

# Gross anatomy and physiology of the oesophagus biology essay

[Science](#), [Biology](#)



## **Introduction**

Oesophageal carcinoma is the eighth most common cancer worldwide with more than 480, 000 new cases annually, and it poses the sixth most common cause of death from cancer, resulting in more than 400, 000 deaths per year (Fiorica et al., 2004). The two major histopathological types are squamous cell carcinoma (SCC) and adenocarcinoma (AC). Incidence rates of oesophageal cancer vary widely internationally, with 80% of all cases occurring in developing countries, particularly the Western Pacific Region and China. However, in developed countries, incidence rates particularly for men have also shown a steady rise over the past two decades, with a projected 24% increase for the period from 2013 to 2017 (Scottish Government, 2010). Advances in the diagnosis and staging of this neoplastic condition have led to small improvements in survival, yet prognosis of patients with either type of oesophageal carcinoma remains very poor and five-year survival rates range around 15 - 34% (Bagheri et al., 2012), depending upon extent of spread at diagnosis as well as type of treatment received. Traditionally, surgical resection of localised oesophageal cancer has been considered the best treatment regimen (Ancona et al., 2001). Unfortunately however, patients treated with surgical techniques alone have a low cure rate regardless of surgical approach or histology of the malignancy and even with a complete resection, loco-regional recurrences and metastatic spread are common. Additionally, perioperative morbidity and mortality mean that the median survival ranges from only 13 - 19 months (Enzinger and Mayer, 2003). Given the disappointing results of surgery only, a multidisciplinary approach including surgery, radiotherapy

and chemotherapy, as well as strategies that combine these three treatment approaches, such as neoadjuvant therapy, have been investigated extensively in order to enhance local control and improve survival among patients. Despite numerous randomised and non-randomised studies and meta-analyses investigating the effectiveness of especially neoadjuvant chemoradiotherapy (NCRT) over the past decade, not all surgeons are convinced of the benefit of this type of adjunctive treatment for oesophageal cancer. In light of the need to define optimum therapeutic strategies for patients suffering from oesophageal carcinoma, this dissertation addresses the following question: what is the role of neoadjuvant chemoradiotherapy in the treatment of squamous cell carcinoma of the oesophagus? The way in which this project intends to answer this question is by analysing the most current clinical trials which are assessing the efficacy and contraindications of NCRT, particularly in squamous cell carcinoma of the oesophagus, to see whether a significant and lasting effect of this type of treatment regimen can be established. Systematic reviews and meta-analyses will also be employed to help analyse the efficiency of the trial designs and provide a grounding for the analysis presented in this dissertation.

## **Background Knowledge**

### **Gross Anatomy and Physiology of the Oesophagus**

The adult human oesophagus is a hollow, muscular tube that forms a conduit for the transport of food from the oral cavity to the stomach, where digestion and absorption takes place. It measures approximately 18 - 26 cm from the upper to the lower physiological sphincter. The oesophagus appears airless

and collapsed at rest, but during swallowing, a food bolus expands its anterior-posterior dimension to approximately 2 cm and its lateral dimension to 3 cm. Food and fluid normally only remain in the oesophagus for a few seconds and reflux is prevented by the sphincter at the gastro-oesophageal junction, acting as a high-pressure zone. Topographically, the oesophagus comprises of three distinct regions (Kuo and Urma, 2006):

### **Cervical Oesophagus**

This cervical part begins in the neck just at the inferior border of the cricoid cartilage at the pharyngo-oesophageal junction between the 5th and 6th cervical vertebral interspace. It then extends about 4 to 5cm down to the suprasternal notch, where it is bordered anteriorly by the trachea, posteriorly by the vertebral column and laterally by the carotid sheaths and the thyroid gland. The oesophageal musculature in this upper third section is comprised of the striated skeletal muscle type and innervated by the vagus nerve with nuclei located within the central medullary swallowing centre.

### **Thoracic Oesophagus**

The thoracic segment extends from the suprasternal notch at the level of T2 and T3 in the superior mediastinum to the diaphragmatic hiatus at the level of the 10th thoracic vertebra (T10) in the posterior mediastinum. On its path, it gradually inclines to the left of the median plane before it returns to the midline in the thorax at the level of T5. At the level of T4, the oesophagus passes posterior and to the right of the aortic arch, but from the level of T8 forward to the diaphragmatic hiatus, it lies anteriorly to the aorta. Other structures it passes are the trachea, the tracheal bifurcation and the left

main stem bronchus. The oesophageal musculature in this middle third section is comprised of a mixture between striated and smooth muscle and innervated by the vagus nerve with nuclei located within the central medullary swallowing centre.

## **Abdominal Oesophagus**

The abdominal oesophagus extends from the diaphragmatic hiatus to cardiac region of the stomach (T11), sitting in the oesophageal groove on the posterior surface of the left lobe of the liver. A 1 cm long, truncated cone forms the area of smooth transition from the base of the oesophagus into the cardiac orifice. The oesophageal musculature in this middle third section is comprised solely of the smooth muscle type and innervated by the vagus nerve with nuclei located within the central medullary swallowing centre. The nature of these regions is of particular interest for the examination and staging of the oesophagus, as oesophageal squamous cell carcinomas (OSCC) and adenocarcinomas cannot be readily distinguished radiographically or endoscopically. OSCC is predominantly located in the thoracic and abdominal oesophagus and only 10 - 15% is situated in the cervical part (Hamilton and Aaltonen, 2000, p. 12). The structure of the oesophageal wall is composed of four layers, from innermost to outermost:

### **Mucosa**

This innermost lining is made up of three components: the stratified squamous epithelium, a supporting lamina propria and the muscularis mucosae, a thin layer of smooth muscle which produces local movement and mucosal folding. The mucosa undergoes abrupt transition known as the Z-

line from a paler pink oesophageal mucosa to a darker gastric mucosa at the gastro-oesophageal junction. As the oesophagus represents a conduit for all external substances entering the digestive tract, any food stuff including potentially harmful liquids such as alcohol and hot beverages may pass the epithelial lining of the mucosa and act as chronic local tissue irritators, ultimately resulting in abnormal tissue growth.

### **Submucosa**

This layer of loose collagenous supporting tissue provides support to the mucosa and contains larger blood vessels, lymphatics and a network of nerves, representing parasympathetic innervation of glands and muscle fibres through the vagus nerve (Izbicki et al., 2009, p. 5). It is the submucosa that, with its many elastic fibres, allows for the considerable distension during passage of a food bolus. Particularly in the upper and lower thirds of the oesophagus, the submucosa also contains small sero-mucous glands which aid lubrication (Young, 2006, p. 267).

### **Muscularis Propria**

This thick layer of muscle fibres is arranged as an internal circular and an external longitudinal layer. The action of the two layers arranged at right angles to one another is the basis of peristaltic contraction. The relatively helical direction of the muscular layer together with the longitudinal course of the lymphatic vessels in the submucosal layer might possibly explain the spreading of carcinoma cells over a long distance before entering the regional lymph nodes both superiorly and inferiorly (Izbicki et al., p. 10). The muscle fibres in the cervical oesophagus are exclusively striated and red in

colour, since this part is under voluntary control to allow for swallowing action. The thoracic part consists predominantly of striated muscle fibres with intermingled smooth muscle fibres, making this the transition zone (Kuo and Urma, 2006). The abdominal segment is mainly made up of smooth muscle fibres. The oesophagus and the left pleura are connected to the root of the left bronchus and the posterior of the pericardium by further accessory muscle bands. This structural proximity may have implications for trans-coelomic tumour spread.

### **Tunica Adventitia**

The oesophagus is connected to the surrounding tissues by the tunica adventitia, which represents a loose supporting tissue investment conducting major vessels, nerves and variable adipose tissue. This outer layer of connective tissue permits some degree of movement.

### **Blood Supply**

The arterial blood supply to the oesophagus is arranged in a segmental fashion due to the length of the structure and the following arteries end in a dense network in the submucosa called the Heller plexus (Kuo and Urma, 2006), providing an extensive anastomotic framework: Inferior thyroid artery: supplies the upper oesophageal sphincter and the cervical part Paired oesophageal arteries of the thoracic aorta: supply the thoracic oesophagus Left gastric artery of the coeliac artery and a branch of the left phrenic artery: supply the lower oesophageal sphincter and the abdominal segment of the oesophagus The segmental venous supply arises from the dense submucosal plexus and drains into the superior vena cava. The veins

of the cervical and abdominal oesophagus drain into the azygous vein, whereas the thoracic oesophageal drainage is into collaterals of the left gastric vein, a branch of the portal vein. Oesophageal cancers typically spread by direct extension or via lymphatics. However, haematogenous spread is also common in advanced disease and these metastases are usually found in lungs and liver.

## **Lymphatics**

Lymphatic drainage of the oesophagus begins in a network of endothelial lymph channels in the oesophageal tissue spaces that continue parallel to the long axis through the oesophageal muscular coat. Electron microscopic studies show anastomotic lymph capillaries to originate in the lower mucosal levels and small lymphatic vessel in the submucosa (Kuo and Urma, 2006), implicating the direction and extent of spread of cancer cells. The direction of lymph flow is governed by paired semilunar valves within the collecting channels, which progress to merge into small trunks that open into the regional lymph nodes. The lymphatic drainage is arranged segmentally, with the cervical part draining into the deep cervical lymph nodes and subsequently into the thoracic duct. The lymphatics from the thoracic part of the oesophagus drain into the superior and posterior mediastinal nodes, whereas lymphatics of the distal third of the oesophagus follow the left gastric artery to the gastric and coeliac lymph nodes. Due to the numerous interconnections among these three drainage regions, a bidirectional lymph flow can be observed which is responsible for the spread of malignancies from the lower to the upper oesophagus. According to Isono et al. (, 1985),



40% of patients with oesophageal squamous cell carcinoma develop isolated cervical nodal metastases following oesophagectomy with curative intent. Therefore, lymphatic spread in oesophageal cancer is an important aspect when considering either neoadjuvant chemoradiotherapy or post-operative chemotherapy in order to optimise local control and ultimately clinical care. The following table taken from Izbicki et al. (2009, p. 85) shows the rate of involvement of lymph nodes for possible sides of primary tumours.

## **Oesophageal Squamous Cell Carcinoma Overview**

Oesophageal cancer is the eighth most common cancer worldwide with more than 480, 000 new cases diagnosed each year (Ferlay et al., 2010) and it carries a particularly poor prognosis unless detected at an early stage when surgical resection for cure may be successful. The average age of onset is between 50 – 60 years of age (Oxbridge Solutions Ltd., 2011). This type of upper gastro-intestinal neoplasm can be subdivided into epithelial tumours, metastatic tumours, lymphomas and sarcomas. Cancers of epithelial origin, predominantly squamous cell carcinomas and adenocarcinomas, are the most common histological types, with the latter possibly showing better long-term prognosis after resection than OSCC (Siewert et al., 2001).

Historically, the large majority of all oesophageal carcinomas were squamous, yet today the incidence of adenocarcinoma is rising rapidly and now accounts for 50% of all cases in the USA (Oxbridge Solutions Ltd., 2011). However, squamous cell carcinoma of the oesophagus still remains the most common neoplasm of the oesophagus and therefore presents an important health problem around the world. The vast majority of these types of cancer

develop from cells of the mucosal layer of the oesophagus, which undergoes structural changes from the proximal to the abdominal part. As the squamous epithelium is most commonly found in the upper and middle non-glandular parts of the oesophagus, this is the area where the majority of squamous cell carcinoma is found.

## **Epidemiology**

### **Incidence**

Oesophageal cancer incidence varies greatly worldwide, with the majority of cases being diagnosed in less developed, low income countries. The highest rates are found in Eastern Asia as well as Southern and Eastern Africa, where annual mortality is as high as 100 per 100, 000. Several well-defined high-risk areas can also be found in Calvados in North-West France, as well as in Northern Italy, where incidence is as high as 30 per 100, 000 population in males (Hamilton and Altonen, 2000, p. 11). By contrast, Northern, Middle and Western Africa exhibit particularly low incidence rates (see Table 2). The majority of diagnoses in these high-risk areas are of squamous cell carcinoma (Cancer Research UK, 2013). However, in most Western industrialized countries, there has been a slight decline in OSCC over the past three decades and a dramatic rise in adenocarcinoma of the distal oesophagus (Abeloff et al., 2008, p. 1400). Both major histological types are directly related to tobacco smoking, but only SCC to alcohol drinking, whilst AC risk is increased by obesity and lack of physical activity. Bosetti et al. (Bosetti et al., 2008) proposed that the increased prevalence of overweight and inactivity in North America and northern Europe has led to the increase

in oesophageal AC reported in recent periods. A high variation between male and female OSCC incidence rates can be seen worldwide, with UK ratios ranging around 2.6 : 1 for males to females (Ferlay et al., 2010). Further incidence variations have been reported in different populations within one and the same country. One example is the USA, where the incidence of OSCC is almost six times higher in black men than in white men, making it the fourth leading cause of death in African Americans (Vizcaino et al., 2002). UK trends show that overall rates for oesophageal cancer in men have increased over the past 30 years with an incidence of around 14 per 100 000, representing 2.2% of all malignant diseases (see Table 2). Both UK men and women show the highest reported incidence of oesophageal cancer in Central Europe, with oesophageal cancer incidence in females being fourteen times higher than the rates reported for Greek women (Ferlay et al., 2010).

## **Aetiology**

No single cause of SCC of the oesophagus can be established. However, current data strongly supports the hypothesis that epithelial tumours arise as a result of chronic tissue irritation from a wide variety of sources (Abeloff et al., 2008). Proven risk factors for OSCC include alcohol and tobacco abuse and the overall risk increase caused by alcohol consumption is thought to be up to 14-fold, with a latency of 15 - 20 years. The type of alcohol plays an important role, with 'hard liquor', i. e. spirits being more harmful than either beer or wine. Abstaining from alcohol for at least 10 years appears to return the risk of oesophageal cancer to the levels of non-drinkers (Castellsagué et al., 1999). Although the exact mechanism responsible for the increased risk

associated with alcohol consumption is not known, the following have all been discussed. (Boffetta and Hashibe, 2006; Holmes and Vaughan, 2007):

- Local action of carcinogens, e. g. nitrosamines, oils, polycyclic hydrocarbons
- Induction of nutritional deficiencies, e. g. riboflavin, nicotinic acid, zinc, etc.
- Decreased chemical detoxification and biotransformation as a result of liver injury

### **Impairment of the immune system**

The adverse effect of smoking is mainly dependent on the duration and dose of tobacco consumption and increases the overall risk by 5-fold (Oxbridge Solutions Ltd., 2011). A cumulative interaction between alcohol intake and tobacco use can further be seen, with an increased risk to nearly 20-fold upon combined exposure (Messmann, 2001). As cited by Messmann (2001), the risk of OSCC decreases by 50% after smoking cessation for 5 years and it has been proposed that the declining OSCC incidence has paralleled the general decline in smoking prevalence in developed countries (Brown and Devesa, 2002). Other implications for oesophageal cancer are as follows:

- Environmental exposure, e. g. lye ingestion; petroleum contaminated water (particularly in Saudi Arabia); molybdenum deficiency in soil (Nouri et al., 2008)
- Dietary deficiencies, e. g. of protein, fibre, folate, vitamin C, riboflavin and trace elements, which may all have a role in lower socio-economic groups (Abeloff et al., 2008, p. 1401)
- Diets high in saturated fat, cholesterol, refined cereals, starch and red processed meat (Oxbridge Solutions Ltd., 2011)
- Foods containing carcinogenic N-nitroso compounds, such as pickled vegetables (Talley et al., 2011, p. 376)
- Hot tea consumption is one of the

most common risk factors worldwide, e. g. Mate tea in South America, which cause thermal injury leading to chronic oesophagitis and then to precancerous lesions (De Stefani et al., 1990; Islami et al., 2009)Coeliac disease (Ribeiro Jr et al., 1996)Achalasia of the oesophagus (Hamilton and Aaltonen, 2000, p. 12)Carcinogenic nitrosamines, e. g. found in food from Northern China contaminated by *Fusarium* spp. mould, may initiate neoplasia (Messmann, 2001)Chronic mucosal irritation, e. g. by radiation therapy for the treatment of breast cancer (Hagendoorn et al., 2010)Infection, e. g. human papilloma virus (HPV, particularly prevalent in high-risk populations in China), Epstein Barr and *Helicobacter pylori* infection increase the risk of chronic inflammation leading to dysplasia (Holmes and Vaughan, 2007)Previous head and neck squamous cell cancer (Oxbridge Solutions Ltd., 2011)Plummer-Vinson syndrome is associated with iron deficiency, glossitis and dysphagia, the latter resulting from functional spasm of the oesophagus and cardia. According to Messmann (2001), 10% of mostly the female patients between the ages of 15 - 50 years develop oesophageal squamous cell carcinomaGenetic predisposition, e. g. tylosis, which is a rare autosomal dominant disorder involving palmer and plantar keratosis that is associated with multiple oesophageal papillomas. Risk et al. (Risk et al., 1994) have located the tylosis oesophageal cancer (TOC) gene locus to 17q25. The subsequent structural loss of the stratified squamous epithelium causes an alteration of the oesophageal integrity and thus makes it more susceptible to environmental mutagens (Montesano et al., 1998). Oesophageal carcinomas tend to arise in areas of partial narrowing, with 40% deriving from the pharyngo-oesophageal junction, 40% from the

junction between the upper and middle third and 20% from the oesophageal hiatus. They usually develop as a nodule which then commences either into a papilliferous mass (60%), an ulcer (25%) or an annular constriction extending variably around the wall of the oesophagus (Oxbridge Solutions Ltd., 2011). OSCC predominantly arises in the middle and lower third oesophagus with only 10 - 15% being situated in the upper third. AC usually arises in Barrett's oesophagus, a specialised columnar epithelium metaplasia in the lower third of the oesophagus. The molecular factors involved in the progression to squamous cell carcinoma are very complex and point mutations, increased copy number and promoter region hypermethylation all appear to play a role in the progression to malignancy. A mutated TP53 gene is involved in 35% - 80% of OSCC cases (Montesano et al., 1998). Other potential prognostic factors as cited by Hamilton and Altonen (2000, p. 19) include p53 protein accumulation in cancer cell nuclei, growth factors, oncogenes such as c-erbB-2 and int-2, cell cycle regulators, tumour suppressor genes, redox defence system components and matrix proteinases. Another important biomarker may be the HER-2/neu status, with rates of overexpression from 0 - 52% in patients suffering from OSCC. According to Aklilu and Ilson (Aklilu and Ilson, 2007), HER-2 overexpression has also been associated with resistance to chemotherapy, extra-mucosal invasion and a increased stage at presentation. As any of the above potential prognostic factors may enhance tumour cell proliferation, invasiveness and metastatic potential, these are important factors to be considered when attempting to prolong patient survival in the future.

## **Clinical Features**

Unfortunately, many oesophageal cancers do not generate symptoms until they reach an advanced stage when the disease has already progressed to infiltrate regional lymph nodes and form distant metastases. The most common initial physical sign of oesophageal cancer is dysphagia, which may be reported as having a progressive onset, initially only affecting solids and gradually also inhibiting swallowing of fluids (Kumar and Clark, 2009, p. 257). Often, patients may be able to precisely locate the level of obstruction, where a carcinoma of the lower third oesophagus for example will be described as a blockage behind the lower part of the sternum. Patients may feel prompted to slowly alter their diet to a more liquid basis, which may delay a timely medical self-referral and thus result in a non-resectable advanced tumour stage that may require neoadjuvant chemoradiation therapy before surgical resection for cure may be attempted. Other local features may include a hard, palpable supraclavicular node, regurgitation of food (due to narrowing of the oesophageal lumen by tumour growth), blood-stained vomit, aspiration pneumonia, retrosternal pain burning sensation that may radiate to the jaws and arms (Hamilton and Aaltonen, 2000, p. 12). General features of malignant disease may include weight loss due to reduced food intake, anorexia, anaemia and oedema, the latter due to a severe reduction in protein intake in later stages. Metastases often occur in the liver, resulting in jaundice.

## **Investigations**

The diagnostic process of oesophageal carcinoma involves a number of modalities and usually begins with the patient's history and examination.

### **Barium Swallow**

The first-line investigation after a history of dysphagia is most frequently a single contrast radiological technique of the oesophagus in form of a barium swallow, primarily used to assess functional and anatomical properties (Talley et al., 2011, p. 318). The patient swallows liquid barium in an upright position and radiographs are taken during the oesophageal phase of transit. The oesophagus can so be visualised lying in the retrocardiac space just in front of the vertebral column. Anteriorly, the normal oesophagus is indented from above downwards by the arch of the aorta, the left bronchus and the left atrium (Ellis, 2006, p. 43). Regurgitation of the gastric contents may subsequently be assessed by taking radiographs with the patient head down and dysphagia may be investigated by soaking bread in the barium suspension (Oxbridge Solutions Ltd., 2011). This type of contrast radiograph may reveal one of the three main oesophageal growth types (Hamilton and Aaltonen, 2000, p. 12): Scirrhus carcinoma with intramural growth and early stenosisUlcerated or medullary carcinoma with ulcerationExophytic, polypoid carcinoma with intraluminal growth and filling defect with irregular surface at the periphery

### **Endoscopy and Biopsy**

Endoscopy with tissue biopsy is the gold standard for the diagnosis of oesophageal cancer and it provides histological proof of the specific cancer



type, confirming 90% of oesophageal carcinomas. It can also be used to therapeutically dilate the oesophagus in order to improve nutrition before a definitive operative intervention (Oxbridge Solutions Ltd., 2011). Early stage superficial oesophageal cancer commonly exhibits only minor morphological changes, such as a slight mucosal elevation or shallow depression, compared to that of advanced cancer. These superficial carcinomas in situ are easily overlooked and cannot be clearly recognised by simple white-light endoscopy. However, as cited by Takubo, (Takubo, 2008, p. 152), mature squamous epithelial cells are rich in cytoplasmic glycogen granules. Lugol iodine spray solution used in chromo-endoscopy offers a convenient approach as it reacts specifically with the glycogen in the normal, non-keratinized squamous epithelium. By contrast, precancerous and cancerous lesions result in negative staining results, helping in the diagnosis of localised oesophageal cancer (see Picture 9). Other diagnostic modalities include cytology using a washing / abrasion technique (used for screening in China), CT scanning to determine mediastinal involvement and liver metastases, bronchoscopy to exclude bronchial involvement in upper and middle-third lesions and ultrasound used to identify secondary liver deposits (Oxbridge Solutions Ltd., 2011). Further, p63 (nuclear) and cytokeratin 5/6 are sensitive and specific immunohistochemistry markers of squamous differentiation and can be used for target antigen detection (Cheng and Bostwick, 2006, p. 1691).

## Staging

The staging of oesophageal carcinoma is the strongest known prognostic factor of survival (Trivers et al., 2005) and plays a further role in determining the optimal therapeutic approach, e. g. for the consideration of possible neoadjuvant treatment. It is performed soon after tissue diagnosis is made, using the TNM staging system, where tumour invasion of the oesophageal wall (T), presence of tumour in lymph nodes (N) or metastases (M) are combined into stage categories (see Figure 1 below). The first staging technique employed is usually a computed tomography (CT) scan of the thorax, identifying distant metastatic disease, as well as excluding T4 lesions by looking for preservation of the anatomic fat plane between the oesophagus and adjacent structures (Talley et al., 2011, p. 318). Endoscopic ultrasound (EUS) is an additional testing method used for patients where CT scans do not show any metastases. EUS provides the most accurate TNM staging with the additional benefit of fine needle aspiration (FNA) for loco-regional lymph node tissue sampling. According to Oxbridge Solutions Ltd. (2011) and Yendamuri et. al (Yendamuri et al., 2009), the stages illustrated in Figure 1 can be translated as follows: Stage I: limited to oesophagus and < 3 cm in length Stage II: limited to oesophagus, > 3 cm in length and with resectable nodes Stage III: > 6 cm in length, extension through oesophagus into adjacent structures, inoperable nodes or inoperable lesion Stage IV: lesion as in stage III with evidence of perforation, fistula or distant metastasis

## **Histology**

### **Macroscopic Appearance**

As mentioned before, the most common sites for OSCC are the middle and lower thirds of the oesophagus. According to Cheng and Bostwick (Cheng and Bostwick, 2006, p. 1691), OSCC may be multifocal in up to 20% of patients and growth usually presents as a grey-white circumferential, sharply demarcated mass which may either be fungating, ulcerative or infiltrative. Superficial carcinomas are limited to the mucosa and submucosa.

### **Microscopic Appearance**

SCC in general and OSCC particularly are invasive and present with enlarged nuclei, densely eosinophilic cytoplasm and intercellular bridges. As cited by Cheng and Boswick (2006, p. 1691), the mitotic rate, desmoplasia and degree of keratin production are variable and most are well or moderately differentiated. Further, submucosal spread can occur up to 5 cm beyond grossly visible margins and vascular invasion occurs in up to 75% of cases

### **Management & Treatment Options**

Management of OSCC depends on the age of the patient, the level of the lesion and the disease stage. Interventions should be undertaken by multidisciplinary teams and treatment options can generally be divided into A) single modality, B) combined modality and C) postoperative adjuvant therapy (Abeloff et al., 2008, pp. 1406-1412).

## **Single Modality**

Surgery alone, i. e. oesophagectomy with reconstruction, has clear curative intent and attempts to locally control the tumour, remove regional lymph nodes and ideally restore swallowing function. Of all the treatment measures for oesophageal carcinoma, complete surgical resection offers the most reasonable chance for a cure, with 80% survival rate if the postoperative pathology confirms the staging (Kumar and Clark, 2009, p. 257). Particularly middle and lower third lesions of the oesophagus are well accessible surgically. However, surgery should only be used for early Stage I OSCC, where the tumour has not yet extended through the oesophageal wall and infiltrated the soft tissues of the neck. The surgical approach depends on the tumour histology and location, overall patient condition and the experience of the surgeon (Allum et al., 2002). Localised tumours are most commonly resected by either a right transthoracic or a transhiatal approach (Enzinger and Mayer, 2003):

### **Right transthoracic approach**

Combines a laparotomy and right-sided thoracotomy, leading to an oesophogastric anastomosis either by the Ivor-Lewis technique in the upper chest or by the three-field technique in the neck

### **Transhiatal approach**

Laparotomy with blunt dissection of the thoracic oesophagus, placing the anastomosis in the neck  
Picture 12: Possible Scar Lines after Surgery for Oesophageal cancer © CancerHelp UK  
Radiotherapy (RT) alone is recommended for Stage I carcinoma and is the definite treatment for

patients with inoperable tumours that are unsuitable for chemoradiation. RT is particularly indicated for lesion up to 5cm long of the upper third oesophagus, as closely related vital mediastinal structures make surgical resection very difficult. RT is also used for palliation of obstructive symptoms, enabling the patient to swallow food and saliva. However, about 70% of patients present with stage II OSCC or greater and thus other management options need to be available for potentially locally advanced presentations. In light of this, this thesis is aimed at investigating the benefits of one type of the following combined modality options.

### **Combined Modality**

Definitive chemoradiation is suitable for patients with more advanced lesions and non-operable disease and eliminates the risk of surgery, but at the cost of inferior local control and poor 5-year survival. Chemotherapy component usually consist of 5- fluorouracil and cisplatin, and sometimes newer agents such as irinotecan or a taxane may be employed (Talley et al., 2011, p. 376). Preoperative Neoadjuvant Chemoradiation (NCR) is still under investigation and will be discussed in a later chapter of this thesis.

### **Postoperative Adjuvant Therapy**

Following NCRT and surgery does not have any demonstrated benefit (Urschel and Vasan, 2003) Following surgery alone is considered for microscopic or gross residual tumours for patients with a good performance status. A significant proportion of OSCC patients are either too old or have too many concurrent illnesses to consider any of the above radical treatment options and require palliation of dysphagia. Treatment of patients in poor

general conditions must be individualised based on stage, patient medical conditions and patient preferences. The aim of palliative treatment is rapid relief of dysphagia without the need for long hospital treatment. Single procedures are often combined according to tumour evolution. When palliation rather than cure is the goal, several options exist, influenced by the severity of symptoms. These include endoscopic laser resection and endoscopic stent placement (Block, 2004, p. 91), oesophago-gastrostomy or Photodynamic therapy (PDT) (Kumar and Clark, 2009, p. 257). The use of indwelling tubes to allow swallowing is also partially successful in very advanced diseases. RT may also be added after endoscopic palliation to increase the durability of local palliation for patients who are likely to survive more than 3 to 6 months. For metastatic disease, chemotherapy is indicated, with the goal of improving survival and preventing or treating symptoms at all locations.

## **Prognosis**

The tumour stage at diagnosis is the strongest known prognostic factor of survival (Trivers et al., 2005). If untreated, oesophageal carcinoma leads to death within 3–6 months after diagnosis. The two-year survival rates after definite radiotherapy are around 20% and results for chemotherapy alone are even worse (Izbicki et al., 2009, p. 89). No differences in survival rates between sex have been established and survival decreases with advanced age at diagnosis. The following Table 4 lists the 5-year survival rates according to TNM classification.

## **Overall Survival Outcomes**

No significant difference in the overall survival (OS) between the NCRT-S and surgery alone groups could be established in two of the trials (Lee et al., 2004; Natsugoe et al., 2006), with p values of 0.580 and 0.690 which did not allow for a rejection of the null hypothesis. However, both of these studies also had the lowest median follow-up out of all the trials with only 24 and 25 months respectively. Further, both studies concluded overall unfavourably towards NCRT and it can thus be speculated that the efficacy of NCRT should be evaluated over a median follow-up of 45 months or longer in order to see a significant improvement in overall survival. According to Table 7 calculations, mean 1-year survival was 80% and 78% respectively in the NCRT and surgery alone groups. Mean 3-year survival was 57% and 38% respectively, showing a difference of 19. Mean 5-year survival was 39% and 27% respectively, giving a 12 difference. All of these mean percentage calculations appear to reflect slightly favourably upon NCRT regimens.