Positive effect of radiotherapy and surgery on hormonally active pulmonary metastases of primary parathyroid carcinoma

Torgny Rasmuson¹, Anders Kristofferson² and Lennart Boquist³
Departments of Radiation Sciences, ¹Oncology, ²Surgery and ³Pathology, Umeå University, SE-901 85 Umeå, Sweden
(Correspondence should be addressed to T Rasmuson; Email: Torgny.Rasmuson@onkologi.umu.se)

Abstract
Objective: Parathyroid carcinoma is a rare cause of primary hyperparathyroidism. Surgery is the primary treatment in recurrent or metastatic disease. Radiotherapy has been used as an adjuvant to control subclinical local disease but is otherwise considered ineffective.

Design: We report on a patient with parathyroid carcinoma with hypercalcaemia and pulmonary metastases, treated with pamidronate and radiotherapy and later with surgery.

Methods: The treatment was evaluated using serial analysis of serum parathyroid hormone (PTH) and calcium, clinical evaluation and chest radiographs.

Results: Intravenous pamidronate alone had limited effect on hypercalcaemia. Following irradiation of the pulmonary lesions (34 Gy in ten fractions), serum levels of calcium and PTH decreased and pamidronate could be discontinued. The patient’s general condition improved parallel to a radiological response. At clinical relapse 18 months following radiotherapy, the pulmonary metastases were resected and serum PTH was normalised.

Conclusions: The results indicate that parathyroid carcinoma can be radiosensitive. Thus radiotherapy may be an alternative to palliate symptoms of hypercalcaemia in patients not suited for surgery.

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Introduction
Carcinoma of the parathyroid glands is a rarity (1). In contrast to the more frequent adenomas, where a female preponderance (2–3:1) is observed, carcinomas are equally frequent in men and women (1, 2). Most carcinomas are actively secreting parathyroid hormone (PTH), and the serum calcium levels are usually higher in patients with carcinomas, compared with those observed in other causes of primary hyperparathyroidism (2). Carcinomas are often palpable in contrast to adenomas. Skeletal involvement, renal calculi, polyuria and peptic ulcers are frequent in patients with parathyroid carcinoma (2, 3).

Therapy is surgical, with en bloc resection (3), and also includes resection of metastases to palliate symptoms of hypercalcaemia (4, 5). Radiotherapy has been used to control tumour growth and hypercalcaemia, but with limited effect (2, 6). The results of adjuvant radiotherapy in parathyroid carcinoma were presented by August et al. (7), and recently by Chow et al. (8), who concluded that this treatment may eliminate the strong predilection for local recurrence after surgery. The present case report demonstrates the palliative effect of radiotherapy, and later of surgery, on hypercalcaemia in a patient with pulmonary metastases secondary to parathyroid carcinoma.

Case report
The patient is a woman born in 1944 with no known hereditary diseases. At the age of 23, and several times later, she was operated on because of osteobromas in the maxilla. At age 37, hysterectomy was performed because of irregular bleedings. Hypercalcaemia was first diagnosed in 1986 but, for no obvious reason, further investigation or therapy was not initiated.

In 1992 she was kicked on the knee and bilateral pretibial swellings were observed. She suffered from bone pain and radiographs of the tibiae showed bilateral signs of metabolic disease with multiple osteolytic lesions. Clinical investigation revealed a palpable mass on the left side of the neck. The patient’s voice was normal, and serum calcium was 3.4 mmol/l (ref. 2.1–2.6), PTH 39 pmol/l (ref. 1.4–5.7) and alkaline phosphatase 28 μkat/l (ref. 0.8–4.6). The parathyroid glands were explored and four normal glands were
A firm nodule was found in the lower pole of the left thyroid lobe, and cytologic examination later indicated malignancy. At reoperation a total thyroidectomy was performed. The left laryngeal nerve was not invaded by the tumour, but postoperatively the patient had a paralysis of her left vocal cord. Histopathology showed a malignant epithelial tumour resected with minimal margin, considered to be a poorly differentiated thyroid carcinoma. Immunohistologic examination was negative for calcitonin, and no amyloid was observed, but immunohistochemistry for PTH was not in clinical use on that occasion. Postoperatively the serum PTH level normalised, and serum calcium was slightly subnormal. Thyroxine substitution was initiated. Postoperative irradiation to the thyroid region was initiated with 2.0 Gy daily dose to a total dose of 48 Gy, with a boost to the tumour area to 68 Gy.

In October 1994 the hypercalcaemia relapsed and a chest radiograph showed two pulmonary lesions, one on each side. Computed tomography of the thyroid region and the thorax showed no signs of local relapse in the thyroid region, and one circular lesion in the upper lobe of the right, and one in the lower lobe of the left lung. The patient had no symptoms and no further therapy was initiated. In June 1996 MIBI scintigraphy was performed and no uptake was found in the thyroid bed or over the pulmonary lesions.

In August 1997 she suffered from weight loss, polydipsia and polyuria. Serum calcium was 4.0 mmol/l and the PTH around 100 pmol/l. There were no signs of local recurrence in the thyroid region. Treatment with intravenous pamidronate was initiated, first biweekly and later weekly, but the effect was limited and of short duration as shown in Fig. 1. Histopathology of the primary tumour was re-examined and the tumour stained positive for PTH but negative for thyroglobulin, and the diagnosis was changed from thyroid to parathyroid carcinoma. Resection of the pulmonary lesions was considered, but the bilaterality, the laryngeal stenosis and the patient’s poor general condition indicated a considerable surgical risk. In December 1997 the two pulmonary lesions, identified by computed tomography, were irradiated with 3.4 Gy daily dose to a total dose of 34 Gy, as shown in Fig. 2. The maximal serum PTH and serum calcium prior to irradiation was 148 pmol/l and 4.2 mmol/l respectively. After radiotherapy the calcium levels gradually decreased and pamidronate was discontinued. Chest radiograph in September 1998 showed a decrease in the size of the lesions compared with December 1997, prior to radiotherapy (Fig. 3). After irradiation the patient gained weight from 37 to 43 kilograms, her general condition improved and she could return to work. In November 1998 PTH was 44 pmol/l and the serum calcium 3.0 mmol/l respectively (Fig. 1).

In February 1999 serum PTH and calcium started to increase (Fig. 1). Computed tomography of the thorax and the abdomen in April showed one lesion in the upper right and two lesions in the lower left pulmonary lobe. No signs of metastases were found in the abdomen. Serum calcium and PTH levels peaked at 4.0 mmol/l and 193 pmol/l respectively. The patient had intravenous pamidronate twice weekly and, in July, a bilateral anterior thoracotomy was performed and four pulmonary lesions were resected. Histopathology identified three of these lesions as metastases of parathyroid carcinoma. Figure 4 shows a comparison between photomicrographs of the primary tumour and one of the pulmonary metastasis. During the postoperative period serum calcium decreased to 1.6 mmol/l and the patient had a slow recovery. Chest radiography
in September 1999 showed bilateral postoperative lesions, but no signs of metastases. At the latest clinical examination in February 2000 the patient was in a good clinical condition. Corrected serum calcium was 2.4 mmol/l and PTH 3 pmol/l.

Methods
Serum PTH was analysed with a chemiluminescent enzyme immunoassay, Immulite Intact PTH (Diagnostic Products Corporation, Los Angeles, CA, USA). Serum calcium and alkaline phosphatase were analysed using the routine procedures of the Clinical Chemical Laboratory, Umeå University Hospital, Sweden. Immunohistochemical staining of PTH was performed on formalin-fixed, paraffin-embedded tumour specimens, using the anti-human parathyroid hormone antibody (DAKO A/S, Glostrup, Denmark). Radiotherapy was planned using the Helax three-dimensional system (MDS Nordian AB, Uppsala, Sweden), and was delivered from a Varian 4.0 Megavolt linear accelerator (Varian Medical Systems Inc., Palo Alto, CA, USA).

Discussion
This patient’s history with relapsing hypercalcaemia illustrates the often protracted natural history of parathyroid carcinoma. Furthermore, it is an illustration of the difficulty that may be associated with the diagnosis of rare diseases. Hypercalcaemia first appeared in 1986, but the correct diagnosis was not made until 1997.

The patient was treated with postoperative adjuvant irradiation to the thyroid region, although the diagnosis
at that time was considered a thyroid carcinoma. August et al. (7), and Chow et al. (8) presented the results of patients treated for microscopic residual disease, and they concluded that adjuvant postoperative radiotherapy in parathyroid carcinoma decreases the risk of local recurrence.

More recent data from the literature on radiotherapy in parathyroid carcinoma are presented in Table 1. The radiotherapy given is often not specified, nor is the mode of evaluation, a fact that makes the evaluation difficult. There are, however, a few case reports that indicate positive effects of radiotherapy (6,10). Our patient was initially treated with intravenous pamidronate for 15 weeks before radiotherapy was started. The effect on serum calcium during this period was limited and of short duration, while PTH steadily increased. Pamidronate treatment was continued throughout the period of irradiation but could later be discontinued. The primary effect of pamidronate is its inhibition of osteoclastic bone resorption. We found no data indicating accumulation of pamidronate in tumour tissue and no reports on radiosensitising effects of this drug. Whether pamidronate in any way could influence the effect of radiotherapy in this patient is unclear.

The effect of radiotherapy in the present patient was demonstrated by a substantial reduction, although not normalisation, of the serum PTH levels as illustrated in Fig. 1. The decrease in serum PTH was paralleled by the reduction of the serum calcium levels, and clinical improvement. The effect of radiotherapy was further verified by chest radiographs (Fig. 3). Radiotherapy has well-documented effects on physiological endocrine activities, for example when menopause is induced after irradiation.

<table>
<thead>
<tr>
<th>Author (Ref. no.)</th>
<th>No. of patients</th>
<th>Radiotherapy</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shane &amp; Bilezikian 1982 (2)</td>
<td>4</td>
<td>1</td>
<td>2 (-), no effect</td>
</tr>
<tr>
<td>Anderson et al. 1983 (9)</td>
<td>3</td>
<td>1</td>
<td>2 (-); 1 no relapse</td>
</tr>
<tr>
<td>McKeown et al. 1984 (10)</td>
<td>1</td>
<td>5</td>
<td>1 (+); 4 (-); 1?</td>
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<tr>
<td>Wynne et al. 1992 (8)</td>
<td>6</td>
<td>1</td>
<td>1 (-)</td>
</tr>
<tr>
<td>Obara et al. 1993 (4)</td>
<td>1</td>
<td>1</td>
<td>1 (-)</td>
</tr>
<tr>
<td>Hakaim &amp; Esselstyn 1993 (11)</td>
<td>2</td>
<td>3</td>
<td>2 Relapse in 1/3</td>
</tr>
<tr>
<td>August et al. 1993 (7)</td>
<td>5</td>
<td>3</td>
<td>2 No relapse</td>
</tr>
<tr>
<td>Chow et al. 1998 (8)</td>
<td>9</td>
<td>6</td>
<td>3 Partial response</td>
</tr>
<tr>
<td>Present study</td>
<td>1</td>
<td>1</td>
<td>1 Partial response</td>
</tr>
</tbody>
</table>

Fig. 3 Chest radiographs on day 117 (left) and day 393 (right). The circular lesions in the right upper and left lower lobes are indicated by arrows. The left radiograph represents the status at the time of initiation of radiotherapy, and the right at follow-up nine months later. (Reproduced with permission from the Department of Radiology, Umeå University Hospital.)
of the ovaries in women with metastatic breast carcinoma, or in pathologic states, as when $^{131}$I is used to treat Graves' disease, or the irradiation of hormone-secreting pituitary adenomas. It therefore seems unlikely that the hormone production of the parathyroid glands would be insensitive to irradiation.

An interesting new approach to treat hyperparathyroidism in a patient with metastatic parathyroid carcinoma by immunisation with PTH was recently presented by Bradwell & Harvey (12). In contrast to our patient who had two distinct pulmonary lesions, their patient had nodular metastases scattered over the visceral pleura and within the lung parenchyma. With this diffuse metastatic pattern, radiotherapy would probably not have been appropriate. Surgical resection of pulmonary metastases of parathyroid carcinoma is recommended (4, 5), and the value of surgery is further supported by the present patient’s history.

The results of the presented patient are in contrast to earlier, generally negative reports on the effect of radiotherapy in parathyroid carcinoma. We conclude that radiotherapy may be considered in the palliation of hypercalcaemia in patients with local manifestations of parathyroid carcinoma not suited for surgery. It would also be of interest to evaluate the effect of radiotherapy on PTH production and release in parathyroid adenomas.

**Acknowledgements**

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*Figure 4* Photomicrograph of the primary parathyroid cancer (A), and a pulmonary metastasis (B). Haematoxylin and eosin; ×180.
References


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