Cancer Association of South Africa (CANSA)

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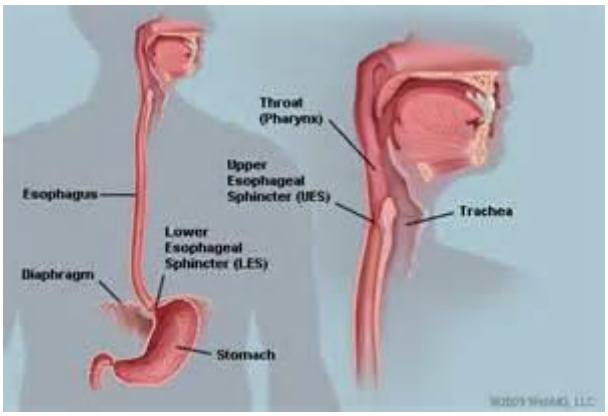
Fact Sheet On Oesophageal Cancer

Introduction

The oesophagus (commonly known as the gullet) is an organ in humans (and other vertebrates) which consists of a muscular tube through which food passes from the pharynx to the stomach. During swallowing, food passes from the mouth through the pharynx into the oesophagus and travels by means of peristalsis to the stomach.



[Picture Credit: Oesophagus picture]

In humans the oesophagus is continuous with the laryngeal part of the pharynx at the level of the 6th cervical (neck) vertebra. The 0esophagus passes through the posterior mediastinum in the thorax (chest) and enters the abdomen through a hole in the diaphragm at the level of the 10th thoracic (chest) vertebrae. It is usually about 25cm long, but variations have been recorded depending on the individual's height. It is divided into the cervical, thoracic and abdominal parts. Due to the lower pharyngeal constrictor muscle, the entry of the oesophagus to the stomach, opens only when swallowing or vomiting.

Oesophageal Cancer

Oesophageal cancer is malignancy of the oesophagus. There are various subtypes, primarily squamous cell cancer and adenocarcinoma. Squamous cell cancer arises from the cells that line the upper part of the oesophagus. Adenocarcinoma arises from glandular cells that are present at the junction of the oesophagus and stomach. A general rule of thumb is that a cancer in the upper two-thirds of the oesophagus is a squamous cell carcinoma and a cancer in the lower one-third of the oesophagus is an adenocarcinoma.

Loots, E., Sartorius, B., Madiba, T.E. Mulder, D.J. & Clarke, D.L. 2017.

"Oesophageal cancer (OC) is responsible for the second highest number of cancer-related deaths in South Africa (SA). Squamous cell carcinoma is the most prevalent type with an incidence of 46.7/100,000 and 19.2/100,000 for males and females. This is a systematic review of the clinical

diagnosis and management of OC within the South African context. This protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42016034053) with adherence to PRISMA guidelines. An online search was performed using MEDLINE, EBSCOHost and PubMed. Eligibility criteria for articles included published, original peer-reviewed research addressing clinical management of oesophageal cancer in South Africa. Review articles, case reports, scientific letters and studies published in languages other than English or Afrikaans were excluded. The research terms were 'etiology', 'human', 'esophageal cancer', 'esophagealcarcinoma', 'oesophageal cancer', and 'oesophageal carcinoma', 'squamous cell carcinoma', 'Africa' and 'South Africa'. A total of 336 articles were identified. Of these, 146 were immediately excluded and a further 159 were excluded after review. A total of 31 appropriate articles, i.e. 9.2% of searched articles, were included. Thirteen articles addressed chemotherapy and/or radiotherapy, 9 oesophageal luminal therapy, 7 oesophageal surgery and 2 screening. OC research of in SA over the last two decades has mainly been in the form of reviews and opinion papers. Clinical research, auditing and prospectively analysing OC management and outcomes in SA hospitals are sorely needed and should be promoted by both healthcare workers and policy makers alike."

Domper, Arnal, M.J., Ferrández Aremas. A. & Lanas Arbeloa, A. 2015.
"Esophageal cancer is one of the most unknown and deadliest cancers worldwide, mainly because of its extremely aggressive nature and poor survival rate. Esophageal cancer is the 6(th) leading cause of death from cancer and the 8(th) most common cancer in the world. The 5-year survival is around 15%-25%. There are clear differences between the risk factors of both histological types that affect their incidence and distribution worldwide. There are areas of high incidence of squamous cell carcinoma (some areas in China) that meet the requirements for cost-effectiveness of endoscopy for early diagnosis in the general population of those areas. In Europe and United States the predominant histologic subtype is adenocarcinoma. The role of early diagnosis of adenocarcinoma in Barrett's esophagus remains controversial. The differences in the therapeutic management of early esophageal carcinoma (high-grade dysplasia, T1a, T1b, N0) between different parts of the world may be explained by the number of cancers diagnosed at an early stage. In areas where the incidence is high (China and Japan among others) early diagnoses is more frequent and has led to the development of endoscopic techniques for definitive treatment that achieve very effective results with a minimum number of complications and preserving the functionality of the esophagus."

Incidence of Oesophageal Cancer in South Africa
According to the outdated National Cancer Registry (2017), known for under reporting, the following number of Oesophageal Cancer cases were histologically diagnosed in South Africa during 2017. Histologically diagnosed means that a specimen of tissue (biopsy) was forwarded to a recognised laboratory where a specially trained pathologist confirmed a diagnosis of cancer.

Group - Males 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	1 008	1:52	2,52%
Asian males	14	1:414	1,34%
Black males	726	1:141	5,49%
Coloured males	92	1:179	1,98%
White males	176	1:199	0,79%

Group - Females 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	788	1:289	1,89%
Asian females	14	1:655	1,01%
Black females	618	1:245	3,29%
Coloured females	64	1:402	1,41%
White females	92	1:435	0,52%

The frequency of histologically diagnosed cases of oesophageal cancer in South Africa for 2017 were 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	2	1	24	97	321	298	173	52
Asian males	0	0	2	2	2	6	2	0
Black males	2	1	16	75	252	244	194	32
Coloured males	0	0	3	12	33	29	11	4
White males	0	0	3	8	34	59	56	16

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	2	1	16	74	216	225	171	83
Asian females	0	0	0	2	5	5	1	1
Black females	1	0	12	56	178	172	136	63
Coloured females	1	1	3	7	17	19	8	8
White females	0	0	1	9	16	29	26	11

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.

He, H., Chen, N., Hou, Y., Wang, Z., Zhang, Y., Zhang, G. & Fu, J. 2020.

Background: Recent studies have indicated that the incidence of esophageal cancer has declined in the past decade in the U.S. However, trends in the incidence and survival have not been thoroughly examined.

Methods: Data from 46 063 patients with esophageal cancer between 1973 and 2015 were collected from the Surveillance, Epidemiology, and End Results database. The trends in the age-adjusted incidence and survival were analyzed using joinpoint regression models.

Results: The age-adjusted incidence of esophageal cancer increased from 5.55 to 7.44 per 100 000 person-years between 1973 and 2004. Later, it decreased at an annual percentage change of 1.23%. In the last 40 years, the strong male predominance increased slightly. Importantly, the percentage of patients with localized stage of squamous cell cancer decreased. It was observed that the incidence of esophageal squamous cell carcinoma declined since 1986, while the incidence of esophageal adenocarcinoma sharply increased since 1973 and surpassed the rate of squamous cell cancer, mainly due to the increase in the incidence among men. Consistently, the estimated 40-year limited-duration prevalence of esophageal adenocarcinoma was higher than that of esophageal squamous cell carcinoma. Additionally, we observed a modest but significant improvement in survival during the study period.

Conclusion: The incidence of esophageal squamous cell carcinoma has decreased significantly over the past four decades in the U.S., while the incidence of adenocarcinoma has increased, particularly among men. Overall, the long-term survival of patients with esophageal cancer is poor but it has improved over the past decades, especially for the localized disease.

Key points: Significant findings of the study The incidence of esophageal cancer has decreased at an annual percentage change of 1.23% since 2004. The incidence of esophageal adenocarcinoma has sharply increased since 1973 and surpassed the rate of squamous cell cancer, mainly due to the increase in the incidence among men. What this study adds There has been a shift in the prevalence of esophageal cancer histological subtypes over the past decades in the U.S. We found that the incidence of esophageal squamous cell carcinoma has continued to decrease, while the esophageal adenocarcinoma rate has continued to increase.

Risk Factors for Oesophageal Cancer

While risk factors for squamous cell carcinoma (SCC) of the oesophagus have been identified, namely tobacco use, alcohol use, malnutrition, and infection with human papillomavirus (HPV), the risk factors associated with oesophageal adenocarcinoma (AC) are less well defined. The most important epidemiological difference between squamous cell cancer and adenocarcinoma of the oesophagus is the strong association between gastro-oesophageal reflux disease (GERD) and adenocarcinoma.

Factors that cause irritation in the cells of the oesophagus which may increases the risk for oesophageal cancer include:

- Drinking alcohol - smoking and drinking combined increase the risk of squamous cell carcinoma (SCC) of the oesophagus 20-fold
- Having bile reflux
- Chewing tobacco (smokeless tobacco) - The International Agency for Research on Cancer (IARC) classifies smokeless tobacco and *betel quid** (with or without tobacco) as a cause of oesophageal cancer. Studies into smokeless tobacco and oesophageal cancer risk in the West have mainly been conducted in the Nordic countries, showing a 60% increase in risk of oesophageal cancer for smokeless tobacco users
- Having difficulty swallowing because of an oesophageal sphincter that will not relax (achalasia)
- Drinking very hot liquids
- Other potential risk factors for oesophageal cancer include oesophageal burns due to accidental or intentional swallowing of caustic materials such as bleach
- Barret's Oesophagus - One of the strongest risk factors for adenocarcinoma of the oesophagus is an acquired premalignant condition known as Barrett's oesophagus (BO, or Barrett's metaplasia)
- Eating few fruits and vegetables - A recent meta-analysis of case-control and cohort studies reported a significant reduction in risk with higher consumption of fruit and a non-significant protective role of vegetable consumption. A study published in December 2011 estimated that more than 46% of oesophageal cancer cases overall in men and around 45% in women in the UK in 2010 were linked to people eating fewer than five portions a day (400g/day) of fruit and vegetables (Cancer Research UK)
- Eating foods preserved in lye, such as lutefisk, a Nordic recipe made from aged stockfish (air-dried whitefish) or dried/salted whitefish (klippfisk) and lye (*lut*) whitefish. Lye-cured olives is another food type in this category
- Certain asthmatic medicines - drugs given to asthmatics such as ?-agonists and aminophyllines also have the effect of relaxing the sphincter and this is the likely reason for the higher incidence of AC observed in asthmatics
- Having gastro-oesophageal reflux disease (GERD)

- Being obese
- Undergoing radiation treatment to the chest or upper abdomen
- Smoking - European studies showed a four-fold risk increase for oesophageal cancer overall among smokers. The effect of smoking is stronger for SCC than adenocarcinoma (AC), with a recent cohort study showing that current smokers have a nine-fold risk increase for oesophageal SCC and a four-fold risk increase for oesophageal AC
- Race - squamous cell cancer of the oesophagus is more common among blacks than whites. Adenocarcinoma is more common in white men than men of other races
- Vitamin Deficiencies - some studies have linked oesophageal cancer with deficiencies in beta carotene, vitamin E, selenium, and iron
- History of other Illnesses - a variety of other illnesses and medical conditions have been associated with an increased risk of oesophageal cancer. These may include:
  - Cancers of the head, neck, or lungs
  - Human papillomavirus (HPV) infection
  - Tylosis, a very rare inherited disease that causes excess skin growth on the palms of the hands and the soles of the feet. People with this disease have a high risk of developing oesophageal squamous cell cancer and should be screened regularly
  - Oesophageal webs - abnormal bands of tissue that extend inward into the oesophagus making it difficult to swallow

Other risk factors include:

- Being male
- Age - being between the ages of 45 and 70

Sheikh, M., Poustchi, H., Pourshams, A., etemadi, A., Islami, F., Koshnia, M., Gharvi, A., Hashemian, M., Roshandel, G., Khademi, H., Zahedi, M., Abedi-Ardekani, B., Boffetta, P., Kamangar, F., Dawsey, S.M., Pharaoh, P.D., Abnet, C.C., Day, N.E., Brennan, P. & Malekzadeh, R. 2019.

BACKGROUND & AIMS: Northeast Iran has one of the highest reported rates of esophageal squamous cell carcinoma (ESCC) worldwide. Decades of investigations in this region have identified some local habits and environmental exposures that increase risk. We analyzed data from the Golestan Cohort Study to determine the individual and combined effects of the major environmental risk factors of ESCC.

METHODS: We performed a population-based cohort of 50,045 individuals, 40-75 years old, from urban and rural areas across Northeast Iran. Detailed data on demographics, diet, lifestyle, socioeconomic status, temperature of drinking beverages, and different exposures were collected using validated methods, questionnaires, and physical examinations, from 2004 through 2008. Participants were followed from the date of enrolment to the date of first diagnosis of esophageal cancer, date of death from other causes, or date of last follow up, through December 31, 2017. Proportional hazards regression models were used to estimate hazard ratios (HRs) and corresponding 95% CIs for the association between different exposures and ESCC.

RESULTS: During an average 10 years of follow up, 317 participants developed ESCC. Opium smoking (HR, 1.85; 95% CI, 1.18-2.90), drinking hot tea (≥60^{o}C) (HR, 1.60; 95% CI, 1.15-2.22), low intake of fruits (HR, 1.48; 95% CI, 1.07-2.05) and vegetables (HR, 1.62; 95% CI, 1.03-2.56), excessive tooth loss (HR, 1.66; 95% CI, 1.04-2.64), drinking un-piped water (HR, 2.04; 95% CI, 1.09-3.81), and exposure to indoor air pollution (HR, 1.57; 95% CI, 1.08-2.29) were significantly associated with increased risk of ESCC, in a dose-dependent manner. Combined exposure to these risk factors was associated with a

stepwise increase in the risk of developing ESCC, reaching a more than 7-fold increase in risk in the highest category. Approximately 75% of the ESCC cases in this region can be attributed to a combination of the identified exposures.

CONCLUSIONS: Analysis of data from the Golestan Cohort Study in Iran identified multiple risk factors for ESCC in this population. Our findings support hypothesis that the high rates of ESCC are due to a combination of factors, including thermal injury (from hot tea), exposure to polycyclic aromatic hydrocarbons (from opium and indoor air pollution), and nutrient-deficient diets. We also associated ESCC risk with exposure to un-piped water and tooth loss.

(*) Betel quid is a combination of betel leaf, areca nut, and slaked lime. In many countries, tobacco is also added, and the product is known as *gutka*, *ghutka*, or *gutkha*. Other ingredients and flavourants are also added according to local preferences and customs (e.g., sweeteners; catechu; or spices such as cardamom, saffron, cloves, anise seeds, turmeric, and mustard). The following cancers have been associated with betel quid use: lip, mouth, tongue, pharynx and oesophagus (Centers for Disease Control and Prevention).

Signs and Symptoms of Oesophageal Cancer

The following are important signs and symptoms that may indicate oesophageal cancer:

- Unintentional weight loss - unintentional weight loss can mean many things, but it is better to have it checked out
- Pain when swallowing (odynophagia) - pain when swallowing is one of the most common symptoms of oesophageal cancer. The throat feels irritated or with pressure. This symptom is not associated with flu or flu-related illnesses. The pain or difficulty swallowing related with oesophageal cancer does not go away. Pain with swallowing is an ominous sign
- Hoarseness - if the voice is hoarse, or the person feels like he/she has to often clear their throat, it should get checked out by a doctor
- Persistent cough - having a cough that does not go away
- Heartburn - having heartburn - pain or burning sensation behind the breast bone. Heart burn that occurs often or increasingly warrants a consultation with a doctor
- Feeling like food is stuck in throat or chest - In certain cases of oesophageal cancer, the oesophagus narrows, thus reducing the amount of space foods have to travel down to the stomach. The sensation of food being stuck in the throat or chest is typical of oesophageal cancer. It is generally not noted until the oesophageal lumen is narrowed to one-half to one-third of normal
- Hiccups with pain – The presence of regular incidents of hiccups requires a visit to a doctor
- Coughing up of blood – the blood is bright red in colour and only a small quantity is vomited at any given time
- Dysphagia - the most common presenting complaint is dysphagia (difficulty in swallowing) which, due to oesophageal elasticity, is generally not noted until the oesophageal lumen is narrowed to one-half to one-third of normal
- Cough - cough that is induced by swallowing is suggestive of local extension into the trachea with resultant trachea-oesophageal fistula and may be a sign of oesophageal cancer
- Hoarseness - hoarseness may be a sign of recurrent laryngeal nerve involvement due to extra-oesophageal spread of cancer
- Metastatic disease - metastatic disease may present as malignant pleural effusion (fluid collection in the lungs) or ascites (fluid collection in the abdomen). Bone metastasis (cancer that

has spread to the bones) can be identified by pain involving the affected site or by associated hypercalcaemia

Diagnosis of Oesophageal Cancer

Screening - Regular screening tests to find oesophageal cancer in people without symptoms are not often used. People with Barrett's oesophagus (see above) may be advised to have endoscopic examinations (looking inside the oesophagus through a flexible, lighted tube) and biopsies (removal of a small amount of tissue for examination under a microscope) regularly to help find cancer early or to find changes that could become cancerous over time.

A diagnosis of oesophageal cancer is usually made following:

Laboratory studies which focused on the evaluation of nutritional status

- Imaging studies that may include the following:
- Barium swallow (very sensitive for helping detect strictures and intraluminal masses, but now rarely used)
- Oesophagogastroduodenoscopy
- Endoscopic ultrasonography (most sensitive test for T and N staging)
- Computed tomography of the abdomen and chest (for M staging and assessing invasion of adjacent structures)
- Bronchoscopy (to help exclude invasion of the trachea or bronchi)
- Bone scan (for patients with complaints suggestive of bone metastases)
- Laparoscopy and thoracoscopy (for staging regional nodes)
- Positron emission tomography (PET for elucidating hypermetabolic foci of disease activity)

Zhu, Y., Fu, L., Jing, W., Guo, D., Chen, Y., Kong, L. & Yu, J. 2019.

"Currently, the use of magnetic resonance imaging (MRI) in patients with esophageal carcinoma is limited. However, the quality of MRI for esophageal carcinoma continues to improve and the importance of MRI in patients with esophageal carcinoma has been gradually recognized. Compared with endoscopic ultrasound and computed tomography applied in T and N staging, MRI has now achieved excellent results after the imaging technique has been optimized. We review the literature on MRI and discuss the future of MRI in esophageal carcinoma. While the role of MRI in staging, tumor volume target delineation and evaluation for preoperative chemoradiotherapy, prognosis and recurrence is still evolving. The application of MRI in esophagealcarcinoma has a bright future and potential to improve precision of T and N staging as well as treatment delivery."

Types of Oesophageal Cancer

There are two main types of oesophageal cancer. Both types are diagnosed, treated, and managed in similar ways.

The two most common types are named for how the cancer cells look under a microscope. Both types begin in cells in the inner lining of the oesophagus:

- Adenocarcinoma (AC) of the oesophagus: This type is usually found in the lower part of the oesophagus, near the stomach.

- Squamous cell carcinoma (SCC) of the oesophagus: This type is usually found in the upper part of the oesophagus.

Reducing the Risk for Oesophageal Cancer

The following can assist in reducing the risk for oesophageal cancer:

- Quit smoking or chewing tobacco. Join the CANSA E-KickButt Programme
- Avoid alcohol consumption. There is no safe limit of alcohol consumption. The risk of various types of cancer — including cancer of the breast, colon, lung, kidney, liver and oesophagus — increases with the amount of alcohol one drinks and the length of time one has been drinking regularly. Alcohol was classified as a Group 1 carcinogen by IARC in 1980
- Eat more fruits and vegetables. Add a variety of colourful fruits and vegetables to the diet. Try and eat at least five portions of vegetables and fresh fruit (in season) every day
- Maintain a healthy weight. If overweight or obese, talk to a doctor about strategies to help lose weight
- Individuals with Barrett's Oesophagus should go for screening every year

Staging of Oesophageal Cancer

The stage of a cancer is the most significant factor when devising a treatment plan.

Prognosis (Outlook)

The likelihood of being cured of cancer depends in large part on the stage of the cancer at the time it is diagnosed. From 80% to 90% of patients with the earliest stage of oesophageal cancer can expect to be alive and cancer free 5 years after treatment. However, since the typical oesophageal cancer is discovered at a relatively advanced stage, the overall success rate in curing oesophageal cancer is often disappointing.

Survival rates are slowly improving as oesophageal cancers are being detected earlier and more effective treatments are developed, but even so they remain poor. Overall, about 40 per cent of people are still alive one year after diagnosis, but currently only about 1 in 8 survive to 5 years. Survival rates are, of course, better for those diagnosed and treated with early stage disease.

Treatment of Oesophageal Cancer

As with most cancers, if a case of oesophageal cancer is found, the first step is to work out what type of cancer it is and how far it has spread. This is called staging, and it helps to predict how the cancer is likely to progress and which treatments are most appropriate

Treatments that may be offered include:

Surgery - what exactly is done will depend on where the tumour is, the stage of the cancer and the person's general level of fitness. In early stage cancer the lining of the oesophagus may simply be

removed, but more often part (or all) of the oesophagus is taken away. Often nearby lymph nodes and other tissues must be removed too. The oesophagus is then repaired so the patient can swallow food. Sometimes a section of the lower intestine may be used to replace the removed part of the oesophagus or to bypass a whole area if the tumour is too large.

During the operation, the surgeon will examine the oesophagus and surrounding area. Some of the lymph nodes will be removed from around the oesophagus. The doctor will send the lymph nodes to the laboratory to check to see if they contain cancer cells. This helps the doctor to know the stage of the cancer.

Endoscopic mucosal resection (EMR) - if the patient has high grade Barrett's oesophagus, or a very early stage cancer which is only on the lining of the oesophagus (the mucosal layer), it may be possible to remove it using endoscopic mucosal resection (EMR). High grade Barrett's oesophagus means that some of the cells are very abnormal. If left untreated, these cells may develop into an invasive cancer. For this procedure, the doctor puts a tube called an endoscope down the patient's throat. The endoscope contains a camera so the doctor can see inside the body. The endoscope can be used to inject fluid into the layer of cells below the cancer or abnormal area, which makes it stand out from the rest of the tissue. Then a thin wire (snare) is used to remove the area.

The most common side effects are bleeding and a narrowing of the oesophagus, which can happen some time after the procedure. There is a very small risk of tearing the oesophageal wall. The patient may also have photodynamic therapy or radiofrequency ablation after EMR, to try to destroy any abnormal areas or cancer cells that may be left.

Yang, A.J., Choi, S.H., Byun, H.K., Kim, H.J., Choi, J., Lee, Y.C., Lee, S.K., Park, K.R. & Kee, C.G. 2018.
BACKGROUND/AIMS: Endoscopic resection is a standard treatment for stage T1a esophageal cancer, with esophagectomy or radical radiation therapy (RT) performed for stage T1b lesions. This study aimed to compare treatment outcomes of each modality for clinical stage T1 esophageal cancer.
METHODS: In total, 179 patients with clinical T1N0M0-stage esophageal cancer treated from 2006 to 2016 were retrospectively evaluated. Sixty-two patients with clinical T1a-stage cancer underwent endoscopic resection. Among 117 patients with clinical T1b-stage cancer, 82 underwent esophagectomy, and 35 received chemoradiotherapy or RT. We compared overall survival (OS) and recurrence-free survival (RFS) rates for each treatment modality.
RESULTS: The median follow-up time was 32 months (range, 1 to 120 months). The 5-year OS and RFS rates for patients with stage T1a cancer receiving endoscopic resection were 100% and 85%, respectively. For patients with stage T1b, the 5-year OS and RFS rates were 78% and 77%, respectively, for the esophagectomy group; 80% and 44%, respectively, for the RT alone group; and 96% and 80%, respectively, for the chemoradiation group. The esophagectomy group showed significantly higher RFS than the RT alone group (p=0.04). There was no significant difference in RFS between the esophagectomy and chemoradiation groups (p=0.922). Grade 3 or higher treatment-related complications occurred in four patients who underwent esophagectomy.
CONCLUSIONS: Endoscopic resection appeared to be an adequate treatment for patients with T1a-stage esophageal cancer. The multidisciplinary approach involving chemoradiation was comparable to esophagectomy in terms of survival outcome without serious complications for T1b-stage esophageal cancer.

Chemotherapy - relieves symptoms and may slow cancer growth. Giving chemotherapy before surgery is called neo adjuvant chemotherapy. This is commonly used for treating oesophageal cancer. The chemotherapy can shrink the cancer, making it easier to remove. It also helps reduce the chances of the cancer coming back.

If there is cancer of the lower oesophagus or where the oesophagus meets the stomach (gastro-oesophageal junction) chemotherapy may be ordered after surgery, as well as before. This also helps to lower the chances of the cancer coming back.

If the oesophageal cancer has spread to other parts of the body (advanced oesophageal cancer) the patient may be given chemotherapy on its own. This may help to control or shrink the cancer and reduce symptoms.

Ota., Ishikawa, T., Endo, Y., Matsumura, S., Yoshida, J., Yasuda, T., Okayama, T., Inoue, K., Dohi, O., Yoshida, N., Sakamoto, N., Kamada, K., Uchiyama, K., Takagi, T., Konishi, H>., Shiozaki, A., Fujiwara, H., Kishimoto, M., Naito, Y. & Itoh, Y. 2019.
"Undernutrition and sarcopenia are associated with a higher incidence of chemotherapy-related toxicity and a poor prognosis in several kinds of cancer, but the impact of sarcopenia on the outcomes of chemotherapy for esophageal cancer remains unclear. Thus, the purpose of this retrospective study was to investigate whether sarcopenia affects the efficacy and toxicities of chemotherapy for advanced esophageal cancer patients. Data were collected from 31 esophageal cancer patients who underwent neo-adjuvant chemotherapy followed by surgery. Body composition was assessed at the start of chemotherapy by bioelectrical impedance analysis, and outcomes of chemotherapy were compared between sarcopenic and non-sarcopenic groups. Of the 31 patients, sarcopenia was observed in 16 (51.6%). The incidence of toxicities was not different between the two groups. However, as for pathologic response, a good therapeutic effect (Grade 2 or higher) was more common in the non-sarcopenic group than in the sarcopenic group (53.3% vs. 25.0%). Multivariate analysis showed that sarcopenia was an independent predictor of poor pathological response (odds ratio 8.02; $P = 0.037$). The results of this study suggest the potential utility of sarcopenia assessment in neoadjuvant patient selection strategies."

Radiotherapy - may be used to shrink a tumour before surgery. It may be given on its own, in combination with chemotherapy or after surgery to try to prevent recurrence. A patient may be given radiotherapy alongside chemotherapy (chemoradiation) before, or instead of, surgery. Or in some cases, the patient may have radiotherapy on its own if he/she is unable to have chemotherapy or surgery. In the case of advanced oesophageal cancer, the patient is most likely to have radiotherapy on its own to help control the cancer and relieve symptoms.

Radiotherapy is painless to have, although it may make the throat sore as the course of treatment goes on. It is usual to have this treatment as an outpatient. The length of the course of radiotherapy treatment will depend on the size and type of oesophageal cancer the patient has. Usual treatment is for a few minutes every day, over a few weeks.

Sometimes radiotherapy is given from inside the body. This is known as internal radiotherapy or brachytherapy. For oesophageal cancer, this means having a radioactive source put down your throat and into the food pipe. The doctor may use a flexible tube known as an endoscope to get the radioactive source in the right place. A patient is most likely to have this treatment if he/she has an advanced cancer that is making it difficult to swallow.

Lian, X., Zhu, C., Lin, H., Gao, Z., Li, G., Zhang, N., Cao, B. & Kang, Y. 2020.
"Radiation therapy is a widely used treatment for esophageal cancer. However, radiation resistance might result in an unsatisfactory prognosis. Overexpression of HER2 has been related to adaptive radiation resistance. Pyrotinib is a HER2 inhibitor that shows an anti-tumor effect in breast cancer. This study aims to explore the influence of pyrotinib combined with radiotherapy on HER2-positive esophageal cancer cells and explore the underlying mechanism. We screened two cell lines (TE-1 and KYSE30) that highly express HER2 from several human esophageal cancer cell lines. Cells were treated with pyrotinib or/and radiation. Cell proliferation, cell cycle distribution, and cell migration were measured. The protein levels involved in cell cycle and DNA repair were measured by western blot. Results showed that pyrotinib inhibited HER2 activation and exerted an anti-proliferative effect in TE-1 and KYSE30 cells. Furthermore, it enhanced the anti-proliferative effect of radiation in these two cell lines. These effects might be via inhibiting HER2 phosphorylation, inducing G0/G1 arrest, and reducing EMT and DNA repair. Our results indicated that pyrotinib sensitivitied HER2 positive esophageal cancer cells to radiation treatment through various mechanisms. These findings may provide a new therapeutic strategy for treating HER2 positive esophageal cancer."

Combined chemotherapy and radiotherapy - In some cases, a patient may have chemotherapy and radiotherapy together. This is called chemoradiation. A patient may have it before surgery to help shrink the cancer, making it easier to remove. If a patient is unable to have surgery, or do not want it, he/she may have chemoradiation on its own. Particularly if they have squamous cell cancer near the top of the oesophagus. Some studies have shown that chemoradiation can be as good as surgery for this type of cancer. Chemoradiation is quite an intensive treatment and there are side effects. The doctor will consider the patient's general health before deciding if this treatment is an option.

Tsou, Y.K., Lee, C.H., Le, P.H. & Chen, B.H. 2020.
"Endoscopic resection (ER) combined with adjuvant therapy appears to be a new treatment for esophageal squamous cell cancers (ESCC) invading to deep mucosa (pT1a-m3) or submucosa (pT1b). Adjuvant therapy can take the form of esophagectomy or chemoradiotherapy (CRT), but it is unclear which treatment is better. This review is to explore the outcomes of adjuvant therapy between esophagectomy and CRT for the treatment of pT1a-m3/pT1b ESCC after ER. Ten relevant studies with a total of 285 patients were included. The reported 5-year overall survival rates ranged between 90-100 % for ER-esophagectomy and 75-85 % for ER-CRT. ESCC with the invasion of ≥ sm2 combined with lymphovascular involvement was associated with a high-risk of relapse in patients receiving ER-CRT, but not in ER-esophagectomy. In conclusion, patients with a high-risk of relapse should be treated with ER-esophagectomy; ER-CRT may be used as an alternative treatment for patients with a nonhigh risk of relapse."

Li, C.C., Fang, H.Y., Lin, C.Y., Shen, W.C. & Chien, C.R. 2019.
BACKGROUND/AIM: The optimal radiotherapy dose for localized esophageal squamous cell carcinoma (ESqCC) patients treated with definitive concurrent chemo-radiotherapy (CCRT) is debated. The aim of our study was to compare patient outcomes using either standard or high radiotherapy dose.
MATERIALS AND METHODS: Eligible patients diagnosed between 2011 and 2015 from the cancer registry of our Institute were identified and a propensity score (PS)-matched cohort (1:1 for high vs. standard dose) was constructed to balance observable potential confounders (including organ at risk dose). The hazard ratio (HR) of death between high and standard dose was compared.

RESULTS: Our study population included 73/36 patients before/after PS matching. The HR of death at the high dose compared to the standard dose was 0.554 (95% confidence interval (CI)=0.308-0.998, p=0.049).
CONCLUSION: Definitive CCRT using a high radiotherapy dose showed improved survival outcomes for localized ESqCC patients compared to standard dose.

Laser treatment - if the cancer is blocking the oesophagus and making it difficult to swallow, the patient may need treatment to clear the blockage. Sometimes laser treatment is used to burn away the tumour. This may help to reduce the size of the tumour and relieve symptoms but is not curative. Laser treatment may be combined with the use of a light-sensitive drug (known as photo-dynamic therapy or PDT).

Insertion of a stent - a rigid tube is placed in the oesophagus to help keep it open and allow food to pass through to the stomach. It can help deal with symptoms but does not treat the cancer itself

Biological (Immuno-) therapies - made from chemicals that occur naturally in the body such as antibodies, or substances that counteract the effect of the protein signalling molecules which naturally stimulate growth of the cells (known as growth factor blockers). Another type of biological therapy is a vaccine, which can stimulate the immune system to identify cancerous cells and destroy them. Biological therapy is not often used, however, if the tumour is in the area where the oesophagus joins the stomach (oesophagogastric junction), doctors sometimes use a biological therapy drug called trastuzumab (Herceptin).

Two main types of cancer affect the oesophagus, a muscular tube through which food passes from the mouth to the stomach: squamous cell carcinoma (cancer that begins in flat cells lining the oesophagus) and adenocarcinoma (cancer that begins in cells that make and release mucus, which are usually associated with ectopic gastric mucosa). Oesophageal cancer is more common in men than in women.

The 5-year relative survival rate for patients with oesophageal cancer is 40% for patients with localised disease; 22% for regional disease; and 4% for metastatic disease.

Surgery remains the most common treatment for oesophageal cancer, though chemotherapy, radiation, and immunotherapy may also be used. The two immunotherapies approved for oesophageal cancer are trastuzumab and ramucirumab. Several approaches to immunotherapy for oesophageal cancer have shown promise in early clinical trials. These treatments can be broken into 5 main categories: checkpoint inhibitors/immune modulators, adoptive cell transfer, monoclonal antibodies, therapeutic vaccines, and cytokines.

Are you a patient or caregiver interested in learning more about cancer immunotherapy treatment and clinical trials?

Immunotherapy has the potential to improve the outlook for patients and families affected by the disease and bring us ever closer to effective, lasting cures for oesophageal cancer. That's why CRI supports scientific research being done to advance the potential of immunotherapies for oesophageal cancers.

Photodynamic Therapy (PDT) - this treatment involves the use of low powered lasers combined with a light sensitive drug to destroy cancer cells. PDT is a relatively new treatment, and one may need to have it repeated a number of times. A patient may be given this:

- as a treatment to try to prevent high grade Barrett's oesophagus developing into cancer, if you are unable to have an endoscopic mucosal resection (EMR) or surgery
- after EMR for high grade Barrett's or very early oesophageal cancer, to treat any abnormal or cancerous cells left behind
- to destroy part of a tumour and improve swallowing when advanced oesophageal cancer is making this difficult

Radiofrequency ablation (RFA) – If a patient has high grade Barrett's oesophagus, he/she may have RFA either on its own or after an endoscopic mucosal resection (EMR). RFA uses heat made by radio waves to destroy the abnormal cells. Radiofrequency is a type of electrical energy. And ablation means 'destroying completely'. A tube with a camera (endoscope) is passed down the throat into the oesophagus. A small balloon or probe is then guided to the area of abnormal cells. A few quick 'pulses' of electrical energy is given to destroy the abnormal cells on the inside of the oesophagus. RFA may also be used after EMR for a very early stage oesophageal cancer.

Argon plasma coagulation (APC) - APC is sometimes recommended after EMR or as a treatment if swallowing remains difficult. Using an endoscope, a probe is placed close to the area to be treated. Using a combination of argon gas and electricity, the doctor can destroy the cancer.

There are Different Types of Treatment for Patients with Oesophageal Cancer.

Different types of treatment are available for patients with oesophageal cancer.. Some treatments are standard (the currently used treatment), and some are being tested in clinical trials. A treatment clinical trial is a research study meant to help improve current treatments or obtain information on new treatments for patients with cancer. When clinical trials show that a new treatment is better than the standard treatment, the new treatment may become the standard treatment. Patients may want to think about taking part in a clinical trial. Some clinical trials are open only to patients who have not started treatment.

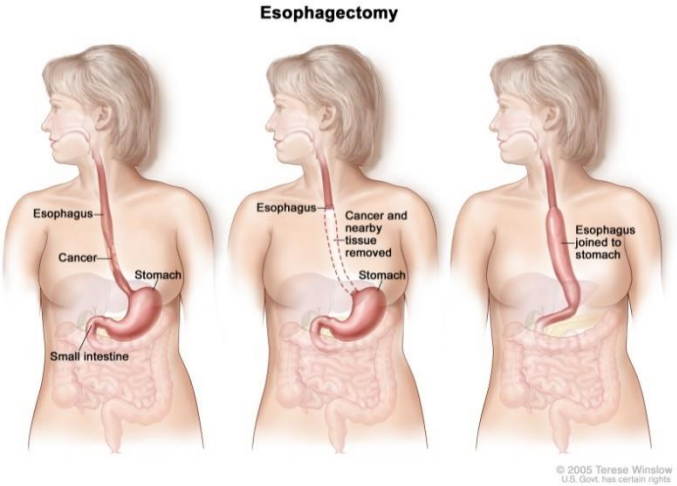
Patients have Special Nutritional Needs During Treatment for Oesophageal Cancer.

Many people with oesophageal cancer find it hard to eat because they have trouble swallowing. The oesophagus may be narrowed by the tumour or as a side effect of treatment. Some patients may receive nutrients directly into a vein. Others may need a feeding tube (a flexible plastic tube that is passed through the nose or mouth into the stomach) until they are able to eat on their own.

Types of Standard Treatment

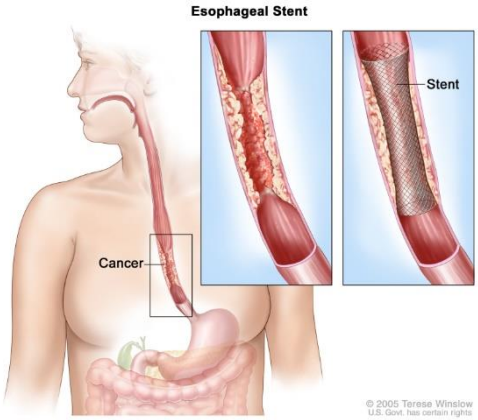
Surgery

Surgery is the most common treatment for cancer of the oesophagus. Part of the oesophagus may be removed in an operation called an oesophagectomy.



Esophagectomy. A portion of the oesophagus is removed and the stomach is pulled up and joined to the remaining oesophagus.

The doctor will connect the remaining healthy part of the oesophagus to the stomach so the patient can still swallow. A plastic tube or part of the intestine may be used to make the connection. Lymph nodes near the oesophagus may also be removed and viewed under a microscope to see if they contain cancer. If the oesophagus is partly blocked by the tumour, an expandable metal stent (tube) may be placed inside the oesophagus to help keep it open.



[Picture Credit: Oesophageal Stent]

Oesophageal stent. A device (stent) is placed in the oesophagus to keep it open to allow food and liquids to pass through into the stomach.

Small, early-stage cancer and high-grade dysplasia of the oesophagus may be removed by endoscopic resection. An endoscope (a thin, tube-like instrument with a light and a lens for viewing) is inserted through a small incision (cut) in the skin or through an opening in the body, such as the mouth. A tool attached to the endoscope is used to remove tissue.

Follow-up tests may be needed.

Some of the tests that were done to diagnose the cancer or to find out the stage of the cancer may be repeated. Some tests will be repeated in order to see how well the treatment is working. Decisions about whether to continue, change, or stop treatment may be based on the results of these tests.

Some of the tests will continue to be done from time to time after treatment has ended. The results of these tests can show if one's condition has changed or if the cancer has recurred (come back). These tests are sometimes called follow-up tests or check-ups.

Changing of Lifestyle Following Oesophageal Cancer Diagnosis

Lifestyle changes following an oesophageal cancer diagnosis can be helpful in a variety of important ways:

- Strengthening the body so that one can withstand some of the rigors of treatment
- Optimising the function of the immune system to aid in the fight against cancer
- Improving one's emotional outlook, so one can enjoy life to the fullest, even during treatment for oesophageal cancer
- Making healthful choices that will help to avoid other medical problems that could complicate health

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/

Sheill, G., Guinan, E., O'Neill, L., Normand, C., Doyle, S.L., Moore, S., Newell, J., McDermott, G., Ryan, R., Reynolds, J.V. & Hussey, J. 2020.

Background: Patients with cancer of the lung or oesophagus, undergoing curative treatment, usually require a thoracotomy and a complex oncological resection. These surgeries carry a risk of major morbidity and mortality, and risk assessment, preoperative optimisation, and enhanced recovery after surgery (ERAS) pathways are modern approaches to optimise outcomes. Pre-operative fitness is an established predictor of postoperative outcome, accordingly, targeting pre-operative fitness through exercise prehabilitation has logical appeal. Exercise prehabilitation is challenging to implement however due to the short opportunity for intervention between diagnosis and surgery. Therefore, individually prescribed, intensive exercise training protocols which convey clinically meaningful improvements in cardiopulmonary fitness over a short period need to be investigated. This project will examine the influence of exercise prehabilitation on physiological outcomes and postoperative recovery and, through evaluation of health economics, the impact of the programme on hospital costs.

Methods: The PRE-HIIT Randomised Controlled Trial (RCT) will compare a 2-week high intensity interval training (HIIT) programme to standard preoperative care in a cohort of thoracic and oesophageal patients who are > 2-weeks pre-surgery. A total of 78 participants will be recruited (39 per study arm). The primary outcome is cardiorespiratory fitness. Secondary outcomes include, measures of pulmonary and physical and quality of life. Outcomes will be measured at baseline (T0), and post-intervention (T1). Post-operative morbidity will also be captured. The impact of PRE-HIIT on well-being will be examined qualitatively with focus groups/interviews post-intervention (T1). Participant's experience of preparation for surgery on the PRE-HIIT trial will also be explored. The

healthcare costs associated with the PRE-HITT programme, in particular acute hospital costs, will also be examined.
Discussion: The overall aim of this RCT is to examine the effect of tailored, individually prescribed high intensity interval training aerobic exercise on pre-operative fitness and postoperative recovery for patients undergoing complex surgical resections, and the impact on use of health services.
Trial registration: The study is registered with Clinical Trials.Gov (NCT03978325). Registered on 7th June 2019.

Lin, S.H., Hobbs, B.P., Verma, V., Tidwell, R.S., Smith, G.L., Lei, X., Corsini, E.M., Mok, I., Wei, X., Yao, L., Wang, X., Komaki, R.U., Chang, J.Y., Chun, S.G., Jeter, M.D., Swisher, S.G., Ajani, J.A., Blum-Murphy, M., Vaporciyan, A.A., Mehran, R.J., Koong, A.C., Gandhi, S.J., Hofstetter, W.L., Hong, T.S., Delaney, T.F., Liao, Z. & Mohan, R. 2020.
Purpose: Whether dosimetric advantages of proton beam therapy (PBT) translate to improved clinical outcomes compared with intensity-modulated radiation therapy (IMRT) remains unclear. This randomized trial compared total toxicity burden (TTB) and progression-free survival (PFS) between these modalities for esophageal cancer.
Methods: This phase IIB trial randomly assigned patients to PBT or IMRT (50.4 Gy), stratified for histology, resectability, induction chemotherapy, and stage. The prespecified coprimary end points were TTB and PFS. TTB, a composite score of 11 distinct adverse events (AEs), including common toxicities as well as postoperative complications (POCs) in operated patients, quantified the extent of AE severity experienced over the duration of 1 year following treatment. The trial was conducted using Bayesian group sequential design with three planned interim analyses at 33%, 50%, and 67% of expected accrual (adjusted for follow-up).
Results: This trial (commenced April 2012) was approved for closure and analysis upon activation of NRG-GI006 in March 2019, which occurred immediately prior to the planned 67% interim analysis. Altogether, 145 patients were randomly assigned (72 IMRT, 73 PBT), and 107 patients (61 IMRT, 46 PBT) were evaluable. Median follow-up was 44.1 months. Fifty-one patients (30 IMRT, 21 PBT) underwent esophagectomy; 80% of PBT was passive scattering. The posterior mean TTB was 2.3 times higher for IMRT (39.9; 95% highest posterior density interval, 26.2-54.9) than PBT (17.4; 10.5-25.0). The mean POC score was 7.6 times higher for IMRT (19.1; 7.3-32.3) versus PBT (2.5; 0.3-5.2). The posterior probability that mean TTB was lower for PBT compared with IMRT was 0.9989, which exceeded the trial's stopping boundary of 0.9942 at the 67% interim analysis. The 3-year PFS rate (50.8% *v* 51.2%) and 3-year overall survival rates (44.5% *v* 44.5%) were similar.
Conclusion: For locally advanced esophageal cancer, PBT reduced the risk and severity of AEs compared with IMRT while maintaining similar PFS.
Trial registration: ClinicalTrials.gov NCT01512589.

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.

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