Cancer Association of South Africa (CANSA)

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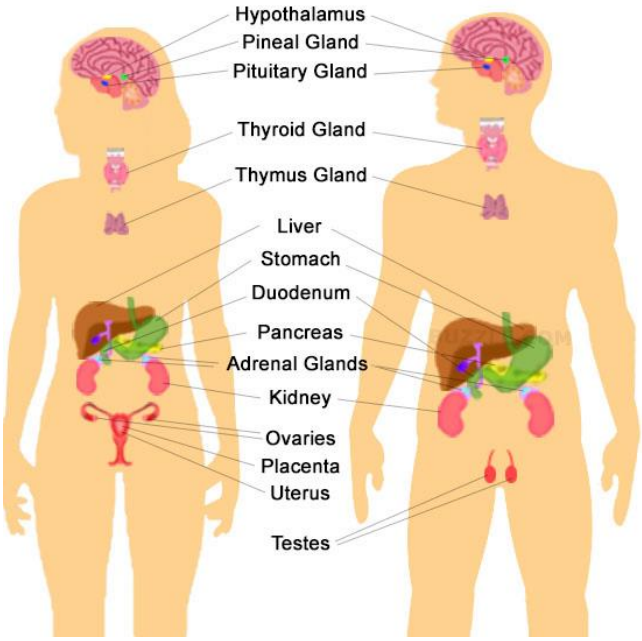
Fact Sheet
on
Parathyroid Gland Cancer

Introduction

The endocrine system is a network of endocrine glands and nerves found throughout the body. Endocrine glands produce and release hormones, which circulate around the body in the blood. Hormones keep an even balance of chemicals and fluid within the body, and help the body respond to changes in the environment. Normally, hormones released by endocrine glands are carefully balanced to meet the body's needs. There are many more organs in the body capable of secreting hormones than is popularly believed.



[Picture Credit: Major Endocrine Organs]

Endocrine organs (those organs that secrete hormones) include:

- Hypothalamus
- Pineal body
- Pituitary gland (anterior lobe)
- Pituitary gland (posterior lobe)
- Thyroid
- Alimentary system
  - Stomach
  - Duodenum
  - Liver
  - Pancreas
- Kidney
- Adrenal cortex
- Adrenal medulla
- Reproductive system
  - Testes

Researched and Prepared by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Diagnostic Radiographer; Dip Audiometry and Noise Measurement; Medical Ethicist]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

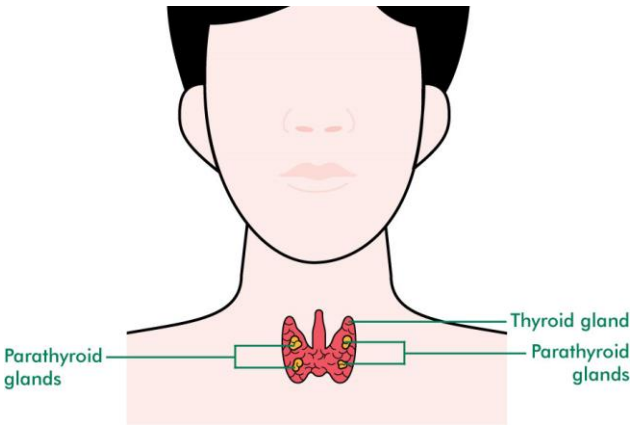
- Ovaries
- Placenta (during pregnancy)
- Uterus (during pregnancy)

- Parathyroid
- Skin

Parathyroid Gland Cancer

Parathyroid gland cancer occurs when the cells of the parathyroid gland multiplies uncontrollably. Parathyroid disease is caused by a single defective parathyroid gland (a benign parathyroid tumour) about 80% of the time. Parathyroid cancer is extremely rare, to the extent that most doctors have never seen it.

[Picture Credit: Parathyroid Glands]



There are four parathyroid glands, which are attached to the thyroid gland in the front of the neck. The parathyroid glands are small, but their function is very important. They maintain the correct levels of calcium in the body. Calcium plays an essential role in controlling muscle and nerve function. A tumour of the parathyroid gland may cause overproduction of the hormone that controls the level of calcium in the body. This hormone is called parathyroid hormone (PTH) or parathormone.

Byrd, C. & Kwartowitz, G. 2019.

"Parathyroid carcinoma is a rare, malignant neoplasm involving the parathyroid gland. The normal weight and size of the parathyroid glands vary. The average weight is about 60 mg. The average dimensions of each gland are 5 mm in length by 3 mm in width and 1 mm in thickness. The color of normal parathyroid glands is a yellow-brown color. There are generally 4 parathyroid glands, 2 superior and 2 inferior glands; they are located on the posterior and lateral surface of the thyroid gland. The location of the glands may vary based on the embryological descent during development. The inferior parathyroids and the thymus both develop from the third branchial pouch, whereas the parafollicular C cells and the superior parathyroids develop from the fourth branchial pouch. The superior parathyroid glands are frequently found near the cricothyroid junction, just superior to the intersection of the recurrent laryngeal nerve and the inferior thyroid artery. The superior parathyroids are closely associated with the posterior capsule of the superior thyroid pole. The inferior parathyroids have a more variable location, and greater than 50% are located at the inferior thyroid pole, but they can be located in the anterior mediastinum along the thyrothymic ligament. Rarely there is the presence of a supernumerary gland. The association of the parathyroid glands to the recurrent laryngeal nerve is an important anatomical relationship. The superior parathyroids are deep to the recurrent laryngeal nerve, and the inferior parathyroids are superficial. In most cases, the parathyroid gland's arterial supply is derived from the inferior thyroid artery, which is a branch of the thyrocervical trunk. In 20% of cases, it may derive its blood supply from the superior thyroid artery, which is a branch from the external carotid artery. There is generally rich anastomosis

between the parathyroids, larynx, pharynx, esophagus, and trachea. The venous drainage parallels the arterial vessels and drains into the internal jugular. The lymphatics of the parathyroid drain into the deep cervical and pretracheal lymph nodes, similar to the lymphatic drainage of the thyroid gland. The major functional cells of the parathyroid are the chief cells, which contain many cytoplasmic secretory granules. These are responsible for producing parathyroid hormone. The second cell type that makes up the parathyroid parenchyma are the oxiphil cells. Their function is unknown, but they tend to be rich in mitochondria. Parathyroid glands with high concentrations of oxiphil cells tend to function abnormally."

Incidence of Parathyroid Gland Cancer in South Africa

The outdated National Cancer Registry (2014), known for under reporting, does not provide any information on the incidence of parathyroid cancer. The Registry combines all endocrine cancers together.

According to the National Cancer Registry (2014) the following number of endocrine cancer cases was histologically diagnosed in South Africa during 2014. Histologically diagnosed means that a tissue specimen (biopsy) was taken and sent to an approved laboratory where a specially trained pathologist confirmed the diagnosis of cancer.

Group - Males 2014	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	24	1:12 300	0,07%
Asian males	0	-	-
Black males	14	1:15 371	0,13%
Coloured males	4	1:13 558	0,10%
White males	6	1:4 796	0,03%

Group - Females 2014	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	21	1:14 555	0,06%
Asian females	1	1:11 478	0,08%
Black females	13	1:22 930	0,08%
Coloured females	2	1:16 352	0,05%
White females	5	1:5 450	0,03%

The frequency of histologically diagnosed cases of endocrine cancer in South Africa for 2014 was as follows (National Cancer Registry, 2014):

Group - Males 2014	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	9	1	1	5	2	4	1	2
Asian males	0	0	0	0	0	0	0	0
Black males	6	0	0	4	0	3	1	0
Coloured males	1	1	1	0	0	0	1	0
White males	2	0	0	1	2	1	0	0

Group - Females 2014	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	8	2	2	3	4	2	1	0
Asian females	0	0	1	0	0	0	0	0
Black females	7	1	1	2	1	1	0	0
Coloured females	0	1	0	0	1	0	0	0
White females	1	0	0	1	1	1	1	0

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females' , however, always reflect the correct totals.

Symptoms of Parathyroid Gland Cancer

Symptoms of parathyroid cancer are mainly caused by high levels of calcium in the blood (hypercalcemia) and may affect different parts of the body.

This may include:

- Bone pain
- Constipation
- Fatigue
- Fractures
- Frequent thirst
- Frequent urination
- Kidney stones
- Muscle weakness
- Nausea
- Poor appetite
- Vomiting

Causes of Parathyroid Gland Cancer

Parathyroid cancer is an extremely rare type of cancer. Men and women are equally affected. It usually occurs in people older than 30.

The cause of parathyroid cancer is unknown. People with a genetic condition called multiple endocrine neoplasia type I have an increased risk for this disease. People who had head or neck radiation may also be at increased risk. Such radiation exposure, however, is more likely to cause thyroid cancer.

Schaaf, L. & Raue, F. 2017.

"Multiple endocrine neoplasia type 1 and 2 are hereditary cancer syndromes. They are characterized by the occurrence of many benign and malignant tumor types, in MEN1 parathyroid tumors, pituitary tumors, and pancreas tumors, in MEN2 medullary thyroid carcinoma, pheochromocytoma, and parathyroid tumors. The autosomal dominant inherited tumor syndromes are caused by mutations in the MEN1 gene, a tumor suppressor gene, and mutations in the RET gene, an activated oncogene, in MEN2. The clinical expression of the different tumors can vary within and between families, with a good genotype-phenotype correlation in MEN2. Early diagnosis and therapy is

possible by using biochemical and imaging screening in the families. Early thyroidectomy in young patients with MEN2 results in a high cure rate of MTC."

Diagnosis of Parathyroid Gland Cancer

The facts about parathyroid cancer:

- Parathyroid cancer is very rare: about one case in every 1 000 patients with parathyroid disease, or possibly even rarer
- Parathyroid cancer is often mild and not very aggressive
- Parathyroid cancer is often hard for the pathologist to diagnose under the microscope. Thus the diagnosis often depends on the clinical picture (very high parathyroid hormone levels, and very high serum calcium levels)
- Parathyroid cancer is *almost always* associated with extremely high parathyroid hormone (PTH) levels (typically in the thousands)
- If the patient's parathyroid hormone level is not in the thousands, and the calcium is not consistently over 14mg/dL, the patient does not have parathyroid cancer (a generalisation, but a good one)
- Most people with calcium levels above 14mg/dL still do not necessarily have parathyroid cancer
- Parathyroid cancer is occasionally associated with a genetic defect, therefore, parathyroid cancer may be found in families

Ferraro, V., Sgaramella, L.I., Di Meo, G., Prete, F.P., Logoluso, F., Minerva, F., Noviello, M., Renzulli, G., Gurrado, A. & Testini. M. 2019.

Background: Parathyroid carcinoma is a rare neoplasm that may present sporadically or in the context of a genetic syndrome. Diagnosis and management are challenging due to the lack of clinical and pathological features that may reliably distinguish malignant from benign disease.

Methods: From January 2013 to December 2017, from 358 consecutive patients affected by parathyroid diseases, 3 patients with parathyroid carcinoma were treated at our academic Department of General Surgery. We present our experience as illustrative of the different features of clinical presentation of parathyroid carcinoma and review its management considering the recent relevant literature.

Results: Case 1: A 62-year-old man was hospitalized for left-sided palpable neck mass, hypercalcemia and elevated PTH. US-guided FNA was suspect for parathyroid carcinoma. A large cystic mass was excised in bloc with total thyroidectomy and central neck dissection. Genetic studies framed a pathologically confirmed parathyroid carcinoma within MEN1 syndrome. Case 2: A 48-year-old woman with hypothyroidism had total thyroidectomy performed for a suspect for right follicular thyroid lesion. Pathology revealed parathyroid carcinoma. Case 3: A 47 year-old man was admitted for hypercalcaemic crisis and renal failure in the context of PHPT. A lesion suggestive on US and MIBI scan for parathyroid adenoma in the right lower position was removed by mini-invasive approach. Pathology revealed parathyroid cancer and patient had completion hemythyroidectomy and central neck dissection.

Conclusion: Parathyroid cancer is a particularly rare endocrine malignancy, however it should be suspected in patients with primary hyperparathyroidism when severe hypercalcemia is associated to cervical mass, renal and skeletal disease. Parathyroid surgery remains the mainstay of treatment. Radical tumour resection and expedited treatment in a dedicated endocrine Center represent crucial prognostic factors.

Yu, Q., Hardin, H., Chu, Y-H., Rehrauer, W. & Lloyd, R.V. 2019.
Parathyroid adenomas are slow growing benign neoplasms associated with hypercalcemia, while atypical parathyroid adenomas and parathyroid carcinomas are uncommon tumors and their histologic features may overlap with parathyroid adenomas. LncRNAs participate in transcription and in epigenetic or post-transcriptional regulation of gene expression, and probably contribute to carcinogenesis. We analyzed a group of normal, hyperplastic, and neoplastic parathyroid lesions to determine the best immunohistochemical markers to characterize these lesions and to determine the role of selected lncRNAs in tumor progression. A tissue microarray consisting of 111 cases of normal parathyroid (n = 14), primary hyperplasia (n = 15), secondary hyperplasia (n = 10), tertiary hyperplasia (n = 11), adenomas (n = 50), atypical adenomas (n = 7), and carcinomas (n = 4) was used. Immunohistochemical staining with antibodies against chromogranin A, synaptophysin, parathyroid hormone, and insulinoma-associated protein 1(INSM1) was used. Expression of lncRNAs including metastasis-associated lung adenocarcinoma transcript one (MALAT1), HOX transcript antisense intergenic RNA (HOTAIR), and long intergenic non-protein coding regulator of reprograming (Linc-ROR or ROR) was also analyzed by in situ hybridization and RT-PCR. All of the parathyroid tissues were positive for parathyroid hormone, while most cases were positive for chromogranin A (98%). Synaptophysin was expressed in only 12 cases (11%) and INMS1 was negative in all cases. ROR was significantly downregulated during progression from normal, hyperplastic, and adenomatous parathyroid to parathyroid carcinomas. These results show that parathyroid hormone and chromogranin A are useful markers for parathyroid neoplasms, while synaptophysin and INSM1 are not very sensitive broad-spectrum markers for these neoplasms. LincRNA ROR may function as a tumor suppressor during parathyroid tumor progression.

Staging of Parathyroid Gland Cancer
There is no standard staging process for parathyroid cancer.

Treatment of Parathyroid Gland Cancer
Different types of treatment are available for patients with parathyroid cancer. Some treatments are standard while some are being tested in clinical trials.

Treatment may include control of hypercalcaemia (high levels of calcium in the blood) in patients who have an overactive parathyroid gland.

Four types of standard treatment may be used:

Surgery - surgery (removing the cancer in an operation) is the most common treatment for parathyroid cancer that is in the parathyroid glands or has spread to other parts of the body. Because parathyroid cancer grows very slowly, cancer that has spread to other parts of the body may be removed by surgery in order to cure the patient or control the effects of the disease for a long time. Before surgery, treatment is usually given to control hypercalcaemia.

Byrd, C. & Kwartowitz, G. 2019.
"Surgery is the preferred treatment for parathyroid carcinoma. If there is a high suspicion for parathyroid carcinoma preoperatively, parathyroidectomy or en bloc resection of the parathyroid tumor and adjacent tissues that have been invaded should be performed. When the diagnosis is

made postoperatively, the patient should be taken back to the operating room for ipsilateral thyroidectomy. In the instance where pathology evaluation reveals positive margins, the patient should be taken back to the operating room to achieve negative margins.
"When parathyroid carcinoma is no longer resectable due to widespread dissemination, medical management is recommended to control hypercalcemia. The prognosis is generally poor with widely disseminated parathyroid carcinoma, but survival can be prolonged with adequate control of serum calcium. Intravenous hydration and bisphosphonates are recommended for the treatment of hypercalcemia. In episodes of hypercalcemia refractory to bisphosphonates, cinacalcet may be attempted to aid in serum calcium reduction.
"In cases of local or regional recurrence, surgical excision is indicated and will provide palliation from hypercalcemia. Long-term cure after recurrence is unknown. In cases with metastasis to the lungs or liver, surgical excision of these areas has been described for palliative care."

No effective medical therapy for parathyroid carcinoma is known. Trials of chemotherapeutic agents have been generally disappointing with only anecdotal reports of success. This tumour is sufficiently rare that controlled trials are impossible.

Medical therapy is usually primarily geared toward management of the hypercalcaemia that is often quite severe. Treatment is similar to hypercalcaemia due to other causes. Hypercalcaemia due to parathyroid cancer is often resistant to long-term medical management and is usually the cause of death in patients with metastatic disease.

Chemotherapy - chemotherapy is a cancer treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing.

Supportive care - supportive care is given to lessen the problems caused by the disease or its treatment. Supportive care for hypercalcaemia caused by parathyroid cancer may include the following:

- Intravenous (IV) fluids.
- Drugs that increase how much urine the body makes.
- Drugs that stop the body from absorbing calcium from the food we eat.
- Drugs that stop the parathyroid gland from making parathyroid hormone.

Wang, B., Zhu, C-R., Liu, H. & Wu, J. 2019.
Objective: We conducted this meta-analysis to assess the effectiveness of parathyroid gland autotransplantation in preserving parathyroid function during thyroid surgery for thyroid neoplasms.
Methods: We conducted a search by using PubMed, Embase, and the Cochrane Library electronic databases for studies that were published up to January 2019. The reference lists of the retrieved articles were also reviewed. Two authors independently assessed the methodological quality and extracted the data. A random-effects model was used to calculate the overall combined risk estimates. Publication bias was evaluated with a funnel plot using Egger's and Begg's tests.
Results: A total of 25 independent studies involving 10,531 participants were included in the meta-analysis. Compared with patients who did not undergo parathyroid gland autotransplantation, the overall pooled relative risks for patients who underwent parathyroid gland autotransplantation were 1.75 (95% CI: 1.51-2.02, p<0.001) for postoperative hypoparathyroidism, 1.72 (95% CI: 1.45-2.05,

p<0.001) for protracted hypoparathyroidism, 1.06 (95% CI: 0.44-2.58, p = 0.894) and 0.71 (95% CI: 0.22-2.29, p = 0.561) for biochemical hypoparathyroidism and biochemical hypocalcemia at 6 months postoperatively, respectively, and 1.89 (95% CI: 1.33-2.69, p<0.001) and 0.22 (95% CI: 0.09-0.52, p = 0.001) for biochemical hypoparathyroidism and biochemical hypocalcemia at 12 months postoperatively, respectively. The pooled relative risks for patients who underwent one parathyroid gland autotransplantation and patients who underwent two or more parathyroid gland autotransplantations were 1.71 (95% CI: 1.25-2.35, p = 0.001) and 2.22 (95% CI: 1.43-3.45, p<0.001) for postoperative hypoparathyroidism, 1.09 (95% CI: 0.59-2.01, p = 0.781) and 0.55 (95% CI: 0.16-1.87, p = 0.341) for hypoparathyroidism at 6 months postoperatively compared with those of patients who did not undergo parathyroid gland autotransplantation.
Conclusions: Parathyroid gland autotransplantation is significantly associated with increased risk of postoperative and protracted hypoparathyroidism, and the number of autoplastic parathyroid glands is positively correlated with the incidence of postoperative hypoparathyroidism.

Winer, K.K., Kelly, A., Johns, A., Zhang, B., Dowdy, K., Kim, L., Reynolds, J.C. Alberts, P.S. & Cutler, G.B. Jnr. 2018.
OBJECTIVE: To determine whether multiple daily injections of parathyroid hormone (PTH) 1-34 are safe and effective as long-term therapy for children with hypoparathyroidism.
STUDY DESIGN: Linear growth, bone accrual, renal function, and mineral homeostasis were studied in a long-term observational study of PTH 1-34 injection therapy in 14 children.
METHODS: Subjects were 14 children with hypoparathyroidism attributable to autoimmune polyglandular syndrome type 1 (N = 5, ages 7-12 years) or calcium receptor mutation (N = 9, ages 7-16 years). Mean daily PTH 1-34 dose was 0.75 ± 0.15 µg/kg/day. Treatment duration was 6.9 ± 3.1 years (range 1.5-10 years). Patients were evaluated semiannually at the National Institutes of Health Clinical Center.
RESULTS: Mean height velocity and lumbar spine, whole body, and femoral neck bone accretion velocities were normal throughout the study. In the first 2 years, distal one-third radius bone accrual velocity was reduced compared with normal children (P < .003). Serum alkaline phosphatase correlated with PTH 1-34 dose (P < .006) and remained normal (235.3 ± 104.8 [SD] U/L, N: 51-332 U/L). Mean serum and 24-hour urine calcium levels were 2.05 ± 0.11 mmol/L (N: 2.05-2.5 mmol/L) and 6.93 ± 1.3 mmol/24 hour (N: 1.25-7.5 mmol/24 hour), respectively-with fewer high urine calcium levels vs baseline during calcitriol and calcium treatment (P < .001). Nephrocalcinosis progressed in 5 of 12 subjects who had repeated renal imaging although renal function remained normal.
CONCLUSIONS: Twice-daily or thrice-daily subcutaneous PTH 1-34 injections provided safe and effective replacement therapy for up to 10 years in children with hypoparathyroidism because of autoimmune polyglandular syndrome type 1 or calcium receptor mutation.

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:
- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers

- Tests to find new ways of screening for cancer

The *South African National Clinical Trials Register* provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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