REVIEW

For reprint orders, please contact: reprints@futuremedicine.com

International Journal of
Endocrine Oncology

Recent advances in the management of endocrine malignancies associated with hereditary hyperparathyroidism syndromes

Yulong Li¹ & William F Simonds^{*,1}

Practice points

- Patients with hereditary syndromes of primary hyperparathyroidism are at risk for development of particular syndrome-specific malignancies.
- Whenever possible, a specific genotype should be established for a patient with a hereditary syndrome of primary hyperparathyroidism since in some cases the genotype may help predict the phenotype of the associated malignancy (e.g., medullary thyroid cancer in multiple endocrine neoplasia type 2A).
- Prospective screening for the syndrome-specific malignancies is recommended by blood testing for characteristic hormonal or biochemical markers and/or imaging.
- Following the earliest recognition of a syndrome-specific malignancy, surgery should be considered with the goal of achieving negative surgical margins.
- Surgery represents the only potentially curative treatment modality.
- For metastatic or nonoperable disease, management may require a multidisciplinary approach.
- Medical management of advanced disease may involve either small molecule inhibitors targeting specific growth-promoting enzymes, agonists at growth-inhibitory receptors or conventional cytotoxic chemotherapeutic agents.
- Other useful treatment options in cases of nonoperable disease include radionuclide therapy, external radiation and local ablative therapy.

Hereditary hyperparathyroidism syndromes, such as multiple endocrine neoplasm type 1, type 2A and the hyperparathyroidism-jaw tumor syndrome, are associated with an increased incidence of malignancies involving the neuroendocrine tissue of the pancreas and thymus, parathyroid and thyroid glands. The natural history of these endocrine tumors can differ from nonhereditary malignancies. The surgical approach, the only potentially curative treatment option for these endocrine malignancies, has evolved considerably in recent years. Newer targeted therapies, such as small molecule kinase inhibitors, somatostatin analogs and peptide receptor radionuclide therapy, are being developed. We provide here a comprehensive review of the current standards of treatment and emerging novel therapies for the endocrine malignancies commonly associated with hereditary hyperparathyroidism syndromes.

First draft submitted: 1 October 2016; Accepted for publication: 13 February 2017; Accepted for publication: 27 April 2017

¹Metabolic Diseases Branch, National Institute of Diabetes & Digestive & Kidney Diseases, National Institutes of Health, MD 20892, USA

*Author for correspondence: Tel.: +1 301 496 9299; Fax: +1 301 402 0374; ws7e@nih.gov

KEYWORDS

• CDC73 • familial hyperparathyroidism syndromes • medullary thyroid cancer • MEN1 • nonfunctioning pancreatic neuroendocrine tumor • parathyroid carcinoma • peptide receptor radionuclide therapy • RET • thymic neuroendocrine tumor • tyrosine kinase inhibitor

IJE-2016-0018 the vast majority of cases of primary hyperparathyroidism (PHPT) are sporadic, familial forms represent some 2–5% of cases and are caused by germline DNA mutations (Table 1). Familial syndromes of PHPT, including multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 2A (MEN2A) and the hyperparathyroidism-jaw tumor syndrome (HPT-JT), are associated with a spectrum of endocrine and nonendocrine neoplasms of varying malignant potential. Some of these familial endocrine neoplasms demonstrate clinical characteristics and disease courses that are distinct relative to their sporadic counterparts. Many of the tumors classically associated with familial syndromes of PHPT have significant malignant potential and present particular challenges to medical management. Knowledge of the unique features and natural history of tumors associated with familial syndromes of PHPT may not only facilitate diagnosis but also help to establish individualized management to improve clinical outcomes. In this review, we summarize current standards of treatment and emerging novel therapies for a key subset of particularly challenging endocrine neoplasms with malignant potential classically associated with familial syndromes of PHPT. These include HPT-JT-associated parathyroid cancer, MEN1-associated thymic carcinoid tumors (a.k.a. thymic neuroendocrine tumors [NET]) and nonfunctioning pancreatic neuroendocrine tumors (pNET), and MEN2A-associated medullary thyroid cancer (MTC). For a detailed discussion of the management of the typically benign parathyroid disease associated with MEN1 and MEN2A, the reader is directed to recent focused reviews on these topics [1–3].

Hyperparathyroidism-jaw tumor syndrome & parathyroid carcinoma

Hyperparathyroidism-jaw tumor syndrome (HPT-JT) is a rare autosomal-dominant familial

PHPT syndrome. HPT-JT is caused by inactivating germline mutations in the *CDC73* gene, with chromosomal location 1q25, which results in the loss-of-function of its gene product named parafibromin [4]. Parafibromin is a presumed tumor-suppressor protein, a component of the PAF1 transcriptional regulatory protein complex that plays a role in the regulation of gene transcription and histone modification [5]. Due to variable penetrance of the trait, patients harboring germline *CDC73* gene mutations may exhibit one of a spectrum of clinical manifestations. Some proven or obligate mutation carriers are asymptomatic while others carrying *CDC73* germline mutations can manifest either one or several features classically associated with HPT-JT. These include PHPT due to parathyroid adenomas or parathyroid carcinomas, benign fibro-osseous tumors of the maxilla or mandible (histologically described as cemento-ossifying fibromas), as well as kidney or uterine tumors.

Diagnosis may be suspected based on a personal history of PHPT and cemento-ossifying jaw tumor, PHPT in the context of a family history of HPT-JT, or parathyroid cancer in the context of familial PHPT, and can be confirmed by germline *CDC73* gene mutation testing [6]. Some 25% of patients with apparently sporadic parathyroid cancer may harbor germline *CDC73* mutation [7,8]. Besides HPT-JT kindreds, a subset of patients with the familial PHPT phenotype also carries germline mutation of *CDC73*, indicating that this disorder may represent an incomplete expression of HPT-JT. HPT-JT patients have a significantly increased risk of developing parathyroid carcinoma, which is otherwise a very rare disease in the general population, with an estimated incidence of 0.015 per 100,000 persons.

Parathyroid carcinoma presents a challenge to medical and surgical management (Table 2). At

Table 1. Endocrine malignancies associated with hereditary hyperparathyroidism syndrome.			
Hereditary hyperparathyroidism syndromes	Germline gene mutation	Tumors that are malignant, or with high malignancy potential	Tumors that are benign, or with lower malignancy potential
Hyperparathyroidism-jaw tumor syndrome	<i>CDC73</i>	Parathyroid carcinoma	Parathyroid adenoma (can be 'atypical')
Multiple endocrine neoplasia type 1 syndrome	<i>MEN1</i>	Pancreatic nonfunctioning neuroendocrine tumors; Thymic neuroendocrine tumor	Anterior pituitary adenomas, parathyroid adenoma/hyperplasia, insulinoma, gastrinoma, bronchial neuroendocrine tumor
Multiple endocrine neoplasia type 2A syndrome	<i>RET</i>	Medullary thyroid carcinoma	Parathyroid adenoma/hyperplasia, pheochromocytoma

initial presentation, a high percentage of parathyroid carcinoma patients have already had lymph node (15–30%) or distal metastasis (33%) [9]. Surgery is the only treatment modality that offers potential cure, but up to 50% of postoperative parathyroid carcinoma patients have persistent or recurrent disease [9].

Refractory hypercalcemia and its systemic complications are the most common cause of mortality and morbidity in patients with parathyroid carcinoma [10,11]. This metabolic disorder may be managed like a chronic disease in many patients with persistent or recurrent parathyroid cancer because of the relatively slow growth of this endocrine cancer.

• Surgery

Survival in patients operated on for parathyroid carcinoma seems to be favorable compared with that with many other malignancies. From large series published in recently, 5-year overall survival rate has been 82.3 and 86.9% and 10-year survival rates are 66 and 72.0% [12,13]. Parathyroidectomy with local resection may be sufficient in selected cases [14].

Because there is a high possibility of lymph node metastasis at initial presentation, a more comprehensive surgery seems to be the optimal choice for patients with parathyroid carcinoma by offering a better chance of local disease control. *En bloc* resection and bilateral neck exploration is an accepted approach in many practices [15]. An observational study reported that *en bloc* oncologic resection of parathyroid carcinoma (defined as *en bloc* resection, ipsilateral thyroid lobectomy, central cervical lymphadenectomy of level VI lymph nodes and/or further locoregional excision) offered better locoregional control and disease-free survival in patients, when compared with local excision alone [16]. In patients with tumor invasion to recurrent laryngeal nerve, trachea or esophagus, surgical resection with immediate structural repair may be attempted [16].

Nevertheless, there is no high-level evidence to support increased survival after aggressive surgical resection. Young *et al.* retrospectively analyzed parathyroid carcinoma patients included in the California Cancer Registry from 1999 to 2012, and found that more extensive surgery did not improve survival when compared with parathyroidectomy alone [12]. In other retrospective studies, neither lymph node status nor type/extension of initial surgery (directed

parathyroidectomy vs *en bloc* surgery) was found to significantly affect survival [13,17–18].

Most parathyroid carcinomas are functioning tumors. Persistent hypercalcemia due to PHPT suggests residual disease. In patients with refractory hypercalcemia, repeated surgery should be considered. The goal is not only to reduce the tumor bulk, but to sustain the calcium level close to the normal range whenever possible [11,19].

Nonfunctional parathyroid carcinoma is quite uncommon, with only about 30 cases reported to date in the literature. Due to normal circulating PTH and calcium levels, medical management is not applicable in those patients. The prognosis is usually poor due to a lack of biomarker for disease surveillance. *En bloc* resection of the cancer with surrounding tissues has been recommended [20].

• Medical management

Medical management plays an important role in controlling persistent hypercalcemia and invisible or nonoperable metastases in patients with parathyroid cancer. Conventional initial management of acute hypercalcemia, including particularly intravenous normal saline hydration, subcutaneous calcitonin and intravenous bisphosphonates, should be instituted whenever applicable, and will not be discussed here.

• Calcimimetics & RANKL-targeting monoclonal antibodies

Calcimimetics (e.g., cinacalcet) are allosteric activators of the calcium-sensing receptor, which act in parathyroid tissue to enhance the effects of extracellular calcium ions, decrease PTH secretion and lower serum calcium levels (Figure 1). This class of drugs has been shown to reduce serum PTH and calcium levels in all forms of PHPT [21]. The US FDA has approved orally administered cinacalcet for the treatment of parathyroid carcinoma in a dose range between 30 mg twice daily and 90 mg four-times a day. It has often been used as a palliative therapeutic measure and typically demonstrates some efficacy in the setting of refractory hypercalcemia secondary to parathyroid carcinoma. In patients with inoperable parathyroid carcinoma, cinacalcet treatment led to a clinically and statistically significant decrease of serum calcium levels among two-thirds of patients, especially those with higher baseline calcium levels. Although PTH levels tended to lower in response to cinacalcet, the reductions were not found to be

Table 2. Parathyroid carcinoma treatment.

Treatment group	Treatment details	Indications	Remarks
Surgery	Parathyroidectomy (simple or <i>en bloc</i> resection), or local resection <i>En bloc</i> resection, with or without hemithyroidectomy and lymph node dissection	Small lesion without clinical evidence of multiglandular involvement Consider <i>en bloc</i> resection for large lesion with high risk of local recurrence or distal metastasis, and for nonfunctioning carcinoma	Aggressive surgical treatment has not shown improvement of survival May offer better local-regional control
Medical management	Conventional treatment (intravenous fluid, diuretic, bisphosphonate, steroid) Cinacalcet in dose range from 30 mg b.i.d. to 90 mg q.i.d. p.o.	First line for acute hypercalcemia whenever applicable Use for palliative or therapeutic purpose, for refractory hypercalcemia secondary to parathyroid carcinoma	Limited efficacy in long-term treatment Approved by US FDA for parathyroid carcinoma; may have tachyphylaxis; may cause nausea, vomiting, hypocalcemia, possible liver function impairment
	Denosumab with varies doses range and frequencies, starting with 60 mg subq once	Symptomatic, refractory hypercalcemia that has failed prior treatment modalities	Can be used in renal insufficiency; may exhibit tachyphylaxis; may cause hypocalcemia
Chemotherapy	Cytotoxic agents (doxorubicin, bleomycin, carboplatin, 5-fluorouracil, mithramycin or dacarbazine)	Palliative treatment, when patient is refractory to all other treatments	Very low response rate
Immunotherapy	Anti-PTH immunotherapy	Under investigation	Seems to improve PTH and calcium levels in treatment sensitive patients; limited experience; efficacy and safety are still unclear
Radiation	External beam radiation	Palliative treatment with mixed results and limited data	Tumor does not seem to be sensitive to the treatment

clinically significant [22]. Any survival benefit of cinacalcet therapy in parathyroid cancer remains to be established.

Common adverse effects of cinacalcet in patients with parathyroid carcinoma include nausea (66%), vomiting (52%) and dehydration (24%). Cinacalcet is a category C drug and requires justification to be used during pregnancy. One case description reported that no teratogenic effect was observed after cinacalcet use in pregnancy [23].

Denosumab is a humanized monoclonal antibody that binds to receptor activator of NF- κ B ligand (RANKL) and prevents activation of the cell surface receptor activator of nuclear factor κ -B (RANK) expressed on osteoclasts, which consequently inhibits recruitment and maturation of osteoclasts and inhibits bone resorption (Figure 2). The FDA approved denosumab for the prevention and treatment of skeletal-related events (i.e., pathologic fracture, radiation to bone, surgery to bone, or spinal cord compression) in patients with bone metastasis from solid tumors. It has been found to be effective to treat refractory hypercalcemia in patients with parathyroid carcinoma, although its efficacy and

adverse effects have not been fully characterized. Like the intravenous bisphosphonates, denosumab has been associated with the development of osteonecrosis of the jaw in a small minority of cases [24].

Because denosumab exerts its effect by decreasing bone absorption, denosumab controls refractory hypercalcemia without decreasing parathyroid hormone [10]. Multiple doses of denosumab are often needed to control hypercalcemia in the setting of parathyroid carcinoma [25–29]. The effectiveness of denosumab in controlling refractory hypercalcemia gradually diminishes over time, and dose escalation and increasing dosing frequency may be required to achieve the target serum calcium level (e.g., 3 mmol/l). It is still unclear whether this decreasing effectiveness to denosumab is caused by downregulation of RANKL/RANK receptor or tumor growth [30].

• Cytotoxic chemotherapy

Like radiotherapy, conventional cancer chemotherapeutic agents have generally been considered ineffective in the treatment of parathyroid carcinoma [9]. The group in the MD Anderson Cancer Center reported that only 1 out of

15 patients had a transient response to chemotherapy [31]. No survival benefit of chemotherapy has been reported. Agents that have been tested include the cytotoxic agents doxorubicin, bleomycin, carboplatin, 5-fluorouracil, mithramycin and dacarbazine [31].

• Somatostatin receptor agonists

If the recurrent or persistent parathyroid carcinoma is positive on somatostatin-receptor scintigraphy, long-acting somatostatin analog may be considered [30]. The results, however, have not been encouraging [30,32].

• Immunotherapy

Anti-PTH immunotherapy has shown promising results by reducing calcium levels and even imageable tumor burden in a few cases [11,33,34]. Its efficacy and safety still need to be further investigated.

• Radiation therapy

Parathyroid carcinoma is radioresistant, and external beam radiation has generally been considered ineffective [9]. In the available small case series of parathyroid carcinoma, only a small percentage of patients (<10%) were reported to have received radiation [35]. Mixed results appeared to show that some patients responded to the radiotherapy while many others had no response [31].

Some small case series have reported that adjuvant radiotherapy after initial surgery may prevent local-regional recurrence [31,36]. In contrast, about 64% of patients treated with radiotherapy developed recurrence [37]. In a large retrospective review of parathyroid carcinoma patients included in the National Cancer Database from 1985 to 2006, adjuvant radiation therapy was not found to be a prognostic factor of survival [13]. The benefit of radiation is therefore not clear with current available data.

• Radiofrequency ablation

Radiofrequency ablation (RFA) has been used in the palliative treatment of distal metastasis (e.g., liver and lung) in several patients with some clinical improvement reported (e.g., reduction in serum calcium and/or PTH level) [38–40].

MEN2A & MTC

Multiple endocrine neoplasia type 2 (MEN2A) is an autosomal dominant disease that is caused by germline gain-of-function missense mutation of the *RET* (REarranged during Transfection)

protooncogene. The *RET* gene encodes a transmembrane receptor tyrosine kinase that involves in regulation of cell growth and survival [41]. Germline *RET* mutations are present in virtually all patients with MEN2A, with close to 100% penetrance for MTC but at a lower frequency for the expression of pheochromocytoma (about 50%) and PHPT (~20%) [41,42]. In MEN2A, parathyroid tumors are typically benign and result in PHPT, while pheochromocytoma has low malignant potential and is not associated with shortened survival [43].

MTC usually develops early in life and is the most common cause of death in MEN2A patients [44]. MTC often presents as a thyroid nodule with neck lymphadenopathy, which can be detected by physical exam or radiologic studies. The diagnosis is confirmed by biopsy. Calcitonin is a sensitive and valuable tumor marker. A high level of calcitonin is indicative of a large tumor mass and possible lymph node metastasis [42,45]. Carcinoembryonic antigen is not a specific marker and should not be used to diagnose MTC, but it can be used in combination with calcitonin to recognize poorly differentiated or invasive MTCs [42]. There is a genotype-phenotype association between specific *RET* missense mutations and the severity and clinical course of MTC. Therefore, *RET*

Figure 1. Cinacalcet binds to the calcium-sensing receptor on the cell surface membrane of parathyroid gland chief cells, and activates the receptor, increasing its sensitivity to calcium. As a consequence, PTH synthesis and secretion are inhibited, and the circulating serum calcium level is lowered. Ca⁺⁺: Ionized calcium; CaSR: Calcium-sensing receptor; PTH: Parathyroid hormone.

germline mutation testing is a critical diagnostic step to help stratify patients for appropriate management (Table 3).

• Surgery

Surgery is the most important treatment modality for MTC and may offer a potential cure. It can be performed either for prophylaxis or for treatment. It is important to keep in mind that screening for and resection of co-existing pheochromocytoma should be done prior to any MTC surgery.

• Prophylactic surgery

MTC has a high penetrance in MEN2A patients and *RET* mutations are predictive of clinical manifestations and prognosis. Therefore, most of the guidelines recommend that prophylactic thyroidectomy should be decided based on the risk stratification of the patient's particular *RET* gene mutation. The American Thyroid Association (ATA)'s current guidelines recommend that total thyroidectomy should be performed at or before age 5 in children with *RET* germline mutations at high risk for aggressive MTC (e.g., *RET* codon 634 mutation), but can be delayed until later childhood in patients possessing moderate risk *RET* germline mutations

(e.g., mutations in *RET* codons 609, 619, 620 or 804) [42]. Bilateral central neck dissection should be considered when there are elevated calcitonin levels or positive neck lymph node(s) [46].

MTC has a high penetrance in MEN2A patients and *RET* mutations are predictive of clinical manifestations and prognosis. Therefore, most of the guidelines recommend that prophylactic thyroidectomy should be decided based on the risk stratification of the patient's particular *RET* gene mutation. Most of *RET* mutations in MEN2A are in moderate or high risk categories as specified in 2015 ATA guideline for the management of MTC. The current guideline recommends that total thyroidectomy should be performed at or before age 5 in children with *RET* germline mutations at high risk for aggressive MTC (e.g., *RET* codon 634 mutation), but can be delayed until later childhood in patients possessing moderate risk *RET* germline mutations (e.g., mutations in *RET* codons 609, 619, 620 or 804) [42]. An abnormally elevated calcitonin level can be an indication for surgery despite of age (or before age 5). Central and lateral neck dissection should be considered when there is elevated calcitonin level or radiological evidence of positive neck lymph node(s) [46].

Figure 2. The monoclonal antibody denosumab binds to receptor activator of nuclear factor κ -B ligand and prevents it from interacting with the receptor activator of NF- κ B on the cell surface membrane of osteoclasts. This decreases osteoclast recruitment, activation and survival, which subsequently results in reduced bone absorption and lowered circulating serum calcium level. RANK: Receptor activator of nuclear factor κ -B; RANKL: Receptor activator of nuclear factor κ -B ligand.

• Surgical treatment

Surgery is the main treatment modality for primary MTC in neck and recurrent cancer in neck or mediastinum [47]. Cure may be achieved by surgery in those patients with no or only limited number of lymph node metastases [48].

Because about 75% of MTC patients with a palpable neck mass have central lymph node metastases, total thyroidectomy with central lymph node dissection is recommended by most surgeons [48,49]. Ipsilateral cervical node and contralateral node metastases are also common in advanced stage cancer. Lateral lymph node dissection may provide a better chance of cure in stage IVa patients with metastasis to cervical, retropharyngeal or superior mediastinal lymph nodes [50], but is associated with a higher morbidity. Spinal accessory nerve damage and lymphatic leakage are two main complications that can lead to shoulder dysfunction. Other complications, such as injury of cervical plexus, sympathetic trunk, phrenic, hypoglossal and vagal nerves, are much less common after lateral compartment dissection and not well studied [51]. The need for lateral lymph node dissection may be determined based on tumor size and location, the extent of lymph node involvement and the degree of calcitonin elevation [52]. Many surgeons determine the need for ipsilateral lymph node dissection based on status of central node involvement and preoperative images, and use imaging and the calcitonin level to guide contralateral neck exploration [49]. Basal calcitonin levels above 20 pg/ml, 50 pg/ml, 200 pg/ml are typically indicative of metastases in ipsilateral central and lateral lymph nodes, contralateral central lymph nodes and contralateral lateral lymph nodes, respectively [42].

In a third of patients with recurrent or persistent local-regional disease, reoperation can achieve long-term control and biochemical cure in experienced hands [49]. Palliative tumor debulking can be considered for clinical symptom relief. In patients with advanced MTCs that have invaded surrounding structures, the decision on whether to perform debulking surgery with laryngectomy, esophagectomy or laryngopharyngectomy should take into consideration the patient's life expectancy and other medical comorbidities, with the goal of maintaining maximal functionality of speech and swallowing. Other treatments, such as cytoreductive surgery, external beam radiotherapy (EBRT), embolization, systemic medical therapy and other

nonsurgical therapies can be considered for local tumor control and life quality improvement in selected cases, as discussed below [42].

• Medical management

About 4–17% of MTC patients have distant metastasis at the time of initial diagnosis, and 18–38% are diagnosed with metastatic disease during subsequent follow-up [47]. Medical management is the main treatment modality for rapidly progressive MTC. Many advances have been made in recent years.

• Tyrosine kinase & mammalian target of rapamycin inhibitors

Various tyrosine kinase inhibitors (TKIs) have been tested in clinical trials, including vandetanib and cabozantinib [44]. These TKIs target the RET tyrosine kinase, and may inhibit many other tyrosine kinases, such as VEGFR (Figure 3).

The US FDA and European Medicines Agency have both approved vandetanib and cabozantinib for use in locally advanced, progressive metastatic disease with significant tumor burden. In randomized, double blind, Phase III trials, both vandetanib and cabozantinib showed statistically significant improvement of progression-free survival (PFS) compared with placebo [53,54].

Vandetanib targets RET, the EGFR and VEGFR-2 and -3. In its pivotal Phase III trial, 331 patients with locally advanced or metastatic MTC, among which 10% had germline *RET* mutation, were treated with vandetanib 300 mg daily or placebo. Partial responses were achieved in 45% of the patients, with median duration of response of 22 months. The median PFS was improved from 19.3 months in the placebo group to 30.5 months in the treatment group. Better quality of life was also observed in the treatment group [53]. Vandetanib has a variety of significant toxicities. It is contraindicated in patients with congenital long QT syndrome (a heart condition in which delayed repolarization of the heart following a heartbeat increases the risk of irregular heart rhythms), and about 55% of patients in the trial experienced adverse events. Side effects can be managed by dose interruption, reduction or symptomatic treatment [55]. The FDA requires providers to receive Risk Evaluation and Mitigation Strategy (REMS) training before prescribing vandetanib [56].

Cabozantinib targets RET, c-Met (also called the hepatocyte growth factor receptor)

Treatment group	Treatment details	Indications	Remarks
Prophylactic surgery	Total thyroidectomy at or before 5 years old	<i>RET</i> germline mutation in high risk category (e.g., p.C634F/G/R/S/W/Y)	Must screen and resect pheochromocytoma prior to MTC surgery
	Total thyroidectomy in childhood	<i>RET</i> germline mutation in moderate or low risk category (e.g., p.C609G/R, p.618F/S)	Approach as clinically indicated
	Central lymph node and bilateral lymph node dissection	Considered in above patients with high calcitonin level, or as clinically indicated	
Surgery	Thyroidectomy with central lymph node dissection	Recommended for most tumors	About 75% patients with palpable neck mass have central lymph node metastases
	Thyroidectomy with central lymph node, ipsilateral or/ and contralateral lymph node dissection	May be considered for advanced stage cancer (e.g., stage IVa)	Perform lateral lymph node dissection based on tumor size, location, lymph node involvement and calcitonin level. It is associated with a higher risk of lateral nerve dysfunction and morbidity
	Repeated surgical resection	Recurrent regional disease; or as palliative tumor debulking	In advanced MTC, surgery can be combined with radiation, radiofrequency ablation, medical therapy to improve local tumor control and life quality
Medical management	Vandetanib (tyrosine kinase inhibitor)	Locally advanced, progressive metastatic disease	Cytostatic instead of cytolytic; secondary resistance may eventually develop. US FDA requires 0 to receive risk evaluation and mitigation strategy training
	Cabozantinib (tyrosine kinase inhibitor)	Locally advanced, progressive metastatic disease	Cytostatic instead of cytolytic; secondary resistance may eventually develop
Peptide receptor radionuclide therapy	⁹⁰ Yttrium-DOTATOC; ¹⁷⁷ Lutetium-DOTATATE	Selected patients with somatostatin receptor positive tumors	Limited data; efficacy and risk need to be further studied
Chemotherapy	Doxorubicin + cisplatin; fluorouracil + dacarbazine	Selected patients with rapid progression	Response rate is poor, and response is partial and short-term
Radiation	External beam radiotherapy	Extensive nodal disease, residual or extrathyroid disease, when surgery is not feasible or incomplete	Has acute and chronic toxicity; may prevent locoregional recurrence; may not improve overall survival; may complicate subsequent surgical procedure

MTC: Medullary thyroid cancer.

and VEGFR-2 kinases (Figure 3). In the Phase III trial of cabozantinib, 330 patients, among which 6% had hereditary MTC, were treated with cabozantinib 140 mg daily or placebo. An objective response rate of 28% was reported, and the median PFS improved from 4 months in the placebo group to 11.2 months in the treatment group [54]. The effectiveness of cabozantinib is independent of prior TKI treatment, indicating a lack of cross-resistance [57]. Adverse events were frequent when cabozantinib was taken at 140 mg per day. The most commonly reported adverse events were diarrhea (63%), stomatitis (51%), palmar plantar erythrodysesthesia (50%) and nausea (43%), while the most common lab abnormalities were increased liver transaminases (86%) and hypocalcemia (52%). The FDA

approved cabozantinib in 2012 for treating progressive, metastatic medullary thyroid cancer, in a dosage of 140 mg once daily [56].

Both vandetanib and cabozantinib should not be used in localized MTC. Their effects are cytostatic instead of cytolytic, and the response is partial and short term. Secondary resistance will eventually develop [44]. Sensitivity to RET-targeting TKIs may depend on the *RET* genotype, as suggested by *in vivo* studies. For example, *RET* mutation at codon 804 may induce resistance to vandetanib [47]. However, no clinical trial has evaluated efficacy of TKI based on stratification of *RET* genotypes.

Several new drugs are currently under clinical development. The selective RET inhibitor (NVP-AST487-NX) and mammalian target of

rapamycin (mTOR) inhibitors have been found to suppress the proliferation of MTC cell lines *in vitro*. An HSP90 inhibitor can induce degradation of RET and several other growth mediating kinases, and is a potential alternative treatment for RET-driven drug-resistant MTC [58]. Cyclic AMP analogues, such as 8-chloro-cAMP, have shown potent antiproliferative effects in MTC cell lines and may potentially be used to treat advanced MTC as well. To date, the mTOR inhibitor everolimus has shown high clinical benefit and low risk profile in a Phase II trial [59].

• Cytotoxic chemotherapy

MTC is not sensitive to chemotherapy and its objective response rate ranged from 0 to 20%. Chemotherapy may be given in selected patients with rapid progression, but offers little benefit in slowly progressive disease. Chemotherapy may be administered as a single agent or used in combination, for example, doxorubicin + cisplatin or 5-fluorouracil + dacarbazine. The response is partial and short-lived [47].

• Radiation therapy

It is still controversial whether EBRT is beneficial in MTC [49]. Some centers report that adjuvant EBRT may help to prevent local-regional recurrence [60], while others found that EBRT did not provide overall survival benefit in the patients with MTC and positive lymph nodes [61].

EBRT to the neck and mediastinum can be considered for local tumor control [47], when surgical resection is incomplete or not feasible or when there is extensive nodal disease, residual or extra-thyroid disease [42]. EBRT can cause both acute and latent side effects, including skin erythema or desquamation, mucositis, esophagitis, laryngeal edema, or even esophageal stricture or tracheal stenosis. EBRT may also complicate subsequent neck surgery [42,49].

• Radionuclide therapy

Peptide receptor radionuclide therapy (PRRT) is a novel treatment targeting the somatostatin receptor (SSTR). PRRT uses somatostatin analogs conjugated with chelators and radionuclide to deliver a tumoricidal dose of radiation to cells expressing SSTRs. Only a fraction of MTC patients have tumors expressing SSTRs. Candidates for this PRRT can be identified by positive tumor imaging with somatostatin-receptor scintigraphy. ⁹⁰Yttrium-labeled DOTA-TOC (edotreotide) binds to SSTR subtype 2

on the surface of MTC tumor cells, and emits β -radiation that causes cytotoxicity. In a Phase II trial, 29% patients with metastatic MTC responded to the ⁹⁰Yttrium-DOTA-TOC treatment, and response to the treatment was associated with a longer survival from time of diagnosis and time of first treatment [62]. Therapy with ¹⁷⁷Lutetium-DOTATATE, a similar type of peptide receptor radionuclide targeting the SSTR, was reported to achieve stable disease for 9–10 months in two cases [63]. PRRT appears to be an alternative therapy for the minority of SSTR-positive MTC tumors, but long-term studies are still needed to understand efficacy and risk profiles of this novel therapy [64].

About 30% of MTC tumors are able to concentrate meta-iodobenzylguanidine (MIBG) and could potentially be treated with ¹³¹I-MIBG. In a retrospective study in Italy, about 35% of patients responded to ¹³¹I-MIBG treatment [65].

• Local ablative therapy

In patients with oligometastatic disease, local ablative therapy, by surgical resection, EBRT, RFA or chemoembolization can all be considered [42]. RFA has been reported to successfully treat liver metastases of MTC associated with low calcitonin level [66]. Embolization and chemoembolization can be considered for rapidly progressive liver metastases, while percutaneous radiofrequency or cryoablation may be used for bone, lung and liver metastases.

Multiple endocrine neoplasia type 1 & pancreatic neuroendocrine tumors

MEN1 is an autosomal-dominant syndrome caused by germline loss-of-function mutation of the *MEN1* tumor suppressor gene [67] that encodes a 610-amino acid protein menin [68]. The protein menin contains multiple nuclear localization signals, interacts with multiple proteins and regulates gene transcription by coordinating chromatin remodeling. It is known to regulate the expression of cell cycle kinase inhibitors and homeobox domain genes via its modulation of histone methyltransferase activity.

MEN1 syndrome manifests as development of multiple endocrine tumors arising from the pituitary, parathyroid, enteropancreatic neuroendocrine system and other endocrine and nonendocrine tissues. About 80–90% MEN1 patients develop pancreatic neuroendocrine tumors (pNETs) in their lifetime, and up to 90% pNETs are nonfunctional. Most pNETs

are small, multifocal and microscopic [69], and larger pNETs tend to be associated with higher rates of lymph node and hepatic metastases [70–74]. Although many of the tumors associated with the MEN1 syndrome are benign, nonfunctional pNET and thymic NET are two NETs in MEN1 with high malignant potential [75].

The natural history of MEN1 has significantly changed over the past decade. The most common cause of death in MEN1 has shifted from functional pNET to nonfunctioning malignant pNET and thymic NETs [76,77]. Malignant pNET is responsible for 58–64% MEN1-related deaths in the NIH series and the pooled literature [76]. The 10-year survival rate of nonfunctioning pNETs is 50%, much lower than the 85% value for functional pNETs [78].

Diagnosis of pNET relies on imaging and biopsy. Endoscopic ultrasound (EUS) has the highest sensitivity to detect pNET, while both CT and MRI have relatively high sensitivity and specificity. In small series, EUS-guided fine-needle aspiration (EUS-FNA) has shown to be effective to make accurate diagnosis and to facilitate treatment selection [79,80]. Immunohistochemical staining for chromogranin A and synaptophysin is recommended. The Ki-67 index and mitotic rate are also used for tumor grading in pathologic exams and are critical determinants when assessing malignant potential. Serum chromogranin A can also be used to evaluate treatment efficacy during follow-up over time in advanced cases [52]. Management of pNETs in MEN1 patients may draw on many treatment modalities (Table 4).

• Surgery

Surgery is the cornerstone, and the only potentially curative treatment for pNETs. The survival benefit of surgery has been demonstrated in different disease stages [72]. The modality and extent of surgery should be decided based on multiple factors, including the patient's genetic background, size and location of tumor and evidence of distant metastasis.

Surgical modalities of pNETs include tumor enucleation, distal pancreatectomy with or without splenectomy, Whipple's procedure and total pancreaticoduodenectomy. Parenchyma-sparing surgery, such as enucleation, risks disease understaging and pancreatic duct leak or fistula formation (50%). More aggressive surgery, such as distal pancreatectomy, which is indicated in patients with large and multiple tumors, confers

a high risk of endocrine and exocrine pancreatic insufficiency [81–83]. Enucleation can be combined with distal pancreatectomy as needed. Laparoscopic surgery is a feasible approach that is associated with less pain, shorter hospital stay and equivalent complication rate when compared with open surgery, especially when the tumor size is <2 cm [84].

The size of nonfunctioning pNETs is often used to guide surgery. The risk of malignancy increases with tumor size [85]. Most authors agree that conservative management should be used for asymptomatic nonfunctioning pNETs <1 cm [70], and surgical intervention should be recommended for tumors >2 cm because about 50–70% pNETs in size of 2–3 cm are associated with lymph node metastases [70–71,83]. Surgical intervention remains controversial in tumors within size of 1–2 cm. Some recommend surgical intervention for nonfunctioning pNET >1 cm in size because of increased risk of hepatic metastasis [86,87], while others argue that nonfunctioning pNET <2 cm in size are indolent with low malignant potential and should be managed conservatively [88]. Because hereditary syndromes like MEN1 are frequently associated with microscopic/multifocal disease and may have an indolent course, conservative management has been advocated by many groups, especially when pNETs are <2 cm in size [72]. A significant size increase over a 6-month interval (e.g., >0.5 cm) is another indication for surgery [83].

In patients with metastatic nonfunctioning pNET, resection of primary tumor is associated with a better survival [89]. Resection of the pancreatic primary tumor may also relieve or prevent pancreatic duct obstruction or complications caused by invasion by the primary tumor [72]. Resection of a single or even multiple surgically amenable hepatic metastatic lesions is recommended by some and can sometimes lead to cure [87].

• Medical management

Large randomized trials have demonstrated efficacy of everolimus and sunitinib in progressive and metastatic pNETs. These small molecule inhibitors prolong PFS in patients with advanced pNETs. Improvement of overall survival was not seen in the Phase III trial of everolimus possibly because crossover was allowed. The impact of these small molecule inhibitors is mainly on delaying progression. Although the Phase III trials of sunitinib and everolimus were designed to

Figure 3. Overview of the molecular mechanisms of different antineoplastic therapies. The chemotherapy agents cause DNA damage that leads to cell death. The TKI, mTOR inhibitors and somatostatin receptor agonists target different intracellular pathways and cause decreased cell growth and survival signaling. Peptide receptor radionuclide therapy also targets somatostatin receptors. AC: Adenyl cyclase; AKT: Protein kinase B; EGFR: Epidermal growth factor receptor; ERK: Extracellular signal-regulated kinases; JAK: Janus kinase; MEK: Mitogen-activated protein kinase; MET: c-Met or hepatocyte growth factor receptor; mTOR: Mammalian target of rapamycin; PI3K: Phosphoinositide 3-kinase; RAF: Rapidly accelerated fibrosarcoma kinase; RET: Rearranged during transfection receptor tyrosine kinase; SSTR: Somatostatin receptor; STAT: Signal transducer and activator of transcription; TKI: Tyrosine kinase inhibitor.

include pNET patients with or without familial syndromes, only a few patients in the sunitinib trial had mutations in MEN1 gene and no information on familial syndromes was specified in the everolimus trial. The FDA approves use of sunitinib and everolimus in pNET patients with unresectable locally advanced or metastatic disease regardless of underlying genetic causes.

• Tyrosine kinase inhibitors

Sunitinib suppresses tumor angiogenesis and cell proliferation by inhibiting PDGFR and VEGFR

(Figure 3). In a Phase III clinical trial, sunitinib improved PFS by 6 months when compared with placebo in advanced pNET patients and had a favorable adverse event profile [90]. Subgroup analysis also showed PFS improvement in non-functioning tumors. The FDA has approved sunitinib for unresectable locally advanced or metastatic pNETs.

• mTOR inhibitors

The enzyme mTOR, a serine-threonine kinase, is a master regulator of cell growth, proliferation

and angiogenesis (Figure 3). Everolimus inhibits mTOR pathway signaling. In patients with advanced, progressive, low- or intermediate-grade pNETs, everolimus resulted in 6.4 months of PFS improvement when compared with placebo [91]. The FDA has approved everolimus for progressive pNETs.

• Medical therapies in development

Other TKIs (such as sorafenib and pazopanib) and monoclonal antibodies against VEGF (such as bevacizumab) have been tested in Phase II clinical trials, and the tumor response rates ranged from 9 to 22% [92]. IGF-1 receptor monoclonal antibody, immunotherapy targeting CTLA-4 and PD-1 are also under clinical investigation for the treatment of pNETs [93].

• Cytotoxic chemotherapy

Streptozocin, an alkylating agent, is the first drug approved for pNETs. It can decrease tumor size in both functioning and nonfunctioning pNETs, and can improve endocrine abnormalities. However, its use is limited because of its difficult dosing schedule and renal toxicities. Like streptozocin, dacarbazine also has demonstrated activity in advanced pNET but its use is limited due to toxicity. Compared with dacarbazine, temozolomide is more tolerable with comparable efficacy [92]. It can be used as a palliative or a second-line therapy for poorly differentiated pNETs, or for palliative purpose in patients with poor performance status [94].

Platinum-based chemotherapy is usually indicated for aggressive pNETs, which may be high-grade or poorly differentiated tumors with high Ki-67 indices upon staining [92]. Poorly differentiated pNETs may be treated with first-line platinum-based regimen for 4–6 cycles. For patients with relapse, the same regimen can be repeated or else second-line chemotherapy can be considered [52]. In contrast, well-differentiated NETs in MEN1 usually respond poorly to platinum-based cytotoxic chemotherapy [52].

Pyrimidine analogs, such as 5-FU, capecitabine and gemcitabine, are often used in combination with an alkylating agent or a platinum. For instance, gemcitabine with oxaliplatin, or capecitabine with temozolomide, have been used in metastatic pNET [72].

• SSTR agonists

About 80% of pNETs possess SSTRs. SSTR2 are more prevalent in pNETs in the context of

MEN syndromes [93], and are expressed in about 80% of pNETs [92]. Octreotide LAR and lanreotide are two long-acting analogs of somatostatin, which act as agonists to G-protein coupled SSTRs in pancreatic neuroendocrine cells and inhibit neurotransmission, hormone secretion and cell proliferation (Figure 3). In randomized trials, somatostatin analogs have demonstrated antiproliferative effects in nonfunctioning NETs including pNET [72] and improved time to progression or PFS [93]. Lanreotide is approved for unresectable, well or moderate differentiated, locally advanced or metastatic gastroenteropancreatic NET.

• Radionuclide therapy

PRRT can be used as neoadjuvant and adjuvant therapy in patients with metastatic pNETs. The most commonly used radionuclides are β -emitting ^{90}Y and β - and γ -emitting ^{177}Lu . ^{90}Y -DOTA and ^{177}Lu -DOTA octreotide have similar response rates in the treatment of pNETs ranging from 10 to 30%, with ^{90}Y -DOTA being associated with a higher risk of nephrotoxicity [72]. Myelodysplastic syndrome and acute leukemia have been observed in patients who received PRRT treatment with prior exposure to alkylating agents [95].

• Local ablative therapy

Local ablative treatment can be used as an alternative therapy in patients who are not candidates for surgery. RFA is the most commonly used technique for this purpose. EUS-guided ethanol ablation offers minimally invasive local treatment of pNET [96], when the size of the pNET is <2 cm [97].

Percutaneous irreversible electroporation uses electrical fields to ablate soft tissue while conserving important blood flow and nerves. It has been tested in small pancreatic NETs (<2 cm) [98], and is currently being studied in clinical trials.

Both intra-arterial therapy and surgical intervention can be used to treat liver metastasis of pNET. There is no high-quality evidence to demonstrate superiority of either approach. When there is a high disease volume in liver, surgical resection is less beneficial [99] and transarterial embolization is preferred. Hepatic transarterial embolization, chemoembolization, or radioembolization (TARE) with Yttrium-90 are commonly used. Yttrium-90 transarterial radioembolization can be associated with biliary damage and liver cirrhosis [100].

Table 4. Pancreatic neuroendocrine tumor treatment.

Treatment group	Treatment details	Indications	Remarks
Conservative management		Stable tumor <1 cm, and may be considered in tumor <2 cm in MEN1 patients	For asymptomatic, nonfunctioning tumor with indolent course
Surgery	Parenchyma sparing surgery, for example, tumor enucleation	Depends on size and location of the tumors; commonly indicated for single lesion; can be considered for patients with multifocal and recurrent disease; and can be combined with distal pancreatectomy	Carries a higher risk for pancreatic duct leak and fistula formation
	Distal pancreatectomy	Depends on size and location of the tumors; commonly indicated for large and multiple tumors	Carries a higher risk for endocrine and exocrine insufficiency
	More aggressive surgery: for example, Whipple's procedure and total pancreaticoduodenectomy	Less favored modalities	Carries the highest risk for endocrine and exocrine insufficiency
Medical management	Tyrosine kinase inhibitor, sunitinib	Unresectable locally advanced or metastatic tumors	Its impact is mainly to delay progression
	mTOR inhibitor, everolimus	Progressive tumors	Its impact is mainly to delay progression
Peptide receptor radionuclide therapy	⁹⁰ Yttrium-DOTATOC; ¹⁷⁷ Lutetium-DOTATATE	Neoadjuvant and adjuvant therapy in patients with metastatic tumors	Only limited data available. ⁹⁰ Yttrium-DOTATOC causes more nephrotoxicity. Both drugs may have myelotoxicity
Chemotherapy	Platinum-based, such as cisplatin, oxaliplatin	Aggressive, high-grade or poorly differentiated tumors	Can be used as first line for poorly differentiated tumors
	Alkylating agent, such as streptozocin, dacarbazine, temozolomide	Palliative or second line for poorly differentiated tumors	Streptozocin and dacarbazine uses are limited by their toxicity; temozolomide is more tolerable
	Pyrimidine analogs, such as 5-FU, capecitabine and gemcitabine	Often used in combination with alkylating or platinum-based agents	
Somatostatin therapy	Octreotide LAR and lanreotide	Lanreotide is approved for unresectable, well or moderate differentiated, locally advanced or metastatic tumor	Has antiproliferative effects
Local ablative therapy	Radiofrequency ablation, endoscopic ultrasound-guided ethanol ablation and percutaneous irreversible electroporation for pNETs; intra-arterial therapy for liver metastases	Patients who are not candidates for surgery with small tumors commonly <2 cm.	Only limited data available

mTOR: Mammalian target of rapamycin.

Multiple endocrine neoplasia type 1 & thymic NETs

Thymic NETs (also known as thymic 'carcinoid tumors'), occur in fewer than 10% of patients with MEN1. These tumors develop more frequently in males and have a high mortality rate, with a 10-year survival rate of between 25–36% [78,101–103]. Analysis of a large cohort of European MEN1 patients confirmed that the presence of thymic NET is associated with a significantly higher mortality rate [77].

Although most thymic NET in MEN1 patients are hormonally nonfunctioning [103], functioning NET can produce symptoms related to the secreted hormone(s) in rare cases. In patients with advanced thymic NET, symptoms and signs can develop from local invasion, mediastinal lymphadenopathy, or distal metastases [104,105]. No genotype-phenotype correlation has been observed between *MEN1* mutation and the presence of thymic NET [106].

• Surgery

Prophylactic transcervical thymectomy at the time of initial parathyroidectomy in MEN1 patients is frequently recommended because of the malignant potential of thymic NET [106–109]. Such prophylactic thymectomy may not prevent the subsequent occurrence of thymic NET, however [106,110]. In one study 30% of MEN1 patients undergoing initial parathyroid surgery for PHPT demonstrated intrathymic parathyroid tissue following prophylactic thymectomy – thus this procedure may have the additional benefit of preventing or delaying recurrent PHPT [111].

Surgery is the primary treatment for MEN1 patients with demonstrated localized thymic NET and is the only potentially curative option. Usually *en bloc* resection of thymus and adjacent involved structures is recommended [108]. One case report describes the successful use of neoadjuvant therapy employing octreotide and sunitinib prior to surgery [112]. Resection with negative tumor margins is a strong prognostic factor for overall survival [113].

• Nonsurgical management

Only very limited data, consisting of case reports or small series, is available regarding nonsurgical therapies for nonresectable thymic NET in MEN1 patients. In patients with metastatic or nonresectable thymic NET, partial responses have been reported with platinum-based chemotherapy and the alkylating agent temozolomide [114]. No remission of disease was reported in a study of two patients with thymic NET treated with ¹⁷⁷Lu-octreotate radionuclide therapy [115]. Radiation therapy can be considered for the palliative management of bone metastases.

Conclusion

As detailed above, patients with hereditary syndromes of PHPT are at increased risk for the development of particular syndrome-specific endocrine malignancies, which result in increased morbidity and mortality rates. Whenever possible, a specific genotype should be established for a patient with a hereditary syndrome of PHPT, since in some cases the genotype may help predict the phenotype of the associated malignancy, as seen in medullary thyroid cancer in MEN2A. Prospective screening for the syndrome-specific malignancies is recommended by blood testing for characteristic hormonal or biochemical markers and/or

imaging. Following the earliest recognition of a syndrome-specific malignancy, surgery should be considered with the goal of achieving negative surgical margins. Surgery represents the only potentially curative treatment modality. For metastatic or nonoperable disease, management may require a multidisciplinary approach. Medical management of advanced disease may involve either small molecule inhibitors targeting specific growth-promoting enzymes, agonists at growth-inhibitory receptors or conventional cytotoxic chemotherapeutic agents. Other useful treatment options in cases of nonoperable disease include radionuclide therapy, external radiation and local ablative therapy.

Future perspective

A unique feature of hereditary hyperparathyroidism syndromes is that the causative gene mutations are frequently known or knowable at the time of patient presentation. The finding of a correlation between the *RET* oncogene genotype and the clinical behavior of MTC has helped to guide and refine the clinical management of MEN2A. It will be interesting to examine whether such genotype and phenotype correlation exists for other hereditary hyperparathyroidism syndromes. So far, analysis of patients with MEN1 has not provided evidence for the existence of such correlation, while little data has been reported in HPT-JT syndrome. With increasing number of cases of the latter syndrome being recognized, it may now be possible to examine the correlation between the *CDC73* mutation genotype and parathyroid neoplasia phenotype in HPT-JT syndrome. Another promising direction will be the identification of predictive biomarkers to guide selection of anti-neoplastic treatments. This is especially relevant given the emergence of many targeted therapies, such as small molecule inhibitors targeting certain tyrosine kinases, mTOR and other critical molecules, SSTR agonists and PRRT (Figure 3). It may be possible to perform such biomarker studies by employing the larger population with the sporadic counterparts of malignancies associated with hereditary hyperparathyroidism syndromes, assuming the findings may be generalizable to the much smaller population of patients with the same neoplasms in the context of hereditary hyperparathyroidism. Finally, management of advanced stage endocrine neoplasm will be multidisciplinary. With emergence of many new therapies, it will be critical to test

combinations and proper sequencing of different treatment modalities in a systematic and controlled fashion.

Financial & competing interests disclosure

WF Simonds is funded by intramural/NIDDK NIH grant DK043012-15 and is a US government employee. The

authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:

• of interest; •• of considerable interest

- Pieterman CR, Van Hulsteijn LT, Den Heijer M *et al.* Primary hyperparathyroidism in MEN1 patients: a cohort study with long-term follow-up on preferred surgical procedure and the relation with genotype. *Ann. Surg.* 255(6), 1171–1178 (2012).
- Scholten A, Schreinemakers JM, Pieterman CR, Valk GD, Vriens MR, Borel Rinkes IH. Evolution of surgical treatment of primary hyperparathyroidism in patients with multiple endocrine neoplasia type 2A. *Endocr. Pract.* 17(1), 7–15 (2011).
- Alevizaki M, Saltiki K. Primary hyperparathyroidism in MEN2 syndromes. *Recent Results Cancer Res.* 204 179–186 (2015).
- Bradley KJ, Cavaco BM, Bowl MR *et al.* Parafibromin mutations in hereditary hyperparathyroidism syndromes and parathyroid tumours. *Clin. Endocrinol.* 64(3), 299–306 (2006).
- Newey PJ, Bowl MR, Thakker RV. Parafibromin-functional insights. *J. Intern. Med.* 266(1), 84–98 (2009).
- Jackson MA, Rich TA, Hu MI, Perrier ND, Waguespack. CDC73-Related Disorders. In: *GeneReviews® [Internet]*. University of Washington, WA, USA (2008).
- Shattuck TM, Valimaki S, Obara T *et al.* Somatic and germ-line mutations of the HRPT2 gene in sporadic parathyroid carcinoma. *N. Engl. J. Med.* 349(18), 1722–1729 (2003).
- Demonstrates the role of somatic and germline CDC73/HRPT2 mutations in the pathogenesis of seemingly sporadic parathyroid cancer.
- Cetani F, Pardi E, Borsari S *et al.* Genetic analyses of the HRPT2 gene in primary hyperparathyroidism: germline and somatic mutations in familial and sporadic parathyroid tumors. *J. Clin. Endocrinol. Metab.* 89(11), 5583–5591 (2004).
- Wei CH, Harari A. Parathyroid carcinoma: update and guidelines for management. *Curr. Treat. Options Oncol.* 13(1), 11–23 (2012).
- Jumpertz Von Schwartzberg R, Elbelt U, Ventz M *et al.* Palliative treatment of uncontrollable hypercalcemia due to parathyrototoxicosis: denosumab as rescue therapy. *Endocrinol. Diabetes Metab. Case Rep.* 2015, 150082 (2015).
- Betea D, Potorac I, Beckers A. Parathyroid carcinoma: challenges in diagnosis and treatment. *Ann. Endocrinol. (Paris)* 76(2), 169–177 (2015).
- Young S, Wu JX, Li N, Yeh MW, Livhits MJ. More extensive surgery may not improve survival over parathyroidectomy alone in parathyroid carcinoma. *Ann. Surg. Oncol.* 23(9), 2898–2904 (2016).
- Asare EA, Sturgeon C, Winchester DJ *et al.* Parathyroid carcinoma: an update on treatment outcomes and prognostic factors from the National Cancer Data Base (NCDB). *Ann. Surg. Oncol.* 22(12), 3990–3995 (2015).
- Basceken SI, Genc V, Ersoz S, Sevim Y, Celik SU, Bayram IK. Is local resection sufficient for parathyroid carcinoma? *Clinics (Sao Paulo, Brazil)* 70(4), 247–249 (2015).
- Mehta A, Patel D, Rosenberg A *et al.* Hyperparathyroidism-jaw tumor syndrome: results of operative management. *Surgery* 156(6), 1315–1324, discussion 1324–1315 (2014).
- Schulte KM, Talat N, Galata G *et al.* Oncologic resection achieving R0 margins improves disease-free survival in parathyroid cancer. *Ann. Surg. Oncol.* 21(6), 1891–1897 (2014).
- Lee PK, Jarosek SL, Virnig BA, Evasovich M, Tuttle TM. Trends in the incidence and treatment of parathyroid cancer in the United States. *Cancer* 109(9), 1736–1741 (2007).
- Harari A, Waring A, Fernandez-Ranvier G *et al.* Parathyroid carcinoma: a 43-year outcome and survival analysis. *J. Clin. Endocrinol. Metab.* 96(12), 3679–3686 (2011).
- Thompson SD, Prichard AJ. The management of parathyroid carcinoma. *Curr. Opin. Otolaryngol. Head Neck Surg.* 12(2), 93–97 (2004).
- Wang L, Han D, Chen W *et al.* Non-functional parathyroid carcinoma: a case report and review of the literature. *Cancer Biol. Ther.* 16(11), 1569–1576 (2015).
- Rodriguez M, Goodman WG, Liakopoulos V, Messa P, Wiecek A, Cunningham J. The use of calcimimetics for the treatment of secondary hyperparathyroidism: a 10-year evidence review. *Semin. Dial.* 28(5), 497–507 (2015).
- Silverberg SJ, Rubin MR, Faiman C *et al.* Cinacalcet hydrochloride reduces the serum calcium concentration in inoperable parathyroid carcinoma. *J. Clin. Endocrinol. Metab.* 92(10), 3803–3808 (2007).
- Nadarasa K, Bailey M, Chahal H *et al.* The use of cinacalcet in pregnancy to treat a complex case of parathyroid carcinoma. *Endocrinol. Diabetes Metab. Case Rep.* 2014 140056 (2014).
- Boquete-Castro A, Gomez-Moreno G, Calvo-Guirado JL, Aguilar-Salvatierra A, Delgado-Ruiz RA. Denosumab and osteonecrosis of the jaw. A systematic analysis of events reported in clinical trials. *Clin. Oral Implants Res.* 27(3), 367–375 (2016).
- Nadarasa K, Theodoraki A, Kurzwinski TR *et al.* Denosumab for management of refractory hypercalcaemia in recurrent parathyroid carcinoma. *Eur. J. Endocrinol.* 171(3), L7–L8 (2014).
- Fountas A, Andrikoula M, Giotaki Z *et al.* The emerging role of denosumab in the long-term management of parathyroid carcinoma-related refractory hypercalcemia. *Endocr. Pract.* 21(5), 468–473 (2015).
- Karuppiah D, Thanabalasingham G, Shine B *et al.* Refractory hypercalcaemia secondary to parathyroid carcinoma: response to high-dose denosumab. *Eur. J. Endocrinol.* 171(1), K1–K5 (2014).
- Bowyer SE, White AM, Ransom DT, Davidson JA. Resistant hypercalcaemia in metastatic parathyroid carcinoma. *Med. J. Aust.* 198(10), 559–561 (2013).
- Vellanki P, Lange K, Elaraj D, Kopp PA, El Muayed M. Denosumab for management of parathyroid carcinoma-mediated hypercalcemia. *J. Clin. Endocrinol. Metab.* 99(2), 387–390 (2014).

- 30 Baretic M. Is denosumab a long-term option for the treatment of parathyroid carcinoma? *QJM* 109(4), 288 (2016).
- 31 Busaidy NL, Jimenez C, Habra MA *et al.* Parathyroid carcinoma: a 22-year experience. *Head Neck*. 26(8), 716–726 (2004).
- 32 Ybarra J, Moises J, Torregrosa JV, Madhun ZT, Schumacher OP. Effects of octreotide on serum and urine electrolytes in a patient with parathyroid carcinoma: clinical case. *Nefrologia* 21(4), 406–410 (2001).
- 33 Horie I, Ando T, Inokuchi N *et al.* First Japanese patient treated with parathyroid hormone peptide immunization for refractory hypercalcemia caused by metastatic parathyroid carcinoma. *Endocr. J.* 57(4), 287–292 (2010).
- 34 Betea D, Bradwell AR, Harvey TC *et al.* Hormonal and biochemical normalization and tumor shrinkage induced by anti-parathyroid hormone immunotherapy in a patient with metastatic parathyroid carcinoma. *J. Clin. Endocrinol. Metab.* 89(7), 3413–3420 (2004).
- 35 Goswamy J, Lei M, Simo R. Parathyroid carcinoma. *Curr. Opin. Otolaryngol. Head Neck Surg.* 24(2), 155–162 (2016).
- 36 Munson ND, Foote RL, Northcutt RC *et al.* Parathyroid carcinoma: is there a role for adjuvant radiation therapy? *Cancer* 98(11), 2378–2384 (2003).
- 37 Erovic BM, Goldstein DP, Kim D *et al.* Parathyroid cancer: outcome analysis of 16 patients treated at the Princess Margaret Hospital. *Head Neck* 35(1), 35–39 (2013).
- 38 Artinyan A, Guzman E, Maghami E *et al.* Metastatic parathyroid carcinoma to the liver treated with radiofrequency ablation and transcatheter arterial embolization. *J. Clin. Oncol.* 26(24), 4039–4041 (2008).
- 39 Tochio M, Takaki H, Yamakado K *et al.* A case report of 20 lung radiofrequency ablation sessions for 50 lung metastases from parathyroid carcinoma causing hyperparathyroidism. *Cardiovasc. Intervent. Radiol.* 33(3), 657–659 (2010).
- 40 Dasgupta R, Shetty S, Keshava SN, Gupta M, Paul MJ, Thomas N. Metastatic parathyroid carcinoma treated with radiofrequency ablation: a novel therapeutic modality. *Australas. Med. J.* 7(9), 372–375 (2014).
- 41 Azar FK, Lee SL, Rosen JE. Medullary thyroid cancer: an update for surgeons. *Am. Surg.* 81(1), 1–8 (2015).
- 42 Wells SA Jr, Asa SL, Dralle H *et al.* Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid* 25(6), 567–610 (2015).
- **Valuable compilation of evidence-based recommendations to assist in the care of patients with sporadic and hereditary medullary thyroid carcinoma.**
- 43 Thosani S, Ayala-Ramirez M, Palmer L *et al.* The characterization of pheochromocytoma and its impact on overall survival in multiple endocrine neoplasia type 2. *J. Clin. Endocrinol. Metab.* 98(11), E1813–E1819 (2013).
- 44 Prazeres H, Torres J, Rodrigues F *et al.* How to treat a signal? Current basis for RET-genotype-oriented choice of kinase inhibitors for the treatment of medullary thyroid cancer. *J. Thyroid. Res.* 2011 678357 (2011).
- 45 Machens A, Dralle H. Biomarker-based risk stratification for previously untreated medullary thyroid cancer. *J. Clin. Endocrinol. Metab.* 95(6), 2655–2663 (2010).
- 46 Niederle B, Sebag F, Brauckhoff M. Timing and extent of thyroid surgery for gene carriers of hereditary C cell disease – a consensus statement of the European Society of Endocrine Surgeons (ESES). *Langenbecks Arch. Surg.* 399(2), 185–197 (2014).
- 47 Hadoux J, Pacini F, Tuttle RM, Schlumberger M. Management of advanced medullary thyroid cancer. *Lancet Diabetes Endocrinol.* 4(1), 64–71 (2016).
- 48 Machens A, Dralle H. Surgical treatment of medullary thyroid cancer. *Recent Results Cancer Res.* 204, 187–205 (2015).
- 49 Rowland KJ, Moley JF. Hereditary thyroid cancer syndromes and genetic testing. *J. Surg. Oncol.* 111(1), 51–60 (2015).
- 50 Bowen A, Mani N, Penney S, Loughran S, Yap B. Surgical management of medullary thyroid cancer: which guidelines should we follow? *J. Laryngol. Otol.* 129(5), 478–483 (2015).
- 51 Dralle H, Machens A. Surgical management of the lateral neck compartment for metastatic thyroid cancer. *Curr. Opin. Oncol.* 25(1), 20–26 (2013).
- 52 Kunz PL, Reidy-Lagunes D, Anthony LB *et al.* Consensus guidelines for the management and treatment of neuroendocrine tumors. *Pancreas* 42(4), 557–577 (2013).
- 53 Wells SA Jr, Robinson BG, Gagel RF *et al.* Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind Phase III trial. *J. Clin. Oncol.* 30(2), 134–141 (2012).
- 54 Elisei R, Schlumberger MJ, Muller SP *et al.* Cabozantinib in progressive medullary thyroid cancer. *J. Clin. Oncol.* 31(29), 3639–3646 (2013).
- 55 Tsang VH, Robinson BG, Learoyd DL. The safety of vandetanib for the treatment of thyroid cancer. *Expert Opin. Drug Saf.* 15(8), 1107–1113 (2016).
- 56 Bible KC, Ryder M. Evolving molecularly targeted therapies for advanced-stage thyroid cancers. *Nat. Rev. Clin. Oncol.* 13(7), 403–416 (2016).
- **Valuable review of molecularly targeted therapies for advanced thyroid cancers including medullary thyroid cancer.**
- 57 Kurzrock R, Sherman SI, Ball DW *et al.* Activity of XL184 (cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. *J. Clin. Oncol.* 29(19), 2660–2666 (2011).
- 58 Gild ML, Bullock M, Pon CK, Robinson BG, Clifton-Bligh RJ. Destabilizing RET in targeted treatment of thyroid cancers. *Endocr. Connect.* 5(1), 10–19 (2016).
- 59 Schneider TC, De Wit D, Links TP *et al.* Beneficial effects of the mTOR inhibitor everolimus in patients with advanced medullary thyroid carcinoma: subgroup results of a Phase II trial. *Int. J. Endocrinol.* 2015 348124 (2015).
- 60 Call JA, Caudill JS, Mciver B, Foote RL. A role for radiotherapy in the management of advanced medullary thyroid carcinoma: the Mayo Clinic experience. *Rare Tumors* 5(3), e37 (2013).
- 61 Martinez SR, Beal SH, Chen A, Chen SL, Schneider PD. Adjuvant external beam radiation for medullary thyroid carcinoma. *J. Surg. Oncol.* 102(2), 175–178 (2010).
- 62 Iten F, Muller B, Schindler C *et al.* Response to [90Yttrium-DOTA]-TOC treatment is associated with long-term survival benefit in metastasized medullary thyroid cancer: a Phase II clinical trial. *Clin. Cancer Res.* 13(22 Pt 1), 6696–6702 (2007).
- 63 Makis W, Mccann K, Mcewan AJ. Medullary thyroid carcinoma (MTC) treated with 177Lu-DOTATATE PRRT: a report of two cases. *Clin. Nucl. Med.* 40(5), 408–412 (2015).
- 64 Vaisman F, De Castro PH, Lopes FP *et al.* Is there a role for peptide receptor radionuclide therapy in medullary thyroid cancer? *Clin. Nucl. Med.* 40(2), 123–127 (2015).
- 65 Castellani MR, Seregini E, Maccauro M *et al.* MIBG for diagnosis and therapy of medullary thyroid carcinoma: is there still a role? *QJ. Nucl. Med. Mol. Imaging.* 52(4), 430–440 (2008).
- 66 Al-Salameh A, Baudry C, Gautier JF, Toubert ME, Bihan H, Cohen R. Late liver metastasis of medullary thyroid cancer with low

- calcitonin levels – successfully cured by radiofrequency. *Endokrynol Pol.* 67(3), 326–329 (2016).
- 67 Marx SJ, Agarwal SK, Kester MB *et al.* Multiple endocrine neoplasia type 1: clinical and genetic features of the hereditary endocrine neoplasias. *Recent Prog. Horm. Res.* 54, 397–438, discussion 438–399 (1999).
- 68 Chandrasekharappa SC, Guru SC, Manickam P *et al.* Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science* 276(5311), 404–407 (1997).
- 69 Vinik A, Casellini C, Perry RR, Feliberti E, Vingan H. Diagnosis and management of Pancreatic Neuroendocrine Tumors (PNETS). In: *Endotext*. De Groot LJ, Beck-Peccoz P, Chrousos G *et al.* (Eds). MDText.com, Inc. MA, USA (2000).
- 70 Sadowski SM, Triponez F. Management of pancreatic neuroendocrine tumors in patients with MEN 1. *Gland Surg.* 4(1), 63–68 (2015).
- 71 Yates CJ, Newey PJ, Thakker RV. Challenges and controversies in management of pancreatic neuroendocrine tumours in patients with MEN1. *Lancet Diabetes Endocrinol.* 3(11), 895–905 (2015).
- 72 Folkert IW, Hernandez P, Roses RE. Multidisciplinary management of nonfunctional neuroendocrine tumor of the pancreas. *World J. Gastroenterol.* 22(11), 3105–3116 (2016).
- 73 Paniccia A, Edil BH, Schulick RD. Pancreatic neuroendocrine tumors: an update. *Indian J. Surg.* 77(5), 395–402 (2015).
- 74 Oditura M, Petrillo A, Ventriglia J *et al.* Pancreatic neuroendocrine tumors: nosography, management and treatment. *Int. J. Surg.* 28(Suppl. 1), S156–S162 (2016).
- 75 Li Y, Simonds WF. Endocrine neoplasms in familial syndromes of hyperparathyroidism. *Endocr. Relat. Cancer* 23(6), R229–R247 (2015).
- 76 Ito T, Igarashi H, Uehara H, Berna MJ, Jensen RT. Causes of death and prognostic factors in multiple endocrine neoplasia type 1: a prospective study: comparison of 106 MEN1/Zollinger-Ellison syndrome patients with 1613 literature MEN1 patients with or without pancreatic endocrine tumors. *Medicine (Baltimore)* 92(3), 135–181 (2013).
- 77 Goudet P, Murat A, Binquet C *et al.* Risk factors and causes of death in MEN1 disease. A GTE (Groupe d'Etude des Tumeurs Endocrines) cohort study among 758 patients. *World J. Surg.* 34(2), 249–255 (2010).
- **A comprehensive analysis of the risk factors and causes of death in a large cohort of multiple endocrine neoplasia type 1 (MEN1) patients from Europe.**
- 78 Jensen RT, Berna MJ, Bingham DB, Norton JA. Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies. *Cancer* 113(Suppl. 7), 1807–1843 (2008).
- 79 Sugimoto M, Takagi T, Hikichi T *et al.* Efficacy of endoscopic ultrasonography-guided fine needle aspiration for pancreatic neuroendocrine tumor grading. *World J. Gastroenterol.* 21(26), 8118–8124 (2015).
- 80 Ito T, Hijioka S, Masui T *et al.* Advances in the diagnosis and treatment of pancreatic neuroendocrine neoplasms in Japan. *J. Gastroenterol.* 52(1), 9–18 (2016).
- 81 Vezzosi D, Cardot-Bauters C, Bouscaren N *et al.* Long-term results of the surgical management of insulinoma patients with MEN1: a Groupe d'étude des Tumeurs Endocrines (GTE) retrospective study. *Eur. J. Endocrinol.* 172(3), 309–319 (2015).
- 82 Bartsch DK, Albers M, Knoop R, Kann PH, Fendrich V, Waldmann J. Enucleation and limited pancreatic resection provide long-term cure for insulinoma in multiple endocrine neoplasia type 1. *Neuroendocrinology* 98(4), 290–298 (2013).
- 83 Harper S, Harrison B. First surgery for pancreatic neuroendocrine tumours in a patient with MEN1: enucleation versus disease-modifying surgery. *Clin. Endocrinol.* 83(5), 618–621 (2015).
- 84 Fernandez Ranvier GG, Shouhed D, Inabnet WB 3rd. Minimally invasive techniques for resection of pancreatic neuroendocrine tumors. *Surg. Oncol. Clin. N. Am.* 25(1), 195–215 (2016).
- 85 Tonelli F. How to follow-up and when to operate asymptomatic pancreatic neuroendocrine tumors in multiple endocrine neoplasia type 1? *J. Clin. Gastroenterol.* 48(5), 387–389 (2014).
- 86 Imamura M. Recent standardization of treatment strategy for pancreatic neuroendocrine tumors. *World J. Gastroenterol.* 16(36), 4519–4525 (2010).
- 87 Machado MC. Surgical treatment of pancreatic endocrine tumors in multiple endocrine neoplasia type 1. *Clinics (Sao Paulo, Brazil)* 67(Suppl. 1), 145–148 (2012).
- 88 Partelli S, Tamburrino D, Lopez C *et al.* Active surveillance versus surgery of nonfunctioning pancreatic neuroendocrine neoplasms ≤2 cm in MEN1 patients. *Neuroendocrinology* 103(6), 779–86 (2016).
- 89 Keutgen XM, Nilubol N, Glanville J *et al.* Resection of primary tumor site is associated with prolonged survival in metastatic nonfunctioning pancreatic neuroendocrine tumors. *Surgery* 159(1), 311–319 (2016).
- 90 Raymond E, Dahan L, Raoul JL *et al.* Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N. Engl. J. Med.* 364(6), 501–513 (2011).
- **A large double-blind, placebo-controlled trial demonstrating the efficacy of the tyrosine kinase inhibitor sunitinib in patients with advanced pancreatic neuroendocrine tumors.**
- 91 Yao JC, Shah MH, Ito T *et al.* Everolimus for advanced pancreatic neuroendocrine tumors. *N. Engl. J. Med.* 364(6), 514–523 (2011).
- 92 Chan JA, Kulke MH. Medical management of pancreatic neuroendocrine tumors: current and future therapy. *Surg. Oncol. Clin. N. Am.* 25(2), 423–437 (2016).
- 93 Berardi R, Morgese F, Torniai M *et al.* Medical treatment for gastro-entero-pancreatic neuroendocrine tumours. *World J. Gastrointest. Oncol.* 8(4), 389–401 (2016).
- 94 De Divitiis C, Von Arx C, Grimaldi AM *et al.* Metronomic temozolomide as second line treatment for metastatic poorly differentiated pancreatic neuroendocrine carcinoma. *J. Transl. Med.* 14(1), 113 (2016).
- 95 Kesavan M, Turner JH. Myelotoxicity of peptide receptor radionuclide therapy of neuroendocrine tumors: a decade of experience. *Cancer Biother. Radiopharm.* 31(6), 189–198 (2016).
- 96 Armellini E, Crino SF, Ballare M, Pallio S, Occhipinti P. Endoscopic ultrasound-guided ethanol ablation of pancreatic neuroendocrine tumours: a case study and literature review. *World J. Gastrointest. Endosc.* 8(3), 192–197 (2016).
- 97 Matsumoto K, Kato H, Tsutsumi K *et al.* Efficacy and safety of endoscopic ultrasound-guided ethanol ablation therapy for pancreatic neuroendocrine tumors. *Acta medica Okayama* 70(4), 313–316 (2016).
- 98 Papamichail M, Ali A, Pizani M, Peddu P, Karani J, Heaton N. Irreversible electroporation for the treatment of pancreatic neuroendocrine tumors. *Korean J. Hepatobiliary Pancreat. Surg.* 20(3), 116–120 (2016).
- 99 Mayo SC, De Jong MC, Bloomston M *et al.* Surgery versus intra-arterial therapy for neuroendocrine liver metastasis: a multicenter international analysis. *Ann. Surg. Oncol.* 18(13), 3657–3665 (2011).

- 100 Loree JM, Hiruki T, Kennecke HF. Case report of cirrhosis following Yttrium-90 radioembolization for pancreatic neuroendocrine liver metastases. *Case Rep. Oncol.* 9(1), 76–82 (2016).
- 101 De Laat JM, Pieterman CR, Van Den Broek MF *et al.* Natural course and survival of neuroendocrine tumors of thymus and lung in MEN1 patients. *J. Clin. Endocrinol. Metab.* 99(9), 3325–3333 (2014).
- **Large natural history study of thymic and bronchial carcinoids in patients with MEN1.**
- 102 Giusti F, Marini F, Brandi ML. Multiple endocrine neoplasia type 1. In: *GeneReviews(R)*. Pagon RA, Adam MP, Ardinger HH *et al.* (Eds). University of Washington, WA, USA (1993).
- 103 Singh ON, Thompson GB, Nichols FC 3rd, Cassivi SD, Young WF Jr. Thymic and bronchial carcinoid tumors in multiple endocrine neoplasia type 1: the Mayo Clinic experience from 1977 to 2013. *Horm. Cancer* 6(5–6), 247–253 (2015).
- 104 Thomas De Montpreville V, Ghigna MR, Lacroix L *et al.* Thymic carcinomas: clinicopathologic study of 37 cases from a single institution. *Virchows Arch.* 462(3), 307–313 (2013).
- 105 Otake Y, Aoki M, Nakanishi T, Hashimoto K. Atypical carcinoid of thymus associated with multiple endocrine neoplasia syndrome type 1. *Gen. Thorac. Cardiovasc. Surg.* 58(10), 534–537 (2010).
- 106 Gouder P, Murat A, Cardot-Bauters C *et al.* Thymic neuroendocrine tumors in multiple endocrine neoplasia type 1: a comparative study on 21 cases among a series of 761 MEN1 from the GTE (Groupe des Tumeurs Endocrines). *World J. Surg.* 33(6), 1197–1207 (2009).
- **Cross-sectional study of the features of thymic carcinoids in a large cohort of MEN1 patients in Europe.**
- 107 Gibril F, Chen YJ, Schrupp DS *et al.* Prospective study of thymic carcinoids in patients with multiple endocrine neoplasia type 1. *J. Clin. Endocrinol. Metab.* 88(3), 1066–1081 (2003).
- 108 Recuero Diaz JL, Embun Flor R, Menal Munoz P, Hernandez Ferrandez J, Arraras Martinez MJ, Rivas De Andres JJ. Thymic carcinoid associated with multiple endocrine neoplasia syndrome type I. *Arch. Bronconeumol.* 49(3), 122–125 (2013).
- 109 Altemir Trallero J, Armengod Grao L, Aguillo Gutierrez E, Cabrejas Gomez C, Ocon Breton J, Garcia Garcia B. Thymic carcinoid in the setting of a multiple endocrine neoplasia syndrome (MEN 1). Prophylactic thymectomy? *Endocrinol. Nutr.* 59(2), 142–144 (2012).
- 110 Burgess JR, Giles N, Shepherd JJ. Malignant thymic carcinoid is not prevented by transcervical thymectomy in multiple endocrine neoplasia type 1. *Clin. Endocrinol.* 55(5), 689–693 (2001).
- 111 Powell AC, Alexander HR, Pingpank JF *et al.* The utility of routine transcervical thymectomy for multiple endocrine neoplasia 1-related hyperparathyroidism. *Surgery* 144(6), 878–883, discussion 883–874 (2008).
- 112 Dham A, Truskinovsky AM, Dudek AZ. Thymic carcinoid responds to neoadjuvant therapy with sunitinib and octreotide: a case report. *J. Thorac. Oncol.* 3(1), 94–97 (2008).
- 113 Filosso PL, Yao X, Ahmad U *et al.* Outcome of primary neuroendocrine tumors of the thymus: a joint analysis of the International Thymic Malignancy Interest Group and the European Society of Thoracic Surgeons databases. *J. Thorac. Cardiovasc. Surg.* 149(1), 103e102–109e102 (2015).
- 114 Crona J, Bjorklund P, Welin S, Kozlovacki G, Oberg K, Granberg D. Treatment, prognostic markers and survival in thymic neuroendocrine tumours. a study from a single tertiary referral centre. *Lung Cancer.* 79(3), 289–293 (2013).
- 115 Van Essen M, Krenning EP, Bakker WH, De Herder WW, Van Aken MO, Kwekkeboom DJ. Peptide receptor radionuclide therapy with ¹⁷⁷Lu-octreotate in patients with foregut carcinoid tumours of bronchial, gastric and thymic origin. *Eur. J. Nucl. Med. Mol. Imaging* 34(8), 1219–1227 (2007).