Diagnosis and management of parathyroid carcinoma: a state-of-the-art review

Diagnosis and Management of Parathyroid Carcinoma: A State-of-the-Art Review

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Funding: National Institute for Health Research (NIHR), South London Clinical Research Network (CRN) "Green shoots" Investigator Award supported Dr Dimitriadis in the writing of this manuscript.

Short title: Parathyroid carcinoma diagnosis and management

Key words: Parathyroid carcinoma, hypercalcaemia, hyperparathyroidism, malignancy, systematic review

Word count: 8315

ABSTRACT

Parathyroid carcinoma is one of the least common endocrine malignancies, and accounts for approximately 1% of all patients with primary hyperparathyroidism. A systematic review of peer-reviewed literature published between January 2000 and March 2022 via Medline, Embase, Cochrane Central Register of Controlled Trials, EudraCT, ClinicalTrials.gov, CINAHL and SCOPUS was conducted. Manuscripts were eligible if they included data on adult non-pregnant populations with parathyroid carcinoma. No restrictions regarding interventions, comparators or duration of follow-up were imposed. Single case reports, reviews or meta-analyses were excluded. Outcomes of interest were molecular pathogenesis, clinical presentation, differential diagnosis, treatment, follow-up and overall survival. Study quality was evaluated using the Newcastle-Ottawa Scale for observational studies.

Seventy-five studies were included from 17 countries, reporting on more than 3000 patients with parathyroid carcinoma. *CDC73* mutation has been recognised as playing a pivotal role in molecular pathogenesis. Parathyroid carcinoma typically presents with markedly increased calcium and parathyroid hormone levels. The most frequently described symptoms were bone and muscle pain or weakness. *En bloc* resection remains the gold standard for the surgical approach. The five-year overall survival ranged from 60% to 93%, with resistant hypercalcaemia a significant cause of mortality. Emerging evidence indicating that targeted therapy, based on molecular biomarkers, presents a novel treatment option. The rarity of PC and need for personalised treatment warrants multidisciplinary management in a ‘centre of excellence’ with a track record in PC management.

INTRODUCTION

Parathyroid carcinoma (PC) is a rare endocrine malignancy which accounts for less than 1% of all cases of primary hyperparathyroidism (PHPT) (Ruda *et al.* 2005). The incidence of PC is increasing, probably secondary to wider routine serum calcium screening (Lee *et al.* 2007). Hypercalcaemia is caused by increased and unregulated secretion of parathyroid hormone (PTH). Compared with patients with benign parathyroid adenomas (BPA), patients with PC are more symptomatic, and present with more significantly raised calcium and PTH concentrations. PC is notable for the fact that it is challenging to diagnose, with confirmation typically only being possible post-operatively on histopathology. Certain histopathological features are suggestive of PC, but definitive diagnosis depends on the presence of invasion into surrounding tissues or distant metastasis (Lloyd *et al*. 2017). Surgery is the mainstay of initial treatment, as well as for local recurrence and distant metastases. There is a lack of data on the effectiveness and appropriate timing of radiotherapy (RT), whilst other treatment options such as chemotherapy or immunotherapy are limited (Wei & Harari, 2012). The major morbidity of PC usually results from intractable hypercalcaemia induced by inoperable recurrent or metastatic lesions. Medical treatment is for symptomatic benefit and directed at managing such hypercalcaemia. Mutation of *CDC73* has been recognised as playing an important role in molecular pathogenesis and has been associated with the predisposition to certain sporadic PCs, as well as hereditary syndromes such as hyperparathyroidism-jaw tumour syndrome (HPT-JT) (Gill 2014). Moreover, deeper understanding of the genetic landscape of PC can help determine the potential scope of new targeted therapy options.
Given the scarce data on PC, this study aims to systematically review the current evidence exploring the clinical manifestations, diagnosis and treatment of PC, and provides recommendations to aid clinicians in the assessment and management of this rare condition.

MATERIALS AND METHODS

Protocol and registration

The protocol was developed according to the *Preferred Reporting Items for Systematic review and Meta-Analysis Protocols* (PRISMA-P), and followed methods outlined in *The Cochrane Handbook for Systematic Reviews of Interventions* (Moher *et al.* 2015). This systematic review has been registered with PROSPERO (International Prospective Register of Systematic Reviews – University of York) with registration number CRD42020223157.

Eligibility criteria

Given the rarity of PC, the restrictions on the inclusion criteria were limited. Manuscripts in English, German and French, published between January 2000 and March 2022, were included for analysis. The search was conducted from 2000 onwards to ensure the most recent relevant literature was included. Single case reports, expert opinion manuscripts, letters to the editor, commentaries, conference papers, animal studies, reviews and meta-analyses were excluded, while all other articles were included. Articles were eligible if they included data on non-pregnant, adult populations with PC. No restrictions regarding type of setting, stage of disease, exposures, interventions or duration of follow-up, were imposed. Where available, comparison with benign parathyroid disease was acknowledged. Outcomes of special interest were related to molecular pathogenesis, clinical presentation, diagnosis, differential diagnosis, treatment, follow-up and overall PC survival.

Information sources and search methods

Systematic searches of the Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica (EMBASE), Cochrane Central Register of Controlled Trials (CENTRAL), European Union Drug Regulating Authorities Clinical Trials (EudraCT), ClinicalTrials.gov, Cumulative Index of Nursing and Allied Health Literature (CINAHL) and SCOPUS databases between 2000 and 2022 were conducted. The search terms included parathyroid carcinoma or neoplasm, or cancer, or malign-, and the search strategy for MEDLINE was constructed as follows: *(parathyroid[Title/Abstract]) AND ((carcinoma[Title/Abstract]) OR neoplasm[Title/Abstract]) OR cancer[Title/Abstract]) OR malign*[Title/Abstract])).* The reference lists and other literature sources were browsed to ensure literature saturation. The final search was conducted in March 2022.

Study selection and data collection process

Study selection was performed independently and in parallel by two reviewers, against the set inclusion criteria and using the systematic reviews software Covidence (Veritas Health Innovation, Melbourne, Australia; http://www.covidence.org). Title and abstract were reviewed for relevance, followed by full-text assessment. Data on the existing evidence around incidence, epidemiology and risk factors, pathogenesis and histopathology, gene expression, clinical presentation, diagnosis, differential

diagnosis, treatment options and outcomes, prognostic factors, follow-up and overall survival of PC, were extracted from the selected articles independently by the two reviewers, using Microsoft Office Excel 2019. All disagreements encountered in the process of selecting articles and extracting data were resolved by consensus or arbitration by a third reviewer, as appropriate.

Study quality

Study quality assessment was performed independently by two reviewers using the Newcastle-Ottawa Scale (NOS) for observational studies. Studies were evaluated on eight items and categorised into three groups: Selection (including whether the cohort is representative of the population), Comparability (assessed on the grounds of study design and the analysis performed) and Outcome (i.e., the assessment of outcome, follow-up rate and adequacy follow-up period). For each question there are several possible answers, using a star system to allow a semi-quantitative assessment of study quality. A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability, with between zero to nine stars attainable (Stang 2010). The scores of the articles using the NOS were translated to the *Agency for Healthcare Research and Quality* - AHRQ - standards (good, fair, and poor), using the conversion thresholds developed by the AHRQ.

Data synthesis

Heterogeneity was visually inspected but, due to high variability and insufficient data, results were not pooled into a meta-analysis. A narrative synthesis was therefore conducted instead.

RESULTS

Study selection

The search retrieved a total of 3097 studies. After removing duplicates and reviewing abstracts, 326 full-text articles were examined in detail for eligibility. The findings from 75 articles have been included in our systematic review. The Prisma flow diagram is shown in Figure 1 (Moher *et al.* 2015).

Study characteristics

Seventy-five studies were systematically reviewed. Of these, 22 studies were laboratory studies. The remaining studies were observational studies (case series, case-control and cohort studies, n=52) and one single-arm prospective study. In total, 38 studies were single-centre, 4 were multicentric and 11 used national databases. It is not possible to report the exact total number of participants with PC described in this paper, as there may be a significant overlap in patient populations given the inclusion of national databases. We report on more than 3000 patients with avoidance of possible overlapping cases through inclusion of only one database at a time when the same database was used in different studies. The sample size ranged from 2 to 1022 patients. Patients were included from 17 different countries. In 21 studies, PC findings were compared to benign disease. The studies informed on different and multiple aspects of PC management – 28 stated clinical manifestations, 42 follow-up and 29 survivorship from PC. Furthermore, 2 studies proposed and validated prognostic classification systems. Tables 2 and 3 summarise each of the selected studies looking at the period of review, setting/country, sample size, and key findings from each study.

Incidence

PC is rare, but its incidence appears to be increasing. Ryhänen *et al.* (2017) and Lo e*t al.* (2014) assessed PC incidence. The latter evaluated the *National Cancer Institute's Surveillance, Epidemiology, and End Results Program* (SEER) database which encompasses approximately 28% of the U.S population. The annual overall incidence of PC increased from 2 to 11 cases per 10 million between 1974 and 2001 and has remained stable around 10 to 13 cases per 10 million per annum since 2001. Lo *et al.* (2014) showed in a subgroup analysis of significant prognostic factors that there was a trend towards increasing incidence of tumours between 0 and 3 cm, and a trend towards increasing incidence of local versus distant disease at the time of initial operation. Likewise, in Finland, the annual incidence of PC has risen over the last decade, with 1.4 cases from 1955 to 2000 to 7.1 cases per 10

million from 2000 to 2013 (Ryhänen *et al.* 2017). A potential explanation is higher detection rates attributable to improved diagnostic methods and greater life-expectancy (Ryhänen *et al.* 2017).

PC is rare, but its incidence has increased over the last decades to 10-13 cases per 10 million per year, which could be explained by higher detection rates due to improved diagnostic methods and greater life-expectancy.

DIAGNOSTIC EVALUATION

Clinical Presentation and Complications at Diagnosis

PC presents equally in males and females (Lo *et al*. 2014, Sadler *et al*. 2014, Ryhänen *et al.* 2017), unlike BPA, which is more common in females (Iacobone *et al*. 2004). The median age of presentation was 44-65 years, with the largest study of 1022 patients having a mean age of 57 years (Sadler *et al.* 2014). No significant correlations have been shown with ethnicity, geographical area or socio-economical level in the current literature. Patients with PC most commonly present with signs and symptoms such as bone and muscle pain, neuropsychiatric symptoms, kidney stones, hypercalcaemic crisis, osteopenia/osteoporosis, pathological fractures and a palpable neck mass. Kowalski *et al.* (2022) suggest the active consideration of PC when the patient presents both renal and bone symptoms simultaneously, because dual presentation is quite rare in BPA. It should be stated that the prevalence of bone and kidney involvement in BPA depends on the definition of “bone and kidney involvement”, and that hypercalciuria or the detection of microcalcification by kidney ultrasound as well as the occurrence of osteopenia, might also occur in patients with BPA.
The clinical presentation of patients from 27 studies, including 932 patients, is summarised in Table 1. Bone manifestations were described most frequently with osteoporosis/osteopenia, fractures,and bone plus muscle pain/weakness, being present in 45.8% (n=427). Renal manifestations including kidney/urinary stones and renal failure were present in 37.2% (n=347), followed by fatigue (13.6%, n=127), a palpable neck mass (11.9%, n=111) and neuropsychiatric symptoms (11.2%, n=104). Of note, only 3% (n=28) of patients were asymptomatic. We found that studies often did not have robust clinical presentation data and many symptoms were not commented upon.

As bone manifestations were the most frequent symptoms/diseases at clinical presentation, Chen *et al.* (2003) analysed age-, gender- and race-adjusted bone mineral density (BMD), measured by dual-energy X-ray absorptiometry (DEXA) in 131 patients with PHPT, of which 20 patients had PC. They reported that the BMD of the distal one-third of the radius was significantly decreased in the PC group, compared to the BPA group. No reduction in BMD occurred in the lumbar spine, suggesting osteopenia was worse in areas rich in cortical bone for PC patients (Chen *et al*. 2003).

PC presents equally in males and females with a median age of presentation of 44-65 years. Clinical symptoms are listed according to their prevalence: bone manifestation > renal manifestation > fatigue > palpable neck mass > neuropsychiatric symptoms

Laboratory findings

PC accounts for only 1-2% of all cases of PHPT. The main laboratory findings in PC are a markedly raised corrected calcium- and PTH-levels. In a retrospective study of 131 consecutive patients with PHPT from Kobe University in Japan, 20 of whom had PC, serum levels of corrected calcium, alkaline phosphatase (ALP) and PTH were significantly higher in the malignant group when compared to the benign group (Chen *et al*. 2003). These biochemical findings are similar to those reported by Bae *et al.* (2012) in a cohort study from Seoul, South Korea, who showed an 83% sensitivity and 97% specificity for PC if ALP levels are greater than 285 IU/L. A nationwide study in Finland advises that PC should be suspected in any patient with PHPT and an ionised calcium concentration above 1.77 mmol/l (standard range 1.15-1.30 mmol/l) (Ryhänen *et al.* 2017). In a Swiss study by Robert *et al*. 2005, which looked at 311 patients with PHPT, they found no patient with PC whose PTH value was under 4-times the upper limit of normal. Absolute levels of PTH tend to be higher in PC than in BPA, but amino-PTH, an N-terminal-extended form of PTH, is overproduced in PC and very rarely seen in BPA (Cavalier *et al*. 2014). Cavalier *et al*. advocate using a $3^{rd}/2^{nd}$-generation PTH ratio which assesses for this over-production of amino-PTH, as only 3^{rd} generation PTH assays can measure amino-PTH. Values >1 of the $3^{rd}/2^{nd}$-generation PTH ratio have a sensitivity of 82% and a specificity of 97% as a marker for PC among PHPT patients. One study investigated human chorionic gonadotrophin (hCG) as a marker for PC, and found that serum malignant hyperglycosylated hCG values, although without a quoted normal range, were higher in all 8 patients with PC when compared to patients with PHPT (Rubin *et al*. 2008).

Absolute levels of PTH and ionised calcium concentrations tend to be significantly higher in PC than in BPA, and the additional use of a 3rd/2nd-generation PTH ratio can help in the detection of PC.

Molecular Pathogenesis

Multiple somatic gene defects have been found in PC samples, including mutations in *CDC73, MEN1, CDKN1B, RET, PRUNE2, ADCK1, FAT3, AKAP9, ZEB1, SDHA, TERT* promoter and *DICER1* (Pandya *et al*. 2017, Cui *et al*. 2019, Kutahyalioglu *et al*. 2019). Mutations *in* Cell Division Cycle-73 gene (*CDC73*, also known as *HRPT2*) were the most commonly implicated cause for PC and identified in 47% to 60% of PC samples (Guarnieri *et al*. 2012, Pandya *et al*. 2017, Cui *et al*. 2019). The *CDC73* gene is a tumour suppressor gene located on chromosome 1q31.2 (Guarnieri *et al*. 2012). This gene encodes parafibromin, a protein involved in the regulation of gene expression and inhibition of cell proliferation. As a result, absence of parafibromin, caused by mutations in *CDC73*, makes parathyroid tissue more prone to carcinoma formation. PC most commonly occurs as a sporadic non-syndromic disorder. However, it has been associated with hereditary conditions that cause PHPT, such as multiple endocrine neoplasia type 1 and 2 (MEN1, MEN2), autosomal dominant familial isolated hyperparathyroidism (FIHP), and hyperparathyroidism-jaw tumour syndrome (HPT-JT). HPT-JT is an autosomal dominant condition characterised by hyperparathyroidism secondary to multi-gland parathyroid neoplasia, and approximately 15% of patients with this syndrome have a risk of developing PC.

The calcium-sensing receptor (CASR) regulates synthesis and secretion of PTH and the proliferation of parathyroid glands (Witteveen *et al.* 2011). The CASR has been found to be downregulated in PC and also HPT-JT when compared to BPA (Witteveen *et al.* 2011). The study by Witteveen *et al.* (2011) of 23 patients with PC has shown CASR downregulation to be a negative prognostic indicator, with a reduced time to development of recurrence/metastasis and a lower 5-year disease-free survival. Condello *et al*. (2021) identified 144 genes that appeared to be associated with the transition from non-metastatic to metastatic PC. The researchers described the acquisition of additional genetic alterations at the late stage of PC, mainly addressing the upregulation of expression of *MMP9, ANGPTL4, BMP7, FGFR1* and *SOX2* genes, and the downregulation of expression of *ERBB3, TBX1, FBP1* and *RAB25*, being potential genes contributing to the metastatic phenotype of PC. Furthermore, the group confirmed

the deregulation of genes already associated with PC, namely *CD24, FAP, FGFR1* and *TBX1.*

PC most commonly occurs as a sporadic non-syndromic disorder but has been associated with hereditary conditions that cause PHPT, such as MEN1, MEN2, FIHP and especially HPT-JT. CDC73 mutations are the most commonly implicated cause for PC.

Imaging studies

Imaging investigation of parathyroid lesions has two different aims: 1. Localisation of the parathyroid lesion prior to surgery, and 2. Distinction of benign from malignant parathyroid lesions.

Regarding the utility of imaging for localising PC prior to surgery, neck ultrasound (US) showed 71% sensitivity with a specificity of 100% (Harari *et al.* 2011). Other imaging modalities which may be considered are 4D-computed tomography (4D-CT), ^{99m}TC Sestamibi imaging SPECT/CT (MIBI), magnetic resonance imaging (MRI) and positron emission tomography (PET)/CT with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (^{18}F-FDG). Of these, 4-DCT and MIBI scanning are most commonly used. According to Christakis *et al*. (2017), combined imaging with US, 4D-CT and MIBI has a 100% sensitivity for PC localisation, whereas imaging with only one modality has a poorer sensitivity (Lo *et al*. 2018, Christakis *et al*. 2017). The use of MRI was recommended by one study as a tool to detect recurrence and metastasis, but data supporting this remain limited (Chen *et al*. 2018).

With respect to the distinction of benign from malignant parathyroid lesions, a tumour size of 30mm (sensitivity 91%, specificity 92%) had a predictive value for the diagnosis of PC in patients with PHPT (Bae *et al*, 2012). Nonetheless, a U.S national database reported that one-third (33.8%) of PCs, in a population of 520 patients, had tumour sizes less than 30 mm (Lo *et al*. 2018). In a retrospective analysis of US features in parathyroid tumours larger than 15mm, infiltration of surrounding tissue and calcification both had a 100% positive predictive value for malignant lesions, while high negative predictive values (NPV) were found for the absence of suspicious vascularity (NPV 97.6%), thick capsule (96.7%) and inhomogeneity (100%) (Sidhu *et al.* 2011). In relation to the the severity of the disease, Calapkulu *et al.* (2021) suggested tumour volume to be a more effective parameter than tumour size.

Combined imaging with US, 4D-CT and MIBI has a 100% sensitivity for PC localisation, whereas imaging with only one modality has a much poorer sensitivity. Infiltration of surrounding tissue and

calcification both have a 100% positive predictive value for malignant lesions, while high negative predictive values (NPV) were found for the absence of suspicious vascularity (NPV 97.6%), thick capsule (96.7%) and inhomogeneity (100%)

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The differential diagnoses of raised PTH and a neck mass include PC and BPA as well as an atypical parathyroid neoplasm (APN). The management of these conditions vastly differs. Accurate assessment is therefore vital in the pre-operative phase to ensure all PCs are managed adequately. Distinguishing between the three entities is challenging, as a diagnosis cannot be based solely on clinical, biochemical or imaging findings. Several studies have demonstrated that PC presents more aggressively with larger tumours (Bae *et al.* 2012), more severe hypercalcaemia (O'Neill *et al.* 2011, Bae *et al.* 2012, Quinn *et al.* 2015) and in younger patients than BPA (Chen *et al.* 2003, Karakas *et al.* 2012, Cavalier *et al.* 2014). Moreover, PC occurs equally between genders, (Sadler *et al.* 2014), whilst BPA is more commonly found in women. Karakas *et al.* (2012) developed a logarithmic formula (Figure 2) to calculate an individual's risk of PC in those presenting with PHPT, based on preoperative serum calcium, PTH and age at diagnosis. They used their formula on 1256 patients presenting with PHPT and, by using a cut-off value of 5% for differentiation of the individual probabilities for the prediction of PC, identified all 19 patients who later were confirmed to have PC. The sensitivity of their algorithm was 100% and the specificity was 98%. While fine needle aspiration and cytology was not recommended by Talat & Schulte *et. al* (Talat & Schulte. 2010) due to fears of disrupting the tumour capsule and increasing the possibility of tumour implantation, Steen *et. al* found cytological differences between BPA and PC, with only PC showing pleomorphism with irregular and prominent nucleoli.

With regard to APN, the diagnosis remains a clinical challenge. APN has characteristics both of BPA and PC and is made through histology when parathyroid neoplasms have cytological features of PC but lack the defining characteristic of invasive growth (Christakis *et al*. 2016). Christakis *et al. (2016)* compared 54 patients with a histopathological diagnosis of PC or APN in a retrospective review, and found no significant group differences when comparing the clinical symptoms, whereas the PC group presented with significant higher PTH levels, with a 5-year disease free survival rate for PC of 59.6 % versus 90.9 % for APN. Patients with tumour recurrence in the APN group presented soft tissue invasion

in the initial histopathology report, but no other discrete features sufficient to be classified as PC. The authors concluded that a high index of clinical suspicion is needed preoperatively and intraoperatively to identify the parathyroid tumours that need oncological operations and recommend constant vigilance to identify early the rare cases that might behave in a malignant manner.

The differential diagnoses of raised PTH and a neck mass include PC and BPA as well as APN. PC presents more aggressively with larger tumours, more severe hypercalcaemia, and in younger patients than BPA, whilst BPA is more commonly found in women. The diagnosis of APN is made through histology and APN seems to have a benign course in the majority of cases, but long-term data are missing. Therefore, constant vigilance is required to identify early the rare cases that might behave in a malignant manner.

PATHOLOGY

The diagnosis of PC can only be confirmed with a detailed histopathology analysis (Talat& Schulte. 2010). The *World Health Organisation* defines the presence of infiltrative growth (capsular and soft tissue invasion) or histological proof of PC vascular invasion as the minimum criteria for diagnosing PC (Lloyd *et al*. 2017). Fine needle aspiration is not recommended as to avoid the incurable state of malignant parathyromatosis (Talat & Schulte. 2010), even though Steen *et al.* found cytological characteristics (larger nuclei with more prominent atypia) that clearly set them apart from the adenomas. Histological features of PC include uniform sheets of cells arranged in a lobulated fashion, intervening fibrous trabeculae, capsule/vascular invasion (Sali *et al.*, 2021) and the presence of mitotic figures. The presence of these findings has been assessed in an analysis of 1036 patients by Talat & Schulte (2010) who found that the presence of fibrous bands and the invasion of surrounding tissues are associated with lower recurrence and mortality rates at 5 years and overall better survival. In contrast, vascular invasion carries a 4-fold higher risk to experience death or recurrence rate at 5 years and a 2.8/2.6-fold higher risk of overall recurrence and death respectively. Capsular invasion was the most reliable marker seen in PC, being present in 84% of cases, but has no prognostic impact (Talat & Schulte. 2010). Liu *et al.* (2021) found that 57.1% (12/21) of patients with recurrent PC were diagnosed with benign

parathyroid disease prior to the recurrence of PC, reflecting the considerable uncertainty regarding the pathological diagnosis of PC.

The histological diagnosis criteria of parathyroid carcinoma have changed between 2000 and 2020 with a number of papers reporting retrospective series of patients from the 1980's. Not all the studies included into this systematic review reported on criteria for PC diagnosis. Therefore, there may have been variability in the diagnostic criteria of studies included in this systematic review, another reason why the data were not pooled into a meta-analysis as stated previously.

Diagnosis of PC can only be confirmed with a detailed histopathology analysis with capsular invasion being the most reliable marker seen in PC, whereas fine needle aspiration is not recommended to avoid malignant parathyromatosis.

IMMUNOHISTOCHEMISTRY AND MOLECULAR ANALYSIS

Immunohistochemical markers are useful in the diagnosis of PC, and there are promising new markers that are potentially useful in the early diagnosis and prognosis of PC. Parafibromin, Ki-67 proliferation index and galectin-3 have the strongest evidence base for use in PC diagnosis. Absence of parafibromin has been assessed in multiple centres and identified in 45%-68% patients with PC (Juhlin *et al*. 2007, Witteveen *et al*. 2011, Guarnieri *et al*. 2012, Wang *et al*. 2012, Erovic et al. 2012, Kumari *et al*. 2016). Parathyroid tumours with low Filamin A expression and positive parafibromin staining, on the other hand, are extremely likely to be benign ($P < 0.001$), and this shows potential as a prognostic predictor of indolent behaviour in parathyroid neoplasms. The Ki-67 proliferation index may be helpful in diagnosing PC (Wang *et al*. 2012). Wang *et al*. (2012) showed that the Ki-67 proliferation index was high in 27% of PC compared to 5% of BPA. Bergero *et al*. (2005) also recommended its use following a study of 56 patients which showed that the Ki-67 proliferation index was higher in PC than BPA (6.7% vs 1.9%). Galectin-3 is recommended by Wang *et al*. (2012), who showed Galectin-3 staining was positive in 73% of PC and 26% of BPA. Bergero *et al*. (2005) also recommended its use with their showing that Galectin 3 levels were expressed by 24 of 26 of the PC patients (92.3%), but only in one (3.3%) out of 30 patients with BPA (P <0.001). Additionally, all metastatic PCs (n=6) were Gal-3–positive. Barazeghi *et al.* (2016) suggest 5-hydroxymethylcytosine (5hmC) as a novel epigenetic marker

for the differentiation between PC and BPA, being negative in patients with PC and positive in patients with BPA.

Emerging evidence supports the potential role of microRNA- (miRNA) and microDNA- (miDNA) molecule expression to PC tumour development (Hu *et al.* (2021), Krupinova *et al.* (2021), Wang *et al.* (2021), with microRNAs (miRNAs) as new group of biomarkers for PC. MiRNAs play an important role in the occurrence and metastasis of tumours as they are involved in almost all biological processes and affect cell proliferation, differentiation, adhesion, migration, invasion and apoptosis. PC cancer can lead to alterations of circulating miRNA expression in the blood as reported by Krupinova *et al.* (2021). The group detected a downregulation of serum miRNA-342-3p in PC patients when compared to patients with BPA, suggesting miRNA-342-3p as promising biomarker for improvement of diagnosis of PC.

Wang *et al.* (2021) investigated miRNAs from serum exosomes of PC and BPA patients and found exosomal hsa-miR-27a-5p in serum exosomes of PC patients as a putative tumuor marker for preoperative identification of PC.

The combination of immunhistochemistry and molecular analysis can offer new perspectives for basic research and for future diagnostic and therapeutic strategies.

TREATMENT

Medical

Medical management is directed towards managing the effects of a raised PTH and subsequent hypercalcaemia. Intravenous fluids, diuretics and bisphosphonates are used to reduce serum calcium as first-line therapy. If first-line therapy is ineffective, the use of calcimimetic agents such as cinacalcet is recommended. Cinacalcet decreases PTH secretion and has been shown to be effective in the management of PC-induced hypercalcaemia, although more advanced tumours may noit express the CASR (Takeuchi *et al*. 2017).

Intravenous fluids, diuretics and bisphosphonates are used to reduce serum calcium as first line therapy, whereas the use of calcimimetic agents such as cinacalcet is recommended as second-line therapy.

Surgical

Surgery is considered the gold standard of treatment for PC and should be performed at a reference centre, specialised in parathyroid surgery, to improve outcomes and provide the best chance of recovery (Kowalski *et al.* 2021). The type of surgery performed can be a localised excision following the parathyroid capsule as dissection plane or an oncological resection (also called “radical resection“ or “*en bloc* resection“) implying that this avoids capsule rupture, with removal of the parathyroid lesion with surrounding fat tissue, ipsilateral thyroid lobe, and possibly the recurrent laryngeal nerve and ipsilateral central neck compartment lymph nodes, with a continuous margin of healthy tissue. Central locoregional lymph node metastasis may be present in around 10% of patients, whilst the lateral compartment is rarely involved (Schulte *et al.,* 2010). There is significant debate as to which surgical technique should be utilised, as different studies have shown contradictory evidence. Schulte *et al*. (2014), in a study of 19 patients with PC, found that a primary oncological resection provides significantly better outcomes than a local excision, due to reduced R1 margins and therefore a lower chance of locoregional recurrence. Likewise, in a study of 38 patients, Iihara *et al*. (2007) found that those who underwent *en bloc* resections (22/38) had significantly longer disease-free survival in univariate analysis. This approach is supported by Lacobone *et al.* (2004), Kirkby-Bott *et al.* (2005), Mucci-Hennekinne *et al.* (2008), Karakas *et al.* (2012), Apaydin *et. al* (2021) and Xue *et al.* (2016), who recommend *en bloc* resection as the first-line option.

On the other hand, some papers support a less extensive surgical approach. (O’Neill *et al.* 2011, Harari *et al.* 2011, Young *et al.* 2016 and Hu *et al*. 2019). For instance, O'Neill *et al.* (2021) attempted to address the question whether further radical surgery is required in patients diagnosed with PC following minimally invasive focused parathyroidectomy (MIP) and report on a small series of 7 patients with diagnosis of PC after MIP. In this series, 6 out of 7 patients underwent revision *en bloc* surgery which did not reveal any residual disease, and after a median follow-up of 44 months there was no clear evidence for recurrence in any of these patients. The authors argue that in such selected patients there might be no need for early completion surgery after PC diagnosis, but also note that long-term data are missing. The authors state that they report on a subgroup of patients with PC, with disease localised to a single site, unlikely to have widespread local involvement, metastatic local nodal disease or distant metastases.

The largest study (n=555) examining the impact of the extent of surgical resection on survival for PC was conducted by Leonard-Murali *et al.* (2021). The group found no significant difference in overall survival between patients with PC treated with local resection (n=522) when compared to radical surgery (n=33). They propose that patients who are found to have parathyroid carcinoma after undergoing local resection for a presumed benign indication may be safely and closely monitored for recurrence, rather than be committed to the morbidity of radical surgery. The study holds several limitations: firstly, Leonard-Murali *et al.* report only overall survival (OS) instead of progression free survival or disease specific survival as suitable parameter to advice for or against the surgical approach; and secondly the groups in this study were stratified according to the operation code providing sufficient detail to distinguish local resection from radical surgery, but further information regarding extent of lymphadenectomy, specific adjacent organs removed, and dissection planes was not available. Another interesting intraoperative approach was presented by Kowalski *et. al* (2021), who suggested intraoperative inspection of all 4 parathyroid glands if the diagnosis of PC is highly suspected during the primary operation.

From all available evidence one must conclude that the gold-standard for PC is still an *en bloc* resection. To ignore this gold- standard may lead to devastating outcomes for some of these patients (Iihara et al., 2007.

Although there is significant debate as to which surgical technique should be utilised, the gold-standard for PC remains an en bloc resection.

Radiotherapy

There are no randomised controlled trials investigating the use of radiotherapy (RT) in PC and a clear consensus has not been reached regarding its use in patients with PC. RT has been used in the adjuvant setting for PC in a small number of patients (Busaidy *et al.* 2004, Erovic *et al.* 2013, Christakis *et al*. 2017). Christakis *et al*. (2017) recommend its use, given its well-tolerated side-effects, in cases where there is concern for recurrence within the central compartment. They do not recommend use of RT as treatment for metastatic disease, and the authors emphasised the need for clinicians to understand possible risks associated with RT, such as increased difficulty of subsequent neck surgery. Munson *et al.* (2003), Kirkby-Bott *et al*. (2005), Selvan *et al*. (2013) and Busaidy *et al.* (2014), also

recommend postoperative RT, supporting its use in reducing local recurrence rates. Apaydin *et al.* (2021) suggest adjuvant radiotherapy to the neck to reduce the risk of local recurrence only in patients with microscopic residual parathyroid carcinoma.

However, the largest series from a single centre, although still only including just 11 patients, observed no significant effects on survival, stating that wide resections in initial surgical management are likely to be of greater importance (Erovic *et al.* 2013). Furthermore, two national registry analyses from the National Cancer Database, USA, independently showed that there was no improvement in overall survival rates in patients who received RT compared with patients who did not receive RT (Asare *et al.* 2015, Limberg *et al.* 2021). More importantly, Limberg *et al.* (2021) reported that 10.5% of patients with completely-resected disease (M0, N0 or Nx) underwent radiotherapy without a benefit in overall survival ($P = 0.183$).

Currently, there are no 17andomized controlled trials investigating the use of RT in PC, and a clear consensus has not been reached regarding its use. Retrospective data show no improvement in OS rates in patients who received RT compared with patients who did not receive RT.

Chemotherapy and immunotherapy

Currently, chemotherapy (CT) and immunotherapy (IT) have not been shown to be effective in treating local or metastatic disease. Given that PC may express *VEGFR-2, PDGFR-α,* and *PDGFR-β* mutations, Erovic *et al*. (2012) have suggested that sunitinib, bevacizumab and pazopanib, which are effective in the treatment of kidney, lung, and breast malignancies, may be useful in PC. However, there are no clinical trials to support this. Silva-Figueroa *et al.* (2018) performed a retrospective study on 17 PC samples assessing the tumour microenvironment. The study showed that the majority of PC is PD-L1 negative, whilst 3 (17.6%) exhibited an adaptive immunotype suggesting suitability for anti-PD-L1 therapy (immunotype 1). The study advocates for more research into immune targeting in PC.

Currently, chemotherapy (CT) and immunotherapy (IT) have not been shown to be effective in treating local or metastatic disease.

FOLLOW-UP

The natural course of the disease is generally slow and inconsistenly progressive, with the eventual development of local recurrence and distant metastases. Recurrence of PC occurs in about 50% of cases (Talat & Schulte, 2010) with a median disease-free interval after the initial surgery of 36 months (Liu et. al., 2021), but longer intervals of 15-20 years have been reported (Lacobone *et al.* 2004). Given that PC can reoccur after 20 years, many centres recommend lifetime follow-up (Christakis *et al*. 2016, Medas *et al.* 2016). In most instances, hypercalcaemia is the initial sign of recurrence (Busaidy *et al.* 2004). Liu *et al. (*2021) evaluated the sonographic findings of locoregional recurrences of PC and found hypoechoic solid nodules in 28 relapses (96.6%), inhomogeneous echotexture in 28 relapses (96.6%) and intralesional echogenic septa-like structures in 21 relapses (72.4%), as well as irregular shape in 22 relapses (75.9%), marked vascularisation on colour Doppler imaging in 19 relapses (65.5%), and multiple lesions in 26 relapses (89.7%). None of the recurrent lesions exhibited calcification, and the total size of all the recurrent lesions at each relapse mildly correlated with the serum intact parathyroid hormone levels (r = 0.450; p = 0.014). Distant metastases most frequently occur within the lungs (Hu *et al.* 2019) and bones (Iacabone *et al*. 2016) As noted above, currently, there is no evidence supporting the routine use of chemotherapy, immunotherapy or radiotherapy in the metastatic setting. Once PC is metastatic, cure is highly unlikely and most patients die from severe hypercalcaemia or metabolic complications rather than metastases *per se*.

Recurrence of PC occurs in about 50% and lifetime follow-up ist recommended with hypercalcaemia being the initial sign of recurrence. Once PC ist metastatic, cure is highly unlikely.

SURVIVORSHIP AND PROGNOSTIC INDICATORS

Five-year overall survival (OS) ranges from 60% to 93% (Busaidy *et al*. 2004, Kleinpeter *et al*. 2005, Karakas *et al.* 2012, Hsu *et al*. 2014, Christakis *et al*. 2016, Christakis *et al*. 2016, Young *et al*. 2016, Ryhänen *et al*. 2017, Kong *et al.* 2021, Wei *et al.* 2022). Combined assessment of prognostic factors is challenging as many studies evaluated different outcomes such as 5-year OS, 10-year OS, disease-free survival (DFS) and disease-specific survival (DSS). Greater age has been found to be a negative prognostic factor by Sadler *et al*. (2014), Hu *et al.* (2019) and Kong *et al.* (2021), but a positive

prognostic factor by Talat & Schulte (2010), and non-significant by Harari *et al.* (2011). In the largest study by Sadler *et al*. (2014), mean OS was lower in patients who were Black, older than 57 years of age, had more than two comorbidities, and whose tumour was a secondary malignancy. Additionally, positive surgical margins, positive lymph nodes, and poorly-differentiated histology all conferred a worse OS. However, in a review of 330 patients by Talat & Schulte (2010), differing results were found, with male gender, younger age and high calcium being adverse clinical prognostic factors. They agreed that positive surgical margins carried a poorer prognosis. An analysis of the SEER registry between 1973 and 2014 revealed that patients with distant metastasis, but not metastatic lymph nodes, and PC tumours > 30mm had worse DSS (Lo *et al*. 2018). Lenschow *et al.* (2022) reported that by TNM a low T status, N0 stage at initial diagnosis and postoperative biochemical remission were beneficial prognostic parameters for recurrence-free survival of PC. The type of surgical procedure to treat PC has been debated heavily, and different centres still disagree over whether it affects prognosis (Kleinpeter *et al*. 2005, Young *et al*. 2016). A decrease in mortality and complication rate was observed when the initial surgery was conducted in an academic tertiary care endocrine surgery referral centre (Harari *et at.* 2011). With respect to revision surgery, Wei *et al.* (2022) and Waechter *et al.* (2019) found different results regarding recurrent or persistent PC, with (extended) *en bloc* resection (EEBR) providing better outcomes than other conventional surgical approaches such as parathyroidectomy only. Wei *et al.* (2022) reported a 5-year OS rate after EEBR of 59.6% compared to 16.7% after less radical procedures, with an improved median expected survival time of 90.0 vs. 13.0 months after local excision. Extended *en bloc* resection might therefore offer a second chance of cure for patients with recurrent or persistent PC in the absence of distant metastasis. Looking at immunhistochemical markers, a study by Hu *et al.* (2019) of 53 patients with PC showed that negative parafibromin correlated with a higher risk of recurrence and metastasis than in patients with positive parafibromin staining (Hu *et al.* 2019). The presence of a high Ki-67 proliferation index (>5%) has also been observed as a negative prognostic indicator in PC, as it was found to be associated with a higher chance of recurrence in a study of 38 patients by Iihara *et al*. (2007). Interestingly, clinicians at the *M. D. Anderson Cancer Center* (Christakis *et al*., 2016) compared the management of PC and outcomes (OS and DFS) in its centre between 1980-2001 and 2002-2015, and no significant changes in OS and DFS were observed over 35 years, highlighting the need to improve oncologic care.

Prognostic indicators vary between studies, but positive surgical margins, a greater age, the presence of a high Ki-67 proliferation index as well as negative parafibromin staining, seem to carry a poorer prognosis. Extended en bloc resection, in an academic tertiary care endocrine surgery referral centre, is the primary mode of therapy for recurrence of PC. However, reoperation is rarely curative and eventual relapse is likely.

PROGNOSTIC TOOLS AND STAGING

Three prognostic tools have been proposed in the management of PC, one by Shaha & Shah (2000), and two by Talat & Schulte (2010). The validity of Shaha & Shah's prognostic tool has been reviewed by Talat & Schulte (2010), who found no significant difference overall between the groups when they used this tool to assess 185 patients with PC. Talat & Schulte (2010) proposed two new prognostic tools which are based on anatomical disease progression: a high and low risk stratifying tool and a stage I to IV based on the TNM scale. Use of these Schulte prognostic tools has been tested by Sadler *et al*. (2014) using 91 patients with PC from a database of 1022 patients with PC, and they found that the high/low-risk tool was an effective method of predicting better outcomes with a 28-month greater mean survival in the low-risk group. Villar-del Moral *et al.* (2014) also support the use of the Schulte tool after their study of 62 patients with PC in Spain showed a significant difference in tumour recurrence in Stage III PC patients when compared to Stage I. Furthermore, they state that the Shaha & Shah system was inferior to Schulte's, as it did not show a stepwise worsening of prognosis at greater stages in the prognostic tool, unlike the Schulte tool. Likewise, Xue *et al.* (2016) advocate for the use of Schulte´s 4 stage classification system and high/low-risk classification for recurrence, finding a significant difference for recurrence in 40 patients with PC in China. Schulte *et al*. (2012) have also validated the use of their prognostic classification system in their review of 82 patients. Their study showed a significant impairment in survival (98.6% I, 79.2% II ,71.4% III, 40.0% IV, $P< 0.05$ between each class). The *American Joint Committee on Cancer* (AJCC) 8th edition of cancer staging has proposed a classification of PC in 2017.

We have created an updated staging system based on the 8th edition of cancer staging of the AJCC, by adding the low and high-risk stratifying tool of Talat & Schulte to the AJCC edition (Table 4).

DISCUSSION

Based on current evidence, we have proposed a diagnostic algorithm for patients presenting with PTHP (Figure 3).

PC should be suspected over other causes of PHPT whenever patients have a personal or family history of HPT-JT, exhibit markedly elevated calcium and PTH levels, or present with severe symptoms. However, anecdoctal cases of normocalcaemic hyperparathyroidism have also been reported (Al-Kurd *et al.* 2014*)*. We recommend that all patients undergo an initial US scan of the neck. The possible parathyroid lesion should then be classified as suspicious or non-suspicious. Thereafter, patients who are severely symptomatic, have a personal or family history of HPT-JT, or have a suspicious lesion on the US, should undergo further investigations including a screening for the most common manifestations involving the bones and kidneys.

If a lesion is classified as non-suspicious, laboratory results must be reviewed and decisions on further management should be taken in a multidisciplinary manner. Unlike Schulte *et al.* (2012) in their diagnostic algorithm, we do not suggest calcium and tumour size cut-offs, given the increasing evidence that PC is also present in smaller tumours and in patients who do not present with severe hypercalcaemia. For further investigations, we recommend the use of a $2^{nd}/3^{rd}$ generation PTH assay ratio and imaging with 4-DCT and MIBI. The use of the tool created by Karakas *et al.* requires validation, but it could be a useful diagnostic adjunct in the pre-operative phase. If the $2^{nd}/3^{rd}$ generation PTH assay ratio and imaging with 4-DCT and MIBI are negative, follow-up as a likely benign PTHP is proposed. If any are positive, we recommend that the patient undergoes an oncological *en bloc* resection with curative intent. Although the extent of surgical resection required to ensure optimal clinical outcomes is not entirely clear, we advise *en bloc* resection as gold standard for the surgical approach due to better outcomes with regard to local disease control. The diagnosis of APN, which is an important differential diagnosis of PC, is made through histology. APN seems to have a benign course in the majority of cases but long-term data are missing. Therefore, constant vigilance is required to identify early the rare cases that might behave in a malignant manner.

In case of PC diagnosis, samples should be sent for genetic and immunohistochemical analysis postoperatively. We recommend that the genetic analysis should be concerned with defects in *CDC73*, and immunohistochemical analysis with parafibromin, Ki-67 proliferation index and galectin-3. Cardoso *et al*. (2017) performed a comprehensive review on the molecular genetics of PC. Their findings, like

others, suggest that *CDC73* mutations are major drivers in the aetiology of PC. They go on to suggest that PC involves other genes such as *MEN1, RET and PRUNE2,* as well as epigenetic mechanisms, alterations in miRNA expression and potentially other, as yet unidentified, genes. In patients with MEN-1, parathyroid tumours are rarely PC (Cardoso *et al.* 2017). With respect to the diagnostic performance of parafibromin, Hu *et al*. (2016) completed a meta-analysis of 10 studies. Their study showed that the pooled specificity of parafibromin staining was satisfactory for the diagnosis of PC (95% CI 85-98%), while the sensitivity was limited 68% (95 % CI 49–82 %). This is in line with the findings of Uljanovs *et al.* (2021). The aim of this study was to assess the molecular landscape and its heterogeneity in primary parathyroid hyperplasia (PPH) and adenoma, compared to carcinoma and normal glands. All carcinomas lacked parafibromin contrasting with invariable positivity in adenomas. Remarkable heterogeneity of cell cycle markers and intermediate filaments must be accounted for in scientific studies and elaboration of diagnostic cut-offs. Given the challenges in characterising PC, a combination of markers may be required to achieve a definitive diagnosis.

With regard to the use of chemotherapy, Adam *et al.* (2010) assessed in a review trial of doxorubicin, cyclophosphamide and 5-flurouracil, and dacarbazine, cyclophosphamide, 5-fluorouracil, and vincristine, which deemed to be ineffective in the management of PC. Given the poor evidence-base supporting use of chemotherapy and immunotherapy, we would currently not recommend their routine use in the management of PC. To date, there are no reports that have shown any survival benefit of radiotherapy in the treatment of PC (Asare *et al.* 2015, Limberg *et al.* 2021). Adjuvant radiotherapy is therefore not recommended as standard therapy for PC and there is a certain risk of overutilisation, without a benefit in OS, particularly in patients with completely resected localised disease undergoing radiotherapy, as reported by Limberg *et al.* (2021). Unlike other endocrine cancers, there is no established TNM classification, due to lack of data. Overall, the evidence supports the use of both of Schulte's criteria for the prognosis of PC to assist in clinical judgement. In terms of follow-up, Schulte & Talat (2012) delineated different follow-up plans depending on whether the patient was classified as high or low risk after the initial surgery. Low risk patients should have circulating PTH and calcium checked at 6-month intervals for the first 5 years, and annually thereafter, while patients with high-risk disease require closer follow-up with 3 monthly reviews for the first decade and 6 monthly reviews thereafter. If PTH or calcium is elevated, it is recommended that patients undergo localising studies such as 4D-CT and MIBI scanning and PTH assay ratio measurements for assessment of recurrent

disease. When PC is no longer amenable to surgical resection, managing hypercalcaemia can prolong survival (Ramos *et al.* 2017). Guise *et al.* (2022) suggested in their review *Cancer-associated Hypercalcaemia,* the correction of volume depletion and the inhibiton of bone resorption are the two basic principles of refractory hypercalcaemia next to the initial treatment of the underlying cancer. Antiresorptive agents include bisphosphonates, calcitonin and denosumab. In particular, denosumab, as a human monoclonal antibody to the receptor activator of NF-κB ligand (RANKL), although not approved for this indication, has been successfully used in PC patients with refractory hypercalcaemia (Karuppiah *et al*. 2015, Vellanki *et al.* 2014, Bowyer *et al*. 2013), leading to an improvement of symptoms and quality of life (Roukain *et al. 2022*). Cinacalcet on the other hand, as an oral calcimimetic agent that reduces PTH secretion and blocks renal tubular reabsorption of calcium, is approved for the treatment of PC-associated hypercalcaemia and reduces calcium levels in approximately 60% of patients with PC (Silverberg *et al.* 2007, Guise *et al*. 2022). Case reports have described its safety and effectiveness in treating several cases of malignancy-associated hypercalcemia alone (Silverberg *et al.* 2007) or in combination with other medications (Tzotzas *et al.* 2022)), and even throughout pregnancy (Nadarasa *et al.* 2014, Horjus *et al.* 2009).

The limitations of this review are due to the significant heterogeneity and retrospective nature of studies, and study design largely limited to single-centre experiences with a reduced sample size. Another limitation is the fact that not all the studies included into this systematic review report on criteria for PC diagnosis. Therefore, there may have been variability in the diagnostic criteria of studies included in this systematic review, which range between 1980´s and 2022.

We believe that the study of rare diseases, such as PC, would benefit from multicentre collaborations with standardised databases. Furthermore, patients with PC would benefit from inclusion in clinical trials of new targeted agents in which the mutation, regardless of the origin of the tumour, is the criteria for eligibility.

CONCLUSIONS

PC is a rare disease which typically presents with hypercalcaemia and often with systemic symptoms. Early recognition of lesions at risk of being PC supported by genetic, biochemistry and imaging is required to determine the surgical approach and extent of resection, with *en bloc* resection remaining the gold standard for surgical approach. Diagnosis is generally confirmed post-operatively by

immunohistochemical and pathological analysis. Given the lack of alternative curative approaches and limited outcome benefit from revisional surgery, we recommend referral to expert centres with experience in oncological parathyroid surgery. However, more evidence is required to ascertain the adequate surgical approach and role of radiotherapy as standards of care. Emerging evidence indicates that targeted therapy based on molecular biomarkers may be a novel treatment option. The rarity of PC and need for personalised treatment warrants multidisciplinary management in an experienced centre.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

LEGENDS

Figures

Figure 1 - Study selection flowchart. The search retrieved a total of 3097 articles. After removing duplicates and reviewing abstracts, 326 full-text articles were analysed in detail for eligibility. 77 studies met the eligibility criteria and 75 studies were included in the review.

Figure 2 - Logarithmic equation calculating preoperative risk of parathyroid cancer in patients with primary hyperparathyroidism by Karakas *et al. (2012).*

Figure 3 – Diagnostic algorithm for parathyroid carcinoma

Tables

Table 1 – Incidence of clinical symptoms/signs in parathyroid carcinoma

Supplementary Material

Table 2 – Study characteristics of observational studies included in this systematic review (between 2000 and 2022) investigating diagnosis and management of parathyroid carcinoma

Abbreviations for table 1 (to be included in word doc):
ALP – Alkaline Phosphatase; APN – Atypical Parathyroid Neoplasm; BPA – Benign Parathyroid Adenoma; Ca – Calcium; BMD - Bone Mineral Density; CND - Central Neck Dissection; CSMR - Cancer Specific Mortality Rate, DFS – Disease-Free Survival; DSS – Disease-Specific Survival; EBRT - External Beam Radiotherapy; EEBR -Extended En-bloc resection; HTx - Hemithyroidectomy; ILND - ipsilateral lymph node dissection; IQR – Interquartile Range; OS – Overall Survival; PC – Parathyroid Carcinoma; PTH – Parathyroid Hormone; NR – Not Reported; Y – Years; LN - lymph node – LN; LR - Local Resection; MIPC - Minimally Invasive Parathyroid Carcinoma; MS - Median Survival, NA - Not Assessed, NCD - National Caner Database; NHIS - National Health Insurace Services; OS - Overall Survial; OMR - Overall Mortality Rate; PH - Parathyroid Hyperplasia; PC - parathyroid carcinoma; PTx – parathyroidectomy; SEER - Surveillance, Epidemiology, and End Results; sTx -Subtotal Thyroidectomy; Tx - Total Thyroidectomy; UNL – Upper Normal Limit; *WIPC - Widely invasive parathyroid carcinoma*

Table 3 – Study characteristics of laboratory studies included in this systematic review (between 2000 and 2022)

Abbreviations for table 2 (to be included in word doc):
APN Atypical Adenoma, EMT epithelial–mesenchymal transition, BPA Parathyroid Adenoma, PH Parathyroid Hyperplasia, PC Parathyroid carcinoma, PHPT Primary Hyperparathyroidism, TA Typical Adenoma

Table 4 - Updated PC Risk Stratifying Tool adapted from Schulte et al. (2012) and the AJCC (2017)