Review

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Review

Synchronous Multiple Parathyroid Carcinoma: A Challenging Diagnosis Influencing Optimal Primary Treatment—A Literature Review

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Abstract: Synchronous multiple parathyroid carcinoma (SMPC) is a rare condition within the already uncommon landscape of parathyroid malignancies, which comprise less than 1% of sporadic primary hyperparathyroidism (sPHP) cases. To date, only seven cases of SMPC in sPHP have been documented. This exceptional rarity complicates both the diagnostic process and therapeutic decision-making. Clinically, parathyroid carcinoma (PC) typically presents as a single mass determining severe symptoms. However, no single clinical, biochemical, or imaging feature allows for definitive preoperative diagnosis. Imaging modalities such as ultrasound (US) and Sestamibi (MIBI) scan exhibit variable sensitivity and may overlook multi-gland involvement. Histopathological examination remains the only reliable diagnostic method. Management strategies are also controversial: while some advocate for conservative surgery, en bloc resection is generally recommended for its association with improved local control and disease-free survival. Given the exceptional occurrence of SMPC, there is a lack of standardized protocols to manage PC in case of synchronous and multiple gland involvement. Early multidisciplinary evaluation and individualized treatment planning are therefore crucial. This review aims to synthesize currently available knowledge about SMPC to assist clinicians with the limited data available and guide decision-making in the management of this rare and challenging entity.

Keywords: synchronous multiple parathyroid carcinoma; primary hyperparathyroidism; parathyroid carcinoma; diagnosis; surgical therapy

1. Introduction

PC is one of the rarest endocrine malignancies, representing less than 1–2% of sPHP cases. It typically presents as a solitary, palpable neck mass, often accompanied by severe hypercalcemia and end-organ complications [1,2]. Despite its rarity, timely recognition and appropriate surgical management are critical, as the initial operation remains the most important determinant of long-term prognosis [2]. Even more exceptional is the occurrence of SMPC, which poses significant challenges in both diagnosis and treatment. Given these uncertainties, surgical expertise plays a crucial role. In PC, especially in its synchronous form, the first surgery offers the best chance for disease control and survival. Inadequate resection due to underdiagnosis can compromise outcomes and lead to persistence or recurrence [3]. This review aims to discuss the peculiarity of presentation and the possible tricks encountered in managing SMPC. Unfortunately, only a very limited number of cases have been described in literature till now. Starting from the available literature resources and

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supported by personal experience we will discuss current knowledge, diagnostic challenges, and the implications of surgical decision-making in this rare and complex clinical scenario.

2. Materials and Methods

This comprehensive review aims to provide a concise yet complete overview of SMPC. We adopted a systematic and targeted literature search strategy in indexed databases such as PubMed/MEDLINE (National Library of Medicine), Scopus, and EMBASE. The search was restricted to English-language publications. Since SMPC is also known as multiple parathyroid carcinoma (MPC) or double parathyroid carcinoma (DPC) in the literature, all searches were conducted using all these terms. This review included all studies published on the subject.

3. Results

From the research conducted, seven studies concerning SMPC were found and included in the review. All the selected articles are case reports and cover the period between 2000 and 2017. Each paper describes only one case. All the cases described were treated at University surgical centers. Demographic, clinical, laboratory findings are described in Table 1. The published series of SMPC included 5 male (71.43%) and 2 female patients (28.57%). The median age was 52 ± 8.18 years (38-67). 6 out of 7 articles describe the clinical presentation of the patients, all of whom were symptomatic [4,5,6,7,8,9]. Among reported cases, the most common symptoms were bone pain (66%), abdominal pain (42%) and fatigue (42%). In 2 out of 6 cases (33.3%) the overt symptoms forced patients to enter emergency department as first evaluation [4,9]. In one of them, the patient manifested neuropsychiatric symptoms such as confusion and depression [4]. In the other case, the patient presented at the emergency department with aspecific symptoms such as dyspnea and tachypnea [9]. In 6 out of 7 cases included in this review, laboratory data at the first patients' evaluation are reported, specifically concerning calcium and parathyroid hormone (PTH) levels [4,5,6,7,8,10]. In only one case blood tests were not initially performed because the PC was misdiagnosed as a thoracic mass of other origin [9]. In 3 out of 6 patients (50 %) calcium level exceeded 14 mg/dl with a median value of 14.4 ± 1.9 mg/dl (11.6 – 17.3) and in 3 out of 6 patients (50 %) PTH was higher than 5 time the normal range with a mean value of 611 ± 449 pg/ml (98 - 1491).

Table 1. Summary of included studies on the clinical presentation and laboratory findings of SMPC.

Reference	Number of Cases	Age	Sex	Symptoms at Presentation	PTH (pg/ml)	Calcium (mg/dl)
Gray JH, Clin Nucl Med 2000	1	50	M	Confusion, depression	437	13
Brown JJ, ENT 2002	1	51	M	Gastrointestinal, bone pain, anxiety	98	14
Kamejana K, Endocr J 2003	1	67	M	Not described	270	11.6
Sahasranam P, South Med J 2007	1	53	M	Hematuria, flank/abdominal pain, bone pain, fatigue, nausea, weight loss, enlarging new neck mass	1491	17.3
Yuan S-F, EJSO 2010	1	38	F	Bone pain, femoral fracture, fatigue,	782	16.3

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				nausea, vomiting, enlarging neck mass		
Haciyanli M, Endocr Pract 2011	1	48	F	Fatigue, joint pain, bone pain	589	14.4
Dikmen K, Pan Afr Med J 2017	1	57	M	Dyspnea, tachypnea	118.7	11.4

M: male; F: female.

Details concerning imaging are reported in Table 2.

Table 2. Summary of included studies on the imaging investigations of SMPC.

Reference	Kind of Centre	Ultrasound Findings	MIBI Scan Findings	Radiological Suspicion of PC	Number of Glands Involved
Gray JH, Clin Nucl Med 2000	University centre	Not reported	Bilateral inferior	Not declared	2
Brown JJ, ENT 2002	University centre	Not reported	Bilateral inferior	Not declared	2
Kamejana K, Endocr J 2003	University centre	Both detected but one suspicious for PTC or PC	Bilateral inferior	Doubtful, only one	2
Sahasranam P, South Med J 2007	University centre	Only one detected and suspicious for PC	Negative	Yes	2
Yuan S-F, EJSO 2010	University centre	Only one detected	Only right	Not declared	2
Haciyanli M, Endocr Pract 2011	University centre	Both detected but only one suspicious for PC	Bilateral	Yes	2
Dikmen K, Pan Afr Med J 2017	University centre	Only one detected (performed after 1st intervention)	Only right (performed after 1st intervention)	No	2

PC: Parathyroid carcinoma; PTC: Papillary thyroid carcinoma.

In the reviewed series, imaging was performed on all the patients. However in the case reported by Dickmen imaging to localize pathological parathyroid tissue was performed only after the first intervention which unexpectedly revealed a mediastinal ectopic PC [9]. The choice to perform more than one single localization study was not homogeneous. MIBI scan was performed in all the cases and in 2 out of 7 (28.6%) it represented the only preoperative investigation [4,5]. In 1 out of 7 cases it was performed only after the primary surgery [9]. When performed before primary surgery (6/7 cases), it exhibited bilateral activity in 4 out of 6 cases (66.67%) [4,5,8,10], unilateral activity in one case (16.67%) [7], and was completely negative in one case (16.67%) [6]. US was performed as first-line imaging in 5 out of 7 cases (71.4%) [6-10]. When performed, it could detect parathyroid enlargement of both the involved glands only in 1 out of 5 cases (20%) [8]. In the remaining 4 cases (80%) US was able to detect only one pathologic parathyroid [6,7,9,10]. In one of these cases, US was unable to recognize one of the parathyroid malignant lesions, misdiagnosing it either with a thyroid nodule or an intrathyroidal parathyroid carcinoma [10]. US features suggested PC in 2 out of 5 cases

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(40%) but never in both the involved glands [6,8]. Only 1 of the 7 cases (14.3%) included in the review involved a patient who received medical treatment designed to reduce calcium levels during the diagnostic workup [6]. Sahasranam et al. described that the patient was treated with adequate hydration for one week, which resulted in improvement in his laboratory tests, showing a decrease in serum calcium to 9.3 mg/dl (from 17.3 mg/dl) [6]. All patients underwent surgical treatment. Surgical approach, histology and follow-up data are reported in Table 3.

Table 3. Summary of included studies on surgical treatment, histology and follow-up of SMPC.

Reference	Emergency Surgery	Type of First Intervention	Need for Completion	Intraoperative Suspicion of PC	Histology PC Criteria	Genetic Testing	Follow-Up (Months)
Gray JH, Clin Nucl Med 2000	Not specified	Double PTX	No	Yes	Yes	No	-
Brown JJ, ENT 2002	No	BNE, double inferior PTX	Yes	No	Yes	No	27
Kamejana K, Endocr J 2003	No	Left PTX + Io-PTH, en-bloc resection of upper right parathyroid + right thyroid lobe	No	Yes, only on right side	Yes	No	8
Sahasranam P, South Med J 2007	No	Total thyroidectomy + PTX (not specified)	No	Not specified	Yes	No	24
Yuan S-F, EJSO 2010	No	En-bloc resection of right parathyroid and thyroid lobe with surrounding tissue	Yes	Yes, only on right side	Yes	No	12
Haciyanli M, Endocr Pract 2011	No	BNE, en-bloc resection of right parathyroid gland + right lobectomy + adherent soft tissue + lower left PTX en-bloc with surrounding tissue	No	Yes, upper right and lower left	Yes	No	48
Dikmen K,	Yes	en bloc resection of	Yes	No	Yes	No	-

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Pan Afr Med J 2017	double left parathyroids + left thyroid lobectomy, left CND	

PC: Parathyroid carcinoma; Io-PTH: Intraoperative PTH; PTX: Parathyroidectomy; BNE: Bilateral neck exploration; CND: Central neck dissection.

A simple parathyroidectomy (PTX) was carried out in 2 cases (28,57%) as first or unique surgical approach [4,5]. Brown et al., described a two stage surgical approach. During the first intervention the patient underwent bilateral neck exploration (BNE) and bilateral inferior PTX due to the intraoperative finding of two enlarged glands adherent to the surrounding tissue. After obtaining definitive histology showing PC in both the removed glands, the surgeon opted for a secondary completion thyroidectomy with central neck lymph node dissection (CND) [5]. In the other case, the authors described a double PTX with no additional notes concerning the intraoperative findings [4]. In these 2 cases, neither a preoperative nor an intraoperative suspicion of PC was referred by the authors. En bloc resection represented the preferred surgical approach in 4 cases (57%) [7-10] in 3 as primary surgery [7,8,10] and in one case as reoperation [9]. In 3 cases (75%) the decision to perform en bloc resection was certainly guided by intraoperative findings [7,9,10]. In the case reported by Yuan et al., preoperative investigations, including neck US and MIBI scan, indicated unilateral glandular hyperactivity [7]. Despite preoperative single-gland localization, the authors planned a BNE. The intraoperative suspicion of single unilateral PC led to an en bloc resection of the involved parathyroid gland along with the ipsilateral thyroid lobe and adjacent soft tissue. Despite the radicality of primary surgery and the bilateral exploration, postoperative PTH levels remained high, necessitating a second intervention consisting of completion thyroidectomy combined with left inferior PTX, performed three months later. Kamejana et al. described the finding of a markedly enlarged left parathyroid gland, which was removed without the surrounding tissue due to the absence of suspected malignancy. A persistent elevation of Intraoperative PTH (Io-PTH) levels led to the identification of the right parathyroid gland, whose appearance was initially uncertain, raising suspicion for either thyroid carcinoma or intrathyroidal PC, and it was removed en bloc with the right thyroid lobe and paratracheal lymph nodes [10]. In the case described by Dikmen et al., the initial chest computed tomography (CT) revealed a mass in the anterior mediastinum, which was thoracoscopically removed. Following the histological diagnosis of PC, the patient underwent further diagnostic investigations and was subsequently treated with en bloc resection of the left superior and inferior parathyroid glands, connected by a fibrous band, en bloc with the left thyroid lobe and left central lymph nodes [9]. Haciyanli et al. instead planned and performed a bilateral en bloc resection of two bilateral suspicious PC [8]. Finally, Sahasranam et al. described bilateral PTX and concomitant total thyroidectomy, but no details about a clear suspicion of PC were reported [6]. Therefore, this case was classified neither as a simple PTX nor as an en-bloc resection. Io-PTH monitoring was employed in 2 of the 7 cases included in the review (28.57%) [9, 10]. In one case, persistently elevated Io-PTH levels led to a BNE, which identified a second diseased parathyroid gland [10]. In the other case, a 70% Io-PTH drop confirmed the correct identification of the affected parathyroid gland [9]. In one case Authors specified that Io-PTH was not used because unavailable at the time of surgery [6]. Histological examination was performed in all the cases included in this review. Detailed reports are available for 6 of the 7 cases [5-10]. In all of these cases, at least one diagnostic criterion for PC is present. Specifically, vascular invasion is reported in 5 (83.3%), capsular and surrounding tissue invasion in 5, and thyroid parenchyma invasion in 3 of the 6 cases (50%). In 2 cases (28,57%), follow-up was not described [4,9]. The mean follow-up registered in the other cases was 23.8 months. In all the cases, patients remained disease-free at the end of the follow-up period. In three of the reported cases, the patient was disease-free with normal postoperative calcium and PTH levels [7,8,10]. In the other 2 cases, the patient continued calcium supplementation therapy [5,6]. No cases mentioned genetic tests to exclude association with syndromic forms.

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4. Discussion

Despite the incidence of PC has increased to 10–13 cases per 10 million per year over the last few decades *[11,12]*, it remains a very rare entity, accounting for only 1% of sPHP *[13]*. SMPC in a setting of sPHP is exceptional. Only seven cases of sporadic SMPC have been previously reported and they were always documented as isolated experiences at different centers. Given the very limited knowledge available in literature, we will combine data from existing sources with our personal experiences to describe and discuss whether, and how, this exceptional entity diverges from the more ordinary form of PC.

4.1. Clinical Presentation

PC presents equally in males and females at a median age of 44–65 years [2]. In published series of SMPC, male sex results more involved than the female counterpart, while the median age of presentation was similar to PC. Unlike the more prevalent types of sPHP linked to adenoma or hyperplasia, PC usually manifests with pronounced signs and symptoms. These include bone and muscle pain, neuropsychiatric issues, kidney stones, hypercalcaemic crises, osteopenia or osteoporosis, pathological fractures, and a noticeable neck mass [1,2]. Also in case of SMPC patients usually presented at diagnosis with overt symptoms (Table 1).

According to literature data, patients with SMPC are always symptomatic presenting to the clinician attention for bone pain (66%), abdominal pain (42%) and fatigue (42%). Moreover, sometimes, the predominant symptoms are neuropsychiatric, such as confusion and depression [4]. In our personal experience the patient was admitted to the emergency room in sleepy state, hyporeactive, with severe weakness and muscle stiffness mimicking a neurological impairment. The severity of clinical picture and symptoms overlapping with other emergent neurological conditions may lead clinicians to perform first-line imaging with low accuracy for PC and SMPC detection. This may influence both the diagnostic pathway and also the therapeutic approach. Notably, regardless of the clinical picture, it should be considered that the overt manifestations due to severe hypercalcemia may help clinicians to suspect malignant parathyroid disease but are useless in distinguishing between single PC and SMPC.

4.2. Laboratory Findings

No strict cut-offs between benign disorders and malignancies of the parathyroid are reported in literature; however, PC typically shows higher laboratory values. A serum calcium level exceeding 14 mg/dl and PTH values greater than 5 times the normal level should raise suspicion of malignancy rather than adenoma [14]. As confirmed in the published series, PC patients usually have absolute levels of PTH and calcium concentrations significantly higher than in other forms of sPHP [15,16]. In SMPC series 50 % of patients presented with calcium level exceeding 14 mg/dl and in 50 % of patients PTH was higher than 5 times the normal range. Only Brown at al. reported quite low levels of PTH [5]. In our case the patient presented with calcium level of 20.1 mg/dl and PTH level of 1470 pg/ml. Unfortunately, no significant difference in blood tests are registered between single and SMPC. Therefore, laboratory findings, though useful in supporting the PC suspicion, cannot help in suggesting a multi-gland involvement.

4.3. Imaging

Imaging investigations of parathyroid lesions are employed to accurately localize the diseased parathyroid gland prior to surgery and to differentiate between benign and malignant lesions in order to plan the best surgical approach. US demonstrated a sensitivity of 71% with a specificity of 100% in localizing the affected parathyroid gland before surgery [17]. According to the malignancy stratification US is considered the most reliable imaging method. A tumour size of 30 mm at US is considered a predictive value for the diagnosis of PC in patients with sPHP with a sensitivity of 91%, specificity of 92% [16]. Both infiltration of surrounding tissue and calcification have a 100% positive predictive value for malignant lesions, while the absence of suspicious vascularity, thick capsule and inhomogeneity

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have high negative predictive values (97.6%; 96.7% and 100% respectively) [2]. MIBI scan is the most sensitive localization technique (95%) for identification of pathological glands [18]. In many Countries, especially in the USA, MIBI scan is considered the most reliable imaging in sPHP and nuclear medicine is largely used but its capability in evaluating the risk of malignancy is very low [19]. Both CT and magnetic resonance imaging (MRI) provide valuable insights into the extent of lesions and potential invasion of adjacent structures, lymph node involvement, or distant metastases. However, CT generally exhibits low sensitivity for detecting PC, whereas MRI is more appropriate for assessing soft tissue involvement [20]. Combined imaging with US, CT and MIBI scan reaches a 100% sensitivity for localization, whereas only one-modality imaging has less sensitivity. Differently from the ordinary form of single gland PC, in case of SMPC imaging plays a determinant role not only in predicting malignancy but also in suspecting multi-gland involvement. For this reason, the decision to perform more than one single localizing study may significantly impact the correct preoperative diagnosis and reduce the risks to underestimate SMPC. In the reviewed SMPC series imaging was performed in all the patients but the choice to perform more than a single one imaging modality was variable. While MIBI scan was performed in all the cases, in 2 out of 7 patients it represented the only imaging modality chosen because US was not performed [4,5]. Concerning the capability of both the imaging modalities to detect more than one gland involvement in SMPC we noticed that unfortunately US was capable to detect parathyroid enlargement of both the involved glands only in 1 out of 5 reviewed cases (20%) [8]. In the remaining 4 cases US was able to detect only one pathologic parathyroid[6,7,9,10]. Considering the dimensions of the involved parathyroids found at surgery it seems quite unreliable that US was not able to detect some of them. Probably they were interpreted as thyroid nodules. In our experience US was able to detect with certainty only one pathologic gland (suspicious for PC) but was not able to predict SMPC. Indeed, the second gland was interpreted as contralateral thyroid carcinoma, maybe because of its intracapsular expression. MIBI scan, instead, showed bilateral activity in 4 out of 7 cases (57%)) [4,5,8,10]. In one case it showed unilateral activity [7], and in the remaining case it was completely negative [6]. In our experience MIBI scan was not performed because the patients followed a different diagnostic pathway. She did not present at our attention in outpatient service but was firstly managed at first aid for relevant neurological symptoms requiring immediate care. Consequently, the patient underwent urgent imaging (MRI, CT and US), with lower accuracy in predicting multi-gland involvement. According to the capability of US to predict parathyroid malignancy, in the reviewed SMPC series we noticed a drop in the US overall accuracy when compared to single PC series. Indeed among the 5 cases in which US was performed, in 2 cases its features suggested PC but only in one of the two involved glands [6,8]. In our personal experience US was able to detect PC but only in one side. The contralateral PC was interpreted as malignant thyroid carcinoma. Probably the preconception of the unlikely occurrence of SMPC in the same patient influences the interpretation of US findings, making more reliable the eventuality of concomitant thyroid nodules. Also for this reason the availability of combined information obtained by a multimodality imaging approach takes on a peculiar role in case of SMPC.

4.4. Treatment

Severe hypercalcemia can lead to cardiovascular, neurological, renal and digestive manifestations. In patients who do not require emergency surgical treatment, the goal of initial clinical management is the reduction of serum calcium levels. The initial treatment for hypercalcemia typically involves intravenous fluids, diuretics, and bisphosphonates, which are intended to lower serum calcium. If these primary therapies prove ineffective, calcimimetic agents such as cinacalcet are recommended. Cinacalcet helps to manage hypercalcemia caused by PC by suppressing PTH secretion; however, its effectiveness may be limited in advanced tumours that do not express the calcium-sensing receptor *[18]*. In only one of the reviewed cases of SMPC the initial medical treatment was described. In order to avoid an incomplete imaging before surgery the possibility to lower the serum calcium is of utmost importance. In our experience, for example, the remarkable neurological symptoms and the limited decrease of serum calcium obtained with diuretics and bisphosphonates

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conditioned the decision to improve the preoperative localization neglecting MIBI scan in favour of urgent surgery based only on US, CT and MRI findings. This choice reduced the possibility to predict multiple PC. Surgery serves as the primary treatment for PC and is the only curative option for localized cases [18,21,22]. Malignancy is seldom suggested by preoperative findings. Nonetheless, intraoperatively, it may be suspected based on the tumour appearance or dissection challenges. If there is a strong suspicion of PC, it is recommended to conduct an "en bloc" tumor removal, ensuring capsule integrity to prevent local spread, along with ipsilateral thyroid lobo-isthmectomy in the presence of adhesions [18]. Reviewing the SMPC cases we noticed a heterogeneous surgical approach. In the reviewed series of SMPC a simple PTX was performed in two cases (28.57%) [4,5]. In both cases neither a preoperative or an intraoperative suspicion of PC was referred by the Authors. En bloc resection was performed in 4 cases (57%) but only in one case surgeons accomplished it for both the involved glands [7-10]. In our case, despite preoperative studies suggested concomitant superior right PC and left thyroid carcinoma, the intraoperative findings demonstrated it was a case of bilateral SMPC. Therefore, in our experience intraoperative interpretation modified the decision-making in favour of bilateral superior right and left parathyroidectomy en bloc along with total thyroidectomy and CND. The cases included in this review illustrate a markedly heterogeneous therapeutic approach tailored to individual clinical scenarios. This variability reflects on one side the ongoing controversies regarding the optimal management of PC and on the other side the lack of univocal strategy in case of the exceedingly rare occurrence of SMPC. According to the guidelines issued by the European Society of Endocrine Surgeons (ESES), en bloc resection of the affected parathyroid gland together with the ipsilateral thyroid lobe and surrounding soft tissue is recommended in patients with T1 PC [18]. However, this recommendation remains subject to debate within the endocrine surgical community [23]. A recent systematic review published by McInerney et al., which included a total of 2,307 patients, concluded that there is no difference in survival between a local resection and extensive radical surgery; and, across all studies, PTX alone (local resection) is the most frequent approach [3]. However, according to an earlier review that included 372 patients, en bloc resection was associated with an 8% local recurrence rate and an 89% long-term overall survival rate (mean follow-up of 69 months) [24]. In contrast, simple PTX resulted in a 51% local recurrence rate and a 53% long-term survival rate (mean follow-up of 62 months). It is worth noting that when only local excision was performed, there was no intraoperative suspicion of malignancy, suggesting that these tumors may have presented at a less advanced stage. Probably most of SMPC described in our review that were treated by simple PTX belonged to such category of PC. Notably, in the reviewed series of SMPC when en bloc resection was the preferred option it was accomplished generally for only one of the two involved glands. This suggests either a variable macroscopic appearance of synchronous PC in the same patient or once again the influencing weight of the extreme rarity of SMPC on the intraoperative judgement of the surgeon. As described above, primary surgery sometimes failed and required reoperative surgery. In one case redo surgery was performed after obtaining histology in order to grant adequate clearance of the surgical field and reduce the risk of recurrence [5]. In another case, the need for reoperation was due to the incomplete removal of PC, attribuited to the inability to recognize multi-glan involvement [7]. In order to reduce the possibility to overlook multi-gland disease, especially in case of incomplete preoperative imaging, BNE should always be the preferred option. Io-PTH demonstrated to reduce the risk of persistence in patients undergoing targeted PTX [25-27]. Io-PTH was used in two of the seven cases included in the review (28.57%) [9,10]. In one case, persistently elevated PTH levels prompted BNE, which led to the identification of a second diseased parathyroid gland [10]. Unfortunately, no studies addressing specifically the usefulness of Io-PTH in case of SMPC are available. However, Dobrinjia et al. reported that the use of Io-PTH could serve as a reliable indicator of malignancy during PTX, as malignant cases tend to show higher baseline Io-PTH levels and a more significant drop compared to benign conditions [28]. Moreover, recently Armstrong et al. showed that >50% Io-PTH decrease into normal reference range may better predict complete excision of malignant tissue in patients with PC compared to >50% Io-PTH decrease alone [29]. The Authors concluded that using Io-PTH with this

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interpretation criterion in addition to a meticulous surgical technique offers the best results in treatment of PC. Another important topic of discussion is the indication whether to perform or not CND in conjunction with en bloc resection of PC. Approximately 10% of PC show initial lymph node involvement [30]. Currently concomitant neck dissection receives general consensus only in cases with clinical suspicion of lymph node metastases. Insufficient non-radical surgery heightens the risk of recurrence and specific mortality. However, there is no proof that preventive neck dissection increases survival rates [31]. In summary, currently no specific guidelines for SMPC are available. Multi-gland involvement and the possibility to present as bilateral makes the optimal strategy of SMPC more complex than in case of usual single PC. First of all, in case of SMPC the risk not to adequately treat the patient at first intervention relies not only in the malignant behavior as in classical single PC but also in its multi-gland expression. For this reason, the preoperative study should be particularly detailed and complete. Unfortunately, the urgent clinical conditions may represent an obstacle to complete all the preoperative studies in favour of an immediate surgical approach. In this sense it is of utmost importance to pursue a multidisciplinary approach ensuring the best medical treatment before surgery. In any case, if the preoperative studies are incomplete, BNE should be always preferred.Also the surgical decision-making has peculiar implications in terms of benefit and risks balance in the case of SMPC, compared to single PC, especially if it is bilateral. As a matter of fact, in case of a radical surgical approach the bilateral gland involvement might imply not only total thyroidectomy but also the possibility to add CND and in some cases also the possibility to achieve more extensive resection of surrounding tissues with consequent significantly increased intraoperative risks and potential complications. On the other hand, insufficient radicality at primary intervention may result in the recurrence of disease, and the need of subsequent surgical procedures that are linked to elevated rates of complications. In case of SMPC surgical expertise is even more crucial than in single PC in order to obtain the best outcome and reduce complications and recurrence. Indeed, an accurate and expert intraoperative evaluation may guide the surgical decision-making in order to achieve the most radical approach only on the side with evident invasion or in case of evident lymph node involvement, and reserving a less extensive surgery if the expression of the disease is limited and not symmetric. Therefore, in case of suspected SMPC, since the expertise and the availability of intraoperative adjuncts plays a decisive role in optimizing outcomes, the patient should be always addressed to specialized centers.

4.5. Pathology and Molecular Analysis

The 2022 World Health Organization (WHO) classification divides parathyroid pathology into three categories: parathyroid adenoma, atypical parathyroid tumor (APT), and PC. From a histopathological perspective, APT and PC share overlapping features. The histological diagnosis of PC still requires the presence of at least one of the following criteria: (i) angioinvasion, defined as tumor infiltration through the vessel wall with associated thrombus, or intravascular tumor cells admixed with thrombus; (ii) lymphatic invasion; (iii) perineural (intraneural) invasion; (iv) direct malignant invasion into adjacent anatomical structures; or (v) histological or cytological evidence of metastatic disease [32]. The classification criteria for PC remained unclear for a long time, and for this reason, it is possible that some of the cases reported in the literature as carcinomas were actually unrecognized APT [22]. Histology data available from the cases of SMPC object of the present review are scarce but sufficient to exclude cases of APT. All the cases reported, independently from the clinical expression or intraoperative appearance, met the criteria for PC diagnosis. From a molecular perspective, there are presently no established clinical guidelines pertaining to the routine investigation of genetic mutations in PC. Nonetheless, one of the most thoroughly examined genes in this context is CDC73 (formerly HRPT2), which encodes parafibromin, a tumor suppressor protein that plays a critical role in transcriptional regulation, cell proliferation, and tumor suppression. Inactivating mutations in CDC73 are often found in both sporadic and syndromic PC, especially linked to hyperparathyroidism-jaw tumor (HPT-JT) syndrome. Other genes associated with PC include NF1, PTEN, and PIK3CA [33]. Molecular sequencing may have clinical value in selected

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cases, as recent studies have identified potentially effective therapies targeting these molecular alterations [34,35]. No data concerning molecular characterization are described in the reviewed cases of SMPC. Complete gene sequencing was performed in the case treated at our centre but no alteration in the genes involved in PC was found.

5. Conclusions

The extreme rarity of SMPC cases reported in the literature and the heterogeneous approach described do not allow us to draw definitive conclusions for its best management. Compared to classical form of PC, peculiarity expression of SMPC relies in multi-gland and potential bilateral involvement. No evident difference in clinical presentation and biochemical findings between classical single PC and SMPC exist and may be used to predict SMPC. Prediction of multi-gland involvement could be improved if complete preoperative localization studies are accomplished. MIBI scan showed the best accuracy in identifying multi-gland involvement in the reviewed cases, but it did not allow to identify malignancy. On the contrary, US proved more effective in detecting malignancy but often failed in identifying the second abnormal gland as parathyroid and malignant. If complete preoperative study is not available before surgery, BNE should always be the preferred surgical option. According to data available, surgical expertise seems to play a crucial role to guide intraoperative decision-making in case of SMPC. Indeed, in case of SMPC compared to single PC the evaluation of balance between surgical outcome, risk of complications and risk of recurrence requires higher expertise to perform tailored surgery. Therefore, SMPC cases, especially in case of redo surgery, should always be addressed to referred centers. Finally, as in case of other rare diseases, all SMPC cases should be collected in international registers and undergo accurate genetic and molecular investigations. Only cumulative and detailed information may allow in the future to better predict SMPC and define specific diagnostic and therapeutic guidelines.

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Abbreviations

The following abbreviations are used in this manuscript:

SMPC	Synchronous multiple parathyroid carcinoma
sPHP	Sporadic primary hyperparathyroidism
PC	Parathyroid carcinoma
US	Ultrasound scan
MIBI	Sestamibi
MPC	Multiple parathyroid carcinoma
DPC	Double parathyroid carcinoma
PTH	Parathyroid Hormone
PTX	Parathyroidectomy
BNE	Bilateral neck exploration
CND	Central neck dissection
IO-PTH	Intraoperative PTH
CT	Computed tomography
MRI	Magnetic resonance imaging
ESES	European Society of Endocrine Surgeons
WHO	World Health Organization

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APT	Atypical parathyroid tumor
HPT-JT	Hyperparathyroidism-jaw tumor

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