Challenges and Pitfalls in the Management of Parathyroid Carcinoma: 17-Year Follow-Up of a Case and Review of the Literature

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Abstract A 29-year-old man presented to his primary care physician with nausea, severe weight loss and muscle weakness. He had a hard, fixed neck swelling. He was severely hypercalcaemic with 10-fold increased parathyroid hormone (PTH) concentrations. A diagnosis of primary hyperparathyroidism was established and the patient was referred for parathyroidectomy. At neck exploration, an enlarged parathyroid gland with invasive growth into the thyroid gland was found and removed, lymph nodes were cleared and hemithyroidectomy was performed. A suspected diagnosis of parathyroid carcinoma was confirmed histologically. Serum calcium and PTH levels normalised post-operatively, but hyperparathyroidism recurred within 3 years of surgery. Over the following 17 years, control of hypercalcaemia represented the most difficult challenge despite variable success achieved with repeated surgical interventions, embolisations, radiofrequency ablation of metastases and treatment with calcimimetics, bisphosphonates and haemodialysis using low-dialysate calcium. In this paper, we report the challenges and pitfalls we encountered in the management of our patient over nearly two decades of follow-up and review recent literature on the topic.

Keywords Parathyroids · Parathyroidectomy · Radiofrequency ablation · Embolisation · Cinacalcet · HRPT2/CDC73

Introduction

Parathyroid carcinoma is a rare disorder, accounting for 0.1% to 5.0% of all cases of primary hyperparathyroidism [1–5]. The disease presents at a mean age of 50 years and is equally likely to occur in males as in females [2–6] (Table 1). Clinical and biochemical manifestations are those of severe primary hyperparathyroidism often with renal and skeletal complications [2–5, 7]. A palpable neck mass can be felt in 30–76% of patients [3, 5, 8, 9]. Parathyroid carcinoma is associated with germline and somatic mutations in the HRPT2 gene [3, 10] and with irradiation of the neck for other pathologies [3, 11].

A diagnosis of parathyroid carcinoma is suggested by the presence of intra-operative features of local invasion and the diagnosis is confirmed by the World Health Organization histopathological criteria for parathyroid carcinoma. These include the presence of vascular invasion, perineural space invasion, capsular penetration with growth into adjacent tissues and/or metastasis [12].

Although parathyroid carcinoma is a slow-growing tumour, it inevitably metastasises and is invariably fatal due to the eventual inability to control hypercalcaemia. Survival is estimated to range from 50% to 86% at 5 years.
## Table 1: Overview of cases of parathyroid carcinoma published between 2001 and 2010

| Author          | Age/sex | Number of operations | Radiotherapy | Chemotherapy | Embolisation | Radiofrequency ablation | PTH immunisation | Calcitonin | Cinacalcet | Bisphosphonates | Development of local recurrence or distant metastasis | Outcome | Follow-up (years) |
|-----------------|---------|----------------------|--------------|--------------|--------------|--------------------------|------------------|-------------|------------|----------------|--------------------------------------------------|---------|-----------------|
| Savli [33]      | 47/F    | 1                    | Yes          |              |              |                          |                  |             |            |                | No                                               | A/FOD   | 1               |
| Tyler [34]      | 44/M    | 2                    | Yes          |              |              |                          |                  |             |            |                | Yes                                              | A/FOD   | 5.5             |
| Dotzenrath [35] | 43/M    | 4                    | Yes          |              |              |                          |                  |             |            |                | Yes                                              | Yes     | DOD 12          |
| Tyler [34]      | 43/F    | 12                   | Yes          |              |              |                          |                  |             |            |                | Yes                                              | Yes     | DOD 8           |
| Tyler [34]      | 62/F    | 2                    | Yes          |              |              |                          |                  |             |            |                | Yes                                              | Yes     | DIOther 9.5     |
| Yamashita [36]  | 43/M    | 2                    | Yes          |              |              |                          |                  |             |            |                | Yes                                              | Yes     | DOD 12          |
| Eurelings [37]  | 45/F    | 1                    | Yes          | Yes          |              |                          |                  |             |            |                | Yes                                              | Yes     | DOD 4           |
| Brown [38]      | 51/M    | 2                    |              |              |              |                          |                  |             |            |                | No                                               | A/FOD   | 2               |
| Bhansali [39]   | 40/M    | 2                    | Yes          |              |              |                          |                  |             |            |                | Yes                                              | No      | DOD 0.5         |
| Hundley [40]    | 33/F    | 5                    | Yes          |              |              |                          |                  |             |            |                | Yes                                              | Yes     | DOD 20          |
| Schmidt [41]    | 76/F    | 1                    |              |              |              |                          |                  |             |            |                | Yes                                              | Yes     | DOD 1           |
| Schoretsanitis [42] | 55/F    | 1                    |              |              |              |                          |                  |             |            |                | No                                               | A/FOD   | 2               |
| Dionisi [43]    | 35/M    | 2                    | Yes          |              |              |                          |                  |             |            |                | Yes                                              | Yes     | DOD 4           |
| Rufener [44]    | 67/M    | 3                    |              |              |              |                          |                  |             |            |                | Yes                                              | Yes     | A/FOD 4         |
| Munson [45]     | 41/F    | 1                    | Yes          |              |              |                          |                  |             |            |                | No                                               | A/FOD   | 5.5             |
|                 | 46/F    | 1                    | Yes          |              |              |                          |                  |             |            |                | No                                               | A/FOD   | 4.5             |
|                 | 49/F    | 1                    | Yes          |              |              |                          |                  |             |            |                | No                                               | A/FOD   | 5.5             |
|                 | 57/F    | 1                    | Yes          |              |              |                          |                  |             |            |                | No                                               | A/FOD   | 4.5             |
| Dogan [46]      | 50/F    | 1                    |              |              |              |                          |                  |             |            |                | No                                               | A/FOD   | 1.5             |
| Betea [23]      | 50/F    | 2                    | Yes          | Yes          | Yes          |                          |                  |             |            |                | Yes                                              | Yes     | AWD 11          |
| Kern [47]       | 54/F    | 2                    | Yes          |              |              |                          |                  |             |            |                | Yes                                              | Yes     | DOD 2.5         |
| Kirkby-Bott [48] | 44/M    | 2                    | Yes          | Yes          |              |                          |                  |             |            |                | Yes                                              | Yes     | DOD 3.5         |
|                 | 70/M    | 1                    | Yes          |              |              |                          |                  |             |            |                | No                                               | A/FOD   | 7               |
|                 | 36/M    | 1                    | Yes          |              |              |                          |                  |             |            |                | No                                               | A/FOD   | 5               |
|                 | 66/M    | 2                    | Yes          |              |              |                          |                  |             |            |                | Yes                                              | Yes     | DOD 8           |
|                 | 46/M    | 1                    | Yes          | Yes          |              |                          |                  |             |            |                | Yes                                              | Yes     | AWD 1           |
|                 | 25/F    | 1                    |              |              |              |                          |                  |             |            |                | No                                               | A/FOD   | 1               |
|                 | 44/M    | 1                    |              |              |              |                          |                  |             |            |                | No                                               | A/FOD   | 1               |
| Lin [49]        | 38/M    | 1                    |              |              |              |                          |                  |             |            |                | No                                               | A/FOD   | 0.5             |
| Ahmad [50]      | 42/F    | 1                    | Yes          |              |              |                          |                  |             |            |                | Yes                                              | Yes     | A/FOD 1         |
| Chiofalo [51]   | 66/M    | 1                    | Yes          |              |              |                          |                  |             |            |                | No                                               | A/FOD   | 1               |
| Cheah [16]      | 32/M    | 2                    | Yes          |              |              |                          |                  |             |            |                | No                                               | A/FOD   | 0.5             |
|                 | 42/F    | 1                    |              |              |              |                          |                  |             |            |                | No                                               | A/FOD   | 0.5             |
|                 | 52/F    | 2                    | Yes          |              |              |                          |                  |             |            |                | Yes                                              | Yes     | A/FOD 5.5       |
| Yoshida [52]    | 61/F    | 2                    |              |              |              |                          |                  |             |            |                | Yes                                              | Yes     | AWD 18.5        |
| Ikeda [53]      | 48/M    | 4                    | Yes          |              |              |                          |                  |             |            |                | Yes                                              | Yes     | AWD 6           |
| Pahlavan [54]   | 21/M    | 2                    | Yes          |              |              |                          |                  |             |            |                | No                                               | A/FOD   | 2               |
| Agarwal [55]    | 22/F    | 2                    |              |              |              |                          |                  |             |            |                | Yes                                              | Yes     | A/FOD 9         |
| Mezhir [56]     | 64/F    | 7                    | Yes          | Yes          | Yes          |                          |                  |             |            |                | Yes                                              | Yes     | A/FOD 8         |
| Name          | Gender | Age | Yes | Yes | Yes | Yes | Yes | A/FOD |
|--------------|--------|-----|-----|-----|-----|-----|-----|-------|
| Placzkowski  | M      | 51  | 4   | Yes | Yes | Yes | Yes | A/FOD |
| Saharzad     | F      | 53  | 1   |     |     |     |     |       |
| Tkaczak      | M      | 55  | 2   | Yes |     |     |     |       |
| Tan          | F      | 55  | 1   |     |     |     |     |       |
| Iwata        | M      | 61  | 1   |     |     |     |     |       |
| Montenegro   | M      | 50  | 2   | Yes | Yes | Yes | DOD | 5     |
| Rath       | F      | 45  | 1   |     |     |     |     |       |
| Artinyan     | M      | 71  | 2   | Yes | Yes | Yes | Yes | A/FOD |
| Cetani       | M      | 53  | 3   | Yes | Yes | Yes | Yes | A/FOD |
| Temmim       | F      | 63  | 1   |     |     |     |     |       |
| Tamura       | M      | 70  | 1   |     |     |     |     |       |
| Schoetsantis | M      | 72  | 1   |     |     |     |     |       |
| Schreiber    | M      | 78  | 1   |     |     |     |     |       |
| Tan          | F      | 75  | 1   |     |     |     |     |       |
| Kung         | F      | 72  | 1   |     |     |     |     |       |
| Marcy        | F      | 42  | 1   |     |     |     |     |       |
| Yuan         | F      | 38  | 2   |     |     |     |     |       |
| Rock         | M      | 60  | 1   | Yes | Yes | Yes | Yes | A/FOD |
| Yong         | M      | 23  | 1   | Yes | Yes | Yes | Yes | A/FOD |
| Chaychi      | F      | 79  | 1   |     |     |     |     |       |
| Todhio       | M      | 42  | 2   | Yes | Yes | Yes | Yes | A/WD  |

| Results are expressed as mean ± SE |
| DOD dead of disease, D/other dead of other cause, A/WD alive with disease, A/FOD alive free of disease |
and 35–70% at 10 years [1–6, 13, 14]. The most effective treatment for parathyroid carcinoma is radical surgery with en bloc removal of the lesion together with the ipsilateral thyroid, thyroid isthmus and lymph nodes [2, 3, 5, 13, 15]. Surgery is also the treatment of choice in case of local recurrence or development of metastases [5, 7, 16], although radiotherapy [2–5, 8, 9], chemotherapy [3, 5, 9, 17, 18], embolisation [19] or radio frequency (RF) ablation [19–21] may also be attempted.

We report here the nearly two decades’ odyssey of a male patient with multiple metastases from parathyroid carcinoma, describing in the process the challenges and pitfalls we encountered in the management of this difficult malignancy. We also review all original case reports and case series on parathyroid carcinoma, fulfilling the WHO criteria and with a follow-up of at least 6 months after initial parathyroidectomy, which were published in the English literature since the last large review on this topic in 2001 [3]. The literature search was conducted in PubMed using the keywords (“Parathyroid Neoplasms” OR “Parathyroid carcinoma” OR “Parathyroid cancer” OR “Parathyroid cancers”) AND (“Case Reports” OR “case report” OR “case” OR “cases”). The last search was conducted on June 2, 2010. Patients with changes suggestive of carcinoma in the context of autonomous (tertiary) hyperparathyroidism were excluded because of the controversy in diagnosing malignancy in this case. Of an initial 872 publications, only 45 fulfilled the WHO criteria for parathyroid carcinoma and follow-up as per our search criteria, and were selected for further analysis.

Case Report

A 29-year-old man presented to his primary care physician with a 2-month history of severe weight loss (20 kg) associated with polyuria, polydipsia, nausea, muscle weakness, difficulty in concentrating and debilitating tiredness. On physical examination, he was clinically dehydrated and had a palpable hard, fixed swelling in the left side of the neck. He was using no medication and had no significant past or family history. Laboratory investigations revealed a severe hypercalcaemia of 4.9 mmol/l (normal range 2.15–2.55 mmol/l), a decreased creatinine clearance of 45 ml/min (normal >120 ml/min) and a 10-fold increased serum intact parathyroid hormone (PTH) concentration: 88 pmol/l (normal <8 pmol/l). These findings suggested a diagnosis of severe primary hyperparathyroidism probably due to parathyroid carcinoma. No further investigations were requested; the patient was intensively rehydrated and referred for parathyroidectomy. At neck exploration, an enlarged parathyroid gland (3.5×3×3.5 cm) invading the ipsilateral thyroid lobe was found and removed from the left side of the neck (Fig. 1). A left hemithyroidectomy was also performed. The diagnosis of parathyroid carcinoma was confirmed histologically by the finding of capsular and vascular invasion. Serum calcium and PTH concentrations normalised within a few days of surgery associated with a significant improvement in renal function. A second surgery was performed within 1 month of the first surgery to ensure complete removal of all malignant tissue and provide a negative surgical margin. The patient was started on a course of radiotherapy, which had to be discontinued before completion because of severe pharyngitis and oesophagitis.

A recurrence of hyperparathyroidism was documented on routine laboratory control 3 years after parathyroidectomy. This was mild, with a serum calcium concentration of 2.74 mmol/l, a PTH concentration of 8.4 pmol/l and a stable creatinine clearance of 75 ml/min. The patient was completely asymptomatic. Tc99m-MIBI-SPECT and ultrasonography identified a lesion in the left side of the neck, which was found to be a local recurrence of the primary tumour at extensive bilateral neck exploration. The recurrent tumour had invaded the oesophagus, part of which was excised and reconstructed using tissue from the sternocleidomastoid muscle. The edges of the excised specimen were tumour free and resected draining lymph nodes were clear of tumour tissue. DNA analysis of the resected recurrent tumour demonstrated a somatic HRPT2 mutation, c.165delC located on exon 2 [22]. Despite the radical nature of the surgery, mild hyperparathyroidism persisted postoperatively, suggesting the presence of residual probably...
metastatic tumour tissue. No further localisation studies or surgery were planned principally because of the patient’s reluctance to undergo further surgery but also because of the mild nature of the hyperparathyroidism. Closer clinical monitoring was arranged.

Over the following 4 years, serum calcium and PTH concentrations and bone turnover markers slowly increased, and periods of dehydration were associated with transient worsening of renal function, which remained, however, on the whole stable despite persistent hypercalciuria and development of nephrocalcinosis. Progressive bone loss, predominantly cortical, was also documented and treatment with the non-nitrogen-containing bisphosphonate clodronate was started, resulting in normalisation of bone turnover and stabilisation of BMD measurements. Rehydration and treatment with bisphosphonates eventually failed in controlling hypercalcaemia and bone loss. Localisation studies were undertaken to identify the source of PTH production. Ultrasound (US), selective venous sampling for PTH (SVS) and CT scan of the neck succeeded in localising a small dense lesion in the left supraclavicular region. CT scan of the thorax also revealed a small solitary lesion of 1-cm radius in the inferior lobe of the right lung (Fig. 2a). The patient refused to undergo a thoracotomy, but did agree to a fourth neck exploration at which a lymph node metastasis was excised from the left supraclavicular region (Fig. 1). Although less severe, hyperparathyroidism persisted postoperatively, as expected due to the unresected lung metastasis. Two attempts at embolisation of the lung metastasis failed to reduce tumour load. In contrast, radiofrequency ablation (RFA) of the lesion, although complicated by an episode of severe pleuritis, was very successful in achieving biochemical remission, with serum PTH concentrations decreasing from 265 pmol/l to <1 pmol/l (Fig. 2), suggesting that the metastasis targeted with RFA was the only source of PTH secretion. However, remission was not permanent and PTH levels started to rise within 9 months of RFA. The patient finally agreed to undergo a right inferior lobectomy (Fig. 3), which was complicated by multiple small cerebral infarcts resulting in right hemianopia, dysphasia, acalculia and transient epilepsy. Disappointingly, there was also only partial improvement in serum calcium and PTH concentrations, which continued to increase within 2 months of lobectomy (Fig. 3).

Further localisation studies, in the form of Tc99m-MIBI-SPECT and a CT scan of the neck and thorax, were unable to localise any residual pathological

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**Fig. 2** Radiological (a pre-RF ablation, b after RF ablation) and biochemical changes after RF ablation of the lung metastasis, demonstrating a severe drop in serum PTH concentrations, which persisted for almost a year
parathyroid tissue suggesting the presence of (micro) metastasis. The now available calcimimetic cinacalcet was prescribed eventually at a maximum dose of 90 mg twice daily, which decreased PTH concentrations from 120 pmol/l to 85 pmol/l, stabilised calcium concentrations to about 2.80 mmol/l and stabilised creatinine clearance at 51 ml/min. In the course of the following year, serum calcium and PTH concentrations further increased, however, despite maximal doses of cinacalcet and intermittent intravenous bisphosphonates.

Repeat Tc99m-MIBI-SPECT and CT scan of the thorax, now demonstrated a new large (4×3×2 cm) subcarinal mediastinal metastasis, which was successfully excised using a transpericardial approach (Fig. 4). The elimination of the source of PTH secretion was associated with a very severe hungry bone syndrome for which the patient needed intensive care for over 2 months, requiring very large doses of iv administered calcium (up to 14 g/day) and maximal doses of active vitamin D metabolites. Remission lasted for more than 1 year, after which PTH levels started to rise again and a new metastatic lesion was localised pretracheally in the upper mediastinum on CT scan of the thorax. There was also suggestion of a second subcarinal lesion at the site of the previously excised metastasis.

In view of the complications associated with his previous surgeries, the patient was at that stage again reluctant to undergo any further surgery. Within the next few months, PTH steadily increased associated with uncontrollable hypercalcaemia and deteriorating renal function eventually requiring haemodialysis using a very-low-dialysate calcium concentration. Localisation studies confirmed the two previously identified pretracheal and subcarinal mediastinal lesions. The pretracheal lesion was accessible from the neck and was radically removed by a cervical approach (Fig. 1). There were no post-operative complications and serum PTH concentration decreased from 590 pmol/l to 155 pmol/l, as expected due to the remaining subcarinal mediastinal metastasis. Surgical removal of this metastasis would have required a third thoracotomy, which would be associated with too high an operative risk, especially in view of the patient’s poor clinical condition. Excision of the metastasis by mediastinoscopy was also not considered to be an option because of multiple scarring due to previous surgeries. The patient remains on haemodialysis and is still treated with cinacalcet, with intermittent courses of intravenous bisphosphonates. The patient was not considered to be a candidate for PTH immunisation [23, 24] because of surgical clearance of cervical and mediastinal lymph nodes, poor general immune status and recurring infections.
Review of the Literature 2001–2010

Sixty-two new cases have been reported in the literature since the last published review in 2001 [3], and data of these cases are summarised in Table 1. The median age of the reported patients was 50 years (21–79) and there was an equal number of men and women reported. Data on initial presentation were available in 43 of the 62 patients (69%), 37 of which were symptomatic (86%). Polyuria and polydipsia were reported in nine patients (21%), constipation in seven (16%), tiredness in 13 (30%), bone and joint pain in 17 (40%), muscle weakness in seven (16%), nausea and vomiting in 10 (23%) and weight loss in seven patients (16%). Seventeen patients (40%) had renal stones and six patients (14%) had sustained a documented fracture. A palpable neck mass was reported in 22 of 27 patients in whom this was checked (81%).

Similar to the review of 2001, surgery is still the most frequently chosen therapy for the initial treatment of parathyroid carcinoma but also for the treatment of recurrent or metastatic parathyroid carcinoma (Table 1). It is of note that the use of both chemotherapy and radiotherapy has decreased over the last 10 years, likely due to several reports and reviews which showed disappointing results [2–5]. The last case report on the use of chemotherapy and radiotherapy dates from 2005 and 2008, respectively (Table 1). In contrast to the review of 2001, reports on the use of the newer techniques embolisation (n=1), radiofrequency ablation (n=3) and PTH immunisation (n=1) have been recently published, although the number of cases reported is still very limited. Use of the calcimimetic, cinacalcet, has increased over the last few years after the first report in 2007, while the use of bisphosphonates has remained stable.

The median follow-up reported in the 62 cases is relatively short at 3 years (range 0.5–20 years), considering that the average time to a first recurrence is also approximately 3 years [1, 3]. This could explain why only 27 of the 62 patients (44%) developed a local recurrence and/or distant metastasis and nine patients (15%) died as a result of parathyroid carcinoma during the reported follow-up period.

Discussion

To our knowledge, we report here one of the longest survival and follow-up in one centre of a patient with recurrent metastatic parathyroid carcinoma. Although parathyroid carcinoma is a slow-growing tumour, it is associated with a relatively high incidence of local recurrence (40–82% within 5 years) [1–3, 5, 6, 13]. Metastases tend to occur later in the course of the disease with spread to cervical nodes (30%), lung (40%) and liver (10%), via both lymphatic and haematogenous routes [3]. Survival is estimated to range from 35% to 70% at 10 years [1–6, 13, 14], with an average survival of 6 years after local recurrence, and of 4.5 years after the development of distant metastases [2].
In patients with parathyroid carcinoma, determinants of survival include delay in diagnosis, the presence of locally invasive features, distant metastasis at diagnosis and the radical nature of initial surgery [3, 6, 13, 14]. A further important determinant of survival and disease-free survival is the due care taken at initial surgery to avoid rupturing the capsule of the gland to prevent local seeding of tumour tissue [3]. Initial surgery has been reported not to be radical in up to 48% of patients because of failure to establish the diagnosis of parathyroid carcinoma pre- or intra-operatively [6, 14]. This was also the case in our patient at initial surgery, despite very suggestive clinical features of parathyroid carcinoma, in the form of severe hyperparathyroidism in a young male patient, palpable neck swelling and intra-operative features of local invasion. A second surgery had to be performed within 1 month of the first to ensure complete removal of all malignant tissue and to provide a negative surgical margin.

The main determinant of survival in all patients remains, however, the eventual inability to control hypercalcaemia [2, 5] and its association with fatal renal and cardiovascular complications [1, 2, 5, 7]. End-stage renal failure has been reported in up to 84% of patients due the deleterious effects of severe persistent hypercalcaemia on kidney function [2, 5, 7]. A persistently elevated circulating PTH level is also associated with increased bone turnover and bone loss predominantly at cortical sites and with increased risk of fractures. In parathyroid carcinoma, the main goal of treatment is control of hyperparathyroidism by eradicating the source of PTH secretion [7, 16].

Although the morbidity associated with re-exploration of the neck is estimated to be 6–17% [7], that of re-exploration of the mediastinum or lungs is clearly much higher. In our patient, the recurrent laryngeal nerve had to be unavoidably sacrificed during the second surgical intervention due to invasive growth of remnants of the primary tumour, resulting in transient loss of voice and permanent hoarseness. Subsequent lung surgery was associated with severe thrombo-embolic complications.

The increasing morbidity attached to repeated surgical interventions has led to the search for other treatment options, such as radiotherapy, chemotherapy, RF ablation, embolisation, use of the calcimimetic cinacalcet and PTH immunisation. Although parathyroid tumours are relatively resistant to radiotherapy [2–5], this management approach showed some promise as adjuvant treatment for microscopic residual disease [8, 9]. In our patient, the prescribed course of radiotherapy could not be completed due to the development of severe side effects in the form of pharyngitis and oesophagitis.

Embolisation of localised and/or ectopic parathyroid adenomas has been reported to have only limited success [19, 25–27], and in metastatic parathyroid carcinoma, embolisation has only been described in combination with RF ablation in one patient [19]. In our patient, the outcome of twice attempted embolisation of a lung metastasis was disappointing, largely because it was not technically possible to selectively embolise the arterial branch that fed the lung metastasis.

The outcome of combined embolisation and RF ablation in a patient with liver metastasis due to parathyroid carcinoma [19], and the effectiveness of RF ablation in various types of cancer [28] has led us to consider RF ablation in our patient. This approach was indeed very successful in eradicating PTH production by the metastasis, as has also been subsequently reported in two patients with parathyroid carcinoma and lung metastases [20, 21]. The beneficial effect was unfortunately transient, lasting only 9 months after the procedure, when PTH production was documented to resume from the same site.

In parathyroid carcinoma, attempts at reducing tumour load are not always successful, in which case control of serum calcium by other means becomes central to prevent the deleterious effects of hypercalcaemia on various organ systems. Intensive rehydration, use of medications such as bisphosphonates and calcimimetics and use of dialysis represent diverse means to control hypercalcaemia and are often used in combination. Bisphosphonates decrease the skeletal efflux of calcium from bone by suppressing osteoclast-mediated bone resorption and overall bone turnover [3]. These agents, however, have no effect on renal tubular reabsorption of calcium so that they improve hypercalcaemia but do not normalise serum calcium [3, 29]. Cinacalcet is a calcimimetic, which reduces parathyroid hormone secretion by binding to the calcium-sensing receptor on parathyroid cells, increasing the sensitivity of these cells to extracellular calcium concentrations [15, 30, 31]. These agents are widely used in the management of secondary and tertiary hyperparathyroidism in renal failure and have been also recently registered for the management of primary hyperparathyroidism, including that due to parathyroid carcinoma. In our patient, combined treatment with bisphosphonates and cinacalcet resulted in reasonable control of the hypercalcaemia initially, but eventually failed to do so, even when used at maximal doses. Dialysing against low-dialysate calcium became necessary in order to better control the hypercalcaemia.

The very high operative risks associated with a third thoracotomy, the patient’s poor lung function and current metabolic status despite regular dialysis, preclude the option of further surgery to remove the identified source of PTH secretion. PTH immunisation is being explored as a potential non-invasive option, although experience with this approach is still limited and the patient’s general condition may not permit its use [23, 24, 32].
Although we are rapidly running out of options in the management of our patient, we believe that we have nonetheless managed to secure for him a longer albeit not disease-free survival. This clinical case with a follow-up spanning over 17 years illustrates that the long-term management of patients with metastatic parathyroid carcinoma remains indeed a daunting task, despite all recent imaging, surgical and medical advances.

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