

CHAPTER 1

Tumours of the Oesophagus

Carcinomas of the oesophagus pose a considerable medical and public health challenge in many parts of the world. Morphologically and aetiologically, two major types are distinguished:

Squamous cell carcinoma

In Western countries, oesophageal carcinomas with squamous cell differentiation typically arise after many years of tobacco and alcohol abuse. They frequently carry G:C >T:A mutations of the *TP53* gene. Other causes include chronic mucosal injury through hot beverages and malnutrition, but the very high incidence rates observed in Iran and some African and Asian regions remain inexplicable.

Adenocarcinoma

Oesophageal carcinomas with glandular differentiation are typically located in the distal oesophagus and occur predominantly in white males of industrialized countries, with a marked tendency for increasing incidence rates. The most important aetiological factor is chronic gastro-oesophageal reflux leading to Barrett type mucosal metaplasia, the most common precursor lesion of adenocarcinoma.

Squamous cell carcinoma of the oesophagus

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Definition

Squamous cell carcinoma (SCC) of the oesophagus is a malignant epithelial tumour with squamous cell differentiation, microscopically characterised by keratinocyte-like cells with intercellular bridges and/or keratinization.

ICD-O Code

8070/3

Epidemiology

Squamous cell carcinoma of the oesophagus shows great geographical diversity in incidence, mortality and sex ratio. In Western countries, the age-standardized annual incidence in most areas does not exceed 5 per 100,000 population in males and 1 in females. There are, however, several well-defined high-risk areas, e.g. Normandy and Calvados in North-West France, and Northern Italy, where incidence may be as high as 30 per 100,000 population in males and 2 in females {1020, 1331}. This type of cancer is much more frequent in Eastern countries and in many developing countries. Regions with very high incidence rates have been identified in Iran, Central China, South Africa and Southern Brazil. In the city of Zhengzhou, capital of Henan province in China, the mortality rate exceeds 100 per 100,000 population in males and 50 in females {1116, 2191}.

In both high-risk and low-risk regions, this cancer is exceedingly rare before the age of 30 and the median age is around 65 in both males and females. Recent changes in the distribution pattern in France indicate that the rate of SCC has increased steadily in low-risk areas, particularly among females, whereas there may be a slight decrease in high-risk areas. In the United States, a search in hospitalisation records of military veterans indicates that SCC is 2-3 times more frequent among blacks than among Asians, Whites or Native Americans {453}.

Aetiology

Tobacco and alcohol. In Western countries, nearly 90% of the risk of SCC can be attributed to tobacco and alcohol. Each of these factors influences the risk of oesophageal cancer in a different way. With regard to the consumption of tobacco, a moderate intake during a long period carries a higher risk than a high intake during a shorter period, whereas the reverse is true for alcohol. Both factors combined show a multiplicative effect, even at low alcohol intake. In high-risk areas of North-West France and Northern Italy, local drinking customs may partially explain the excess incidence of SCC {523, 1020}. In Japanese alcoholics, a

polymorphism in *ALDH2*, the gene encoding aldehyde dehydrogenase 2, has been shown to be significantly associated with several cancers of the upper digestive tract, including squamous cell cancer. This observation suggests a role for acetaldehyde, one of the main carcinogenic metabolites of alcohol in the development of oesophageal carcinoma {2177}.

Nutrition. Risk factors other than tobacco and alcohol play significant roles in other regions of the world. In high-risk areas of China, a deficiency in certain trace elements and the consumption of pickled or mouldy foods (which are potential sources of nitrosamines) have been suggested.

Hot beverages. Worldwide, one of the most common risk factors appears to be the consumption of burning-hot beverages (such as Mate tea in South America) which cause thermal injury leading to chronic oesophagitis and then to precancerous lesions {1116, 2191, 387}.

HPV. Conflicting reports have proposed a role for infectious agents, including human papillomavirus (HPV) infection. Although HPV DNA is consistently detected in 20 to 40% of SCC in high-risk areas of China, it is generally absent in the cancers arising in Western countries {954, 679}.

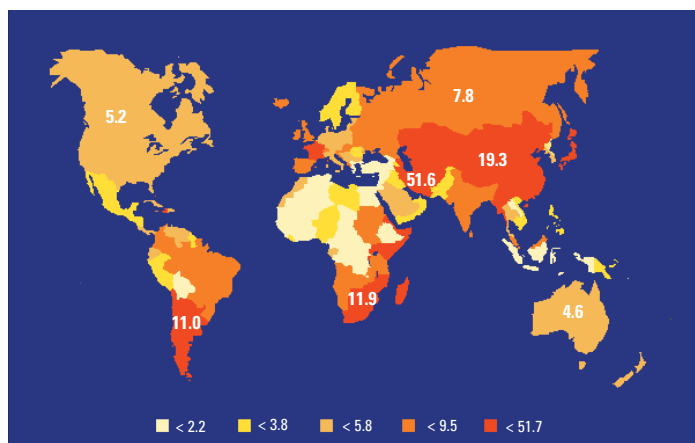


Fig. 1.01 Worldwide annual incidence (per 100,000) of oesophageal cancer in males. Numbers on the map indicate regional average values.

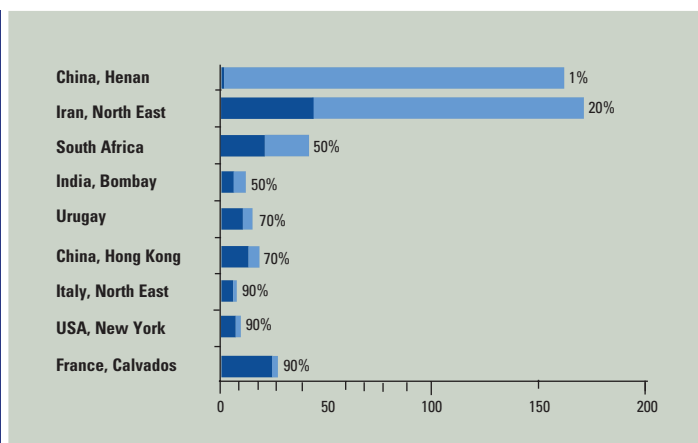


Fig. 1.02 Squamous cell carcinoma of the oesophagus. Age-standardized incidence rates per 100,000 and proportions (%) due to alcohol and tobacco (dark-blue).

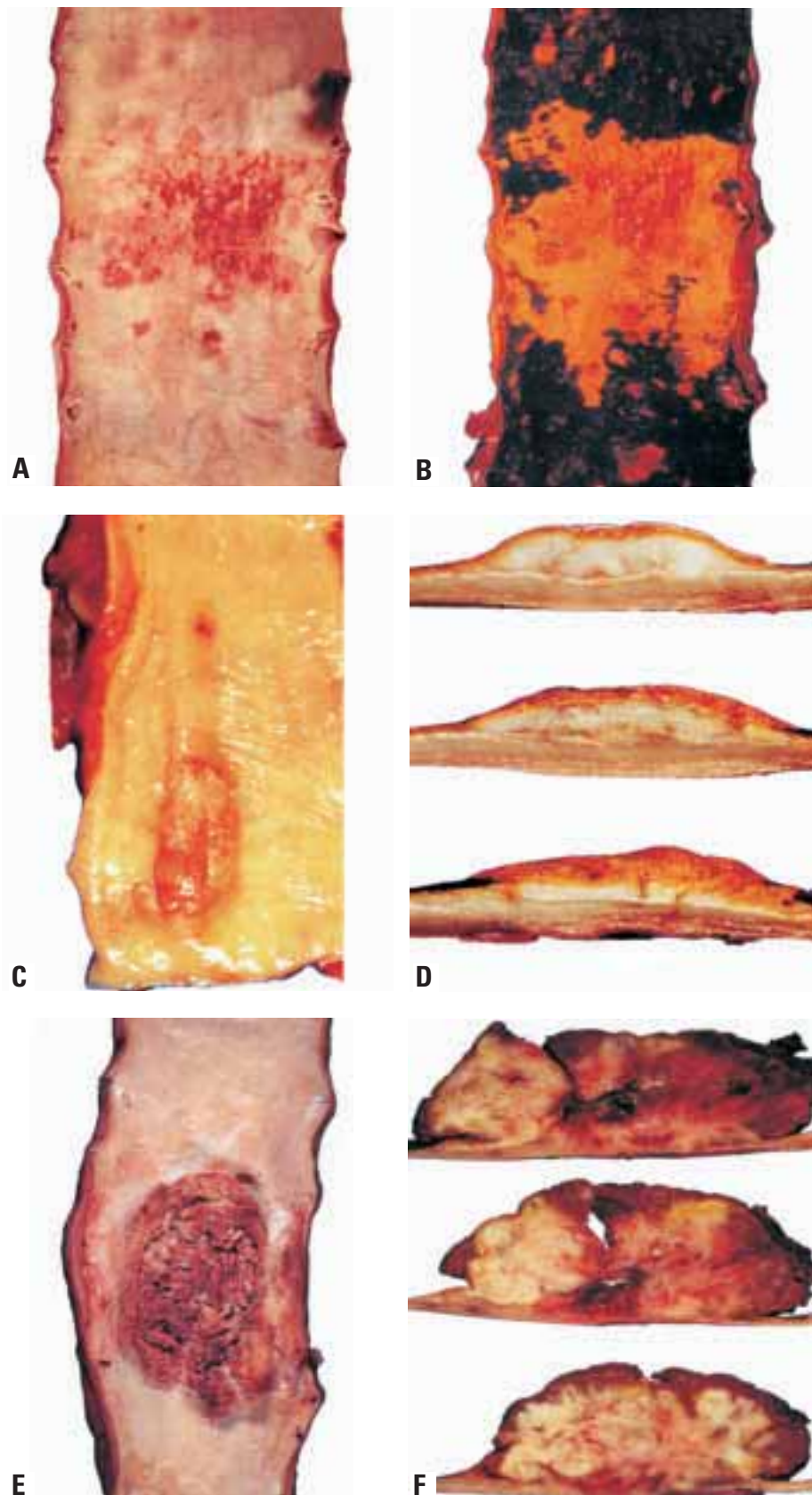


Fig. 1.03 Macroscopic images of squamous cell carcinoma (SCC) of the oesophagus. **A** Flat superficial type. **B** Lugol iodine staining of the specimen illustrated in A. **C** Polypoid SCC. **D** Longitudinal sections of carcinoma illustrated in C. **E** Deeply invasive polypoid SCC. **F** Longitudinal sections of carcinoma illustrated in E.

Associations between achalasia, Plummer-Vinson syndrome, coeliac disease and tylosis (focal nonepidermolytic palmo-plantar keratoderma) with oesophageal cancer have also been described.

Localization

Oesophageal SCC is located predominantly in the middle and the lower third of the oesophagus, only 10-15% being situated in the upper third {1055}.

Clinical features

Symptoms and signs

The most common symptoms of advanced oesophageal cancer are dysphagia, weight loss, retrosternal or epigastric pain, and regurgitation caused by narrowing of the oesophageal lumen by tumour growth {606}. Superficial SCC usually has no specific symptoms but sometimes causes a tingling sensation, and is, therefore, often detected incidentally during upper gastrointestinal endoscopy {464, 1874}.

Endoscopy and vital staining

Superficial oesophageal cancer is commonly observed as a slight elevation or shallow depression on the mucosal surface, which is a minor morphological change compared to that of advanced cancer. Macroscopically, three types can be distinguished: flat, polypoid and ulcerated. Chromoendoscopy utilizing toluidine blue or Lugol iodine spray may be of value {465, 481}. Toluidine blue, a metachromatic stain from the thiazine group, has a particular affinity for RNA and DNA, and stains areas that are richer in nuclei than the normal mucosa. Lugol solution reacts specifically with glycogen in the normal squamous epithelium, whereas precancerous and cancerous lesions, but also inflamed areas and gastric heterotopia, are not stained. However, the superficial extension of carcinomas confined to the mucosa can not be clearly recognized by simple endoscopy.

Endoscopic ultrasonography

Endoscopic ultrasonography is used to evaluate both depth of tumour infiltration and para-oesophageal lymph node involvement in early and advanced stages of the disease {1509, 1935}. For the evaluation of the depth of infiltration, high frequency endoscopic ultrasonography may be used {1302}. In general,

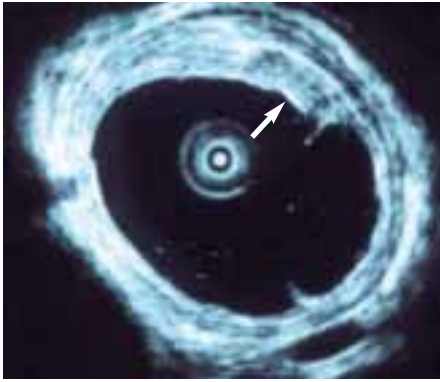


Fig. 1.04 Catheter probe ultrasonograph of a squamous cell carcinoma, presenting as hypoechoic lesion (arrow).

oesophageal carcinoma presents on endosonography as a circumscribed or diffuse wall thickening with a predominantly echo-poor or echo-inhomogeneous pattern. As a result of tumour penetration through the wall and into surrounding structures, the endosonographic wall layers are destroyed.

Computed tomography (CT) and magnetic resonance imaging (MRI)

In advanced carcinomas, CT and MRI give information on local and systemic spread of SCC. Tumour growth is characterized as swelling of the oesophageal wall, with or without direct invasion to surrounding organs {1518}. Cervical, abdominal and mediastinal node enlargement is recorded. Three-dimensional CT or MRI images may be presented as virtual endoscopy, effectively demonstrating T2-T4 lesions, but not T1 lesions.

Macroscopy

The gross appearance varies according to whether it is detected in an early or an advanced stage of the disease. Among early SCC, polypoid, plaque-like, depressed and occult lesions have been described {161, 2183}. For the macroscopic classification of advanced oesophageal SCC, Ming {1236} has proposed three major patterns: fungating, ulcerative, and infiltrating. The fungating pattern is characterized by a predominantly exophytic growth, whereas in the ulcerative pattern, the tumour growth is predominantly intramural, with a central ulceration and elevated ulcer edges. The infiltrative pattern, which is the least common one, also shows a predominantly intramural growth, but causes only a small mucosal defect. Similar types of macroscopic

growth patterns have been defined in the classification of the Japanese Society for Esophageal Diseases {58}.

Tumour spread and staging

For the staging of SCC, the TNM system (tumour, node, metastasis) established by the International Union Against Cancer (UICC) is the most widely used system. Its usefulness in the planning of treatment and in the prediction of prognosis has been validated {1104, 895, 66, 1, 772}.

Superficial oesophageal carcinoma.

When the tumour is confined to the mucosa or the submucosa, the term superficial oesophageal carcinoma is used irrespective of the presence of regional lymph node metastases {58, 161}. In China and in Japan, the term early oesophageal carcinoma is often used defining a carcinoma that invades no deeper than the submucosa but has not metastasised {609}. In several studies from Japan, superficial carcinomas accounted for 10-20% of all resected carcinomas, whereas in Western countries

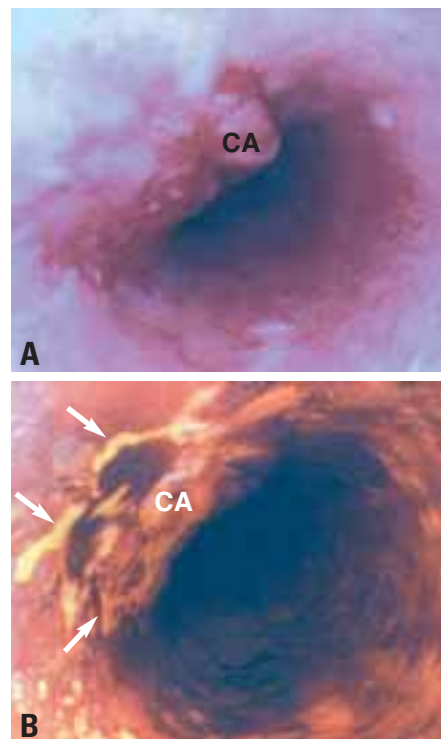


Fig. 1.05 **A** Endoscopic view of a superficial squamous cell carcinoma presenting as a large nodule (CA) in a zone of erosion. **B** After spraying of 2% iodine solution, the superficial extent of the tumour becomes visible as unstained light yellow area (CA, arrows).

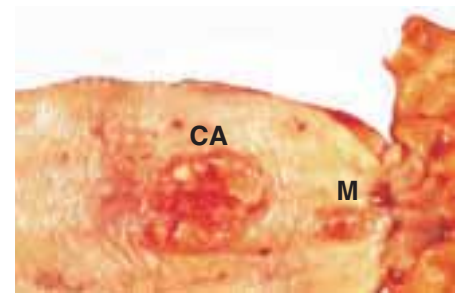


Fig. 1.06 Primary squamous cell carcinoma (CA) of oesophagus with an intramural metastasis (M) near the oesophagogastric junction.

superficial carcinomas are much less frequently reported {543}. About 5% of superficial carcinomas that have invaded the lamina propria display lymph node metastases, whereas in carcinomas that invade the submucosa the risk of nodal metastasis is about 35% {1055}. For tumours that have infiltrated beyond the submucosa, the term advanced oesophageal carcinoma is applied.

Intramural metastases. A special feature of oesophageal SCC is the occurrence of intramural metastases, which have been found in resected oesophageal specimens in 11-16% of cases {896, 987}. These metastases are thought to result from intramural lymphatic spread with the establishment of secondary intramural tumour deposits. Intramural metastases are associated with an advanced stage of disease and with shorter survival.

Second primary SCC. Additionally, the occurrence of multiple independent SCC has been described in between 14 and 31% of cases, the second cancers being mainly carcinomas *in situ* and superficial SCC {1154, 989, 1507}.

Treatment groups. Following the clinical staging, patients are usually divided into two treatment groups: those with locoregional disease in whom the tumour is potentially curable (e.g. by surgery, radiotherapy, multimodal therapy), and those with advanced disease (metastases outside the regional area or invasion of the airway) in whom only palliative treatment is indicated {606}. Oesophageal SCC limited to the mucosa may be treated by endoscopic mucosal resection due to its low risk of nodal metastasis. Endoscopic mucosal resection is also indicated for high-grade intraepithelial neoplasia. Tumours that have invaded the submucosa or those in more advanced tumour stages have

more than 30% risk of lymph node metastasis, and endoscopic therapy is not indicated [465]. Additionally, clinical staging is performed in order to determine the success of treatment, e.g. following radio- and/or chemotherapy.

Tumour spread

The most common sites of metastasis of oesophageal SCC are the regional lymph nodes. The risk of lymph node metastasis is about 5% in carcinomas confined to the mucosa but over 30% in carcinomas invading the submucosa and over 80% in carcinomas invading adjacent organs or tissues [772]. Lesions of the upper third of the oesophagus most frequently involve cervical and mediastinal lymph nodes, whereas those of the middle third metastasise to the mediastinal, cervical and upper gastric lymph nodes. Carcinomas of the lower third preferentially spread to the lower mediastinal and the abdominal lymph nodes [28]. The most common sites of haematogenous metastases are the lung and the liver [1153, 1789]. Less frequently affected sites are the bones, adrenal glands, and brain [1551]. Recently, disseminated tumour cells were identified by means of immunostaining in the bone marrow of about 40% of patients with oesophageal SCC [1933]. Recurrence of cancer following oesophageal resection can be locoregional or distant, both with approximately equal frequency [1185, 1027].

Histopathology

Oesophageal SCC is defined as the penetration of neoplastic squamous epithelium through the epithelial basement membrane and extension into the lamina propria or deeper tissue layers. Invasion commonly starts from a carcinoma in situ with the proliferation of rete-like projections of neoplastic epithelium that push into the lamina propria with subsequent dissociation into small carcinomatous cell clusters. Along with vertical tumour cell infiltration, usually a horizontal growth undermines the adjacent normal mucosa at the tumour periphery. The carcinoma may already invade intramural lymphatic vessels and veins at an early stage of disease. The frequency of lymphatic and blood vessel invasion increases with increasing depth of invasion [1662]. Tumour cells in lymphatic vessels and in blood vessels may be found progressively several centimetres beyond the gross

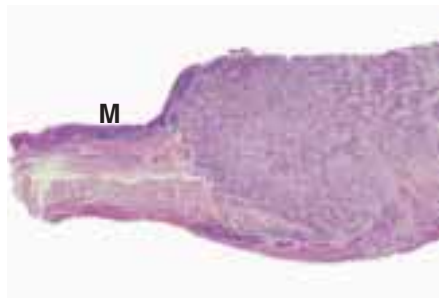


Fig. 1.07 Squamous cell carcinoma with transmural invasion. M, remaining intact mucosa.

tumour. The carcinoma invades the muscular layers, enters the loose fibrous adventitia and may extend beyond the adventitia, with invasion of adjacent organs or tissues, especially the trachea and bronchi, eventually with the formation of oesophagotracheal or oesophago-bronchial fistulae [1789]. Oesophageal SCC displays different microscopic patterns of invasion, which are categorised as 'expansive growth' or 'infiltrative growth'. The former pattern is characterized by a broad and smooth invasion front with little or no tumour cell dissociation, whereas the infiltrative pattern shows an irregular invasion front and a marked tumour cell dissociation. The degree of desmoplastic or inflammatory stromal reaction, nuclear polymorphism and keratinization is extremely variable. Additionally, otherwise typical oesophageal SCC may contain small foci of glandular differentiation, indicated by the formation of tubular glands or mucin-producing tumour cells [987].

Verrucous carcinoma (ICD-O 8051/3)

This rare variant of squamous cell carcinoma [19] is histologically comparable to verrucous carcinomas arising at other sites [969]. On gross examination, its appearance is exophytic, warty, cauliflower-like or papillary. It can be found in any part of the oesophagus. Histologically, it is defined as a malignant papillary tumour composed of well differentiated and keratinized squamous epithelium with minimal cytological atypia, and pushing rather than infiltrating margins [2066]. Oesophageal verrucous carcinoma grows slowly and invades locally, with a very low metastasising potential.

Spindle cell carcinoma (ICD-O 8094/3)

This unusual malignancy is defined as a squamous cell carcinoma with a variable

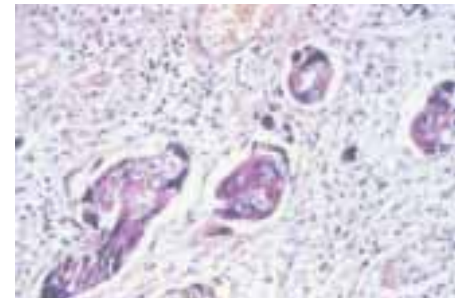


Fig. 1.08 Squamous cell carcinoma invading thin-walled lymphatic vessels.

sarcomatoid spindle cell component. It is also known by a variety of other terms, including carcinosarcoma, pseudosarcomatous squamous cell carcinoma, polypoid carcinoma, and squamous cell carcinoma with a spindle cell component [1055]. Macroscopically, the tumour is characterized by a polypoid growth pattern. The spindle cells may be capable of maturation, forming bone, cartilage and skeletal muscle cells [662]. Alternatively, they may be more pleomorphic, resembling malignant fibrous histiocytoma. In the majority of cases a gradual transition between carcinomatous and sarcomatous components has been observed on the light microscopic level. Immunohistochemical and electron microscopic studies indicate that the sarcomatous spindle cells show various degrees of epithelial differentiation. Therefore, the sarcoma-

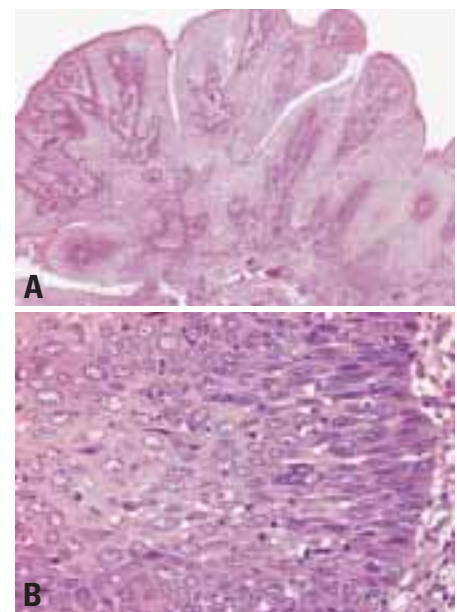


Fig. 1.09 Verrucous carcinoma. **A** Typical exophytic papillary growth. **B** High degree of differentiation.

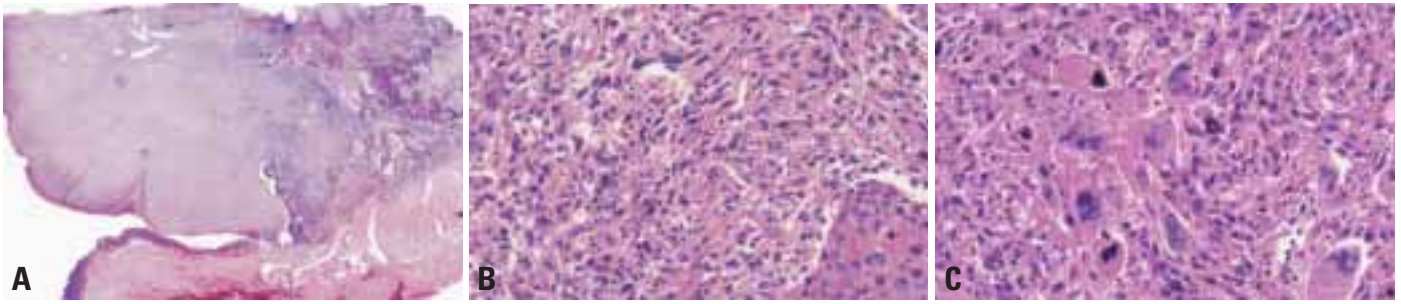


Fig. 1.10 Spindle cell carcinoma. **A** Typical polypoid appearance. **B** Transition between conventional and spindle cells areas. **C** Malignant fibrous histiocytoma-like area in a spindle cell carcinoma.

tous component may be metaplastic. However, a recent molecular analysis of a single case of a spindle cell carcinoma showed divergent genetic alterations in the carcinomatous and in the sarcomatous tumour component suggesting two independent malignant cell clones {823}.

Basaloid squamous cell carcinoma (ICD-O 8083/3)

This rare but distinct variant of oesophageal SCC {1961} appears to be identical to the basaloid squamous cell carcinomas of the upper aerodigestive tract {109}. Histologically, it is composed of closely packed cells with hyperchromatic nuclei and scant basophilic cytoplasm, which show a solid growth pattern, small gland-like spaces and foci of comedo-type necrosis. Basaloid squamous cell carcinomas are associated

with intraepithelial neoplasia, invasive SCC, or islands of squamous differentiation among the basaloid cells {2036}. The proliferative activity is higher than in typical SCC. However, basaloid squamous cell carcinoma is also characterized by a high rate of apoptosis and its prognosis does not differ significantly from that of the ordinary oesophageal SCC {1663}.

Precursor lesions

Most studies on precursor lesions of oesophageal SCC have been carried out in high-risk populations, especially in Iran and Northern China, but there is no evidence that precursor lesions in low-risk regions are substantially different. The development of oesophageal SCC is thought to be a multistage process which progresses from the conversion of normal squamous epithelium to that with basal cell hyperplasia, intraepithelial neoplasia (dysplasia and carcinoma in situ), and, finally, invasive SCC {354, 1547, 377}.

Intraepithelial neoplasia. This lesion is about eight times more common in high cancer-risk areas than in low-risk areas {1547}, and is frequently found adjacent to invasive SCC in oesophagectomy specimens {1154, 988}. Morphological features of intraepithelial neoplasia include both architectural and cytological abnormalities. The architectural abnormality is characterized by a disorganisation of the epithelium and loss of normal cell polarity. Cytologically, the cells exhibit irregular and hyperchromatic nuclei, an increase in nuclear/cytoplasmic ratio and increased mitotic activity. Dysplasia is usually graded as low or high-grade. In low-grade dysplasia, the abnormalities are often confined to the lower half of the epithelium, whereas in high-grade dysplasia the abnormal cells also occur in

the upper half and exhibit a greater degree of atypia. In carcinoma *in situ*, the atypical cells are present throughout the epithelium without evidence of maturation at the surface of the epithelium {1154}. In a two-tier system, severe dysplasia and carcinoma-in-situ are included under the rubric of high-grade intraepithelial neoplasia, and may have the same clinical implications {1055}.

Epidemiological follow-up studies suggest an increased risk for the subsequent development of invasive SCC for patients with basal cell hyperplasia (relative risk: 2.1), low-grade dysplasia (RR: 2.2), moderate-grade dysplasia (RR: 15.8), high-grade dysplasia (RR: 72.6) and carcinoma in situ (RR: 62.5) {377}.

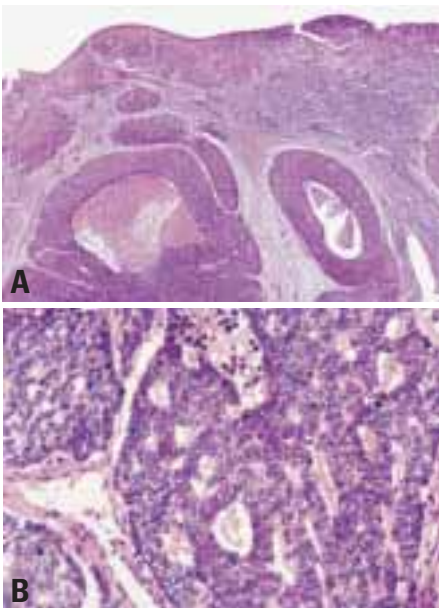


Fig. 1.11 Basaloid squamous cell carcinoma. **A** Typical comedo-type necrosis. **B** Small gland-like structures.

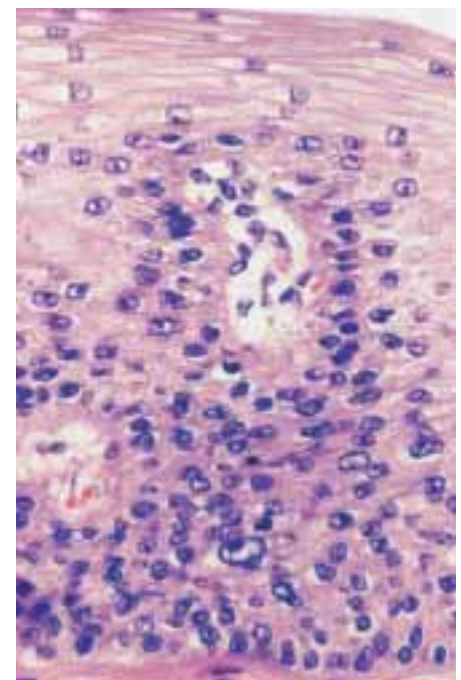


Fig. 1.12 Low-grade intraepithelial neoplasia with an increase in basal cells, loss of polarity in the deep epithelium and slight cytological atypia.

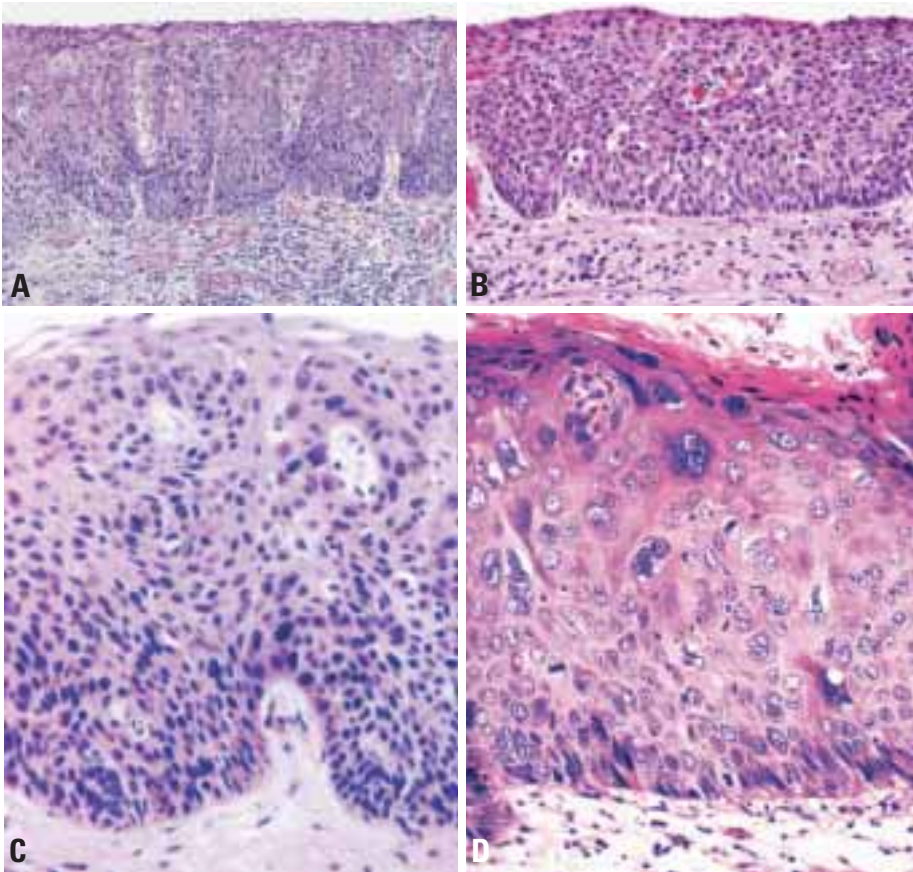


Fig. 1.13 High grade intraepithelial neoplasia of oesophageal squamous epithelium. Architectural disarray, loss of polarity and cellular atypia are much greater than shown in Fig. 1.12. Changes in **D** extend to the parakeratotic layer of the luminal surface.

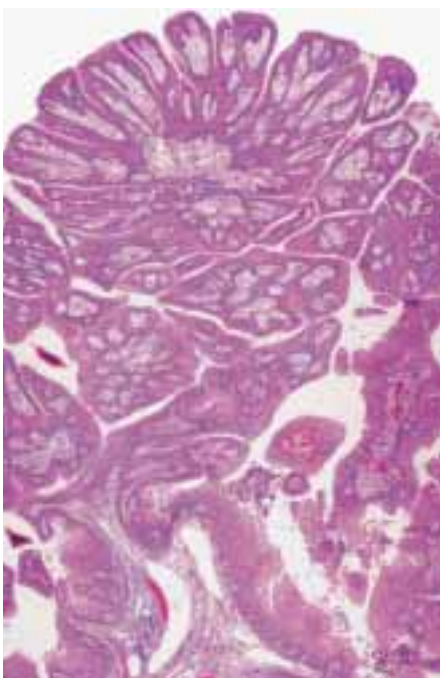


Fig. 1.14 Squamous cell papilloma of distal oesophagus. This lesion was negative for human papillomavirus by in situ hybridisation.

Basal cell hyperplasia

This lesion is histologically defined as an otherwise normal squamous epithelium with a basal zone thickness greater than 15% of total epithelial thickness, without elongation of lamina propria papillae {377}. In most cases, basal cell hyperplasia is an epithelial proliferative lesion in response to oesophagitis, which is frequently observed in high-risk populations for oesophageal cancer {1547}.

Squamous cell papilloma (ICD-O 8052/0)

Squamous cell papilloma is rare and usually causes no specific symptoms. It is a benign tumour composed of hyperplastic squamous epithelium covering finger-like processes with cores derived from the lamina propria. The polypoid lesions are smooth, sharply demarcated, and usually 5 mm or less in maximum diameter {249, 1428}. Rarely, giant papillomas have been reported, with sizes up to 5 cm {2037}. Most squamous cell papillomas represent single isolated lesions, typically located in the distal to

middle third of the oesophagus, but multiple lesions occur.

Histologically, cores of fibrovascular tissue are covered by mature stratified squamous epithelium. The aetiological role of human papillomavirus (HPV) infection has been investigated in several studies, but the results were inconclusive {248}. Malignant progression to SCC is extremely rare.

In Japan, oesophageal squamous cell carcinoma is diagnosed mainly based on nuclear criteria, even in cases judged to be non-invasive intraepithelial neoplasia (dysplasia) in the West. This difference in diagnostic practice may contribute to the relatively high rate of incidence and good prognosis of superficial squamous cell carcinoma reported in Japan {1682}.

Grading

Grading of oesophageal SCC is traditionally based on the parameters of mitotic activity, anisonucleosis and degree of differentiation.

Well differentiated tumours have cytological and histological features similar to those of the normal oesophageal squamous epithelium. In well differentiated oesophageal SCC there is a high proportion of large, differentiated, keratinocyte-like squamous cells and a low proportion of small basal-type cells, which are located in the periphery of the cancer cell nests {1055}. The occurrence of keratinization has been interpreted as a sign of differentiation, although the normal oesophageal squamous epithelium does not keratinize.

Poorly differentiated tumours predominantly consist of basal-type cells, which usually exhibit a high mitotic rate.

Moderately differentiated carcinomas, between the well and poorly differentiated types, are the most common type, accounting for about two-thirds of all oesophageal SCC. However, since no generally accepted criteria have been identified to score the relative contribution of the different grading parameters, grading of SCC suffers from a great inter-observer variation.

Undifferentiated carcinomas are defined by a lack of definite light microscopic features of differentiation. However, ultrastructural or immunohistochemical investigations may disclose features of squamous differentiation in a subset of light-microscopically undifferentiated carcinomas {1881}.

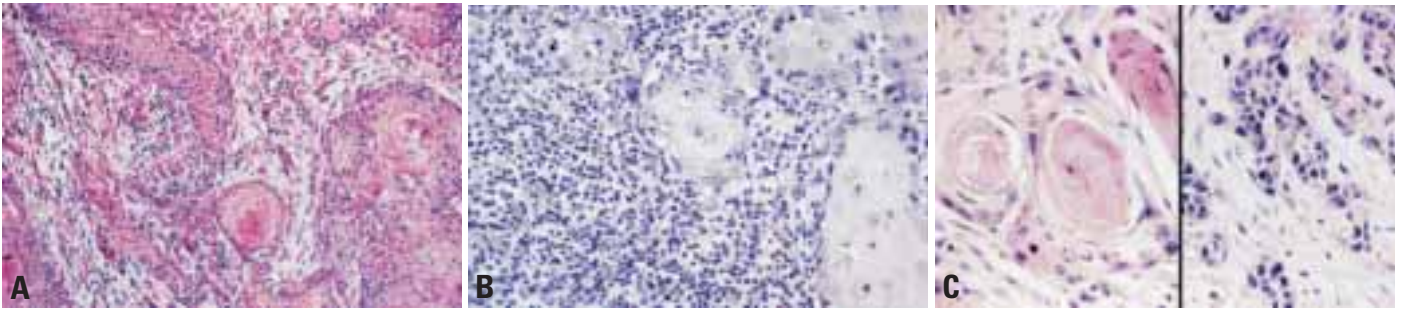


Fig. 1.15 Squamous cell carcinoma. **A** Moderately differentiated. **B** Well differentiated with prominent lymphoid infiltrate. **C** Well differentiated areas (left) contrast with immature basal-type cells of a poorly differentiated carcinoma (right).

Genetic susceptibility

Familial predisposition of oesophageal cancer has been only poorly studied except in its association with focal non-epidermolytic palmoplantar keratoderma (NEPPK or tylosis) {1279, 1278, 752}. This autosomal, dominantly inherited disorder of the palmar and plantar surfaces of the skin segregates together with oesophageal cancer in three pedigrees, two of which are extensive {456, 1834, 693}. The causative locus has been designated the tylosis oesophageal cancer (TOC) gene and maps to 17q25 between the anonymous microsatellite markers D17S1839 and D17S785 {1594, 899}. The genetic defect is thought to be in a molecule involved in the physical structure of stratified squamous epithelia whereby loss of function of the gene may alter oesophageal integrity thereby making it more susceptible to environmental mutagens.

Several structural candidate genes such as envoplakin (*EVPL*), integrin $\beta 4$ (*ITGB4*) and plakoglobin have been excluded as the TOC gene following integration of the genetic and physical maps of this region {1595}. The importance of this gene in a larger population than those afflicted with the familial disease is indicated by the association of the genomic region containing the TOC gene with sporadic squamous cell oesophageal carcinomas {2020, 823}, Barrett adenocarcinoma of the oesophagus {439}, and primary breast cancers {549} using loss of heterozygosity studies.

Genetics

Alterations in genes that encode regulators of the G1 to S transition of cell cycle are common in SCC. Mutation in the *TP53* gene (17p13) is thought to be an early event, sometimes already

detectable in intraepithelial neoplasia. The frequency and type of mutation varies from one geographic area to the other, suggesting that some *TP53* mutations may occur as the result of exposure to region-specific, exogenous risk factors. However, even in SCC from Western Europe, the *TP53* mutation spectrum does not show the same tobacco-associated mutations as in lung cancers {1266}. Amplification of cyclin D1 (11q13) occurs in 20-40% of SCC and is frequently detected in cancers that retain expression of the Rb protein, in agreement with the notion that these two factors cooperate within the same signalling cascade {859}. Inactivation of *CDKN2A* occurs essentially by homozygous deletion or de novo methylation and appears to be associated with advanced cancer. Other potentially important genetic alterations include transcriptional inactivation of the FHIT gene (fragile histidine triad, a

presumptive tumour suppressor on 3p14) by methylation of 5' CpG islands, and deletion of the tylosis oesophageal cancer gene on 17q25 {2020, 1264}. Furthermore, analysis of clones on 3p21.3, where frequent LOH occurs in oesophageal cancer {1274}, recently led to identification of a novel gene termed *DLC1* (deleted in lung and oesophageal cancer-1) {365}. Although the function of the *DLC1* gene remains to be clarified, RT-PCR experiments indicated that 33% of primary cancers of lung and oesophagus lacked *DLC1* transcripts entirely or contained increased levels of nonfunctional *DLC1* mRNA. Recent evidence suggests that LOH at a new, putative tumour suppressor locus on 5p15 may occur in a majority of SCC {1497}. Amplification of several proto-oncogenes has also been reported (*HST-1*, *HST-2*, *EGFR*, *MYC*) {1266}. How these various genetic events correlate with phenotypic

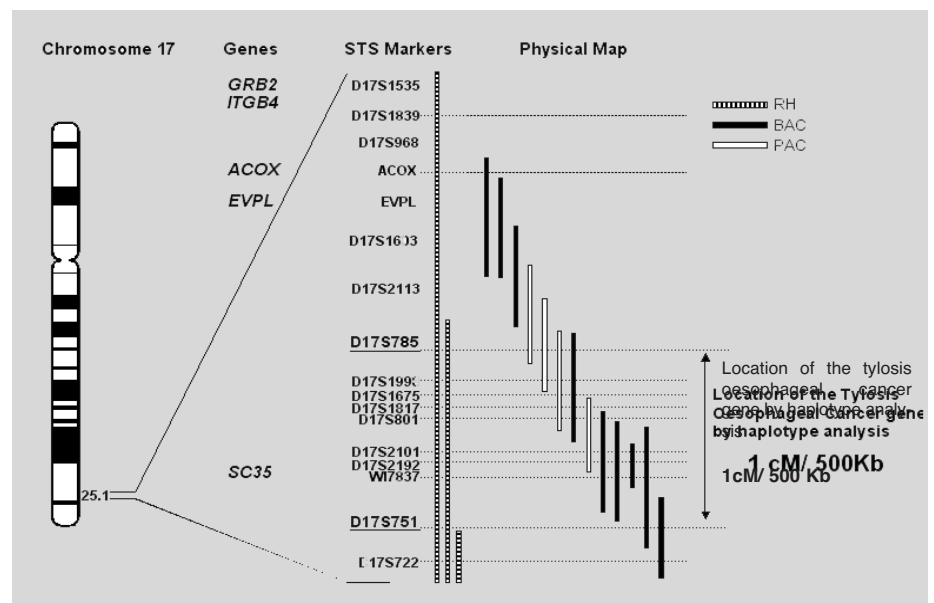


Fig. 1.16 Location of the tylosis oesophageal cancer gene on chromosome 17q.

changes and co operate in the sequence of events leading to SCC is still speculative.

Prognosis and prognostic factors

Overall, the prognosis of oesophageal SCC is poor and the 5-year survival rates in registries are around 10%. Cure is foreseen only for superficial cancer. The survival varies, depending upon tumour stage at diagnosis, treatment received, patient's general health status, morphological features and molecular features of the tumour. In the past, studies on prognostic factors were largely focused on patients who were treated by surgery, whereas factors influencing survival of patients treated by radiotherapy or by multimodal therapy have been investigated only rarely.

Morphological factors

The extent of spread of the oesophageal SCC is the most important factor for prognosis, the TNM classification being the most widely used staging system.

Staging. All studies indicate that the depth of invasion and the presence of nodal or distant metastases are independent predictors of survival {1104, 895, 772}. In particular, lymph node involvement, regardless of the extent of the primary tumour, indicates a poor prognosis {1862, 912, 1873}. More recently, the prognostic significance of more sophisticated methods for the determination of tumour spread have been evaluated, including the ratio of involved to resected lymph nodes {1603}, immunohistochemically determined lymph node micrometastases {824, 1327} and micrometastases in the bone marrow {1933}. However, current data are still too limited to draw final conclusions on the prognostic value.

Differentiation. The prognostic impact of tumour differentiation is equivocal, possibly due to the poor standardisation of the grading system and to the high prognostic power of tumour stage. Although some studies have shown a significant influence of tumour grade on survival {709, 772}, the majority of studies have not {443, 1858, 1601, 1660}. Other histopathological features associated with a poor prognosis include the presence of vascular and/or lymphatic invasion {772, 1662} and an infiltrative growth pattern of the primary tumour {1660}.

Lymphocytic infiltration. Intense lympho-

Table 1.01

Genetic alterations in squamous cell carcinoma of the oesophagus.

Gene	Location	Tumor abnormality	Function
<i>TP53</i>	17p13	Point mutation, LOH	G1 arrest, apoptosis, genetic stability
<i>p16, p15, ARF/CDKN2</i>	9p22	Homozygous loss Promoter methylation	CDK inhibitor (cell cycle control)
<i>Cyclin D1</i>	11q13	Amplification	Cell cycle control
<i>EGFR</i>	17p13	Amplification, overexpression	Signal transduction (membrane Tyr kinase)
<i>c-myc</i>	8q24.1	Amplification	Transcription factor
<i>Rb</i>	13q14	LOH Absence of expression	Cell cycle control
<i>TOC</i>	17q25	LOH	Tumour suppressor
<i>FEZ1</i>	8p22	Transcription shutdown	Transcription factor
<i>DLC1</i>	3p21.3	Transcription shutdown	Growth inhibition

cytic response to the tumour has been associated with a better prognosis {1660, 443}.

Proliferation. The cancer cell proliferation index, determined immunohistochemically by antibodies such as PCNA or Ki-67 / MIB-1, have been studied extensively. However, the proliferation index does not appear to be an independent prognostic factor {2189, 1005, 1659, 779}.

DNA ploidy. Aneuploidy of cancer cells, as determined by flow cytometry or by image analysis, has been identified in 55% to 95% of oesophageal SCC {935}. Regarding the prognostic impact, patients with diploid tumours usually survive longer than those with aneuploid tumours. However, a prognostic impact independent of tumour stage has been shown only in two studies {422, 1195}, whereas the majority of studies have not verified this

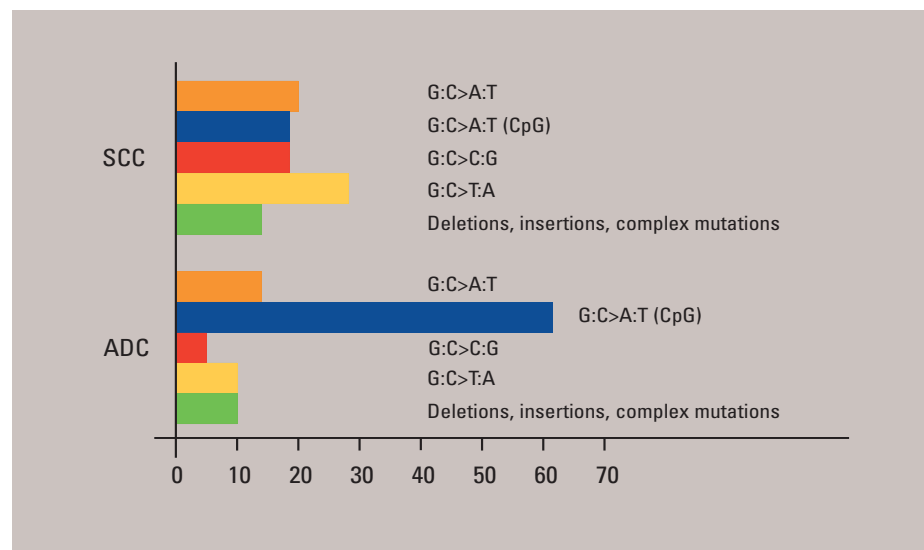


Fig. 1.17 Spectrum of *TP53* mutations in squamous cell carcinoma (SCC) and adenocarcinoma (ADC) of the oesophagus.

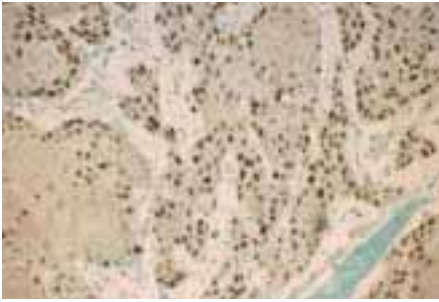


Fig. 1.18 *TP53* immunoreactivity in squamous cell carcinoma of the oesophagus.

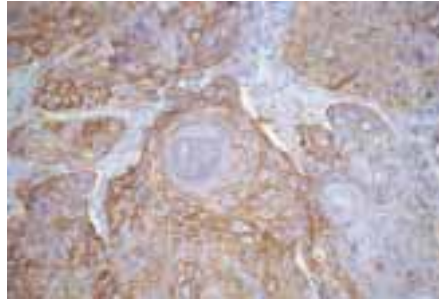


Fig. 1.19 Immunoreactivity for epidermal growth factor receptor (EGFR) in oesophageal squamous cell carcinoma.

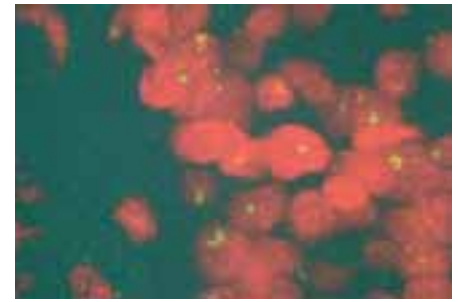


Fig. 1.20 Fluorescence in situ hybridisation demonstrating cyclin D1 in squamous carcinoma cells.

finding {935}. Therefore, the determination of DNA ploidy is currently not considered to improve the prognostic information provided by the TNM system {1055}.

Extent of resection. The frequency of locoregional recurrence is negatively correlated with the distance of the primary tumour to the proximal resection margin and possibly to preoperative chemotherapy {1890, 1027}.

Molecular factors

The *TP53* gene is mutated in 35% to 80%

of oesophageal SCC {1266}. Whereas some studies indicated a negative prognostic influence of p53 protein accumulation in cancer cell nuclei {1743, 277}, others did not observe any prognostic value of either immunoeexpression or *TP53* mutation {2014, 1661, 1008, 779, 319}.

Other potential prognostic factors include growth factors and their receptors {927}, oncogenes, including *c-erbB-2* and *int-2* {778}, cell cycle regulators {1748, 1297}, tumour suppressor genes {1886}, redox

defence system components, e.g., metallothionein and heat shock proteins {897}, and matrix proteinases {1303, 1947, 2155}. Alterations of these factors in oesophageal SCC may enhance tumour cell proliferation, invasiveness, and metastatic potential, and thus may be associated with survival. However, none of the factors tested so far has entered clinical practice.

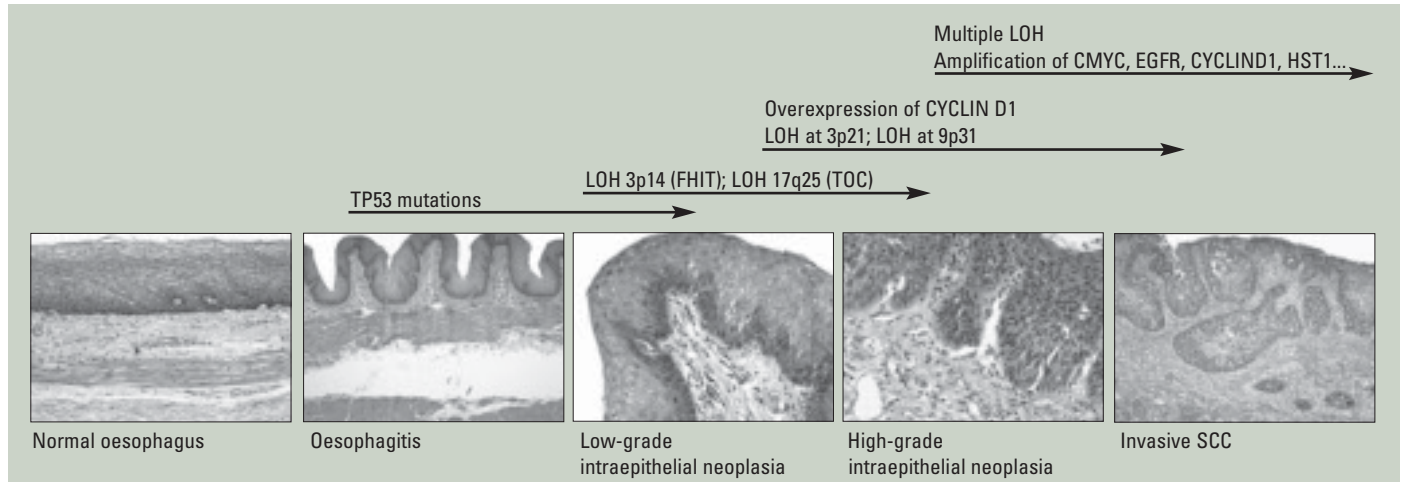


Fig. 1.21 Putative sequence of genetic alterations in the development of squamous cell carcinoma of the oesophagus.

Adenocarcinoma of the oesophagus

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P. Hainaut
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R. Lambert
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H.J. Stein

Definition

A malignant epithelial tumour of the oesophagus with glandular differentiation arising predominantly from Barrett mucosa in the lower third of the oesophagus. Infrequently, adenocarcinoma originates from heterotopic gastric mucosa in the upper oesophagus, or from mucosal and submucosal glands.

ICD-O Code

8140/3

Epidemiology

In industrialized countries, the incidence and prevalence of adenocarcinoma of the oesophagus has risen dramatically {1827}. Population based studies in the U.S.A. and several European countries indicate that the incidence of oesophageal adenocarcinoma has doubled between the early 1970s to the late 1980s and continues to increase at a rate of about 5% to 10% per year {152, 153, 370, 405, 1496}. This is paralleled by rising rates of adenocarcinoma of the gastric cardia and of subcardial gastric carcinoma. It has been estimated that the rate of increase of oesophageal and oesophagogastric junction adenocarcinoma in the U.S.A. during the past decade surpassed that of any other type of cancer {152}. In the mid 1990s the incidence of oesophageal adenocarcinoma has been estimated between 1 and 4 per 100,000 per year in the U.S.A. and several European countries and thus approaches or exceeds that of squamous cell oesophageal cancer in these regions. In Asia and Africa, adenocarcinoma of the oesophagus is an uncommon finding, but increasing rates are also reported from these areas.

In addition to the rise in incidence, adenocarcinoma of the oesophagus and of the oesophagogastric junction share some epidemiological characteristics that clearly distinguish them from squamous cell oesophageal carcinoma and adenocarcinoma of the distal stomach. These include a high preponderance for the male sex (male:female ratio 7:1), a

higher incidence among whites and an average age at the time of diagnosis of around 65 years {1756}.

Aetiology

Barrett oesophagus

The epidemiological features of adenocarcinoma of the distal oesophagus and oesophagogastric junction match those of patients with known intestinal metaplasia in the distal oesophagus, i.e. Barrett oesophagus {1605, 1827}, which has been identified as the single most important precursor lesion and risk factor for adenocarcinoma of the distal oesophagus, irrespective of the length of the segment with intestinal metaplasia.

Intestinal metaplasia of the oesophagus develops when the normal squamous oesophageal epithelium is replaced by columnar epithelium during the process of healing after repetitive injury to the oesophageal mucosa, typically associated with gastro-oesophageal reflux disease {1798, 1799}.

Intestinal metaplasia can be detected in more than 80% of patients with adenocarcinoma of the distal oesophagus. {1756, 1824}. A series of prospective endoscopic surveillance studies in patients with known intestinal metaplasia of the distal oesophagus has shown an incidence of oesophageal adenocarcinoma in the order of 1/100 years of follow up {1799}. This translates into a life-time risk for oesophageal adenocarcinoma of about 10% in these patients. The length of the oesophageal segment with intestinal metaplasia, and the presence of ulcerations and strictures have been implicated as further risk factors for the development of oesophageal adenocarcinoma by some authors, but this has not been confirmed by others {1799, 1797, 1827}.

The biological significance of so-called ultrashort Barrett oesophagus or intestinal metaplasia just beneath a normal Z line has yet to be fully clarified {1325}. Whether adenocarcinoma of the gastric cardia or subcardial gastric cancer is also related to foci of intestinal metapla-

sia at or immediately below the gastric cardia {715, 1797, 1722} is discussed in the chapter on adenocarcinoma of the oesophagogastric junction. Despite the broad advocacy of endoscopic surveillance in patients with known Barrett oesophagus, more than 50% of patients with oesophageal adenocarcinoma still have locally advanced or metastatic disease at the time of presentation {1826}.

Chronic gastro-oesophageal reflux is the usual underlying cause of the repetitive mucosal injury and also provides an abnormal environment during the healing process that predisposes to intestinal metaplasia {1799}. Data from Sweden have shown an odds ratio of 7.7 for oesophageal adenocarcinoma in persons with recurrent reflux symptoms, as compared with persons without such symptoms {1002, 1001}.

The more frequent, more severe, and longer-lasting the symptoms of reflux, the greater the risk. Among persons with long-standing and severe symptoms of reflux, the odds ratio for oesophageal adenocarcinoma was 43.5. Based on these data a strong and probably causal relation between gastro-oesophageal reflux, one of the most common benign disorders of the digestive tract, and oesophageal adenocarcinoma has been postulated.

Factors predisposing for the development of Barrett oesophagus and subsequent adenocarcinoma in patients with gastro-oesophageal reflux disease include a markedly increased oesophageal exposure time to refluxed gastric and duodenal contents due to a defective barrier function of the lower oesophageal sphincter and ineffective clearance function of the tubular oesophagus {1823, 1827}. Experimental and clinical data indicate that combined oesophageal exposure to gastric acid and duodenal contents (bile acids and pancreatic enzymes) appears to be more detrimental than isolated exposure to gastric juice or duodenal contents alone {1241, 1825}. Combined reflux is thought to increase cancer risk

by promoting cellular proliferation, and by exposing the oesophageal epithelium to potentially genotoxic gastric and intestinal contents, e.g. nitrosamines {1825}.

Tobacco

Smoking has been identified as another major risk factor for oesophageal adenocarcinoma and may account for as much as 40% of cases through an early stage carcinogenic effect {562, 2204}.

Obesity

In a Swedish population-based case control study, obesity was also associated with an increased risk for oesophageal adenocarcinoma. In this study the adjusted odds ratio was 7.6 among persons in the highest body mass index (BMI) quartile compared with persons in the lowest. Obese persons (BMI > 30 kg/m²) had an odds ratio of 16.2 as compared with the leanest persons (persons with a BMI < 22 kg/m²) {1002}. The pathogenetic basis of the association with obesity remains to be elucidated {310}.

Alcohol

In contrast to squamous cell oesophageal carcinoma, there is no strong relation between alcohol consumption and adenocarcinoma of the oesophagus.

Helicobacter pylori

This infection does not appear to be a predisposing factor for the development of intestinal metaplasia and adenocarcinoma in the distal oesophagus. According to recent studies, gastric *H. pylori* infection may even exert a protective effect {309}.

Localization

Adenocarcinoma may occur anywhere in a segment lined with columnar metaplastic mucosa (Barrett oesophagus) but develops mostly in its proximal verge. Adenocarcinoma in a short segment of Barrett oesophagus is easily mistaken for adenocarcinoma of the cardia. Since adenocarcinoma originating from the distal oesophagus may infiltrate the gastric cardia and carcinoma of the gastric cardia or subcardial region may grow into the distal oesophagus these entities are frequently difficult to discriminate (see chapter on tumours of the oesophago-gastric junction). As an exception, adenocarcinoma occurs also in the middle or proximal third of the oesophagus, in the

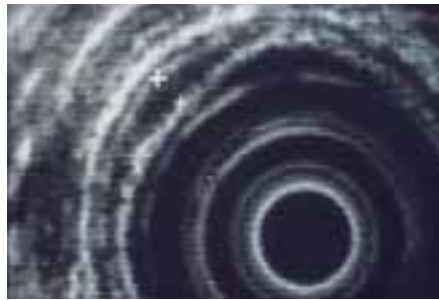


Fig. 1.22 Endoscopic ultrasonograph of Barrett T1 adenocarcinoma. The hypoechoic tumour lies between the first and second hyperechoic layers (markers). The continuity of the second layer (submucosa) is respected.

latter usually from a congenital islet of heterotopic columnar mucosa (that is present in up to 10% of the population).

Barrett oesophagus

Symptoms and signs

Barrett oesophagus as the precursor of most adenocarcinomas is clinically silent in up to 90% of cases. The symptomatology of Barrett oesophagus, when present, is that of gastro-oesophageal reflux {1011}. This is the condition where the early stages of neoplasia (intraepithelial and intramucosal neoplasia) should be sought.

Endoscopy

The endoscopic analysis of the squamo-columnar junction aims at the detection of columnar metaplasia in the distal oesophagus. At endoscopy, the squamo-columnar junction (Z-line) is in the thorax, just above the narrowed passage across the diaphragm. The anatomical landmarks in this area are treated in the chapter on tumours of the oesophago-gastric junction.

If the length of the columnar lining in this distal oesophageal segment is ≥ 3 cm, it is termed a long type of Barrett metaplasia. When the length is < 3 cm, it is a short type. Single or multiple finger-like (1-3 cm) protrusions of columnar mucosa are classified as short type. In patients with short segment (< 3 cm) Barrett oesophagus the risk for developing adenocarcinoma is reported to be lower compared to those with long segment Barrett oesophagus {1720}.

As Barrett oesophagus is restricted to cases with histologically confirmed intestinal metaplasia, adequate tissue sampling is required.

Histopathology

Barrett epithelium is characterized by two different types of cells, i.e. goblet cells and columnar cells, and has also been termed 'specialized', 'distinctive' or Barrett metaplasia. The goblet cells stain positively with Alcian blue at low pH (2.5). The metaplastic epithelium has a flat or villiform surface, and is identical to gastric intestinal metaplasia of the incomplete type (type II or III). Rarely, foci of complete intestinal metaplasia (type I) with absorptive cells and Paneth cells may be found. The mucous glands beneath the surface epithelium and pits may also contain metaplastic epithelium. Recent studies suggest that the columnar metaplasia originates from multipotential cells located in intrinsic oesophageal glands {1429}.

Intraepithelial neoplasia in Barrett oesophagus

Macroscopy

Intraepithelial neoplasia generally has no distinctive gross features, and is detected by systematic sampling of a flat Barrett mucosa {634, 1573}. The area involved is variable, and the presence of multiple dysplastic foci is common {226, 1197}. In some cases, intraepithelial neoplasia presents as one or several nodular masses resembling sessile adenomas. Rare dysplastic lesions have been considered true adenomas, with an expanding but localised growth resulting in a well demarcated interface with the surrounding tissue {1459}.

Microscopy

Epithelial atypia in Barrett mucosa is usually assessed according to the system

Table 1.02

Pattern of endoscopic ultrasound in oesophageal cancer. There are three hyper- and two hypoechoic layers; the tumour mass is hypoechoic.

T1	The 2nd hyperechoic layer (submucosa) is continuous
T2	The 2nd hyperechoic layer (submucosa) is interrupted The 3rd hyperechoic layer (adventitia) is continuous
T3	The 3rd hyperechoic layer (adventitia) is interrupted
T4	The hypoechoic tumour is continuous with adjacent structures

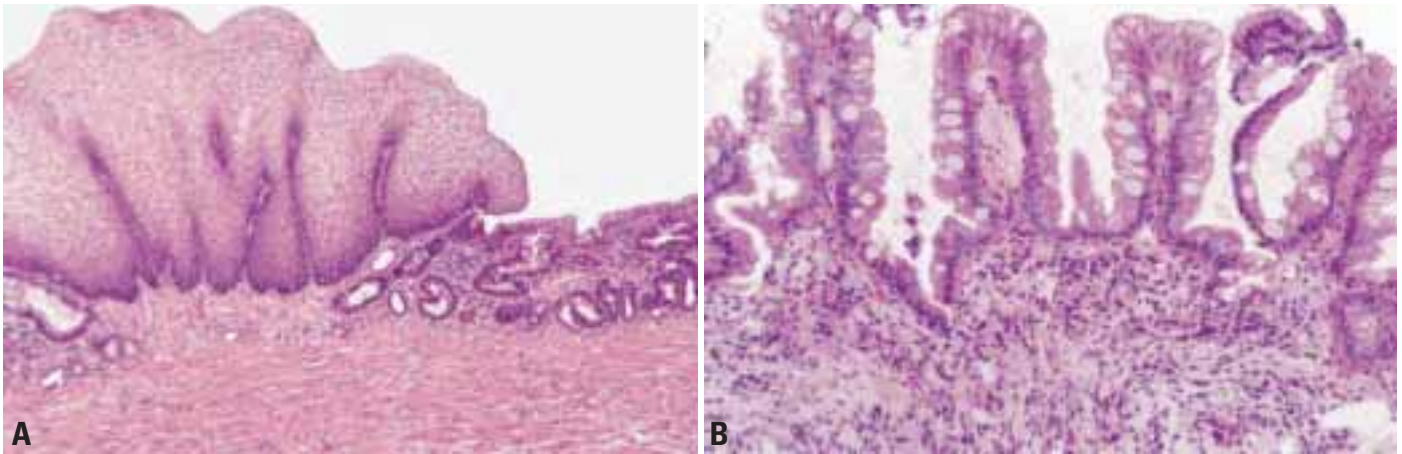


Fig. 1.23 Barrett oesophagus. **A** Haphazardly arranged glands (right) adjacent to hyperplastic squamous epithelium (left). **B** Goblet cells and columnar cells form villus-like structures over chronically inflamed stroma. There is no intraepithelial neoplasia.

devised for atypia in ulcerative colitis, namely: negative, positive or indefinite for intraepithelial neoplasia. If intraepithelial neoplasia is present, it should be classified as low-grade (synonymous with mild or moderate dysplasia) or high-grade (synonymous with severe dysplasia and carcinoma *in situ*) {1582, 1685}. The criteria used to grade intraepithelial neoplasia comprise cytological and architectural features {75}.

Negative for intraepithelial neoplasia

Usually, the lamina propria of Barrett mucosa contains a mild accompanying inflammatory infiltrate of mononuclear cells. There may be mild reactive

changes with enlarged, hyperchromatic nuclei, prominence of nucleoli, and occasional mild stratification in the lower portion of the glands. However, towards the surface there is maturation of the epithelium with few or no abnormalities. These changes meet the criteria of atypia negative for intraepithelial neoplasia, and can usually be separated from low-grade intraepithelial neoplasia.

Atypia indefinite for intraepithelial neoplasia. One of the major challenges for the pathologist in Barrett oesophagus is the differentiation of intraepithelial neoplasia from reactive or regenerative epithelial changes. This is particularly difficult, sometimes even impossible, if

erosions or ulcerations are present {1055}. In areas adjacent to erosions and ulcerations, the metaplastic epithelium may display villiform hyperplasia of the surface foveolae with cytological atypia and architectural disturbances. These abnormalities are usually milder than those observed in intraepithelial neoplasia. There is a normal expansion of the basal replication zone in regenerative epithelium *versus* intraepithelial neoplasia, where the proliferation shifts to more superficial portions of the gland {738}. If there is doubt as to whether reactive and regenerative changes or intraepithelial neoplasia is present in a biopsy, the category atypia indefinite for intraepithelial neoplasia is appropriate and a repeat biopsy after reflux control by medical acid suppression or anti-reflux therapy is indicated.

Low-grade and high-grade intraepithelial neoplasia. Intraepithelial neoplasia in Barrett metaplastic mucosa is defined as a neoplastic process limited to the epithelium {1582}. Its prevalence in Barrett mucosa is approximately 10%, and it develops only in the intestinal type metaplastic epithelium.

Cytological abnormalities typically extend to the surface of the mucosa. In low-grade intraepithelial neoplasia, there is decreased mucus secretion, nuclear pseudostratification confined to the lower half of the glandular epithelium, occasional mitosis, mild pleomorphism, and minimal architectural changes.

High-grade intraepithelial neoplasia shows marked pleomorphism and decrease of mucus secretion, frequent mitosis, nuclear stratification extending

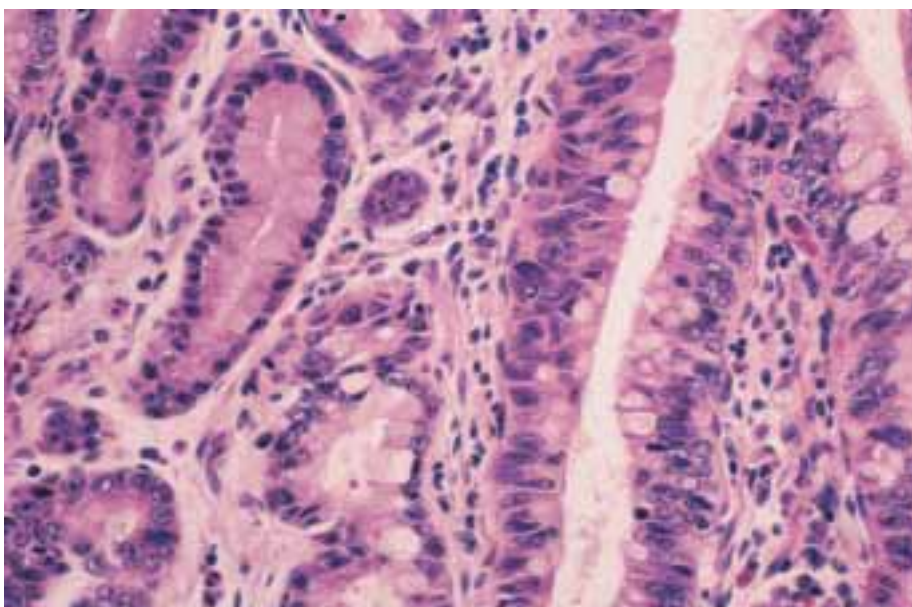


Fig. 1.24 Barrett oesophagus with low-grade intraepithelial neoplasia on the left and high-grade on the right. Note the numerous goblet cells showing a clear cytoplasmic mucous vacuole indenting the adjacent nucleus.

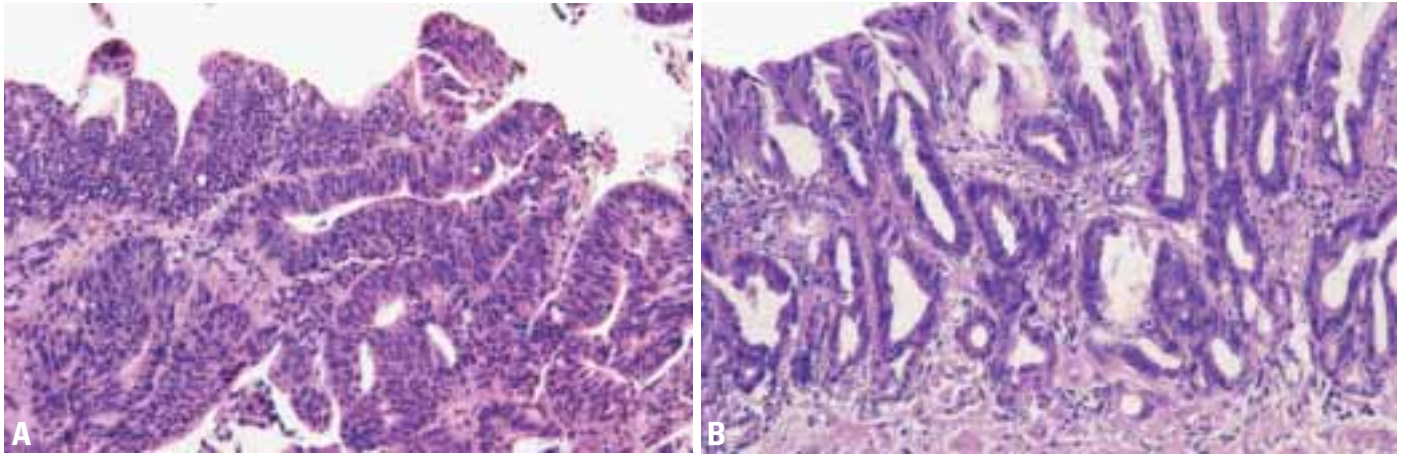


Fig. 1.25 High-grade intraepithelial neoplasia in Barrett oesophagus. **A** Marked degree of stratification with nuclei being present throughout the thickness of the epithelium. Foci of cribriform, back-to-back glands. **B** Highly atypical cells lining tubular structures.

to the upper part of the cells and glands, and marked architectural aberrations. The most severe architectural changes consist of a cribriform pattern that is a feature of high-grade intraepithelial neoplasia as long as the basement membrane of the neoplastic glands has not been disrupted. The diagnostic reproducibility of intraepithelial neoplasia is far from perfect; significant interobserver variation exists {1572}.

Adenocarcinoma

Symptoms and signs

Dysphagia is often the first symptom of advanced adenocarcinoma in the oesophagus. This may be associated with retrosternal or epigastric pain or cachexia.

Endoscopy

The endoscopic pattern of the early tumour stages may be that of a small polypoid adenomatous-like lesion, but more often it is flat, depressed, elevated or occult {1011, 1009}. Areas with high

grade intraepithelial neoplasia are often multicentric and occult. Therefore a systematic tissue sampling has been recommended when no abnormality is evident macroscopically {483}. The usual pattern of advanced adenocarcinoma at endoscopy is that of an axial, and often tight, stenosis in the distal third of the oesophagus; with a polypoid tumour, bleeding occurs at contact.

Radiology

This approach is still proposed in the primary diagnosis of oesophageal cancer when endoscopic access is not easily available {1058}. Today, barium studies are helpful mostly for the analysis of stenotic segments; they are less efficient than endoscopy for the detection of flat abnormalities. Computerised tomography will detect distant thoracic and abdominal metastases.

Endoscopic ultrasonography

At high frequency, some specificities in the echoic pattern of the mucosa and submucosa of the columnar lined oesophagus are displayed. However, the procedure is only suitable for the staging of tumours previously detected at endoscopy; the tumour is hypoechoic. Lymph nodes adjacent to the oesophageal wall can also be visualised by this technique {1614}.

Macroscopy

The majority of primary adenocarcinomas of the oesophagus arise in the lower third of the oesophagus within a segment of Barrett mucosa {1055}. Adjacent to the tumour, the typical salmon-pink mucosa

of Barrett oesophagus may be evident, especially in early carcinomas. In the early stages, the gross findings of Barrett adenocarcinoma may be subtle with irregular mucosal bumps or small plaques. At the time of diagnosis, most tumours are advanced with deep infiltration of the oesophageal wall. The advanced carcinomas are predominantly flat and ulcerated with only one third having a polypoid or fungating appearance. Occasionally, multifocal tumours

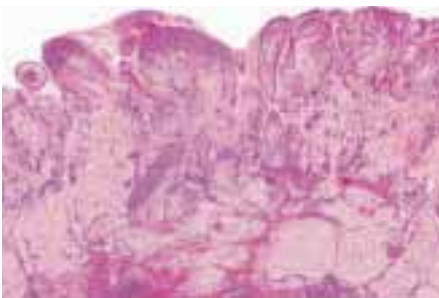


Fig. 1.26 Mucinous adenocarcinoma arising in Barrett oesophagus. Large mucinous lakes extend throughout the oesophageal wall.



Fig. 1.27 Highly infiltrative adenocarcinoma in Barrett oesophagus (pT3), with extension into the cardia.

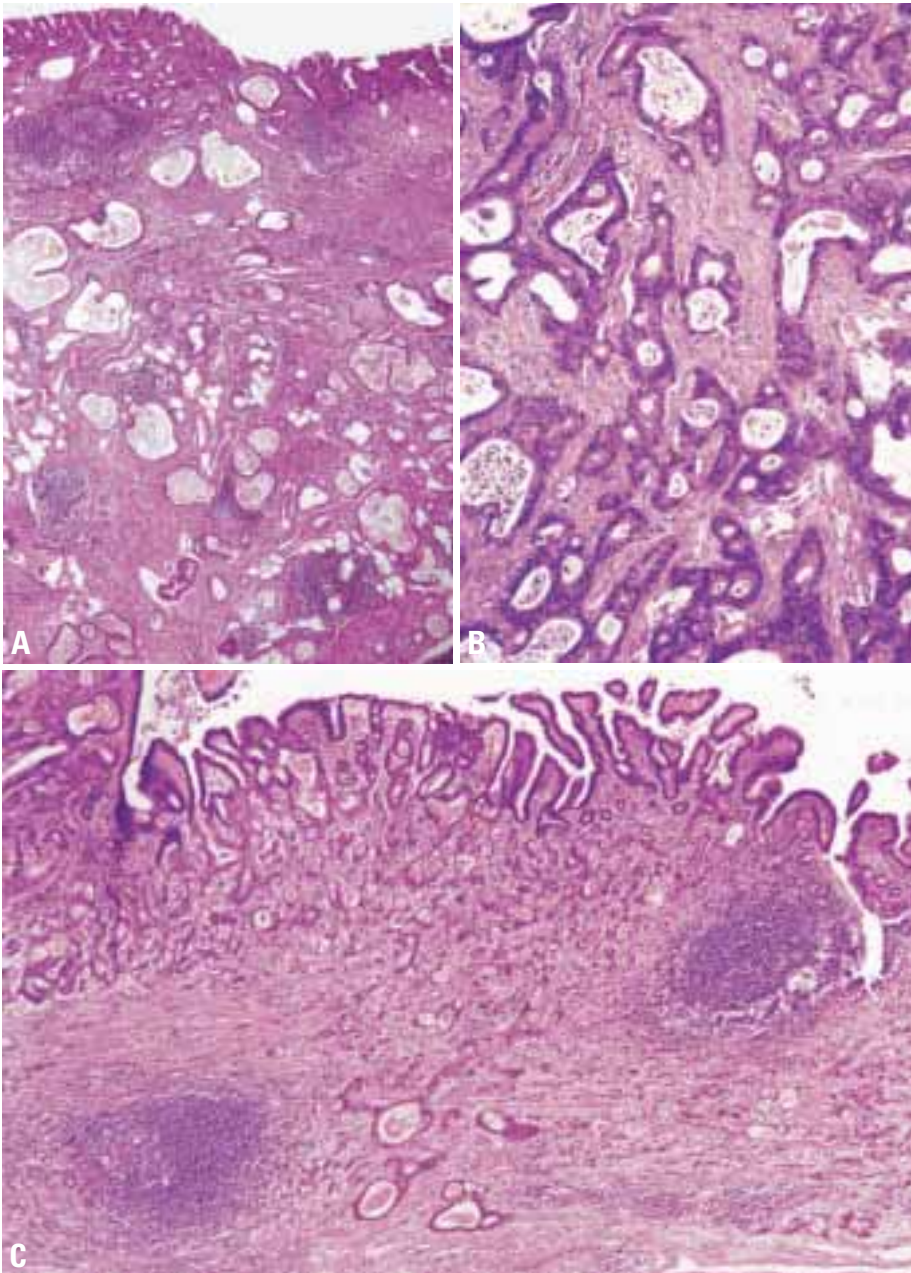


Fig. 1.28 Adenocarcinoma, tubular type. **A** Well differentiated, **B** moderately differentiated and **C** poorly differentiated.

may be present {1055, 1770}. The rare adenocarcinomas arising independently of Barrett oesophagus from ectopic gastric glands and oesophageal glands display predominantly ulceration and polypoid gross features, respectively. These tumours are also found in the upper and middle third of the oesophagus {265, 1204}, but are rare.

Histopathology

Adenocarcinomas arising in the setting of Barrett oesophagus are typically papillary and/or tubular. A few tumours are of

the diffuse type and show rare glandular formations, and sometimes signet ring cells {1458, 1770}. Differentiation may produce endocrine cells, Paneth cells and squamous epithelium. Mucinous adenocarcinomas, i.e. tumours with more than 50% of the lesion consisting of mucin, also occur.

Grading

Most adenocarcinomas arising from Barrett mucosa are well or moderately differentiated {1458}, and display well formed tubular or papillary structures.

The well differentiated tumours may pose a diagnostic problem in biopsy specimens because the infiltrating component may be difficult to recognize as invasive {1055} since Barrett mucosa often has irregular dispersed glands. Glandular structures are only slightly formed in poorly differentiated adenocarcinomas and absent in undifferentiated tumours.

Small cell carcinoma may show foci of glandular differentiation. It is discussed in the chapter on endocrine neoplasms of the oesophagus.

Tumour spread and staging

Adenocarcinomas spread first locally and infiltrate the oesophageal wall. Distal spread to the stomach may occur. Extension through the oesophageal wall into adventitial tissue, and then into adjacent organs or tissues is similar to squamous cell carcinoma. Common sites of local spread comprise the mediastinum, tracheobronchial tree, lung, aorta, pericardium, heart and spine {1055, 1789}. Barrett associated adenocarcinoma metastasizes to para-oesophageal and paracardial lymph nodes, those of the lesser curvature of the stomach and the celiac nodes. Distant metastases occur late. The TNM classification used for SCC is applicable to Barrett adenocarcinoma and provides prognostically significant data {1945}.

Other carcinomas

Adenosquamous carcinoma

(ICD-O code: 8560/3)

This carcinoma has a significant squamous carcinomatous component that is intermingled with a tubular adenocarcinoma.

Mucoepidermoid carcinoma

(ICD-O code: 8430/3)

This rare carcinoma shows an intimate mixture of squamous cells, mucus secreting cells and cells of an intermediate type.

Adenoid cystic carcinoma

(ICD-O code: 8200/3)

This neoplasm is also infrequent and believed to arise, like the mucoepidermoid variant, from oesophageal glands {265, 2066}. Both lesions tend to be of salivary gland type, and small tumours may be confined to the submucosa. However, the ordinary oesophageal adenocarcinoma can also arise from ectopic gastric glands, or oesophageal glands {1204, 1055}.

Genetic susceptibility

Several lines of evidence suggest that there is a genetic susceptibility to oesophageal adenocarcinoma arising from Barrett oesophagus. The almost exclusive occurrence of Barrett oesophagus in whites and its strong male predominance hint at the involvement of genetic factors {1605}. Several reports describe familial clustering of Barrett oesophagus, adenocarcinoma and reflux symptoms in up to three generations, with some families showing an autosomal dominant pattern of inheritance with nearly complete penetrance {470, 480, 482, 569, 861, 1537, 1610, 1959}. Although shared dietary or environmental factors in these families could play a role, the earlier age of onset of Barrett in some families suggests the influence of genetic factors {861}. The molecular factors that determine this genetic susceptibility are largely unknown and linkage analysis in families has not been reported. Recently, an association between a variant of the *GSTP1* (glutathione S-transferase P1) gene and Barrett oesophagus and adenocarcinoma has been demonstrated {1994}. GSTs are responsible for the detoxification of various carcinogens, and inherited differences in carcinogen detoxification capacity may contribute to the development of Barrett epithelium and adenocarcinoma.

Genetics

In Barrett oesophagus a variety of molecular genetic changes has been correlated with the metaplasia-dysplasia-carcinoma sequence (Fig. 1.21) {2091}. Prospective follow-up of lesions biopsied at endoscopy show that alterations in *TP53* and *CDKN2A* occur at early stages {112, 1337}.

***TP53*.** In high-grade intraepithelial neoplasia a prevalence of *TP53* mutations of approximately 60% is found, similar to adenocarcinoma {789}. Mutation in one allele is often accompanied by loss of the other (17p13.1). Mutations occur in diploid cells and precede aneuploidy. The pattern of mutations differs significantly from that in squamous cell carcinomas. This is particularly evident for the high frequency of G:C>A:T transition mutations, which prevail in adenocarcinomas but are infrequent in SCC (Fig. 1.17).

***CDKN2A*.** Alterations of *CDKN2A*, a locus on 9p21 encoding two distinct tumour suppressors, p16 and p19^{arf}

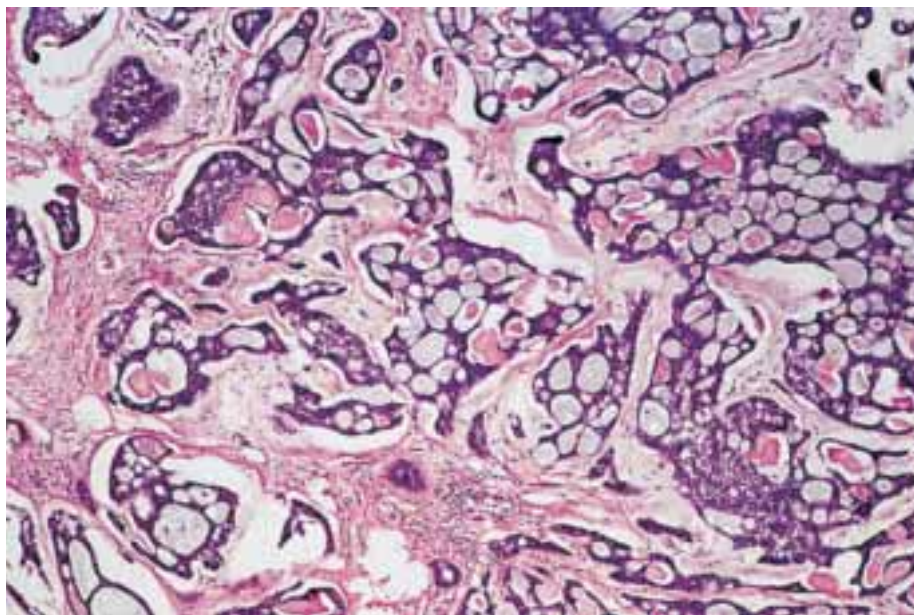


Fig. 1.29 Adenoid cystic carcinoma showing typical cribriform pattern resembling its salivary gland counterpart.

include hypermethylation of the p16 promoter and, more rarely, mutations and LOH {948}.

***FHIT*.** Among other early changes in the premalignant stages of metaplasia are alterations of the transcripts of *FHIT*, a presumptive tumour suppressor gene spanning the common fragile site FRA3B {1222}.

LOH and gene amplification. A number of other loci are altered relatively late during the development of adenocarcinoma, with no obligate sequence of events. Prevalent changes (> 50%) include LOH on chromosomes 4 (long arm) and 5 (several loci including APC) and amplification of *ERBB2* {1266, 1264}.

Phenotypic changes in Barrett oesopha-

Table 1.03

Genes and proteins involved in carcinogenesis in Barrett oesophagus.

Factor	Comment
<i>Tumour suppressor genes</i>	
<i>TP53</i>	60% Mutation – high-grade intraepithelial neoplasia and carcinoma
<i>APC</i>	Late in intraepithelial neoplasia-carcinoma sequence
<i>FHIT</i>	Common, early abnormalities
<i>CDKN2A</i> (p16)	Hypermethylation common in intraepithelial neoplasia
<i>Growth factor receptors</i>	
CD95/AP0/Fas	Shift to cytoplasm in carcinoma
EGFR	Expressed in 60% carcinomas, gene amplification
c-erbB2	Late in dysplasia-carcinoma sequence, gene amplification
<i>Cell adhesion</i>	
E-cadherin	Loss of expression in intraepithelial and invasive carcinoma
Catenins	Similar loss of expression to E-cadherin
<i>Proteases</i>	
UPA	Prognostic factor in carcinoma
<i>Proliferation</i>	
Ki-67	Abnormal distribution in high-grade intraepithelial neoplasia
<i>Membrane trafficking</i>	
rab11	High expression in low-grade intraepithelial neoplasia

gus include expansion of the Ki-67 proliferation compartment correlating with the degree of intraepithelial neoplasia {738}. Molecules involved in membrane trafficking such as rab11 have been reported to be specific for the loss of polarity seen in low-grade intraepithelial neoplasia {1566}. In invasive carcinoma, reduced expression of cadherin/catenin complex and increased expression of various proteases are detectable. Non-neoplastic Barrett oesophagus expresses the MUC2 but not the MUC1 mucin gene product, whereas neither is expressed in intraepithelial neoplasia in Barrett

oesophagus {298}. Invasive lesions exhibit variable expression of MUC1 and MUC2.

Prognostic factors

The major prognostic factors in adenocarcinoma of the oesophagus are the depth of mural invasion and the presence or absence of lymph node or distant metastasis {734, 1049, 1458, 1945}. Gross features and histological differentiation do not influence prognosis. The overall 5-year survival rate after surgery is less than 20% in most series including a majority of advanced carcinomas. The

survival rates are better in superficial (pT1) adenocarcinoma, ranging from 65% to 80% in different series {735, 1219}.

Since the stage at the time of diagnosis is the most important factor affecting outcome, endoscopic surveillance of Barrett patients with early detection of their adenocarcinomas, results in better prognosis in most cases {1995}.

Endocrine tumours of the oesophagus

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L.H. Sobin
R. Arnold

Definition

Endocrine tumours of the oesophagus are rare and include carcinoid (well differentiated endocrine neoplasm), small cell carcinoma (poorly differentiated endocrine carcinoma), and mixed endocrine-exocrine carcinoma.

ICD-O codes

Carcinoid	8240/3
Small cell carcinoma	8041/3
Mixed endocrine-exocrine carcinoma	8244/3

Epidemiology

In an analysis of 8305 carcinoid tumours of different sites, only 3 (0.04%) carcinoids of the oesophagus were reported {1251}. They represented 0.05% of all gastrointestinal carcinoids reported in this analysis and 0.02% of all oesophageal cancers. All cases were in males and presented at a mean age of 56 years {1251}. Small cell carcinoma occurs mainly in the sixth to seventh decade and is twice as common in males as females {190, 421, 765, 1026}. The reported frequencies among all oesophageal cancers were between 0.05% to 7.6% {190, 421, 765, 1026}.

The few mixed endocrine-exocrine carcinomas were in males at the sixth decade {256, 301}.

Aetiological factors

Patients with small cell carcinomas often have a history of heavy smoking and one reported case was associated with long standing achalasia {93, 1539}. A case of combined adenocarcinoma and carcinoid occurred in a patient with a Barrett oesophagus {256}. Small cell carcinoma has also been associated with Barrett oesophagus {1678, 1813}.

Localization

Carcinoid tumours are typically located in the lower third of the oesophagus {1329, 1567, 1754}. Almost all small cell carcinomas occur in the distal half of the oesophagus {190, 421}.

Clinical features

Dysphagia, severe weight loss and sometimes chest pain are the main symptoms of endocrine tumours of the oesophagus. Patients with small cell carcinomas often present at an advanced stage {765, 1026}. Inappropriate antidiuretic hormone syndrome and hypercalcemia have been reported {421}. In addition, a case

of watery diarrhoea, hypokalaemia-achlor-hydrria (WDHA) syndrome, due to ectopic production of VIP by a mixed-cell (squamous-small cell) carcinoma of the oesophagus has been described {2070}.

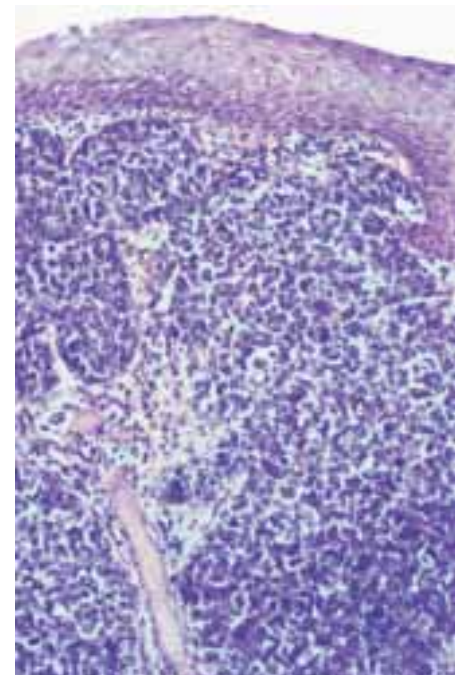


Fig. 1.30 Small cell carcinoma of the oesophagus.

Macroscopy

All reported oesophageal carcinoids were of large size (from 4 to 7 cm in diameter) and infiltrated deeply the oesophageal wall {1329, 1567, 1754}. Small cell carcinomas usually appear as fungating or ulcerated masses of large size, measuring from 4 to 14 cm in greatest diameter.

Histopathology

Carcinoid (well differentiated endocrine neoplasm)

All carcinoids so far reported in the literature have been described as deeply infiltrative tumours, with high mitotic rate and metastases {1329, 1567, 1754}. Microscopically, they are composed of solid nests of tumour cells that show positive stain for Grimelius and neuron-specific enolase {1567}, and characteristic membrane-bound neurosecretory granules at ultrastructural examination {1754}.

Small cell carcinoma (poorly differentiated endocrine carcinoma)

Small cell carcinoma of the oesophagus is indistinguishable from its counterpart

in the lung according to histological and immunohistochemical features as well as clinical behaviour. The cells may be small with dark nuclei of round or oval shape and scanty cytoplasm, or be larger with more cytoplasm (intermediate cells) forming solid sheets and nests. There may be foci of squamous carcinoma, adenocarcinoma, and/or mucoepidermoid carcinoma, a finding that raises the possibility of an origin of tumour cells from pluripotent cells present in the squamous epithelium or ducts of the submucosal glands {190, 1887}. Argyrophilic granules can be demonstrated by Grimelius stain, and small dense-core granules are always detected by electron microscopy {781}.

Immunohistochemical reactions for neuron-specific enolase, synaptophysin, chromogranin and leu7 usually are positive and represent useful diagnostic markers {723}. Some cases have been associated with calcitonin and ACTH production {1272}.

Mixed endocrine-exocrine carcinoma

In the few reported cases {256, 301}, the

tumours combined a gastrointestinal-type adenocarcinoma with the trabecular-acinar component of a carcinoid. In one case the carcinoid component was positive for Grimelius stain, Fontana argentaffin reaction and formaldehyde induced fluorescence for amines {301}.

Prognostic factors

Two of three oesophageal carcinoids from the analysis of 8305 cases of carcinoid tumours {1251} were associated with distant metastases and one {1567} of the three reported cases {1329, 1567, 1754} died 29 months after surgery.

The prognosis of small cell carcinoma of the oesophagus is poor, even when the primary growth is limited {190, 421}. The survival period is usually less than 6 months {816 and thus similar to that of patients with small cell carcinoma of the colon {765, 1026}. Multidrug chemotherapy may offer temporary remission {765, 816, 1026, 1678}.

Lymphoma of the oesophagus

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Definition

Primary lymphoma of the oesophagus is defined as an extranodal lymphoma arising in the oesophagus with the bulk of the disease localized to this site {796}. Contiguous lymph node involvement and distant spread may be seen but the primary clinical presentation is in the oesophagus with therapy directed at this site.

Clinical features

The oesophagus is the least common site of involvement with lymphoma in the digestive tract, accounting for less than 1% of lymphoma patients {1399}. Oesophageal involvement is usually second-

ary either from the mediastinum, from nodal disease or from a primary gastric location. Patients are frequently male and usually over 50 years old. Tumours involving the distal portion of the oesophagus may cause dysphagia {644}.

Histopathology

Primary oesophageal lymphomas may be of the large B-cell type or may be low-grade B-cell MALT lymphomas {1794}. MALT lymphomas show morphological and cytological features common to MALT lymphomas found elsewhere in the digestive tract. Lymphoid follicles are surrounded by a diffuse infiltrate of centrocyte-like (CCL) cells showing a vari-

able degree of plasma cell differentiation. Infiltration of these cells into the overlying epithelium is usually seen. Characteristically the CCL cells express pan-B-cell markers CD20 and CD79a and they are negative for CD5 and CD10. They express bcl-2 protein and may be positive with antibodies to CD43. Due to the rarity of these lesions, molecular genetics data are not available.

In common with other sites in the digestive tract, secondary involvement of the oesophagus may occur in dissemination of any type of lymphoma.

Primary oesophageal T-cell lymphoma has been described but is exceedingly rare {547}.

Mesenchymal tumours of the oesophagus

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Definition

A variety of rare benign and malignant mesenchymal tumours that arise in the oesophagus. Among these, tumours of smooth muscle or 'stromal' type are most common.

ICD-O codes

Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Gastrointestinal stromal tumour (GIST)	8936/3
Granular cell tumour	9580/0
Rhabdomyosarcoma	8900/3
Kaposi sarcoma	9190/3

Classification

The morphological definitions of these lesions follow the WHO histological classification of soft tissue tumours {2086}. Stromal tumours are described in detail in the chapter on gastric mesenchymal tumours.

Epidemiology

Leiomyoma is the most common mesenchymal tumour of the oesophagus. It occurs in males at twice the frequency

as females and has a median age distribution between 30 and 35 years {1712, 1228}. *Sarcomas* of the oesophagus accounted for 0.2% of malignant oesophageal tumours in SEER data from the United States from 1973 to 1987. Males were more frequently affected than females by nearly 2:1 {1928}. Adults between the 6th and 8th decades are primarily affected. Oesophageal stromal tumours show demographics similar to those of sarcomas {1228}.

Localization

Leiomyomas and *stromal tumours* are most frequent in the lower oesophagus and begin as intramural lesions. The larger tumours can extend to mediastinum and form a predominantly mediastinal mass. *Leiomyomatosis* forms worm-like intramural structures that may extend into the upper portion of the stomach.

Clinical features

Dysphagia is the usual complaint, but many leiomyomas and a small proportion of stromal tumours are asymptomatic and are incidentally detected by X-ray as mediastinal masses. Since most sarcomas project into the lumen, they are relatively easy to diagnose by endoscopy or imaging studies. The endoscopic pattern is that of a submucosal tumour with a swelling of a normal mucosa. Endoscopic ultrasound helps in determining the actual size of the tumour, its position in the oesophageal wall and its eventual position in the mediastinum. A CT scan of the mediastinum is then a useful complement. Most tumours less than 3 cm in diameter are benign. Endoscopic tissue sampling (large biopsy or fine needle aspiration) is difficult and not very reliable for the assessment of malignancy.

Macroscopy

Leiomyomas vary in size from a few millimeters up to 10 cm in diameter (average 2-3 cm). They may be spherical, or when larger they can form sausage-like masses with a large longitudinal dimension

or dumb-bell shaped masses with circular involvement {1712, 1228}. Large leiomyomas (over 0.5 kg) have been described {968}. *Sarcomas*, most of them representing malignant gastrointestinal stromal tumours (GISTs), are typically multinodular or less commonly plaque-like masses resembling sarcomas of the soft tissues. Many oesophageal sarcomas protrude into the mediastinum.

Histopathology

Leiomyoma is composed of bland spindle cells and shows low or moderate cellularity and slight if any mitotic activity. There may be focal nuclear atypia. The cells have eosinophilic, fibrillary, often clumped cytoplasm. Eosinophilic granulocytes and spherical calcifications are sometimes present. Leiomyomas are typically globally positive for desmin and smooth muscle actin, and are negative for CD34 and CD117 (KIT) {1228}.

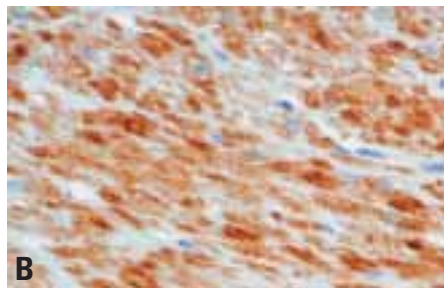
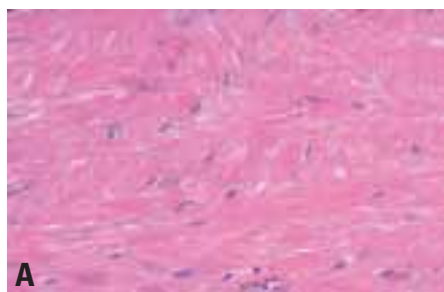


Fig. 1.31 Leiomyoma of oesophagus. **A** Haematoxylin and eosin stain. **B** Immunoreactivity for desmin.

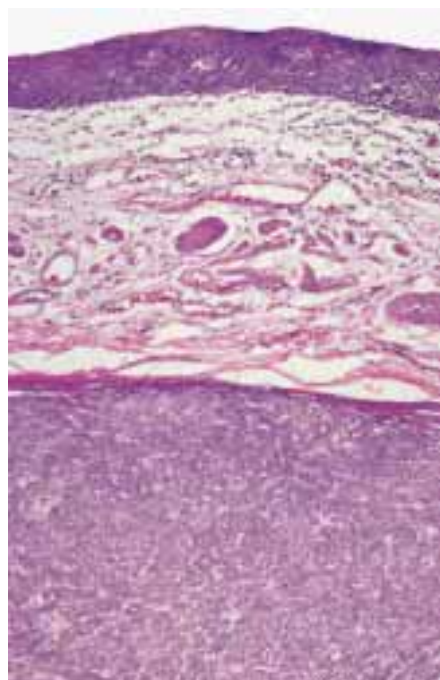


Fig. 1.32 Stromal tumour of the oesophagus, involving the oesophageal muscle layer beneath a normal mucosa.

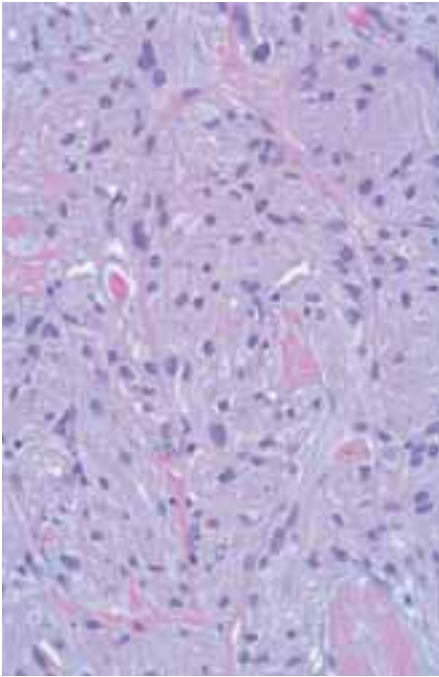


Fig. 1.33 Granular cell tumour of oesophagus.

Leiomyosarcoma, a malignant tumour featuring differentiated smooth muscle cells, is rare in the oesophagus. In a recent series, such tumours comprised 4% of all combined smooth muscle and stromal tumours. They were large tumours that presented in older adults, and all patients died of disease. Diagnosis is based on demonstration of smooth muscle differentiation by α -smooth muscle actin, desmin or both, and lack of KIT expression {1228}.

Stromal tumours (GISTs) are rare in the oesophagus, and comprise 20-30% of the combined cases of smooth muscle and stromal tumours. Like elsewhere in the digestive system, they predominantly occur in older adults between the 6th and 8th decades; oesophageal stromal tumours may have a male predominance. Most oesophageal examples are spindle cell tumours, and a minority are epithelioid. Oesophageal GISTs are identical with their gastric counterparts by their positivity for KIT and CD34, variable reactivity for smooth muscle actin and general negativity for desmin. Most are clinically malignant, and commonly develop liver metastases. The oesophageal tumours analyzed to date have shown similar *c-kit* mutations (exon 11) as observed in gastric and intestinal GISTs {1228}. The pathological features are described with gastric GISTs.

Granular cell tumours are usually detected endoscopically as nodules or small sessile polyps predominantly in the distal oesophagus {1216, 7}. Benign behaviour is the rule, but a case of malignant oesophageal granular cell tumour has been reported. The tumours are usually small, up to 1-2 cm in diameter, and are grossly yellow, firm nodules. Histologically they are composed of sheets of oval to polygonal cells with a small central nucleus and abundant granular slightly basophilic cytoplasm. This is due to extensive accumulation of lysosomes filled with lamellar material. Granular cell tumours are typically PAS- and S100-protein positive and negative for desmin, actin, CD34 and KIT. Tumours that encroach upon the mucosa may elicit a pseudocarcinomatous squamous hyperplasia {862, 1710}.

Rhabdomyosarcoma has been reported in older adult patients in distal oesophagus. A few well-documented cases have shown features similar to embryonal rhabdomyosarcoma {2002}. Demonstration of skeletal muscle differentiation by the presence of cross-striations, electron microscopy, or immunohistochemistry is required for the diagnosis.

Synovial sarcoma has been reported in children and in older adults. These tumours usually present as polypoid masses in the proximal oesophagus {168, 149}.

Kaposi sarcoma may appear as a mucosal or less commonly more extensive mural lesion, usually in HIV-positive patients. Histologically typical are spindle cells with vascular slit formations and scattered PAS-positive globules. The tumour cells are positive for CD31 and CD34.

Grading

Histological grading follows the systems commonly used for soft tissue tumours. Mitotic activity is the main criterion for grading stromal sarcomas and leiomyosarcomas, namely those tumours with over 10 mitoses per 10 HPF are considered high-grade.

Genetics

Somatic deletions and gene rearrangements involving the genes encoding alpha5 and 6 chains of collagen type IV have been described in oesophageal leiomyomatosis associated with Alport syndrome {1704, 1982} and in sporadic



Fig. 1.34 Kaposi sarcoma in a patient with acquired immunodeficiency syndrome.

leiomyoma {683}, whereas these tumours do not have *c-kit* gene mutations commonly found in GISTs {1018}. Comparative genomic hybridization studies have shown that oesophageal leiomyomas do not have losses of chromosome 14, as often seen in GIST, but instead have gains in chromosome 5 {450, 1664}. Oesophageal stromal tumours show similar *c-kit* mutations as observed in gastric and intestinal GISTs (see stomach mesenchymal tumours) {1228}.

Kaposi sarcoma is positive for human herpesvirus 8 by PCR.

Prognosis

The prognosis of oesophageal sarcomas, like carcinomas, is largely dependent on the size, depth of invasion, and presence or absence of metastasis.

Secondary tumours and melanoma of the oesophagus

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Secondary tumours

Definition

Tumours of the oesophagus that originate from but are discontinuous with a primary tumour elsewhere in the oesophagus or an extra-oesophageal neoplasm.

Incidence

Metastatic spread to the oesophagus is uncommon. An unusually high frequency (6.1% of autopsy cases) was reported from Japan {1249}.

Origin of metastases

The concept of intramural metastasis in oesophageal squamous cell carcinoma is discussed in the chapter on squamous cell carcinoma of the oesophagus. Neoplasms of neighbouring organs such as pharynx or gastric cardia {714} can spread to the oesophagus via lymphatics. Haematogenous metastases from any primary localization may occur. Reported primary sites include thyroid {335}, lung {1416, 1249}, breast {2143,

1249, 545}, skin {1569, 1203}, kidney {1956}, prostate {1318} and ovary {1249}.

Localization

The most common site of involvement is the middle third of the oesophagus.

Clinical features

The leading symptom is dysphagia, whereas achalasia and upper gastrointestinal bleeding with anemia are unusual {545}. Barium swallow examination, endoscopy, computed tomography and magnetic resonance imaging demonstrate in most cases a submucosal tumour, but any aspect resembling a primary oesophageal carcinoma may be observed {545, 1318, 714}.

Histopathology and predictive factors

Submucosal localization without invasion of the mucosa is characteristic for a metastasis. Early metastases of gastric and oesophageal tumours into the oesophagus may be local indicators of systemic spread {896, 714}. The pres-

ence of metastasis in the oesophagus is a sign of poor prognosis, but the outcome is much better when the primary tumour growth rate is slow, and when other metastases are excluded {1416, 1249}.

Melanoma

ICD-O Code

8720/3

Malignant melanoma in the oesophagus is much more commonly metastatic than primary. Primary oesophageal melanomas are usually polypoid and are clinically aggressive lesions {400, 353}. They are believed to arise from a zone of atypical junctional proliferation of melanocytes and such a proliferation is often present adjacent to the invasive tumour, although it may not be observed in advanced disease. The histology of the invasive component is indistinguishable from cutaneous melanoma {409}. Growth is typically expansile rather than infiltrative.

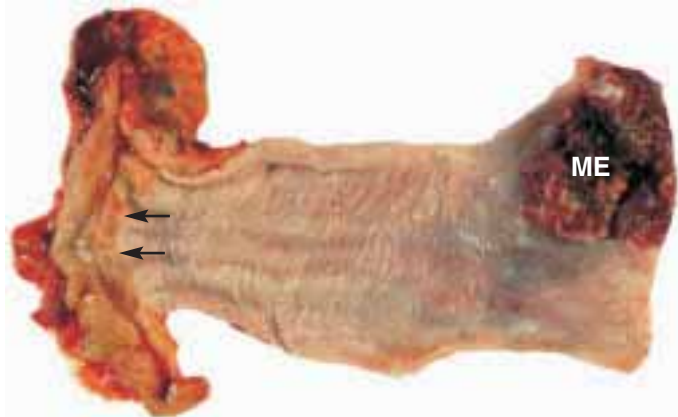


Fig. 1.35 Primary melanoma of the oesophagus (ME). The gastro-oesophageal junction is on the left (arrows).

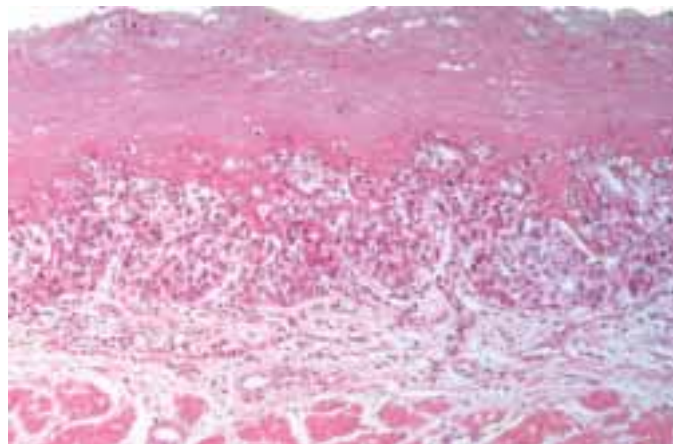


Fig. 1.36 Primary malignant melanoma of the distal oesophagus. Zone of atypical junctional proliferation of melanocytes located adjacent to the invasive tumour. This supports the diagnosis of a primary melanoma.