<span style="color:maroon">**CASE REPORT**</span>

# Severe Hyperparathyroidism Versus Parathyroid Carcinoma
## A clinical dilemma

Mariam Al-Fadhli,[1] *Suhail A R Doi,[1,4] Thomas Muttikkal,[2] Basel Al-Sumait[3]

فرط نشاط الغُدَدُ الدُّرَيقِيَّة الشديد مقابــــل سرطانة الغدة الدُّرَيقِيَّة

معضلة سريرية

مريم الفضلي، سهيل دوي، توماس متكال، باسل السميط

**الملخص**: لا توجد معطيات سريرية أو مختبرية تتيح تشخيص سرطانة الغدد الدريقية قبل الجراحة، ولكن نادرا ما توجد نتيجة نهائية تفرق ما بين الورم الحميد والخبيث، نستعرض هنا حالة فرط نشاط الغدد الدريقية والمعروض على شكل ارتفاع أولي شديد لهرمون الغدد الدريقية وفي مستوى الكالسيوم في المصل وكذلك في مضاعفاتها. كما نناقش هذه الحالة على ضوء مراجعة الأدبيات. شدة ارتفاع هرمون الغدد الدريقية وكذلك التغيرات الكيميائية الأخرى، ومضاعفاتها على الهيكل العظمي والكلى وكتلة الرقبة يجب أن تنبه الطبيب المختص لإحتمال الإصابة بسرطانة الغدة الدريقية. تعتبر العملية الجراحية هي العلاج الوحيد الفعال لسرطانة الغدة الدريقية، والتي يجب أن تجرى في حالة وجود أدنى شك.

**مفتاح الكلمات**: فرط نشاط الغدد الدريقية، سرطانة الغدد الدريقية، جراحة ، مضاعفات، علاج.

**ABSTRACT:** No clinical or laboratory data allow a preoperative diagnosis of parathyroid carcinoma and only occasionally does a definitive finding differentiate an adenoma from a carcinoma. We present a case of primary hyperparathyroidism presenting with severe elevation of parathyroid hormone and serum calcium as well as complications. We go on to discuss the case in the light of a literature review. The severity of the elevation of the parathyroid hormone, other biochemical alterations, the presence of skeletal and renal complications and of a neck mass should alert the clinician to a possible parathyroid carcinoma. Radical surgery is the only effective therapy for parathyroid carcinoma, and should always be performed if a preoperative suspicion is entertained.
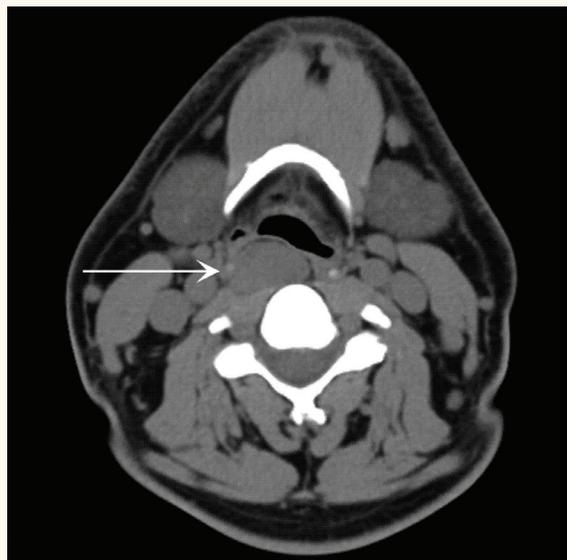
*Keywords:* Hyperparathyroidism; Parathyroid carcinoma; Surgery; Complications; Treatment; Case report; Kuwait

Asymptomatic hypercalcaemia is a common metabolic derangement, usually detected incidentally on routine biochemical screening. The most common aetiologies are primary hyperparathyroidism and cancer. Primary hyperparathyroidism is usually mild and asymptomatic. Only a few patients with primary hyperparathyroidism develop severe hypercalcaemia with serum calcium concentrations above 3.5mmol/L and evidence of end-organ involvement, such as bone or kidney. In contrast, a severe hyperparathyroid state is usually present in parathyroid carcinoma. We present a case of severe primary hyperparathyroidism and then discuss in what circumstances it should be treated as parathyroid carcinoma as well as review the evidence for what action clinicians should take when faced with such a dilemma.

## Case Report

A 44 year-old male with a 4 year history of renal calculi, but no other chronic illness, was admitted to the Urology service at Mubarak Al-Kabeer Teaching Hospital, Jabriya, Kuwait with an impacted urethral stone. He was a naval officer working outdoors, on a normal diet with no symptoms of malabsorption, no neck masses on clinical exam and no cervical lymphadenopathy. He had normal renal and liver functions. He was found to be severely

Departments of [1]Medicine, [2]Radiology and [3]Surgery, Mubarak Al-Kabeer Teaching Hospital, Jabriya, Kuwait and [4]School of Population Health, University of Queensland, Brisbane, Australia
To whom correspondence should be addressed. Email: goldlife203@hotmail.com

**Figure 1a:** Pre-contrast and post-contrast axial images showing soft tissue density lesion (parathyroid carcinoma) with intense enhancement.

**Figure 1b:** The lesion (arrow) is indenting the posterior aspect of pharynx and shows preserved fat planes.

hypercalcaemic (corrected calcium 3.4 mmol/L) and subsequent investigations revealed severe hyperparathyroidism (intact parathyroid hormone (iPTH) 84 pmol/l (normal range 2.2–7.1 pmol/L) and alkaline phosphatase (ALP) 1200 IU/L (normal range 26–88 IU/L). Hypercalcaemia was controlled with saline diuresis, calcitonin (200 units twice daily subcutaneous) and pamidronate (initially a 60 mg infusion followed by 30 mg 10 days later), but despite these intensive measures, there was only a transient drop in serum calcium down to a nadir of 2.7 mmol/L corrected, after which it slowly began to rise again.

Although, on evaluation, he had vitamin D deficiency: 25-hydroxy (OH) vitamin D was 22 nmol/L (Low < 30 nmol/L; insufficient 30–80 nmol/L; normal > 80 nmol/L), his bone mineral density (BMD) T-scores were normal at anterior-posterior (AP) spine and femoral neck suggesting that this state of severe hyperparathyroidism was not long-standing. Given the previous data and the severity of the hyperparathyroidism plus raised ALP and the presence of radiological evidence of metabolic bone disease, it was suspected that he might have parathyroid carcinoma (PTC) which could have evolved from a state of preceding mild primary hyperparathyroidism (accounting for renal calculi over the preceding 4 years). His normal BMD, in retrospect, was attributed to a possibility of recent PTC transformation. Localisation studies confirmed the presence of a large tumour posterior to the trachea and just above the superior pole of the right thyroid lobe by both sestamibi scanning and a computed tomography (CT) scan of his neck [Figures 1 and 2], but was missed by ultrasound (US) in view of its ectopic location. The CT scan also showed the presence of three large (1cm) lymph nodes in the upper jugular group close to the tumour.

He was booked for radical excision (based only on clinical suspicion of PTC) and had this done about 2 weeks after being reviewed by the endocrine team, with central and paratracheal lymph node dissection and right hemithyroidectomy. The three enlarged superior jugular lymph nodes were removed and sent for frozen section that showed no evidence of metastases from the possible parathyroid tumour. This was confirmed by the final pathology report. As expected, he went into hungry bone syndrome post surgery and was managed on parenteral calcium for the first 72 hours. There were no surgical complications and he had complete surgical recovery. He was placed subsequently on alfacalcidol 0.25 mcg twice a day and calcium (Sandoz) 1 gm thrice daily. Histopathology revealed no morphologic features of PTC within the tumour and there was no capsular or vascular invasion. Immumohistochemical studies revealed 5% Ki67 protein positivity and a weakly positive B-cell leukaemia/lymphoma 2 (BCL2). He is doing well
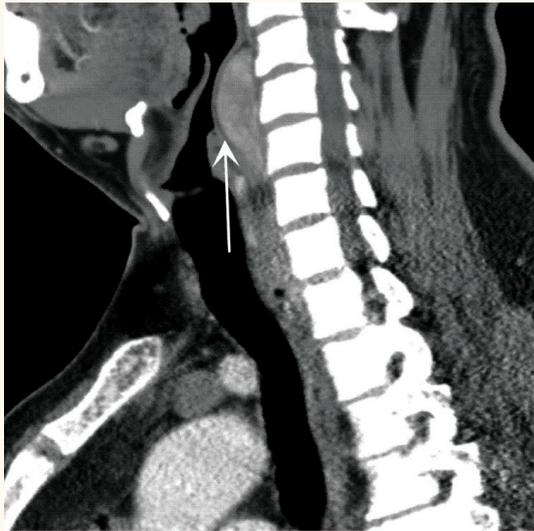
**Figure 2:** Post-contrast sagittal reformat showing the extent of the lesion (arrow).

post surgery and is currently normocalcaemic.

Fourteen months after surgery, he had a traumatic fracture of the right neck of his femur. A repeat iPTH was 3.3 pmol/L, calcium 2.6 mmol/L, albumin 32 g/L and BMD revealed normal T-scores. This was thus not attributed to a recurrence of his underlying disease.

## Discussion

PTC is often misdiagnosed preoperatively as primary hyperparathyroidism secondary to parathyroid adenoma or hyperplasia. The clinician's suspicion of malignancy should be aroused in the presence of severe hyperparathyroidism and such suspicion is the most valuable tool in planning surgery thereby optimising the outcome. Although such clinical and laboratory findings may suggest carcinoma,[1] these findings are non-specific and there are no obvious clinical or biochemical markers that can clearly differentiate patients with carcinoma from adenomas.

An important clue is very high serum calcium, although this is not diagnostic. Calcium levels above 3.5 mmol/L are common in contrast to the typical elevation of 0.25 to 0.5 mmol/L above normal seen in benign primary hyperparathyroidism.[2] A majority of patients with subsequently proved PTC have been shown to have a calcium level in excess of 3.8 mmol/L, and indeed 12% of patients present with hypercalcaemic crisis.[3] Alkaline phosphatase is also more commonly elevated in

patients with PTC, this finding is thought to result from the higher incidence of bone degradation in this population.[4] Another clue is a severely elevated parathyroid hormone (PTH) levels in patients with subsequently proven PTC. Levels up to 12 times those in normal subjects are the norm in these patients, whereas PTH levels approximately two times normal are the more common presentation in primary hyperparathyroidism.[4] Occasionally, values as high as 75-fold may occur.[5] This is in contrast to benign adenomas where no correlation exists between clinical variables and preoperative biochemical markers of calcium homeostasis and adenoma weight or volume.[6]

The most commonly affected organ systems in patients with primary hyperparathyroidism are the renal and skeletal systems.[7] Benign hyperparathyroidism is reported to cause renal impairment (nephrolithiasis, nephrocalcinosis, impaired glomerular filtration) in fewer than 20% of patients. In contrast, Wynne et al. reported a 56% prevalence of nephrolithiasis and an 84% prevalence of renal insufficiency in PTC.[8] Radiological hyperparathyroid skeletal features such as osteitis fibrosa cystica, subperiosteal erosion and 'salt and pepper ' skull, are more commonly observed in PTC (39-91%);[5] less than 10% of patients with benign disease have these features. Patients with PTC are also at higher risk for developing complications in other organ systems (severe pancreatitis, peptic ulcer disease and anaemia) than patients with primary hyperparathyroidism.[5,9] Although none of these findings is specific to the diagnosis of PTC, they should alert the surgeon to the possibility of it.

In addition to severe hyperparathyroidism, careful neck examination may reveal the presence of a palpable firm lump within the neck which has been reported in approximately half of patients with PTC, but in less than 10% of patients with benign primary hyperparathyroidism.[2,9] Paralysis of the recurrent laryngeal nerve is also a sign of late invasive PTC, but is noted to be rare.[9] At the time of presentation 15-20% of patients with cancer have lymph node metastasis and up to one-third have distant metastasis, usually to lung or bone.[3,10,11] Despite the easy access to the tumour in PTC, the use of fine needle aspiration in suspected cases is not recommended for several reasons. First, the diagnosis of PTC can be extremely difficult

cytologically and, further, sampling errors may lead to significant false negative results. Second, by violating the fibrous capsule, there is a risk of seeding of parathyroid tissue. It is noteworthy that one case report of cutaneous seeding of a lesion subsequently proved to be PTC followed a fine needle aspiration which itself showed no cellular atypia.[12]

While not being specific for malignancy, sestamibi scanning is also an excellent modality to detect the presence of local and distant metastasis.[13] US of the neck is the most useful initial method for localisation of parathyroid glands. Distinguishing features of PTC, noted on the US, include a depth-width ratio greater than 1 in 94% of cases in contrast to 5% of patients with adenoma. The US scan may also indicate the lobulated appearance and inhomogeneous echogenicity often associated with PTC.[14] Our patient had an ectopic tumour (hence missed on ultrasonography), being in one of the four most common ectopic locations which are: retrotracheal adenoma, mediastinal adenoma, intrathyroid, and carotid sheath adenoma. Finally, bone mineral density scans have been used to detect significant skeletal abnormalities and, when correlated with grossly abnormal laboratory values (calcium, PTH and alkaline phosphatase), have been found helpful in distinguishing patients with PTC from those with adenoma.[4]

Normalisation of hypercalcaemia prior to surgery is essential for patients with PTC to prevent possible renal failure and cardiac arrest. Adequate rehydration with intravenous normal saline increases renal calcium excretion. The additional use of frusemide or other loop diuretics promotes sodium and calcium diuresis. Bisphosphonates inhibit bone resorption and have become the main line treatment for lowering severe hypercalcaemia. Intravenous pamidronate is commonly used and produces a striking, but transient, fall in serum calcium. Routine blood tests and adequate renal function must be checked prior to surgery. In patients with persistent hypercalcaemia and those with unresectable tumours, medical treatment aimed at reducing calcium levels has been implemented. Also the use of octreotide can inhibit parathyroid hormone secretion from some PTCs. Conservative treatment with saline and loop diuretics is typically not sufficient, and more aggressive medical therapy is required.[5] Medications that have been used with some success include pamidronate

(bisphosphonates),[15] mithramycin,[16] calcitonin[17] and cinacalcet.[18]

Surgery is currently the only effective treatment for PTC. The diagnosis of PTC should be suspected in patients with primary hyperparathyroidism if at the time of neck exploration a large white or grey adherent mass is seen (the majority of them weigh in between 2 and 10 gm).[8] This is in contradistinction to benign parathyroid neoplasias, which tend to be soft, flattish, and red-brown in colour.[9] Frozen section often provides results of little value as microscopic infiltration of tumours can be missed. En bloc resection of the PTC, avoiding capsular rupture with widely adjacent tissue, is the treatment of choice.[10] This usually involves a large collar incision with ipsilateral thyroid lobectomy and excision of paratracheal alveolar tissue, lymph nodes and thymic tongue. Sacrifice of the recurrent laryngeal nerve may be required if involved. Although cervical lymph node metastasis occurs in less than 20% of cases, most authors recommend routine dissection of the tracheo-oesophageal groove.[10] Surgery offers the patient the best chance of a cure. Unfortunately, the diagnosis of PTC is often made following pathologic review, but if carcinoma is suspected based on laboratory values and intraopreoperative findings are consistent with PTC, en bloc resection should be completed at the time of initial surgery, before definitive pathologic assessment.[5,19] Controversy exists as to whether the patient without obvious tumour extension should be taken back to the operating room for thyroidectomy, isthmusectomy and excision of paratracheal and central neck nodes after the diagnosis of PTC is obtained from the pathology report. If preoperative diagnosis of PTC is suspected, we advocate pre-emptive radical surgery with en bloc resection of the tumour, together with ipsilateral thyroid lobe, paratracheal and central lymph node dissection and adjacent structures (only if involved) avoiding any capsular rupture of the mass. This represents the gold standard of surgical treatment of patients.[20]

Regular postoperative calcium levels must be monitored after resection as calcium levels may fall rapidly due to the 'hungry bone syndrome' where high levels of parathyroid hormone have depleted bone stores of calcium. Intravenous calcium as well as oral calcium and vitamin D may be required for a variable amount of time. After the operation, all patients require careful long-term monitoring.

In the early postoperative period, symptomatic hypocalcaemia may occur secondary to redeposition of calcium into the bones (hungry bone syndrome);[21] this requires treatment with intravenous calcium and we usually start immediately post surgery with a continuous infusion starting at 0.5 mg/kg/h of elemental calcium. Supplemental calcium and calcitriol must be prescribed to maintain calcium at the lower limit of the normal range.[5] Once the suppressed parathyroid glands recover and adequate bone deposition has taken place, the requirement for supplemental calcium and calcitriol will drop and eventually these agents can be stopped. Thereafter, serum calcium and PTH levels should be monitored every 3 months.

Although the post-operative diagnosis of PTC relies often on histological examination, the histological criteria for this diagnosis are not definitive. Several authors have suggested that criteria for pathologic diagnosis of PTC should include the presence of a fibrous capsule, fibrous trabeculae, trabecular or rosette-like cellular architecture, presence of mitotic figures and presence of capsular or vascular invasion.[22] However, other authors have pointed out that mitotic activity can occasionally be seen in adenoma and hyperplastic glands. McKeown et al. have noted that the presence of cellular pleomorphism and atypia per se are not reliable indicators of malignancy, and mitotic activity in parenchymal cells must be distinguished from mitotic activity in endothelial cells.[23] Others have suggested that spindle cells and coagulation necrosis on standard slides may suggest PTC with a poorer prognosis. However, in the absence of pathognomonic diagnostic criteria, a definitive pathological diagnosis of PTC may not be possible, especially in its less aggressive forms.[23] Nonetheless, diagnostic accuracy should be improved by recognition of the constellation of macroscopic and microscopic features in combination with multidisciplinary correlation.

With immunohistochemical staining, several cellular proteins have been found to occur more commonly in specimens of PTC than in the parathyroid adenoma.[22] Ki-67 has been found in about 11%, (range 3-65%) of patients with PTC in contrast to 2% of those with a parathyroid adenoma.[22,24] The retinoblastoma (Rb) protein has been found to be present in most patients with parathyroid adenoma and to be significantly reduced or entirely absent in various studies in patients with PTC.[22] Stojadinovic et al. tested several molecular phenotypes and found that 76% of patients with a parathyroid adenoma and no patients with carcinoma had the phenotype "p27(+) bcl-2(+) Ki-67(-) mdm2(+)".[22] Although these immunohistochemical markers have shown potential to discriminate between benign and malignant parathyroid disease, probably only vascular invasion that correlates with tumour recurrence and metastases should be considered useful in confirming malignancy.[20]

Recurrence of tumours can be monitored by calcium and parathyroid hormone levels. Most recurrences occur 2-3 years after the initial operation, but this period is variable and a prolonged disease-free interval of as long as 23 years has been reported in the literature.[5,11] This emphasises the importance of long-term follow-up of patients who have had a parathyroidectomy for malignant disease. A short disease free interval is associated with poor prognosis. Recurrent disease presents with rising levels of serum calcium and PTH. Rarely, a patient may present with a severe hypercalcaemic crisis. Parathyroid carcinoma metastasises through both lymphatic and haematogenous routes. The regional lymph nodes are common sites of metastatic disease (30%) and distant metastases most frequently involve the lungs and bones, followed by the liver and other visceral organs. Cervical recurrences are frequently palpable in patients.

Modified radical neck dissection has not been reported to improve survival and is associated with higher operative complications.[11] Therefore modified radical neck dissection may only be indicated in patients with cervical lymph node metastasis, local invasion or with local recurrence.[11] The lung is the most common site of distant metastasis, followed by the bones and the liver. For localised distant metastasis, multiple, aggressive surgical resection is recommended by most authors as it reduces tumour bulk, thereby reducing the serum calcium and parathyroid hormone levels. When hypercalcaemia is refractory to surgical resection, medical treatment is required. Radiation therapy has been described in the literature with limited data and conflicting results.[8] Data from treatment groups receiving adjuvant radiation therapy following surgical excision, where margins were positive, have shown evidence of possible improvement in preventing recurrence of disease. Limited data exist regarding

primary treatment with radiation therapy, but there may be a role for adjuvant radiotherapy as it may provide a survival benefit.[25] Data are also limited for the treatment of PTC with chemotherapy.

## Conclusion

There are no clinical or laboratory data which allow a preoperative diagnosis of parathyroid carcinoma and only occasionally does a definitive histopathologic finding differentiate an adenoma from a carcinoma. We have argued that this sort of presentation should alert the clinician to the presence of a possible parathyroid carcinoma. This should then lead to radical surgery since this is the only effective therapy for parathyroid carcinoma, and it should always be performed if a preoperative suspicion is entertained. Finally, at the time of publication of this report, our patient had been followed for 2 years, and had a normal calcium, iPTH and BMD. He did have a fracture neck of femur that occurred on minimal trauma, but there is no evidence to suggest a recurrence of his disease at this point. It can be argued that this could be a case of primary hyperparathyroidism complicated by vitamin D deficiency, and this is probably true even though there were no features of severe vitamin D deficiency (other than vitamin D levels) including a normal skeletal status. While the Vitamin D deficiency may be aetiologic in the pathogenesis of such a severely hyperparathyroid state, our focus nevertheless is not on why the hyperparathyroidism was so severe. Rather the focus here is that such severe hyperparathyroidism is also seen in parathyroid carcinoma and as such we should have a high index of suspicion for parathyroid carcinoma whenever we are faced with this severity of hyperparathyroidism, as it is the more serious condition and should not be missed. Conversely, parathyroid carcinoma is extremely uncommon and thus, if there is a clear vitamin D deficiency clinically and biochemically with tertiary hyperparathyroidism and hypercalcaemia, the likelihood of carcinoma is extremely low and need not be considered further. –

## References

1. Robert JH, Trombetti A, Garcia A, Pache JC, Herrmann F, Spiliopoulos A, et al. Primary hyperparathyroidism: can parathyroid carcinoma be anticipated on clinical and biochemical grounds? Report of nine cases and review of the literature. Ann Surg Oncol 2005; 12:526–32.

2. Fernandez–Ranvier GG, Khanafshar E, Jensen K, Zarnegar R, Lee J, Kebebew E, et al. Parathyroid carcinoma, atypical parathyroid adenoma, or parathyromatosis? Cancer 2007; 110:255–64.

3. Kebebew E, Clark OH. Parathyroid adenoma, hyperplasia, and carcinoma: localization, technical details of primary neck exploration, and treatment of hypercalcemic crisis. Surg Oncol Clin N Am 1998; 7:721–48.

4. Chen Q, Kaji H, Nomura R, Sowa H, Yamauchi M, Tsukamoto T, et al. Trial to predict malignancy of affected parathyroid glands in primary hyperparathyroidism. Endocr J 2003; 50:527–34.

5. Shane E. Clinical review 122: Parathyroid carcinoma. J Clin Endocrinol Metab 2001; 86:485–93.

6. Randhawa PS, Mace AD, Nouraei SA, Stearns MP. Primary hyperparathyroidism: do perioperative biochemical variables correlate with parathyroid adenoma weight or volume? Clin Otolaryngol 2007; 32:179–84.

7. Rao SR, Shaha AR, Singh B, Rinaldo A, Ferlito A. Management of cancer of the parathyroid. Acta Otolaryngol 2002; 122:448–52.

8. Wynne AG, van Heerden J, Carney JA, Fitzpatrick LA. Parathyroid carcinoma: clinical and pathologic features in 43 patients. Bull Sch Med Univ Md 1992; 71:197–205.

9. Fujimoto Y, Obara T. How to recognize and treat parathyroid carcinoma. Surg Clin North Am 1987; 67:343–57.

10. Obara T, Fujimoto Y. Diagnosis and treatment of patients with parathyroid carcinoma: an update and review. World J Surg 1991; 15:738–44.

11. Kebebew E. Parathyroid carcinoma. Curr Treat Options Oncol 2001; 2:347–54.

12. Spinelli C, Bonadio AG, Berti P, Materazzi G, Miccoli P. Cutaneous spreading of parathyroid carcinoma after fine needle aspiration cytology. J Endocrinol Invest 2000; 23:255–7.

13. Al–Sobhi S, Ashari LH, Ingemansson S. Detection of metastatic parathyroid carcinoma with Tc-99m sestamibi imaging. Clin Nucl Med 1999; 24:21–3.

14. Hara H, Igarashi A, Yano Y, Yashiro T, Ueno E, Aiyoshi Y, et al. Ultrasonographic features of parathyroid carcinoma. Endocr J 2001; 48:213–7.

15. Newrick PG, Braatvedt GD, Webb AJ, Sheffield E, Corrall RJ. Prolonged remission of hypercalcaemia due to parathyroid carcinoma with pamidronate. Postgrad Med J 1994; 70:231–2.

16. Singer FR, Neer RM, Murray TM, Keutmann HT, Deftos LJ, Potts JT Jr. Mithramycin treatment of intractable hypercalcemia due to parathyroid

carcinoma. N Engl J Med 1970; 283:634–6.

17. Bhansali A, Kataria RN, Dutta P, Saha MM, Singh P, Dash RJ. Parathyroid carcinoma: difficult management options. Indian J Cancer 2002; 39:119–22.

18. Silverberg SJ, Rubin MR, Faiman C, Peacock M, Shoback DM, Smallridge RC, et al. Cinacalcet hydrochloride reduces the serum calcium concentration in inoperable parathyroid carcinoma. J Clin Endocrinol Metab 2007; 92:3803–08.

19. Fujimoto Y, Obara T, Ito Y, Kanazawa K, Aiyoshi Y, Nobori M. Surgical treatment of ten cases of parathyroid carcinoma: importance of an initial en bloc tumor resection. World J Surg 1984; 8:392–400.

20. Lumachi F, Basso SM, Basso U. Parathyroid cancer: etiology, clinical presentation and treatment. Anticancer Res 2006; 26:4803–7.

21. Brasier AR, Nussbaum SR. Hungry bone syndrome: clinical and biochemical predictors of its occurrence after parathyroid surgery. Am J Med 1988; 84:654–60.

22. Stojadinovic A, Hoos A, Nissan A, Dudas ME, Cordon-Cardo C, Shaha AR, et al. Parathyroid neoplasms: clinical, histopathological, and tissue microarray-based molecular analysis. Hum Pathol 2003; 34:54–64.

23. McKeown PP, McGarity WC, Sewell CW. Carcinoma of the parathyroid gland: is it overdiagnosed? A report of three cases. Am J Surg 1984; 147:292–8.

24. Lumachi F, Ermani M, Marino F, Iacobone M, Baldessin M, Cappuzzo G, et al. PCNA-LII, Ki-67 immunostaining, p53 activity and histopathological variables in predicting the clinical outcome in patients with parathyroid carcinoma. Anticancer Res 2006; 26:1305–8.

25. Rawat N, Khetan N, Williams DW, Baxter JN. Parathyroid carcinoma. Br J Surg 2005; 92:1345–53.