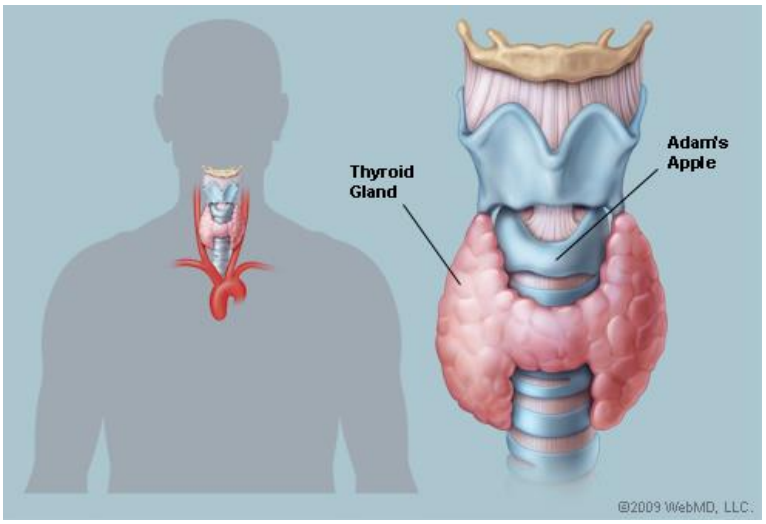
Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet
on
Cancer of the Thyroid

Introduction

The thyroid is a butterfly-shaped gland that sits low on the front of the neck. The thyroid lies below the Adam's apple, along the front of the windpipe. It has two side lobes, connected by a bridge (isthmus) in the middle. When the thyroid is its normal size, it cannot be felt.



[Picture Credit: Thyroid Gland]

Brownish-red in colour, the thyroid is rich with blood vessels. Nerves important for voice quality also pass through the thyroid.

The thyroid secretes several hormones, collectively called thyroid hormones. The main hormone is thyroxine, also called T4. Thyroid hormones act throughout the body, influencing metabolism, growth and development, and body temperature. During infancy and childhood, adequate thyroid hormone is crucial for brain development.

The C cells in the thyroid make calcitonin. This hormone plays a small role in keeping a healthy level of calcium in the body. Four or more tiny parathyroid glands are on the back of the thyroid. These glands make parathyroid hormone. This hormone plays a big role in helping the body maintain a healthy level of calcium.

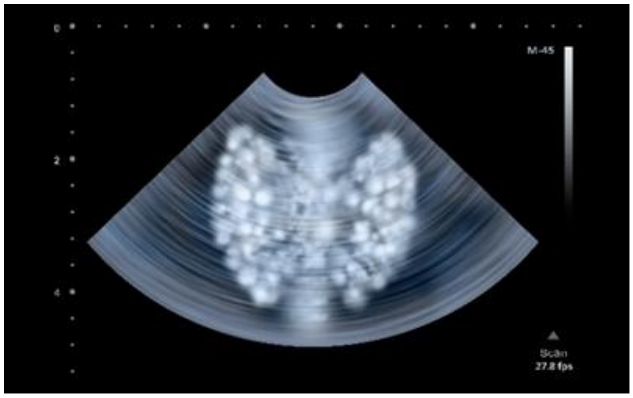
Thyroid Cancer

Thyroid cancer is when cancer develops in the cells of the thyroid. Cancer begins in cells, the building blocks that make up tissues. Tissues make up the thyroid and other organs of the body. Normal

Researched and Authored 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; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

thyroid cells grow and divide to form new cells as the body needs them. When normal cells grow old or get damaged, they die, and new cells take their place.

Sometimes, this process goes wrong. New cells form when the body does not need them, and old or damaged cells do not die as they should. The build-up of extra cells often forms a mass of tissue called a nodule. It may also be called a growth or tumour. Most thyroid nodules are benign. Benign nodules are not cancer (malignant).



[Picture Credit: Thyroid]

Thyroid cancer cells can spread by breaking away from the thyroid tumour. They can travel through lymph vessels to nearby lymph nodes. They can also spread through blood vessels to the lungs, liver, or bones. After spreading, cancer cells may attach to other tissues and grow to form new tumours that may damage those tissues.

Araque, K.A., Gubbi, S. & KlubooGwiezdzinska, J. 2020.
"The diagnostic modalities, stratification tools, and treatment options for patients with thyroid cancer have rapidly evolved since the development of the American Thyroid Association (ATA) guidelines in 2015. This review compiles newer concepts in diagnosis, stratification tools and treatment options for patients with differentiated thyroid cancer (DTC), medullary thyroid carcinoma (MTC) and anaplastic thyroid cancer (ATC). Newer developments apply precision medicine in thyroid cancer patients to avoid over-treatment in low risk disease and under-treatment in high risk disease. Among novel patient-tailored therapies are selective RET inhibitors that have shown efficacy in the treatment of MTC with limited systemic toxicity compared with non-specific tyrosine kinase inhibitors. The combination of BRAF and MEK inhibitors have revolutionized management of *BRAF V600E* mutant ATC. Several immunotherapeutic agents are being actively investigated in the treatment of all forms of thyroid cancer."

Botezatu, A., Iancu, I.V., Plesa, A., Manda, D., Popa, O., Bostan, M., Mihaila, M., Albulescu, A., Fudulu, A., Vladoiu, S.V., Huica, I., Dobrescu, R., Anton, G. & Badiu, C. 2019.
BACKGROUND: Thyroid carcinoma is the most common endocrine malignancy worldwide. Changes in DNA methylation can cause silencing of normally active genes, especially tumour suppressor genes (TSG) or activation of normally silent genes.
OBJECTIVE: The aim of this study is to evaluate the degree of promoter methylation for a panel of markers for thyroid neoplasms and to establish their relationship with thyroid oncogenesis.
METHODS: To generate a comprehensive DNA methylation signature of TSGs involved in thyroid neoplasia, we use Human TSG EpiTect Methyl II Signature PCR Array-Qiagen for 24 samples (follicular adenomas and papillary thyroidcarcinomas) compared with normal thyroid tissue. We extended the evaluation for three TSGs (TP73, WIF1, PDLIM4) using qMS-PCR. Statistical analysis was performed with GraphPad Prism.
RESULTS: We noted four important genes NEUROG1, ESR1, RUNX3, MLH1, which presented methylated promoter in tumour samples compared to normal. We found new characteristic

of thyroid tumours: methylation of TP73, WIF1 and PDLIM4 TSGs, which can contribute to thyroid neoplasia. A significant correlation between BRAF V600E mutation and RET/PTC rearrangements with TIMP3 and CDH13, RARB methylation, respectively was observed.
CONCLUSIONS: TSGs promoter hypermethylation is a hallmark of cancer and a test that uses methylation quantification method is suitable for diagnosis and prognosis of thyroid cancer.

Incidence of Thyroid Cancer in South Africa

According to the outdated National Cancer Registry (2016), known for under reporting, the following number of cases of the thyroid gland was histologically diagnosed in South Africa during 2016. Histologically diagnosed means that a tissue sample (biopsy) was forwarded to an approved pathology laboratory where a specially trained pathologist confirmed a cancer diagnosis:

Group - Males 2016	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	126	1:1 496	0,32%
Asian males	9	1:1 172	0,82%
Black males	41	1:3 195	0,30%
Coloured males	12	1:2 130	0,26%
White males	64	1:494	0,31%

Group - Females 2016	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	485	1:550	1,15%
Asian females	25	1:356	1,85%
Black females	192	1:1 061	0,93%
Coloured females	50	1:602	1,04%
White females	218	1:148	1,31%

The frequency of histologically diagnosed cases of cancer of the thyroid gland in South Africa for 2016 was as follows (National Cancer Registry, 2016):

Group - Males 2016	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	1	7	18	21	38	21	14	6
Asian males	0	2	1	3	3	0	0	0
Black males	1	2	5	9	16	2	5	1
Coloured males	0	0	5	0	6	1	0	0
White males	0	3	7	9	13	15	12	5

Group - Females 2016	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	13	35	99	112	92	82	43	9
Asian females	3	2	4	8	1	6	0	1
Black females	5	15	46	39	37	30	17	2
Coloured females	2	1	12	13	11	8	3	0
White females	2	17	37	52	43	38	23	6

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.

According to **Bruni, *et al*.,** (2019), the burden of cancer of the Thyroid for South Africa for 2018 is estimated as (based on Globocan estimates):

- Annual number of cancer of the Thyroid cases 2 408
- Annual number of cancer of the Thyroid deaths 157

Signs and Symptoms of Thyroid Cancer

Thyroid cancer does not always have symptoms, so it can be hard to detect and diagnose. In fact, some of the possible symptoms are not actually caused by thyroid cancer itself. Instead, these symptoms can be caused by a thyroid nodule - and thyroid nodules are not necessarily cancerous.

People may visit a doctor because they notice one or more of the following symptoms and signs:

Lump in the Neck - Not all thyroid nodules are big enough to cause a noticeable lump. The most common way that a thyroid lump (and potential thyroid cancer) is detected, however, is when a doctor performs a thyroid examination and feels the thyroid.

Swollen Lymph Node - Swollen lymph nodes in the neck are another symptom of thyroid cancer (a symptom not related to thyroid nodules). Thyroid cancer can spread to the lymph nodes. The lymph nodes in one's neck become swollen when one has a cold or sore throat, for example. When the infection is gone, they should return to their normal size, so if the lymph nodes in one's neck stay enlarged for an extended period one should talk to one's doctor.

[Picture Credit: Lump in Neck]

Hoarse Voice - The thyroid gland sits just below the larynx (more commonly known as the voice box or Adam's apple). A thyroid nodule (which may be thyroid cancer) may be pressing on the voice box, causing hoarseness or voice changes. This is an uncommon way that thyroid cancer is detected.

Difficulty Swallowing or Breathing - The thyroid is on top of the trachea or windpipe. A developing thyroid cancer may put pressure on the trachea, making breathing more difficult. The oesophagus is below the trachea, so again, a developing thyroid cancer can cause trouble swallowing. This is also an uncommon way that thyroid cancer is detected.

Risk Factors for Thyroid Cancer

The following risk factors for thyroid cancer have been identified:

Gender and age - for unclear reasons thyroid cancers (like almost all diseases of the thyroid) occur about 3 times more often in women than in men. Thyroid cancer can occur at any age, but the risk peaks earlier for women (who are most often in their 40s or 50s when diagnosed) than for men (who are usually in their 60s or 70s).

Johar, J., Britton, H. & Wiseman, S.M. 2020.
"Differentiated thyroid cancer (DTC) has long been recognized as having a worse prognosis in older people. We retrospectively evaluated the clinical and pathological characteristics of 973 sequentially treated patients with primary DTC stratified into 2 age groups, ≥ 55 or < 55 years, based on the current American Joint Committee on Cancer (AJCC) DTC staging system. We found that older patients had a higher frequency of extrathyroidal cancer extension and larger cancers, and that their cancers were less commonly completely resectable."

Diet low in iodine - follicular thyroid cancers are more common in areas of the world where people's diets are low in iodine. A diet low in iodine may also increase the risk of papillary cancer if the person also is exposed to radioactivity.

Radiation - exposure to radiation is a proven risk factor for thyroid cancer. Sources of such radiation include certain medical treatments and radiation fallout from power plant accidents or nuclear weapons.

Hereditary conditions and family history - several inherited conditions have been linked to different types of thyroid cancer, as has family history. Still, most people who develop thyroid cancer do not have an inherited condition or a family history of the disease.

Medullary thyroid cancer
About 1 out of 3 medullary thyroid carcinomas (MTCs) result from inheriting an abnormal gene.

Other thyroid cancers
People with certain inherited medical conditions have a higher risk of more common forms of thyroid cancer.

Higher rates of thyroid cancer occur among people with uncommon genetic conditions such as:

- familial adenomatous polyposis (FAP): People with this syndrome develop many colon polyps and have a very high risk of colon cancer. They also have an increased risk of some other cancers, including papillary thyroid cancer. *Gardner syndrome* is a subtype of FAP in which patients also get certain benign tumours. Both Gardner syndrome and FAP are caused by defects in the gene *APC*.

- Cowden disease: People with this syndrome have an increased risk of thyroid, endometrial (uterine), and breast cancers. The thyroid cancers tend to be either the papillary or follicular type. This syndrome is caused by defects in the gene *PTEN*.

Papillary and follicular thyroid cancers do seem to run in some families. Having a first-degree relative (parent, brother, sister, or child) with thyroid cancer, even without a known inherited syndrome in the family, increases one's risk for thyroid cancer. The genetic basis for these cancers is not totally clear.

Diagnosis of Thyroid Cancer
Diagnosis of thyroid cancer typically involves a number of procedures and tests.

Physical Exam - the doctor should conduct a thorough physical examination, including palpation of the thyroid to feel for enlargement and lumps, as well as the gland's size and firmness. The doctor will also look for any enlarged lymph nodes in the neck.

Biopsy - doctors often will do a biopsy of suspicious thyroid nodules, to evaluate for potential cancer. Typically thyroid nodules are biopsied using a needle, in a procedure known as 'fine needle aspiration biopsy' -- sometimes abbreviated FNA. Some patients have a surgical biopsy, where the nodule, or the thyroid gland itself, is removed surgically.

Erkinuresin, T. & Demirci, H. 2020.
"Background Routine application of fine needle aspiration cytology (FNAC) has decreased unnecessary referral of thyroid nodules for surgical treatment and has also increased the cancer rates found in surgery materials. Success of thyroid FNAC depends on skilled aspiration, skilled cytological interpretation and rational analysis of cytological and clinical data. The aim of this study was to determine the diagnostic accuracy rates of thyroid FNAC results obtained in our institution. Methods The data from FNAC and thyroidectomy reports of patients presenting with goiter and who had been evaluated from 1st January 2014 to 1st March 2018 were used. There were 149 patients in total who had undergone thyroidectomy following FNAC. The Bethesda System for Reporting Thyroid Cytology was used in all cytological diagnoses. Results The sensitivity of thyroid FNAC for malignant cases was 57.89%, specificity was 88.10%, false-positive rate was 11.90%, false-negative rate was 42.11%, positive predictive value was 52.38%, negative predictive value was 90.24% and accuracy rate was 82.52%. "Focus number" variable was detected as the factor that affected the accurate prediction of FNAC and thyroidectomy results by the pathologist. Conclusions This study showed that there was a moderate conformity between thyroid FNAC and thyroidectomy cyto-histopathological diagnosis in malignant cases. As two or more nodules have a negative effect on the physician's diagnosis of malignant nodules, we think that a more sensitive approach is needed in the determination of these cases. Sampling defects may affect this non-matching."

Imaging Tests - A variety of imaging scans are used to evaluate thyroid nodules for possible thyroid cancer. These may include:

- Nuclear scan, also known as radioactive iodine uptake (RAI-U) scan. Nodules that absorb more radioactive iodine, and therefore are more visible, are known as "hot nodules" and are more likely to be benign.
- CT scan, known as computed tomography or a "cat scan," is a specialized type of x-ray that is sometimes used to evaluate the thyroid. A CT scan can't detect smaller nodules, but may help detect and diagnose a goiter, or larger thyroid nodules.
- Magnetic resonance imaging (MRI), can help detect enlargement in the thyroid, as well as tumours, tumour size, and may be able to detect tumour spread.
- Thyroid ultrasound, can tell whether a nodule is a fluid-filled cyst, or a mass of solid tissue, but it cannot determine if a nodule or lump is malignant.

Wang, L., Kou, H., Chen, W., Lu, M. Zhou, L. & Zou, C. 2020.
PURPOSE: To explore the clinical value of ultrasound in the diagnosis of medullary thyroid carcinoma by comparing with enhanced computed tomography.

METHODS: This retrospective study was performed on 62 patients with pathologically confirmed medullary thyroid carcinoma. All patients underwent ultrasound and enhanced computed tomography examinations before surgery. The findings of the pathologic examination of resected specimens were considered as gold standard and were compared with the results of these 2 methods.
RESULTS: There were 73 medullary thyroid carcinoma lesions and 29 benign lesions in 62 patients. In all, 55 of 73 medullary thyroid carcinoma lesions and 27 of 29 benign lesions were correctly diagnosed by ultrasound; and 45 of 73 medullary thyroid carcinoma lesions and 24 of 29 benign lesions were correctly diagnosed by enhanced computed tomography. The accuracy of ultrasound and enhanced computed tomography was 80.4% and 67.6%, respectively. There was significant difference between 2 methods ($P < .05$).
CONCLUSIONS: Ultrasound can be used to observe the location, number, size, shape, border, internal echo, calcification, and blood flow of the lesion. It is a convenient, inexpensive, and nonradiative method with higher accuracy than enhanced computed tomography.

Blood Tests - blood tests cannot diagnose thyroid cancer itself, or detect a cancerous thyroid nodule. Thyroid stimulating hormone (TSH) blood tests, however, may be used to evaluate the thyroid's activity and test for hypothyroidism or hyperthyroidism.

Other Tests - when medullary thyroid cancer is suspected, doctors will typically test for high levels of calcium, as this can be an indicator. They may also do genetic testing to identify the abnormal gene associated with some cases of medullary thyroid cancer.

How Thyroid Cancer Can Spread
Should Cancer of the thyroid spread to organs in the body, it may spread as indicated below:

Cancer Type:	**Main Sites of Metastasis (Spread)**
Bladder	Bone, liver, lung
Breast	Bone, brain, liver, lung
Colon	Liver, lung
Colorectal	Liver, lung, peritoneum (lining of abdomen)
Kidney	Adrenal gland, bone, brain, liver, lung
Lung	Adrenal gland, bone, brain, liver, other lung
Melanoma	Bone, brain, liver, lung, skin, muscle
Ovary	Liver, lung, peritoneum (lining of abdomen)
Pancreas	Liver lung, peritoneum (lining of abdomen)
Prostate	Adrenal gland, bone, liver, lung
Stomach	Liver, lung, peritoneum (lining of abdomen), ovaries
Thyroid	Bone, liver, lung
Uterus	Boner, liver, lung, peritoneum (lining of abdomen), vagina
Non-melanoma skin cancer	Very rare: lymph nodes, lung, bone (if in head/neck region)

Treatment of Thyroid Cancer
Thyroid cancer treatment options depend on the type and stage of the thyroid cancer, the overall health of the patient and his/her preferences. Most cases of thyroid cancer can be cured with treatment. Treatment may include:

Surgery
Most people with thyroid cancer undergo surgery to remove all or most of the thyroid.

Thyroid hormone therapy
After thyroid cancer surgery, patients are given thyroid hormone medication for life.

Radioactive iodine
Radioactive iodine treatment uses large doses of a form of iodine that is radioactive. Radioactive iodine treatment is often used after thyroidectomy to destroy any remaining healthy thyroid tissue, as well as microscopic areas of thyroid cancer that were not removed during surgery. Radioactive iodine treatment may also be used to treat thyroid cancer that recurs after treatment or that spreads to other areas of the body.

External radiation therapy
Radiation therapy can also be given externally using a machine that aims high-energy beams at precise points on the body. Called external beam radiation therapy, this treatment is typically administered a few minutes at a time, five days a week, for about six weeks.

Chemotherapy
Chemotherapy is a drug treatment that uses chemicals to kill cancer cells. Chemotherapy is typically given as an infusion through a vein. Chemotherapy is not commonly used in the treatment of thyroid cancer, but it may benefit some people who do not respond to other, more standard therapies.

Targeted therapy
In general, thyroid cancers do not respond well to chemotherapy. But exciting data are emerging about some newer targeted drugs. Unlike standard chemotherapy drugs, which work by attacking rapidly growing cells (including cancer cells), these drugs attack specific targets on cancer cells.

PDQ Adult Treatment Editorial Board. 2019.
Six types of standard treatment for thyroid cancer are used:

Surgery
Surgery is the most common treatment for thyroid cancer. One of the following procedures may be used:

- Lobectomy: Removal of the lobe in which thyroid cancer is found. Lymph nodes near the cancer may also be removed and checked under a microscope for signs of cancer.
- Near-total thyroidectomy: Removal of all but a very small part of the thyroid. Lymph nodes near the cancer may also be removed and checked under a microscope for signs of cancer.
- Total thyroidectomy: Removal of the whole thyroid. Lymph nodes near the cancer may also be removed and checked under a microscope for signs of cancer.
- Tracheostomy: Surgery to create an opening (stoma) into the windpipe to help you breathe. The opening itself may also be called a tracheostomy.

Radiation therapy, including radioactive iodine therapy
Radiation therapy is a cancer treatment that uses high-energy X-rays or other types of radiation to kill cancer cells or keep them from growing. There are two types of radiation therapy:

- External radiation therapy uses a machine outside the body to send radiation toward the cancer. Sometimes the radiation is aimed directly at the tumour during surgery. This is called intraoperative radiation therapy.
- Internal radiation therapy uses a radioactive substance sealed in needles, seeds, wires, or catheters that are placed directly into or near the cancer.

Radiation therapy may be given after surgery to kill any thyroid cancer cells that were not removed. Follicular and papillary thyroid cancers are sometimes treated with radioactive iodine (RAI) therapy. RAI is taken by mouth and collects in any remaining thyroid tissue, including thyroid cancer cells that have spread to other places in the body. Since only thyroid tissue takes up iodine, the RAI destroys thyroid tissue and thyroid cancer cells without harming other tissue. Before a full treatment dose of RAI is given, a small test-dose is given to see if the tumour takes up the iodine.
The way the radiation therapy is given depends on the type and stage of the cancer being treated. External radiation therapy and radioactive iodine (RAI) therapy are used to treat thyroid cancer.

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. When chemotherapy is taken by mouth or injected into a vein or muscle, the drugs enter the bloodstream and can reach cancer cells throughout the body (systemic chemotherapy). When chemotherapy is placed directly into the cerebrospinal fluid, an organ, or a body cavity such as the abdomen, the drugs mainly affect cancer cells in those areas (regional chemotherapy).
The way the chemotherapy is given depends on the type and stage of the cancer being treated.

Thyroid hormone therapy
Hormone therapy is a cancer treatment that removes hormones or blocks their action and stops cancer cells from growing. Hormones are substances made by glands in the body and circulated in the bloodstream. In the treatment of thyroid cancer, drugs may be given to prevent the body from making thyroid stimulating hormone (TSH), a hormone that can increase the chance that thyroid cancer will grow or recur.
Also, because thyroid cancer treatment kills thyroid cells, the thyroid is not able to make enough thyroid hormone. Patients are given thyroid hormone replacement pills.

Targeted therapy
Targeted therapy is a type of treatment that uses drugs or other substances to identify and attack specific cancer cells without harming normal cells. There are different types of targeted therapy:

- Tyrosine kinase inhibitor. Tyrosine kinase inhibitor therapy blocks signals needed for tumours to grow. Sorafenib, lenvatinib, vandertanib, and cabozantinib are used to treat certain types of thyroid cancer. New types of tyrosine kinase inhibitors are being studied to treat advanced thyroid cancer.
- Protein kinase inhibitor**.** Protein kinase inhibitor therapy blocks proteins needed for cell growth and may kill cancer cells. dabrafenib and tramatinib are used to treat anaplastic thyroid cancer in patients with a certain mutation in the BRAF gene.

Watchful waiting
Watchful waiting is closely monitoring a patient's condition without giving any treatment until signs or symptoms appear or change.

New types of treatment are being tested in clinical trials.

Immunotherapy

Immunotherapy is a treatment that uses the patient's immune system to fight cancer. Substances made by the body or made in a laboratory are used to boost, direct, or restore the body's natural defenses against cancer. This type of cancer treatment is also called biotherapy or biologic therapy. Immunotherapy is being studied as a treatment for thyroid cancer.

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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Lump in Neck
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