

# Cancer Association of South Africa (CANSA)



## Fact Sheet on Parathyroid Gland Cancer

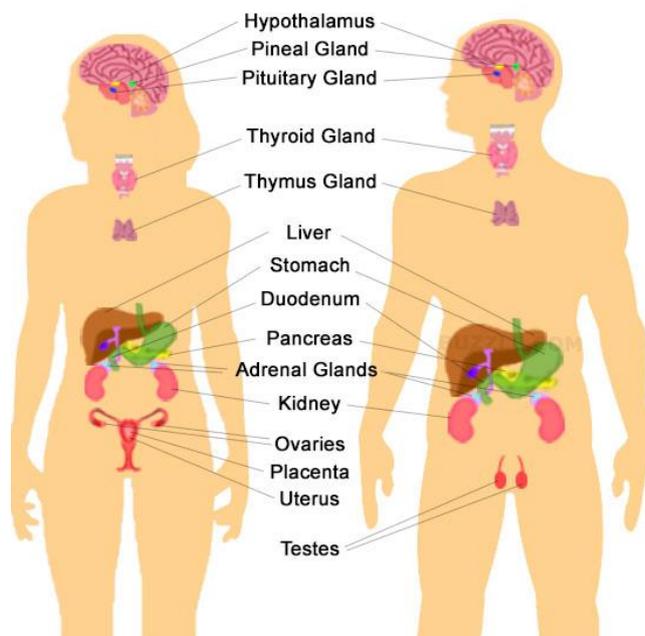
### Introduction

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



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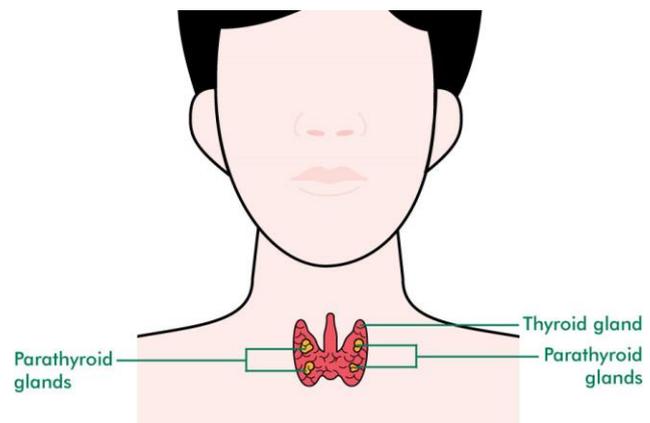
- Ovaries
- Placenta (during pregnancy)
- Uterus (during pregnancy)
- Parathyroid
- Skin

### 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.



**Rodrigo, J.P., Hernandez-Prera, J.C., Randolph, G.W., Zafereo, M.E., Hartl, D.M., Silver, C.E., Suárez, C., Owen, R.P., Bradford, C.R., Mäkitie, A.A., Shaha, A.R., Bishop, J.A., Rinaldo, A. & Ferlito, A. 2020.**

“Parathyroid cancer (PC) is a rare malignant tumor which comprises 0.5-5% of patients with primary hyperparathyroidism (PHPT). Most of these cancers are sporadic, although it may also occur as a feature of various genetic syndromes including hyperparathyroidism-jaw tumor syndrome (HPT-JT) and multiple endocrine neoplasia (MEN) types 1 and 2A. Although PC is characterized by high levels of serum ionized calcium (Ca) and parathyroid hormone (PTH), the challenge to the clinician is to distinguish PC from the far more common entities of parathyroid adenoma (PA) or hyperplasia, as there are no specific clinical, biochemical, or radiological characteristic of PC. Complete surgical resection is the only known curative treatment for PC with the surgical approach during initial surgery strongly influencing the outcome. In order to avoid local recurrence, the lesion must be removed en-bloc with clear margins. PC has high recurrence rates of up to 50% but with favorable long-term survival rates (10-year overall survival of 60-70%) due to its slow-growing nature. Most patients die not from tumor burden directly but from uncontrolled severe hypercalcemia. In this article we have updated the information on PC by reviewing the literature over the past 10 years and summarizing the findings of the largest series published in this period.”

**Byrd, C., Kashyap, S. & Kwartowitz, G. 2021.**

“Parathyroid carcinoma is a rare, malignant neoplasm originating from 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

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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, each 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 is the oxyphil cell. Their function is unknown, but they tend to be rich in mitochondria. Parathyroid glands with high concentrations of oxyphil cells may be more prone to hyperfunction.

As with all malignancy, parathyroid carcinoma is a result of the uncontrolled or unregulated growth of the parathyroid cells, and most parathyroid carcinomas are functional - meaning they secrete parathyroid hormone (PTH). Parathyroid carcinoma can occur in any of the parathyroids and does not appear to have a predilection for either the superior or inferior glands (or supernumerary glands), though the rarity of the disease precludes any definitive conclusions. The hallmark characteristic is a very high serum PTH level, often into the thousands, which is rare in benign hyperparathyroidism.”

### **Incidence of Parathyroid Gland Cancer in South Africa**

The outdated National Cancer Registry (2017), 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 (2017) the following number of endocrine cancer cases was histologically diagnosed in South Africa during 2017. The term ‘histologically diagnosed’ means that a biopsy specimen was forwarded to an approved laboratory where a specially qualified pathologist confirmed the diagnosis of cancer:

Group - Males 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	36	1:6 290	0,09%
Asian males	1	1:8 889	0,10%
Black males	16	1:16 000	0,12%
Coloured males	7	1:3 040	0,15%
White males	12	1:2 353	0,06%

Group - Females 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	29	1:10 696	0,07%
Asian females	2	1:4 717	0,16%
Black females	15	1:18 019	0,08%
Coloured females	1	-	0,02%
White females	11	1:2 696	0,06%

The frequency of histologically diagnosed cases of endocrine cancer in South Africa for 2017 was as follows (National Cancer Registry, 2017):

Group - Males 2017	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	10	3	3	5	7	4	3	1
Asian males	0	0	0	0	1	0	0	0
Black males	8	0	2	2	3	1	0	0
Coloured males	1	1	0	1	2	2	0	0
White males	1	2	1	2	1	1	3	1

Group - Females 2017	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	10	1	4	2	6	4	1	1
Asian females	0	1	0	0	1	0	0	0
Black females	9	0	1	1	2	2	0	0
Coloured females	0	0	0	0	0	0	0	1
White females	1	0	3	1	3	2	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

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- 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.

### **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

**Itani, M. & Middleton, W.D.** 2020.

“Primary hyperparathyroidism (PHPT) is a common endocrine abnormality, caused in most cases by a single parathyroid adenoma. Surgery remains the first-line curative therapy in PHPT. Imaging plays a vital role in presurgical localization of parathyroid adenomas. Ultrasound provides a safe and quick imaging modality free of ionizing radiation, but is operator dependent. Sestamibi scan offers comparable sensitivity to ultrasound, improved with concurrent tomographic imaging. 4DCT remains a problem-solving technique in challenging cases and after failed neck exploration. We present an overview of various parathyroid imaging modalities, including protocols and findings, in addition to relevant pearls and pitfalls.”

**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 hemithyroidectomy 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 reprogramming (LincROR 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 INSM1 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.

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## **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 autoplasmic parathyroid glands is positively correlated with the incidence of postoperative hypoparathyroidism.

### 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

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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/](http://www.sanctr.gov.za/)

### Medical Disclaimer

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#### KidsHealth

[http://kidshealth.org/parent/general/body\\_basics/endocrine.html](http://kidshealth.org/parent/general/body_basics/endocrine.html)

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### MacMillan Cancer Support

<http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Endocrine/Adrenalglands.aspx>

<http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Endocrine/Parathyroidglands.aspx>

### Major Endocrine Organs

[https://www.google.co.za/search?q=endocrine+system&source=Inms&tbm=isch&sa=X&ei=q9c2UtvmtSrAex2ICQCw&sqi=2&ved=0CAcQ\\_AUoAQ&biw=1366&bih=614&dpr=1#facrc=\\_&imgdii=\\_&imgrc=5SC7Bq5sKebYrM%3A%3BF72pBXaoZEytXM%3Bhttp%253A%252F%252Fbuzzle.com%252Fimages%252Fdiagrams%252Fhuman-body%252Fendocrine-glands.jpg%3Bhttp%253A%252F%252Fwww.buzzle.com%252Farticles%252Fendocrine-system-facts.html%3B550%3B550](https://www.google.co.za/search?q=endocrine+system&source=Inms&tbm=isch&sa=X&ei=q9c2UtvmtSrAex2ICQCw&sqi=2&ved=0CAcQ_AUoAQ&biw=1366&bih=614&dpr=1#facrc=_&imgdii=_&imgrc=5SC7Bq5sKebYrM%3A%3BF72pBXaoZEytXM%3Bhttp%253A%252F%252Fbuzzle.com%252Fimages%252Fdiagrams%252Fhuman-body%252Fendocrine-glands.jpg%3Bhttp%253A%252F%252Fwww.buzzle.com%252Farticles%252Fendocrine-system-facts.html%3B550%3B550)

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### Parathyroid Glands

[https://www.google.co.za/search?q=parathyroid+gland+cancer+diagnosis&source=Inms&tbm=isch&sa=X&ei=yA04UtLAHc bJhAej5YHAAQ&ved=0CAcQ\\_AUoAQ&biw=1366&bih=614&dpr=1#facrc=\\_&imgdii=\\_&imgrc=mWDTuopsebG4BM%3A%3BSBf82gFf0ztnqM%3Bhttp%253A%252F%252Fwww.macmillan.org.uk%252Fimages%252FCancerinfo%252FLongdescriptions%252FCancertypes%252FParathyroid\\_2012\\_accessible.jpg%3Bhttp%253A%252F%252Fwww.macmillan.org.uk%252FCancerinformation%252FCancertypes%252FEndocrine%252FParathyroidglands.aspx%3B900%3B602](https://www.google.co.za/search?q=parathyroid+gland+cancer+diagnosis&source=Inms&tbm=isch&sa=X&ei=yA04UtLAHc bJhAej5YHAAQ&ved=0CAcQ_AUoAQ&biw=1366&bih=614&dpr=1#facrc=_&imgdii=_&imgrc=mWDTuopsebG4BM%3A%3BSBf82gFf0ztnqM%3Bhttp%253A%252F%252Fwww.macmillan.org.uk%252Fimages%252FCancerinfo%252FLongdescriptions%252FCancertypes%252FParathyroid_2012_accessible.jpg%3Bhttp%253A%252F%252Fwww.macmillan.org.uk%252FCancerinformation%252FCancertypes%252FEndocrine%252FParathyroidglands.aspx%3B900%3B602)

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### Wikipedia

[http://en.wikipedia.org/wiki/Endocrine\\_system](http://en.wikipedia.org/wiki/Endocrine_system)

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