**Updates on World Health Organization Classification and Staging of oesophageal
tumours: Implications for future clinical practice**

Alfred King-yin Lam¹, MBBS, MD, FRCPA, PhD,

¹School of Medicine, Griffith University, Gold Coast, Australia

Correspondence to: Professor Alfred Lam, Head of Pathology, Griffith Medical School,
Gold Coast Campus, Gold Coast QLD 4222, Australia. a.lam@griffith.edu.au

Telephone +61 7 56780718 Fax +61 7 56780303

Short title: Classification and Staging of oesophageal tumours

Keywords: oesophagus; staging; AJCC; WHO; pathology

Conflicts of interest: none

Funding source: none

Acknowledgements

The author would like to thank Dr, Dr Elaine Cheung from Queen Elizabeth Hospital of
Hong Kong for her contribution to Figure 1C.

25 **Abstract**

26 The Fifth edition of the World Health Organization Classification of Digestive system and
27 American Joint Committee on Cancer (AJCC) staging manual contain substantial refinements
28 of information for oesophageal tumours. The epithelial tumours of oesophagus are classified
29 as benign, dysplasia and malignant groups. Dysplasia is divided into Barrett dysplasia and
30 squamous dysplasia and graded into either low grade or high grade. Malignant oesophageal
31 tumours are often adenocarcinoma or squamous cell carcinoma. The main update in cancer
32 staging in oesophageal tumours is the subdivision of the prognostic staging into 3 groups;
33 squamous cell carcinoma, adenocarcinoma and carcinoma after adjuvant therapy. HER-2
34 amplification is recognized as a molecular target for therapy of oesophagogastric
35 adenocarcinoma. The other oesophageal tumours are adenoid cystic carcinoma,
36 mucoepidermoid/ adenosquamous carcinoma, undifferentiated carcinoma and neuroendocrine
37 neoplasms. Overall, the incorporation of new data and definitions on histopathology,
38 prognostic factors and genetics are important for personalized management of patients with
39 oesophageal tumours.

40

41 **Keywords:** oesophagus; WHO; staging; dysplasia; carcinoma

1. Introduction

The histology and function of the mucosal lining of the oesophagus and oesophagogastric junction are different from the rest of gastrointestinal tract. It follows that the epidemiology, pathogenesis, morphology, classification as well as clinical management of the tumours of the region are different from the other portions of gastrointestinal tract. These unique features and complexity of tumours from oesophagus and oesophagogastric junction are reflected in the updated information provided by the current edition of American Joint Committee on Cancer (AJCC) cancer staging manual [1] and the World Health Organization (WHO) classification of digestive system.[2]

The 8th edition of the AJCC cancer staging manual published in 2016 [1], adopted for use in 2017 and with its web updates for use in 2018 (www.cancerstaging.org) contains extensive modifications of the pathological staging of oesophageal cancers which were different from the 7th edition published in 2010.[3] The changes are based on machine learning of data of the prognostic impacts of different clinicopathological parameters collected from patients with oesophageal cancers worldwide.[1]

In 2018, an editorial board formed for editing the oesophageal tumours in the 5th edition of the World Health Organization (WHO) classification of digestive system and the classification was published in 2019.[2] The WHO group adopted the new staging criteria (8th edition of the AJCC cancer staging manual) as well as substantial modifications of the classification of oesophageal cancers documented in the fourth edition of WHO classification that was published in 2010.[4] These modifications are based on new knowledge of the pathogenesis, molecular markers, clinical behaviour of these tumours as well as the clinical management.

In the current WHO classification of digestive system, only the epithelial tumours (including neuroendocrine neoplasms) of the oesophagus were grouped in the Chapter 2 –

“Tumours of the oesophagus” with sections for different classes of benign, pre-invasive and malignant tumours. The other tumours in the oesophagus was described together with tumours in other sites of the gastrointestinal tract in other Chapters.

The following review will discuss the classification, provide updates, and highlight the changes in new WHO classification and pathological staging which are important for the management of patients with oesophageal tumours.

2. Benign epithelial tumour and precursors

2.1 Squamous cell papilloma

Squamous cell papilloma is the most common benign epithelial tumour in the oesophagus. The tumour is first described in a separate section in the current WHO classification of Digestive system tumours.[5] The prevalence of squamous cell papilloma in endoscopic series ranges from 0.01% to 0.45%.[6] The low prevalence of the tumour could be related to the fact that this benign tumour is often small (median diameter = 3mm) and asymptomatic.[6] In large endoscopic series from France, the tumour is more common in middle age (median age =50) and located mostly in lower oesophagus.[6] The aetiologies of the tumour include chronic mucosal irritation, human papilloma virus (HPV) and genetic syndrome.[6] In rare instances, especially in the setting of genetic syndrome (e.g. Goltz-Gorlin syndrome/focal dermal hypoplasia), multiple squamous cell papillomas may arise in the oesophagus.[7] On histological examination, squamous cell papilloma shows papillary proliferation of non-dysplastic squamous epithelium with a fibrovascular core of lamina propria. Although squamous cell carcinoma has been associated with squamous cell papilloma [6,8], it is unlikely that squamous cell papilloma could progress to squamous cell carcinoma.

3. Pre-invasion Lesions/Dysplasia

3.1. Barrett dysplasia

Barrett dysplasia is a neoplastic epithelium without invasion occurring in area of metaplastic columnar epithelium in the oesophagus. Gastroesophageal reflux with inflammation and columnar/glandular metaplasia (mostly intestinal metaplasia) is the fundamental factor for occurrence of Barrett dysplasia and to adenocarcinoma.[9] In the current WHO classification, the term “Barrett dysplasia” is adopted as nearly all of the cases were related to the pathogenesis of metaplastic columnar epithelium. Barrett dysplasia is mostly of intestinal type and occasional of foveolar type (non-intestinal type) without goblet cells but with prominent cytoplasmic mucin. Endoscopic resection is often used to treat Barrett dysplasia and early staged adenocarcinoma.[10] The two-tier system (high-grade and low-grade) have been important in the selection of high-grade Barrett dysplasia for treatment. However, in the recent years, there is shift of management approach for ablation even for low-grade Barrett dysplasia. The differentiation of high grade versus low grade dysplasia is based on cytological and architectural abnormalities. Low-grade Barrett dysplasia shows cytological atypia but no architectural atypia whereas high-grade Barrett dysplasia reveals a greater degree of cytological atypia and often with architectural atypia (back to back and cribriform arrangement of glands) (Figure 1A and 1B). In a meta-analysis, the pooled annual incidence rate of progression to oesophageal adenocarcinoma was 0.5%.[11]

3.2. Squamous dysplasia

Squamous dysplasia is the precursor of squamous cell carcinoma. Thus, the aetiological factors and epidemiological features follow that of squamous cell carcinoma.[11] In areas with high incidence of squamous cell carcinoma with screening on high-risk patients, the prevalence of squamous dysplasia could be high.[12] In a study in China, over a follow-

up period of 3.5 years, oesophageal squamous cell carcinoma develops in 5% of patients with low-grade dysplasia.[13]

It is important to identify squamous dysplasia or early stages squamous cell carcinoma as endoscopic resection could be used to manage this group of lesions.[14] The current WHO classification has adopted the two-tier (low grade and high grade) for grading of oesophageal squamous dysplasia (Figure 1C and 1D). Low grade squamous dysplasia shows squamous cells with mild cytological atypia and limits to the lower half of the squamous epithelium. In contrast, high grade squamous dysplasia consists of squamous cells with either cytological atypia involves more than half of the squamous epithelium or with severe cytological atypia.[15] High grade squamous dysplasia includes the lesion labelled as “carcinoma-in-situ”. The use of the terminology “mild dysplasia”, “moderate dysplasia”, “severe dysplasia”, “carcinoma-in-situ” is not recommended.

4. Malignant epithelial tumours and neuroendocrine neoplasms

Malignant oesophageal epithelial tumours comprised mainly of adenocarcinoma and squamous cell carcinoma. Pathological staging applies predominately to these two carcinomas.

4.1 Pathological Staging and prognostic factors

The purpose of staging of cancer is to provide guide to prognosis and plan for treatment for patients with malignant oesophageal epithelial tumours. Thus, the various groups defined in the AJCC cancer staging Manuel are now termed “prognostic staging groups”. One of the unique features of prognostic stage grouping in oesophageal cancer which is different from the stage grouping of cancers in other portions of the gastrointestinal tract is the separation of stage grouping for two categories of histology, adenocarcinoma group and squamous cell carcinoma group based on data showing that difference in patients’

prognosis. The other unique feature is starting from the current edition of AJCC, separate pathological prognostic stage grouping of those patients with post neoadjuvant therapy (ypTNM) and those without neoadjuvant therapy is adopted (pTNM) (Table 1).

In the current AJCC prognostic stage grouping, in contrast to stage grouping in AJCC in 7th edition, stage IV is subdivided into stage IVA and stage IVB (Table 1). A couple of adverse pathological factors could upgrade an oesophageal cancer into stage IVA (cancer with these parameters were classified as stage IIIC in the previous edition). In addition, the presence of distant metastases (identified as stage IV in previous edition) will upgrade the pathological stage of a carcinoma to stage IVB. Stage III is only subdivided into stage IIIA and IIIB (without IIIC in the previous edition). Stage III cancers comprise mainly cancers with lymph node metastases but without distant metastases (M0). There are two exceptions of “lymph node positive = stage III” rules. One is T4a N0 oesophageal cancer, which is labelled as prognostic staging group IIIB although there is no lymph node metastasis. The other one is oesophageal cancer of early T stage (T1) and presence of small number of lymph node (N1) is classified as a stage IIB cancer instead of stage III cancer.

For adenocarcinoma of oesophagus and oesophagogastric without treatment by neoadjuvant therapy, the parameters used for prognostic stage grouping are T, N, M and tumour grade.[16] Stage I is divided into 3 subgroups, stage IA, IB and IC (instead of no division of stage I in seventh edition of AJCC cancer staging Manuel) whereas Stage II is divided into stage IIA and stage IIB. The tumour grade is an important prognostic marker only in subgrouping for early stages oesophageal cancers (stage I and stage II) (Table 1).

For oesophageal squamous cell carcinoma without treatment by neoadjuvant therapy, the parameters used for prognostic stage grouping are T, N, M, tumour grade and tumour location (Table 1).[17] Like in the subgrouping of oesophageal adenocarcinoma, tumour grade is important in subgrouping squamous carcinoma of early stages cancers (stage I and

stage II). Stage I and II oesophageal squamous cell carcinomas are divided into 2 subgroups each, namely stage IA, IB, IIA and IIB respectively. The location of oesophageal squamous cell carcinoma is a parameter used to subgroup stage II cancers. Patients with cancer in the lower oesophagus is in subgroup with better prognosis than those with cancer in upper or middle oesophagus.

In patients after receiving neoadjuvant therapy, the prognostic stage subgrouping for adenocarcinoma and squamous cell carcinoma is identical (Table 1). In addition, in ypTNM stage grouping, there is no subgrouping for stage I and stage II cancers (in contrast to pTNM stage grouping for oesophageal adenocarcinoma or squamous cell carcinoma). The presence of lymph node metastases (either N1 or N2) or with tumour extent of T4a will make a cancer stage III. Thus, in contrast to stage grouping of those without receiving neoadjuvant therapy, T1N1 cancer is grouped into stage III cancer (instead of being stage IIB in pTNM stage grouping). The presence of T4b or N3 will classify a cancer as stage IVA. The grade or location of the cancer do not affect the prognostic stage grouping.

Apart from the parameters mentioned in the stage grouping, other pathological features were shown to be associated with prognosis of oesophageal cancer.[1] These include tumour size, status of surgical margins and presence of lymphovascular permeation and extra-nodular extension of cancer. HER-2 status of cancer is important in prediction of response to target therapy to HER-2 in patient with oesophagogastric adenocarcinoma. Tumour regression grade and lymph node downstaging after neoadjuvant therapy are also of prognostic importance. Grading of the tumour regression is commonly done either by the proportion of cancer as detected by the amount of therapy-induced fibrosis in relation to the residual cancer (Mandard system) or estimated percentage of residual cancer in relation to the previous cancer site (Becker system).[18]

4.2 Histological types of malignant epithelial tumours

4.2.1. Adenocarcinoma

Oesophageal adenocarcinoma is the most common oesophageal malignancy in the Western populations. The most common aetiological factor is gastro-oesophageal disease with precursor lesion identified as Barrett oesophagus. [9,18] As a result, adenocarcinomas mainly occur either in the lower oesophagus or oesophagogastric junction. Thus, in the current WHO classification of Digestive system tumours, adenocarcinomas in the oesophagus and oesophagogastric junction were described together in a single section. There is a change in anatomical definition of adenocarcinoma of the oesophagogastric junction which now includes adenocarcinoma with epicentre within 20mm (instead of 50mm) of the oesophagogastric junction. [1,16]

The adenocarcinoma had a 3-tier grading system depends on the percentage of glandular formation (well differentiated = >95%; moderately differentiated 50% to 95%; poorly differentiated <50%). The 3-tier grading is adopted because the 3-tier grading was used in stage subgrouping in the current AJCC staging of oesophageal cancers.[1] Histologically, oesophageal adenocarcinoma could be arranged in tubular, papillary, mucinous and signet-ring patterns (Figure 2A, 2B).[18] They are often in mixture patterns. There are limited data on the clinical impacts of these patterns. Thus, they are labelled as patterns and not as subtypes of adenocarcinoma.

Amplification of the *ERBB2* (*HER2*) gene with resulting overexpression of HER-2 protein is the molecular target for approved therapy for treatment of advanced stages or metastatic oesophagogastric/lower oesophageal adenocarcinoma.[18] Thus, *in-situ* hybridisation for detection of the amplification of the *EBER* gene and immunohistochemical assessment of increase expression of HER-2 protein are used in the management of patients with oesophagogastric/lower oesophageal adenocarcinoma. It is worth noting that HER-2

staining is often in basolateral or lateral membrane in cancer cells of oesophagogastric/lower oesophageal adenocarcinoma which contrasts with the complete membrane staining of cells in breast carcinomas.

4.2.2. Adenoid cystic carcinoma

Oesophageal adenoid cystic carcinoma is first being described in a separate section in the current WHO classification of Digestive system tumours.[19] It was included as a subtype of oesophageal adenocarcinoma in the previous edition of WHO classification of Digestive system tumours.[4]

Oesophageal adenoid cystic carcinoma is an oesophageal carcinoma with morphology identical to the adenoid cystic carcinoma of the salivary gland. It is likely the carcinoma differentiates in the direction of oesophageal glands. The carcinoma comprises epithelial and myoepithelial tumour cells forming true glands and pseudo glands and arranged in cribriform, tubular and solid architecture (Figure 2C). Immunohistochemical stains could be used to highlight the epithelial and myoepithelial cells in the carcinoma. Oesophageal adenoid cystic carcinoma should be differentiated from oesophageal basaloid squamous carcinoma. Adenoid cystic carcinoma does not have squamous differentiation, central necrosis, prominent mitotic figures and high-grade squamous dysplasia in the mucosa. In addition, markers for myoepithelial differentiation (S-100, smooth muscle actin) are negative in basaloid squamous cell carcinoma.

Oesophageal adenoid cystic carcinoma is uncommon with slightly more than 100 reported cases in the literature. It accounts for approximately 0.1% of all oesophageal neoplasms.[20] The carcinoma most often located in the middle third of the oesophagus.[21] Like the oesophageal squamous or adenocarcinoma, oesophageal adenoid cystic carcinoma is more common in men and occurs often in seventh decade of life.[22, 23] The prognosis of

patients with oesophageal basaloid squamous cell carcinoma is variable and depends on the pathological stage.[22, 23] In AJCC cancer staging grouping, oesophageal adenoid cystic carcinoma follows that of oesophageal adenocarcinoma.

4.2.3. Mucoepidermoid carcinoma and Adenosquamous carcinoma

Mucoepidermoid carcinoma and adenosquamous carcinoma are carcinomas with both squamous and mucinous containing (glandular) components (Figure 2D). They are first described in a separate section in the 2019 WHO classification of Digestive system tumours.[3] They were included as subtypes of oesophageal adenocarcinoma in the previous edition of WHO classification of Digestive system tumours.[4] In adenosquamous carcinoma, the squamous and mucinous containing components are separate. On the other hand, in mucoepidermoid carcinoma, the squamous, mucinous containing as well as intermediate components are mixed. In large series, this group of carcinomas comprised approximately 2% of oesophageal carcinomas.[24] Mucoepidermoid carcinoma is more commonly reported than adenosquamous cell carcinoma.[25] In addition, most of the large series being reported in Asian populations.[26]

The diagnosis of these carcinomas often requires resection specimen as the glandular component may not be apparent in the biopsy specimens. Retrospective analysis of endoscopic biopsy specimens of these carcinomas showed that only 42% of the cases showed the mucin containing component in the biopsy.[27] In fact, there is no established guidelines of the proportion of mucin containing (glandular) component or squamous component needs in the definition. Japanese Esophageal Society [28] requires at least 20% of either component whereas Lam et al. [27] documented a requirement of at least 10% of mucin containing component to be selected into this group of carcinomas.

Like squamous cell carcinoma, these carcinomas are often noted in the mid portion of the oesophagus. In general, the results of a few studies suggest that these carcinomas may be more aggressive than conventional squamous cell carcinoma. [27,29,30] Thus, these carcinomas should not be in the stage grouping of oesophageal adenocarcinomas. There is no current recommendation of stage grouping for this group of oesophageal carcinomas.

4.2.4. Squamous cell carcinoma

Squamous cell carcinoma is the most common type of oesophageal carcinoma and occur mainly in Asian populations.[11] The aetiology of the carcinoma is multifactorial and the main environmental risk factors are heavy smoking, high consumption of alcohol and various dietary factors.[11,31] Human papilloma virus (HPV) was identified in a portion of the squamous cell carcinoma.[11, 32, 33] Nevertheless, HPV is not found in many oesophageal squamous cell carcinomas. Thus, the virus is unlikely to be the major cause of the cancer. Approximately half of the squamous cell carcinoma located in the middle portion of the oesophagus. [34,35]

Squamous cell carcinoma is graded on a 3-tier system. The grading criteria are more subjective when compared with adenocarcinoma and depend on cytological atypia, mitotic activity and presence of keratinization. The current AJCC staging group for oesophageal squamous cell carcinoma is based on three grades of the tumour. [1] (Table 1) (Figure 3A). Nevertheless, it is difficult to differentiate grade 1 from grade 2 squamous cell carcinoma.

Apart from the conventional squamous cell carcinoma, there are 3 subtypes of squamous cell carcinoma, namely verrucous squamous cell carcinoma, basaloid squamous cell carcinoma and spindle cell squamous cell carcinoma.

Verrucous squamous cell carcinoma is rare with approximately eighty cases reported in the literature.[36] It is often located in the lower oesophagus.[37] A small number of cases

were associated with HPV.[38, 39] However, a recent Italian study on nine verrucous squamous cell carcinomas using three different molecular methods failed to detect any HPV.[36] It is a well differentiated squamous cell carcinoma with minimal cytological atypia and mitotic activity. The carcinoma is characterized by papillary architecture and broad bulbous pushing fronts.[15] The carcinoma is often superficial (early T stage) and seldom have lymph node metastasis (in only 7.5% of patients).[36] Distant metastasis has not been reported. Thus, the prognosis of patients with this subtype of squamous cell carcinoma is good.[40] and the tumour could be treated by endoscopic resection in appropriate cases. [41, 42]

Basaloid squamous carcinoma accounts for 4 to 5% of primary oesophageal carcinoma. [43,44] The carcinoma has carcinoma with basaloid appearance (resemble basal cells in stratified squamous epithelium) with abrupt transition with squamous carcinoma cells. It shows frequent tumour mitosis and often with comedonecrosis (necrosis in the centre of tumour nests).[15] Patients with oesophageal basaloid squamous cell carcinoma often show shorter overall survival than conventional squamous cell carcinoma though the difference may not be significant. [43, 44, 45]

Spindle cell squamous cell carcinoma comprises neoplastic spindle cells (Figure 4A). The carcinoma accounts for approximately 1 to 2 % of oesophageal carcinomas. [46, 47] It has also been labelled as “sarcomatoid carcinoma” or carcinosarcoma”. The neoplastic spindle cell component is likely to be dedifferentiated from the squamous carcinoma component via epithelial-mesenchymal transition (EMT) and could show osseous, cartilaginous or skeletal muscle differentiation.[47] The spindle cell carcinoma component could show weak positivity to cytokeratins. The poorly differentiated region may be negative to cytokeratins.[48] In this instance, the carcinoma may be difficult to differentiate from sarcomas. The identification of epithelial component is important to making the

diagnosis of spindle cell squamous cell carcinoma. Sometimes, the only prominent abnormal epithelial component may be seen as high grade squamous dysplasia and tiny islands of early invasive squamous cell carcinoma.[14] (Figure 4B) Some of the spindle cell squamous cell carcinoma has a polypoid growth pattern (Figure 4C) which shows a better patients' prognosis than those with ulcerative growth pattern or those with conventional squamous cell carcinoma.[48]

4.2.5. Undifferentiated carcinoma

Oesophageal undifferentiated carcinoma is first described in a separate section in the current WHO classification [49]. It is defined as carcinoma lacking squamous, glandular or neuroendocrine differentiation. Thus, in depth histological examination, use of histochemical stains (mucins) as well as immunohistochemical markers are needed to exclude the presence of squamous (p40, p63 and CK5/6), glandular or neuroendocrine differentiation. In addition, immunohistochemical markers (positivity to cytokeratin) could be used to confirm the epithelial differentiation and differentiate from rare non-epithelial tumours such as melanoma, lymphoma and sarcomas. The carcinoma often shows a syncytial pattern of carcinoma cells with giant tumour cells, large pleomorphic nuclei and prominent macronucleoli and necrosis.[50] Sometimes, there could be dispersed large atypical cells with rhabdoid morphology which show loss expression of SMRCA2/SMARCA4. Many oesophageal undifferentiated carcinomas were of advanced pathological stages and thus the prognosis of patients with undifferentiated carcinoma was often poor.[50] In the previous WHO classification, undifferentiated carcinoma was presented as a grade 4 squamous carcinoma.[4] Thus, it has been suggested that the staging could follow oesophageal squamous cell carcinoma staging group. However, there is no evidence-based study to support this approach.

There is a carcinoma subtype with characteristic pathological features termed “lymphoepithelioma-like carcinoma”. The carcinoma has heavy lymphocytes and plasma cell infiltrates in the stroma (Figure 5A and 5B). Cytokeratin is needed to confirm the epithelial nature of the tumour (Figure 5C). Some cases are positive for Epstein Barr virus.[51] (Figure 5D). Slightly more than 20 cases were reported worldwide. [52,53] The carcinoma is mainly reported in Asian populations with a few exceptions. This subtype of oesophageal carcinoma appears to have a better prognosis than other oesophageal carcinomas.[54]

4.2.6. Neuroendocrine neoplasms (NEN)

In the 2000’s WHO classification of tumours of the Digestive system, this group of tumours is labelled “endocrine tumours of the oesophagus”.[55] In the 2010’s WHO classification of tumours of the Digestive system, the term “neuroendocrine neoplasms of the oesophagus” (NENs) was introduced.[4] In the current WHO classification of the Digestive system tumours, oesophageal NEN is classified in the line with the neuroendocrine neoplasms of the other parts of the gastro-entero-pancreatic tract.[56, 57] and are classified into neuroendocrine tumour (NET), neuroendocrine carcinoma (NEC) and mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN).

More than 95% of oesophageal NENs are NECs.[58] NEC could be small cell type (SCNEC) or large cell type (LCNEC). In the literature, 98% of oesophageal NENs are SCNEC and more than three quarters (>75%) are from Eastern countries. Like oesophageal squamous cell carcinoma, oesophageal SCNEC occurs mostly in middle oesophagus and with higher incidence in men, patients of advanced age and association with heavy smoking and high alcohol consumption. It accounts for approximately 1% of oesophageal neoplasms in surgical series [59] and 3% of oesophageal neoplasms in autopsy series [60]. The tumour is

often large and have primitive tumour cells with high nuclear to cytoplasmic ratio as in the counterpart in lung (Figure 6). The carcinoma may resemble basaloid squamous carcinoma, in the biopsy specimen. Use of neuroendocrine markers (chromogranin A, synaptophysin, etc.) and squamous cell differentiation markers (p63, p40, CK5/6) is useful to differentiate these two subtypes of oesophageal carcinomas.

Oesophageal LCNEC comprises of approximately 1% of NENs and mostly (>90%) reported in Western countries. Oesophageal NET is extremely rare and comprise less than 1% of oesophageal NEN. NET occurs in approximately same prevalence in Eastern and Western populations. Less than 50 oesophageal NETs were reported in the literature. Most oesophageal NETs are either grade 1 or 2.

In the current WHO classification, “MiNEN” was used instead of “mixed adeno-neuroendocrine carcinomas (MANECs)” used in the 2010 WHO classification to include a border classification. [4,57] In the oesophagus, MiNEN often comprise of NEC combine with adenocarcinoma or squamous cell carcinoma. Rarely, mixed adenocarcinoma and NET occurs in the oesophagus.[61]

The two subtypes of oesophageal NEC show no difference in patients’ prognosis. In the current AJCC staging manual, there is no stage grouping for staging of oesophageal NEC. The overall survival rates of the patients with NEC is significantly lower than those with oesophageal adenocarcinoma.[62] Surgical resection is achievable in less than half of the cases with oesophageal NEC and majority of the non-resection cases had distant metastases at presentation.[63] In addition, patients with oesophageal NEC has lower survival rates than those having oesophageal MiNEN with NEC as the neuroendocrine component.[64] Distant metastases are the strongest adverse prognostic factor for NEC. Thus, it is advised that NEC should be categorized using TNM grouping as in other oesophageal carcinomas. Rarely, oesophageal NEC and MiNEN of type - NEC and adenocarcinoma could arise in patients

with Barrett oesophagus. They are often being detected at early stage and might show better patients' survival compared with oesophageal NEC.[65] Furthermore, in patient having MiNEN with adenocarcinoma component, the carcinoma is staged as adenocarcinoma.

5. Non-epithelial tumours

This group of tumours are described with their counterparts in separate chapters. Hematolymphoid tumours are very rare in the oesophagus and could comprise of a variety of histological types. [66 – 68] Many of the reported cases are extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma).

Different mesenchymal tumours have been reported in the oesophagus. Of these, leiomyoma and granular cell tumour are the most common benign mesenchymal tumour in the oesophagus.[69] In a large series (n=36), the mean age of patients with leiomyoma at presentation was 62 years and multiple leiomyomas was seen in 11% of the patients.[70] Granular cell tumour of oesophagus has a predilection for lower oesophagus and more often occur in females.[71] The tumour mainly occurs in patients in the fifth decade of life.

In the other tumour category, mucosal melanoma could occur in the oesophagus. It is the most common non-epithelial malignancy noted in the oesophagus. The tumour comprises approximately 0.2% of oesophageal cancers.[72] A review of literature reveals that the tumour was noted in patients with mean age of 61. The tumour usually developed in the lower oesophagus (with slightly less than half in the lower oesophagus).[73] The survival rate of patients with mucosal melanoma of the oesophagus is poor. The median survival of a large series (n=70) of mucosal melanoma from China is 13.5 months.[74]

Other than direct infiltration of oesophagus, metastatic tumour could occur in the oesophagus, they could be from breast carcinoma, lung carcinoma or cutaneous melanoma.[75]

6. Conclusion

Tumours of different morphological features occur in oesophagus and oesophagogastric junction. Table 2 summarizes the categories of this group of tumours mentioned in the current WHO classification. The commonest tumours are squamous cell carcinoma and adenocarcinoma. The two carcinomas are differences in aetiopathogenesis, epidemiology, patients' prognosis and treatment protocols. Adjuvant therapy is being employed for treatment of many oesophageal carcinomas. Pathological stage groupings for oesophageal carcinomas are updated based on the variance in these two carcinomas as well as the use of adjuvant therapy. Pathological parameters are more important for staging of early-stage oesophageal carcinomas. On the other hand, advanced stage cancers are often treated by neoadjuvant therapy and pathological parameters such as grade and location lose their clinical relevance. Overall, the incorporation of new data on histopathology, prognostic factors and genetics are important for current personalized management of patients with oesophageal tumours.

FIGURE LEGENDS

Figure 1 Oesophageal dysplasia

1A. Low grade Barrett dysplasia

1B. High grade Barrett dysplasia

1C. Low grade squamous dysplasia

1D. High grade squamous dysplasia

Figure 2. Oesophageal glandular malignancy

2A. Adenocarcinoma, tubular pattern

2B. Adenocarcinoma, signet ring pattern

2C. Adenoid cystic carcinoma

2D. Mucoepidermoid carcinoma (mucin stain highlighted the glandular component)

Figure 3. Oesophageal squamous cell carcinoma, conventional and basaloid variants

3A. Squamous cell carcinoma, grade 2 with keratin pearls

3B. Squamous cell carcinoma, grade 3 with focal squamous differentiation

3C. Squamous cell carcinoma, basaloid squamous variant with fibrotic stroma and encasement of nerve

3D. Squamous cell carcinoma, basaloid squamous variant with focal squamous area and necrosis

Figure 4. Oesophageal squamous cell carcinoma, spindle cell variant

4A. Microscopic appearance showing malignant spindle cells

4B. Microscopic appearance showing the malignant spindle cells and the overlying malignant squamous epithelium.

4C. Macroscopic appearance of the tumour showing the characteristics polypoid appearance

Figure 5 Oesophageal undifferentiated carcinoma

5A. Undifferentiated carcinoma underneath the squamous epithelium

5B. Undifferentiated carcinoma composed of tumour cells in inflammatory stroma

5C. Undifferentiated carcinoma highlighted by positive to cytokeratin (AE1/3)

5D. Undifferentiated carcinoma which is EBER positive

Figure 6. Oesophageal small cell neuroendocrine carcinoma

6A. Macroscopic appearance showing a large ulcerative tumour

6B. Microscopic appearance showings of tumour cells with high nuclear to cytoplasmic ratio.

REFERENCES

1. Rice TW, Kelsen D, Blackstone E, Ishwaran H, Patil DT, Bass AJ, Erasmus JJ, Gerdes H, Hofstetter WL. Esophagus and Esophagogastric junction. In: Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM, Meyer LR, editors. AJCC Cancer staging Manual. 8th ed. New York: Springer; 2016, Chapter 16, p.185-202.
2. Edge S, Byrd DR, Compton CC, Fritz AG, Greene F, Trotti A. Esophagus and Esophagogastric junction. In: AJCC Cancer Staging Manual, 7th ed. New York: Springer; 2010, Part 3, chapter 10, p.103-155.
3. Lam AK, Ochiai A, Odze RD. Tumours of the oesophagus: Introduction. In: Odze RD, Lam AK, Ochiai A, Washington MK, editors. WHO Classification of Tumours-Digestive System Tumours, 5th ed. Lyon: IARC; 2019, Chapter 2, p. 28-9.
4. Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO classification of tumours of the Digestive System, 4th ed. Lyon: IARC; 2010, Chapter 2, p.15-37.
5. Lam AK. Oesophageal squamous papilloma. In: In: Odze RD, Lam AK, Ochiai A, Washington MK editors, WHO Classification of Tumours, edition, 5th ed. Lyon: IARC; 2019, Chapter 2, p. 30-1.
6. d'Huart MC, Chevaux JB, Bressenot AM, Froment N, Vuitton L, Degano SV, et al. Prevalence of esophageal squamous papilloma (ESP) and associated cancer in northeastern France. *Endosc Int Open*. 2015;3:E101-6.
7. Pasman EA, Heifert TA, Nylund CM. Esophageal squamous papillomas with focal dermal hypoplasia and eosinophilic esophagitis. *World J Gastroenterol*. 2017;23:2246-50.

- 495 8. Jideh B, Weltman M, Wu Y, Chan CHY. Esophageal squamous papilloma lacks clear
496 clinicopathological associations. *World J Clin Cases*. 2017;5:134-9.
- 497 9. Lam AK. Introduction: Esophageal adenocarcinoma: updates of current status.
498 *Methods Mol Biol*. 2018;1756:1-6.
- 499 10. Kumarasinghe MP, Brown I, Raftopoulos S, Bourke MJ, Charlton A, de Boer WB, et
500 al. Standardised reporting protocol for endoscopic resection for Barrett oesophagus
501 associated neoplasia: expert consensus recommendations. *Pathology*. 2014;46:473-80.
- 502 11. Lam AK. Introduction: Esophageal squamous cell carcinoma-current status and future
503 advances. *Methods Mol Biol*. 2020;2129:1-6.
- 504 12. Yang J, Wei WQ, Niu J, Liu ZC, Yang CX, Qiao YL. Cost-benefit analysis of
505 esophageal cancer endoscopic screening in high-risk areas of China. *World J*
506 *Gastroenterol*. 2012;18:2493-501.
- 507 13. Dawsey SM, Lewin KJ, Wang GQ, Liu FS, Nieberg RK, Yu Y, et al. Squamous
508 esophageal histology and subsequent risk of squamous cell carcinoma of the
509 esophagus. A prospective follow-up study from Linxian, China. *Cancer*.
510 1994;74:1686-92.
- 511 14. Fujii S, Lam AK. Macroscopic assessment and sampling of endoscopic resection
512 specimens for squamous epithelial malignancies with superficial involvement of
513 esophagus. *Methods Mol Biol*. 2020;2129:63-81.
- 514 15. Lam AK. Histopathological assessment for esophageal squamous cell carcinoma.
515 *Methods Mol Biol*. 2020;2129:7-18.
- 516 16. Lam AK. Application of pathological staging in esophageal adenocarcinoma.
517 *Methods Mol Biol*. 2018;1756:93-103.
- 518 17. Lam AK. Application of pathological staging in esophageal squamous cell carcinoma.
519 *Methods Mol Biol*. 2020;2129:19-31.

18. Lam AK, Kumarasinghe MP. Adenocarcinoma of the oesophagus and oesophagogastric junction NOS. In: Odze RD, Lam AK, Ochiai A, Washington MK, editors. WHO Classification of Tumours, 5th ed. Lyon: IARC; 2019, Chapter 2, p.38-43.
19. Lam AK. Oesophageal adenoid cystic carcinoma. In: Odze RD, Lam AK, Ochiai A, Washington MK, editors. WHO Classification of Tumours, 5th ed. Lyon: IARC; 2019, Chapter 2, p. 44-5.
20. Karaoglanoglu N, Eroglu A, Turkyilmaz A, Gursan N. Oesophageal adenoid cystic carcinoma and its management options. *Int J Clin Pract.* 2005;59:1101-3.
21. Guo XF, Mao T, Gu ZT, Fang WT, Chen WH, Shao JC. Adenoid cystic carcinoma of the esophagus: report of two cases and review of the Chinese literature. *Diagn Pathol.* 2012;7:179.
22. Sawada G, Moon J, Saito A, Odagiri K, Kimura Y, Takahashi G, et al. A case of adenoid cystic carcinoma of the esophagus. *Surg Case Rep.* 2015;1:119.
23. Petursson SR. Adenoid cystic carcinoma of the esophagus. Complete response to combination chemotherapy. *Cancer.* 1986;57:1464-67.
24. Fegelman E, Law SY, Fok M, Lam KY, Loke SL, Ma LT, Wong J. Squamous cell carcinoma of the esophagus with mucin-secreting component. Mucoepidermoid carcinoma. *J Thorac Cardiovasc Surg.* 1994;107:62-7.
25. Lam KY, Dickens P, Loke SL, Fok M, Ma L, Wong J. Squamous cell carcinoma of the oesophagus with mucin-secreting component (muco-epidermoid carcinoma and adenosquamous carcinoma): a clinicopathologic study and a review of literature. *Eur J Surg Oncol.* 1994;20:25-31.
26. Lam AK. Histopathological Assessment for Esophageal Adenocarcinoma. *Methods Mol Biol.* 2018; 1756: 67-76.

27. Lam KY, Loke SL, Ma LT. Histochemistry of mucin secreting components in mucoepidermoid and adenosquamous carcinoma of the oesophagus. *J Clin Pathol.* 1993;46:1011-5.
28. Japan Esophageal Society. Japanese Classification of Esophageal Cancer, 11th Edition: part II and III. Esophagus. 2017;14:37-65.
29. Hagiwara N, Tajiri T, Tajiri T, et al. Biological behavior of mucoepidermoid carcinoma of the esophagus. *J Nippon Med Sch.* 2003;70:401-7.
30. Yendamuri S, Malhotra U, Hennon M, Miller A, Groman A, Halloon A, Reid ME. Clinical characteristics of adenosquamous esophageal carcinoma. *J Gastrointest Oncol.* 2017;8:89-95.
31. Brown IS, Fujii S, Kawachi H, Lam AK, Saito T. Oesophageal squamous cell carcinoma NOS. In: Odze RD, Lam AK, Ochiai A, Washington MK, editors, WHO Classification of Tumours, 5th ed. Lyon: IARC; 2019, Chapter 2, p.48-53.
32. He D, Zhang DK, Lam KY, Ma L, Ngan HY, Liu SS, Tsao SW. Prevalence of HPV infection in esophageal squamous cell carcinoma in Chinese patients and its relationship to the p53 gene mutation. *Int J Cancer.* 1997;72:959-64.
33. Lam KY, He D, Ma L, Zhang D, Ngan HY, Wan TS, Tsao SW. Presence of human papillomavirus in esophageal squamous cell carcinomas of Hong Kong Chinese and its relationship with p53 gene mutation. *Hum Pathol.* 1997;28:657-63.
34. Lam KY, Law S, Tin L, Tung PH, Wong J. The clinicopathological significance of p21 and p53 expression in esophageal squamous cell carcinoma: an analysis of 153 patients. *Am J Gastroenterol.* 1999;94:2060-8.
35. Ando N, Ozawa S, Kitagawa Y, Shinozawa Y, Kitajima M. Improvement in the results of surgical treatment of advanced squamous esophageal carcinoma during 15 consecutive years. *Ann Surg.* 2000;232:225-32.

36. Cappellesso R, Coati I, Barzon L, Peta E, Masi G, Scarpa M, et al. Human papillomavirus infection is not involved in esophageal verrucous carcinoma. *Hum Pathol.* 2019;85:50-7.
37. Tabuchi S, Koyanagi K, Nagata K, Ozawa S, Kawachi S. Verrucous carcinoma of the esophagus: a case report and literature review. *Surg Case Rep.* 2020;6:35.
38. Tonna J, Palefsky JM, Rabban J, Campos GM, Theodore P, Ladabaum U. Esophageal verrucous carcinoma arising from hyperkeratotic plaques associated with human papilloma virus type 51. *Dis Esophagus.* 2010;23:E17-20.
39. Vieira CL, Lopes JC, Velosa J. A case of esophageal squamous cell carcinoma with positive HPV 11. *Gastroenterol Hepatol.* 2013;36:311-5.
40. Egeland C, Achiam MP, Federspiel B, Svendsen LB. Verrucous squamous cell cancer in the esophagus: an obscure diagnosis. *Case Rep Gastroenterol.* 2016;10:466-471.
41. Behrens A, Stolte M, Pech O, May A, Ell C. Verrucous oesophageal carcinoma: single case report and case series including 15 patients - issues for consideration of therapeutic strategies. *Viszeralmedizin.* 2014;30:346-52.
42. Soota K, Tirumanisetty P, Lee YJ, Holm A. Experience with endoscopic resection of oesophageal verrucous carcinoma and literature review. *BMJ Case Rep.* 2019;12:pii: e229576.
43. Li TJ, Zhang YX, Wen J, Cowan DF, Hart J, Xiao SY. Basaloid squamous cell carcinoma of the esophagus with or without adenoid cystic features. *Arch Pathol Lab Med.* 2004;128:1124-30.
44. Lam KY, Law S, Luk JM, Wong J. Oesophageal basaloid squamous cell carcinoma: a unique clinicopathological entity with telomerase activity as a prognostic indicator. *J Pathol.* 2001;195:435-42.

45. Salami A, Abbas AE, Petrov R, Jhala N, Bakhos CT. Comparative analysis of clinical, treatment, and survival characteristics of basaloid and squamous cell carcinoma of the esophagus. *J Am Coll Surg*. 2018;226:1086-1092.
46. Lam KY, Law SY, Loke SL, Fok M, Ma LT. Double sarcomatoid carcinomas of the oesophagus. *Pathol Res Pract*. 1996;192:604-9.
47. Raza MA, Mazzara PF. Sarcomatoid carcinoma of esophagus. *Arch Pathol Lab Med*. 2011;135:945-8.
48. Hashimoto M, Kitagami H, Niwa H, Kikkawa T, Ohuchi T, Takenouchi T, Hosokawa M. Prognosis and prognostic factors of esophageal spindle cell carcinoma treated by esophagectomy: a retrospective single-institution analysis. *Esophagus*. 2019;16:292-9.
49. Kawachi H, Saito T. Oesophageal undifferentiated carcinoma NOS. In: Odze RD, Lam AK, Ochiai A, Washington MK (ed), *WHO Classification of Tumours*, 5th ed. Lyon: IARC; 2019, Chapter 2, p. 54-5.
50. Singhi AD, Seethala RR, Nason K, Foxwell TJ, Roche RL, McGrath KM, Levy RM, Luketich JD, Davison JM. Undifferentiated carcinoma of the esophagus: a clinicopathological study of 16 cases. *Hum Pathol*. 2015;46:366-75.
51. Terada T. Epstein-Barr virus associated lymphoepithelial carcinoma of the esophagus. *Int J Clin Exp Med*. 2013;6:219-26.
52. Khokhar N, Nasir H, Amir M, Hassan S, Khan K, Ahmed M. Lymphoepithelioma-like carcinoma of the esophagus: a rare tumor. *J Coll Physicians Surg Pak*. 2017;27:S114-6.
53. Okata T, Uno K, Fujishima F, Saito M, Jin X, Hatta W, Asanuma K, et al. Difficult preoperative diagnosis of lymphoepithelioma-like carcinoma of the esophagus. *ACG Case Rep J*. 2019;6:e00163.

54. Sashiyama H, Nozawa A, Kimura M, Nomura E, Tamaru JI, Ninomiya E, Koide Y, Iino M, Ozawa K. Case report: A case of lymphoepithelioma-like carcinoma of the oesophagus and review of the literature. *J Gastroenterol Hepatol*. 1999;14:534-9.
55. Capella C, Solcia E, Sobin LH, Arnold R. Endocrine tumours of the oesophagus. In: Hamilton SR, Aaltonen LA, editors. *World Health Organization Classification of Tumours - Pathology and Genetics: Tumours of the Digestive System*, 3rd. Lyon; IARC; Chapter 1, p. 26-7.
56. Ishida H, Lam AK. Pancreatic neuroendocrine neoplasms: The latest surgical and medical treatment strategies based on the current World Health Organization classification. *Crit Rev Oncol Hematol*. 2020;145:102835.
57. Scoazec JY, Randi G. Oesophageal neuroendocrine neoplasms. In: Odze RD, Lam AK, Ochiai A, Washington MK, editors. *WHO Classification of Tumours*, 5th ed. Lyon: IARC; 2019, Chapter 2, p. 56-8.
58. Giannetta E, Guarnotta V, Rota F, de Cicco F, Grillo F, Colao A, et al. A rare rarity: Neuroendocrine tumor of the esophagus. *Crit Rev Oncol Hematol*. 2019;137:92-107.
59. Lam KY, Law S, Tung PH, Wong J. Esophageal small cell carcinomas: clinicopathologic parameters, p53 overexpression, proliferation marker, and their impact on pathogenesis. *Arch Pathol Lab Med*. 2000;124:228-33.
60. Lam KY, Law S, Wong J. Low prevalence of incidentally discovered and early-stage esophageal cancers in a 30-year autopsy study. *Dis Esophagus*. 2003;16:1-3.
61. Hoang MP, Hobbs CM, Sobin LH, Albores-Saavedra J. Carcinoid tumor of the esophagus: a clinicopathologic study of four cases. *Am J Surg Pathol*. 2002;26:517-22.

62. Cai W, Ge W, Yuan Y, Ding K, Tan Y, Wu D, Hu H. A 10-year population-based study of the differences between NECs and carcinomas of the esophagus in terms of clinicopathology and survival. *J Cancer*. 2019;10:1520-7.
63. Law SY, Fok M, Lam KY, Loke SL, Ma LT, Wong J. Small cell carcinoma of the esophagus. *Cancer*. 1994;73:2894-9.
64. Ye L, Lu H, Wu L, Zhang L, Shi H, Wu HM, Tu P, Li M, Wang FY. The clinicopathologic features and prognosis of esophageal neuroendocrine carcinomas: a single-center study of 53 resection cases. *BMC Cancer*. 2019;19:1234.
65. Doi S, Matsumoto S, Wakatsuki K, Migita K, Ito M, Kunishige T, Nakade H, Hatakeyama K, Ohbayashi C, Sho M. A neuroendocrine carcinoma with a well-differentiated adenocarcinoma component arising in Barrett's esophagus: a case report and literature review. *Surg Case Rep*. 2018;4:103.
66. George MK, Ramachandran V, Ramanan SG, Sagar TG. Primary esophageal T-cell non-Hodgkin's lymphoma. *Indian J Gastroenterol*. 2005;24:119-20.
67. Tabibian JH, Kalani A, Moran AM, Panganamamula K. Extranodal marginal zone B cell (MALT) lymphoma of the esophagus. *J Gastrointest Cancer*. 2019;50:1034-36.
68. Kobayashi S, Iwamuro M, Nishida K, Tanaka T, Kawano S, Kawahara Y, Yoshino T, Okada H. Primary localized esophageal mucosa-associated lymphoid tissue lymphoma treated by endoscopic submucosal dissection. *Intern Med*. 2018;57:2347-52.
69. Terada T. Benign Tumors of the Esophagus: A histopathologic study of 49 cases among 931 consecutive esophageal biopsies. *Gastroenterology Res*. 2009;2:100-3.
70. Lam KY. Oesophageal mesenchymal tumours: clinicopathological features and absence of Epstein-Barr virus. *J Clin Pathol*. 1999;52:758-60.

71. Ofori E, Ramai D, Lui YX, Reddy M. Esophageal granular cell tumor: a case and review of the literature. *Gastroenterology Res.* 2017;10:372-5.
72. Lam KY, Law S, Wong J. Malignant melanoma of the oesophagus: clinicopathological features, lack of p53 expression and steroid receptors and a review of the literature. *Eur J Surg Oncol.* 1999;25:168-72.
73. Schizas D, Mylonas KS, Bagias G, Mastoraki A, Ioannidi M, Kanavidis P et al. Esophageal melanoma: a systematic review and exploratory recurrence and survival analysis. *Dis Esophagus.* 2019;32:1-9.
74. Dai L, Wang ZM, Xue ZQ, He M, Yuan Y, Shang XQ, Chen KN; Chinese Cooperative Primary Malignant Melanoma of the Esophagus Group (CCPMMEG). Results of surgical treatment for primary malignant melanoma of the esophagus: A multicentre retrospective study. *J Thorac Cardiovasc Surg.* 2020 (in press).
75. Mizobuchi S, Tachimori Y, Kato H, Watanabe H, Nakanishi Y, Ochiai A. Metastatic esophageal tumors from distant primary lesions: report of three esophagectomies and study of 1835 autopsy cases. *Jpn J Clin Oncol.* 1997;27:410-4.

Table 1. Comparisons of the staging group of oesophageal carcinomas in patients with and without neoadjuvant therapy

Yp TNM (post neoadjuvant therapy)				p TNM (pathological) Squamous cell carcinoma						p TNM (pathological) Adenocarcinoma				
Stage	T	N	M	Stage	T	N	M	Grade	Location	Stage	T	N	M	Grade
I	T0	N0	M0	0	Tis	N0	M0	NA	Any	0	Tis	N0	M0	NA
	T1	N0	M0	IA	T1a	N0	M0	G1/GX	Any	IA	T1a	N0	M0	G1/GX
				IB	T1a	N0	M0	G2	Any	1B	T1a	N0	M0	G2
					T1b	N0	M0	G1-2/GX	Any		T1b	N0	M0	G1-2/GX
					T1a	N0	M0	G3	Any	1C	T1a	N0	M0	G3
					T1b	N0	M0	G3			T1b	N0	M0	G3
II	T2	N0	M0		T2	N0	M0	G1	Any	IIA	T2	N0	M0	G1
				IIA	T2	N0	M0	G2	Any		T2	N0	M0	G2
					T2	N0	M0	G3/GX	Any		T2	N0	M0	G3/GX
	T3	N0	M0		T3	N0	M0	Any	Lower	IIB	T3	N0	M0	Any
					T3	N0	M0	G1	Upper/middle					
IIIA	T0	N1	M0	IIB	T3	N0	M0	G2-3/X	Upper/middle					
	T1	N1	M0		T1	N1	M0	Any	Any	IIIA	T1	N1	M0	Any
	T2	N1	M0	IIIA	T2	N1	M0	Any	Any		T2	N1	M0	Any
IIIB	T0	N2	M0		T1	N2	M0	Any	Any		T1	N2	M0	Any
	T1	N2	M0											
	T2	N2	M0	IIIB	T2	N2	M0	Any	Any	IIIB	T2	N2	M0	Any
	T3	N1	M0		T3	N1	M0	Any	Any		T3	N1	M0	Any
	T4a	N0	M0		T4a	N0	M0	Any	Any		T4a	N0	M0	Any
IVA	T3	N2	M0		T3	N2	M0	Any	Any		T3	N2	M0	Any
	T4a	N1	M0		T4a	N1	M0	Any	Any		T4a	N1	M0	Any
	T4a	N2	M0	IVA	T4a	N2	M0	Any	Any	IVA	T4a	N2	M0	Any
	T4b	Any N	M0		T4b	Any N	M0	Any	Any		T4b	Any N	M0	Any
	Any T	N3	M0		Any T	N3	M0	Any	Any		Any T	N3	M0	Any
IV	Any T	Any N	M1	IVB	Any T	Any N	M1	Any	Any		Any T	Any N	M1	Any

T stage measures the depth of involvement of the oesophageal carcinoma. It can be classified into T0 (no malignancy), Tis (high grade dysplasia), T1 (T1a and T1b), T2, T3 and T4 (T4a and T4b). T0 is only used for staging after post-neoadjuvant therapy with no residual malignancy. T1 is subdivided T1a and T1b (as opposite to only T1 used in the 7th edition of AJCC cancer staging Manual). T1a carcinoma is intramucosal carcinoma in which the carcinoma invades lamina propria or muscularis mucosae. T1b carcinoma is submucosal carcinoma in which the carcinoma invades submucosa. T2 carcinoma involves to the muscularis propria whereas T3 carcinoma infiltrates to the adventitia of the oesophagus. T4 is carcinoma invades structure adjacent to the oesophagus. The documentation of T4 needs surgical or radiological findings. T4a is generally resectable tumour invading the pleura, pericardium, azygous vein or diaphragm or peritoneum. T4b is usually unresectable tumour that invades the other structures such as the aorta, vertebral body or trachea, etc. The lymph node status (N) depends on the number of positive lymph nodes found near the oesophagus (including cervical nodes to coeliac lymph nodes). N is divided into N0, N1(1 to 2 positive lymph nodes), N2 (3 to 6 positive lymph nodes) and N3 (7 or more positive lymph nodes) whereas M is divided into M0 (without distant metastasis) and M1 (with distant metastasis)

Table 2 Tumours of the Oesophagus and Oesophagogastric junction

Epithelial tumours

Benign – squamous cell papilloma

Pre-invasive

Barrett dysplasia - low grade and high grade

Squamous dysplasia - low grade and high grade

Malignant

Adenocarcinoma

Adenoid cystic carcinoma

Mucoepidermoid carcinoma/Adenosquamous carcinoma

Squamous cell carcinoma – conventional, verrucous, spindle cell, basaloid squamous

Undifferentiated carcinoma and lymphoepithelioma-like carcinoma

Neuroendocrine neoplasms

Neuroendocrine tumour (NET) – grade 1, grade 2 and grade 3

Neuroendocrine carcinoma (NEC) – small cell and large cell

Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs)

Mixed squamous - NEC

Mixed adenocarcinoma - NEC

Mixed adenocarcinoma – NET

Non-epithelial tumours

Hematolymphoid tumours

Mesenchymal tumours

Gastrointestinal stromal tumour

Adipose tissue and (myo)fibroblastic tumours

Inflammatory myofibroblastic tumour

Solitary fibrous tumour

Lipoma

Inflammatory fibroid polyp

Smooth muscle and skeletal muscle tumours

Leiomyoma

Leiomyosarcoma

Rhabdomyosarcoma

Vascular tumours

Hemangioma

Kaposi sarcoma

Angiosarcoma

Glomus tumour

Lymphangioma and lymphangiomatosis

Neural tumours

Schwannoma

Granular cell tumour

Synovial sarcoma

Other tumours

Mucosal melanoma

Metastatic tumours

A **B** **C** **D**