Oesophageal Cancer
- All you need to know

Is it really just Heartburn?
Introduction

The oesophagus is a hollow muscular tube that connects the mouth to the stomach. It is around 25 cm long in adults. The inside of the oesophagus is normally lined by flat “paving slab” like cells called a stratified squamous epithelium. These sit upon a membrane that separates the lining from the muscle layers of the oesophagus.

Cancer can occur at any point along its length & the structure of the oesophagus can contribute to cancer progression. For example, unlike the rest of the digestive tract the oesophagus does not have an outer covering layer, which means that cancer cells can spread more easily and quickly to neighbouring organs.

There are two predominant types of oesophageal cancer: squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma (SCC) arises from the normal stratified squamous lining cells. Adenocarcinoma arises in fields of lining cells that have changed shape and size due to long-term exposure to stomach and bile acids. These cells change from looking like “paving slabs” under the microscope, to looking more like piled up columns, a condition known as Barrett’s oesophagus.

Worldwide the most common form of oesophageal cancer is squamous cell carcinoma. In many developed countries, however, the incidence of adenocarcinoma exceeds that of SCC. This is especially true of the UK and The Netherlands but is also true in North America, Australasia and Scandinavia.
How common in oesophageal cancer?

UK Mortality Rates from Oesophageal Cancer
- There were around 7,800 oesophageal cancer deaths in the UK in 2014, that’s 21 deaths every day
- Oesophageal cancer is the sixth most common cause of cancer death in the UK (2014)
- Oesophageal cancer accounts for 5% of all cancer deaths in the UK (2014).
- In males in the UK, oesophageal cancer is the fourth most common cause of cancer death, with around 5,200 deaths in 2014
- In females in the UK, oesophageal cancer is the sixth most common cause of cancer death, with around 2,600 deaths in 2014

UK Incidence of Oesophageal Cancer
- The United Kingdom has the highest incidence of oesophageal adenocarcinoma in the world: 7.2 per 100,000 in men and 2.5 per 100,000 in women
- There were around 8,900 new cases of oesophageal cancer in the UK in 2014, that’s 24 cases diagnosed every day
- Oesophageal cancer is the 14th most common cancer in the UK (2014)
- Oesophageal cancer accounts for 2% of all new cases in the UK (2014)
- In males in the UK, oesophageal cancer is the ninth most common cancer, with around 6,000 cases diagnosed in 2014
- In females in the UK, oesophageal cancer is the 14th most common cancer, with around 2,900 cases diagnosed in 2014

Global Incidence of Oesophageal Cancer
- There were 456,000 new cases of oesophageal cancer worldwide in 2012.
- The majority, 398,000, were squamous cell carcinomas (SCC)
- 315,000 of those cases were in Central & South-East Asia (210,000 in China alone)
- 52,000 were adenocarcinomas
- The worldwide incidence of oesophageal SCC is 5.2 per 100,000 but is substantially higher in males (7.7 per 100,000) than in females (2.8 per 100,000).
- Oesophageal adenocarcinoma has a global incidence of 0.7 per 100,000.


Figure 1: Age standardised incidence of oesophageal cancer.
(Adapted from Arnold M et al. 2015)
What are the outcomes for people with oesophageal cancer?

Cancer of the oesophagus is the 14th most common cancer in the UK but the 6th most common cause of cancer death. In England 40% of all sufferers will survive for one year, but by 5 years only 14% will still be alive. This is because the majority of patients present with incurable disease; It has either spread too far from the oesophagus into local organs or secondary tumours (metastasis) have developed at other sites in the body (typically lymph glands, liver and lungs).

The prognosis is dependent on the stage of the cancer and whether or not it can be cured with the best current treatments.

Less than 40% of patients can be offered curative treatment. These patients have a 74% chance of surviving for one year after diagnosis compared to 30% if the cancer is too advanced for curative therapy.

What causes oesophageal cancer?

Squamous Cell Carcinoma

Oesophageal squamous cell carcinoma arises through chronic irritation and inflammation of the oesophageal lining. Risk factors vary between countries and cultures but in general it is a disease of poor nutrition, poor-oral hygiene and poverty. The strongest associations are smoking and alcohol but consumption of hot beverages, high intake of barbecued meat and human papilloma virus infection have all been implicated.

Adenocarcinoma

Adenocarcinoma is rare globally but more common in wealthy, industrialised western nations. It is most common in middle-aged, caucasian, obese males with a history of excess alcohol consumption and smoking. Male-pattern obesity (fat carried around the waist and inside the abdomen) may be responsible for increased abdominal pressure and therefore acid reflux (often causing heartburn), going some way to explain why adenocarcinoma is seen far more commonly in men than women.

Adenocarcinoma of the oesophagus is strongly associated with gastro-oesophageal reflux disease (GORD) often described as Heartburn.

GORD is a common disease whereas adenocarcinoma of the oesophagus is not. GORD affects 1 in 10 adults on a daily basis and up to 2 in 10 weekly. Of these a further 1 in 10 will have Barrett’s oesophagus, the only known precursor for adenocarcinoma, the risk of progression to cancer in this population is around 1 in every 1000 patients per year.
How do our genes contribute to Oesophageal Cancer?

Heartburn Cancer UK trustee Professor Rebecca Fitzgerald has led a worldwide effort to understand the genetic basis of oesophageal adenocarcinoma as part of the International Cancer Genome Consortium. Supported by HCUK Vice-Chair Professor Tim Underwood, Prof Fitzgerald and her team have demonstrated that adenocarcinoma of the oesophagus is a highly disordered cancer containing many DNA mutations. Several well-known cancer causing genes have been identified. Unfortunately the complexity of mutations in oesophageal cancer means that no new single gene target has so far been identified for new treatments.

However, taking a genome-wide view of oesophageal adenocarcinoma has identified six patterns of mutation. These “mutational signatures” give clues as to the underlying causes of the disease and go some way to explaining the huge variations shown in response to current treatment. They also allow a broad molecular classification of adenocarcinoma with implications for treatment.

Over 50% of these tumours carry the ‘typical’ mutational signature of oesophageal adenocarcinoma caused by acid reflux. It is hoped that these tumours will be amenable to new immunotherapy drugs in the future. Our understanding of the molecular biology of oesophageal cancer is rapidly progressing and HCUK trustees are at the forefront of these efforts.
How is oesophageal cancer diagnosed?

The typical symptoms of oesophageal cancer are of difficulty swallowing (food getting stuck), at first solids and then sometimes liquids. There may be weight loss and anaemia (a low red blood cell count). Whilst a number of other conditions can lead to difficulty swallowing, anyone who has this symptom should see their doctor.

The first test performed is usually an endoscopy (a camera test to view the inside of the oesophagus and stomach) with biopsies (small samples of the lining are painlessly removed and examined under a microscope).

The majority of patients are diagnosed with oesophageal cancer following a referral from their general practitioner (GP) or another hospital doctor (85%). A very small number (less than 1%) are identified because they are known to have Barrett’s oesophagus and undergo regular surveillance endoscopy. The remaining 14% present as an emergency.

If oesophageal cancer is found how far has it spread?

Once a diagnosis of oesophageal cancer has been made it is important for the patient and doctors to understand how far the cancer has spread. This allows accurate treatment planning and gives an idea of the likely prognosis. A series of tests will be performed that are referred to as “staging investigations”.

The first staging investigation will usually be a CT scan of the chest, abdomen and pelvis. The patient lies flat on a bench while they are slowly moved through a large donut shaped x-ray machine. At the same time a dye is injected into a vein to help improve the detail of the x-ray pictures. This is often performed straight after the endoscopy when the cancer is first seen.

The purpose of a CT is to assess the size and spread of the primary cancer and identify any secondary (metastatic) disease. In those patients where the cancer has not spread on CT and possible curative treatment is proposed then further imaging in the form of Positron Emission Tomography (PET)-CT and Endoscopic Ultrasound (EUS) may be performed.

A PET CT is similar to a CT scan but involves a special dye that will show up brightly on the scan pictures wherever cells in the body are working hard and using a lot of energy. Cancer cells tend to use a lot of energy and therefore appear as bright areas on these images.
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An EUS is very similar to an endoscopy except the scope that the doctor uses will have a small ultrasound probe on the end which will help to assess the depth of any tumours in the wall of the oesophagus.

In some patients a small operation called a staging laparoscopy will be performed. This allows doctors to examine the inside of the abdomen to check for cancer spread not seen on the scans and to plan surgery.
Once all the staging investigations are complete the team of specialists called a multi-disciplinary team (MDT) will meet to agree on the stage of the disease and the most appropriate treatment plan or plans to offer to the patient.

The MDT will have specialist cancer doctors (oncologists), cancer surgeons, endoscopy doctors and x-ray doctors as well as cancer nurses, dieticians and a variety of other experts.

Tumours are given a score known as the TNM stage.

- **T** stands for tumour. Each tumour is given a score between 0 (no tumour) and 4 (a deep tumour that has spread into a neighbouring organ).
- **N** stands for lymph node. A score of 0 means no lymph nodes have cancer whereas a score of 3 means that seven or more lymph nodes have cancer within them.
- **M** stands for metastasis or spread. A cancer has either not spread (0) or has spread (1).
- The final stage will be given as each letter followed by the number (eg T3N2M0)

How is oesophageal cancer treated?

Once staging has been completed a management plan will be developed and tailored to individual patients. This will include the stage of disease and other medical conditions, taking into account the wishes of the patient and their family.

Treatment of advanced and incurable cancer.

In this setting treatment is aimed at improving the length and quality of life. Doctors may suggest a number of potential treatments or no treatment at all, depending on individual circumstances.

In very advanced cases the most appropriate treatment will be supportive care aimed at alleviating symptoms. Local treatment is directed at controlling difficult and painful swallowing. This is often achieved by the placement of an oesophageal stent, a reinforced plastic tube that can be placed into the oesophagus to “open-up” the tumour to allow eating and drinking.

Radiotherapy can be used to treat the primary tumour and to treat symptomatic metastases such as those in bones.

If chemotherapy is considered then a combination of three drugs: Epirubicin, Oxaliplatin and Capecitabine (EOX) is the current standard for incurable disease in the UK.
In a small number of cases the cancer will be suitable for treatment with Trastuzumab (Herceptin), best known for its role in breast cancer treatment. Oesophageal tumours are now routinely tested to see whether or not Herceptin is likely to work.

A range of new treatments, including immunotherapies (treatments that enhance the body's own ability to kill cancer), are being tested in clinical trials in the UK and elsewhere, but these are yet to become standard treatments.

Treatment of curable cancer

If oesophageal cancer is diagnosed early it can be cured. For the earliest stage cancers the tumour can be removed endoscopically (from the inside of the oesophagus in a similar way to the camera test used for diagnosis) without the need for major surgery or other treatments. If any Barrett's oesophagus is present this will also be removed completely. More than one endoscopic treatment may be required.

Squamous cell cancer of the oesophagus often responds well to a combination of chemotherapy and radiotherapy.

Patients whose tumours have advanced beyond the oesophageal lining (mucosa) and/or have evidence of cancer cells in local lymph glands, and are fit enough to undergo aggressive treatment are considered for pre-operative (neo-adjuvant) therapies followed by surgery. A number of large clinical trials conducted in the UK, Europe and the USA have proven that this strategy of giving anti-cancer treatment before surgery offers the best chance of long-term survival and cure. Uncertainty remains regarding whether this pre-operative treatment should be chemotherapy alone or chemotherapy and radiotherapy together. A current clinical trial called NeoAegis is running in the UK and Ireland and aims to answer this question.

Unfortunately, the survival benefit of neoadjuvant therapy in oesophageal cancer is limited to only about 20% of patients, at the expense of the many who derive no benefit at all, and who may be harmed by over-treatment. Current research being conducted by Prof Underwood and a large UK team is striving to predict who these patients will be before and during therapy in order to spare patients unnecessary treatments.
Surgery

Surgery remains the mainstay of curative treatment for oesophageal cancer. The aim of surgery is to remove the tumour, the oesophagus, the lymph nodes (that may contain cancer cells) and the surrounding tissue and to restore continuity of the digestive tract. By far the most commonly performed operation is an Ivor-Lewis oesophagectomy that involves operating in the abdomen and the chest. In the UK 96% of operations are performed in this way.

Minimally Invasive and Robotic Oesophagectomy

The role of key hole (minimally invasive) and robotic surgery is expanding in oesophageal cancer. The perceived advantages are shorter recovery times, a reduction in complications and less post-operative pain. The UK’s ROMIO clinical trial (Randomised controlled trial of minimally invasive or open oesophagectomy) coupled with similar trials in France (MIRO) and Holland (TIME), is designed to compare the clinical and cost-effectiveness of minimally invasive and open surgical procedures in terms of recovery, health related quality of life, cost and survival. At present there is no convincing evidence that key hole surgery is better or worse than traditional open surgery and patients should be reassured that the type of operation that they receive will not determine their chances of survival or quality of life.

Improvements in care for patients undergoing oesophageal surgery

In recent years there has been a significant improvement in the quality of care for patients who need to have oesophageal surgery for cancer.
Historically oesophagectomy was a high-risk procedure with a 10% (1 in 10) chance of death in hospital after surgery. In the UK this risk has fallen dramatically, to less than 2% (1 in 50), and continues to improve.

One of the ways this has been achieved is through the implementation of Enhanced recovery.

Enhanced Recovery

Enhanced recovery is a pathway that the specialist team and the patient follow together.

Before the operation patients, their families and carers are taught about the surgery and what to expect. They are also told what will be expected of them and what steps they can take before and after surgery to improve and optimise their recovery. Usually this involves increasing their activity levels before the operation (like an athlete training for a big race) and starting to walk again as soon as possible after the operation. Patients are given dietary advice and drink high calorie liquids on the day of surgery.

During the operation the surgical team and the anaesthetist work together taking steps to minimise the impact of the surgery and to make sure that pain is well controlled.

After the operation there will be many drains, catheters and tubes attached to the patient that will be removed as soon as possible by the medical team. Patients will start to drink as soon as it is safe to do so and will start a puree diet soon afterwards with guidance from the dieticians. Patients will be given a mobility goal for each day and help from specialist nurses and physiotherapists to achieve that goal.

Although enhanced recovery and similar projects are continue to improve the experience of cancer sufferers oesophagectomy remains a major procedure and the consequences may continue to affect the lives of patients long after they have left the hospital. Patients must learn a new way of eating meals in order to avoid problems such as malnutrition. Complications do occur and it can take many weeks, months and sometimes years to recover.
Future Developments

Despite improving outcomes oesophageal cancer still carries a dismal prognosis. Heartburn Cancer UK has identified oesophageal cancer as a cancer of unmet need and a research priority. We are supported in this view by Cancer Research UK and others.

In July 2017 a group of charities launched the Less Survivable Cancers Taskforce, a collaboration designed to highlight the need for further research and funding for the six deadliest cancers including oesophageal cancer.

Immunotherapy

One of the reasons cancer is so hard to treat is that the body struggles to recognise cancer cells and kill them. Immunotherapy is a relatively new approach to treating cancer. Medication is designed to improve the body’s own ability to find and kill cancer cells.

Cancer cells can often have high numbers of the same molecule on their surface. Immunotherapy drugs called monoclonal antibodies can bind to these molecules and allow the body’s immune system to recognise them as cancer. Several immunotherapy drugs are being trialled in oesophageal cancer.

Unfortunately not all immunotherapies work for all cancers. Researchers are developing tests that will enable doctors to know which drugs will help destroy which tumours.

In the past, studies have treated all oesophageal cancer as though it is one disease. It is, however, becoming increasingly clear that oesophageal cancer is far more complex than that. Some small groups of patients do much better than other groups using standard therapy.

The next generation of clinical trials will involve stratification of patients according to the molecular features of their tumours and their predicted response to therapy.

Immunotherapy is likely to transform the way we think about oesophageal cancer. The increase in survival and reduction in side effects means there is a great deal of optimism and hope for patients, relatives, carers and those involved in treating oesophageal cancer. Research funded and supported by charities such as Heartburn Cancer UK are developing a new wave of intelligent, precision-guided treatments in the fight against cancer.
Help us by donating now!

HCUK relies on public support to do their vital work.

Donating to HCUK is easy.

You can donate:

• on-line through justgiving.com and virgin money,
• by cheque made payable to: Heartburn Cancer UK
• through a payroll giving scheme,
• with regular standing orders,
• as part of your legacy,
• or every time you shop online.

If you are a current UK taxpayer we would encourage you to complete a gift aid declaration which allows us to reclaim the tax so a donation of £10 is worth £12.50 to us.

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