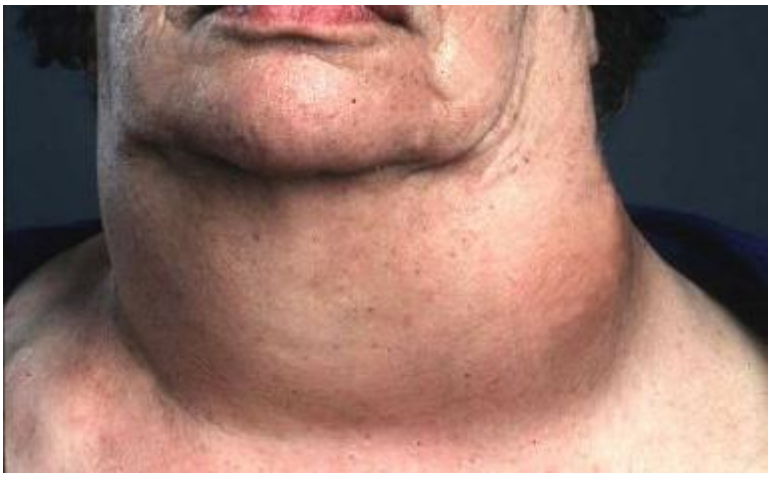
Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet
on
Anaplastic Thyroid Cancer

Introduction

Thyroid cancer occurs in the cells of the thyroid - a butterfly-shaped gland located at the base of one's neck, just below the Adam's apple. The thyroid produces hormones that regulate heart rate, blood pressure, body temperature and weight.



Picture Credit: Anaplastic Thyroid Cancer

Although thyroid cancer is not common, rates seem to be increasing. Doctors think this is because new technology is allowing them to find small thyroid cancers that may not have been found in the past.

Most cases of thyroid cancer can be cured following early diagnosis and treatment.

Anaplastic Thyroid Cancer

Anaplastic thyroid cancer (ATC) is one of the most aggressive tumours known in medicine. Even though a multimodal approach is used in treating these patients, average survival rate is expressed in months, and one-year survival is 15%

Anaplastic thyroid cancer is the least common of the thyroid cancers accounting for 0.5-1.5% of the total. Its peak incidence is in patients over 60 years of age, and is most common in areas of endemic goitre where there is chronic iodine deficiency. The incidence of ATC has steadily decreased over the past few decades, although the reason for this decline is not completely understood, and several factors may be involved.

There are three main types of anaplastic cancer, each with a differing likelihood of being able to be resected. First there is the previously unsuspected rapidly growing mass (can rarely resect), second is the PTC or FTC transforming into ATC (resection may be possible), and third is the ATC arising in a goitre (8% of ATC), usually found incidentally, occurring in an endemic goitrous region (resection often already done, but if not, worth trying).

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]

The cancer may arise in pre-existing follicular tumours. The progression of PTC or FTC to ATC has been well documented at a clinical and molecular level with the loss of the *p53* tumour suppressor gene. In one study up to 76% of ATC had previous or concurrent thyroid disorders, with 47% related to well differentiated thyroid cancer.

There are four major groups of Thyroid Cancer:

Papillary Thyroid Cancer – it is the most common type of all thyroid cancers. Papillary thyroid cancer can occur at any age. It tends to grow slowly and spread to lymph nodes in the neck, and generally has an excellent outlook.
Follicular Thyroid Cancer - it makes up about 10% of all thyroid cancers. Follicular thyroid cancer can spread to lymph nodes in the neck, but is more likely than papillary cancer to spread to distant organs, particularly the lungs and bones.
Medullary Thyroid Cancer - it accounts for approximately 2% of all thyroid cancers. Approximately 25% of all medullary thyroid cancer is inherited, and a test for a genetic mutation in the RET proto-oncogene can lead to an early diagnosis and, thus, to curative surgery.
Anaplastic Thyroid Cancer - it is the most advanced and aggressive thyroid cancer. Anaplastic thyroid cancer is very rare and is found in less than 2% of patients with thyroid cancer. It most commonly occurs in people over the age of 60 years. The information in this brochure pertains to Anaplastic thyroid cancer.

Ashorobi, D. & Lopez, P.P. 2020.
"The thyroid is an endocrine gland located just below the cricoid cartilage in the neck, and it is composed of both the right and the left lobes separated by an isthmus. The thyroid gland functions to produce the thyroid hormone which is needed by the body to carry out different metabolism. Follicles comprise the thyroid and are the functional and structural units of the gland. Epithelial cells line the follicles, which could be cuboidal, columnar depending on the state of activity. These cells could develop abnormal growth causing follicular malignancy. Thyroid cancer is one of the most common endocrine tumors and classifies as either differentiated or undifferentiated cancer. Differentiated cancers include papillary and follicular thyroid carcinoma, and undifferentiated types include medullary thyroid cancer and anaplastic cancer. Papillary thyroid cancer accounts for most varieties. Follicular thyroid cancer is the second most prevalent type, and it accounts for 10 to 15% of all thyroid cancer. The undifferentiated types are rare when compared to the differentiated type.
Follicular thyroid cancer is a tumor of the follicular cells that are lined by cuboidal epithelial cells and have capsular and vascular invasive properties. Compared to follicular carcinoma, follicular adenoma is benign and occurs more commonly with a ratio estimated to be 5 to 1. This article will focus more on the follicular type of thyroid cancer, discussing the etiology, epidemiology, histology, evaluation, staging, and complications of follicular thyroid cancer."

Limaiem, F., Kashyap, S. & Giwa, A.O. 2020.
"Anaplastic thyroid carcinoma also known as undifferentiated carcinoma is a rare, highly aggressive malignant tumor accounting for 2% to 3% of all thyroid gland neoplasms. It is composed of undifferentiated thyroid follicular cells, requiring immunohistochemical or ultrastructural support to determine their epithelial origin. Anaplastic thyroid carcinoma continues to rank as one of the most deadly diseases worldwide and carries a very poor prognosis. In addition to considerable local invasion, anaplastic thyroid carcinoma often presents with metastatic spread to regional lymph nodes and distant sites."

De Leo, S., Trevisan, M. & Fugazzola, L. 2020.
"Anaplastic thyroid cancer (ATC) is undoubtedly the thyroid cancer histotype with the poorest prognosis. The conventional treatment includes surgery, radiotherapy, and conventional chemotherapy. Surgery should be as complete as possible, securing the airway and ensuring access for nutritional support; the current standard

of care of radiotherapy is the intensity-modulated radiation therapy; chemotherapy includes the use of doxorubicin or taxanes (paclitaxel or docetaxel) generally with platin (cisplatin or carboplatin). However, frequently, these treatments are not sufficient and a systemic treatment with kinase inhibitors is necessary. These include multitarget tyrosine kinase inhibitors (Lenvatinib, Sorafenib, Sunitinib, Vandetanib, Axitinib, Pazopanib, Pyrazolo-pyrimidine compounds), single target tyrosine kinase inhibitors (Dabrafenib plus Trametinib and Vemurafenib against BRAF, Gefitinib against EGFR, PPARγ ligands (e.g. Efatutazone), Everolimus against mTOR, vascular disruptors (e.g. Fosbretabulin), and immunotherapy (e.g. Spartalizumab and Pembrolizumab, which are anti PD-1/PD-L1 molecules). Therapy should be tailored to the patients and to the tumor genetic profile. A BRAF mutation analysis is mandatory, but a wider evaluation of tumor mutational status (e.g. by next-generation sequencing) is desirable. When a $BRAF^{V600E}$ mutation is detected, treatment with Dabrafenib and Trametinib should be preferred: this combination has been approved by the Food and Drug Administration for the treatment of patients with locally advanced or metastatic ATC with $BRAF^{V600E}$ mutation and with no satisfactory locoregional treatment options. Alternatively, Lenvatinib, regardless of mutational status, reported good results and was approved in Japan for treating unresectable tumors. Other single target mutation agents with fair results are Everolimus when a mutation involving the PI3K/mTOR pathway is detected, Imatinib in case of PDGF-receptors overexpression, and Spartalizumab in case of PD-L1 positive tumors. Several trials are currently evaluating the possible beneficial role of a combinatorial therapy in ATC. Since in this tumor several genetic alterations are usually found, the aim is to inhibit or disrupt several pathways: these combination strategies use therapy targeting angiogenesis, survival, proliferation, and may act against both MAPK and PI3K pathways. Investigating new treatment options is eagerly awaited since, to date, even the molecules with the best radiological results have not been able to provide a durable disease control."

Rashid, M., Agarwal, A., Pradhan, R., George, N., Kumari, N., Sabaretnam, M., Chand, G., Mishra, A., Agarwal, G. & Mishra, S.K. 2019.
Introduction: Anaplastic thyroid cancer (ATC) is rare but fatal thyroid cancer responsible for majority of thyroid cancer related mortality. ATC may originate de novo or from preexisting differentiated thyroid cancer. Complex interaction between different gene mutation has been suggested to be the main causative factor for origin of ATC in both pathways. Mostly affected pathways are MAP kinase and PI3CA kinase. Hence, we decided to study the frequent alterations in both the pathways in ATC patients.
Methodology: Clinico-pathological data of 34 ATC patients were collected retrospectively and Formalin Fixed Paraffin Embedded (FFPE) blocks were taken out for genetic analysis. DNA and RANA were isolated from FFPE tissues. BRAF V600E mutations were screened by RFLP PCR method and confirmed by sequencing. RAS, PI3CA and p53 mutations were checked by sequencing. RET/PTC translocations were screened by Real Time PCR.
Results: A total of 34 patients were studied: Mean age 58.6+ 11.6 years with F:M- 1.8:1, 60% had history of goiter. Most common presenting symptom was rapidly growing thyroid mass followed by dyspnea, dysphasia and hoarseness of voice. Extent of disease was local, locoregional and metastatic in 32%, 35% and 33% respectively. 57.6% were euthyroid, 20.5 % were hyperthyroid while functional status were not available in 11.7%. FNAC was suggestive of ATC only in 52.9% cases. 15 (44%) were operated. BRAF V600E mutations were observed in 10/34 (29.4%). Interestingly, all three ATC patients with DTC components had previous history of goiter with rapid increase in size and BRAF V600E mutation, while BRAF was positive only in 7/31 (22.5%) of patients with no DTC component. Mean survival of 3.5 months in BRAF positive cases in comparison to 5.5 months in BRAF negative ATC. RAS mutations were found to be positive in 5.8%, and none had RET-PTC/PI3CA mutations. P53 mutation was positive in 7 patients. 3 patients presented with history of rapid increase in size of previous goiter while rest 4 patients presented with rapidly increasing thyroid swelling of 1 to 3 months. At presentation 2 patients has disease localized to thyroid, 4 has loco-regional disease and one patient presented with metastasis. 5 out of these 7 patients were operated (Total thyroidectomy:3, thyroidectomy with neck dissection:2). Mean survival was 4 months (1-6 months).

Conclusion: BRAF V600E was the commonest mutation followed by p53 of the 5 genes tested and BRAF was more common in patients with previous history of longstanding goiter or differentiated thyroid cancer. This provides an indirect evidence of neoplastic transformation of PTC to ATC.

Incidence of Anaplastic Thyroid Cancer

The outdated South African National Cancer Registry (2017), known for under reporting, does not provide any information regarding Anaplastic Thyroid Cancer. According to the National Cancer Registry (2016) 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 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	188	1:1 035	0,47%
Asian males	13	1:783	1,34%
Black males	48	1:2 555	0,35%
Coloured males	24	1:940	0,51%
White males	103	1:302	0,49%

Group - Females 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	559	1:506	1,34%
Asian females	41	1:225	3,18%
Black females	205	1:1 035	1,05%
Coloured females	73	1:387	1,56%
White females	240	1:136	1,41%

The frequency of histologically diagnosed cases of cancer of the thyroid gland 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	5	13	26	32	41	42	25	4
Asian males	0	3	1	4	3	1	1	0
Black males	2	2	10	7	14	8	4	1
Coloured males	1	1	4	5	3	6	2	2
White males	2	7	11	16	21	27	18	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	9	54	114	118	113	77	58	16
Asian females	1	6	13	10	6	3	2	0
Black females	4	18	37	50	40	26	21	9
Coloured females	1	7	18	13	12	11	8	3
White females	3	23	46	45	55	37	27	4

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.

Risk Factors for Anaplastic Thyroid Cancer
The following factors may raise a person's risk of developing thyroid cancer:
Gender -women are diagnosed with 3 of every 4 thyroid cancers

Age - thyroid cancer can occur at any age, but about two-thirds of all cases are found in people between the ages of 20 and 55. Anaplastic thyroid cancer is usually diagnosed after age 60. Older infants (10 months and older) and adolescents can develop MTC, especially if they carry the *RET*proto-oncogene mutation

Genetics - some types of thyroid cancer are associated with genetics.

Radiation exposure - exposure to moderate levels of radiation to the head and neck may increase the risk of papillary and follicular thyroid cancers. Such sources of exposure include:

- low-dose to moderate-dose x-ray treatments used before 1950 to treat children with acne, tonsillitis, and other head and neck problems.
- radiation therapy for Hodgkin Lymphoma or other forms of Lymphoma in the head and neck.
- exposure to radioactive iodine, also called I-131 or RAI, especially in childhood.
- exposure to ionizing radiation, including radioactive fallout from atomic weapons testing during the 1950s and 1960s and nuclear power plant fallout. Examples include the 1986 Chernobyl nuclear power plant accident and the 2011 earthquake that damaged nuclear power plants in Fukushima, Japan. Another source of I-131 is environmental releases from atomic weapon production plants.

Diet low in iodine - iodine is needed for normal thyroid function. In the United States, iodine is added to salt to help prevent thyroid problems.

Race - white people and Asian people are more likely to develop thyroid cancer, but this disease can affect a person of any race or ethnicity.

Breast cancer - a recent study showed that breast cancer survivors may have a higher risk of thyroid cancer, particularly in the first 5 years after diagnosis and for those diagnosed with breast cancer at a younger age. This finding continues to be examined by researchers.

Demeter, J.G., De Jong, S.A. Lawrence, A.M. & Paloyan, E. 1991.
"Anaplastic thyroid carcinoma, in contrast to well-differentiated thyroid carcinoma, has a dismal prognosis, and little progress has been made in improving survival for this disease. We reviewed our experience during a 23-year period to identify risk factors and possible methods to improve outcome. Between 1966 and 1989, 340 patients with thyroid carcinoma underwent operation. Of these, 17 (5%) were undergoing operative treatment of anaplastic or undifferentiated thyroid carcinoma. The female/male ratio was 3.5:1, and mean age at presentation was 63 years. The most common presenting symptoms included neck mass, voice change, or dysphagia. Unusual presentations included symptomatic bradycardia from compression of the vagus nerve and superior vena cava syndrome. Four patients had a history of well-differentiated thyroid carcinoma. Nine patients had been diagnosed or treated in the past for "goiter" or a neck mass, and four patients had concurrent differentiated thyroid carcinoma associated with the anaplastic tumor. Thus 13 (76%) of 17 patients had a previous thyroiddisorder, benign or differentiated malignant, and eight (47%) of 17 patients had previous or concurrent differentiated thyroidcarcinoma. At the time of presentation, six patients had unilateral true vocal cord paralysis. At operation, 14 patients had local extension of the tumor and four required tracheostomy. Only five of 12 patients showed response to postoperative radiation therapy. Overall median survival was 12 months, and 13 (76%) of 17 patients died. The two patients alive longer than 12 months had only small foci of anaplastic carcinoma in association with well-differentiated carcinoma. Anaplastic thyroid carcinoma is a locally and systemically aggressive disease, with long-term survival seen only in those

with well-localized anaplastic tumor. The major risk factor in this series is a history of previous benign or malignant thyroid disease. Because of this, a more aggressive approach to thyroid masses may be warranted. Long-standing goiters or benign nodules should be followed carefully and considered for resection if they grow or do not respond to medical therapy, and total thyroidectomy for malignant disease may obviate the subsequent development of anaplastic carcinoma. This method of early diagnosis and resection of abnormal thyroid tissue seems to be the only method currently available to improve the nearly uniform fatality of this disease."

Signs and Symptoms of Anaplastic Thyroid Cancer

Unlike most thyroid cancers which do not cause symptoms, anaplastic cancers tend to grow very quickly (sometimes over a few weeks) and cause compressive symptoms which include difficulty swallowing, food or pills getting "stuck" when they swallow, and pressure or shortness of breath when lying flat.

Patients typically notice a rock-hard mass they can feel or a visible mass (i.e. a mass they can see). In cases of advanced cancer that are growing (i.e. invading) into surrounding structures, patients may develop hoarseness or difficulty swallowing. Patients with compressive symptoms, enlarged lymph nodes, hoarseness, and/or a rapidly growing mass in the neck, especially if they have a known thyroid goiter, should seek medical evaluation right away.

Anaplastic thyroid cancer is the rarest type of thyroid cancer. It is fast-growing and mostly affects people over 60. The causes of anaplastic thyroid cancer are unknown.

The most common symptom is:

- a mass or lump in the neck which grows quickly

Other symptoms include:

- difficulties breathing or swallowing
- a cough
- a hoarse voice
- discomfort in the neck

If one has symptoms, one should see one's physician. If the treating physician thinks one may have cancer, he/she will refer the patient to a hospital for specialist advice and treatment. At the hospital, the doctor will ask about one's general health and any previous medical problems. The patient will have a physical examination and some tests.

Characteristics of Anaplastic Thyroid Cancer

Key characteristics of anaplastic thyroid cancer usually include:

- Peak onset of anaplastic thyroid cancer is age 65 years old and older
- It is very rare in young patients
- It is more common in males than females by a 2:1 ratio
- It typically presents as a rapidly growing neck mass
- It can occur many years after radiation exposure

- The spread to lymph nodes of the neck is present in more than 90% of cases
- The distant spread (to lungs or bones) is very common even when it's first diagnosed
- The overall cure rate is very low
- It typically requires a very aggressive treatment plan with surgery, radiation, and sometimes even chemotherapy
- It often requires a tracheostomy to maintain the patient's airway

Diagnosis of Anaplastic Thyroid Cancer
A physical examination almost always shows a growth in the neck region.

The following may contribute towards a diagnosis:
- An MRI or CT scan of the neck may show a tumour growing from the thyroid gland.
- A thyroid biopsy makes the diagnosis.
- An examination of the airway with a fiberoptic scope (laryngoscopy) may show a paralyzed vocal cord.
- A thyroid scan shows this growth to be "cold," meaning it does not absorb a radioactive substance.
- Thyroid function blood tests are normal in most cases.

Yamazaki, H., Iwasaki, H., Suganuma, N., Toda, S., Masudo, K., Nakayama, H., Rino, Y. & Masuda, M. 2019.
Summary: Anaplastic transformation of a primary thyroid tumor whose process can be followed is rare. The objective this study is to report a case of anaplastic transformation of locally advanced papillary thyroid carcinoma after treatment with lenvatinib. A 74-year-old woman consulted a local physician because of cough and bloody sputum. Thyroid cancer with tracheal invasion was suspected on computed tomography (CT) imaging, and she visited our hospital for treatment. We suspected anaplastic thyroid cancer (ATC) and core needle biopsy was performed. Histologic sections of the core needle biopsy showed that the tumor formed a papillary structure, and we diagnosed papillary thyroid carcinoma. Surgery would have been difficult, and we initiated lenvatinib at a low dose of 8 mg/day. CT on day 40 of lenvatinib treatment revealed that the thyroid tumor had shrunk remarkably. CT on day 111 revealed that tumor regrowth and tracheal invasion had been exacerbated. Core needle biopsy was performed, and histologic sections of the core needle biopsy that was performed after regrowth of the tumor showed that individual cancer cells had large, irregular nuclei, and necrosis was also observed. The immunohistochemical findings were negative for thyroglobulin, and only a few cells were positive for thyroid transcription factor 1, and we diagnosed ATC. Anaplastic transformation of the target lesion may be one of the causes of lenvatinib treatment failure in differentiated thyroid carcinoma.
Learning points: Anaplastic transformation of a primary thyroid tumor whose process can be followed is rare. The resistance mechanism of lenvatinib in treatment for differentiated thyroid carcinoma has not been clarified. Anaplastic transformation of the target lesion may be one of the causes of lenvatinib treatment failure in differentiated thyroid carcinoma.
Keywords: 2019; Adult; Anaplastic thyroid cancer; Asian - Japanese; Bronchoscopy*; CT scan; Core needle biopsy; Coughing; FT3; FT4; Female; Haemoptysis; Histopathology; Immunohistochemistry; Japan; Levatinib; October; Papillary thyroid cancer; TSH; Thyroglobulin; Thyroid; Thyroid antibodies; Thyroid carcinoma; Thyroid transcription factor-1; Thyroid ultrasonography; Thyroxine (T4); Triiodothyronine (T3); Unique/unexpected symptoms or presentations of a disease.

Treatment for Anaplastic Thyroid Cancer
Treatment of anaplastic thyroid carcinoma (ATC) is mostly palliative. Surgical resection with adjuvant radiation therapy and chemotherapy may prolong survival somewhat and improve quality of life.

The role of adjuvant therapy in ATC has not been clearly defined.

Radiotherapy and chemotherapy regimens continue to be investigated.

Alobuia, W., Gillis, A. & Kebebew, E. 2020.
"Anaplastic thyroid cancer (ATC) is a rare but very aggressive form of undifferentiated thyroid cancer. Due to its rapid rate of progression and invasive nature, ATC poses significant risks of morbidity and mortality. The cornerstone in the management of ATC remains a prompt diagnosis of the disease and timely management of complications depending on the stage of disease. Surgery continues to offer a higher chance of a cure, although not all patients are candidates for surgical management. Patients with advanced disease may be considered for palliative surgery to reduce morbidity and complications from advanced disease. With the advent of new molecular testing and improved methods of diagnosis, novel therapeutic targets have been identified. Systemic therapy (chemotherapy and radiation therapy) as well as novel immunotherapy have shown some promise in patients with targetable genetic mutations. Patients should therefore have molecular testing of their tumor-if it is unresectable-and be tested for mutations that are targetable. Mutation-targeted therapy may be effective and may result in a significant response to allow surgical intervention for exceptional responders. Overall, patients who receive all three modalities of therapy (surgery, chemotherapy, and radiation therapy) have the highest overall survival."

Ma, M., Lin, B., Wang, M., Liang, X., Su, L. Okose, O., Ly, W. & Li, J. 2020.
"Anaplastic thyroid cancer (ATC) is one of the worst human malignancies, with an associated median survival of only 5 months. It is resistant to conventional thyroid cancer therapies, including radioiodine and thyroid-stimulating hormone suppression. Cancer immunotherapy has emerged over the past few decades as a transformative approach to treating a wide variety of cancers. However, immunotherapy for ATC is still in the experimental stage. This review will cover several strategies of immunotherapy and discuss the possible application of these strategies in the treatment of ATC (such as targeted therapy for tumor-associated macrophages, cancer vaccines, adoptive immunotherapy, monoclonal antibodies and immune checkpoint blockade) with the hope of improving the prognosis of ATC in the future."

Amaral, M., Afonso, R.A., Gaspar, M.M. & Reis, C.P. 2020.
"Globally, thyroid cancer accounts for 2 % of all cancer diagnoses, and can be classified as well-differentiated or undifferentiated. Currently, differentiated thyroid carcinomas have good prognoses, and can be treated with a combination of therapies, including surgical thyroidectomy, radioactive iodine therapy and hormone-based therapy. On the other hand, anaplastic thyroid carcinoma, a subtype of undifferentiated thyroid carcinoma characterized by the loss of thyroid-like phenotype and function, does not respond to either radioactive iodine or hormone therapies. In most cases, anaplastic thyroid carcinomas are diagnosed in later stages of the disease, deeming them inoperable, and showing poor response rates to systemic chemotherapy. Recently, treatment courses using multiple-target agents are being explored and clinical trials have shown very promising results, such as overall survival rates, progression-free survival and tumor shrinkage. This review is focused on thyroid carcinomas, with particular focus on anaplastic thyroid carcinoma, exploring its undifferentiated nature. Special interest will be given to the treatment approaches currently available and respective obstacles or drawbacks. Our purpose is to contribute to understand why this malignancy presents low responsiveness to current treatments, while overviewing novel therapies and clinical trials."

Pozdeyev, N., Rose, M.M., Bowles, D.Q. & Schweppe, R.E. 2020.
"Anaplastic thyroid cancer (ATC) represents one of the most lethal human cancers and although this tumor type is rare, ATC accounts for the majority of deaths from thyroid cancer. Due to the rarity of ATC, a comprehensive genomic characterization of this tumor type has been challenging, and thus the development of new therapies has been lacking. To date, there is only one mutation-driven targeted therapy for BRAF-mutant ATC. Recent genomic studies have used next generation sequencing to define the genetic landscape of ATC in order to identify new therapeutic targets. Together, these studies have confirmed the role of oncogenic mutations of MAPK pathway as key drivers of differentiated thyroid cancer (BRAF, RAS), and that additional genetic alterations in the PI3K pathway, TP53, and the TERT promoter are necessary for anaplastic transformation. Recent novel findings have linked the high mutational burden associated with ATC with mutations in the Mismatch Repair (MMR) pathway and overactivity of the AID/APOBEC family of cytidine deaminases. Additional novel mutations include cell cycle genes, SWI/SNF chromatin remodeling complex, and histone modification genes. Mutations in RAC1 were also identified in ATC, which have important implications for BRAF-directed therapies. In this review, we summarize these novel findings and the new genetic landscape of ATC."

Ferrari, S.M., Elia, G., Ragusa, F., Ruffilli, I., La Motta, C., Paparo, S.R., Patrizio, A., Vita, R., Benvenga, S., Matarazzi, G., Fallahi, P. & Antonelli, A. 2020.
"Anaplastic thyroid cancer (ATC) is one of the deadliest human cancers and it is less than 2% of thyroid carcinomas (TCs). The standard treatment of ATC includes surgical debulking, accelerated hyperfractionated external beam radiation therapy (EBRT), and chemotherapy, in particular with cisplatin or doxorubicin, achieving about 10 months of median survival. Since ATC is a rare and aggressive tumor, it is still challenging to predict the patient clinical therapy responsiveness. Several genetic mutations have been described in ATC, involved in different molecular pathways linked to tumor progression, and novel therapies acting on these molecular pathways have been investigated, to improve the quality of life in these patients. Here we review the new targeted therapy of ATC. We report interesting results obtained with molecules targeting different pathways: angiogenesis (vandetanib, combretastatin, sorafenib, lenvatinib, sunitinib, CLM94, CLM3, etc.); EGFR (gefitinib, docetaxel); BRAF (dabrafenib/trametinib, vemurafenib); PPARγ agonists (rosiglitazone, pioglitazone, efatutazone); PD-1 and PD-L1 (pembrolizumab); TERT. To escape resistance to monotherapies, the evaluation of combination strategies with radiotherapy, chemotherapy, or targeted drugs is ongoing. The results of clinical trials with dabrafenib and trametinib led to the approval from FDA of this combination for patients with BRAF V600E mutated ATC with locally advanced, unresectable, or metastatic ATC. The anti-PD-L1 antibody immunotherapy, alone or combined with a BRAF inhibitor, has been shown also promising in the treatment of ATC. Furthermore, to increase the therapeutic success and not to use ineffective or even harmful treatments, a real tailored therapy should be pursued, and this can be achieved thanks to the new available genomic analysis methods and to the possibility to test in vitro novel treatments directly in primary cells from each ATC patient. Exploring new treatment strategies is mandatory to improve the survival of these patients, guaranteeing a good quality of life."

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/

Salehian, B., Liem, S.Y., Mojazi Amiri, H. & Maghami, E. 2019.
CONTEXT: Anaplastic thyroid carcinoma (ATC) is associated with rapid tumor growth and extremely poor prognosis. Although ATC is found in only 2% of all thyroid carcinomas, it accounts for up to 50% of thyroid cancer mortality.
OBJECTIVE: To understand the effect of different treatment modalities upon anaplastic thyroid cancer outcomes.
METHODS: A systematic review of studies from 1995 to 2017 was performed employing the search terms "anaplasticthyroid" and "treatment" in PubMed. Studies comparing patients receiving any type of therapy for ATC and measuring either survival as primary outcome or the percentage of patient surviving more than 1 year as secondary outcome were included for review. We did not limit sample size or subject condition. A total of 40 articles were returned from our database search, of which 25 met the inclusion criteria.
RESULTS: A review of the 25 published studies indicated that early multidisciplinary approaches using extensive radical surgery, in combination with adjuvant chemo-radiation using either docetaxel/pacitaxel or cisplatin, provided the best chance of disease control. Targeted multi-tyrosine kinases inhibitors helped to limit disease progression. Also, the finding of foci of differentiated thyroid cancer within the anaplastic tumor was associated with increased long-term survival.
CONCLUSIONS: ATC remains a fatal disease. Despite aggressive therapy the median survival has not significantly changed over the last 20 years. However, the percentage of patients surviving longer than 1 year continues to increase. Novel approaches incorporating multiple targeted therapy and immune therapies are critically needed.

Medical Disclaimer

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

Whilst the Cancer Association of South Africa (CANSA) has taken every precaution in compiling this Fact Sheet, neither it, nor any contributor(s) to this Fact Sheet can be held responsible for any action (or the lack thereof) taken by any person or organisation wherever they shall be based, as a result, direct or otherwise, of information contained in, or accessed through, this Fact Sheet.

Sources and References Consulted and/or Utilised

Alobuia, W., Gillis, A. & Kebebew, E. 2020. Contemporary management of anaplastic thyroid cancer. *Curr Treat Options Oncol.* 2020 Aug 7;21(10):78.

Amaral, M., Afonso, R.A., Gaspar, M.M. & Reis, C.P. 2020. Anaplastic thyroid cancer: how far can we go? *EXCLI J.* 2020 Jun 15;19:800-812.

Anaplastic Thyroid Cancer
http://www.endocrinesurgery.net.au/anaplastic-cancer/
https://www.hindawi.com/journals/ije/2014/815070/
http://columbiasurgery.org/conditions-and-treatments/anaplastic-thyroid-cancer
https://www.cancer.net/cancer-types/thyroid-cancer/risk-factors
https://www.thyroidcancer.com/thyroid-cancer/anaplastic
https://www.macmillan.org.uk/information-and-support/thyroid-cancer/understanding-cancer/types-of-thyroid-cancer/anaplastic-thyroid-cancer.html
https://www.endocrineweb.com/conditions/thyroid-cancer/thyroid-cancer-anaplastic-cancer
https://medlineplus.gov/ency/article/000352.htm
https://www.thyroidcancer.com/thyroid-cancer/anaplastic/treatment
https://emedicine.medscape.com/article/283165-treatment

Ashorobi, D. & Lopez, P.P. 2020. Follicular thyroid cancer. ***In***: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. 2020 Dec 18.

Clinical Trials
www.sanctr.gov.za/

De Leo, S., Trevisan, M. & Fugazzola, L. 2020. Recent advances in the management of anaplastic thyroid cancer. *Thyroid Res*. 2020 Nov 24;13(1):17.

Demeter, J.G., De Jong, S.A. Lawrence, A.M. & Paloyan, E. 1991. Anaplastic thyroid carcinoma: risk factors and outcome. *Surgery*. 1991 Dec;110(6):956-61; discussion 961-3.

Ferrari, S.M., Elia, G., Ragusa, F., Ruffilli, I., La Motta, C., Paparo, S.R., Patrizio, A., Vita, R., Benvenga, S., Matarazzi, G., Fallahi, P. & Antonelli, A. 2020. Novel treatments for anaplastic thyroid carcinoma.
Gland Surg, 9 (Suppl 1), S28-S42, Jan 2020.

Huang, N.S., Shi, X., Lei, B.W., Wei, W.J., Lu, Z.W., Yu, P.C., Wang, Y., Ji, Q.H. & Wang, Y.L. 2019. An update of the appropriate treatment strategies in anaplastic thyroid cancer: a population-based study of 735 patients. *Int J Endocrinol*. 2019 Feb 19;2019:8428547. doi: 10.1155/2019/8428547. eCollection 2019.

Li, Z., Zhang, Y., Wang, R., Zou, K. & Zou, L. 2019. Genetic alterations in anaplastic thyroid carcinoma and targeted therapies. *Exp Ther Med*, 18 (4), 2369-2377, Oct 2019.

Limaiem, F., Kashyap, S. & Giwa, A.O. 2020. Anaplastic thyroid cancer. ***In***: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. 2020 Oct 16.

Ma, M., Lin, B., Wang, M., Liang, X., Su, L. Okose, O., Ly, W. & Li, J. 2020. Immunotherapy in analplastic thyroid cancer. *Am J Transl Res*. 2020 Mar 15;12(3):974-988. eCollection 2020.

Pozdeyev, N., Rose, M.M., Bowles, D.Q. & Schweppe, R.E. 2020. Molecular therapeutics for anaplastaic thyroid cancer. *Semin Cancer Biol*. 2020 Apr;61:23-29.

Rashid, M., Agarwal, A., Pradhan, R., George, N., Kumari, N., Sabaretnam, M., Chand, G., Mishra, A., Agarwal, G. & Mishra, S.K. 2019. Genetic alterations in anaplastic thyroid carcinoma. *Indian J Endocrinol Metab*, 23 (4), 480-485, Jul-Aug 2019.

Salehian, B., Liem, S.Y., Mojazi Amiri, H. & Maghami, E. 2019. Clinical trials in management of anaplastic thyroid carcinoma; progaressions and set backs: a systematic review. *Int J Endocrinol Metab*. 2019 Jan 13;17(1):e67759. doi: 10.5812/ijem.67759. eCollection 2019 Jan.

Thyroid Cancer
https://www.mayoclinic.org/diseases-conditions/thyroid-cancer/symptoms-causes/syc-20354161

Yamazaki, H., Iwasaki, H., Suganuma, N., Toda, S., Masudo, K., Nakayama, H., Rino, Y. & Masuda, M. 2019.
Anaplastic Thyroid Carcinoma Diagnosed After Treatment of Lenvatinib for Papillary Thyroid Carcinoma. Endocrinol Diabetes Metab Case Rep, 2019, 2019 Oct 1[Online ahead of print].

Yu, Q., Jiang, W., Li, D., Gu, M., Liu, K., Dong, L., Wang, C., Jiang, H. & Dai, W. 2019. Sodium arthovanadate inhibits growth and triggers apoptosis of human anaplastic thyroid carcinoma cell in vitro and in vivo. *Oncol Lett*. 2019 May;17(5):4255-4262. doi: 10.3892/ol.2019.10090. Epub 2019 Feb 28.