

# Long-term follow-up after parathyroidectomy for radiation-induced hyperparathyroidism

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**Background.** External radiation is associated with a risk of hyperparathyroidism. We reviewed the outcomes after operation for radiation-induced hyperparathyroidism (R-HPT).

**Methods.** We conducted a retrospective review of all patients who had operative therapy for R-HPT from 1980 to 2003 in our department with a minimum of 3 years of follow-up after operative therapy.

**Result.** Between 1980 and 2003, 1932 patients underwent parathyroidectomy for primary hyperparathyroidism. Thirty-seven (1.92%) patients had a history of neck irradiation. Thirty-two patients underwent a bilateral exploration (BE), and 5 patients had a focused approach (FA). Thirty-five patients presented with single gland disease, and 2 patients had multiple gland disease. In the BE group, 26 patients remained cured biochemically after a median follow-up of 10.3 years (range, 3-21 years), and 6 patients had recurrence after a median of 13.2 years (range, 7-22 years). In the FA group, all 5 patients remained cured biochemically; however, the median follow-up remained shorter (6.4 years; range, 3-8 years).

**Conclusion.** In R-HPT, the incidence of multiple gland disease at the time of initial operation was comparable with sporadic HPT. In the absence of thyroid disease, an FA may be proposed for R-HPT. Metachronous pathologic glands may develop several years after successful parathyroidectomy in R-HPT. Hence, lifelong follow-up of these patients is essential. (*Surgery* 2007;142:819-22.)

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IN THE PAST, THERAPEUTIC EXTERNAL BEAM IRRADIATION has been used widely for the treatment of benign conditions of the head, neck, and upper thorax in both children and adults. These patients have an increased frequency of tumors of the skin, breast, thyroid, salivary, and parathyroid glands as compared with the general population.<sup>1</sup> The risk of developing hyperparathyroidism after radiation exposure has been estimated to be 2.9 times that of the general population.<sup>2</sup> Although radiation is used infrequently for benign conditions, it remains one of the treatment modalities for malignant conditions in adults as well as in pediatric pathology, such as Hodgkin's lymphoma, neuroblastoma, and Wilms's tumors.

It has been suggested that because all parathyroid glands are at risk for adenomatous transformation after radiation exposure, all 4 parathyroid glands should be inspected in cases of radiation-induced hyperparathyroidism (R-HPT).<sup>3</sup> Until 1995, it was our departmental policy that the suspicion of R-HPT was an absolute indication for a 4 parathyroid gland exploration via a conventional cervicotomy. Since 1995, based on our experience of a high rate of single adenomas in R-HPT, a focused approach (FA) has been adopted for patients that did not require simultaneous thyroid operative therapy and in which no other contraindications to minimal access parathyroidectomy existed. The aim of this study was to determine the pattern of presentation, recurrence and the long-term outcomes after operative therapy for R-HPT. We also reviewed the associated histologic findings.

## MATERIALS AND METHODS

A retrospective review was performed on R-HPT in patients operated on from 1980 to 2003. All patients with familial HPT or multiple endocrine neoplasia types 1 or 2 were excluded from the

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study. Irradiated patients were defined as those who had received 1 or more therapeutic doses of external beam radiation to the head and neck area for the treatment of benign or malignant disease. A minimum of 3 years of follow-up after operative therapy was required for inclusion.

All irradiated patients underwent an evaluation for thyroid and parathyroid disease that included a clinical examination, thyroid stimulating hormone, parathyroid hormone (PTH), and calcium measurements, as well as a neck ultrasound. Preoperative data, pathologic findings, and long-term outcome were analyzed. The coexistence of thyroid disease and previous thyroid operative therapy was also documented. Serum calcium and intact PTH levels were measured postoperatively, at 6 months, and yearly thereafter. Operative failure (ie, persistent disease) was defined as hypercalcemia and high or inappropriately unsuppressed PTH within 6 months of operative therapy. Recurrent disease was defined as disease recurrence presenting at greater than 6 months after operative therapy.

Through 1995, R-HPT patients underwent a bilateral neck exploration automatically via a conventional cervicotomy. After 1995, our departmental policy changed and patients who present without clinical and imaging evidence of thyroid disease and who present concordant Mibi-spect and ultrasound findings of a single parathyroid gland underwent an FA in the form of an endoscopic parathyroidectomy, as practiced in our department since 1998.<sup>4</sup> All patients who presented with a history of neck irradiation with combined thyroid and parathyroid disease continue to undergo thyroidectomy and bilateral parathyroid exploration by a conventional cervicotomy.

Histologically, parathyroid adenomas were classified as encapsulated parathyroid tumors in which a rim of normal parathyroid gland tissue was clearly identifiable. In the absence of these histologic features, abnormally enlarged parathyroid glands were classified as hyperplastic.

## RESULTS

Between 1980 and 2003, 1932 patients with primary HPT underwent parathyroidectomy in our department. Thirty-seven patients (1.92%; 3 men and 34 women) presented with a history of neck irradiation and were therefore considered to be cases of R-HPT. The median age at which patients received radiation was 17 years (range, 1-57 years). The indications for radiation treatment are summarized in the Table. Thirty-four patients were irradiated before 1965, and data of the radiation dose were not available. The remaining 3 patients

**Table.** Indication for radiation treatment in R-HPT patients

<i>Indication for radiation treatment</i>	<i>Patients (n = 37)</i>
Goiter	2
Cervical pain	4
Hemangiomas	4
Skin lesions	3
Thymus enlargement	5
Hodgkin's lymphoma	2
Keloid scar	1
Cervical adenopathy	6
Abscess	2
Tonsils	8

were treated after 1965 and received a mean dose of 3500 rad for the treatment of Hodgkin's lymphoma (2 patients) and malignant melanoma (1 patient).

Nine patients had undergone thyroid operative therapy previously with a median interval between radiation and thyroid operative therapy of 19.5 years (range, 12-31 years). None of the patients that had undergone thyroid operative therapy previously presented with either biochemical hyperparathyroidism preoperatively or enlarged parathyroid glands intraoperatively. Thyroid histology was benign goiter in 7 patients and papillary thyroid cancer in 2 patients.

Of the 37 patients who were studied, 18 were referred to our institution originally for thyroid disease and 19 patients received a diagnosis of hyperparathyroidism. The patients referred originally with HPT included 13 patients with symptomatic hyperparathyroidism and 6 patients with asymptomatic HPT identified incidentally on routine serum biochemistry. In the 18 patients referred with thyroid disease, HPT was diagnosed during routine evaluation before thyroid operation. In addition, 5 patients referred originally with HPT were found on clinical examination or imaging to have concomitant thyroid disease. Altogether, 23 patients presented with concurrent thyroid and parathyroid disease. The median interval between radiation and the diagnosis of HPT was 43 years (range, 5-85 years).

Thirty-two patients underwent a bilateral neck exploration, including 9 patients who had had previous thyroid operative therapy and 5 patients who had endoscopic parathyroidectomy. In the bilateral exploration (BE) group, 4 parathyroid glands were identified in all except 8 patients who underwent thyroid operative therapy previously; 3 glands were identified in 3 patients, 2 glands in 4 patients, and

1 gland in 1 patient. Overall, a single, enlarged parathyroid gland was found in 30 of 32 patients. Two patients presented with multiglandular disease. Histology confirmed the macroscopic findings of a single hyperplastic gland in 30 patients (among whom 19 patients had lesions classified as parathyroid adenomas), double adenomas in 1 patient, and triple adenomas in another patient. Thyroid histologic findings were thyroid papillary cancer in 14 patients and multinodular goiter in 9 patients. No nerve palsies were reported on routine postoperative laryngoscopy. Transitory hypocalcaemia occurred in 1 patient who had undergone thyroidectomy previously and in 8 other patients that underwent a simultaneous parathyroidectomy and thyroidectomy. Follow-up showed that 26 patients remain cured after a median follow-up of 10.3 years (range, 3-21 years) with 6 patients with recurrent disease at a median time of 13.2 years (range, 7-22 years) after operation. Three of these 6 patients have undergone successful reoperation. Two patients underwent a Mibi-directed open FA with resection of an adenoma confirmed on histology. The other patient had negative preoperative studies and underwent a BE with identification of all 3 remaining glands, 2 of which were abnormal and confirmed on histology as hyperplastic. Postoperative calcium and PTH confirmed a cure in all patients. No hypocalcaemia, nerve palsies, and recurrences have occurred in these patients after a median follow-up of 3 years (range, 1-5 years). The remaining 3 patients refused operative therapy and underwent medical surveillance; they have ongoing disease, but they all have a serum calcium level lower than 2.75 mmol/L.

Since 1995, 7 patients without any associated thyroid disease were considered potential candidates for a focused parathyroidectomy. Five of these 7 patients had concordant Mibi-spect and ultrasound localization findings and underwent an endoscopic parathyroidectomy, whereas the other 2 patients with negative localization findings underwent a BE by a conventional cervicotomy. In the FA group, intraoperative PTH decreased by more than 50% within 15 min in all patients. At histology, all 5 lesions were parathyroid adenomas. No transitory hypocalcaemia or nerve palsies were reported. All patients remain cured at a comparatively shorter median follow-up of 6.4 years (range, 3-8 years).

## **DISCUSSION**

The reports of increased thyroid cancer risk that follows exposure to radiation<sup>5</sup> have focused interest on the relationship between radiation exposure and subsequent development of both benign and

malignant endocrine tumors. External beam irradiation to the neck, especially during childhood, increases the risk of thyroid cancer. The most frequent radioinduced thyroid cancer is papillary carcinoma. In our series of R-HPT, papillary thyroid cancer occurred in over one third of patients (14 of 37 patients; 37.8%). Among 6 patients who had undergone subtotal thyroidectomy previously, 3 patients with papillary thyroid cancer were identified when parathyroid operative therapy was later performed. Indeed this highlights why total thyroidectomy has become the treatment of choice for patients with a history of radiation exposure presenting as a thyroid nodule.<sup>6</sup>

Patients who have been exposed to external beam radiation have an increased risk of developing HPT that has been quantified at 2.9 times the risk of nonexposed controls.<sup>2</sup> A Swedish series reported a 14% incidence of R-HPT in a group of 170 patients with HPT.<sup>7</sup> R-HPT shows the same clinical course as sporadic non-R-HPT.<sup>8</sup>

It has been reported that the association of thyroid cancer with HPT occurred 9 times more frequently in irradiated patients<sup>9</sup> than in nonirradiated patients.<sup>8</sup> Therefore, both pathologies must be kept in mind in radiation-exposed patients and the screening and evaluation of both pathologies must be undertaken. Serum calcium estimation is measured routinely before all thyroid operative therapy to establish a baseline level and importantly to avoid inadvertent concomitant undiagnosed HPT. Patients with a history of radiation exposure may also benefit from a PTH estimation because this may reveal an unaccommodated PTH that may precede overt hypercalcaemic hyperparathyroidism. In patients with R-HPT, preoperative diagnosis of associated thyroid disease is mandatory by clinical and ultrasound evaluation. The presence of solitary or multiple thyroid nodules that require operative treatment should be assessed carefully before parathyroid operative therapy.

The appropriate operative strategy in suspected R-HPT remains unproven. This series of patients with R-HPT demonstrates that single gland disease was responsible for HPT at the time of initial operation in 35 of 37 patients. Other reports have confirmed parathyroid pathology as similar in R-HPT and sporadic HPT.<sup>3,8,10</sup> Altogether, 6 patients experienced disease recurrence, so the overall proportion of multiple gland disease was 8 of 37 patients when long-term follow-up was taken into consideration. Five of these 6 patients had 1 pathologic gland removed and 3 normal parathyroid glands left in situ at the time of the original parathyroidectomy. In the last patient, who underwent

total thyroidectomy previously, only 1 parathyroid gland had been identified: This gland was pathologic and was removed. Overall, these 6 patients had a median disease-free interval of 13.2 years. Why parathyroid disease recurred after such a delay is unclear, but it is known that HPT may follow neck irradiation with a latency period between 18 and 65 years. However, a shorter latency period has been reported after high-dose radiation in malignant disease.<sup>3</sup> Overall, parathyroid glands seem to have a relatively low sensitivity to radiation and induced changes may not become manifest until many years after irradiation.<sup>11</sup> The parathyroid glands may reveal no macroscopic abnormalities when inspected at the time of thyroid operation for radiation-induced thyroid disease because this seems to precede parathyroid disease by at least a decade. The delayed recurrent disease may suggest that not all parathyroids manifest the same degree of radiosensitivity, even in the same patient. Metachronous pathologic glands may develop over time, and lifelong follow-up is mandatory in irradiated patients. Our data suggest that BE does not seem to reduce late recurrences. A higher rate of postoperative complications is reported after BE in comparison with FA,<sup>12,13</sup> even if in our experience concomitant thyroidectomy could explain this higher morbidity. If BE is performed to conduct a subtotal parathyroidectomy, what is the evidence for removing or leaving in situ a normal-appearing gland? In a series of 34 patients who presented with R-HPT, all underwent total parathyroidectomy with autotransplantation despite macroscopic evidence of uniglandular disease in 25 of 34 patients, and recurrence occurred in 2 patients caused by an autotransplanted normal parathyroid gland.<sup>10</sup> After subtotal PTX, postoperative morbidity, and in the event of reoperation, a risk of leaving the patient a parathyroid should be borne in the mind of the operating surgeon. In R-HPT, up to one third of patients may have had a previous thyroid operation<sup>3</sup> because of the greater lag between exposure to radiation and disease. In these patients who have undergone neck operative therapy, attempts to identify all glands embedded in scar tissue may result in their devascularization and destruction. An FA reduces the need for exploration in scar tissue and reduces the formation of adherence in the other parathyroid sites, which is an important point in patients in which reexploration is needed later. In our experience, FA also has a low associated morbidity and offers long-term cure. Concomitant thyroid disease remains a contraindication to FA, however, and this approach is of course limited by negative localization findings.

Given that image-guided, minimal access parathyroidectomy with intraoperative PTH measurement offers a cure in sporadic non-R-HPT,<sup>14</sup> the same should apply to patients with R-HPT when such operative therapy is not contraindicated. In the absence of other contraindications, it would seem appropriate to propose focused parathyroid operation in R-HPT, and lifelong thyroid and parathyroid surveillance should be undertaken in irradiated patients.

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## DISCUSSION

**Dr Bradford K. Mitchell** (Morgantown, West Virginia): None of your patients were treated with radioactive iodine in this group. Are you looking at that group separately and would you handle those patients any differently?

**Dr Giuseppe Ippolito** (Marseille, France): We have no experience with patients presenting HPT who have a previous history of radioactive iodine treatment. Indeed, we do not routinely screen for HPT in patients previously treated with radioactive iodine.

**Dr Bradford K. Mitchell** (Morgantown, West Virginia): No treatment for Graves' disease with radioactive iodine?

**Dr Giuseppe Ippolito** (Marseille, France): In the series presented, the 2 patients presenting with an enlarged thyroid gland had received only external beam irradiation.

**Dr Scott Wilhelm** (Cleveland, Ohio): In your flow chart where you said how you worked up these patients up, you did an ultrasound of the neck first, if you found a thyroid nodule and parathyroid disease, you went directly to surgery. Did you FNA those people in between to determine if the nodule was cancer?

Second question. In your reoperative patients, did you evaluate them by the same flow chart criteria, meaning ultrasound and then Sestamibi, to try to localize the other gland to do a focused operation or did you go back and reexplore all the glands?

Last question. You said, by the literature, you mentioned that there was a higher risk of morbidity with bilateral neck exploration. Are you referring to Dr. Westerdahl's study where they took the 50 patients in each arm and in the bilateral group they had a slightly higher rate of transient hypocalcemia, but no difference in nerve and no difference in long term? Or is there something else you are referring to there?

**Dr Giuseppe Ippolito** (Marseille, France): In our series, the presence of thyroid disease in the context of a previous history of irradiation was an indication per se for surgery because of the known high risk of thyroid malignancy. FNA is therefore not utilized during work-up of irradiated patients. In irradiated patients presenting unilateral or bilateral thyroid disease, we always performed a total thyroidectomy.

**Dr Scott Wilhelm** (Cleveland, Ohio): The second question was, in the reoperative patients did you follow the same algorithm?

**Dr Giuseppe Ippolito** (Marseille, France): Yes, we did.

**Dr Scott Wilhelm** (Cleveland, Ohio): The last question was, by the literature you mentioned higher rate of morbidity.

**Dr Giuseppe Ippolito** (Marseille, France): Yes, I was referring to Dr Westerdahl and Dr Anders Bergenfelz's study. In our experience, we can explain a higher morbidity rate after bilateral exploration in comparison to focused approach because we also performed a simultaneous total thyroidectomy in the former group.

**Dr Lawrence T. Kim** (Little Rock, Arkansas): Exactly what is the risk of developing hyperparathyroidism after neck irradiation? Is it similar? You had, what, 18 or 20% recurrence after ten years? Is it in the same ballpark? If you take all patients with neck irradiation, what is the actual risk of developing hyperparathyroidism due to that?

**Dr Giuseppe Ippolito** (Marseille, France): The relative risk is reported to be about 3 times than that of not irradiated population. In our experience, 2% of primary HPT patients had a history of previous irradiation. A higher incidence of previous irradiation in patients with HPT is also reported in a Swedish series. The real incidence may be underestimated because often patients do not recall previous radiation treatment.

**Dr Carmen C. Solorzano** (Miami, Florida): Can you define for us exactly what you mean by neck radiation? Maybe I missed it. Some people get radiated for lymphoma of the thyroid or lymphoma of other things. Were these all patients that got it from a young age for acne or thymus, et cetera?

Secondly, did you use the intraoperative hormone assay in any of these patients, and did you see any differences in what the assay tells you or not?

**Dr Giuseppe Ippolito** (Marseille, France): Irradiated patients were defined as those who had received one or more therapeutic doses of external beam radiation to the head and neck area for the treatment of benign or malignant disease. When we perform a focused approach parathyroidectomy we routinely utilize intraoperative PTH to confirm cure. Patients that underwent bilateral exploration, intraoperative PTH was utilized only if one pathological gland and less than 2 normal appearing glands were identified.

**Dr Carmen C. Solorzano** (Miami, Florida): After the last gland you took out?

**Dr Giuseppe Ippolito** (Marseille, France): After we took out the pathological gland.