THEMATIC REVIEW

HEREDITARY ENDOCRINE TUMOURS: CURRENT STATE-OF-THE-ART AND RESEARCH OPPORTUNITIES

New and future perspectives for parathyroid carcinoma

Nancy D Perrier[1], Andrew Arnold[2], Jessica Costa-Guda[3], Naifa L Busaidy[4], Ha Nguyen[5], Hubert H Chuang[6] and **Maria Luisa Brandi[7]**

[1]Department of Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas, USA
[2]Center for Molecular Oncology and Division of Endocrinology & Metabolism, University of Connecticut School of Medicine, Farmington, Connecticut, USA
[3]Center for Regenerative Medicine & Skeletal Development, Center for Molecular Oncology, University of Connecticut School of Medicine/Dental Medicine, Farmington, Connecticut, USA
[4]Department of Endocrine Neoplasia & Hormonal Disorders, University of Texas MD Anderson Cancer Center, Houston, Texas, USA
[5]Department of Medicine-Endocrinology, Baylor College of Medicine, Houston, Texas, USA
[6]Department of Nuclear Medicine, University of Texas MD Anderson Cancer Center, Houston, Texas, USA
[7]Department of Endocrinology, University of Florence, Medical School, Florence, Italy

Correspondence should be addressed to N D Perrier: NPerrier@mdanderson.org

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Abstract

This report summarizes published data on parathyroid cancer, with the inclusion of topics discussed at MEN2019: 16th International Workshop on Multiple Endocrine Neoplasia, 27–29 March 2019, Houston, TX, USA. An expert panel on parathyroid cancer was constituted by the Steering Committee to address key questions in the field. The objectives were to recap open forum discussion of interested parties from multiple disciplines. The expert panel met in a closed session to consult on the data to be highlighted on the evidence-based results and on the future directions. Preceding the Conference, members of the expert panel conducted an extensive literature search. All presentations were based upon the best peer-reviewed information taking into account the historical and current literature. Questions were developed by the expert panel on parathyroid carcinoma. A comprehensive literature search for relevant studies was undertaken. This report represents the expert panel's synthesis of the conference material placed in a context designed to be relevant to clinicians and those engaged in cutting-edge studies of parathyroid carcinoma. This document not only provides a summary of our current knowledge but also places recent advances in its management into a context that should enhance future advances in our understanding of parathyroid carcinoma.

Key Words

- hyperparathyroidism
- parathyroid carcinoma
- hyperparathyroidism-jaw tumor syndrome
- CDC73/HRPT2 gene
- surgery of parathyroid carcinoma

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Introduction

Because parathyroid disease is a critical part of several endocrine syndromes and the carcinomatous process does have genetic predisposition, it was believed to be an important aspect of the 16th International Workshop on Multiple Endocrine Neoplasia (MEN2019), whose main focus was on malignancy in hereditary endocrine tumor syndromes.

Parathyroid carcinoma (PC), first described by Sainton & Millot (1933), is a rare malignant neoplasm involving the parathyroid gland and one of the rarest causes of primary hyperparathyroidism (PHPT) (~1%), with the tendency to present with more severe symptoms of hypercalcemia than its benign counterparts (adenomas and hyperplasia) (Lee *et al.* 2007, Fraser 2009). PC is the least common endocrine cancer worldwide; however, there have been reports of higher incidence of PC in different parts of the world in the last few decades (Lee *et al.* 2007, Brown *et al.* 2011, Ryhanen *et al.* 2017, Machado & Wilhelm 2019). Possible explanation for this increased incidence of the PC could be improvement in diagnosis, increased screening and referrals to parathyroid surgery centers or true increase in disease incidence.

PC can be sporadic or familial. The familial form is known as hyperparathyroidism-jaw tumor (HPT-JT) syndrome (OMIM# 145001), a cancer syndrome whose features include PHPT, resulting from parathyroid tumors (typical, adenoma, atypical adenoma or carcinoma (in 10–15% of cases)), fibro-osseous jaw tumors, and/or tumors in uterus and kidney (Li & Simonds 2016). HPT-JT syndrome was originally linked to germline mutations of the tumor suppressor gene *CDC73* (formerly known as *HRPT2*) (Carpten *et al.* 2002, Newey *et al.* 2010). Further, mutation of *CDC73* is the most frequent pathogenic molecular defect in sporadic PC, found in roughly 40–75% of cases, although the percentage of mutation-positive tumors has varied widely across studies, with 9–100% harboring at least one mutant allele (Howell *et al.* 2003, Shattuck *et al.* 2003, Pandya *et al.* 2017, Brewer *et al.* 2019, Clarke *et al.* 2019, Cui *et al.* 2019). Factors potentially contributing to this variability include small sample sizes, non-uniform clinical/pathologic case selection criteria, inclusion of lower-quality DNA from formalin-fixed paraffin-embedded tissues in some studies, and NGS bioinformatics filtering protocols that could miss many inactivating mutations. Of particular significance for clinical DNA testing, about one quarter of seemingly sporadic PC harbor germline mutations in the *CDC73* gene (Shattuck *et al.* 2003, Pandya *et al.* 2017, Brewer *et al.* 2019, Clarke *et al.* 2019, Cui *et al.* 2019). Consistent with a classic two-hit tumor suppressor mechanism, biallelic inactivation of *CDC73* is often detectable, with roughly half of this subset exhibiting intragenic, inactivating mutations of the second allele and the other half containing large deletions involving the whole gene. Only rarely has PC been seen in the context of other familial endocrine syndromes, as multiple endocrine neoplasia type 1 (MEN1) and multiple endocrine neoplasia syndrome type 2 (Christakis *et al.* 2016, Cardoso *et al.* 2017).

Challenging aspects in the management of this malignancy include the only recent availability of preclinical models; the late diagnosis due to the lack of specific symptoms and signs (but very severe symptomatic hypercalcemia and a younger age at diagnosis), lack of specific histopathologic definition of PC and of radiological exams to be performed in follow-up, with consequent high recurrence and low survival rates in metastatic disease (Wei & Harari 2012, Lo *et al.* 2018); the limited experience in the surgical approach to PC due to the rarity of the disease; the absence of efficacious targeted pharmacological therapeutics in PC. Only with combined efforts to coalesce data will there be an ability to make an impact on the morbidity and mortality of this disease. Knowing the current shortcomings in the diagnosis and management of PC offers the opportunity to fill the gaps and to develop a strategy to solve the unsolved.

This document not only provides a summary of current knowledge about the outlined criticisms but also places advances in the field into a context that should enhance future advances in our understanding of this disorder.

Materials and methods

A panel of 25 world experts with a committed interest in parathyroid disease convened during the 16th International Workshop on Multiple Endocrine Neoplasia (MEN2019). Panel leaders pre-defined critical questions in the management of PC and an extensive literature search was performed in the selected topics. Panel leaders organized active discussions where a multidisciplinary, international group composed of patient advocacy, genetic counselors, pathologists, nuclear medicine physicians, endocrinologists and surgeons was fully engaged over a 2-day period. The experts also discussed opportunities for future growth and discovery to advance the science of parathyroid carcinoma. This summary discusses advances in pathology reporting, basic science preclinical models,

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advances in pathology and radiology in diagnosis, extent of surgical intervention, systemic therapy and future steps.

Pre-clinical models

Advances in the understanding and treatment of parathyroid carcinoma have been slowed by the dearth of preclinical models. Ideally, a preclinical model system would mimic the clinical course of recurrent and metastatic parathyroid carcinoma, allowing for (a) careful study of the biologic contributors of recurrence and metastasis and (b) testing of therapeutic interventions. The currently available model systems fall short of these goals. Several are discussed below.

Although cell culture-based models are invaluable in short-term study and can provide a cost-effective means of prioritizing further studies in more complex biologic systems, only a few parathyroid cell lines have been developed. PT-r (Sakaguchi *et al.* 1987) and its subclone PTH-C1 (Fabbri *et al.* 2014) were developed from the hyperplastic parathyroid glands of vitamin D-deficient rats. The original PT-r cells did not generally express the *Pth* gene, but certain subclones, including PTH-C1, were reported to express *Pth* and maintain some degree of calcium responsiveness (Kawahara *et al.* 2008). Similarly, a cell line developed from a PC from a patient with secondary hyperparathyroidism, Pt.Kich-1, did not maintain the ability to produce PTH or respond to calcium beyond the 6th–8th passage (Gogusev *et al.* 2015). Another cell line, sHPT-1, was developed from the hyperplastic parathyroid gland of a patient with secondary hyperparathyroidism. While PTH expression is seen in sHPT-1 cells, it is unclear if these cells are responsive to calcium (Bjorklund *et al.* 2007). No parathyroid cell line system has been widely used and validated across multiple independent research laboratories. Several groups have reported success in primary culture of parathyroid cells (Corbetta *et al.* 2002, Ritter *et al.* 2004), including from parathyroid carcinoma (Falchetti *et al.* 2005), particularly when maintained in 3D culture, but such systems have not been extensively evaluated.

Several genetically engineered mouse models (GEMMs) involving parathyroid tumor-driver genes have been developed. One such model is informed by the fact that inactivating mutations of *CDC73* and loss of expression of its encoded protein, parafibromin, are the most frequent findings in parathyroid cancer. Homozygous germline deletion of *Cdc73* is embryonic lethal by day 6.5 and initially, no parathyroid phenotype was noted (Wang *et al.* 2008). In a follow-up study, 68% of germline heterozygous *Cdc73*-knockout mice ≥18 months of age developed biochemical hyperparathyroidism and/or histologic features of parathyroid tumors. Although some tumors displayed features such as nuclear pleomorphism and/or fibrous septation, which can be suggestive of atypical parathyroid adenoma or parathyroid carcinoma in humans, the tumors did not exhibit the definitively malignant features of local invasion or distant metastasis (Walls *et al.* 2017). Similar parathyroid gland abnormalities were reported after parathyroid-targeted deletion of *Cdc73*, by crossing floxed-*Cdc73* mice (Wang *et al.* 2008) with transgenic *PTH-Cre* mice (Libutti *et al.* 2003); 58% of heterozygous and 50% of homozygous null mice ≥18 months of age were affected (Walls *et al.* 2017).

Several additional genes have been implicated in the development of parathyroid carcinoma. Somatic *CCND1* gene amplification (Zhao *et al.* 2014, Pandya *et al.* 2017) and cyclin D1 overexpression (Vasef *et al.* 1999, Zhao *et al.* 2014) are seen in approximately 41 and 82% of parathyroid carcinomas, respectively. A transgenic mouse model, harboring a *PTH-CCND1* transgene, containing the *PTH* promoter and enhancer elements juxtaposed to genomic *CCND1*, resulting in parathyroid-specific overexpression of cyclin D1, has been developed. These mice develop chronic biochemical hyperparathyroidism and parathyroid gland hypercellularity by about 8–12 months of age. However, specific features of parathyroid carcinoma have not been observed (Imanishi *et al.* 2001).

The role of *MEN1* inactivation in parathyroid carcinoma remains unclear, as only small subset of patients with parathyroid carcinoma harbor *MEN1* intragenic mutations (Haven *et al.* 2007, Enomoto *et al.* 2010, Clarke *et al.* 2019) and similarly, fewer than 1% of MEN1 patients appear to develop parathyroid carcinoma in the course of their lifetime (Di Meo *et al.* 2018). In mice, homozygous germline knockout of *Men1* is embryonic lethal; however, heterozygous knockouts develop a spectrum of tumors similar to human MEN1 syndrome, including parathyroid adenoma (Crabtree *et al.* 2001, Bertolino *et al.* 2003, Harding *et al.* 2009). Parathyroid-targeted deletion of *Men1* resulted in hypercalcemia by 7 months of age and enlarged parathyroid glands in 80% of mice over 9 months of age but histologic features suggestive of carcinoma were not described (Libutti *et al.* 2003).

Additional recurrently mutated genes reported in PC include *PIK3CA, MTOR, AKAP9, ZEB1, KDM5C, ADCK1* and *PRUNE2* (Brewer *et al.* 2019). While a number of mouse models for the study of *PIK3CA/MTOR* in cancer have

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been developed, these models are largely tissue specific and would not be expected to result in a parathyroid gland phenotype (Mitchell & Phillips 2019). Additionally, a parathyroid phenotype has not been described in mouse knockouts of *AKAP9* (Schimenti *et al.* 2013, Venkatesh *et al.* 2016), *ZEB1* (Takagi *et al.* 1998, Liu *et al.* 2008), *KDM5C* (Iwase *et al.* 2016, Scandaglia *et al.* 2017); GEMMs involving *ADCK1* or *PRUNE2* have not been reported.

To be ideally positioned to tie in work on these preclinical models with the most relevant clinical and biologic questions will require a multipronged approach and will require collaboration across institutions worldwide. Ideally, tissue from all known or suspected parathyroid carcinoma specimens would be preserved for research purposes at the time of surgery and made accessible to collaborating investigators. Fresh tumor tissue could then be used for primary culture into organoids/pseudoglands and/or patient-derived xenografts (PDX). Additional frozen and/or formalin-fixed paraffin embedded material could be utilized for next-generation sequence-based screening for relevant genetic, genomic and/or epigenetic alterations. Additional screening for genetic aberrations, and particularly for combinations of such alterations, remains a vital step in advancing our understanding of this disease. Such information can be used to aid in predicting which patients are likely to develop advanced/refractory disease and to develop GEMMs harboring combinations of genetic modifications. This information could be used to develop adjuvant therapies designed to prevent recurrence and progression. A biobank of tumor organoids and pseudoglands can be used to develop and screen for non-surgical therapeutic strategies likely to be effective against tumors harboring specific genetic alterations and combinations thereof. Promising therapies can then be further tested in PDX models.

Pathologic reporting

Since pathology details are fundamental for appropriate cancer staging and treatment, the need for a standard nomenclature to more consistently capture details of this rare disease was acknowledged. The recent creation of a global nomenclature by the International Collaboration on Cancer Reporting (ICCR) to facilitate harmonization of pathology reporting worldwide will contribute as an important step (Williams *et al.* 2019). The data elements have been defined for improved consistency in reporting across users. This initiative for universal data collection will also allow for the amalgamation of data in rare disease types to augment understanding of the clinical, pathologic, and biologic outcomes. The ICCR dataset for parathyroid neoplasia is a template that includes reporting for both parathyroid carcinoma and atypical parathyroid neoplasms. This data set includes both core elements agreed upon to be key factors for the management and/or staging along with non-core elements which may not directly impact prognosis, are not widely available, and/or are awaiting further validation. Core elements for parathyroid neoplasia require clinical information along with the surgical specimens for pathologic evaluation. Non-core elements include pre-operative biochemical evaluation and operative findings that aid in defining this disease. Pathologic elements for classifying, grading and staging parathyroid neoplasms will be documented including tumor site, size and weight, extent of tumor invasion, along with cytologic features of necrosis, mitoses, and margin status. If available, ancillary testing for parafibromin and ki67 proliferation index and other testing will be included. It is anticipated that ultimately this collective data will allow for the broader spectrum of parathyroid carcinomas to be delineated and studied and offer the chance to correlate these variables with long-term clinical outcomes. With uniform collection as the first step, the criteria for diagnosis will be subject to validation testing.

Imaging

The literature primarily consists of case reports without systematic comparison of various imaging studies. Routine cervical ultrasonography for anatomical localization can be suggestive of the diagnosis and initial sestamibi with SPECT provides functional information. Preoperative neck ultrasound may show suspicious features suggestive of PC such as infiltration, calcification, heterogeneous cystic structure, irregular borders or signs of local invasion (Sidhu *et al.* 2011, Clark *et al.* 2016). When the diagnosis of carcinoma is suspected based on clinical presentation and ultrasonographic findings, cross section imaging can be used to plan the operation. As the initial definitive diagnosis of parathyroid carcinomas is often only determined by pathologic evaluation, there is minimal use for additional functional imaging in the pre-operative setting.

Similarly, following surgical resection, surveillance for tumor recurrence is largely based upon clinical and biochemical assessments (calcium, iPTH) rather than

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stand-alone imaging findings. It was expert opinion that postoperative imaging of neck and, perhaps chest and abdomen, should be done at 3–6 months postop with biochemical laboratory evaluation. It was agreed upon that while there are no trials to prove best imaging modalities, repeat neck ultrasound and/or Sestamibi or 4D CT neck can be done in that timeframe.

The role of imaging is in localization for directed therapy with recurrent/refractory disease. Although the most commonly used and most widely available functional imaging agent for parathyroid tissue is ^{99m}Tc-sestamibi, conflicting case reports report its efficacy to identify local recurrence or distant metastases. One older but larger series reported the sensitivity of sestamibi scans in the re-operative setting at 79% (Kebebew *et al.* 2001). In particular, when biochemical evidence of recurrent disease is present, whole body planar imaging, in addition to focused views of the neck, are most helpful in evaluating for distant metastases. Although PET/CT generally improves lesion detection compared to studies with planar or SPECT/CT imaging, and provides whole body tomographic imaging, a PET/CT imaging agent equivalent to sestamibi has not been identified. ^{18}F-fluorodeoxyglucose (FDG) is a glucose analog with wide use in oncologic imaging, with only case reports of parathyroid carcinoma detection (Gardner *et al.* 2010). Research trials comparing sestamibi to 18-FDG PET should be analyzed for primary disease, surveillance, local-regional recurrence and distant disease.

Somatostatin receptor PET/CT, for example with ^{68}Ga-DOTATATE, is being more widely used for detection of neuroendocrine tumors. However, other cells and tumors express somatostatin receptors, including parathyroid tissue (Reubi *et al.* 1997). Anecdotally, there are single scans reported as falsely negative in recurrent parathyroid carcinoma but a systematic study is warranted to clarify if these scans show any added benefit compared to other studies discussed above. ^{18}F-choline PET/CT, which is an indicator of lipid synthesis, has shown promise in detecting benign parathyroid adenomas but its utility in localizing initial or recurrent parathyroid carcinoma is unknown; only case reports have shown some promise thus far (Deandreis *et al.* 2015, Morand *et al.* 2018).

Key questions that arose include should imaging recommendations for localization of local disease recurrence be different from imaging modalities suggested for distant metastatic disease? The role and timing of molecular imaging complementary to cross-sectional anatomical imaging for surveillance needs further evaluation. Expert opinion agreed that imaging without biochemical evidence of residual or recurrent disease is unlikely to show true positive findings unless it was known that the tumor had de-differentiated and is non-functional. No evidence exists with regard to timing of imaging for surveillance and with regard to treatment and administration of calcimimetics.

It was anticipated that there would be prognostic information gained with FDG. Future studies should consider PET/CT with other radiopharmaceuticals utilizing uptake of specific nuclear and cytoplasmic receptors for diagnosis and treatment. A systemic radiotherapy using radiolabeled receptor ligands (e.g. ^{177}Lutetium DOTATATE) to treat recurrent/metastatic parathyroid carcinomas has potential. Targeted therapies show a satisfying safety profile and in other neuroendocrine tumors is manageable with a low rate of grade 3–4 adverse events. However, there is no current published data on its effectiveness with parathyroid carcinoma and prospective studies on these topics would be valuable.

Extent of surgery

The mainstay of treatment for parathyroid carcinoma is surgery. There was expert opinion that there is no role for prophylactic parathyroidectomy to prevent malignancy in individuals with germline *CDC73* mutation carriers who have no manifestation of PC. In patients with germline *CDC73* mutation undergoing initial surgery for hyperparathyroidism, the recommended approach should be bilateral exploration to identify and inspect all four glands, with resection only of those that appear abnormal. Multi-gland resection is not necessary for patients at high risk with only one gland enlarged and/or clinically malignant. There was no agreement as to the benefit of unilateral parathyroid tissue clearance when operating for proven single gland disease. There was expert opinion that *en bloc* resection is the preferred operation. This requires a comprehensive excision of all gross tumor burden at the time of initial surgery with the goal to include resection of adjacent and involved structures (R0) (Cetani *et al.* 2019). This includes concomitant thyroid lobectomy and if necessary, overlying strap musculature and adjacent soft tissues removal. A functional recurrent laryngeal nerve should be left intact unless it is circumferentially involved by malignancy. There is no evidence that concomitant prophylactic lymph node dissection has disease free or survival benefit (Asare *et al.* 2019).

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Emerging therapies

Patients with locally advanced or distant metastasis parathyroid carcinoma usually undergo multiple surgical interventions and medical therapies to control hypercalcemia including antiresorptive therapies with bisphosphonate, denosumab and calcimimetic agents (Busaidy *et al.* 2004, DasGupta *et al.* 2014, Christakis *et al.* 2017, Salcuni *et al.* 2018). In patients with advanced disease, multimodality treatment rarely achieves cure. Systemic therapies, sometimes in conjunction with external beam radiation therapy and conventional chemotherapy, have failed to demonstrate efficacy (Salcuni *et al.* 2018). There is a clinical need to find more effective and durable therapeutic options to control both hormonal complications of hypercalcemia and tumor burden. Molecular profiling of PC tumors with germline testing when indicated have the potential to improve patient outcomes. Tumor genetic pathways have been studied and provided important information. That said, such studies in parathyroid carcinoma have been challenging to interpret, due to differences in case selection criteria and differences in assay and bioinformatics methodologies. Going forward, case selection criteria should be defined in detail, and best practices in next generation sequencing (NGS) methodology and interpretation should be followed. Recent studies have suggested that in addition to *CDC73*, MAPK signaling of the AKT/mTOR/PI3K pathways may be oncogenic pathways (Kasaian *et al.* 2013, Pandya *et al.* 2017, Clarke *et al.* 2019, Cui *et al.* 2019, Kang *et al.* 2019). Mutations involving PI3K or TP53 pathways have been reported in about 10–30% of PC in several genomic profiling studies in PC (Yu *et al.* 2015, Pandya *et al.* 2017, Kutahyalioglu *et al.* 2019). Recurrent genetic alterations in other genes such as *AKAP9*, *ZEB1*, *KDM5C, ADCK1,* and *PRUNE2* have been reported. Mutations in *NF1, SDHA, FAT3, TNRC6A, PTEN, KDR, TERT* promoter, *DICER1, TSC1* and *TSC2* have also been found (Yu *et al.* 2015, Pandya *et al.* 2017, Kang *et al.* 2019, Kutahyalioglu *et al.* 2019), as has amplification and overexpression of the cyclin D1 gene *CCND1* (Vasef *et al.* 1999, Zhao *et al.* 2014, Pandya *et al.* 2017) are common in parathyroid carcinoma. A number of these genes, but not all, can potentially be targeted by newer or emerging therapeutic agents.

Tyrosine kinase inhibitors (TKIs) have shown efficacy in suppressing the angiogeneic and proliferative signaling in tumorigenesis. VEGF is overexpressed in parathyroid tumors and another potential target for therapy, although this is not proven (Lazaris *et al.* 2006). Only a few case studies from various institutions have reported experience of patients with advanced PC who were given various targeted therapies cabozantinib (Kang *et al.* 2019), sorafenib (Kutahyalioglu *et al.* 2019, Rozhinskaya *et al.* 2017), lenvatinib and everolimus (Kutahyalioglu *et al.* 2019). In some of the reported cases drug selection was guided by patient-specific mutation pathways and in others multikinase antiangiogenics were given.

In a few cases, patients achieved radiographic and hormonal control with normalization of calcium while demonstrating good drug tolerability, although selection bias was likely in place. Additionally, some patients were able to stop anti-resorptive agents while on TKIs presumably from therapeutic effects on calcium and PTH levels (Kutahyalioglu *et al.* 2019). In one patient with a *TSC1* mutation, vandetanib (an anti-angiogenic drug) and everolimus (mTOR inhibitor) were initiated and disease stability was observed within two and a half months and the serum calcium levels were better controlled; later at progression, patient developed normocalcemia on lenvatinib (Kutahyalioglu *et al.* 2019). Another report of cabozantinib use in a patient with a tumor that harbored *KDR T668K* mutation. While on cabozantinib, biochemical and partial radiographic response shrinkage in one cervical lymph node was noted (Kang *et al.* 2019). Sorafenib has also shown benefits to refractory hypercalcemia and tumor control (Rozhinskaya *et al.* 2017).

Several TKIs, in addition to the anti-angiogenic properties, have been shown to inhibit bone resorption (Aleman *et al.* 2014). This impact on bone resorption in advanced PC could potentially be quite beneficial. The major contributor to poor quality of life and mortality in patients is from hypercalcemia. Different mechanisms of TKI's inhibitory effects on bone resorption have been proposed to be direct effects on osteoblasts and osteoclasts (Dewar *et al.* 2005, Sahi *et al.* 2009, Vandyke *et al.* 2010, Aleman *et al.* 2014); indirect actions via different pathways include osteoblast-derived RANKL, VEGF inhibition, PDGFR inhibition, macrophage colony-stimulating factor, SRC kinase, decrease in vitamin D-mediated intestinal calcium absorption, and altered calcium and phosphorus metabolism (Dewar *et al.* 2005, Sahi *et al.* 2009, Vandyke *et al.* 2010, Aleman *et al.* 2014). Sorafenib is such a multi-target TKI with anti-angiogenesis effect achieved by inactivating VEGFR-2, VEGFR-3, PDGFR-β, FGF receptor 1, c-Kit, Flt-3, and RET (http://hcp.nexavar-us.com/mechanism-of-action/). It is unclear whether the drug affects tumor shrinkage, directly on osteoblasts/osteoclasts or indirect pathways through bone regulatory hormones

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but use can be considered as a part of hypercalcemia treatment in conjunction with established anti-resorptive or calcimimetic agents.

Other agents have also been investigated in PC. One notable case in particular is a single patient with metastatic PC whose tumor harbored high O6-methylguanine DNA methyltransferase (MGMT) promoter methylation status was reported to achieve long-term remission for 17 years after multiple lines of treatment with surgery, radiation, zolendronic acid, cinacalcet, and temozolomide (Storvall *et al.* 2019*a*). Successful treatment in this patient could be from synergistic effects of combined therapies. However, interestingly, the tumor also had high MGMT promoter methylation which is suggestive of a low MGMT enzyme activity, a known predictor of positive temozolomide treatment response in other tumors (Thomas *et al.* 2017). High MGMT methylation status seems to be an uncommon finding in PC although additional studies are needed to investigate the role of MGMT methylation status in PC (Storvall *et al.* 2019*b*).

In the search for other therapeutic agents and the potential role immunotherapy plays in advanced PC, some recent studies have been conducted. Kang *et al.* had tested for tumor mutation burden in patients (Kang *et al.* 2019). Sixteen patients with advanced or metastatic PC had their tumors tested. The median TMB was 1.7 mutations per mega base (m/Mb). Across all cancer types, median TMB was 3.6 mutations/Mb. Three out of 16 (19%) cases were found to have high TMB (defined as greater than 20 m/Mb). Those patients with high TMB in the study had microsatellite stability and intact DNA mismatch repair. Silva and colleagues evaluated the immunophenotype of parathyroid carcinomas and found the microenvironment within the neoplasm to be immune-ignorant and immune-tolerant (immunetype II and IV), but the surrounding microenvironment to have increased programmed death ligand I and tumor-infiltrating lymphocyte expression (Silva-Figueroa *et al.* 2018). Together these studies suggest that a subset of PC patients may benefit from immunotherapy.

Additional research to better understand PC tumorigenesis and explore the use of TKI and/or immunotherapy, or other targeted therapies, is needed. Based on the limited available data, we recommend precision oncology approach utilizing comprehensive genetic and epigenetic analysis, and tumor immune profiling. The expert group felt acquired information can be used to guide targeted therapies and/or immunotherapy. In patients with no targetable mutations, multi-target TKI with anti-angiogenesis such as sorafenib/lenvatinib/cabozantinib could be considered. Patients whose tumors have high MGMT methylation status might be candidates for agents such as temozolomide. Patients with parathyroid cancer are best discussed and treated in a multidisciplinary team approach and, ideally, in the context of clinical trials.

The expert group discussed the timing of initiation of new therapies. Whether at time of diagnosis or at time of carcinoma recurrence remains unclear or whether there was a role for adjuvant therapy. Knowledge of the risk factors associated with distant metastasis will help clinicians tailor a surveillance strategy after initial curative resection, and help identify patients at particularly high risk who might be candidates for early systemic therapy. Also, aggressive treatment of early metastasis may reduce the incidence, and mitigate the implications of hypercalcemia-associated sequelae. Finding the optimal timing and management strategy for patients with advanced, metastatic parathyroid carcinoma is a work in progress. The only level I evidence for parathyroid carcinoma was published by the AJCC in the 8th Edition of the Cancer Staging System (Landry *et al.* 2017). It noted increased risk of death with metastases (Fig. 1). Recently a single institution large database found that patients with metastatic PC have significantly decreased survival compared to those without distant metastasis, and suggested that patients with bony metastasis may have higher rates of death compared to other sites of metastases (Asare *et al.* 2015). The work confirmed

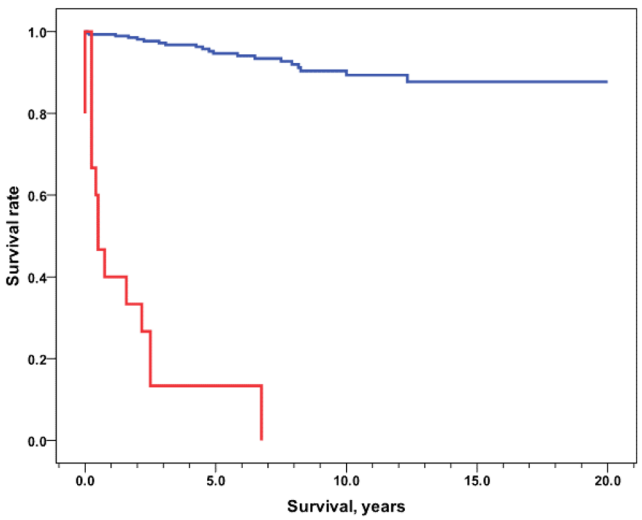

Figure 1
Cancer-specific survival comparing patients with disease localized to the neck versus patients with distant metastasis. Data was obtained from the Surveillance, Epidemiology, and End Results Program (SEER) for patients diagnosed from 1973 to 2012 (patients with multiple primary tumors excluded) (Landry *et al.* 2017).

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that continued close surveillance of patients with PC is warranted because the cumulative incidence of distant metastasis increases with time. The MD Anderson series acknowledging sample size limitations of only 75 patients, but noted in recursive partitioning analysis that patients with tumor size greater than 3.15 cm and age less than 47.5 years had the highest cumulative incidence of distant metastasis (Asare *et al.* 2015). The 5-year overall survival of 16% was noted for patients with distant metastasis compared to 87% for those without metastasis. Closer surveillance and consideration for adjuvant therapies should be considered in this cohort. Future work will seek to assess the mutational profiles of patients with PC to look for molecular predictors of metastasis and potential targets of salvage therapies.

Clinical trials

Clinical trials are a must to move the PC field forward. Given the rarity of the disease, consideration should be given for enrolling PC patients in genomically driven basket trials which include patients with certain genetic mutation in common regardless of tumor sites. Both mutational and immune profiling have important potential. The choice of targeted therapy ± immunotherapy can be driven by the findings of the precise molecular alterations based on mutation and signature of the tumor. The initial therapy should include a precision-medicine based clinical trial (CLIA lab actionable mutation) and if no mutation or particular immune signature, a standard dose of a multikinase inhibitor can be given.

Although improving overall survival (OS) is the ultimate goal for any cancer therapy, the variable, and at times long survival time in many PC patients, may prove OS to be a difficult trial endpoint in this heterogeneous and rare disease. There was much discussion as to carefully designing clinical trials and considering other cleverly designed and unique endpoints including composite endpoints of survival (hormonal and hypercalcemia-free survival, skeletal event-related free survival and other quality of life measures). The group felt that while progression free survival and OS are important measures and need to be analysed, perhaps the aforementioned composite endpoints may have more clinical meaning and prove better measures given the unique morbidities of this disease. In addition, prevention of recurrence and metastasis needs to be an endpoint in future trials begging for appropriately designed surgical, adjuvant and perhaps neoadjuvant trials in this setting.

The consolidation of databases and tumor banks internationally is a must. The group discussed that such an approach in this rare cancer will allow generation of enough data to determine best clinical trial feasible designs and whether pursuing further study is warranted in any one particular area. In addition, future work investigating cell free DNA, cell surface markers, circulating tumor cells and metabolomic biomarkers are needed. As collaborators we should be looking for opportunities to find funding for registries to link all clinical path samples, outcome and collectable data. We should also strive to utilize the rare tumor initiative at the NCI and other rare tumor consortiums that have virtual cohorts.

Patient support groups

There is a need for parathyroid cancer-specific advocacy groups to serve patients suffering from this small subset of endocrine tumors. Other support groups such as the American Cancer Society exist but have little knowledge of this rare tumor. The Neuroendocrine Tumor Research Foundation (NETRF), Carcinoid Cancer Foundation, and Thyroid Cancer Survivors' Association exist and serve as models to specifically focus on catering to the unique challenges of having a rare tumor. A specialized group can provide additional support to those whose disease course requires multidisciplinary care and complications of treatment. Deliberate attendance at conferences and networking can be accomplished to minimize redundant efforts for a broader audience with a diverse view. Web conference and communication platforms can be strategically created.

Summary

Approximately two-thirds of seemingly sporadic PC harbor somatic and/or germline mutations in the *CDC73* gene. Several additional genes have been implicated in the development of parathyroid carcinoma, for example *CCND1* gene amplification and cyclin D1 overexpression have also been noted. The recent inclusion of parathyroid carcinoma in the AJCC 8th edition and creation of a global nomenclature by the International Collaboration on Cancer Reporting (ICCR) will facilitate harmonization of pathology reporting. Since the diagnosis is confirmed pathologically the role of imaging is largely in localization for directed therapy when recurrent/refractory disease occurs. The data elements have been defined

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for improved consistency in reporting across users. Although radioisotope therapy is being used for other neuroendocrine tumors, there is no current published data on its effectiveness with parathyroid carcinoma and prospective studies on these topics would be valuable. Complete surgical extirpation remains the mainstay of treatment and there is no evidence that concomitant prophylactic lymph node dissection has disease free or survival benefit. The major contributor to poor quality of life and mortality in patients is from hypercalcemia. Therefore, therapeutic agents aimed at control of hypercalcemia including varying calcimimetic agents are first line. However, beyond that, the initial systemic therapy should include a personalized precision-medicine based clinical trial (CLIA lab actionable mutation) and if no mutation or particular immune signature, a standard dose of an antiangiogenic multikinase inhibitor can be given. The consolidation of databases and tumor banks internationally is a must. Advances in the field are to enhance future directives in our understanding of this rare and potentially fatal disorder.

Declaration of interest

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