Case Report

Parathyroid Carcinoma in Tertiary Referral Centre: A 12-Year Case Series

Napas Tanamai MD[1]

[1] Center of Excellence in Otolaryngology Head and Neck Surgery, College of Medicine, Rajavithi Hospital, Rangsit University, Bangkok, Thailand

Background: Parathyroid carcinoma (PC) is a rare malignancy that is difficult to diagnose preoperatively, and when it is suspected from clinical features and laboratory results, en-bloc resection is performed.

Objective: To retrospectively review the prevalence, clinical presentations, laboratory findings, management modalities, and treatment outcomes of PC cases in the present study tertiary referral hospital.

Materials and Methods: Patients with PC that attended the present center between 2008 and 2019 were included. Demographic data, clinical presentations, preoperative laboratory results, management, and outcomes were retrospectively reviewed.

Results: Ten of 102 cases (9.8%) of the primary hyperparathyroidism were diagnosed as PC. Five were male (50%), and the mean age at diagnosis was 47.90±15.50 years. All PC patients presented with renal or bony manifestations, and five out of nine (45.5%) had palpable neck mass. Mean preoperative parathyroid hormone and serum calcium were 1,688.56±858.84 pg/mL and 15.30±3.27 mg/dL, respectively. In eight of these PC cases (80%), en-bloc resection was performed, and six patients underwent postoperative radiation treatment. Two patients died due to uncontrolled hypercalcemia with distant metastasis at 5.5- and 8-years after diagnosis.

Conclusion: The prevalence of PC among primary hyperparathyroidism is as high in Thailand as in other Asian countries. En-bloc resection is performed when clinical presentations and laboratory results are suggestive of PC. Postoperative radiation is considered in selected cases. Intractable hypercalcemia is the main cause of death.

Keyword: Parathyroid cancer; Parathyroid carcinoma; Primary hyperparathyroidism; Hypercalcemia; Parathyroid carcinoma case series

Received 5 February 2021 | Revised 20 April 2021 | Accepted 21 April 2021

J Med Assoc Thai 2021;104(6):1033-8

Website: http://www.jmatonline.com

Parathyroid carcinoma (PC) is a rare endocrine malignancy that accounts for 0.005%[1] of all cancers and 0.5% to 5% of primary hyperparathyroidism[2-7]. It can occur as a part of multiple endocrine tumor type I (MEN1) or hyperparathyroidism-jaw tumor (HPT-JT) syndrome that caused by a mutation of the HRPT2 gene, which is found approximately 67% inactive in sporadic PC[8]. Gender distribution is fairly equal[9-11], and the most common age of diagnosis is in the fifth decade of life[9,11-13].

Most cases of PC involve excessive secretion of the parathyroid hormone (PTH), and present with the symptoms of hypercalcemia, which include nausea, vomiting, constipation, lethargy, fatigue, mood disturbance, weight loss, and bone and renal involvement. It is difficult to diagnose carcinoma of the parathyroid preoperatively[4,6] because its manifestations are similar to those of parathyroid adenoma or hyperplasia. Diagnosis is usually made after permanent pathologic results are obtained. Some researchers in the literature have proposed that markedly elevated PTH levels at three to 10 times above upper normal limits, profound hypercalcemia of 14 or more mg/dL, and palpable neck mass may predict of PC[10-13].

Suspicion of PC at the initial evaluation helps to decide the extent of surgery. En-bloc resection of parathyroid tumors is currently recommended for cure including ipsilateral thyroidectomy and removal of surrounding involved tissue with grossly free margins[3,14-17]. Postoperative PTH and serum calcium levels are monitored to confirm that all hyperfunctioning parathyroid tissue has been removed.

The role of radiotherapy remains inconclusive because of the small number of cases of PC and it is considered not to be radiosensitive[12,18]. Some

Correspondence to:

Tanamai N.

Center of Excellence in Otolaryngology Head and Neck Cancer, Rajavithi Hospital, College of Medicine, Rangsit University, 2, Phayathai Road, Ratchathewi district, Bangkok 10400, Thailand.

Phone: +66-2-2062900 ext. 21101, +66-81-3461616, **Fax**: +66-2-2062927

Email: ntanamai@gmail.com

How to cite this article:

Tanamai N. Parathyroid Carcinoma in Tertiary Referral Centre: A 12-Year Case Series. J Med Assoc Thai 2021;104:1033-8.

doi.org/10.35755/jmedassocthai.2021.06.12435

studies have suggested that postoperative radiation may reduce locoregional recurrence and improve disease-free survival[19,20].

Local recurrence and uncontrolled hypercalcemia are the main causes of mortality in PC. The 5-year and 10-year overall survival rates have been found to vary from 78% to 82% and 60% to 65%, respectively[13,21-23].

In the current retrospective study, the authors reviewed the prevalence of parathyroid cancer, its clinical presentations, laboratory findings, management modalities, and treatment outcomes in the present study tertiary referral hospital.

Materials and Methods

The authors included all patients that presented with primary hyperparathyroidism at the Center of Excellence in Otolaryngology Head and Neck Surgery, Rajavithi Hospital, Thailand between January 2008 and December 2019. Patients with histopathological diagnosis of PC were included in the present study series. The demographic data, brief clinical presentations, preoperative laboratory results, management, and outcomes were retrospectively reviewed. The study was approved by the Ethics Committee of Rajavithi Hospital (No.169/2563). The patients were informed about the study and data collection, and they signed the consent forms. The study was registered in the Thai Clinical Trial Registry and the identification number was TCTR20201223002. The present case series has been reported in the line with PROCESS Guideline.

Results

The authors enrolled 102 patients with primary hyperparathyroidism, 10 of whom (9.8%) were diagnosed with PC postoperatively from the pathological results. Of these, five (50.0%) were male, and their mean age at diagnosis was 47.90±15.50 years with a median of 53 years and a range of 15 to 63 years (Table 1).

Clinical presentations suggested the symptoms of hypercalcemia such as nausea and vomiting, fatigue, constipation, pancreatitis, renal calculi, and bone pain. Three had pathological fracture, four had renal impairment, and five had palpable neck mass (45.5%). Preoperative intact PTH levels were very high, with most exceeding a thousand, and just two below that level (776 and 469 pg/mL), with a mean of 1,688.56±858.84 pg/mL and a range of 469 to 2,913. The mean serum calcium level was 15.30±3.27 mg/dL with a range of 11.4 to 22 mg/dL. The laboratory results are shown in Table 1 (one patient's data were missing).

Most patients (80.0%) underwent en-bloc resection with ipsilateral thyroidectomy and central neck dissection, while one had parathyroidectomy, and another underwent parathyroidectomy with ipsilateral thyroidectomy. Six patients received postoperative radiotherapy (60.0%), and one also received chemotherapy due to lung and bone metastasis with persistent hypercalcemia (Table 1).

Patients were followed up until 2019. The mean period of follow-up was 9.9 years with a range of three to 18 years, and most (80.0%) were still alive at the end of the period without recurrent hyperparathyroidism. However, two died from intractable hypercalcemia with local recurrence and distant metastasis (Table 1).

Patient no.5 had recurrent hyperparathyroidism from lung metastasis two years after en-bloc resection, followed by postoperative radiation due to positive margin, and she underwent right lower lung lobectomy. Two years later, she had recurrent hypercalcemia, and complete thyroidectomy was performed with central neck dissection, but hyperparathyroidism persisted. PET scan was done and showed positive result at the midline and right side of the neck. The patient refused further operative treatment, and she subsequently passed away due to intractable hypercalcemia 5.5 years after diagnosis.

Patient no.6 underwent en-bloc resection because of suspicion of parathyroid cancer preoperatively, but the final pathologic result was reviewed with pathologist, and confirmed parathyroid adenoma size 2.5 centimeters without characteristic of carcinoma in the specimen, he had hypoparathyroidism and hypocalcemia postoperatively. Two years later, he developed hyperparathyroidism, and MIBI scan and neck ultrasound revealed uptake lateral to the right side of the thyroid, size 0.75×0.75 centimeters. Right thyroidectomy with paratracheal dissection was performed, and as the pathological report revealed PC with infiltrative subcutaneous tissue, he received postoperative radiation. After the second surgery, he had persistent hypercalcemia with progressively higher PTH levels, MIBI scan did not show any uptake in the following year, and two years later, another MIBI scan showed no uptake at thyroid bed but increased uptake at the left shoulder and right hemithorax. He was found to have bilateral multiple pulmonary nodules in a chest computed tomography (CT) scan, and chemotherapy was administered. This was not effective, and he died from intractable hypercalcemia due to lung and bone metastasis eight

Table 1. Demographic data, clinical presentations, preoperative laboratory results, management, duration of follow-up and status of 10 patients who were diagnosed with parathyroid cancer

No.	Sex	Age (years)	Clinical presentations	Serum PTH (pg/mL)	Serum calcium (mg/dL)	Surgery	Tumor size (cm)	Other treatments	Follow-up period (years)/status
1	F	47	Neck mass, renal impairment	776	13.0	Parathyroidectomy	NA	RT	18 ears/disease free
2	F	62	Fatigue, constipation, bone pain, pathological fracture	1,229	17.0	En-bloc resection	1×2	-	17 ears/disease free
3	F	56	Constipation, neck mass	2,510	22.0	En-bloc resection	1.7×1.5×1	-	12 years/disease free
4	M	15	Neck mass, pathological fracture, renal calculi	1,164	17.1	En-bloc resection	2.5×2	-	12 years/disease free
5	F	61	NA	NA	NA	En-bloc resection	NA	RT	5.5 years/death (lung metastasis, local recurrence, intractable hypercalcemia)
6	M	33	Bone pain, pathological fracture, renal impairment	2,500	14.2	En-bloc resection	1×0.8×0.6	RT, CMT	8 years/death (lung and bone metastasis, intractable hypercalcemia)
7	M	36	Neck mass, hoarseness	469	16.9	Parathyroidectomy with ipsilateral thyroidectomy	9×5.5×4.5	-	9 years/disease free
8	M	63	Constipation, neck mass, bone pain, renal impairment	1,480	11.4	En-bloc resection	4×2	RT	8 years/disease free
9	M	58	Pancreatitis, bone pain, renal impairment	2,913	13.4	En-bloc resection	3.8×3×2.5	RT	6 years/disease free
10	F	53	Fatigue, nausea, vomiting	2,156	12.7	En-bloc resection	3×2×2	RT	3 years/disease free

F=female; M=male; PTH=parathyroid hormone; NA=not available; RT=radiotherapy; CMT=chemotherapy

years after diagnosis.

Discussion

PC is a rare malignancy, accounting for 0.5% to 5% of the patients presenting with primary hyperparathyroidism[2-7]. The prevalence in the present study was rather high, at 9.8%. In the literature, a high proportion of PC has been found in Asian populations, for example, 4.7% and 5.7% in Korea[3,4], and 8.1% in China[22]. This high rate is due to the studies were conducted in the referral hospitals. The high (5%) prevalence in Japan[24] could be attributable to the possibility that asymptomatic primary hyperparathyroidism may not have been detected.

There has been only one study in Thailand[25], reporting PC at 9% (4/45) of the primary hyperparathyroidism, which is close to the prevalence found in the present study. In common with the reports from Korea and China, the present research was performed in a tertiary care hospital that accepts referrals of severe primary hyperparathyroidism suspected of cancer. The uncomplicated cases are treated at the patients' primary hospital. Sometimes, they follow up at an Internal Medicine department if they did not meet the indications for surgery, and some cases of asymptomatic hypercalcemia may be missed, as there is no routine calcium screening in Thailand.

The gender distribution was equal with five men and five women, similar to the findings of other reports in the literature[9,11,21-23]. However, this differs from the benign primary hyperparathyroidism that occurs more commonly in women. In the present series of 102 patients with primary hyperparathyroidism, 9.8% were diagnosed with parathyroid cancer, with 14.29% (5/35) of males compared to only 7.46% (5/67) of females. Mean age at diagnosis was 53 years, similar to the reports from Korea[4], Japan[24], and China[26], which was between 50 and 54 years.

All patients presented with symptomatic hypercalcemia, and half had renal problems such as renal calculi or renal impairment, or skeletal complaints such as bone pain or pathological fracture. The authors found 45.5% had palpable neck mass, which is similar to other reports in the literature in which the proportion ranged from 30% to 70%[10,15,18,24]. However, it is different from the only other study in Thailand in which none of the four parathyroid cancer patients had neck mass[25]. This may be due to the small number of patients in that study.

Preoperative PTH levels in PC patients have been reported at 3 to 10 times higher than the normal upper

limits. In the present series, most patients had PTH more than 10 times higher. This was in line with the findings of Shulte et al[27] in which mean PTH was 11.6±12.5 times higher than normal upper limits, and Xue et al[22] in which a median PTH of 1,622.5 pg/mL with a range of 200 to 3,251 was found. While mean serum calcium level was 15.30±3.27 mg/dL, this was similar to the levels in other studies that found levels between 14.03 and 19.8 mg/dL[10,12,27].

Preoperative diagnosis of PC is challenging because there are no definite parameters to differentiate it from benign parathyroid lesions, which are usually impalpable neck mass, intact PTH level at two to three times more than upper normal limit, and serum calcium level at just above upper normal limit[4,10,18]. Furthermore, fine needle aspiration for cytology is not advised because it cannot evaluate capsular invasion of the tumor, and there is a risk of tumor seeding in the needle tract. PTH levels of more than 560 pg/mL, serum calcium levels of over 12.5 mg/dL and large parathyroid volume above 2.55 centimeters have been flagged as suggestive of PC[22], with a sensitivity of 73.7% and specificity of 75.6%. A Korean series concluded that tumor size of more than 3 centimeters and serum alkaline phosphatase above 285 IU/L, may be the predictors of PC, with sensitivity of 90.1% and 83.3% and specificity of 92.1% and 97%, respectively[4].

In the present study, the authors suspected PC when the patient had very high PTH of more than a thousand, symptomatic high serum calcium, and palpable neck mass. In these circumstances, the authors decided to perform oncologic en-bloc resection. This was similar to the decisions made in several other studies[16,18,22,28]. Intraoperative finding of tumor invasion also prompted the surgeon to perform oncologic resection, even if preoperative parameters did not indicate parathyroid cancer.

Performing en-bloc resection of parathyroid tumor, and ipsilateral thyroidectomy with paratracheal lymph node dissection while avoiding tumor rupture and spillage in the surgical field form the mainstay management for cure. Schulte and Talat[29] found that en-bloc resection with clear margin reduced local recurrence and improved disease-free survival. Some studies[6,9,23] have proposed that parathyroidectomy is sufficient in selected cases because en-bloc resection does not show improved survival, but the results of these studies were limited by the small numbers of patients. In the present series, two patients had PTH of less than one thousand and underwent parathyroidectomy and thyroid lobectomy in the event of palpable neck treatment, is at the discretion of the surgeon (patient no.1 and 7) (Table 1).

PC is considered radioresistant[18], so that the role of postoperative radiation is still controversial. Some studies in the literature have suggested that adjunctive radiation may reduce locoregional recurrence[20,30] and that it is indicated when there is local invasive disease such as invading esophagus, trachea, vascular, or soft tissue, persistent high PTH, or locally recurrent tumor[31]. In the current study, six patients underwent postoperative radiation due to positive margin (no.1 and 5), local recurrence (no.6), and vascular or lympho-vascular invasion (no.8 to 10) (Table 1). There was no evidence of clinical benefits of chemotherapy[7,29]. In the present series, one patient received chemotherapy when he was found to have pulmonary and bone metastasis, but the treatment was not effective.

Intractable hypercalcemia is the main cause of death in parathyroid cancer with 5-year and 10-year overall survival rates of 80% to 85% and 60.7% to 77%, respectively[10,19,21-23,32]. Being older than 65 years, having a serum calcium greater than 15 mg/dL and having vascular invasion were prognostic signs of local recurrence proposed by Silva-Figueroa et al[32]. Meanwhile, tumor recurrence could be predicted by such variables as intraoperative tumor rupture, presence of mitotic figures in tumor cells, and tumor invasion of vital structures or node metastasis[5]. In the present study, no patient died at 5-years follow-up but patient no.10 was lost to follow-up after three years. Two patients passed away at 5.5- and 8-years after diagnosis of PC due to local recurrence (no.5) and distant metastasis (no.6) with uncontrolled hypercalcemia.

This current study is the first series to collect the data of PC in a Thai tertiary hospital. Making preoperative diagnosis is challenging, and further data comparing variables between benign and malignant primary hyperparathyroidism should be collected to establish whether there are any parameters to differentiate in the Thai population. All PC patients should be followed up for surveillance of locoregional recurrence or distant metastasis to determine survival rates in Thailand.

Conclusion

PC has a high rate of diagnosis in Thailand as in other Asian countries, and the authors suspects cancer when the patient has PTH level of more than a thousand, symptomatic hypercalcemia, and palpable neck mass. En-bloc resection is the authors' main

choice of surgery. Adjuvant radiation in selected cases when there is positive margin, invasion to other structures, or recurrent tumor after second resection would be considered. Intractable hypercalcemia from local recurrence or distant metastasis is the main cause of death.

What is already known on this topic?

Parathyroid carcinoma is a rare malignancy with a high proportion in Asian literatures. There is no definite parameter to diagnose parathyroid cancer preoperatively.

What this study adds?

The study found a higher prevalence of parathyroid carcinoma among Thai population of 9.8% comparing to 0.5% to 5% in the literatures. The authors suggest performing oncologic resection when preoperative PTH level is more than a thousand, symptomatic hypercalcemia, and palpable neck mass.

Acknowledgement

The author would like to thank Dr. Porn-ake Apipan and Dr. Somjin Chindavijak for their advice and support, and Department of Research and Technology Assessment for their help.

The data can be shared on request.

Conflicts of interest

The author has no conflicts of interest to declare.

References

1. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. Two hundred eighty-six cases of parathyroid carcinoma treated in the U.S. between 1985-1995: a National Cancer Data Base Report. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer 1999;86:538-44.
2. Hakaim AG, Esselstyn CB Jr. Parathyroid carcinoma: 50-year experience at The Cleveland Clinic Foundation. Cleve Clin J Med 1993;60:331-5.
3. Lee YS, Hong SW, Jeong JJ, Nam KH, Chung WY, Chang HS, et al. Parathyroid carcinoma: a 16-year experience in a single institution. Endocr J 2010;57:493-7.
4. Bae JH, Choi HJ, Lee Y, Moon MK, Park YJ, Shin CS, et al. Preoperative predictive factors for parathyroid carcinoma in patients with primary hyperparathyroidism. J Korean Med Sci 2012;27:890-5.
5. Villar-del-Moral J, Jiménez-García A, Salvador-Egea P, Martos-Martínez JM, Nuño-Vázquez-Garza JM, Serradilla-Martín M, et al. Prognostic factors and staging systems in parathyroid cancer: a multicenter cohort study. Surgery 2014;156:1132-44.
6. Basceken SI, Genc V, Ersoz S, Sevim Y, Celik SU, Bayram IK. Is local resection sufficient for parathyroid carcinoma? Clinics (Sao Paulo) 2015;70:247-9.
7. Medas F, Erdas E, Loi G, Podda F, Pisano G, Nicolosi A, et al. Controversies in the management of parathyroid carcinoma: A case series and review of the literature. Int J Surg 2016;28 Suppl 1:S94-8.
8. Shattuck TM, Välimäki S, Obara T, Gaz RD, Clark OH, Shoback D, et al. Somatic and germ-line mutations of the HRPT2 gene in sporadic parathyroid carcinoma. N Engl J Med 2003;349:1722-9.
9. Lee PK, Jarosek SL, Virnig BA, Evasovich M, Tuttle TM. Trends in the incidence and treatment of parathyroid cancer in the United States. Cancer 2007;109:1736-41.
10. Schaapveld M, Jorna FH, Aben KK, Haak HR, Plukker JT, Links TP. Incidence and prognosis of parathyroid gland carcinoma: a population-based study in The Netherlands estimating the preoperative diagnosis. Am J Surg 2011;202:590-7.
11. Sadler C, Gow KW, Beierle EA, Doski JJ, Langer M, Nuchtern JG, et al. Parathyroid carcinoma in more than 1,000 patients: A population-level analysis. Surgery 2014;156:1622-30.
12. Erovic BM, Goldstein DP, Kim D, Mete O, Brierley J, Tsang R, et al. Parathyroid cancer: outcome analysis of 16 patients treated at the Princess Margaret Hospital. Head Neck 2013;35:35-9.
13. Allen ME, Semrad A, Yang AD, Martinez SR. Parathyroid carcinoma survival: improvements in the era of intact parathyroid hormone monitoring? Rare Tumors 2013;5:e12.
14. Schulte KM, Talat N, Galata G, Gilbert J, Miell J, Hofbauer LC, et al. Oncologic resection achieving r0 margins improves disease-free survival in parathyroid cancer. Ann Surg Oncol 2014;21:1891-7.
15. Givi B, Shah JP. Parathyroid carcinoma. Clin Oncol (R Coll Radiol) 2010;22:498-507.
16. Cetani F, Pardi E, Marcocci C. Update on parathyroid carcinoma. J Endocrinol Invest 2016;39:595-606.
17. Dąbrowska A, Tarach J, Zwolak A. Primary hyperparathyroidism due to parathyroid cancer - a diagnostic and management challenge. Endokrynol Pol 2015;66:150, 7-67.
18. Wei CH, Harari A. Parathyroid carcinoma: update and guidelines for management. Curr Treat Options Oncol 2012;13:11-23.
19. Busaidy NL, Jimenez C, Habra MA, Schultz PN, El-Naggar AK, Clayman GL, et al. Parathyroid carcinoma: a 22-year experience. Head Neck 2004;26:716-26.
20. Munson ND, Foote RL, Northcutt RC, Tiegs RD, Fitzpatrick LA, Grant CS, et al. Parathyroid carcinoma: is there a role for adjuvant radiation therapy? Cancer 2003;98:2378-84.
21. Asare EA, Sturgeon C, Winchester DJ, Liu L, Palis B, Perrier ND, et al. Parathyroid carcinoma: an update on treatment outcomes and prognostic factors from the

National Cancer Data Base (NCDB). Ann Surg Oncol 2015;22:3990-5.
22. Xue S, Chen H, Lv C, Shen X, Ding J, Liu J, et al. Preoperative diagnosis and prognosis in 40 parathyroid carcinoma patients. Clin Endocrinol (Oxf) 2016;85:29-36.
23. Hsu KT, Sippel RS, Chen H, Schneider DF. Is central lymph node dissection necessary for parathyroid carcinoma? Surgery 2014;156:1336-41.
24. Obara T, Okamoto T, Kanbe M, Iihara M. Functioning parathyroid carcinoma: clinicopathologic features and rational treatment. Semin Surg Oncol 1997;13:134-41.
25. Prasarttong-Osoth P, Wathanaoran P, Imruetaicharoenchoke W, Rojananin S. Primary hyperparathyroidism: 11-year experience in a single institute in Thailand. Int J Endocrinol 2012;2012:952426.
26. Cao J, Chen C, Wang QL, Xu JJ, Ge MH. Parathyroid carcinoma: A report of six cases with a brief review of the literature. Oncol Lett 2015;10:3363-8.
27. Schulte KM, Gill AJ, Barczynski M, Karakas E, Miyauchi A, Knoefel WT, et al. Classification of parathyroid cancer. Ann Surg Oncol 2012;19:2620-8.
28. Machado NN, Wilhelm SM. Parathyroid cancer: a review. Cancers (Basel) 2019;11:1676.
29. Schulte KM, Talat N. Diagnosis and management of parathyroid cancer. Nat Rev Endocrinol 2012;8:612-22.
30. Selvan B, Paul MJ, Seshadri MS, Thomas N, Paul T, Abraham D, et al. High index of clinical suspicion with optimal surgical techniques and adjuvant radiotherapy is critical to reduce locoregional disease progression in parathyroid carcinoma. Am J Clin Oncol 2013;36:64-9.
31. Christakis I, Silva AM, Williams MD, Garden A, Grubbs EG, Busaidy NL, et al. Postoperative local-regional radiation therapy in the treatment of parathyroid carcinoma: The MD Anderson experience of 35 years. Pract Radiat Oncol 2017;7:e463-70.
32. Silva-Figueroa AM, Hess KR, Williams MD, Clarke CN, Christakis I, Graham PH, et al. Prognostic scoring system to risk stratify parathyroid carcinoma. J Am Coll Surg 2017;224:980-7.