avoided unless it is involved circumferentially by malignancy.[38]

Moreover, prophylactic and radical neck dissection is controversial. Rates of lymph node involvement have varied from 32% in a series published in 1969[71] to as low as 3% in the 1999 series published by Hundal et al. [1] However, the high rates of lymph node involvement may not actually be as high as some reports suggest, since not all series distinguished cases with metachrouous lymph node metastases, often occurring in the setting of local recurrence from primary cases, thus inflating the lymph node involvement rate to >30%. This suggests that primary lymph node metastasis in parathyroid carcinoma is rare and radical neck dissection does not improve overall survival. In addition, unnecessary prophylactic radical neck dissection may increase the risk of postoperative complications.[21] Therefore, comprehensive lymphadenectomy is not recommended except in cases, in which lymph node enlargement is apparent, there is extensive local invasion, or local recurrence is present.[21,30,38]

There is also controversy regarding the management of parathyroid carcinoma initially treated as primary hyperparathyroidism and diagnosed postoperatively by histology. While some authors suggest follow-up at intervals of 3 months with serial measurements of serum calcium and PTH,[78] others recommend re-exploration of the neck and completion surgery particularly if the gross characteristics were suggestive and the subsequent pathology is aggressive, with vascular or capsular invasion.[35] Given the high recurrence rate of simple parathyroidectomy discussed earlier in this section, the majority of surgeons tend to agree with the later view because the first reoperation may offer the last chance for cure.

3.2. Radiotherapy

Following complete surgical resection, the most common relapse pattern is local recurrence and distant metastases.[43] In spite of an extensive and a potentially curative surgery, recurrence rates as high as 80% has been reported with the neck being the most

common site of local recurrence.[43,79] Until recently, this malignancy was considered to be not a radiosensitive neoplasm because in the majority of patients studied, radiotherapy failed to slow tumor growth and reduce metabolic complications.[29,71,80] However, some recent reports have advocated postoperative radiation therapy as a strategy for optimizing local control.[38,76,81] In selected patients, it appears to decrease the local recurrence rate effectively and improves the disease-free interval.[82] While this approach offers a theoretical benefit, the available literature on adjuvant radiotherapy following resection of parathyroid carcinoma is absent of prospective, randomized trials, mainly due to the rarity of the disease. Therefore, most knowledge so far is from case reports and small retrospective series and the role of adjuvant radiation therapy following surgery remains unclear.

3.3. Chemotherapy

Chemotherapy has not been shown to improve survival or correct hypercalcemia in patients with wide spread or unresectable disease.[19,45] A large number of agents including cyclophosphamide, 5-fluorouracil and decarbazine, have been tested as single or combination therapies without appreciable effects.[83] Partial responses with a marked drop in serum calcium lasting from weeks to several months have been observed in some individual cases[84]; however, in general the results are largely disappointing.

3.4. Management of hypercalcemia

Patients with functioning parathyroid carcinoma who die of disease do so as a result of complications of hypercalcemia rather than from the tumor load itself.[24,45,55,78], Control of hypercalcemia resulting from parathyroid carcinoma can be best achieved through surgical resection. Aggressive, often repeated resection of functional local and distant recurrences is the most effective means of achieving this end.[47] However, in some patients, hypercalcemia may be refractory to surgery, especially in those with unresectable or widely metastatic disease, and these patients require other treatment options. Management of hypercalcemic crisis initially involves rehydration with intravenous 0.9% NaCl along with the administration of loop diuretics to promote excretion of calcium.[24] Most patients will be fluid depleted and can require up to 4 L of fluid within the first 24 h. Effective long-term control of hypercalcemia requires the addition of drugs that interfere with osteoclast-mediated bone resorption or target the calcium-sensing receptor (CaSR). Clodronate, etidronate and pamidronate are the most widely used bisphosphnates that inhibit bone resorption.[23,24] However, owing to significant problems related to hypocalcemia after surgery, intravenous use of bisphosphonates should be avoided if the patient is to undergo surgery within a few days. Moreover, most patients become unresponsive to bisphosphonates. Plicamicin, although not very effective and toxic, is indicated as a reserve drug for life-threatening hypercalcemia, unresponsive to bisphosphonates.[35] Calcitonin in the dose of 200 IU every 8 h might be helpful in decreasing albumin-adjusted calcium. Furthermore, there is good evidence that calcimimetics, agents that suppress the secretion of PTH by increasing the sensitivity of CaSR, such as cinacalcet, can also be of value to control symptomatic hypercalcemia in parathyroid carcinoma patients.[85,86] Likewise, immunization with PTH peptides and dendritic cell immunotherapy are newer approaches that may have a promising future.[87–91]

3.5. Non-functioning parathyroid carcinoma

While functioning parathyroid carcinoma is a rare malignancy, non-functioning parathyroid carcinoma is exceedingly rare with only 19 reported cases in the last 100 years.[4,81] Patients have normal serum calcium and PTH levels and do not present with symptoms of hypercalcemia. Therefore, non-functioning parathyroid carcinoma is usually clinically silent until it presents with advanced disease. A palpable neck mass is present in more than 80% of patients.[4,8,24] Other presenting symptoms may include dysphagia and hoarseness due to involvement of the recurrent laryngeal nerve.[81] Similar to functioning parathyroid carcinoma, the mainstay of treatment of non-functioning parathyroid cancer is surgery. At present, only en bloc resection of all detectable tumor is associated with improvement in long-term prognosis. However, overall outcome is dismal, in part because there is no specific serologic marker and early detection of recurrence is almost impossible. In contrast to patients with functioning parathyroid carcinoma who die of metabolic complications of hypercalcemia, Patients who die of non-functioning parathyroid carcinoma succumb to systemic tumor burden, mostly within the first two years of diagnosis.[4,92,93]

3.6. Staging and prognosis

When a diagnosis of cancer is suspected, the initial priority is to determine staging for treatment, particularly resectability. Unfortunately, there are no accepted staging criteria for parathyroid carcinoma. The usual TNM staging system cannot be applied to parathyroid carcinoma for the following reasons: first, parathyroid carcinoma spreads to adjacent lymph nodes, but usually after local recurrence and primary lymph node metastasis is infrequent[1,38]; and second, tumor size does not appear to play a role in prognosis.[1,30,85] So, staging is clinical and best done with an interdisciplinary input.

Regarding prognosis, parathyroid carcinoma is a disease with an often indolent but progressive course. It has a tendency to infiltrate in to the surrounding muscles, and vital anatomical structures. Its prognosis is quite variable; and no one characteristic correlates predictably with outcome. Neither tumor size nor lymph node status appears to predict survival.[1] Early recognition and en bloc resection of the primary lesion at the time of the initial operation carry the best prognosis.[35] The mean time to recurrence is approximately 3 years (range 1–20 years).[21,79] Five-year survival rates vary from 40% to 86%.[35] The overall 10-year survival rate is reported to be 49%.[1] However, 10-year survival rates as high as 77% have been also reported.[38] The higher survival rate at 10 years in this group may relate to an improvement in supportive care in general and, more specifically, in the control of hypercalcemia.

4. Summary

Parathyroid carcinoma is an extremely rare tumor that continues to present formidable challenges in diagnosis and treatment. It is an aggressive disease with propensity to multiple recurrences that portends poor outcome. In spite of the best surgical effort, the recurrence rate of parathyroid carcinoma is as high as 80% with survival rates $<$50% at 10 years. It is likely that the diagnostic uncertainty which mainly results from the unusual biological behavior of this malignancy contributes to inadequate initial surgical treatment. This decreases the possibility of achieving a histological margin-negative resection, as this is the patient's only hope for cure and prolonged disease-free survival. It means, major improvement in the survival of patients with this cancer will probably not result from more aggressive or advanced surgical techniques only. Instead, additional efforts should be directed at early detection, which is the main problem, and novel additional treatments derived from basic research. Effort should be taken to establish more reliable diagnostic tools. New molecular studies,

including evaluation of HRPT2/parafibromin as well as advances in imaging, may aid to achieve this objective and improve outcomes in this devastating disease. Furthermore, there are only sporadic reports of successful adjuvant radiation therapy and currently there are no data supporting the routine use of chemotherapy outside a clinical trial. These are additional avenues of study that need to be undertaken.

Conflict of interest

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