Oncology

Clinical Study

Oncology
DOI: 10.1159/000541543

Received: March 24, 2024
Accepted: September 10, 2024
Published online: September 19, 2024

Predictive Ability of Rule of 3 in Parathyroid Cancer: Outcomes from a South Asian Cohort

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Keywords
Parathyroid surgery · Cancer · Hyperparathyroidism · Parathyroidectomy · Predictive factor

Abstract

Background: Preoperative diagnosis of parathyroid cancer (PC) where possible allows for en-bloc resection of the tumour, which is associated with excellent prognosis. The rule of >3 (size of tumour larger than 3 cm; corrected calcium more than 3 mmol/L) as proposed by Schulte and Talat has a specificity of 95% in predicting malignancy in parathyroid neoplasms. We looked at the impact of rule of 3 in predicting malignancy and outcomes on intervention in a South Asian cohort. ***Methods:*** Patients who underwent parathyroid surgery between 2010 and 2023 at two tertiary referral centres were assessed. Patients with PC were selected and their clinicopathological parameters, treatment modalities, and outcomes were analysed. ***Results:*** Thirteen of 336 (3.8%) patients with a mean age of 61.8 (±17.5) years were diagnosed with PC during the study period. The highest mean preoperative values were PTH (92.4 ± 66.27 pmol/L), highest corrected calcium (3.21 ± 0.28 mmol/L), and alkaline phosphatase (419 IU/mL). Nine patients underwent en-bloc excision while the other had focussed parathyroidectomy. Recurrences were recorded in 2 (28.5%) patients over a mean follow-up period of 69 (±48.6) months. One patient with lung metastasis underwent video-assisted thoracic surgery. There was no disease specific mortality in this cohort during the study period. ***Conclusions:*** In our experience, the predictive rule of 3 has low sensitivity to suspect PC preoperatively, resulting in limited usefulness in clinical practice. Outcomes appear to be less favourable with higher recurrence rates in cases where less than en-bloc resection is performed.

Introduction

Parathyroid carcinoma (PC) is a rare malignant tumour, was first described by Quervain [1], is an uncommon cause of primary hyperparathyroidism [2]. The condition has an estimated prevalence of 0.005% of all

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malignancies, with early over 1,000 cases reported in the literature [3, 4]. Preoperative distinction between an adenoma and carcinoma based on the symptoms alone may be difficult, but a malignant parathyroid lesion may be considered in the presence of a palpable neck mass, demonstration of metastasis, significantly elevated serum calcium (>3 mmol/L; >12 mg/dL) and PTH (>3 times the upper limit of normal; usually 10 times the upper limit of normal), specific ultrasonographic features, and a ratio >1 for the results of 3rd:2nd generation parathyroid hormone assays [5, 6]. There remains a challenge to identify parathyroid cancer early to enable cure before metastasis develops.

Given the lack of prospective data, the preferred surgical approach for the treatment of PC is not clear at index surgery or where second stage surgery may be required [7]. The current consensus is for an en-bloc excision (affected parathyroid + ipsilateral hemithyroidectomy +/− ipsilateral central neck dissection) and has shown to result in improved local control. This strategy is associated with better long-term outcomes in terms of cure as adjuvant therapy has not proven successful [8, 9]. As the rate of recurrence is about 50% in most cases, life-long follow-up is mandatory following initial surgical excision [5, 10].

The aim of the study was to look at the predictive impact of rule of 3 in parathyroid cancers and evaluate the outcomes of surgical intervention. We also compared the outcomes from other published series from Asia.

Methodology

The study is a retrospective cohort evaluation of patients with a diagnosis of parathyroid cancer treated at two tertiary referral centres in Singapore and India. All patients who underwent some form of parathyroidectomy between the period from 2010 to 1st quarter of 2023 were included in the study. Clinical suspicion of parathyroid cancer was entertained in patients with rule of 3 (severe hypercalcaemia, very elevated serum parathyroid hormone, tumour with a size of more than 3 cm), with or without the presence of a palpable neck mass [5]. A suspicion of parathyroid cancer was also considered intraoperatively, where the adenomatous lesion was found to be have dense fibrosis or infiltration into the thyroid gland or surrounding structures.

The histological diagnosis was based on one of the following criteria as proposed by the 2022 WHO classification of parathyroid tumours: features of vascular, lymphatic, or neural (perineural or intraneural) invasion, angioinvasion (vascular invasion), invasion into contiguous anatomic structures, and or histologically/cytologically documented metastatic disease [11]. Patients with a diagnosis of atypical adenomas were excluded from the study.

Clinical data on symptomatology, biochemistry, imaging, surgical interventions, histology, adjuvant therapies, and follow-up were collected on patients with PC. PTH was detected by 3rd generation assays and serum calcium corrected against the serum albumin levels. The laboratory reference values for the biochemical parameters collected included serum total calcium (2.10–2.60 mmol/L), serum phosphorus (1.12–1.45 mmol/L), serum alkaline phosphatase (35–129 U/L), and serum PTH (1.6–6.9 pmol/L). The details pertaining to medications such as calcimimetics, bisphosphonates, calcitonin, and diuretics were also collected.

The follow-up was analysed to detect the remission and recurrence of the disease in all patients until death or last documented follow-up. Biochemical remission after the surgery was defined as a drop of serum calcium and intact PTH below the upper level of the reference range. Persistent disease was defined as presence of disease before 6 months of follow-up and recurrence as hyperparathyroidism present after 6 months of follow-up.

Statistical data analysis was performed by using SPSS version 27 (IBM Corporation, New York, USA) and the clinicopathological variables compared by rates and proportions with χ^2 (χ^2 test). The variables with normal distribution are presented as mean with standard deviation (SD). Kaplan-Meier survival curves were generated for the cohort and compared using the log-rank (Mantel-Cox) test. Multivariate analysis was performed using Cox regression analysis to calculate predictors affecting overall survival (OS) with calculation of hazard ratio. The sensitivity and specificity of the rule of 3 in predicting malignancy was evaluated with receiver operating characteristic curve analysis. p values less than 0.05 were considered to be statistically significant. The study was approved by the Institutional Review Board (IRB 2020/00524).

Results

The flow chart of the patients included in the review is shown in Figure 1. A total of 13 of 336 (3.8%) patients with primary hyperparathyroidism were diagnosed to have parathyroid cancer. The mean age of the cohort was 61.8 (±17.5) years with a female ratio of 1.2:1 as shown in Table 1. All patients were symptomatic with nausea,

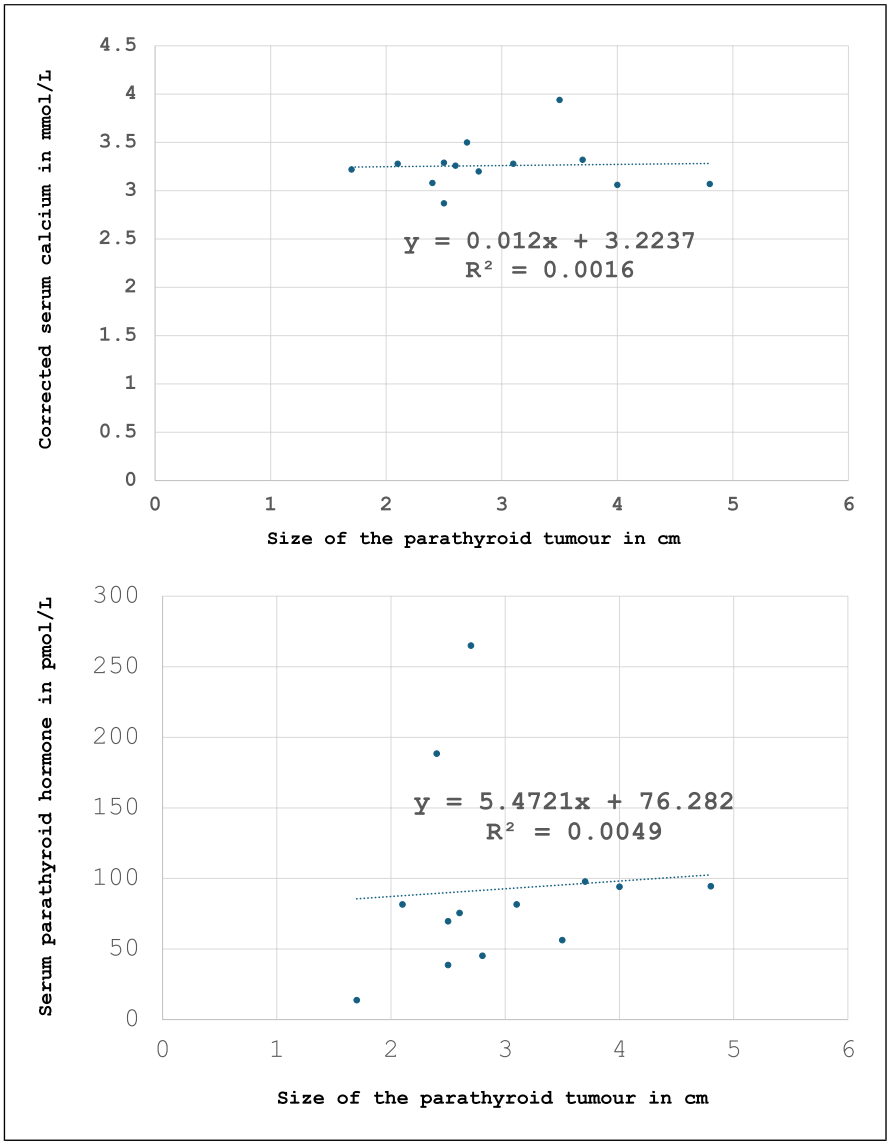

Fig. 1. Correlation between size of parathyroid tumour and serum levels of PTH and calcium.

vomiting, abdominal pain, and confusion being the main symptoms. All patients had hypercalcaemia on presentation and over 60% of them presented with complications like renal stones or pathological fractures.

Palpable neck mass was only detected in 6 patients (46%) with the largest being 3.7 cm and the mean 2.95 cm (range 2.1–4.8 cm). All the tumours were classically demonstrated on ultrasound scans of the neck and ^{99}mTc-MIBI parathyroid scintigraphy. The mean serum PTH level was 92.44 (SD ± 66.27) pmol/L and the mean albumin-corrected serum calcium 3.21 (SD ± 0.28) mmol/L. The correlation coefficient for tumour size and PTH value demonstrated a weak relationship as shown in Figure 1. The preoperative diagnosis of PC based on the rule of 3 was only possible in 6 (46%) of cases and showed no correlation with any parameters as shown in Table 2. The sensitivity and specificity to predict malignancy based on the rule of 3 in our cohort was low as shown by the receiver operating characteristic curve (Fig. 2).

More than 70% of these patients required 3 types of drugs to control their hypercalcaemia prior to surgery (diuretics/bisphosphonates and cinacalcet). All had to use the calcimimetic cinacalcet and 2 patients had to use calcitonin as a 4th drug. Nine patients (69%) underwent the ideal surgical management of PC: parathyroidectomy + ipsilateral hemithyroidectomy with/without central node dissection. Four patients (31%) underwent simple parathyroidectomy (Table 3). The preoperative understanding

Table 1. Demographics of the study population (n = 13)

Parameter	*N* (%)
Age, mean (range), years	61.8 (36–89)
Gender (F:M)	7F:6M
Site of surgery (cancer/% of PHPT)	
India	4 (3.8%)
Singapore	9 (3.8%)
Symptoms	
Abdominal pain	7 (54%)
Renal stones	9 (69%)
Confusion	8 (62%)
Fractures and osteoporosis	7 (54%)
Lethargy and weakness	6 (46%)
Palpable mass	7 (54%)
Imaging	
US	13 (100%)
MIBI	13 (100%)
CT	2 (15%)
PET-FDG	1 (8%)
Size of tumour, mean (range), cm	2.95 (1.7–4.8)
Invasion	
Capsular	11 (85%)
Vascular	11 (85%)
Soft tissue	9 (69%)
Lymph nodes	0 (0%)
Surgery	
Parathyroidectomy alone	4 (31%)
En-bloc resection	9 (69%)
Recurrence	
Parathyroidectomy alone	2 (15%)
En-bloc resection	0 (0%)
Metastasis	1 (8%)
Disease-specific mortality	0 (0%)
Follow-up time, months	69

of these patients was that they harboured an adenoma than a carcinoma.

In this cohort, recurrences were noted in 2 patients who had focussed parathyroidectomy and the specimen was fractured during the surgery. In both patients, there was no preoperative suspicion of parathyroid cancer. One patient developed a local recurrence of PC at 11 months post-op, with neck parathyromatosis, indicating R1 resection. During the next 3 years, this patient had to undergo multiple neck surgeries and radiotherapy to clear away the local disease burden. She is currently disease free. The other patient developed lung metastases at 18 months post-op and had to undergo video-assisted thoracic surgical excision twice. Despite the 2 surgeries, she continued to remain hypercalcaemic and started on cinacalcet again as palliative therapy.

Unilateral recurrent laryngeal nerve palsy was noted in 2 patients. One was temporary and the other permanent. Only 1 patient developed hungry bone syndrome following excision and had a prolonged hospital stay of over a month. The mean follow-up for these patients was 69 months (months with a mean of 69.9 [±48.6] months). Only 1 patient died in this cohort due to an unrelated cardiovascular event, with all the other patients alive and with continuing follow-up. The Kaplan-Meier survival for the cohort is shown in Figure 3. The results from this study report of lower mortality and lower incidence as a cause of PHPT when compared with other published series from South and South East Asia (Table 4). The difference in the outcomes is possibly due to early intervention with en-bloc surgery for most patients, with no disease-specific mortality in the cohort.

Discussion

The rule of 3 in predicting parathyroid cancer preoperatively is less than that as proposed in the literature. The other significant findings from the study were as follows: 3% incidence of parathyroid cancer as a cause of PHPT, higher mean age of onset of disease (61.8 vs. 46.6), lower mortality rate (0% vs. 22%), and recurrence (15% vs. 34%) when compared to other published series from Asia. The incidence of parathyroid cancer reported here as a cause of PHPT is similar to the large published series from around the world, in contrast to the cumulative rate of 12% published series from China [12, 15, 16], Japan [13, 14] and Korea [17]. PC commonly affects a single gland, but multiglandular PC and PC in renal hyperparathyroidism are very rare [18].

Most parathyroid cancers are functional and symptomatic but rarely can be asymptomatic as shown in a few case reports published recently [19–21]. All the patients reported in this cohort were symptomatic and 46% had a palpable neck mass. The rare (2%) non-functioning PC, which would present late with local invasion, mass effects, and distal metastasis, was not detected in this cohort [22]. It is not uncommon for parathyroid cancer patients to present with acute hypercalcaemic crisis, which is a medical emergency as was the case in 31% of our patients. However, to make a diagnosis of parathyroid cancer based on symptoms and hypercalcaemia alone is impossible as patients with benign parathyroid adenomas can also have profound symptoms.

Table 2. Univariate and multivariate analysis of rule of 3 with the various clinicopathological parameters in the cohort

Parameter	Univariate analysis ($p < 0.05$)	Multivariate analysis (log-rank test) ($p < 0.05$)
Age	0.56	NS
Gender	0.43	NS
Tumour size	0.09	NS
Preoperative corrected serum calcium	0.57	NS
Preoperative serum PTH	0.32	NS
Preoperative alkaline phosphatase	0.08	NS
Palpable tumour	0.43	NS
Vomiting	0.19	NS
Abdominal pain	0.19	NS
Renal stones	0.19	NS
Fractures	0.81	NS
Confusion	0.05	0.74
Lethargy	0.006	0.62
Surgery	0.78	NS
Adjuvant therapy	0.37	NS
Recurrence	0.18	NS
Mortality	0.91	NS

NS, not significant.

One thing to note though is the changing trend in the presentation of benign parathyroid disease from symptomatic to asymptomatic disease detected on incidental biochemical screening, even in developing countries [23, 24]. Due to the nonspecific nature of the symptoms and examination, only a high degree of suspicion is required to entertain the possibility of the diagnosis of PC. Schulte et al. describe a useful clinical tool to raise the suspicion of PC based on "the rule of 3" – when a parathyroid of more than 3 cm is present and albumin-corrected calcium is >3 mmol/L, the index of suspicion of PC is higher [5]. With the limited numbers in this cohort, the correlation of size with PTH and calcium was only weakly positive and seen in only 46% of cases.

All the patients in the cohort underwent dual imaging studies (ultrasound thyroid and ^{99}mTc-MIBI parathyroid scintigraphy) to localize the lesion. Some pointers that should raise the suspicion of PC on ultrasound scan include irregular shape and margins with heterogenous echotexture, depth-width ratio >1, cystic change, intra-lesional calcifications, and local invasion [25]. A study by Christakis et al. [26] showed that the specificity of PC localization can go up to 95% when all ultrasound, MIBI, and 4D-CT are utilized. The utility of cytology in making a diagnosis of PC is unproven. Biopsy is contraindicated as rupture and seedling of the tract allow parathyromatosis and in the case of PC, the patient will have no chance of cure even after standard clearance [25, 27]. Besides, interpretation of cancer in parathyroid lesions using a cytological evaluation is inadequate and most often the cytology usually mimics a follicular neoplasm [28, 29].

The mainstay of treatment for PC is *en-bloc* resection, although the ideal treatment strategy is a subject of controversy [30–33]. Minimally, *en-bloc* resection entails the excision of the parathyroid lesion with ipsilateral hemithyroidectomy to avoid spillage of the tumour contents and central node dissection. Longer relapse-free survival and OS has been shown in patients having en-bloc resection compared to parathyroidectomy alone [12, 14, 30, 34]. In this series, 69% of patients underwent en-bloc resection, which is much higher than the other reported series from Asia [10, 12–17] and probably accounts for the better survival in this cohort. The extent of lymph node dissection has

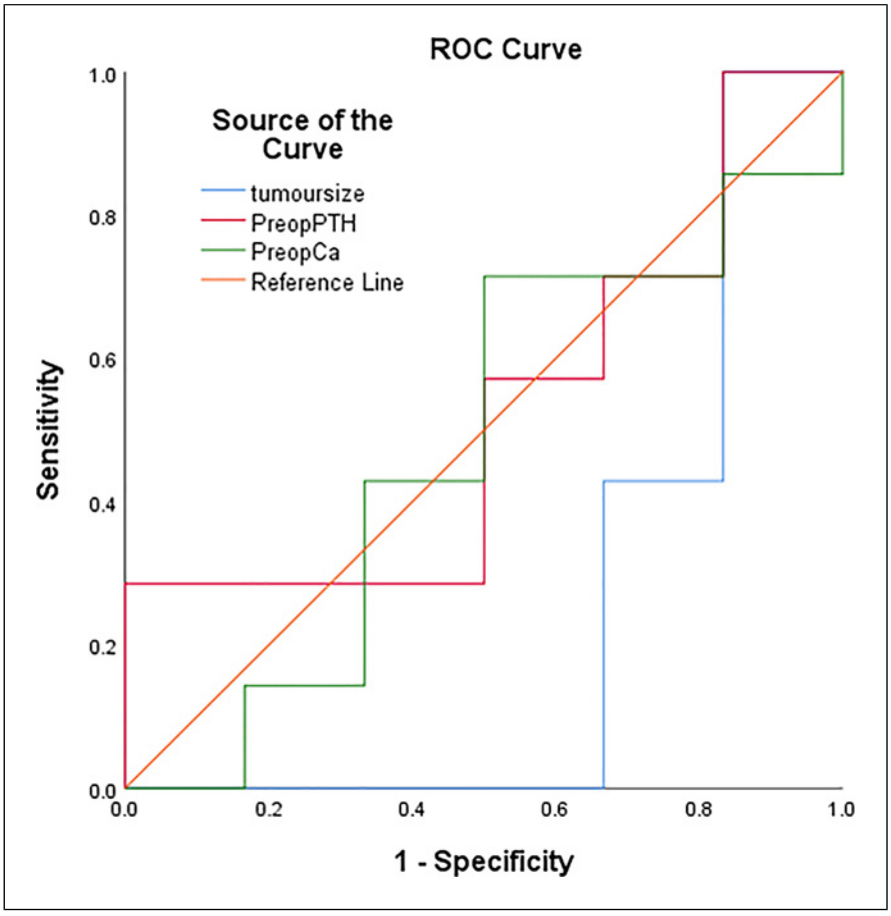

Fig. 2. ROC curve showing the poor sensitivity and specificity of rule of 3 in predicting malignancy in the cohort.

Table 3. Clinicopathological profiles of the cohort (n = 13)

Patient No.	Year of diagnosis	Nature of surgery performed	Pathology	Revision surgery	Follow-up
1	2014	Left inf. PTx with HT	Chief cell type; clear margins	No	Alive
2	2017	Right sup. PTx with HT + CND	Chief cell type; clear margins	No	Dead
3	2018	Left inf. PTx with HT + CND	Chief cell type; clear margins	No	Dead
4	2010	Left inf. PTx with HT + CND	Chief cell type; clear margins	No	Alive
5	2018	Left sup. PTx	Chief cell type; margins positive	Yes	Alive
6	2015	Left inf. PTx	Chief cell type; margins positive	Yes	Alive
7	2016	Left inf. PTx with HT	Chief cell type; clear margins	No	Alive
8	2023	Right inf. PTx with HT	Chief cell type; clear margins	No	Alive
9	2023	Right inf. PTx with HT	Chief cell type; clear margins	No	Alive
10	2019	Right inf. PTx with HT + CND	Chief cell type; clear margins	No	Alive
11	2010	Focussed PTx	Chief cell type; clear margins	No	Alive
12	2012	Right inf. PTx with HT + CND	Chief cell type; clear margins	No	Alive
13	2022	Focussed PTx	Chief cell type; clear margins	No	Alive

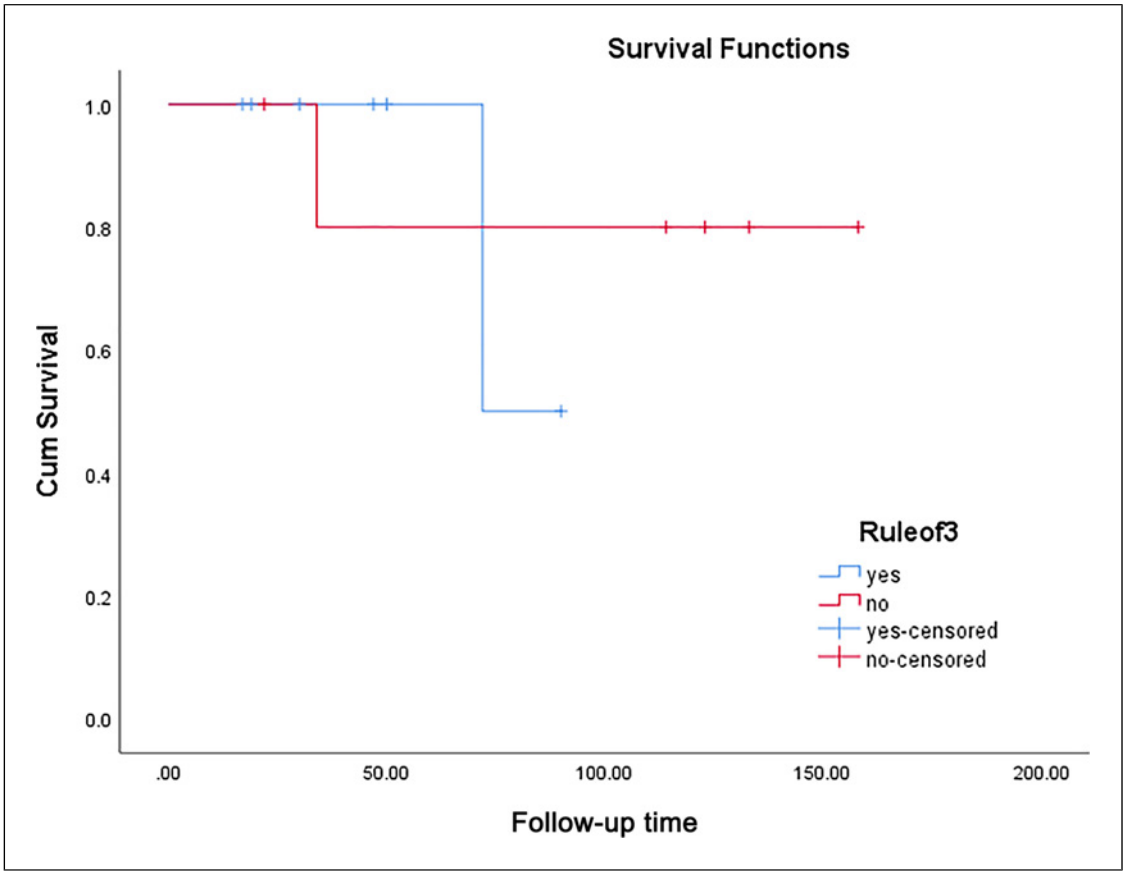

Fig. 3. Kaplan-Meier survival curve of the cohort based on the rule of 3 showed no significant impact on mortality.

not proven consistently to be of benefit as the incidence of lymph node involvement varies between 3 and 32% [35, 36]. Lymph node involvement was not seen in any of the patients who underwent nodal dissection concurrently with en-bloc excision.

A common clinical situation is post-operative diagnosis of PC in a patient who was suspected to have a benign pathology. Previously, a repeat neck exploration with ipsilateral hemithyroidectomy was almost always performed, but this approach has not been clearly shown to reduce local recurrence or improve OS. The clinical management in the above-mentioned scenario is controversial: some authors deem necessary a re-exploration in case of gross characteristics typical of a carcinoma and pathological features of aggressive tumour as extensive vascular or capsular invasion, or persistent post-operative hypercalcaemia, while others consider a re-exploration only in case of clear involvement of thyroid lobe or other structures. We had 3 cases of previously unsuspected PC; we did not go for re-exploration in any case. However, we want to stress the importance of involving the patients in the decision citing the lack of conclusive data in literature.

Disease progression is generally very slow, with a few patients developing local recurrence or distant metastasis following treatment. Recurrences and distant metastasis are seen in 50% of patients who only undergo a parathyroidectomy alone [37]. On review of the Asian cohort, recurrences reported range from 5 to 39% over a mean follow-up period of 53 months [12–15, 17]. Only 2 patients in our cohort developed recurrences that required further intervention in the form of surgery, and both of them continue to be disease free. Once distant metastasis develops, treatment options are limited and cure is unlikely. Mortality has been reported be between 8 and 50% in parathyroid cancers, but there was no disease-specific mortality in our cohort. The difference in mortality could be explained by the en-bloc clearance and early intervention adopted in most of our patients and delayed presentation in other reported cohorts from Asia.

Table 4. Comparative studies of parathyroid cancer from Asia and their reported outcomes

Author	Centre	*N*	Study period	% of PHPT	Mean age	Surgery	Outcomes	Mortality	Follow-up, months
Xue et al. [12] (2016)	China	40	2000–2015	12.4	49	14 PTx 17 en bloc	Recurrence 12 (30%)	9 (22.5%)	49
Okhuwa et al. [13] (2023)	Japan	38	1979–2020	2.5	57	21 en bloc 17 PTx	Recurrence 9 (13%)	3 (7.9%)	63
Iihara et al. [14] (2007)	Japan	38	1981–2005	NR	51	22 en bloc 16 PTx	Recurrence 15 (39%)	9 (23.6%)	119
Hu et al. [15] (2022)	China	68	1992–2021	3.9	43	42 en bloc 26 PTx	Recurrence 41 (60%)	17 (25%)	62
Chen et al. [16] (2023)	China	79	1992–2019	24.6	46	43 en bloc 36 Ptx	Recurrence 25 (31.6%)	NR	44
Shah et al. [38] (2021)	India	19	2010–2018	13.2	46	10 Ptx 9 en bloc	4 (21%)	3 (15.7%)	29
Kong et al. [17] (2021)	Korea	255	2002–2017	16.9	53	172 Ptx 83 en bloc	14 (5.5%)	32 (12.5%)	67
Agarwal et al. [39] (2006)	India	4	1990–2004	4	37	En bloc	3 (75%)	2 (50%)	39
Pinto et al. (this study)	India and Singapore	13	2010–2023	3	62	9 en bloc 4 PTx	2 (15%)	0	69

Conclusions

Parathyroid cancer is rare cancer and early recognition is important for good outcomes. The predictive rule of 3 has low sensitivity to suspect parathyroid cancer, resulting in limited usefulness in clinical practice. Outcomes appear to be less favourable with higher recurrence rates in cases where less than en-bloc resection is performed.

Statement of Ethics

This study protocol was reviewed and approved by National University Hospital (Approval No. IRB 2020/00524).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Author Contributions

All authors contributed to the study conception and design and read and approved the final manuscript. Material preparation and data collection and analysis were performed by Diluka Pinto, George He, Jolene Chia, and Mallika Dhanda. The first draft of the manuscript was written by Diluka Pinto and Mallika Dhanda and all authors commented on previous versions of the manuscript. Conceptualization was by Amit Agrawal and Rajeev Parameswara.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

References

1 De Quervain F. Parastruma maligna aberrata. Langenbeck's Arch Surg. 1909;100(1):334–53. https://doi.org/10.1007/bf02819737

2 Marcocci C, Cetani F, Rubin MR, Silverberg SJ, Pinchera A, Bilezikian JP. Parathyroid carcinoma. J Bone Miner Res. 2008;23(12):1869–80. https://doi.org/10.1359/jbmr.081018

3 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 Database Report. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer. 1999;86(3):538–44. https://doi.org/10.1002/(sici)1097-0142(19990801)86:3<538::aid-cncr25>3.0.co;2-k

4 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(9):1736–41. https://doi.org/10.1002/cncr.22599
5 Schulte K-M, Talat N. Diagnosis and management of parathyroid cancer. Nat Rev Endocrinol. 2012;8(10):612–22. https://doi.org/10.1038/nrendo.2012.102
6 Roser P, Leca BM, Coelho C, Schulte K-M, Gilbert J, Drakou EE, et al. Diagnosis and management of parathyroid carcinoma: a state-of-the-art review. Endocr Relat Cancer. 2023;30(4):e220287. https://doi.org/10.1530/ERC-22-0287
7 Pelizzo MR, Piotto A, Bergamasco A, Rubello D, Casara D. Parathyroid carcinoma. Therapeutic strategies derived from 20 years of experience. Minerva Endocrinol. 2001;26(1):23–9.
8 Cetani F, Pardi E, Marcocci C. Parathyroid carcinoma. Front Horm Res. 2019;51:63–76. https://doi.org/10.1159/000491039
9 Rodrigo JP, Hernandez-Prera JC, Randolph GW, Zafereo ME, Hartl DM, Silver CE, et al. Parathyroid cancer: an update. Cancer Treat Rev. 2020;86:102012. https://doi.org/10.1016/j.ctrv.2020.102012
10 McClenaghan F, Qureshi YA. Parathyroid cancer. Gland Surg. 2015;4(4):329–38. https://doi.org/10.3978/j.issn.2227-684X.2015.05.09
11 Erickson LA, Mete O, Juhlin CC, Perren A, Gill AJ. Overview of the 2022 WHO Classification of Parathyroid Tumors. Endocr Pathol. 2022;33(1):64–89. https://doi.org/10.1007/s12022-022-09709-1
12 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. 2016;85(1):29–36. https://doi.org/10.1111/cen.13055
13 Ohkuwa K, Katoh R, Sugino K, Nagahama M, Kitagawa W, Matsuzu K, et al. Evaluation of factors predicting postoperative recurrence and metastasis of parathyroid cancer: a single-center study. World J Surg Oncol. 2023;21(1):32. https://doi.org/10.1186/s12957-023-02912-2
14 Iihara M, Okamoto T, Suzuki R, Kawamata A, Nishikawa T, Kobayashi M, et al. Functional parathyroid carcinoma: long-term treatment outcome and risk factor analysis. Surgery. 2007;142(6):936–43.e1; discussion 43 e1. https://doi.org/10.1016/j.surg.2007.09.014
15 Hu Y, Cui M, Chang X, Wang O, Chen T, Xiao J, et al. Patterns and predictors of cervical lymph node metastasis in parathyroid carcinoma. Cancers. 2022;14(16):4004. https://doi.org/10.3390/cancers14164004
16 Chen Y, Song A, Nie M, Jiang Y, Li M, Xia W, et al. Clinical and genetic analysis of atypical parathyroid adenoma compared with parathyroid carcinoma and benign lesions in a Chinese cohort. Front Endocrinol. 2023;14:1027598. https://doi.org/10.3389/fendo.2023.1027598
17 Kong SH, Kim JH, Park MY, Kim SW, Shin CS. Epidemiology and prognosis of parathyroid carcinoma: real-world data using nationwide cohort. J Cancer Res Clin Oncol. 2021;147(10):3091–7. https://doi.org/10.1007/s00432-021-03576-9
18 Zivaljevic V, Zivic R, Slijepcevic N, Buzejic M, Dundjerovic D, Trbojevic Stankovic J, et al. Parathyroid carcinoma in chronic renal disease: a case series of three patients and review of literature. Acta Chir Belg. 2023;123(2):199–206. https://doi.org/10.1080/00015458.2021.1970438
19 Poortmans N, Verfaillie G, Unuane D, Raeymaeckers S, Lamote J. Intrathyroidal parathyroid carcinoma presenting as an asymptomatic hypercalcemia: a case report. Acta Chir Belg. 2020;120(6):433–6. https://doi.org/10.1080/00015458.2019.1631626
20 Kim E, Bondarenko E, Eremkina A, Nikiforovich P, Mokrysheva N. Silent intrathyroid parathyroid carcinoma. Endocrinol Diabetes Metab Case Rep. 2023;2023(2):23–0027. https://doi.org/10.1530/EDM-23-0027
21 Wang S, Cui G, Pan Z, Gong Z. A case of asymptomatic giant parathyroid carcinoma. Asian J Surg. 2024;47(1):542–3. https://doi.org/10.1016/j.asjsur.2023.09.098
22 Cetani F, Pardi E, Marcocci C. Parathyroid carcinoma. In: Brandi ML, editor. Parathyroid disorders: focusing on unmet needs. S.Karger AG; 2018. p. 0.
23 Yadav SK, Johri G, Bichoo RA, Jha CK, Kintu-Luwaga R, Mishra SK. Primary hyperparathyroidism in developing world: a systematic review on the changing clinical profile of the disease. Arch Endocrinol Metab. 2020;64(2):105–10. https://doi.org/10.20945/2359-3997000000211
24 Arya AK, Kumari P, Bhadada SK, Agrawal K, Singh P, Mukherjee S, et al. Progressive rise in the prevalence of asymptomatic primary hyperparathyroidism in India: data from PHPT registry. J Bone Miner Metab. 2021;39(2):253–9. https://doi.org/10.1007/s00774-020-01142-w
25 Liu J, Zhan WW, Zhou JQ, Zhou W. Role of ultrasound in the differentiation of parathyroid carcinoma and benign parathyroid lesions. Clin Radiol. 2020;75(3):179–84. https://doi.org/10.1016/j.crad.2019.10.004
26 Christakis I, Vu T, Chuang HH, Fellman B, Figueroa AMS, Williams MD, et al. The diagnostic accuracy of neck ultrasound, 4D-computed tomography and sestamibi imaging in parathyroid carcinoma. Eur J Radiol. 2017;95:82–8. https://doi.org/10.1016/j.ejrad.2017.07.026
27 Wilhelm SM, Wang TS, Ruan DT, Lee JA, Asa SL, Duh QY, et al. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. JAMA Surg. 2016;151(10):959–68. https://doi.org/10.1001/jamasurg.2016.2310
28 Weymouth MD, Serpell JW, Chambers D. Palpable parathyroid adenomas presenting as clinical solitary thyroid nodules and cytologically as follicular thyroid neoplasms. ANZ J Surg. 2003;73(1–2):36–9. https://doi.org/10.1046/j.1445-2197.2003.02636.x
29 Cetani F, Frustaci G, Torregrossa L, Magno S, Basolo F, Campomori A, et al. A nonfunctioning parathyroid carcinoma misdiagnosed as a follicular thyroid nodule. World J Surg Oncol. 2015;13:270. https://doi.org/10.1186/s12957-015-0672-9
30 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(6):1891–7. https://doi.org/10.1245/s10434-014-3530-z
31 Rodrigo JP, Hernandez-Prera JC, Randolph GW, Zafereo ME, Hartl DM, Silver CE, et al. Parathyroid cancer: an update. Cancer Treat Rev. 2020;86:102012. https://doi.org/10.1016/j.ctrv.2020.102012
32 Leonard-Murali S, Ivanics T, Kwon DS, Han X, Steffes CP, Shah R. Local resection versus radical surgery for parathyroid carcinoma: a National Cancer Database analysis. Eur J Surg Oncol. 2021;47(11):2768–73. https://doi.org/10.1016/j.ejso.2021.06.026
33 Roser P, Leca BM, Coelho C, Schulte KM, Gilbert J, Drakou EE, et al. Diagnosis and management of parathyroid carcinoma: a state-of-the-art review. Endocr Relat Cancer. 2023;30(4):e220287. https://doi.org/10.1530/ERC-22-0287
34 Iacobone M, Lumachi F, Favia G. Up-to-date on parathyroid carcinoma: analysis of an experience of 19 cases. J Surg Oncol. 2004;88(4):223–8. https://doi.org/10.1002/jso.20152
35 Hsu KT, Sippel RS, Chen H, Schneider DF. Is central lymph node dissection necessary for parathyroid carcinoma? Surgery. 2014;156(6):1336–41; discussion 41. https://doi.org/10.1016/j.surg.2014.08.005
36 Quaglino F, Manfrino L, Cestino L, Giusti M, Mazza E, Piovesan A, et al. Parathyroid carcinoma: an up-to-date retrospective multicentric analysis. Int J Endocrinol. 2020;2020:7048185. https://doi.org/10.1155/2020/7048185
37 Talat N, Schulte KM. Clinical presentation, staging and long-term evolution of parathyroid cancer. Ann Surg Oncol. 2010;17(8):2156–74. https://doi.org/10.1245/s10434-010-1003-6
38 Shah R, Gosavi V, Mahajan A, Sonawane S, Hira P, Kurki V, et al. Preoperative prediction of parathyroid carcinoma in an Asian Indian cohort. Head Neck. 2021;43(7):2069–80. https://doi.org/10.1002/hed.26677