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Updates on World Health Organization classification and staging of esophageal tumors: implications for future clinical practice☆

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Summary The Fifth edition of the World Health Organization classification of digestive system and American Joint Committee on Cancer staging manual contain substantial refinements of information for esophageal tumors. The epithelial tumors of esophagus are classified as benign, dysplasia, and malignant groups. Dysplasia is divided into Barrett dysplasia and squamous dysplasia and graded into either low-grade or high-grade. Malignant esophageal tumors are often adenocarcinoma or squamous cell carcinoma. The main update in cancer staging in esophageal tumors is the subdivision of the prognostic staging into 3 groups; squamous cell carcinoma, adenocarcinoma, and carcinoma after adjuvant therapy. HER-2 amplification is recognized as a molecular target for therapy of esophagogastric adenocarcinoma. The other esophageal tumors are adenoid cystic carcinoma, mucoepidermoid/adenosquamous carcinoma, undifferentiated carcinoma and neuroendocrine neoplasms. Overall, the incorporation of new data and definitions on histopathology, prognostic factors, and genetics are important for personalized management of patients with esophageal tumors.

1. Introduction

The histology and function of the mucosal lining of the esophagus and esophagogastric junction are different from the rest of gastrointestinal tract. It follows that the epidemiology, pathogenesis, morphology, classification, as well as clinical management of the tumors of the region are different from the other portions of gastrointestinal tract. These unique features and complexity of tumors from esophagus and esophagogastric 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

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of esophageal 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 esophageal cancers worldwide [1].

In 2018, an editorial board formed for editing the esophageal tumors in the 5th edition of the 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 esophageal 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 behavior of these tumors, as well as the clinical management.

In the current WHO classification of digestive system, only the epithelial tumors (including neuroendocrine neoplasms [NENs]) of the esophagus were grouped in the chapter 2 — *Tumors of the esophagus* with sections for different classes of benign, preinvasive, and malignant tumors. The other tumors in the esophagus was described together with tumors 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 esophageal tumors.

2. Benign epithelial tumor and precursors

2.1. Squamous cell papilloma

Squamous cell papilloma is the most common benign epithelial tumor in the esophagus. The tumor is first described in a separate section in the current WHO classification of digestive system tumors [5]. The prevalence of squamous cell papilloma in endoscopic series ranges from 0.01% to 0.45% [6]. The low prevalence of the tumor could be related to the fact that this benign tumor is often small (median diameter = 3 mm) and asymptomatic [6]. In large endoscopic series from France, the tumor is more common in middle age (median age = 50) and located mostly in lower esophagus [6]. The aetiologies of the tumor 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 esophagus [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. Preinvasive lesions/dysplasia

3.1. Barrett dysplasia

Barrett dysplasia is a neoplastic epithelium without invasion occurring in area of metaplastic columnar epithelium in the esophagus. 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 (nonintestinal 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) (Fig. 1A and B). In a meta-analysis, the pooled annual incidence rate of progression to esophageal 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, esophageal squamous cell carcinoma develops in 5% of patients with low-grade dysplasia [13].

It is important to identify squamous dysplasia or early-stage 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 esophageal squamous dysplasia (Fig. 1C and D). 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 labeled as *carcinoma-in-situ*. The use of

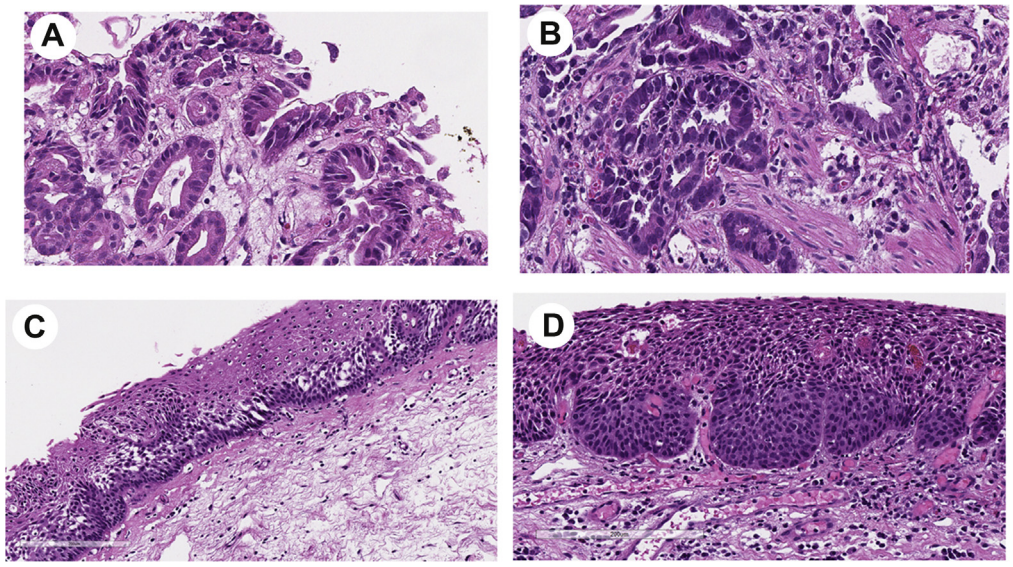

Fig. 1 Esophageal dysplasia. (1A) Low-grade Barrett dysplasia. (1B) High-grade Barrett dysplasia. (1C) Low-grade squamous dysplasia. (1D) High-grade squamous dysplasia.

the terminology *mild dysplasia*, *moderate dysplasia*, *severe dysplasia*, *carcinoma-in-situ* is not recommended.

4. Malignant epithelial tumors and NENs

Malignant esophageal epithelial tumors 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 esophageal epithelial tumors. 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 esophageal 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 esophageal 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 esophageal cancer, which is labeled as prognostic staging group IIIB although there is no lymph node metastasis. The other one is esophageal 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 esophagus and esophagogastric without treatment by neoadjuvant therapy, the parameters used for prognostic stage grouping are T, N, M, and tumor 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 tumor grade is an important prognostic marker only in subgrouping for early-stage esophageal cancers (stage I and stage II) (Table 1).

For esophageal squamous cell carcinoma without treatment by neoadjuvant therapy, the parameters used for prognostic stage grouping are T, N, M, tumor grade, and tumor location (Table 1) [17]. Similar to that in the subgrouping of esophageal adenocarcinoma, tumor grade is important in subgrouping squamous carcinoma of early-stage cancers (stage I and stage II). Stage I and II esophageal squamous cell carcinomas are divided into 2 subgroups each, namely stage IA, IB, IIA, and IIB, respectively. The location of esophageal squamous cell carcinoma is a parameter used to subgroup stage II cancers. Patients with cancer in the lower esophagus is in subgroup

Table 1 Comparisons of the staging group of esophageal 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
	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
II	T3	N0	M0		T3	N0	M0	Any	Lower	IIB	T3	N0	M0	Any
					T3	N0	M0	G1	Upper/middle					
				IIB	T3	N0	M0	G2-3/X	Upper/middle					
IIIA	T0	N1	M0											
	T1	N1	M0		T1	N1	M0	Any	Any		T1	N1	M0	Any
	T2	N1	M0	IIIA	T2	N1	M0	Any	Any	IIIA	T2	N1	M0	Any
IIIB	T0	N2	M0											
	T1	N2	M0		T1	N2	M0	Any	Any		T1	N2	M0	Any
	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
	T3	N2	M0		T3	N2	M0	Any	Any		T3	N2	M0	Any
IVA	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 esophageal 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 mucose. 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 esophagus. T4 is carcinoma invades structure adjacent to the esophagus. The documentation of T4 needs surgical or radiological findings. T4a is generally resectable tumor invading the pleura, pericardium, azygous vein, or diaphragm or peritoneum. T4b is usually unresectable tumor that invades the other structures such as the aorta, vertebral body, or trachea, and so on. The lymph node status (N) depends on the number of positive lymph nodes found near the esophagus (including cervical nodes to coeliac lymph nodes). N is divided into N0, N1(1−2 positive lymph nodes), N2 (3−6 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).

with better prognosis than those with cancer in upper or middle esophagus.

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 esophageal adenocarcinoma or squamous cell carcinoma). The presence of lymph node metastases (either N1 or N2) or with tumor extent of T4a will make a cancer stage III. Thus, in contrast to stage groping 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 esophageal cancer [1]. These include tumor size, status of surgical margins, and presence of lymphovascular permeation and extranodular extension of cancer. HER-2 status of cancer is important in prediction of response to target therapy to HER-2 in patients with esophagogastric adenocarcinoma. Tumor regression grade and lymph node downstaging after neoadjuvant therapy are also of prognostic importance. Grading of the tumor 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].

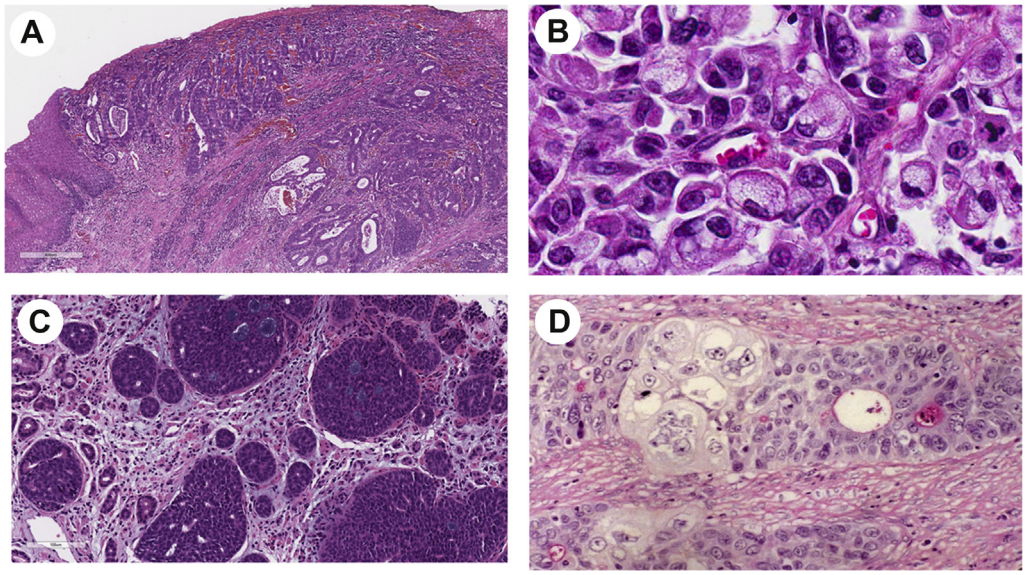

Fig. 2 Esophageal glandular malignancy. (2A) Adenocarcinoma, tubular pattern. (2B) Adenocarcinoma, signet ring pattern. (2C) Adenoid cystic carcinoma. (2D) Mucoepidermoid carcinoma (mucin stain highlighted the glandular component).

4.2. Histological types of malignant epithelial tumors

4.2.1. Adenocarcinoma

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

The adenocarcinoma had a 3-tier grading system depends on the percentage of glandular formation (well differentiated = >95%; moderately differentiated 50%–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 esophageal cancers [1]. Histologically, esophageal adenocarcinoma could be arranged in tubular, papillary, mucinous, and signet ring patterns (Fig. 2A and B) [18]. They are often in mixture patterns. There are limited data on the clinical impacts of these patterns. Thus, they are labeled as patterns and not as subtypes of adenocarcinoma.

Amplification of the *ERBB2* (*HER-2*) gene with resulting overexpression of HER-2 protein is the molecular target for approved therapy for treatment of advanced stages or metastatic esophagogastric/lower esophageal adenocarcinoma [18]. Thus, *in situ* hybridization 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 esophagogastric/lower esophageal adenocarcinoma. It is worth noting that HER-2 staining is often in basolateral or lateral membrane in cancer cells of esophagogastric/lower esophageal adenocarcinoma which contrasts with the complete membrane staining of cells in breast carcinomas.

4.2.2. Adenoid cystic carcinoma

Esophageal adenoid cystic carcinoma is first being described in a separate section in the current WHO classification of digestive system tumors [19]. It was included as a subtype of esophageal adenocarcinoma in the previous edition of WHO classification of digestive system tumors [4].

Esophageal adenoid cystic carcinoma is an esophageal carcinoma with morphology identical to the adenoid cystic carcinoma of the salivary gland. It is likely the carcinoma differentiates in the direction of esophageal glands. The carcinoma comprises epithelial and myoepithelial tumor cells forming true glands and pseudo glands and arranged in cribriform, tubular, and solid architecture (Fig. 2C). Immunohistochemical stains could be used to highlight the epithelial and myoepithelial cells in the carcinoma. Esophageal adenoid cystic carcinoma should be differentiated from esophageal 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.

Esophageal adenoid cystic carcinoma is uncommon with slightly more than 100 reported cases in the literature. It accounts for approximately 0.1% of all esophageal neoplasms [20]. The carcinoma most often located in the middle third of the esophagus [21]. Similar to the esophageal squamous or adenocarcinoma, esophageal adenoid cystic carcinoma is more common in men and occurs often in seventh decade of life [22,23]. The prognosis of patients with esophageal basaloid squamous cell carcinoma is variable and depends on the pathological stage [22,23]. In AJCC cancer staging grouping, esophageal adenoid cystic carcinoma follows that of esophageal adenocarcinoma.

4.2.3. Mucoepidermoid carcinoma and adenosquamous carcinoma

Mucoepidermoid carcinoma and adenosquamous carcinoma are carcinomas with both squamous and mucinous containing (glandular) components (Fig. 2D). They are first descripted in a separate section in the 2019 WHO classification of digestive system tumors [3]. They were included as subtypes of esophageal adenocarcinoma in the previous edition of WHO classification of digestive system tumors [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 esophageal 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.

Similar to squamous cell carcinoma, these carcinomas are often noted in the mid portion of the esophagus. 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 esophageal adenocarcinomas. There is no current recommendation of stage grouping for this group of esophageal carcinomas.

4.2.4. Squamous cell carcinoma

Squamous cell carcinoma is the most common type of esophageal carcinoma and occur mainly in Asian populations [11]. The etiology of the carcinoma is multifactorial, and the main environmental risk factors are heavy smoking, high consumption of alcohol, and various dietary factors [11,31]. HPV was identified in a portion of the squamous cell carcinoma [11,32,33]. Nevertheless, HPV is not found in many esophageal squamous cell carcinomas. Thus, the virus is unlikely to be the major cause of the cancer. Approximately half of the squamous cell carcinoma are located in the middle portion of the esophagus [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 esophageal squamous cell carcinoma is based on three grades of the tumor [1]. (Table 1) (Fig. 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 esophagus [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 miotic 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 tumor could be treated by endoscopic resection in appropriate cases [41,42].

Basaloid squamous carcinoma accounts for 4–5% of primary esophageal 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 tumor mitosis and often with comedonecrosis (necrosis in the center of tumor nests) [15]. Patients with esophageal basaloid squamous cell carcinoma often show shorter overall survival than conventional squamous cell carcinoma though the difference may not be significant [43–45].

Spindle cell squamous cell carcinoma comprises neoplastic spindle cells (Fig. 4A). The carcinoma accounts for approximately 1–2% of esophageal carcinomas [46,47]. It has also been labeled as *sarcomatoid carcinoma* or *carcinosarcoma*. The neoplastic spindle cell

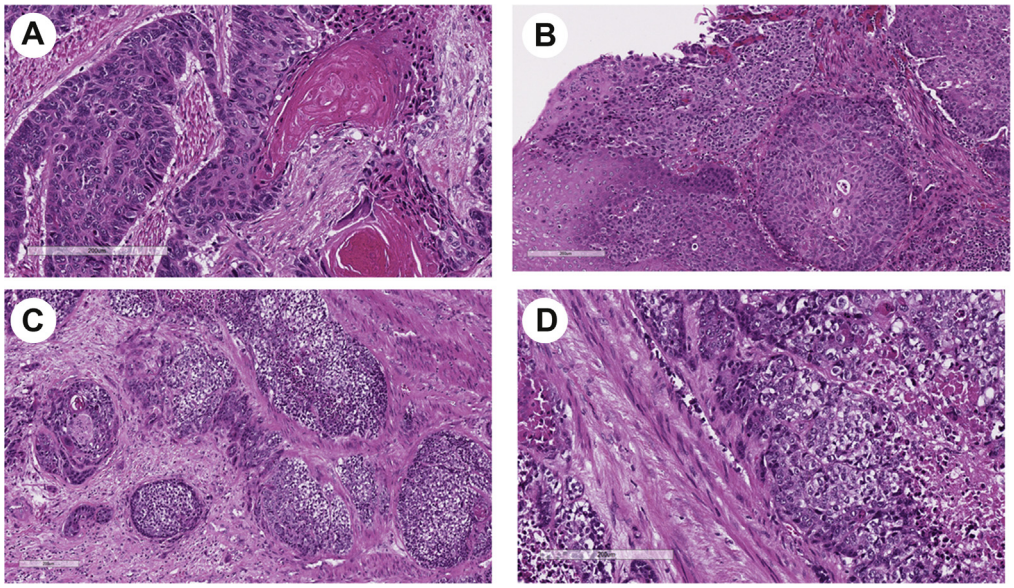

Fig. 3 Esophageal squamous cell carcinoma, conventional and basaloid variants. (3A) Squamous cell carcinoma, grade 2 with keratin pearls. (3B) Squamous cell carcinoma, grade 3 with focal squamous differentiation. (3C) Squamous cell carcinoma, basaloid squamous variant with fibrotic stroma and encasement of nerve. (3D) Squamous cell carcinoma, basaloid squamous variant with focal squamous area and necrosis.

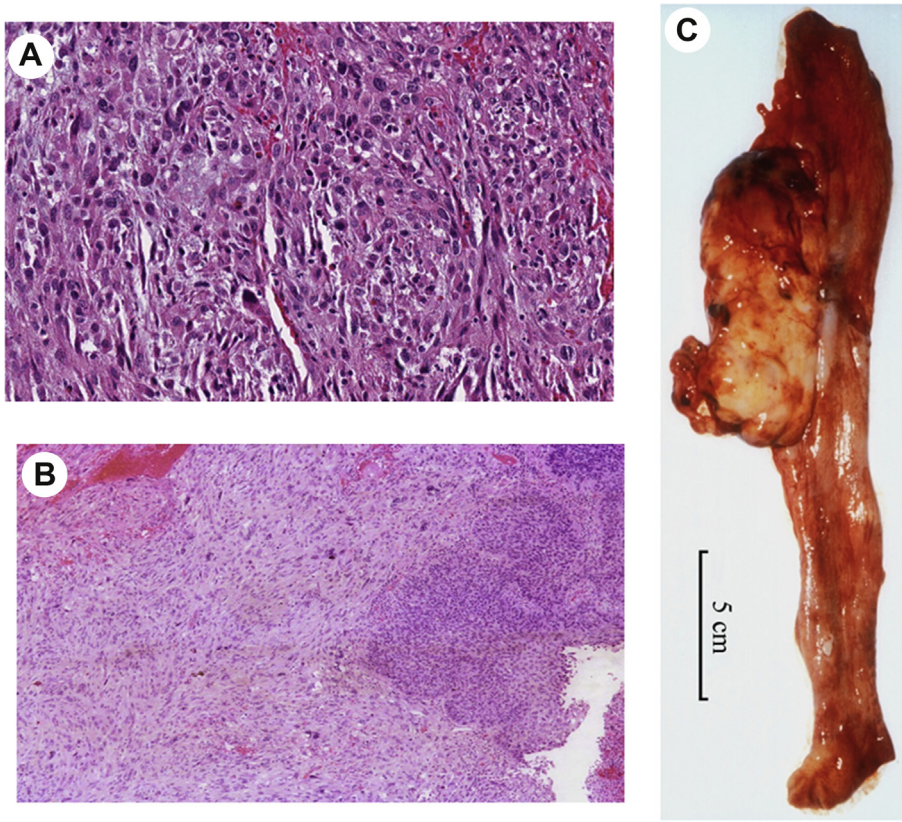

Fig. 4 Esophageal squamous cell carcinoma, spindle cell variant. (4A) Microscopic appearance showing malignant spindle cells. (4B) Microscopic appearance showing the malignant spindle cells and the overlying malignant squamous epithelium. (4C) Macroscopic appearance of the tumor showing the characteristics polypoid appearance.

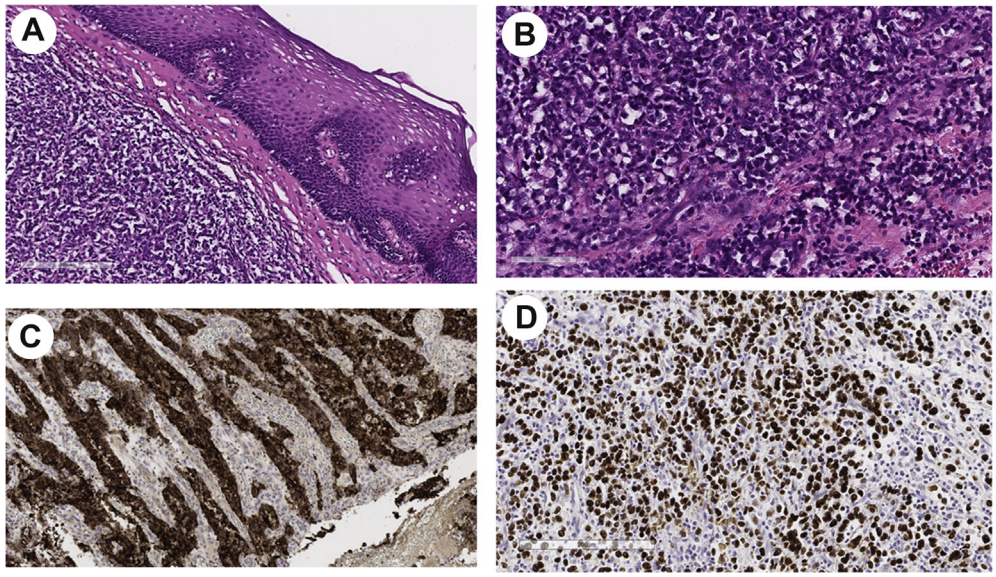

Fig. 5 Esophageal undifferentiated carcinoma. (5A) Undifferentiated carcinoma underneath the squamous epithelium. (5B) Undifferentiated carcinoma composed of tumor cells in inflammatory stroma. (5C) Undifferentiated carcinoma highlighted by positive to cytokeratin (AE1/3). (5D) Undifferentiated carcinoma which is EBER-positive.

component is likely to be dedifferentiated from the squamous carcinoma component via epithelial-mesenchymal transition 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 in 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]. (Fig. 4B) Some of the spindle cell squamous cell carcinoma has a polypoid growth pattern (Fig. 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

Esophageal 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 nonepithelial tumors such as melanoma, lymphoma, and sarcomas. The carcinoma often shows a syncytial pattern of carcinoma cells with giant tumor 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 esophageal 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 esophageal 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 (Fig. 5A and B). Cytokeratin is needed to confirm the epithelial nature of the tumor (Fig. 5C). Some cases are positive for Epstein-Barr virus [51]. (Fig. 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 esophageal carcinoma appears to have a better prognosis than other esophageal carcinomas [54].

4.2.6. Neuroendocrine neoplasms

In the 2000's WHO classification of tumors of the digestive system, this group of tumors is labeled *endocrine tumors of the esophagus* [55]. In the 2010s WHO classification of tumors of the digestive system, the term *neuroendocrine neoplasms of the esophagus* (NENs) was introduced [4]. In the current WHO classification of the digestive system tumors, esophageal NEN is classified in the line with the NENs of the other parts of the gastro-entero-pancreatic tract [56,57] and are classified into

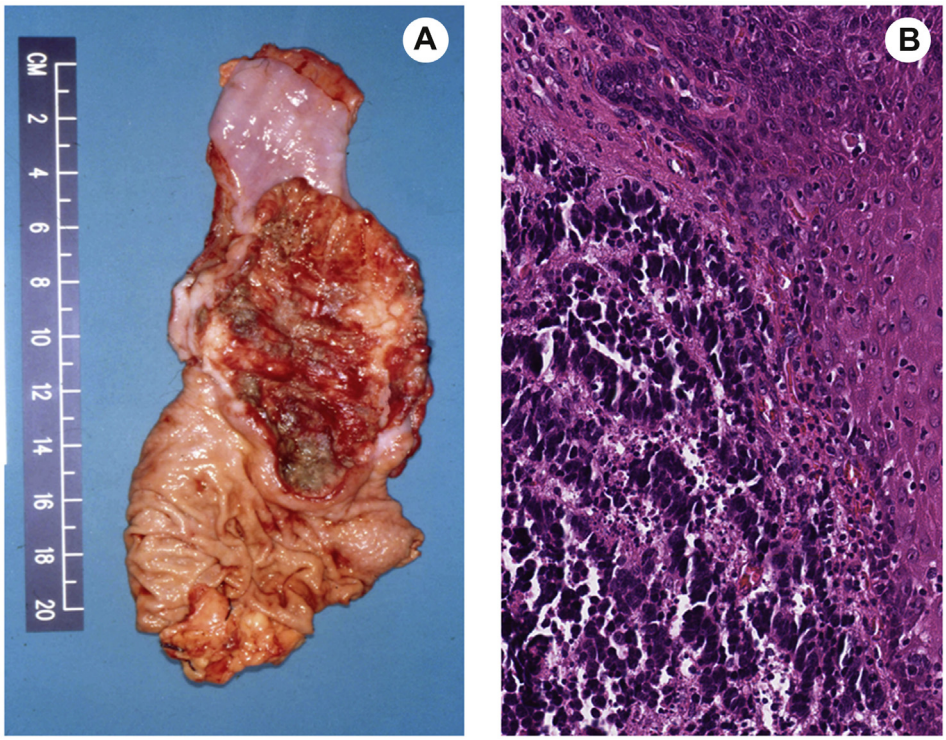

Fig. 6 Esophageal small-cell neuroendocrine carcinoma. (6A) Macroscopic appearance showing a large ulcerative tumor. (6B) Microscopic appearance showings of tumor cells with high nuclear to cytoplasmic ratio.

neuroendocrine tumor (NET), neuroendocrine carcinoma (NEC) and mixed neuroendocrine-non-NEN (MiNEN).

More than 95% of esophageal NENs are NECs [58]. NEC could be small cell type (SCNEC) or large cell type (LCNEC). In the literature, 98% of esophageal NENs are SCNEC and more than three quarters (>75%) are from Eastern countries. Similar to esophageal squamous cell carcinoma, esophageal SCNEC occurs mostly in middle esophagus 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 esophageal neoplasms in surgical series [59] and 3% of esophageal neoplasms in autopsy series [60]. The tumor is often large and have primitive tumor cells with high nuclear to cytoplasmic ration as in the counterpart in lung (Fig. 6). The carcinoma may resemble basaloid squamous carcinoma, in the biopsy specimen. Use of neuroendocrine markers (chromogranin A, synaptophysin, and so on) and squamous cell differentiation markers (p63, p40, CK5/6) is useful to differentiate these two subtypes of esophageal carcinomas.

Esophageal LCNEC comprises approximately 1% of NENs and mostly (>90%) reported in Western countries. Esophageal NET is extremely rare and comprise less than 1% of esophageal NEN. NET occurs in approximately same prevalence in Eastern and Western populations. Less than 50 esophageal NETs were reported in the literature. Most esophageal 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 esophagus, MiNEN often comprise NEC combine with adenocarcinoma or squamous cell carcinoma. Rarely, mixed adenocarcinoma and NET occurs in the esophagus [61].

The two subtypes of esophageal NEC show no difference in patients' prognosis. In the current AJCC staging manual, there is no stage grouping for staging of esophageal NEC. The overall survival rates of the patients with NEC is significantly lower than those with esophageal adenocarcinoma [62]. Surgical resection is achievable in less than half of the cases with esophageal NEC and majority of the nonresection cases had distant metastases at presentation [63]. In addition, patients with esophageal NEC have lower survival rates than those having esophageal 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 esophageal carcinomas. Rarely, esophageal NEC and MiNEN of type − NEC and adenocarcinoma could arise in patients with Barrett esophagus. They are often being detected at early stage and might show better patients' survival compared with esophageal NEC [65]. Furthermore, in patient having MiNEN with adenocarcinoma component, the carcinoma is staged as adenocarcinoma.

Table 2 Tumors of the Oesophagus Esophagus and Oesophagogastric Esophagogastric junction.

Epithelial tumors

Benign − squamous cell papilloma

Preinvasive

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

Nonepithelial tumors

Hematolymphoid tumors

Mesenchymal tumors

Gastrointestinal stromal tumor

Adipose tissue and (myo)fibroblastic tumors

Inflammatory myofibroblastic tumour

Solitary fibrous tumour

Lipoma

Inflammatory fibroid polyp

Smooth muscle and skeletal muscle tumors

Leiomyoma

Leiomyosarcoma

Rhabdomyosarcoma

Vascular tumors

Hemangioma

Kaposi sarcoma

Angiosarcoma

Glomus tumour

Lymphangioma and lymphangiomatosis

Neural tumors

Schwannoma

Granular cell tumour

Synovial sarcoma

Other tumors

Mucosal melanoma

Metastatic tumors

5. Nonepithelial tumors

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

Different mesenchymal tumors have been reported in the esophagus. Of these, leiomyoma and granular cell tumor are the most common benign mesenchymal tumor in the esophagus [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 tumor of esophagus has a prediction for lower esophagus and more often occur in women [71]. The tumor mainly occurs in patients in the fifth decade of life.

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

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

6. Conclusion

tumors of different morphological features occur in esophagus and esophagogastric junction. Table 2 summarizes the categories of this group of tumors mentioned in the current WHO classification. The commonest tumors are squamous cell carcinoma and adenocarcinoma. The two carcinomas are differences in aetiopathogenesis, epidemiology, patients' prognosis, and treatment protocols. Adjuvant therapy is being used for treatment of many esophageal carcinomas. Pathological stage groupings for esophageal 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 stating of early-stage esophageal carcinomas. On the other hand, advanced stage cancers are often treated by neoadjuvant therapy and pathological parameters such as grade and location loss its clinical relevance. Overall, the incorporation of new data on histopathology, prognostic factors, and genetics is important for current personalized management of patients with esophageal tumors.

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