Ministry of Defence

Synopsis of Causation

Cancer of the Oesophagus

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

1.1. **Carcinoma of the oesophagus** is a cancer that arises in the mucosa of the oesophagus and then invades the submucosa, the muscular layer and then the surrounding structures. It may penetrate into the trachea or bronchial tree and/or involve the recurrent laryngeal nerve or the aorta.

1.2. There are two histological types - squamous cell carcinoma and adenocarcinoma. Tumours in the middle and upper third of the oesophagus are almost invariably squamous cell carcinoma. Although adenocarcinoma is usually confined to the lower third of the oesophagus, only about half of the tumours at this level are adenocarcinoma, the remainder being of the squamous cell type. Carcinoma may arise within Barrett's oesophagus (See 3.4.7 below) or may spread from a malignancy of the fundus of the stomach.

1.3. Staging of the cancer is important to determine prognosis and the most appropriate management. Staging can be by simple numerical staging or by the TNM system (tumour, node, metastasis), which has been validated as an indicator of prognosis.[1]

1.4. Numerical staging starts with stage 0 or *carcinoma in situ*. This is rarely detected, since there are no symptoms to prompt investigation, but it may be found in a biopsy of Barrett's oesophagus (See 3.4.7 below).

- Stage 1 is confined to the mucosa and submucosa. It is equivalent to T1,N0,M0 (see 1.5 below)
- In stage 2a there is penetration into the muscular layer but no lymph node involvement. In stage 2b there is involvement of regional lymph nodes
- Stage 3 includes spread to regional nodes and adjacent tissues
- Stage 4 is where there is distant spread

1.5. In the TNM system, the letter T indicates the size and penetration of the tumour.

- T1 is confined to the mucosa and submucosa. T2 penetrates the muscularis. T3 denotes that the tumour has penetrated the outer wall of the oesophagus and in T4 it directly infiltrates other organs such as the liver, lungs or stomach

- N0 signifies no lymph node involvement. N1 denotes up to 6 affected regional lymph nodes. N2 indicates that 7 to 15 regional nodes are affected and in N3, 16 or more nodes are involved

- M0 indicates that there is no metastasis. M1 denotes metastatic spread. Recently there has been a further subdivision: M1a means that in carcinoma of the lowest third of the oesophagus there is involvement of the local or coeliac lymph nodes, and in M1b there is involvement of any other nodes. In the middle third this classification is not applicable. In the highest third M1a is involvement of the local and cervical nodes. M1b is any other involvement

2. Clinical features

2.1. **Incidence** The incidence of carcinoma of the oesophagus varies markedly throughout the world. In China it is the commonest cause of death from cancer and it is also very common in Southern Russia, Northern Iran and the Transkei region of South Africa. In the UK it accounts for 1-2% of cancer deaths and has an incidence of about 10 per 100,000 population per year.

2.2. In Western societies squamous cell carcinoma used to represent about 90% of cases but this proportion is falling both relatively and in absolute terms as adenocarcinoma has become more common over the last 20 years.[2] In the UK, adenocarcinoma now accounts for half of all new cases of cancer of the oesophagus and this pattern is typical of developed countries. Worldwide, the squamous cell variety accounts for 95% of cases.

2.3. Over the last 20 years the incidence of adenocarcinoma has risen more than threefold in the UK. This is a trend in most Western societies but the figures for adenocarcinoma in the UK are the highest of those available. It presents most often in the 6th and 7th decades, and there is a male preponderance of about 2:1 for squamous cell carcinoma and around 7:1 for adenocarcinoma.

2.4. Oesophageal cancers often present late in the progress of the disease because approximately 75% of the circumference of the oesophagus must be involved before symptoms of food sticking are experienced. As a result, approximately half of patients who present with developing symptoms will already have a tumour which cannot be removed surgically or has resulted in distant metastases.

2.5. The classical presenting feature is progressive dysphagia. Initially there is only a problem with substances like meat but as the disease progresses more foodstuffs cause difficulty with swallowing until even sloppy food like porridge does not pass easily.

2.6. Heartburn, chest pain, dysphagia and weight loss are all other possible presenting features. A less common feature is persistent cough and wheeze due to aspiration of food and acid or sometimes perforation into the bronchial tree.

2.7. Other rarer presentations include hoarseness, intractable hiccoughs and enlarged lymph nodes. Features such as progressive dysphagia and weight loss require urgent investigation.[3]

2.8. Investigation is by barium swallow X-ray followed by endoscopy and biopsy. Barium swallow precedes endoscopy to obtain as much information as possible about the tumour because it is very easily perforated with an endoscope. Endoscopic ultrasound examination together with fine needle aspiration biopsy is used for staging.[4]

2.9. Surgery requires a clearance of at least 10cm to avoid submucosal spread. A total gastrectomy via a thoraco-abdominal approach is used for adenocarcinoma. For squamous cell carcinoma the options are a 2 stage subtotal oesophagectomy (Ivor Lewis), a subtotal 3 stage oesophagectomy (McKeown) or a trans-hiatal oesophagectomy. There is dispute about the value of block dissection of lymph nodes.[5]

2.10. Squamous cell carcinoma is radiosensitive and radiotherapy offers an alternative to surgery. adenocarcinoma is not radiosensitive and surgery is the mainstay of treatment.

3. Aetiology

3.1. The aetiology of oesophageal cancer is poorly understood, but is probably multifactorial. A wide variety of agents have been implicated in both causation and protection including dietary, constitutional and genetic factors, some specific disorders and medications.

3.2. Factors that affect the risk of carcinoma of the oesophagus can be divided into three main categories:

- Genetic influences
- Predisposing conditions
- External factors – diet, toxins, other exposures

3.3. **Genetic factors** The risk of adenocarcinoma may have a genetic component, and this may be helpful in deciding who to screen and in defining modes of progression of the disease.[6] OMIM (Online Mendelian Inheritance in Man – a database of human genes and genetic disorders maintained by the Johns Hopkins Hospital) lists a number of other conditions associated with oesophageal cancer, and so a family history may be relevant. Further implications with regard to screening those deemed to be at risk have not been ascertained.

3.4. **Predisposing conditions** A number of constitutional conditions have been linked to cancer of the oesophagus. These include obesity, achalasia of the cardia, coeliac disease and tylosis.

3.4.1. **Obesity** is associated with an increased risk of gastro-oesophageal reflux and associated disease like oesophagitis but a possible link with Barrett's oesophagus (see 3.4.6 below) has not been explored. The risk of all these diseases, including cancer, rises with increasing obesity.[7] Although the link between obesity and cancer of the oesophagus is very strong, it is unlikely to be a completely independent risk factor in that people who are obese probably have a diet that is high in fat and low in fresh fruit, vegetables and fibre, and consumption of alcohol may also be high. They are in addition more likely to suffer from gastro-oesophageal reflux disease.

3.4.2. **Achalasia of the cardia** has been identified as a risk factor.[8] In achalasia there is a disorder of innervation of the lower oesophagus so that food does not pass freely and this causes stasis with dilatation, often gross, of the oesophagus behind it. The risk of cancer in achalasia is probably related to this stasis and thus increased exposure to carcinogens.[9]

3.4.3. **Coeliac disease** is an allergic reaction to gluten in food that produces atrophy of the small intestinal villi and malabsorption. Avoiding gluten in the diet reverses the process but failure to comply fully with this is associated with the risk of developing malignancies of the upper gastrointestinal tract. Most, but not all, are lymphomatous in type. Some are adenocarcinoma. It has been suggested that the increased risk of carcinoma of the oesophagus is related to failure of absorption of vitamin A.[10]

3.4.4. **Tylosis** is part of a set of conditions of which one is a hereditary form with hyperkeratosis of the palms and soles. It appears to be inherited as an autosomal dominant and there is a lifetime risk of carcinoma of the oesophagus of 45%. The

abnormal gene has been mapped to 17q25.

3.4.5. **The Plummer-Vinson syndrome**, also known as the **Paterson-Brown-Kelly syndrome** is due to iron deficiency, and is associated with a post-cricoid web of tissue and possible malignant change. It is typically a disease of middle-aged women. In Northern Sweden, where the incidence in women has historically been very high, prevention of iron deficiency has almost eradicated the condition, along with post-cricoid carcinoma.[11] Any existing histological changes are fully reversed by iron therapy provided that malignant change has not yet occurred.[12] The associated carcinoma of the oesophagus is squamous cell in type.

3.4.6. **Barrett's oesophagus** Adenocarcinoma tends to occur in pre-existing Barrett's oesophagus, first described in 1950. Barrett's oesophagus is found in about 1% of the older population, the incidence rising with age, and in 3 to 5% of those with gastro-oesophageal reflux.[13] It is rare in people of African ancestry. The normal columnar lined lower oesophagus undergoes metaplasia. This change occurs in response to acid reflux, but reflux of bile would also seem to be important. There is a risk of change to dysplasia or adenocarcinoma at the rate of 1% per year. Barrett's oesophagus increases the risk of cancer 30-fold. Acid suppression along with muscular stimulant drugs to reduce reflux of bile can reverse the condition. There is, however, doubt about whether this prevents malignant change.[14] The incidence of adenocarcinoma continues to climb despite effective acid suppression, even by powerful modern agents such as proton pump inhibitors (PPIs). There is evidence that the more severe and the more prolonged the symptoms of acid reflux, the greater the risk of subsequent malignancy.[15]

3.5. **External factors** A number of dietary factors are thought to predispose to cancer of the oesophagus. Smoking and alcohol ingestion probably have an important aetiological role. Associations have been demonstrated with low intake of fruit, vegetables, and cereal fibres, and deficiencies of molybdenum, zinc and of vitamins A, C or E. Nitrosamines and aflatoxins have also been implicated as causative agents. Radiation may also have a role.

3.5.1. **Smoking and alcohol** The main established risk factors for squamous cell carcinoma of the oesophagus appear to be high consumption of tobacco and alcohol.[16] The World Health Organisation (WHO) estimates that in developed countries around 75% of cancers of the oral cavity, pharynx and oesophagus are caused by tobacco and alcohol. The risk of cancers of various tissues seems to be related to the level of consumption of tobacco, being higher in those who smoke more. There is no appreciable difference between the risk for men and women and reviews suggest that there is no threshold below which smoking can be deemed safe.[17] In adenocarcinoma there still appears to be a link with alcohol consumption and smoking in both men and women although it is not as strong as for squamous cell carcinoma.[18]

3.5.2. **Low intake of fruit, vegetables and cereal fibre** may be important. There is evidence that greater intake of dietary fibre, certain carotenoids and vitamins may decrease the risk of adenocarcinoma, whereas greater intake of saturated fat may increase the risk of adenocarcinoma and distal stomach cancer.[19] A diet high in fibre and vitamin C is usually low in fat. The protective effect of vitamins A, C and E may be due to their reducing powers helping to prevent the effects of nitrosamines. The role of dietary fat may be to retard gastric emptying and thus encourage gastro-oesophageal reflux (see 3.5.3).

3.5.3. **High intake of fat** has been identified as a risk factor in a number of studies. One from France identified high consumption of butter as accounting for about one third of the excess number of cases. It estimated that the combination of high fat in the diet and drinking hot Calvados (a local liquor) accounted for 57% of the excess incidence.[20] The consumption of hot beverages has been identified in other studies as a risk factor for this disease.[21]

3.5.4. **Molybdenum deficiency** has been suggested as being relevant to the disease. Molybdenum is a trace element, only required in minute amounts, but dietary deficiency can occur. There is a small amount of evidence relating molybdenum to cancer of oesophagus. A study in which tumours were induced in rats by the addition of nitrosamines to their diet showed some protection by molybdenum and riboflavin.[22] However in one trial in China, where the incidence of carcinoma of oesophagus is extremely high, the addition to the diet of molybdenum and other supplements failed to produce any significant difference in outcome with regard to oesophageal cancer.[23]

3.5.5. **Vitamin A, C, E, and zinc deficiencies.** The role these vitamins in the causation of cancer of the oesophagus is as yet poorly defined. The evidence suggests that the reducing power of these vitamins C and E may be important in protecting against the potential carcinogenic effects of nitrosamines. Both these vitamins seem to give protection against both squamous cell carcinoma and adenocarcinoma in men.[24] It has been more difficult to ascertain the relationship in women in whom oesophageal carcinoma is less common. Vitamin A appears to have a general protective effect against carcinogens in animals and there is some evidence that deficiency of zinc and vitamin A may play a part in the aetiology of carcinoma of the oesophagus in humans.[25]

3.5.6. **Nitrosamines** are a class of chemicals that are formed from amines and nitrate. Amines and nitrosating agents occur together, and the chemical reaction to produce nitrosamines follows. About 300 of these chemicals have been tested and around 90% have been shown to be carcinogenic in animal experimental models.

- Nitrosamines occur in tobacco and in cured meat, of which bacon has been most extensively studied. The high temperature involved in cooking bacon facilitates the chemical reaction but it can be impeded by the reducing agents ascorbic acid (vitamin C) and alpha-tocopherol (vitamin E). An isomer of ascorbic acid (erythorbic) acid is often added to such food and it is equally effective at retarding nitrosamine production

- Nitrosamines used to be found in beer from the drying process of malt, but refinement of the process has reduced the nitrosamine content to about 2% of the level of 20 years ago. Nitrosamines can also form in the stomach from the reaction of gastric acid and bacteria. A diet rich in vitamin C will impede this process

- A report from the American National Academy of Sciences in 1981 estimated that the average daily consumption of nitrosamines was approximately 1 microgram per person, mostly from beer and bacon. This has probably fallen to around 0.1 microgram currently, but cigarette smokers average 17 micrograms daily and workers in rubber and chemical industries have a high exposure

- The precise relationship between nitrosamines in food and drink and carcinoma

of the oesophagus in humans is difficult to define, but experimental studies in rats have shown a very strong causal relationship between diethylnitrosamine and carcinoma of the oesophagus[26]

3.5.7. **Aflatoxins** are produced by the organisms *Aspergillus flavus* and *Aspergillus parasiticus*. *Aspergillus* spp. are common and widespread in nature and are most often found when crops are exposed to a high humidity over a long period of time or are damaged in drought conditions. Crops which are frequently affected include cereals such as maize, rice and wheat, oilseeds including peanut, soybean and sunflower, spices including chilli peppers, black pepper, coriander and turmeric and tree nuts including almond, pistachio, walnut and coconut. Aflatoxins are most noted for their association with carcinoma of the liver but although it has been suggested that there may be some relationship with carcinoma of oesophagus there is little or no evidence for any link.

3.5.8. **Participation in the UK atmospheric tests** has not been shown to produce any excess mortality from carcinoma of the oesophagus.[27]

3.5.9. **Radiotherapy** following mastectomy for breast cancer results in an increased incidence of squamous carcinoma in the upper and middle thirds of the oesophagus beginning five years after the radiotherapy.[28] This was found in a study examining data derived between 1973 and 2000, with relatively high doses of therapeutic irradiation and less focussed targeting than is currently used. There is no evidence that exposure to ionising radiation in the natural environment or at work (with normal precautions) is a risk factor.

3.5.10. There is no evidence linking exposure to **electromagnetic radiation** or **lasers** with carcinoma of the oesophagus.

3.5.11. Reduced exposure to **UV-B irradiation** from sunlight has been shown to increase the incidence of oesophageal cancer in several epidemiological studies.[29]

3.6. **Therapeutic drugs** Medications which relax the lower oesophageal sphincter might contribute to the risk by encouraging reflux of gastric contents. Such agents include nitroglycerine, anticholinergics, beta-adrenergic agonists, theophyllines, and benzodiazepines. This may account for approximately 10% of all cases.[30]

3.7. **Factors which appear to reduce the risk of oesophageal cancer** include infection with *Helicobacter pylori* and anti-inflammatory agents.

3.7.1. The picture is rather complicated. It seems that whilst infection with *H. pylori* is associated with an increased risk of gastric cancer in as well as to peptic ulceration, it has a protective effect against carcinoma of oesophagus and the gastric cardia.[31]

3.7.2. Anti-inflammatory analgesics may have a protective effect. There is evidence that cyclooxygenase-2 (COX-2) inhibits tumour formation in the entire upper digestive and respiratory tracts.[32] This is supported by the finding that carcinoma of oesophagus appears to be less common in those who use regular non-steroidal anti-inflammatory agents (NSAIDs) or the more specific COX-2 inhibitors.

4. Prognosis

4.1. The disease tends to present late, and only 40% of tumours are operable. The operative mortality is now under 10%, but only 40% of patients survive one year after surgery. The prognosis for oesophageal carcinoma varies depending on the stage at presentation. The overall 5 year survival rate for resectable tumours ranges from 10 to 25%. 5 year survival rates for stage 1 oesophageal cancer range from 80 to 94% but for stage 3 it is 10 to 14%.[33] These figures demonstrate that comparatively few patients present at an early stage.

4.2. The value of **preoperative chemotherapy** has been disputed.[34]

4.3. As many cases are not amenable to **curative surgery** and even those that are have a high rate of recurrence, **palliative surgery** is commonly employed. Oesophageal intubation is often required to permit food and drink to pass and to swallow saliva. Tubes are usually placed under endoscopic or radiological control. Risks include oesophageal perforation, tube displacement or blockage. Expanding stents provide cost-effective palliation.[35]

4.4. **Laser therapy** produces good palliation in about 60% of cases but it may need to be repeated every 4 to 6 weeks, and perforation occurs in about 5%.[36] External beam radiotherapy, brachytherapy, diathermy and alcohol injection are also used.

4.5. **Barrett's oesophagus** is often asymptomatic, and a frequent incidental finding at endoscopy. The significance of a short segment of less than 3cms is unclear. If it is recognised at endoscopy, most patients are started on life-long acid suppression, although there is little evidence that this causes regression of metaplasia. Recent interest has been shown in endoscopic mucosal ablation with photosensitisers and laser treatment. The role of endoscopic surveillance is controversial. The aim is to detect dysplasia before progression to carcinoma. An unexpected focus of adenocarcinoma is often found in biopsy specimens taken at endoscopy,[37] and oesophagectomy for dysplasia has a 5 year survival rate of 80%. Endoscopic treatment with photodynamic therapy, laser treatment, and endoscopic mucosal resection may offer a more acceptable mode of treatment that reduces the risk of malignant change.[38]

4.6. In one study,[39] very intensive treatment of non-neoplastic Barrett's oesophagus with **complete acid suppression**, laser treatment, and intensive endoscopic follow-up produced a recurrence rate of 3% with no malignant change.

4.7. Despite recent advances in diagnosis and treatment the outcome of oesophageal cancer remains very poor.[40]

5. Summary

5.1. There are two histological types of carcinoma of the oesophagus. About half of those in the lowest third are adenocarcinoma and the remainder at all levels are squamous cell carcinoma.

5.2. The incidence of carcinoma of the oesophagus varies considerably throughout the world. Overall, squamous cell carcinoma accounts for about 95%, but in the UK adenocarcinoma now accounts for 50%.

5.3. In Western societies, the incidence of squamous cell carcinoma is falling but the incidence of adenocarcinoma is rising rapidly, especially in white males, and there is no adequate explanation for this. One possibility is that increasing obesity is associated with more gastro-oesophageal reflux disease.

5.4. The median age of presentation is 60 and there is a male preponderance.

5.5. The clinical presentation of carcinoma of the oesophagus is usually due to obstruction, and as it has to be about 75% obstructed to cause symptoms, the disease is often advanced by the time it presents.

5.6. The risk of squamous cell carcinoma is increased by tobacco and alcohol consumption, but in regions of very high incidence there are often toxins implicated. Nitrosamines are probably the most important and these are found in food and drink as well as in tobacco. A diet high in fat and low in vitamins A,C and E as well as zinc increases risk. There is also an association with previous radiotherapy for breast cancer, and with reduced exposure to solar UV-B.

5.7. For adenocarcinoma, the association with smoking is much less and that with alcohol is possibly non-existent. Most adenocarcinoma is thought to arise within the metaplasia of Barrett's disease of the oesophagus. Acid suppression does not appear to reduce the risk of malignant change, although an aggressive regime of laser coagulation of abnormal mucosa along with an exceptionally high dose of a PPI may be of value. The possible protective effect of NSAIDs or COX-2 inhibitors is being investigated.

5.8. The rate of malignant change in Barrett's oesophagus is only about 1% per annum, but endoscopic surveillance is regarded as an effective intervention since the prognosis of the clinical disease is so poor. Unsuspected foci of malignancy within metaplasic areas are common.

5.9. Only about 40% of cases of oesophageal cancer are amenable to curative surgery, and most of those who undergo such surgery will be dead within a year.

5.10. The 5 years survival rate for stage 1 tumours is 80 to 94% whilst for stage 3 the figures are 10 to 14%. The overall figures for resectable tumours are 10 to 25%. It is a cancer with a poor prognosis, not least because it tends to be fairly advanced at presentation. An overall 5 year survival of 10% gives it one of the worst prognoses of all cancers.[41]

5.11. A number of palliative procedures are available, such as the insertion of stents to allow the passage of food and saliva through the oesophagus. Squamous cell carcinoma is radiosensitive and radiotherapy may be a very acceptable alternative. Adenocarcinoma does not respond to this form of treatment.

6. Related Synopses

Cancer of the stomach

7. Glossary

ablation	Removal or destruction of tissue.
achalasia	A rare disorder of the oesophagus where the muscle at the lower end of the oesophagus does not relax enough for the passage to open properly.
adenocarcinoma	Cancer that begins in cells that line certain internal organs and that have glandular (secretory) properties.
aspiration	Inhalation or spill-over into the respiratory tract.
atrophy	Wasting of tissues.
biopsy	Removal of tissue for laboratory analysis.
block dissection	Surgical removal of all lymph glands from a region of the body.
brachytherapy	Internal radiation therapy using an implant of radioactive material placed directly into or near the tumour.
cardia	Upper part of the stomach, adjacent to the oesophagus.
columnar	Refers to a shape of cells which often line ducts or glands within the body.
cricoid	A solid ring of cartilage located below and behind the thyroid cartilage.
diathermy	The use of heat to destroy abnormal cells. Also called cauterisation.
dysphagia	Difficulty in swallowing.
dysplasia	Abnormal development or growth of cells and tissues; precancerous tissue changes.
endoscopy	The use of an endoscope, a flexible, lighted tube, for examining body cavities.
epithelium	A specialized type of tissue that normally lines the surfaces and cavities of the body.
fundus	The part of a hollow organ that is farthest away from the organ's opening.

gastrectomy	Surgical removal of the stomach.
histology	Study of the microscopic structure of tissues.
hyperkeratosis	A skin condition characterised by thickening and hardening of the skin.
metaplasia	A change of cells to a form that does not normally occur in the tissue in which it is found.
metastasis	The spread of cancer from one part of the body to another.
mucosa	A mucous membrane lining a hollow organ or body cavity, such as the gastrointestinal tract.
muscularis	The muscular layer surrounding a hollow organ.
neoplastic	Abnormal and uncontrolled cell growth.
oesophagectomy	Surgical removal of the oesophagus.
photosensitiser	An agent that enhances a tumour's sensitivity to light.
radiosensitive	Of a tumour which responds to radiotherapy.
reflux	Backward flow.
resection	Surgical removal.
sphincter	A ringlike band of muscle that constricts a passage or closes a natural orifice.
squamous	Thin flat cells with an irregular shape.
stent	A device implanted in a hollow organ used to help keep it open.
submucosa	The layer deep to the mucosa.
thoraco-abdominal	Through the chest and abdomen.
trans-hiatal	Through the gap in the diaphragm.
tylosis	A genetic disorder characterized by thickening (hyperkeratosis) of the palms and soles, and a high risk of developing oesophageal cancer.

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