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Ana Filipa Teixeira Peres

Adenocarcinoma do Esófago – Abordagem Atual / Esophageal Adenocarcinoma – Current Paradigm

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Adenocarcinoma do Esófago – Abordagem Atual / Esophageal Adenocarcinoma – Current Paradigm

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E sob a Coorientação de:

Professor Doutor José Adelino Lobarinhas Barbosa

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TÍTULO ~~DISSERTAÇÃO~~/MONOGRAFIA (riscar o que não interessa)

Esophageal Adenocarcinoma - Current Paradigm

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Esophageal adenocarcinoma – current paradigm

Adenocarcinoma do esófago – abordagem atual

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Esophageal adenocarcinoma – current paradigm

Resumo

Introdução

O cancro do esófago é uma doença neoplásica agressiva, com uma incidência crescente e um prognóstico pobre. O adenocarcinoma e o carcinoma epidermóide são os dois tipos histológicos mais comummente associados a este cancro e compõem mais de 95% de todos os tumores esofágicos. O carcinoma epidermóide era anteriormente o tipo histológico predominante globalmente, enquanto o adenocarcinoma era raramente observável. No entanto, com o passar das décadas e a melhoria na qualidade de vida, a incidência do adenocarcinoma tem subido drasticamente no Ocidente, sendo responsável pela maioria dos cancros do esófago no Norte da Europa, América do Norte e Austrália. A doença do refluxo gastroesofágico é considerada preponente desta tendência epidemiológica; não-obstante exploram-se outras hipóteses causais menos bem-estabelecidas.

Métodos

Seguindo as *guidelines* SANRA, realizou-se uma revisão narrativa da literatura incidindo amplamente na temática do adenocarcinoma do esófago (epidemiologia, patofisiologia, fatores de risco, clínica, diagnóstico, estadiamento, tratamento e prognóstico). Recorreu-se a duas bases de dados de referências, a *Medline* e a *ScienceDirect*.

Resultados

Identificaram-se um total de 353 referências. Após exclusão de duplicados, artigos não disponíveis ou irrelevantes, analisaram-se qualitativamente 142 artigos.

Discussão

Toda a bibliografia atual considera o Esófago de Barret como o último estadio pré-invasivo na sequência metaplasia-displasia-neoplasia do adenocarcinoma do esófago, sendo assim o melhor preditor do risco de cancro. A vigilância dos pacientes com Esófago de Barrett oferece, assim, a oportunidade de deteção precoce do adenocarcinoma. As opções de tratamento incluem técnicas endoscópicas diretas, cirurgia de resseção, quimioterapia perioperatória e radioterapia preoperatória – sendo que a evidência recente de mais alta qualidade apoia a terapia multimodal e abordagens minimamente invasivas como o padrão de cuidados de saúde.

Conclusão

O corpo de conhecimento em torno do adenocarcinoma do esófago está maioritariamente bem descrito. Todavia, o prognóstico da doença permanece precário, que coloca o cancro esofágico no sexto lugar global de maior mortalidade.

Abstract

Introduction

Esophageal cancer is an aggressive malignancy with an increasing incidence and a poor prognosis. Esophageal adenocarcinoma (EAC) and squamous cell carcinoma (SCC) are the two most common histologic types and make up over 95% of all esophageal malignant tumors. In the past, SCC was the predominating type, while EAC was a rarely seen condition. However, over time, as a result of better quality of life, the incidence of EAC has increased dramatically in Western countries, accounting for the majority of all esophageal cancers in Northern Europe, North America and Australia. Gastroesophageal reflux disease is consensually regarded as the main culprit. Regardless, we explore other less well-established hypothesis.

Methods

Following the SANRA guidelines, we performed a narrative review of literature regarding epidemiology, pathophysiology, risk factors, clinical manifestations, diagnosis, staging, treatment, and prognosis of Esophageal Adenocarcinoma. We used both Medline and ScienceDirect libraries.

Results

We identified a total of 353 records. After exclusion of duplicates, unavailable and non-relevant articles, we included 142 papers in our broad scope narrative review.

Discussion

All contemporary works consider Barrett's Esophagus (BE) as the last preinvasive stage in the metaplasia-dysplasia-neoplasia sequence of EAC, thus remaining the single best surrogate marker for cancer risk. BE surveillance offers the opportunity of early EAC diagnosis. Treatment options include novel direct endoscopic therapies, esophagectomy, perioperative chemotherapy and preoperative radiation therapy – with the most recent and highest-standard evidence pointing towards multimodality therapy & minimally invasive strategies as the standard of care.

Conclusion

The EAC landscape is for the most part well-described. Nevertheless, prognosis remains substandard and incidence is ever-increasing, which leads to esophageal cancer being the sixth most deadly worldwide.

Key words

Esophageal Adenocarcinoma, Epidemiology, Pathophysiology, Diagnosis, Management

Introduction

Esophageal cancer is currently the eighth most incident neoplastic disease worldwide and the sixth most common cause of cancer-related mortality. According to the WHO Global Cancer Observatory 2020 (GCO), it accounted for an estimated 604 thousand new cases, having been responsible for around 544 thousand deaths[1] – which demonstrates its often-poor prognosis[2].

Esophageal adenocarcinoma (EAC) and squamous cell carcinoma (SCC) are the two most common histologic types and make up over 95% of all esophageal malignant tumors. Less than 1% to 2% are sarcomas or small cell carcinomas. Very rarely lymphomas, neuroendocrine tumors, carcinoids, gastrointestinal stromal tumors, and melanomas may arise in the esophagus[3].

For most of the 20th century, SCC was the predominating type (mainly in the upper esophagus), while EAC was a rarely seen condition. However, over time with improving quality of life, the incidence of EAC (predominantly in the distal esophagus) has increased dramatically in Western countries. Nowadays EAC accounts for the majority of all esophageal cancers in Northern Europe, North America and Australia[2]. In contrast, globally, SCC still predominates[4].

These two major subtypes are epidemiologically and biologically distinct entities, with different risk factors. Tobacco smoking and alcohol consumption are major risk factors for SCC, while gastroesophageal reflux disease (GERD) and other causes of increased esophageal acid exposure, Barrett's esophagus (BE), obesity and metabolic syndrome are some of the most important risk factors for EAC. Most of these aspects reflect underlying demographic and socioeconomic issues[2].

In this review, we will focus on EAC and cover its specific epidemiology, pathophysiology, clinical manifestations, diagnosis, staging, treatment, and prognosis.

Materials & methods

A review of literature was performed according to the Scale for the Assessment of Narrative Review Articles (SANRA) checklist. Both Medline (via PubMed) and ScienceDirect databases were surveyed, using the following search terms: esophageal adenocarcinoma (MeSH and non-MeSH Terms). The exclusion criteria were: full-text non-availability, non-human study subjects, and the language of the article being other than English, Spanish or Portuguese.

All references with a relevant title or abstract were retrieved and screened. This study included scientific studies, meta-analysis, review papers and other documents published between 2016 and February 2021. Titles, abstracts, and full texts of the reference lists of included studies were also screened for additional relevant papers. This review included 142 papers, selected based on theme relevance and evidence quality. Additionally, reference works in the area such as book chapters and clinical practice guidelines were also screened.

Epidemiology

Esophageal cancer is the eighth most common cancer, being the sixth-most common cause of cancer-related death worldwide[1]. For most of the 20th century, SCC comprised the vast majority of esophageal cancers globally. However, for the past three decades, the frequency of adenocarcinoma of the esophagus and esophagogastric junction (EGJ) cancers has increased dramatically, a finding initially observed in Western countries and more recently in some Eastern countries as well [2].

In 2020, World Health Organization's GLOBOCAN database[1] estimates that it has accounted for 604 100 new cases and has caused 544 076 deaths – one of the most fatal malignancies worldwide, with very poor survival rates (overall 5-year survival rate of about 10% and 5-year post-surgical resection survival rate around 15-40%).[5]

The majority of cases worldwide are SCC histology; nonetheless, the incidence and most prevalent histology type vary by location[4].

The highest incidence rates are found in Eastern Asia and Southeastern Africa, and the lowest in West-Central Africa and Central America. In the highest-risk area, stretching from Iran's Caspian coast, through the central Asian republics, to North-Central China (usually referred to as the "esophageal cancer belt"), nearly 90% of cases are SCC [2].

Major risk factors in these areas are not completely understood but are thought to include dietary habits such as low intake of fruits and vegetables and ingestion of hot beverages[6]. In contrast, in low-risk areas for SCC, such as the United States and several Western countries, tobacco smoking and excessive alcohol consumption are the main contributive causes, in approximately 90% of the total cases of SCC [6].

Chronological trends in esophageal cancer vary between its two major histologic types. Incidence rates for EAC have grown steeply in several Western countries in the last three decades, in part due to increasing in known risk factors such as higher BMI. When stratified according to anatomic location, most of the increased incidence involves tumors at the EGJ and gastric cardia[7].

Conversely, rates for SCC are steadily decreasing in these same countries because of longstanding public health-related reductions in tobacco and alcohol consumption[7].

Notwithstanding, esophageal SCC remains the most common histology worldwide and is increasing in certain Asian countries such as Taiwan[7]. Its incidence varies considerably among geographic regions, but the highest rates are concentrated in the aforementioned “esophageal cancer belt”. Geographic variation is also reported within individual countries (rural versus urbanized areas)[7].

Besides lower socioeconomic status, smoking and alcohol consumption and dietary factors, risk factors for SCC are: previous esophageal disease, prior gastrectomy, atrophic gastritis, HPV infection, biphosphonate use, upper aerodigestive tract cancer and poor oral hygiene[6].

After the twentieth century, the disease burden of esophageal carcinoma in industrialized countries has been overtaken by EAC[8-11] – a finding originally witnessed in Western countries and, more recently, in some Eastern countries as well[2]. Caucasian people have a higher risk of being affected by this histologic subtype in comparison with Black people (3-4-fold increased risk) and Hispanics (2-fold). Regarding sex differences, the incidence of esophageal adenocarcinoma is about 7 times higher in males, although the incidence among white women is increasing[5,12]. The risk of being diagnosed peaks after the age of 50 [5].

Etiologic / Risk Factors

Cumulative evidence states that gastroesophageal reflux disease (GERD), a history of smoking, being overweight or obese, a low-fiber diet and other means of increased esophageal acid exposure are the main risk factors for the development of EAC[13]. Some data suggest that interactions between risk factors and age may be more important than individual risk factors. In one study, early-onset EAC was more strongly associated with recurrent gastroesophageal reflux and high BMI rather than EAC in older age groups[13].

Gastroesophageal reflux disease

Most, if not all, EACs arise from a region of Barrett's metaplasia in the lower esophagus caused by GERD. Thus, it is the single most important risk factor for esophageal cancer – an association established in the late 1990s [14].

In population-based case-control studies and meta-analysis, gastroesophageal reflux is associated with an odds ratio (OR) of 12.0 (95% Confidence Interval (CI) 7.64-18.7) for BE and 4.64 (95% CI 3.28 - 6.57) for EAC. [11,15,16]

Among patients who have BE, the risk of developing EAC is increased at least 30-fold above that of the general population, but the absolute risk of developing cancer in patients with Barrett's metaplasia is low[17].

Obesity and metabolic syndrome

Following reflux, obesity, and in particular central obesity [18,19], is the second strongest risk factor for EAC and these two factors display synergy. [12,15,20]

Obesity is associated with a higher risk for esophageal and gastric cardia adenocarcinoma[21] and with BE [20,22]. A meta-analysis identified a relative risk for EAC or gastric cardia AC of 1.71 (95% CI 1.5-1.96) for BMIs between 25-30 kg/m^2, and 2.34 (95% CI 1.95-2.81) for BMIs equal or higher than 30 kg/m^2 [23]. Obesity does not, however, appear to affect the risk of SCC. [14,21]

Obesity may represent an indirect risk factor for both EAC and BE's metaplasia because it increases the risk of GERD through mechanical effects (elevated intra-abdominal pressure, disrupted function of the lower esophageal sphincter, and increased risk of a hiatal hernia). [12,20,24-26]

The augmented risk of EAC due to obesity is also attributable to metabolic syndrome alone [7,12,13,28]. This proinflammatory status encompasses a myriad of biomolecular effects such as increased production of insulin and insulin-like growth factors, release of multiple inflammatory cytokines, macrophage activation, decreased adiponectin, and

increased leptin (EGF-R activator), cumulating in cell proliferation, angiogenesis, and reduced apoptosis. [20,26,28]

Some meta-analysis data correlate dietary cholesterol intake[29] and diabetes mellitus[30] with an increased risk of developing esophageal cancer, specifically in Europe and North America. No such correlation was found in Asian subjects[30].

A 2017 systematic review collected evidence from 57 cohort studies and suggested a protective role of vegetable intake and body weight control in EAC development[31].

Tobacco smoking

Smoking elevates the risk of developing EAC, particularly in patients with BE [32,33]. In a pooled analysis from the International BE and Esophageal Adenocarcinoma Consortium (BEACON), the risk of EAC or EGJ adenocarcinoma was two-times greater in smokers than in controls[32].

Despite being a moderately strong risk factor for EAC [10], smoking is a major risk factor for SCC [6] and, contrary to SCC, smoking cessation has limited influence on reducing the initial risk of EAC [34].

Helicobacter pylori infection

Helicobacter pylori infection, especially with the CagA+ strain, demonstrates an inverse association with EAC risk, as supported by several recent meta-analysis [35,36,37,38]. Declining population seropositivity to H. pylori due to improved socioeconomic and health-care conditions may also contribute to rising rates of EAC [12].

The absence/eradication of *H. pylori* may be a risk factor for the development of esophageal AC, although disparate data exist [38].

As to why this relationship exists, there are several theories. For instance, H. pylori-related atrophic gastritis that conducts to the destruction of gastric parietal cells impairs acid secretion [19].

Consequently, the reduced acidity of the refluxate lessens the risk of complications of GERD, such as BE and EAC. Another speculation is that H. pylori infection might be associated with reduced risk for obesity, reducing the mechanical and biological obesity complications previously discussed [38]. Some literature states complex interactions between H. pylori and esophageal microbiome in individuals affected by BE [39,40].

Since H. pylori infection strongly increases the risk of gastric cancer (it being a Class I human carcinogen), no evidence should prevent clinicians from eradication treatment, regardless of coexisting reflux esophagitis or BE [38].

Proton-pump inhibitors (PPIs) plus aspirin

The best evidence supporting the combination of aspirin and PPIs in reducing EAC progression risk is well illustrated in the Aspirin and Esomeprazole Chemoprevention in Barrett's Metaplasia Trial (AspECT) randomized controlled trial. At a median follow-up of nearly 9 years, daily high-dose esomeprazole plus aspirin showed the strongest effect compared with low-dose esomeprazole alone (time ratio 1.59, 95% CI 1.14–2.23, *P* = 0.0068). The composite end points were time to all-cause mortality, adenocarcinoma, or high-grade dysplasia[41].

Later in 2019, Zhang and colleagues[42] established the pathophysiologic foundations to these findings, laying the groundwork for the introduction of this combination as a strategy for EAC chemoprevention.

Statins

Statin use is associated with a significantly lower incidence of EAC. This effect is seen both Barrett's cohorts and general populations[43].

In addition to lowering plasma cholesterol, statins have antiproliferative, pro-apoptotic, anti-angiogenic, and immunomodulatory effects, aiding in a 41% risk reduction of adenocarcinoma in patients with BE in one study[44].

A meta-analysis also showed that statin use was associated with a lower risk of BE progression (OR 0.48, 95% CI 0.31–0.73)[45]. In general, statins appear promising for chemoprevention, but further study is needed [46].

Pathophysiology

EAC is commonly preceded by the development of Barrett's esophagus, which in turn emerges in the setting of GERD. This is a metaplastic response of the esophageal mucosa in the face of repeated erosion, due to gastric acid, bile salts and nitroso compounds, generating a cycle of damage and repair, in a context of chronic inflammation [47]. In Barret's esophagus the epithelium becomes more akin to intestinal mucosa, which is better suited to withstand the damage caused by these agents. The stratified squamous epithelium of the esophagus acquires an intestinal phenotype, morphologically characterized by a columnar epithelium with goblet cells forming glandular structures [48]. This change in phenotype also manifests itself in the change of

the cells' transcription program, with the downregulation of esophagus-specific transcription factors, particularly p63 and SOX2, and increased expression of intestinal transcription factors, such as SOX9, CDX2 and FOXA2 [49]. It is not currently clear whether this change of phenotype results from the transdifferentiation of mature squamous epithelial cells into mature intestinal cells, or from the transcommitment to an intestinal lineage by progenitor cells originating in the esophagus or migrating from other places, particularly from the gastric cardia, bone marrow or the GEJ [48,49].

While it was initially believed that gastric acid, pepsin, and bile acids were responsible for acute damage and necrosis of esophageal epithelium, resulting in erosion and acute inflammation, more recent research has shifted the role of these aggressors. According to the research conducted by Souza[50] erosive esophagitis is not caused by an acidic "burn" that kills off epithelial cells, instead the aggressors activate the NF-κB pathway and cause the epithelium to secrete pro-inflammatory cytokines (mainly Il-8 and IL-1 β), that recruit T lymphocytes to the submucosa. The chronic inflammation shifts the gene expression of the epithelium from an esophageal program, to an intestinal one [48]. Additionally, immune cells produce oxygen reactive species (ROS) resulting in DNA damage, an effect aggravated by the direct oxidative and genotoxic effect of bile salts [48]. The exposure of actively replicating cells to a mutagenic environment promotes, then, the transmission of acquired mutations to a large population of cells.

Cancerization in the setting of Barrett's esophagus follows two main pathways, both of which have the deletion or inactivation of the TP53 gene as an early event [48]. In the classical pathway, the neoplastic process results from the stepwise acquisition of mutation in tumor suppressor genes, such as TP53, CDKN2A or SMAD4, followed by genomic instability and oncogene amplification [48]. However, more recent evidence suggests that the most prevalent pathway might be the genome duplication pathway. According to this model, after the early inactivation of TP53, the tissue progresses to dysplasia after whole-genome duplication and to neoplasia once genomic instability and oncogene amplification are attained [48].

These genetic and genomic changes that characterize EAC are also accompanied by morphological changes, with low-grade dysplasia (LGD) and high-grade dysplasia (HGD) appearing in Barrett's metaplasia and, possibly, progressing to invasive adenocarcinoma. It is well established that Barrett's esophagus affords a small risk of developing EAC, at an annual incidence rate of 0,65% [51]. In contrast, HGD affords an equally well-established high risk of EAC, at an annual incidence rate of 28,63% [51]. However, the natural history and progression potential of LGD is far more dubious, largely due to the difficult histopathological diagnosis of this morphological entity. This difficulty is highlighted by the fact that diagnoses by consensus usually result in higher

progression rates than diagnosis by a single pathologist [52]. As a further complicating matter, one study has shown that around 65% of histopathological LGD diagnosis suffer histological regression at follow-up [53]. Whether this constitutes a true biological regression or a misdiagnosis at first diagnosis is not apparent. As such, there is no clear-cut sequence of events along the biological natural history of the precursor lesions of EAC firmly established.

Clinical presentation and diagnosis

Due to the muscular and compliant nature of the esophagus, symptoms from an obstructing or stricturing lesion may only become apparent when the tumor has reached a relatively locally advanced or even metastatic stage. In contemporary Italian series, approximately 6-10% of patients are asymptomatic at the time of diagnosis [54]. Warning symptoms include progressive dysphagia and/or odynophagia (difficulty or pain on swallowing), significant involuntary weight loss, and hoarseness or persistent cough (which can denote laryngeal nerve involvement, by either the primary tumor or associated nodal metastases, or aspiration). Occasionally patients may vomit blood or void melena. Commonly, fatigue may occur due to iron deficiency anemia due to occult bleeding or the chronic disease burden. Clinical examination should focus on the assessment of performance status and search for clinically apparent metastatic disease (e.g., supraclavicular lymph nodes and hepatomegaly), but esophagogastroduodenoscopy is the mainstay of evaluation since the clinical examination is often unremarkable even with locally advanced disease.[12] The differential diagnosis of dysphagia is broad and includes nonmalignant strictures, achalasia and other esophageal motility disorders, esophagitis from diverse etiologies, and esophageal webs and rings.

Tumor characteristics which should be documented at esophagogastroduodenoscopy include its exact site (relative to the GEJ, extension into the stomach and distance from incisive teeth), length of the lesion, circumferential involvement, and presence of obstruction[55]. For instance, early esophageal cancers may appear endoscopically as superficial plaques or nodules, and lesions as strictures, large ulcerations and ulcerated or circumferential masses. Any adjacent pre-malignant lesions such as BE should be documented and measured [56].

Histology should be classified according to WHO criteria [57] and histological subtype and grade should be documented. In the presence of a poorly differentiated tumor,

immunohistochemistry and molecular biomarkers may help to distinguish between adenocarcinoma (e. g., p53 overexpression or cytokeratin 7/20) and squamous cell carcinoma (p63 or cytokeratin 5/6 and) [52]. Identification of rare histologies, which have individual treatment paradigms, is also essential. Assessment of HER2 staining is useful and should be performed in patients with advanced tumors not suitable for curative therapy in whom trastuzumab or other HER2-directed monoclonal antibodies might be a treatment option [12,58,59].

Staging of esophageal cancer

The clinical staging of esophageal cancer is assessed through the widely accepted tumor-node-metastasis (TNM) system developed by the American Joint Committee on Cancer (AJCC) (Table 1).

Accurate pretreatment staging is essential because it determines overall treatment options available, provides important information regarding prognosis, and properly allocates patients in clinical trial groups.

The T staging focuses on identifying the depth of invasion of the primary tumor (from mucosa deep to muscularis, adventitia, and beyond the esophagus). A critical aspect of the T staging focuses on establishing whether the primary tumor has invaded the surrounding mediastinal structures, given that these patients with locally spread disease would no longer be suitable for surgery.

This aspect of staging is crucial in defining stage-specific protocols for treatment. (Table 2). For instance, regarding T3 or T4 tumors, multidisciplinary oncology teams usually adopt preoperative chemotherapy or combination chemoradiotherapy in order to condense primary tumor mass and render it surgically resectable. In contrast, T1 or T2 tumors are primarily treated with surgical resection[3].

The N staging focuses on lymph-node neoplastic dissemination. Segregation between N1 to N3 is made by the number of involved regional lymph nodes. Regional lymph nodes for all esophageal cancer locations encompass the periesophageal cervical nodes, subcarinal nodes, right and left bronchial nodes until the celiac nodes.

Location of the tumor is defined by the position of its epicenter in the esophagus and classified as X: location unknown; upper: cervical esophagus to lower border of azygos vein; middle: lower border of azygos vein to lower border of inferior pulmonary vein; and lower: lower border of inferior pulmonary vein to stomach, including GEJ.

There is some controversy regarding whether adenocarcinoma of the GEJ should be staged as esophageal or gastric cancer. Adenocarcinoma of the cardia was staged as esophageal cancer according to the 7th edition of the AJCC staging system. However, assigning tumors at this location as one or the other is somewhat arbitrary. Since the launch of the previous edition of the AJCC staging system in 2010, cumulative evidence, especially from the East[60,61] has suggested that Siewert type III tumors should be staged as gastric cancer instead of esophageal cancer. The definition of EGJ is thus revised in the 8th edition of AJCC system stating that cancer involving it with epicenters no more than 2cm into the gastric cardia are staged as adenocarcinoma of the esophagus and those with more than 2cm involvement of the gastric cardia are staged as stomach cancer, even if the tumor margins invade the esophagogastric junction.

In daily practice, an anatomic classification system for adenocarcinoma of the GEJ that is broadly used is the Siewert classification. It assigns tumors into type I (esophageal), type II (cardiac) and type III (subcardiac), according to their epicenter location relatively to the GEJ: 1-5cm above, within 1cm above and 2cm below, and 2-5cm below, respectively. Classically the three types of cancers differed regarding patient demographics, possible etiology, histopathologic features, treatment approach, and prognosis. Although widely accepted with historical data to support the classification, there are certain drawbacks to this system. First, assigning tumors to type I to III may lack accuracy preoperatively, especially when advanced tumors may have obliterated the endoscopic landmarks. Second, treatment, especially surgical approaches, would more depend on the extent of the tumor rather than its epicenter. Clinicians should be mindful of these limitations — thus, favoring more systematic classifications, as the one previously discussed [62].

The two most prevalent histology types are stage-grouped differently. Stage-groups of both tumor types are further sub-classified as clinical (cTNM); post-neoadjuvant (ypTNM) and pathological (pTNM) stage, according to the latest 8th edition of AJCC staging system[62].

Methods of staging

Given the importance of staging in treatment options and overall prognosis, many modalities have been utilized to precisely establish it. These include, in a typical order, barium contrast studies, esophagogastroduodenoscopy with endoscopic ultrasound (EUS), bronchoscopy, computed tomography (CT) scan, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET scan) [63], percutaneous ultrasound of cervical

lymph nodes with or without fine-needle aspiration (FNA) cytology, and finally, laparoscopy and/or thoracoscopy.

Nowadays the availability of more advanced staging modalities makes barium contrast studies much less essential. Features indicative of possible malignancy include mucosal irregularities, lumen stenosis, shouldering appearance, and dilatation of the proximal segments. Other signs suggestive of advanced-stage or infiltrative disease comprise tortuosity, angulation, axis deviation, sinus formation, and fistulation to the tracheobronchial tree[64].

EUS is the only imaging modality capable of differentiating the various structures of the esophageal wall, usually seen as five alternating hyper- and hypoechoic layers. It is the most accurate technique for locoregional staging of invasive esophageal cancer. Sensitivity and specificity rates of EUS for the correct evaluation of T stage are 81-92%, and 94-97%, respectively; in general, EUS performs better with advanced than with early disease [65]. T2, T3, and T4 tumors appear as strictures, ulcerations, or exophytic masses, each to their relative extent. The echographic finding of an irregular outer border with invasion through the adventitia of the esophagus may or may not indicate local unresectability. In the 8th edition of the TNM classification (Table 1), tumors classified as T4 are divided into those that are potentially resectable (T4a: tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum) and those that are categorically unresectable (T4b: invasion of other adjacent structures, such as the aorta, vertebral body, or airway). A caveat for EUS staging of esophageal wall penetration is that the instrument may not cross a tumor-induced stenosis. In these settings, EUS might under-stage the tumor because the entirety of the lesion may not be visualized. Suggested ways to overcome this problem are pre-dilation[66] or miniature ultrasound catheter probes that are passed through the working channel of a conventional endoscope[67].

Echographic features of lymph nodes that suggest malignant involvement include diameter greater than 10mm, rounded contour, sharp borders and hypoechogenic appearance, in decreasing order of importance. When all four features are present, there is an 80-100% chance of metastatic involvement.

The accuracy of EUS may understandably fluctuate for different lymph node locations because it is related to the depth of penetration of the sonogram (about 3 cm). It is best for detecting paraesophageal nodes, as the sensitivity varies inversely with axial distance. The ability to perform EUS-guided FNA cytology of suspicious nodes (such as paratracheal or celiac nodes) is another factor that makes EUS superior to CT scanning. Sensitivity, specificity, and accuracy of EUS-guided FNA for locoregional lymph nodes are all over 85% [65].

Bronchoscopy is performed to assess tumor invasion of the tracheobronchial tree, especially for upper and middle located tumors. Bronchoscopic findings that show tumor involvement include widening of carina, extrinsic compression (particularly from posterior tracheal wall), direct tumor infiltration, and fistulization. Airway invasion excludes patients from resection surgery.

As in other digestive tumors, the main value of a CT scan in esophageal cancer is its ability to detect distant metastasis, such as those in the liver, lungs, bones, and adrenal glands. Adenocarcinomas most frequently metastasize to intra-abdominal sites. The sensitivity for liver metastases larger than 2 cm is approximately 70-80%, but it is reduced to 50% if the lesion is <1 cm [68]. Lung metastases related to a primary esophageal tumor are seldomly solitary lesions. If a solitary mass appears, investigation should be directed to a primary lung cancer or a benign nodule. Regarding the evaluation of a primary esophageal tumor, the precision of the CT scan is inferior to the EUS. In the diagnosis of T4 disease by CT scan, obliteration of the fat plane between the esophagus and the aorta, trachea and bronchi, and pericardium is suggestive of invasion, but the scarcity of fat in cachectic patients makes this criterion rather useless. Another image cue suggestive of infiltration is the contact area of the esophagus and the aorta exceeding 90 degrees of the circumference, with accuracy of 80% [69]. Additionally, the sensitivity of detecting mediastinal and abdominal nodal involvement is suboptimal with CT scans, because the diagnostic criteria are reduced to nodal. Nevertheless, normal-sized lymph nodes may contain metastatic deposits. On the other hand, enlargement of lymph nodes may be due to reactive and inflammatory hyperplasia.

CT scans are nowadays commonly performed together with PET scans. A composite picture of both is generated to correlate detailed anatomic irregularities with metabolic uptake of a glucose analogue. This improved anatomic definition explains why FDG-PET scan is gaining popularity in esophageal cancer staging. The sensitivity ranges from 78% to 95% for detecting the primary tumor, with most false-negative tests occurring in patients with T1 or small T2 tumors [70,71].

FDG-PET alone does not provide enough definition of the esophageal wall, having no value in determining T stage. For locoregional nodal metastases, spatial resolution is also insufficient to distinguish the primary tumor from juxta-tumoral lymph nodes because of the former's interference. This is especially true in the middle and lower mediastinum, where most primary tumors are found in close anatomic relation to lymph node clusters, causing a low sensitivity in node-involvement detection. In contrast, specificity is usually much better, reaching 95% to 100% in some studies [71,72,73]. FDG-PET's main advantage is that it is more sensitive than contrast-enhanced CT or EUS in the detection of distant metastases[74,75].

The addition of PET to the preoperative assessment alters management in 5-20% of cases, mainly by detecting occult metastases (thus increasing M status) which reduces the number of patients with advanced disease who undergo surgery [76]. The improved sensitivity of PET scans for the detection of metastatic disease makes it potentially the most cost-effective method of identifying patients with occult metastases for whom curative therapy should not be pursued [76].

Percutaneous ultrasound is particularly useful for obtaining FNA biopsies of cervical lymph nodes. It has high diagnostic sensitivity, specificity, and accuracy for affected nodes, confirmed by histopathology in patients who underwent subsequent lymphadenectomy[77]. Information acquired by combining preoperative cervical ultrasound and EUS has high prognostic value, bearing in mind that both these procedures are operator-dependent [78].

Thoracoscopy and laparoscopy are the least consensual staging modalities. Thoracoscopic staging usually involves a right-sided approach, with opening of the mediastinal pleura from below the subclavian vessels to the inferior pulmonary vein with lymph node sampling. Laparoscopic staging can include celiac lymph node biopsy, laparoscopic ultrasound for detecting liver metastases, and peritoneal carcinomatosis diagnosis. It can be performed as a preliminary procedure during the surgical time of esophagogastrectomy. The CALGB 9380 multi-centric study reported results in 113 patients, and the strategy was feasible in 73% of them. Thoracoscopy and laparoscopy identified nodes or metastatic disease missed by CT scan in 50% of patients, and by EUS in 30%. Although no deaths nor major complications occurred, this approach required general anesthesia, one-lung anesthesia, a median operating duration of 210 minutes, and a hospital stay of 3 days[79]. Given their invasiveness, these methods should be reserved for patients in whom confirmation of metastatic disease is not otherwise obtainable and is essential for treatment decisions.

Treatment

In the past, treatment options for esophageal cancer were limited to surgical resection, radiotherapy, and palliative plastic stenting. Technological advances have increased the number of therapeutic options. Stage-directed therapy has become the norm, offering patients appropriate treatment methods, comprising either single techniques or combined strategies.

Early esophageal adenocarcinoma

High-grade dysplasia in BE, synonymous with intraepithelial cancer, is the last preinvasive stage in the metaplasia-dysplasia-neoplasia sequence, thus remaining the best surrogate marker for cancer risk[80]. Treatment options include intensive surveillance, direct endoscopic therapies, and esophagectomy.

The main goal of endoscopic surveillance is to identify precancerous lesions early in time and then intent curative interventions[81]. Its proponents claim that such a strategy can diagnose invasive cancer at an early stages and treatment can be delayed until then without compromising prognosis. The assumed high morbidity and mortality rates of esophagectomy are also a deterrent to immediate surgical resection [82].

High-grade dysplasia is currently the only reliable marker of preinvasive cancer, but interobserver concordance is suboptimal in distinguishing invasive and noninvasive lesions. Expert GI pathologists' assessment must be taken in consideration in those cases[83].

When esophagectomy is carried out in patients who have high-grade dysplasia, invasive adenocarcinoma (at least submucosal cancer) is identified in the surgical specimen in up to 12.7% of patients, according to a meta-analysis, and most of these patients had visible lesions such as nodularity at endoscopy, a known risk for invasive cancer. In the absence of visible lesions, this figure is as low as 6.7%[82].

To our knowledge, there are no controlled randomized prospective studies that show the efficacy and superiority of these surveillance strategies to identify patients at risk, knowing that the yearly incidence of EAC is overall low and a significative proportion of patients didn't suffer from BE previously to developing cancer. In a Netherlandish cohort study, only 5.6% of BE patients died from EAC[84].

Most would regard the finding of high-grade dysplasia as a threshold for intervention, but not necessarily a surgical one. In patients who have visibly suspicious lesions (such as raised nodules suggesting submucosal invasion or size being greater than 1.5cm), and not just a flat Barrett mucosa, endoscopic resection is recommended to ensure no invasive cancer is present [85], followed by ablative therapy of the remaining metaplastic mucosa (to address possible occult lesions) [86]. Given the high incidence of progression from high-grade dysplasia to early adenocarcinoma, current guidelines preferably recommend endoscopic intervention [55,58,87].

The rationale of endoscopic mucosal treatments is that the incidence of nodal metastases in high-grade dysplasia or T1a (intramucosal) tumors is low, and therefore, exclusive intervention on mucosal disease will most likely result in cure. In T1a lesions,

the rate of nodal metastases is reported as 0-6%. Once the submucosa is invaded (as in T1b lesions), this figure rises to around 20% [88].

Several specialty associations have launched practice guidelines for endoscopic treatment for BE (Tables 26-2 and 26-9). Options of endoscopic approach for high-grade dysplastic BE and early adenocarcinoma include endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), photodynamic therapy (PDT), and radiofrequency ablation (RFA).

EMR can be used to resect localized visible lesions in BE. The resection of localized lesions is done not only for therapeutic purposes but also for staging [89]. A study of EMR reported by Ell and colleagues included 100 patients, of whom complete local remission was achieved in 99. 11% of patients developed recurrence (6% locally and 5% at different locations), but successful repeated treatments were possible in all. The 5-year survival rate was 98%. In this study, all patients had mucosal lesions of up to 20 mm arising in Barrett metaplasia, and no lymphovascular invasion [90]. In addition to resecting localized lesions, circumferential EMR makes it possible to approach the whole length of the Barrett's mucosa. Another larger and more recent study showed its high effectiveness and long-term results. Of 1,000 patients, 96.3% had achieved complete response; only 3.7% of which underwent surgery after eradication failed during a follow-up of almost 5 years. Metachronous lesions or recurrence of cancer developed during the follow-up period in 14.5% of patients but most were successfully treated endoscopically, resulting in a long-term complete remission rate of 93.8% [91].

ESD is a technique developed in Japan in the late 1990's that allows for *en bloc* resection of superficial lesions. The technique consists of marking the perimeter of the lesion with cautery, then creating a circumferential mucosal incision around the lesion. The mucosa is then freed by carefully dissecting through the submucosa via endoscopic cautery. ESD has similar indications to EMR, but offers the advantage of deeper resection, thus leading to a higher probability of curative removal of lesions and potentially reducing the incidence of recurrence. The larger specimens retrieved also allow more precise histological analysis[89]. A recent meta-analysis of 15 non-randomized studies comparing ESD to EMR for superficial tumors of the gastrointestinal tract showed much higher curative resection rates (odds ratio, 13.87 and 3.53, respectively) with ESD, regardless of lesion size, as well as decreased local recurrence rate (odds ratio, 0.09). However, compared to EMR, ESD is associated with longer procedure times, and increased complications, such as bleeding and perforation[91]. Studies have shown endoscopic resection to be effective in eradicating HGD or T1a EAC in 91% to 98% of cases [93]. Retrospective data collected by James and colleagues[94] suggests cure and survival

rates of endoscopic resection of T1a disease to be comparable to outcomes following surgery, but with substantially decreased procedure-related morbidity and mortality.

Besides excisional therapy, ablative methods are available. A randomized trial demonstrated that PDT could reduce the cancer risk in BE. In this study, 208 patients with high-grade dysplasia were randomized to ablation using PDT post porfimer sodium intake plus a PPI versus PPI alone. High-grade dysplasia was eliminated in 77% of patients in the PDT group, although in 39% of patients in the PPI group, high-grade dysplasia was also not found on subsequent biopsies. Barrett's epithelium elimination was achieved in 52% of patients in the PDT group compared to only 7% in the PPI group. Adenocarcinoma developed in 15% of the patients in the PDT group compared with 29% in the PPI group, with a longer time to progression to cancer favoring PDT [95]. The downsides of PDT treatment include the need for repeated sessions, generalized photosensitivity, possible stricture formation, and pseudo-regression (with incidence as high as 51%), making continued surveillance necessary. Since PDT does not treat nodal disease and there is no specimen for histologic examination, accurate pretherapy diagnosis of noninvasiveness is needed.

RFA has been shown to be effective in treating both nondysplastic and dysplastic BE [96]. RFA energy is delivered by a bipolar electrode, causing frictional heating of intracellular water molecules. The most commonly used system comes with circumferential (HALO360) and focal ablative probes (HALO90). This technical procedure is performed under sedation. For HALO360, a sizing balloon is first introduced into the esophagus and an appropriate size of probe is chosen and then inserted into the esophagus. For HALO90, the probe is mounted at the tip of an endoscope. It is best used for ablating residual Barrett's mucosa after some other first treatment. A trial examined the use of the HALO system in ablating dysplastic BE in which patients were randomly assigned to RFA or to a placebo procedure. Randomization was stratified according to grade of dysplasia and length of BE. In the intention-to-treat analyses, among patients with low-grade dysplasia, complete eradication of dysplasia occurred in 90.5% of patients in the ablation group compared to 22.7% in the control group. Among patients with high-grade dysplasia, the respective figures were 81% and 19%. Overall, 77.4% of patients in the ablation group had complete eradication of intestinal metaplasia, compared with 2.3% of patients in the control group. Patients in the ablation group had less disease progression (3.6% vs 16.3%) and fewer cancers (1.2% vs 9.3%). Stricture only developed in 6% of ablated patients [97].

A popular endoscopic multimodal approach involves combining focal EMR with RFA. Ablation is typically performed 6-12 weeks following the focal resection to allow the esophageal wound to heal. A systematic review by Desai and colleagues has established

its efficacy and safety, making this approach the preferred combined treatment technique[98].

Other state-of-the art endoscopic technologies for early diagnosis and minimally invasive treatment are reviewed by di Petro and colleagues [99].

Despite all methods revised, surgical resection is the only method to ensure complete eradication of the dysplastic mucosa and the frequently undetected invasive cancer. Surgical resection was considered a standard treatment in the past because of the high frequency of invasive cancers found in surgical specimens when resection was performed for high-grade dysplasia. The supposedly high morbidity and mortality rates of esophagectomy are the bigger deterrents against surgical resection. However, in specialized high-volume centers, the mortality rate from esophagectomy, especially in early cases, is minimal. Minimally invasive surgical methods, including thoracoscopy, laparoscopy, or esophageal stripping, further reduce the trauma of surgical access. The Merendino procedure, with limited surgical resection of the distal esophagus and GEJ, together with lymphadenectomy of the lower mediastinum and upper abdominal compartment, has been advocated. An isoperistaltic jejunal interposition graft is used to restore intestinal continuity. This method combines the adequacy of nodal dissection and improved quality of life, as the jejunal loop helps against gastroesophageal reflux[100].

In summary, in patients with high-grade dysplasia or early intramucosal cancer, treatment is indicated, preferably with endoscopic modalities. When the histopathologic findings of the specimen indicate stages more advanced than T1a, a multidisciplinary approach, much like for advanced-stage disease, should be considered. Ideal management should include a gastroenterologist, thoracic surgeon, oncologist, pathologist, and radiation oncologist[46].

Advanced Esophageal Cancer

Surgical resection remains the mainstay treatment for localized esophageal cancer. Surgery in combination with multimodality oncology treatments is the new standard of care. Palliative methods, whenever cure is not attainable, have also evolved.

Excellent surgical outcomes after esophagectomy are now achievable in dedicated high-volume centers; centralization of services with specialized management teams reasonably improves outcomes[101].

Utmost aspects to enhance post-esophagectomy outcomes are 1) appropriate patient selection, 2) choice and execution of surgical techniques, and 3) perioperative care.

Patient Selection for Esophagectomy

How strictly a surgical team selects patients for esophagectomy will influence the success rate. Selection typically depends on many factors, including 1) the referral policy of each center, 2) the prevailing treatment philosophy, 3) the availability of alternative therapies, and 4) the possible mortality and morbidity that the surgeon and patient are willing to accept.

In studies that report on improvement of surgical results over time, a stricter patient selection often comes into play, either by excluding high-risk patients or by treating advanced disease by nonoperative means. Resection with a clear aim for palliation is becoming uncommon, and most would only operate on patients for potential cure.

The evaluation of the fitness of a patient to undergo esophagectomy is an imperfect science. Many poor-risk indicators have been identified, such as Karnofsky Performance Scale score of less than 80, poor nutritional status as defined as more than 10% weight loss, preexisting cirrhosis, and cardiopulmonary disease. Other factors reported to be predictive of increased morbidity and mortality include advanced age, proximally located tumor, high alcohol intake, and heavy smoking[102] and all of these are relative contraindications.

One must emphasize that obesity is not associated with any increase in overall morbidity following esophagectomy and should not be considered a contraindication for esophagectomy[103].

Candidates for upfront esophagectomy usually consist of patients with clinical T1N0M0 lesions and, in many centers, with clinical T2N0M0 lesions (Table 2).

Indicators of unresectability

The presence of metastatic disease (staged as M1), such as in peritoneal, lungs, bones, adrenal glands, brain, or liver metastases, or extraregional lymph node spread (e. g., paraaortic or mesenteric lymphadenopathy), precludes an attempt at resection. Celiac nodal metastases and mediastinal/supraclavicular nodes are scored as regional nodal disease in the TNM staging system, regardless of the primary tumor location; it is the number of involved nodes rather than location that determines the N stage [104].

Choice of Surgical Approaches

Esophagectomy is a technically difficult operation, and the complication rate is high due to the anatomic challenges of the procedure. There are many important variables in esophagectomy, such as surgical access, extent of resection and lymphadenectomy, type and method of preparation of the esophageal substitute, the route of reconstruction, and the technique of esophageal anastomosis. Many of these variables are associated and could affect immediate morbidity and mortality rates, long-term quality of life, and survival. Tumor location and stage, patient risk profile, and surgeon preference and experience are important variables in deciding the surgical procedure. Surgical teams' diversified expertise is crucial in order to adapt to the different presentations of esophageal cancer. We will focus our attention onto operative procedures targeting thoracic and abdominal esophageal cancer, as EAC generally arises in those locations.

Transhiatal esophagectomy – This procedure can be performed to resect cervical, thoracic, and EGJ esophageal cancers; it is performed through an upper midline laparotomy incision and a left neck incision, typically without a thoracotomy[105]. The thoracic esophagus is bluntly dissected through the diaphragmatic hiatus superiorly and via the neck inferiorly. A cervical anastomosis is created most often with a gastric pull-up approach. Disadvantages include the inability to perform a full thoracic lymphadenectomy and lack of visualization of the midthoracic dissection.

In the largest prospective series of 2007 patients, the in-hospital mortality rate decreased throughout the years (comparing the 1998-2006 cohort to the 1976-1998) reaching 1% in 2006, reflecting increasing surgical safety [106]. In addition, the anastomotic leak rate was also lower in the most recent cohort (9% versus the previous 14%). Other postoperative complications included atelectasis, pneumonia, intrathoracic hemorrhage, recurrent laryngeal nerve paralysis, chylothorax, and tracheal laceration in less than 1% each[106].

Ivor-Lewis transthoracic esophagectomy – The Ivor-Lewis esophagectomy can be used to resect cancers in the lower third of the esophagus but is not the optimal approach for cancers located in the middle third because of the limited proximal margin that can be achieved. This procedure combines a laparotomy with a right thoracotomy and an intrathoracic esophagogastric anastomosis. This approach permits direct visualization of the thoracic esophagus and allows the surgeon to perform a full thoracic lymphadenectomy. A minimally invasive Ivor-Lewis approach to a thoracotomy is preferred. Disadvantages of the transthoracic esophagectomy include a limitation to the length of proximal esophagus that can be resected to achieve a histologically negative

margin, an intrathoracic location of the esophagogastric anastomosis, and a 3-20% risk of severe bile reflux [107]. A leak occurring at the intrathoracic anastomosis has been associated with morbidity and mortality rates as high as 64% [108]. With current techniques, mortality rates are substantially lower [109].

Several centers report favorable results using the conventional Ivor-Lewis esophagectomy with a right thoracic anastomosis [110,111]. At least one meta-analysis [112] suggests similar long-term outcomes compared to the transhiatal esophagectomy[111]. In one of the largest series of 228 patients undergoing an Ivor-Lewis subtotal esophagectomy, perioperative mortality rate was 4%, and major respiratory and cardiovascular and/or thromboembolic complications occurred in 17% and 7%, respectively[111]. Nine patients (4%) developed a mediastinal leak, which was anastomotic in five, and due to either an ischemic gastric conduit or gastrotomy dehiscence in the remainder.

Tri-incisional esophagectomy (modified McKeown technique) — The tri-incisional esophagectomy combines the transhiatal and transthoracic approaches into a transthoracic total esophagectomy with a thoracic lymphadenectomy and cervical esophagogastric anastomosis [113]. The three-incisional technique allows the surgeon to perform a complete two-field (mediastinal and upper abdominal) lymphadenectomy under direct vision and a cervical esophagogastric anastomosis. A thoracoscopic approach to the chest rather than a thoracotomy is preferred to minimize the risk of respiratory complications.

Abdominal and EGJ esophageal cancer resection — GEJ or intra-abdominal esophageal cancers have been traditionally managed surgically with either an esophagectomy with partial gastrectomy or an extended gastrectomy, with or without thoracotomy. Regardless of the approach, R0 resection, a 4cm gastric margin, a 5cm esophageal margin, and resection of at least 15 nodes appropriate for the primary tumor location is necessary[114]. The extent of the esophageal resection that can be achieved solely via a transabdominal approach without thoracoabdominal incision or transhiatal esophagectomy is limited, and therefore this approach is not accepted for tumors that involve the distal esophagus due to difficulties in achieving an adequate negative proximal margin[115].

Minimally invasive approaches — An Ivor-Lewis esophagectomy can be performed through open incisions, total minimally invasive (thoracoscopic/laparoscopic), or hybrid approach. The hybrid approach can either combine thoracoscopic resection of the

thoracic esophagus and mediastinal nodes with open laparotomy or combine laparoscopic resection of the intra-abdominal esophagus, stomach, and lymph nodes with an open right thoracotomy. The transhiatal esophagectomy can be performed open or laparoscopically.

A 2019 systematic review and meta-analysis of 55 studies, including over 14,000 patients, concluded that minimally invasive esophagectomy was associated with an 18% lower five-year all-cause mortality compared with open esophagectomy (hazard ratio 0.82, 95% CI 0.76-0.88) [116]. Additional data available from an analysis of over 5500 patients from the National Cancer Database who underwent esophagectomy between 2010 and 2015, found comparable survival between minimally invasive, robotic-assisted, and open approaches[117]. Both minimally invasive and robotic approaches produced a higher median lymph node yield than the open approach.

The robot-assisted minimally invasive thoraco-laparoscopic esophagectomy (RAMIE) technique was evaluated in a trial of 112 patients with esophageal cancer [118].

Compared with open transthoracic esophagectomy, RAMIE resulted in fewer complications, faster functional recovery, and better short-term quality of life. Oncologic outcomes were comparable at a medium follow-up of 40 months.

Although data suggest potential benefit for a total minimally invasive approach to Ivor-Lewis esophagectomy, they are not sufficient to conclude that this is a standard approach [118].

Extent of lymphadenectomy — The appropriate extent of lymphadenectomy during esophageal cancer surgery is still debated. The minimum number of lymph nodes that should be removed during potentially curative esophagectomy is yet to be established. However, as many lymph nodes should be removed as is feasible since more extensive lymphadenectomy has been associated with better survival [119]. For example, in a retrospective review of 972 patients with node-negative esophageal cancer, the five-year disease-specific survival was 55% when fewer than 11 nodes were resected, 66% for 11 to 17 nodes resected, and 75% for 18 or more nodes resected [120]. A greater number of retrieved lymph nodes generally reflects more accurate staging, which generally comes with more extensive resections.

Many high-volume surgical centers routinely perform “en bloc” esophagectomy with a two-field (mediastinal and upper abdomen) lymph node dissection in the belief that this contributes to better locoregional control because of removal of metastatic lymph nodes. An even more extensive lymphadenectomy, three-field lymphadenectomy of the mediastinal, abdominal, and cervical nodes, is commonly practiced in Asian countries for upper thoracic esophageal cancers, as Japan Esophageal Society advises [121,122].

Proponents of extended lymphadenectomy emphasize the relationship between total lymph node count and prognosis and quote long-term survival rates as evidence of its therapeutic benefit[119]. In the United States and most Western countries, “en bloc” resection of the mediastinal and upper abdominal lymph nodes is considered a standard component of transthoracic esophagectomy, and a three-field lymphadenectomy is not considered a standard treatment for patients with esophageal cancer. The location of the tumor (upper versus middle to lower third) may have an influence on the frequency of finding cervical nodal metastases, as it is tightly related with histology subtype[123].

Esophageal reconstruction – There are various methods of esophageal reconstruction that have been previously described in the literature. The main conduits used for esophageal reconstruction after esophagectomy include interposition grafts such as gastric, colon, and jejunum. There are also several free flaps that can be utilized, including pedicled, local flaps such as the pectoralis major and supraclavicular island flaps, or free flaps such as the radial forearm free flap, anterolateral thigh free flap, but these are usually not first-line options [124]. Overall, “gastric pull-up” isoperistaltic technique[125] is the most used for surgical reconstruction following esophagectomy. The stomach is reshaped into a tube, preserving the right gastroepiploic artery along the greater curvature. The rich supply of submucosal vascular networks can preserve the stomach on this single vessel. Once the stomach conduit is made, it is pulled into the chest or neck for the anastomosis execution. The single anastomosis of the gastric esophageal conduit makes it less technically demanding than any of the other conduit choices [126]. Jejunal loops or colon segments can also be used. These are resistant to the effects of gastric acid and have a similar shape to the native esophagus. However, their use requires two additional anastomoses, and in the case of the jejunal interposition, the fixed mesenteric length limits transposition to the proximal esophagus [124].

Combined modality therapy – general recommendations

Surgery is the most effective strategy to cure EAC in early-stage. However, surgery alone is usually inadequate in more advanced cases. Preoperative (neoadjuvant) chemoradiation or perioperative (neoadjuvant and adjuvant) chemotherapy are currently used as an adjunct to surgery. This is the recommendation for patients with T3N0, T4aN0, and clinically node-positive thoracic esophageal cancer. Concurrent chemoradiotherapy is advised instead of chemotherapy alone [127].

Although the optimal category, dose, combination, and schedule of drugs has not been definitively established for chemoradiotherapy, evidence from the Dutch CROSS trial proposes the low-dose weekly carboplatin plus paclitaxel regimen (rather than two courses of cisplatin plus fluorouracil as was used in CALGB 9781).

According to from the CROSS trial, after a median follow-up of 105 months, health-related quality of life in patients treated with neoadjuvant chemoradiotherapy was not statistically different than of those treated with surgery alone [128].

The optimal dose-fractionation radiotherapy schedule for concurrent chemoradiotherapy regimens remains to be determined. However, three-dimensional conformal techniques should be used for modern treatment planning to minimize toxicities to adjacent vital organs. Standard preoperative RT dose in once-daily schedule currently practiced is between 41.4 and 50.4 Gy (values based on the CROSS[128] and the CALBG 9781 trials, respectively).

Tri-modality therapy rather than definitive chemoradiotherapy for clinically resectable adenocarcinomas is recommended given the higher rate of local recurrence after chemoradiotherapy alone and a lack of data on nonsurgical management of patients with adenocarcinoma. There are no randomized trials directly comparing tri-modality versus bimodality, but some data from retrospective analyses support this claim [129,130]. Tri-modality therapy is also superior to preoperative chemotherapy. The addition of radiotherapy resulted in higher histological complete response rate, higher R0 resection rate, and a lower frequency of lymph-node metastases, without significantly affecting survival [131].

For chemoradiotherapy non-responders, surgery is rationally the cornerstone of therapy, for patients who remain operable after chemoradiotherapy.

The benefit of preoperative chemoradiotherapy for patients with clinical stage T2N0 adenocarcinomas is less clear. Nevertheless, these patients were included in three trials that demonstrated a survival benefit for neoadjuvant chemoradiotherapy, and we suggest combined modality therapy rather than resection alone. For patients with T1N0

EAC, upfront surgery or endoscopic resection is preferred rather than neoadjuvant chemotherapy or chemoradiotherapy [55,58].

In patients who are not surgical nor endoscopic candidates, definitive chemoradiotherapy is a reasonable approach.

Patients with completely resected pT3-4 adenocarcinomas who have not received neoadjuvant therapy should be advised to undergo postoperative adjuvant therapy [55,132].

National Comprehensive Cancer Network (NCCN) guidelines suggest adjuvant therapy for selected patients with high-risk resected pT2N0 adenocarcinomas, including those with poorly differentiated histology, with lymphovascular or perineural invasion, and arising in patients younger than age 50 [55].

Patients with residual disease in the esophagectomy specimen after preoperative chemoradiotherapy should be offered adjuvant nivolumab for up to one year. In the CheckMate 577 randomized controlled trial disease-free survival was significantly longer among those who received nivolumab adjuvant therapy than among those who received placebo [133].

There are no randomized trials to guide postoperative surveillance strategy and no data that demonstrates improvement in quality of life or longevity from earlier detection of asymptomatic recurrences. Clinical history, physical examination, and targeted blood work (if symptomatic, or if there was an elevated serum tumor marker preoperatively) should be performed every four months for the first three years. Restaging CT scans of the chest and abdomen should also be carried out at four-month intervals [55].

Consensus [55] has determined that surveillance endoscopy should only be carried out if there was a preoperative history of BE, a questionable resection margin, or if the patient has an unmanageable stricture that is worrisome for an occult local recurrence. Strict surveillance in the first two years after treatment may be warranted in patients who underwent definitive chemoradiotherapy.

Palliative treatment

Patients unable to tolerate neoadjuvant chemoradiotherapy or with a short estimated life-expectancy (i.e., six months or less) are advised to undergo alternative approaches to palliation of dysphagia, such as endoscopic therapy or brachytherapy, rather than concurrent chemoradiotherapy.

Endoscopic interventions may be appropriate for palliation of dysphagia in patients who have advanced esophageal cancer in the following settings:

– Patients for whom definitive management is planned, but have severe dysphagia at presentation requiring intervention prior to therapy;
– Failure to achieve adequate palliation of dysphagia with initial therapy;
– Recurrent dysphagia due to locoregional failure;
– Recurrent dysphagia due to benign strictures in patients who are successfully treated with radiotherapy;
– Patients who are poor candidates for either chemotherapy or radiotherapy.

There are several endoscopic approaches that provide palliation from malignant dysphagia: placement of a prosthetic self-expanding metal stent, dilation, laser therapy, endoscopic injection therapies, photodynamic therapy, and brachytherapy.

Stenting is the preferred method for patients with a malignant stricture and/or fistula. In the absence of a fistula, optimal therapy remains controversial. A systematic review of interventions for palliation of dysphagia associated with locally advanced esophageal cancer concluded that insertion of a self-expanding stent is safe and provides rapid relief of dysphagia, while thermal and chemical ablative therapy provided comparable dysphagia palliation but with an increased requirement for reintervention and adverse effects [134].

Brachytherapy is a suitable alternative that may be associated with improved survival and quality of life. It permits treatment of a targeted area of the esophagus with high radiation doses, sparing the surrounding structures from its damage. It should be for palliation of dysphagia, particularly when the extent of extraluminal disease is limited, and long-term palliation is likely. Although stenting has the advantage of palliating dysphagia immediately, the palliative effect of brachytherapy is frequently more durable with lower complication rates[135].

Palliative resection surgery is usually not considered for patients with locally advanced disease and distant metastases. It is also no longer considered a valid concept for patients with locally advanced non-metastatic esophageal cancer. Perioperative morbidity and mortality rates are high, hindering the opportunity for safer alternatives, such as definitive chemoradiotherapy.

Like palliative esophagectomy, surgical bypass provides limited benefit and is associated with substantial morbidity in patients with clearly unresectable disease [136]. Although these palliative bypasses relieve symptoms, complication rates usually exceed 50%-60%, and mortality rates are between 5 and 10% [137]. As a result, these procedures are nowadays rarely attempted.

Prognosis

The prognosis of esophageal cancer is strongly associated with disease stage. Accurate clinical staging of both local tumor extent and the existence of distant metastases is critical for estimating prognosis and selecting the appropriate treatment strategy.
Esophageal cancer is highly lethal, with a 5-year survival of 15%-25% [138]. The majority of cases present with advanced disease at the time of diagnosis, hence the dismal prognosis. These patients have a median survival of 3-6 months [139].
English cancer patient database points out that 47.1% of males survived esophageal cancer for at least one year. This number falls to 16.3% surviving five years or more, in age-standardized net survival in 2013-2017 period. Survival for females at one year is 46.0% and falls to 18.7% surviving for at least five years [140]. For this reason, nowadays global attempts are made to more diagnose and treat both BE (the known precursor to invasive disease) and neoplastic disease in early stages [141].
Over the past decade, the multimodality therapy previously discussed has improved survival for patients with operable esophageal adenocarcinoma.
Current available prognostication tools exist but are yet to be validated for use in clinical practice. One important limitation Gupta and colleagues describe is the fact that these tools frequently exclude adenocarcinoma histology [142].

Discussion and Conclusions

Esophageal cancer is an aggressive malignancy with an increasing incidence and a poor prognosis. Much of this increase is at the expense of the adenocarcinoma subtype, “an emerging disease”. The other main histologic type is the squamous cell carcinoma, with divergent etiology and epidemiology. They present almost-complementary incidence trends. Whereas the incidence of SCC is declining in most parts of the world, EAC incidence rates have shown a significant and sustained rise, especially in Western industrialized countries over the past four decades. The most well established EAC risk factors are GERD and obesity, two highly prevalent conditions in the Western World. Both might be modifiable with lifestyle and anti-reflux therapy, where EAC prevention probably lies. This tumor is known to arise from a metaplastic BE mucosa, namely when high grade dysplasia is present. Since BE patients are much more likely to develop cancer of the esophagus, they require close medical surveillance to manage potential

emerging tumors in a timely manner. Once high-grade dysplasia or invasive disease are diagnosed, depth and extension of cancer spread should be promptly evaluated.

Accurate cTNM and staging must be pursued, taking advantage of imaging modalities, such as EUS and FDG-PET scan, in order to establish treatment strategy.

Early-stage EAC patients are allocated to endoscopic therapy, a modern area offering diverse and efficacious techniques, devoid of the traditional surgery risks[99].

Whenever possible, effort should be made to assign advanced-stage patients to tri-modality therapy: neoadjuvant chemoradiotherapy, resection surgery and adjuvant chemotherapy[129]. For these patients, conjunctive therapy is the standard of care, demonstrably improving survival without decline of quality of life. If feasible, minimally invasive surgery is always recommended[55]. Reconstruction of the esophageal tract is generally made resorting to a gastric conduit. Unlike what happened in the past, perioperative mortality and morbidity are nowadays diminished in high-volume specialized centers. Whether this volume-outcome relationship is due to repeated practice and skill-share or selective referral patterns is up to debate[101].

Despite EAC landscape being relatively well described – as shown by this narrative review, prognosis remains substandard, making esophageal cancer one of the top ten most lethal globally.

This paper's core strength is the broad scope of subjects examined. Conversely, its main limitation is the heterogeneity of bibliographic sources used, which was expected from the diversity of specialty backgrounds.

Future investigation areas that would benefit patient outcomes should focus on prevention strategies (beyond lifestyle changes and including pharmacological chemoprevention); tailored molecular therapies (in the personalized medicine field); refining optimal radiotherapy and chemotherapy dosing and timing; and, finally, perfecting prognostication assessment tools.

Table 1: Cancer staging categories for cancer of the esophagus and esophagogastric junction [62]

Category	***Criteria***
T category	
TX	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined by the basement membrane
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
*T1a**	Tumor invades the lamina propria or muscularis mucosae
*T1b**	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
*T4a**	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
*T4b**	Tumor invades other adjacent structures, such as aorta, vertebral body, or trachea
N category	
NX	Regional lymph nodes* cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
M category	
M0	No distant metastasis
M1	Distant metastasis
Adenocarcinoma G Category	
GX	Differentiation cannot be assessed
G1	Well differentiated. >95% of tumor is composed of well-formed glands
G2	Moderately differentiated. 50% to 95% of tumor shows gland formation
G3[†]	Poorly differentiated. Tumors composed of nest and sheets of cells with <50% of tumor demonstrating glandular formation
Squamous cell carcinoma G category	
GX	Differentiation cannot be assessed
G1	Well-differentiated. Prominent keratinization with pearl formation and a minor component of nonkeratinizing basal-like cells. Tumor cells are arranged in sheets, and mitotic counts are low
G2	Moderately differentiated. Variable histologic features, ranging from parakeratotic to poorly keratinizing lesions. Generally, pearl formation is absent
G3[‡]	Poorly differentiated. Consists predominantly of basal-like cells forming large and small nests with frequent central necrosis. The nests consist of sheets or pavement-like arrangements of tumor cells, and occasionally are punctuated by small numbers of parakeratotic or keratinizing cells
*Squamous cell carcinoma L category***	
LX	Location unknown
Upper	Cervical esophagus to lower border of azygos vein
Middle	Lower border of azygos vein to lower border of inferior pulmonary vein
Lower	Lower border of inferior pulmonary vein to stomach, including esophagogastric junction

* Regional lymph nodes encompass areas from the neck and through the mediastinum to the upper abdomen, including the celiac nodes.

Table 2: TNM staging is essential in determining stage-specific protocols for treatment [63]

Stage	*Tumor*	*Node*	*Metastasis*	*Therapeutic options*
0	Tis	N0	M0	Local ablative therapy
I	T1	N0	M0	Surgery
IIA	T2	N0	M0	Surgery
	T3	N0	M0	
IIB	T1	N1	M0	Neoadjuvant therapy with or without surgery
	T2	N1	M0	
III	T3	N1	M0	Neoadjuvant therapy with or without surgery
	T4	Any N	M0	
IVA	Any T	Any N	M1a	Chemotherapy or radiation therapy with or without surgery
IVB	Any T	Any N	M1b	Palliative treatment

References

1. GCO.IARC.fr/today/home: International Agency for Research on Cancer, WHO, Global Cancer Observatory [Webpage]; [visited on 2021 Feb 9] Available at: https://gco.iarc.fr/today/online-analysis-multi-bars?v=2020&mode=cancer&mode_population=countries&population=900&populations=&key=total&sex=0&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=15&group_cancer=1&include_nmsc=1&include_nmsc_other=1&type_multiple=%257B%2522inc%2522%253Atrue%252C%2522mort%2522%253Atrue%252C%2522prev%2522%253Afalse%257D&orientation=horizontal&type_sort=0&type_nb_items=%257B%2522top%2522%253Atrue%252C%2522bottom%2522%253Afalse%257D
2. Wong MCS, Hamilton W, Whiteman DC, Jiang JY, Qiao Y, Fung FDH, et al. Global Incidence and mortality of oesophageal cancer and their correlation with socioeconomic indicators temporal patterns and trends in 41 countries. Sci Rep. 2018;8(1):4522.
3. Napier KJ, Scheerer M, Misra S. Esophageal cancer: A Review of epidemiology, pathogenesis, staging workup and treatment modalities. World J Gastrointest Oncol. 2014;6(5):112-20.
4. Zhang Y. Epidemiology of esophageal cancer. World J Gastroenterol. 2013;19(34):5598-5606.
5. Huang FL, Yu SJ. Esophageal cancer: Risk factors, genetic association, and treatment. Asian J Surg. 2018;41(3):210-215.
6. Abnet CC, Arnold M, Wei WQ. Epidemiology of Esophageal Squamous Cell Carcinoma. Gastroenterology. 2018;154(2):360-373.
7. Thrift AP. The epidemic of oesophageal carcinoma: Where are we now?. Cancer Epidemiol. 2016;41:88-95
8. Edgren G, Adami HO, Weiderpass E, Nyrén O. A global assessment of the oesophageal adenocarcinoma epidemic. Gut. 2013;62(10):1406-1414.
9. Cook MB, Chow WH, Devesa SS. Oesophageal cancer incidence in the United States by race, sex, and histologic type, 1977-2005. Br J Cancer. 2009;101(5):855-9.
10. Lagergren J, Mattsson F. No further increase in the incidence of esophageal adenocarcinoma in Sweden. Int J Cancer. 2011;129(2):513-516.
11. Schmassmann A, Oldendorf MG, Gebbers JO. Changing incidence of gastric and oesophageal cancer subtypes in central Switzerland between 1982 and 2007. Eur J Epidemiol. 2009;24(10):603-9.
12. Smyth EC, Lagergren J, Fitzgerald RC, Lordick F, Shah MA, Lagergren P, et al. Oesophageal cancer. Nat Rev Dis Primers. 2017;3:17048.
13. Drahos J, Li L, Jick SS, Cook MB. Metabolic syndrome in relation to Barrett's esophagus and esophageal adenocarcinoma: Results from a large population-based case-control study in the Clinical Practice Research Datalink. Cancer Epidemiol. 2016;42:9-14.

14. Lagergren J, Bergström R, Lindgren A, Nyrén O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med. 1999;340(11):825-831.
15. Anderson LA, Watson RG, Murphy SJ, Johnston BT, Comber H, McGuigan J, et al. Risk factors for Barrett's oesophagus and oesophageal adenocarcinoma: results from the FINBAR study. World J Gastroenterol. 2007;13(10):1585-1594.
16. Cook MB, Corley DA, Murray LJ, Liao LM, Kamangar F, Ye W, et al. Gastroesophageal reflux in relation to adenocarcinomas of the esophagus: a pooled analysis from the Barrett's and Esophageal Adenocarcinoma Consortium (BEACON). PLoS One. 2014;9(7):e103508.
17. Hvid-Jensen F, Pedersen L, Drewes AM, Sørensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus. N Engl J Med. 2011;365:1375–1383.
18. Du X, Hidayat K, Shi BM. Abdominal obesity and gastroesophageal cancer risk: systematic review and meta-analysis of prospective studies. Biosci Rep. 2017;37(3):BSR20160474.
19. McColl KEL. What is causing the rising incidence of esophageal adenocarcinoma in the West and will it also happen in the East?. J Gastroenterol. 2019;54(8):669-673.
20. Camilleri M, Malhi H, Acosta A. Gastrointestinal Complications of Obesity. Gastroenterology. 2017;152(7):1656-1670.
21. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body Fatness and Cancer – Viewpoint of the IARC Working Group. N Engl J Med. 2016;375(8):794-798.
22. Thrift AP, Shaheen NJ, Gammon MD, Bernstein L, Reid BJ, Onstad L, et al. Obesity and risk of esophageal adenocarcinoma and Barrett's esophagus: a Mendelian randomization study. J Natl Cancer Inst. 2014;106(11):dju252. doi: 10.1093/jnci/dju252.
23. Turati F, Tramacere I, La Vecchia C, Negri E. A meta-analysis of body mass index and esophageal and gastric cardia adenocarcinoma. Ann Oncol. 2013;24(3):609-617.
24. Cook MB, Greenwood DC, Hardie LJ, Wild CP, Forman D. A systematic review and meta-analysis of the risk of increasing adiposity on Barrett's esophagus. Am J Gastroenterol. 2008;103(2):292-300.
25. Corley DA, Kubo A, Levin TR, et al. Abdominal obesity and body mass index as risk factors for Barrett's esophagus. Gastroenterology. 2007;133(1):34-311.
26. Maret-Ouda J, El-Serag HB, Lagergren J. Opportunities for Preventing Esophageal Adenocarcinoma. Cancer Prev Res (Phila). 2016;9(11):828-834.
27. Leggett CL, Nelsen EM, Tian J, Schleck CB, Zinsmeister AR, Dunagan KT, et al. Metabolic syndrome as a risk factor for Barrett esophagus: a population-based case-control study. Mayo Clin Proc. 2013;88(2):157-65.

28. Chandar AK, Iyer PG. Role of Obesity in the Pathogenesis and Progression of Barrett's Esophagus. Gastroenterol Clin North Am. 2015;44(2):249-64.
29. Jin Y, Yang T, Li D, Ding W. Effect of dietary cholesterol intake on the risk of esophageal cancer: a meta-analysis. J Int Med Res. 2019;47(9):4059-4068.
30. Xu B, Zhou X, Li X, Liu C, Yang C. Diabetes mellitus carries a risk of esophageal cancer: A meta-analysis. Medicine (Baltimore). 2017;96(35):e7944
31. Vingeliene S, Chan DSM, Vieira AR, Polemiti E, Stevens C, Abar L, et al. An update of the WCRF/AICR systematic literature review and meta-analysis on dietary and anthropometric factors and esophageal cancer risk. Ann Oncol. 2017;28(10):2409-2419.
32. Cook MB, Kamangar F, Whiteman DC, Freedman ND, Gammon MD, Bernstein L, et al. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. J Natl Cancer Inst. 2010;102(17):1344-53.
33. Tramacere I, La Vecchia C, Negri E. Tobacco smoking and esophageal and gastric cardia adenocarcinoma: a meta-analysis. Epidemiology. 2011;22(3):344-349.
34. Wang QL, Xie SH, Li WT, Lagergren J. Smoking Cessation and Risk of Esophageal Cancer by Histological Type: Systematic Review and Meta-analysis. J Natl Cancer Inst. 2017;109(12):10.1093/jnci/djx115.
35. Polk DB, Peek RM Jr. Helicobacter pylori: gastric cancer and beyond. Nat Rev Cancer. 2010;10(6):403-414.
36. Mungan Z, Pınarbaşı Şimşek B. Gastroesophageal reflux disease and the relationship with Helicobacter pylori. Turk J Gastroenterol. 2017;28(1):S61-S67.
37. Fischbach LA, Nordenstedt H, Kramer JR, Gandhi S, Dick-Onuoha S, Lewis A, et al. The association between Barrett's esophagus and Helicobacter pylori infection: a meta-analysis. Helicobacter. 2012;17(3):163-175
38. Erőss B, Farkas N, Vincze Á, Tinusz B, Szapáry L, Garami A, et al. Helicobacter pylori infection reduces the risk of Barrett's esophagus: A meta-analysis and systematic review. Helicobacter. 2018;23(4):e12504.
39. Snider EJ, Freedberg DE, Abrams JA. Potential Role of the Microbiome in Barrett's Esophagus and Esophageal Adenocarcinoma. Dig Dis Sci. 2016;61(8):2217-2225.
40. Lv J, Guo L, Liu JJ, Zhao HP, Zhang J, Wang JH. Alteration of the esophageal microbiota in Barrett's esophagus and esophageal adenocarcinoma. World J Gastroenterol. 2019;25(18):2149-2161.
41. Jankowski JAZ, de Caestecker J, Love SB, Reilly G, Watson P, Sanders S, et al. Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial. Lancet. 2018;392(10145):400-408.

42. Zhang T, Wang Q, Ma WY, Wang K, Chang X, Johnson ML, et al. Targeting the COX1/2-Driven thromboxane A2 pathway suppresses Barrett's esophagus and esophageal adenocarcinoma development. EBioMedicine. 2019;49:145-156.
43. Thomas T, Loke Y, Beales ILP. Systematic Review and Meta-analysis: Use of Statins Is Associated with a Reduced Incidence of Oesophageal Adenocarcinoma. J Gastrointest Cancer. 2018;49(4):442-454..
44. Singh S, Singh AG, Singh PP, Murad MH, Iyer PG. Statins are associated with reduced risk of esophageal cancer, particularly in patients with BE: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013;11(6):620-9.
45. Krishnamoorthi R, Singh S, Ragunathan K, Visrodia K, Wang KK, Katzka DA, Iyer PG. Factors Associated With Progression of BE: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2018;16(7):1046-1055.e8.
46. Singh T, Sanghi V, Thota PN. Current management of Barrett esophagus and esophageal adenocarcinoma. Cleve Clin J Med. 2019;86(11):724-732.
47. Spechler J, (2021) Barrett's esophagus: Pathogenesis and malignant transformation. [Webpage] In NJ Tlley and S Grover (Ed), UpToDate. [Visited on 2021 March 10] Available at: (https://www.uptodate.com/contents/barretts-esophagus-pathogenesis-and-malignant-transformation?search=adenocarcinoma%20of%20the%20esophagus%20patophysiology&source=search_result&selectedTitle=1~57&usage_type=default&display_rank=1#H2680220180)
48. Peters Y, Al-Kaabi A, Shaheen NJ, Chak A, Blum A, Souza RF et al. Barrett oesophagus. Nat Rev Dis Primers 5, 35 (2019).
49. Que J, Garman KS, Souza RF, Spechler SJ. Pathogenesis and Cells of Origin of Barrett's Esophagus. Gastroenterology. 2019;157(2):349-364.e1.
50. Souza RF. Reflux esophagitis and its role in the pathogenesis of Barrett's metaplasia. J Gastroenterol. 2017;52(7):767-776.
51. Moole H, Patel J, Ahmed Z, Duvvuri A, Vennelaganti S, Moole V, et al. Progression from low-grade dysplasia to malignancy in patients with Barrett's esophagus diagnosed by two or more pathologists. World J Gastroenterol. 2016;22(39):8831-8843.
52. Naini BV, Souza RF, Odze RD. Barrett's Esophagus: A Comprehensive and Contemporary Review for Pathologists. Am J Surg Pathol. 2016;40(5):e45-6
53. Picardo SL, O'Brien MP, Feighery R, O'Toole D, Ravi N, O'Farrell NJ, et al. A Barrett's esophagus registry of over 1000 patients from a specialist center highlights greater risk of progression than population-based registries and high risk of low grade dysplasia. Dis Esophagus 2015;28:121-126
54. Cavallin F, Scarpa M, Cagol M, Alfieri R, Ruol A, Sileni VC, et al. Esophageal Cancer Clinical Presentation: Trends in the Last 3 Decades in a Large Italian Series. Ann Surg. 2018;267(1):99-104.

55. Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Corvera C, Das P, et al. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019;17(7):855-883.
56. Graham DY, Schwartz JT, Cain GD, Gyorkey F. Prospective evaluation of biopsy number in the diagnosis of esophageal and gastric carcinoma. Gastroenterology. 1982;82(2):228
57. Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO classification of tumours of the digestive system. World Health Organization; 2010
58. Lordick F, Mariette C, Haustermans K, Obermannova R, Arnold D. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27:v50–v57.
59. Bartley AN, Washington MK, Ventura CB, Ismaila N, Colasacco C, Benson AB 3rd, et al. HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma: Guideline From the College of American Pathologists, American Society for Clinical Pathology, and American Society of Clinical Oncology. Am J Clin Pathol. 2016;146(6):647-669.
60. Sano T, Aiko T. New Japanese classifications and treatment guidelines for gastric cancer: revision concepts and major revised points. Gastric Cancer. 2011;14(2):97-100.;
61. Suh YS, Han DS, Kong SH, et al. Should adenocarcinoma of the esophagogastric junction be classified as esophageal cancer? A comparative analysis according to the seventh AJCC TNM classification. Ann Surg. 2012;255(5):908-915.
62. Rice TW, Patil DT, Blackstone EH. 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to clinical practice. Ann Cardiothorac Surg. 2017;6(2):119-130.
63. Kim TJ, Kim HY, Lee KW, Kim MS. Multimodality assessment of esophageal cancer: preoperative staging and monitoring of response to therapy. Radiographics. 2009;29:403–421
64. Maingot R, Zinner M, Ashley SW, Hines OJ. Maingot's Abdominal Operations. McGraw-Hill Education; 2019.
65. Puli SR, Reddy JB, Bechtold ML, Antillon D, Ibdah JA, Antillon MR. Staging accuracy of esophageal cancer by endoscopic ultrasound: a meta-analysis and systematic review. World J Gastroenterol. 2008;14(10):1479-90
66. Wallace MB, Hawes RH, Sahai AV, Van Velse A, Hoffman BJ. Dilation of malignant esophageal stenosis to allow EUS guided fine-needle aspiration: safety and effect on patient management. Gastrointest Endosc. 2000;51(3):309-313)
67. Hünerbein M, Ghadimi BM, Haensch W, Schlag PM; Transendoscopic ultrasound of esophageal and gastric cancer using miniaturized ultrasound catheter probes. Gastrointest Endosc. 1998;48(4):371.

68. Rice TW. Clinical staging of esophageal carcinoma. CT, EUS, and PET. Chest Surg Clin N Am. 2000;10(3):471-485
69. Picus D, Balfe DM, Koehler RE, Roper CL, Owen JW. Computed tomography in the staging of esophageal carcinoma. Radiology. 1983;146(2):433-438
70. Kato H, Kuwano H, Nakajima M, et al. Comparison between positron emission tomography and computed tomography in the use of the assessment of esophageal carcinoma. Cancer. 2002;94(4):921-928.
71. Flamen P, Lerut A, Van Cutsem E, et al. Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. J Clin Oncol. 2000;18(18):3202-3210.
72. Rasanen JV, Sihvo EI, Knuuti MJ, et al. Prospective analysis of accuracy of positron emission tomography, computed tomography, and endoscopic ultrasonography in staging of adenocarcinoma of the esophagus and the esophagogastric junction. Ann Surg Oncol. 2003;10(8):954-960.
73. van Westreenen HL, Westerterp M, Bossuyt PM, et al. Systematic review of the staging performance of 18F-fluorodeoxyglucose positron emission tomography in esophageal cancer. J Clin Oncol. 2004;22(18):3805-3812.
74. van Vliet EP, Heijenbrok-Kal MH, Hunink MG, Kuipers EJ, Siersema PD. Staging investigations for oesophageal cancer: a meta-analysis.; Br J Cancer. 2008;98(3):547.
75. Meyers BF, et al. he utility of positron emission tomography in staging of potentially operable carcinoma of the thoracic esophagus: results of the American College of Surgeons Oncology Group Z0060 trial. J Thorac Cardiovasc Surg. 2007;133(3):738.
76. van Westreenen HL, Heeren PA, van Dullemen HM, van der Jagt EJ, Jager PL, Groen H, Plukker JT. Positron emission tomography with F-18-fluorodeoxyglucose in a combined staging strategy of esophageal cancer prevents unnecessary surgical explorations. J Gastrointest Surg. 2005;9(1):54.
77. Rosch T. Endosonographic staging of esophageal cancer: a review of literature results. Gastrointest Endosc Clin N Am. 1995;5(3):537-547.
78. Natsugoe S, Yoshinaka H, Shimada M, et al. Number of lymph node metastases determined by presurgical ultrasound and endoscopic ultrasound is related to prognosis in patients with esophageal carcinoma. Ann Surg. 2001;234(5):613-618.
79. Krasna MJ, Reed CE, Nedzwiecki D, et al. CALGB 9380: a prospective trial of the feasibility of thoracoscopy/laparoscopy in staging esophageal cancer. Ann Thorac Surg. 2001;71(4):1073-1079.

80. Reed CC, Shaheen NJ, Endoscopic Treatment of High-Grade Dysplasia and Intramucosal Esophageal Adenocarcinoma, J Laparoendosc Adv Surg Tech A. 2016;26(10):768–772
81. Thoguluva V, Chandrasekar P, Vennalaganti P, Sharma P, Management of BE: From screening to newer treatments, Revista de Gastroenterología de México 2016;81(2):91-102
82. Wang VS, Hornick JL, Sepulveda JA, Mauer R, Poneros JM. Low prevalence of submucosal invasive carcinoma at esophagectomy for high-grade dysplasia or intramucosal adenocarcinoma in Barrett's esophagus: a 20-year experience. Gastrointest Endosc. 2009;69(4):777-783.
83. Duits LC, Phoa KN, Curvers WL, Ten Kate FJ, Meijer GA, Seldenrijk CA, et al. Bergman JJ Barrett's oesophagus patients with low-grade dysplasia can be accurately risk-stratified after histological review by an expert pathology panel. Gut. 2015; 64(5):700-6.
84. Benaglia T, Sharples LD, Fitzgerald RC, et al. Health benefits and cost effectiveness of endoscopic and nonendoscopic cytosponge screening for BE Gastroenterology. 2013;144:62-73e6
85. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy 2015;47(9):829-854.
86. Milano RV, Bergman JJ, Pouw RE. Endoscopic treatment of early esophageal adenocarcinoma. Minerva Chir. 2018;73(4):355-365.
87. Shaheen NJ, Falk GW, Iyer PG, Gerson LB. ACG clinical guideline: diagnosis and management of BE. Am J Gastroenterol. 2016;111(1):30-50.
88. Altorki NK, Lee PC, Liss Y, et al. Multifocal neoplasia and nodal metastases in T1 esophageal carcinoma: implications for endoscopic treatment. Ann Surg. 2008;247(3):434-439
89. Ishihara R, Goda K, Oyama T. Endoscopic diagnosis and treatment of esophageal adenocarcinoma: introduction of Japan Esophageal Society classification of BE. J Gastroenterol. 2019;54(1):1-9.
90. Ell C, May A, Pech O, et al. Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). Gastrointest Endosc. 2007;65(1):3-10.)
91. Pech O, May A, Manner H, et al. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. Gastroenterology 2014;146(3):652–660.e1.
92. Cao Y, Liao C, Tan A, et al. Meta-analysis of endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract. Endoscopy. 2009;41:751-757.

93. Pech O, Behrens A, May A, et al. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. Gut 2008;57:1200-6.
94. James A. Kim, Pari M. Shah, Screening and prevention strategies and endoscopic management of early esophageal cancer, Chin Clin Oncol. 2017;6(5):50.
95. Overholt BF, Wang KK, Burdick JS, et al. Five-year efficacy and safety of photodynamic therapy with Photofrin in Barrett's high-grade dysplasia. Gastrointest Endosc. 2007;66(3):460-468.
96. Krajciova J, Vackova Z, Spicak J, Martinek J. Radiofrequency ablation for BE-related neoplasia. Minerva Chir. 2018;73(4):366-377.
97. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in BE with dysplasia. N Engl J Med. 2009;360(22):2277-2288.
98. Desai M, Saligram S, Gupta N, Vennalaganti P, Bansal A, Choudhary A, et al. Efficacy and safety outcomes of multi-modal endoscopic eradication therapy in BE-related neoplasia: a systematic review and pooled analysis. Gastrointest Endosc 2017;85:482-495.e4.
99. di Pietro M, Canto MI, Fitzgerald RC. Endoscopic Management of Early Adenocarcinoma and Squamous Cell Carcinoma of the Esophagus: Screening, Diagnosis, and Therapy. Gastroenterology. 2018;154(2):421-436.
100. Stein HJ, Feith M, Mueller J, Werner M, Siewert JR. Limited resection for early adenocarcinoma in BE. Ann Surg. 2000; 232(6):733-742.
101. Markar SR, Karthikesalingam A, Thrumurthy S, Low DE. Volume-outcome relationship in surgery for esophageal malignancy: systematic review and meta-analysis 2000-2011. J Gastrointest Surg. 2012;16(5):1055.)
102. Bartels H, Stein HJ, Siewert JR. Preoperative risk analysis and postoperative mortality of oesophagectomy for resectable oesophageal cancer. Br J Surg. 1998;85(6):840-844.
103. Miao L, Chen H, Xiang J, Zhang Y. A high body mass index in esophageal cancer patients is not associated with adverse outcomes following esophagectomy. J Cancer Res Clin Oncol. 2015;141(5):941-50.
104. Rice TW, Kelsen D, Blackstone EH, et al. Esophagus and esophagogastric junction. In: AJCC Cancer Staging Manual, 8th ed, Amin MB (Ed), AJCC, Chicago 2017. p.185
105. Rao YG, Pal S, Pande GK, Sahni P, Chattopadhyay TK. Transhiatal esophagectomy for benign and malignant conditions. Am J Surg. 2002;184(2):136-42.
106. Orringer MB, Marshall B, Chang AC, Lee J, Pickens A, Lau CL. Two thousand transhiatal esophagectomies: changing trends, lessons learned. Ann Surg. 2007;246(3):363-72.
107. Orringer MB, Marshall B, Iannettoni MD. Transhiatal esophagectomy: clinical experience and refinements. Ann Surg. 1999;230(3)

108. Urschel JD. Esophagogastrostomy anastomotic leaks complicating esophagectomy: a review. Am J Surg. 1995;169(6):634-40.
109. Price TN, Nichols FC, Harmsen WS, Allen MS, Cassivi SD, Wigle DA, et al. A comprehensive review of anastomotic technique in 432 esophagectomies. Ann Thorac Surg. 2013;95(4):1154-60.
110. Visbal AL, Allen MS, Miller DL, Deschamps C, Trastek VF, Pairolero PC. Ivor Lewis esophagogastrectomy for esophageal cancer. Ann Thorac Surg. 2001;71(6):1803-8.
111. Griffin SM, Shaw IH, Dresner SM. Early complications after Ivor Lewis subtotal esophagectomy with two-field lymphadenectomy: risk factors and management. J Am Coll Surg. 2002;194(3):285-97
112. Hulscher JB, Tijssen JG, Obertop H, van Lanschot JJ. Transthoracic versus transhiatal resection for carcinoma of the esophagus: a meta-analysis. Ann Thorac Surg. 2001;72(1):306-13.
113. Swanson SJ, Sugarbaker DJ. The three-hole esophagectomy. The Brigham and Women's Hospital approach (modified McKeown technique). Chest Surg Clin N Am. 2000 Aug;10(3):531-52. PMID: 10967755.
114. Barbour AP, Rizk NP, Gonen M, Tang L, Bains MS, Rusch VW, et al. Adenocarcinoma of the gastroesophageal junction: influence of esophageal resection margin and operative approach on outcome. Ann Surg. 2007;246(1):1-8.
115. Omloo JM, Lagarde SM, Hulscher JB, Reitsma JB, Fockens P, van Dekken H, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. Ann Surg. 2007;246(6):992.
116. Gottlieb-Vedi E, Kauppila JH, Malietzis G, Nilsson M, Markar SR, Lagergren J. Long-term Survival in Esophageal Cancer After Minimally Invasive Compared to Open Esophagectomy: A Systematic Review and Meta-analysis. Ann Surg. 2019;270(6):1005-1017.
117. Espinoza-Mercado F, Imai TA, Borgella JD, Sarkissian A, Serna-Gallegos D, Alban RF, Soukiasian HJ. Does the Approach Matter? Comparing Survival in Robotic, Minimally Invasive, and Open Esophagectomies. Ann Thorac Surg. 2019;107(2):378-385.
118. van der Sluis PC, van der Horst S, May AM, Schippers C, Brosens LAA, Joore HCA, et al. Robot-assisted Minimally Invasive Thoracolaparoscopic Esophagectomy Versus Open Transthoracic Esophagectomy for Resectable Esophageal Cancer: A Randomized Controlled Trial. Ann Surg. 2019;269(4):621-630.
119. Rizk NP, Ishwaran H, Rice TW, Chen LQ, Schipper PH, Kesler KA, et al. Optimum lymphadenectomy for esophageal cancer. Ann Surg. 2010;251(1):46-50.

120. Greenstein AJ, Litle VR, Swanson SJ, Divino CM, Packer S, Wisnivesky JP. Effect of the number of lymph nodes sampled on postoperative survival of lymph node-negative esophageal cancer. Cancer. 2008;112(6):1239-46.
121. Japan Esophageal Society. Japanese Classification of Esophageal Cancer, 11th Edition: part I. Esophagus. 2017;14(1):1-36.
122. Kitagawa Y, Uno T, Oyama T, et al. Esophageal cancer practice guidelines 2017 edited by the Japan esophageal society: part 2. Esophagus 2019;16:25-43.
123. Fujita H, Sueyoshi S, Tanaka T, Fujii T, Toh U, Mine T, et al. Optimal lymphadenectomy for squamous cell carcinoma in the thoracic esophagus: comparing the short- and long-term outcome among the four types of lymphadenectomy. World J Surg. 2003;27(5):571-9.
124. Baldwin D, Gonzalez SR, Anand S. Esophageal ReconstructionIn: StatPearls [Internet - Updated 2021 May 14]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK564336/ [visited on 2021 June 29]
125. Bakshi A, Sugarbaker DJ, Burt BM. Alternative conduits for esophageal replacement. Ann Cardiothorac Surg. 2017;6(2):137-143.
126. Manghelli JL, Ceppa DP, Greenberg JW, Blitzer D, Hicks A, Rieger KM, Birdas TJ. Management of anastomotic leaks following esophagectomy: when to intervene? J Thorac Dis. 2019;11(1):131-137.
127. Harada K, Rogers JE, Iwatsuki M, Yamashita K, Baba H, Ajani JA. Recent advances in treating oesophageal cancer. F1000Res. 2020;9:F1000 Faculty Rev-1189.
128. Noordman BJ, Verdam MGE, Lagarde SM, Shapiro J, Hulshof MCCM , van Berge Henegouwen MI, et al., for the CROSS Study Group. Impact of neoadjuvant chemoradiotherapy on health-related quality of life in long-term survivors of esophageal or junctional cancer: results from the randomized CROSS trial. Annals of Oncology 2018;29:445-451.
129. Goense L, van Rossum PSN, Xi M, Maru DM, Carter BW, Meijer GJ, et al. Preoperative Nomogram to Risk Stratify Patients for the Benefit of Trimodality Therapy in Esophageal Adenocarcinoma. Ann Surg Oncol. 2018;25(6):1598-1607.
130. Sun L, Zhao F, Zeng Y, Yi C. Risks and Benefits of Multimodal Esophageal Cancer Treatments: A Meta-Analysis. Med Sci Monit. 2017;23:889-910.
131. Klevebro F, Alexandersson von Döbeln G, Wang N, Johnsen G, Jacobsen AB, Friesland S, et al. A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction. Ann Oncol. 2016;27(4):660-7.

132. Shah MA, Kennedy EB, Catenacci DV, Deighton DC, Goodman KA, Malhotra NK, et al. Treatment of Locally Advanced Esophageal Carcinoma: ASCO Guideline. J Clin Oncol. 2020;38(23):2677-2694.
133. Kelly RJ, Ajani JA, Kuzdzal J, Zander T, Van Cutsem E, Piessen G, et al; CheckMate 577 Investigators. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. N Engl J Med. 2021;384(13):1191-1203.
134. Sreedharan A, Harris K, Crellin A, Forman D, Everett SM. Interventions for dysphagia in oesophageal cancer. Cochrane Database Syst Rev. 2009;(4):CD005048.
135. Homs MY, Steyerberg EW, Eijkenboom WM, Tilanus HW, Stalpers LJ, Bartelsman JF, et. al. Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: multicentre randomised trial. Lancet. 2004;364(9444):1497-504.
136. Bolton JS, Fuhrman GM, Richardson WS. Esophageal resection for cancer. Surg Clin North Am. 1998;78(5):773-94.
137. Mannell A, Becker PJ, Nissenbaum M. Bypass surgery for unresectable oesophageal cancer: early and late results in 124 cases. Br J Surg. 1988;75(3):283-6.
138. Enzinger PC, Mayer RJ. Barrett's esophagus: a review of the literature. N Engl J Med. 2003;349(23):2241-52.
139. Adamson D, Byrne A, Porter C, et al. Palliative radiotherapy after oesophageal cancer stenting (ROCS): a multicentre, open-label, phase 3 randomised controlled trial. Lancet Gastroenterol Hepatol. 2021;6(4):292-303.
140. Office for National Statistics, Cancer survival by stage at diagnosis for England [Webpage] [visited on 2021 Jan 9] Available at: (https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed)
141. Evans RP, Mourad MM, Fisher SG, Bramhall SR. Evolving management of metaplasia and dysplasia in Barrett's epithelium. World J Gastroenterol. 2016;22(47):10316-10324.
142. Gupta V, Coburn N, Kidane B, Hess KR, Compton C, Ringash J, et al. Survival prediction tools for esophageal and gastroesophageal junction cancer: A systematic review. J Thorac Cardiovasc Surg. 2018;156(2):847-856.

Annex 1

Normas de Publicação da Acta Médica Portuguesa

Acta Médica Portuguesa's Publishing Guidelines

Conselho Editorial ACTA MÉDICA PORTUGUESA
Acta Med Port 2016, 30 dezembro 2016

1. MISSÃO

Publicar trabalhos científicos originais e de revisão na área biomédica da mais elevada qualidade, abrangendo várias áreas do conhecimento médico, e ajudar os médicos a tomar melhores decisões.

Para atingir estes objectivos a Acta Médica Portuguesa publica artigos originais, artigos de revisão, casos clínicos, editoriais, entre outros, comentando sobre os factores clínicos, científicos, sociais, políticos e económicos que afectam a saúde. A Acta Médica Portuguesa pode considerar artigos para publicação de autores de qualquer país.

2. VALORES

Promover a qualidade científica.
Promover o conhecimento e actualidade científica.
Independência e imparcialidade editorial.
Ética e respeito pela dignidade humana.
Responsabilidade social.

3. VISÃO

Ser reconhecida como uma revista médica portuguesa de grande impacto internacional.

Promover a publicação científica da mais elevada qualidade privilegiando o trabalho original de investigação (clínico, epidemiológico, multicêntrico, ciência básica).

Constituir o fórum de publicação de normas de orientação.

Ampliar a divulgação internacional.

Lema: "Primum non nocere, primeiro a Acta Médica Portuguesa"

4. INFORMAÇÃO GERAL

A Acta Médica Portuguesa é a revista científica com revisão pelos pares (*peer-review*) da Ordem dos Médicos. É publicada continuamente desde 1979, estando indexada na PubMed / Medline desde o primeiro número. Desde 2010 tem Factor de Impacto atribuído pelo Journal Citation Reports - Thomson Reuters.

A Acta Médica Portuguesa segue a política do livre acesso. Todos os seus artigos estão disponíveis de forma integral, aberta e gratuita desde 1999 no seu site www.actamedicaportuguesa.com e através da Medline com interface PubMed.

A Acta Médica Portuguesa não cobra quaisquer taxas relativamente ao processamento ou à submissão de artigos.

A taxa de aceitação da Acta Médica Portuguesa, em 2014, foi de aproximadamente de 20% dos mais de 700 manuscritos recebidos anualmente.

Os manuscritos devem ser submetidos *online* via "Submissões Online" http://www.actamedicaportuguesa.com/revista/index.php/amp/about/submissions#onlineSubmissions.

A Acta Médica Portuguesa rege-se de acordo com as boas normas de edição biomédica do International Committee of Medical Journal Editors (ICMJE), do Committee on Publication Ethics (COPE), e do EQUATOR Network Resource Centre Guidance on Good Research Report (desenho de estudos).

A política editorial da Revista incorpora no processo de revisão e publicação as Recomendações de Política Editorial (*Editorial Policy Statements*) emitidas pelo Conselho de Editores Científicos (Council of Science Editors), disponíveis em http://www.councilscienceeditors.org/i4a/pages/index.cfm?pageid=3331, que cobre responsabilidades e direitos dos editores das revistas com arbitragem científica. Os artigos propostos não podem ter sido objecto de qualquer outro tipo de publicação. As opiniões expressas são da inteira responsabilidade dos autores. Os artigos publicados ficarão propriedade conjunta da Acta Médica Portuguesa e dos autores.

A Acta Médica Portuguesa reserva-se o direito de comercialização do artigo enquanto parte integrante da revista (na elaboração de separatas, por exemplo). O autor deverá acompanhar a carta de submissão com a declaração de cedência de direitos de autor para fins comerciais.

Relativamente à utilização por terceiros a Acta Médica Portuguesa rege-se pelos termos da licença *Creative Commons* 'Atribuição – Uso Não-Comercial – Proibição de Realização de Obras Derivadas (by-nc-nd)'.

Após publicação na Acta Médica Portuguesa, os autores ficam autorizados a disponibilizar os seus artigos em repositórios das suas instituições de origem, desde que mencionem sempre onde foram publicados.

5. CRITÉRIO DE AUTORIA

A revista segue os critérios de autoria do "International

Commitee of Medical Journal Editors" (ICMJE).

Todos designados como autores devem ter participado significativamente no trabalho para tomar responsabilidade pública sobre o conteúdo e o crédito da autoria.

Autores são todos que:

1. Têm uma contribuição intelectual substancial, directa, no desenho e elaboração do artigo
2. Participam na análise e interpretação dos dados
3. Participam na escrita do manuscrito, revendo os rascunhos; ou na revisão crítica do conteúdo; ou na aprovação da versão final
4. Concordam que são responsáveis pela exactidão e integridade de todo o trabalho

As condições 1, 2, 3 e 4 têm de ser reunidas.

Autoria requer uma contribuição substancial para o manuscrito, sendo pois necessário especificar em carta de apresentação o contributo de cada autor para o trabalho.

Ser listado como autor, quando não cumpre os critérios de elegibilidade, é considerado fraude.

Todos os que contribuíram para o artigo, mas que não encaixam nos critérios de autoria, devem ser listados nos agradecimentos.

Todos os autores, (isto é, o autor correspondente e cada um dos autores) terão de preencher e assinar o "Formulário de Autoria" com a responsabilidade da autoria, critérios e contribuições; conflitos de interesse e financiamento e transferência de direitos autorais / *copyright (modelo disponível em http://www.actamedicaportuguesa.com/info/AMP_template-Declaracao-Responsabilidade-Autoral.doc)*.

O autor Correspondente deve ser o intermediário em nome de todos os co-autores em todos os contactos com a Acta Médica Portuguesa, durante todo o processo de submissão e de revisão. O autor correspondente é responsável por garantir que todos os potenciais conflitos de interesse mencionados são correctos. O autor correspondente deve atestar, ainda, em nome de todos os co-autores, a originalidade do trabalho e obter a permissão escrita de cada pessoa mencionada na secção "Agradecimentos".

6. *COPYRIGHT* / DIREITOS AUTORAIS

Quando o artigo é aceite para publicação é mandatório o carregamento na plataforma electrónica de documento digitalizado, assinado por todos os Autores, com a partilha dos direitos de autor entre autores e a Acta Médica Portuguesa.

O(s) Autor(es) deve(m) assinar uma cópia de partilha dos direitos de autor entre autores e a Acta Médica Portuguesa quando submetem o manuscrito, conforme minuta publicada em anexo:

Nota: Este documento assinado só deverá ser enviado quando o manuscrito for aceite para publicação.

Editor da Acta Médica Portuguesa

O(s) Autor(es) certifica(m) que o manuscrito intitulado: _____ (ref. AMP_____) é original, que todas as afirmações apresentadas como factos são baseados na investigação do(s) Autor(es), que o manuscrito, quer em parte quer no todo, não infringe nenhum *copyright* e não viola nenhum direito da privacidade, que não foi publicado em parte ou no todo e que não foi submetido para publicação, no todo ou em parte, noutra revista, e que os Autores têm o direito ao *copyright*.

Todos os Autores declaram ainda que participaram no trabalho, se responsabilizam por ele e que não existe, da parte de qualquer dos Autores conflito de interesses nas afirmações proferidas no trabalho.

Os Autores, ao submeterem o trabalho para publicação, partilham com a Acta Médica Portuguesa todos os direitos a interesses do *copyright* do artigo.

Todos os Autores devem assinar

Data:_____

Nome (maiúsculas):_____

Assinatura:_____

7. CONFLITOS DE INTERESSE

O rigor e a exactidão dos conteúdos, assim como as opiniões expressas são da exclusiva responsabilidade dos Autores. Os Autores devem declarar potenciais conflitos de interesse. Os autores são obrigados a divulgar todas as relações financeiras e pessoais que possam enviesar o trabalho.

Para prevenir ambiguidade, os autores têm que explicitamente mencionar se existe ou não conflitos de interesse.

Essa informação não influenciará a decisão editorial mas antes da submissão do manuscrito, os autores têm que assegurar todas as autorizações necessárias para a publicação do material submetido.

Se os autores têm dúvidas sobre o que constitui um relevante interesse financeiro ou pessoal, devem contactar o editor.

8. CONSENTIMENTO INFORMADO e APROVAÇÃO ÉTICA

Todos os doentes (ou seus representantes legais) que possam ser identificados nas descrições escritas, fotografias e vídeos deverão assinar um formulário de consentimento informado para descrição de doentes, fotografia e vídeos. Estes formulários devem ser submetidos com o manuscrito (modelo disponível em http://www.actamedicaportuguesa.com/info/consentimento_informado_do_doente.doc).

A Acta Médica Portuguesa considera aceitável a omissão de dados ou a apresentação de dados menos específicos para identificação dos doentes. Contudo, não aceitaremos a alteração de quaisquer dados.

Os autores devem informar se o trabalho foi aprovado pela Comissão de Ética da instituição de acordo com a declaração de Helsínquia.

9. LÍNGUA

Os artigos devem ser redigidos em português ou em inglês. Os títulos e os resumos têm de ser sempre em português e em inglês.

10. PROCESSO EDITORIAL

O autor correspondente receberá notificação da recepção do manuscrito e decisões editoriais por *email*.

Todos os manuscritos submetidos são inicialmente revistos pelo editor da Acta Médica Portuguesa. Os manuscritos são avaliados de acordo com os seguintes critérios: originalidade, actualidade, clareza de escrita, método de estudo apropriado, dados válidos, conclusões adequadas e apoiadas pelos dados, importância, com significância e contribuição científica para o conhecimento da área, e não tenham sido publicados, na íntegra ou em parte, nem submetidos para publicação noutros locais.

A Acta Médica Portuguesa segue um rigoroso processo cego (*single-blind*) de revisão por pares (*peer-review*, externos à revista). Os manuscritos recebidos serão enviados a peritos das diversas áreas, os quais deverão fazer os seus comentários, incluindo a sugestão de aceitação, aceitação condicionada a pequenas ou grandes modificações ou rejeição. Na avaliação, os artigos poderão ser:

a) aceites sem alterações;

b) aceites após modificações propostas pelos consultores científicos;

c) recusados.

Estipula-se para esse processo o seguinte plano temporal:

• Após a recepção do artigo, o Editor-Chefe, ou um dos Editores Associados, enviará o manuscrito a, no mínimo, dois revisores, caso esteja de acordo com as normas de publicação e se enquadre na política editorial. Poderá ser recusado nesta fase, sem envio a revisores.

• Quando receberem a comunicação de aceitação, os Autores devem remeter de imediato, por correio electrónico, o formulário de partilha de direitos que se encontra no *site* da Acta Médica Portuguesa, devidamente preenchido e assinado por todos os Autores.

• No prazo máximo de quatro semanas, o revisor deverá responder ao editor indicando os seus comentários relativos ao manuscrito sujeito a revisão, e a sua sugestão de quanto à aceitação ou rejeição do trabalho. O Conselho Editorial tomará, num prazo de 15 dias, uma primeira decisão que poderá incluir a aceitação do artigo sem modificações, o envio dos comentários dos revisores para que os Autores procedam de acordo com o indicado, ou a rejeição do artigo.

Os Autores dispõem de 20 dias para submeter a nova versão revista do manuscrito, contemplando as modificações recomendadas pelos peritos e pelo Conselho Editorial. Quando são propostas alterações, o autor deverá no prazo máximo de vinte dias, carregar na plataforma electrónica da Acta Médica Portuguesa uma versão revista do artigo, com as alterações inseridas destacadas com cor diferente, bem como um novo Documento Suplementar respondendo a todas as questões colocadas.

• O Editor-Chefe dispõe de 15 dias para tomar a decisão sobre a nova versão: rejeitar ou aceitar o artigo na nova versão, ou submetê-lo a um ou mais revisores externos cujo parecer poderá, ou não, coincidir com os resultantes da primeira revisão.

• Caso o manuscrito seja reenviado para revisão externa, os peritos dispõem de quatro semanas para o envio dos seus comentários e da sua sugestão quanto à aceitação ou recusa para publicação do mesmo.

• Atendendo às sugestões dos revisores, o Editor-Chefe poderá aceitar o artigo nesta nova versão, rejeitá-lo ou voltar a solicitar modificações. Neste último caso, os Autores dispõem de um mês para submeter uma versão revista, a qual poderá, caso o Editor-Chefe assim o determine, voltar a passar por um processo de revisão por peritos externos.

• No caso da aceitação, em qualquer das fases anteriores, a mesma será comunicada ao Autor principal. Num prazo inferior a um mês, o Conselho Editorial enviará o artigo para revisão dos Autores já com a formatação final, mas sem a numeração definitiva. Os Autores dispõem de cinco dias para a revisão do texto e comunicação de quaisquer erros tipográficos. Nesta fase, os Autores não podem fazer qualquer modificação de fundo ao artigo, para além das correcções de erros tipográficos e/ou ortográficos de pequenos erros. Não são permitidas, nomeadamente, alterações a dados de tabelas ou gráficos, alterações de fundo do texto, etc.

• Após a resposta dos Autores, ou na ausência de resposta, após o decurso dos cinco dias, o artigo considera-se concluído.

• Na fase de revisão de provas tipográficas, alterações de fundo aos artigos não serão aceites e poderão implicar a sua rejeição posterior por decisão do Editor-Chefe.

Chama-se a atenção que a transcrição de imagens, quadros ou gráficos de outras publicações deverá ter a prévia autorização dos respectivos autores para dar cumprimentos às normas que regem os direitos de autor.

11. PUBLICAÇÃO *FAST-TRACK*

A Acta Médica Portuguesa dispõe do sistema de publicação *Fast-Track* para manuscritos urgentes e importantes desde que cumpram os requisitos da Acta Médica Portuguesa para o *Fast-Track*.

a) Os autores para requererem a publicação *fast-track* devem submeter o seu manuscrito em http://www.actamedicaportuguesa.com/ “submeter artigo” indicando claramente porque consideram que o manuscrito é adequado para a publicação rápida. O Conselho Editorial tomará a decisão sobre se o manuscrito é adequado para uma via rápida (*fast-track*) ou para submissão regular;

b) Verifique se o manuscrito cumpre as normas aos autores da Acta Médica Portuguesa e que contém as informações necessárias em todos os manuscritos da Acta Médica Portuguesa.

c) O Gabinete Editorial irá comunicar, dentro de 48 horas, se o manuscrito é apropriado para avaliação *fast-track*. Se o Editor-Chefe decidir não aceitar a avaliação *fast-track*, o manuscrito pode ser considerado para o processo de revisão normal. Os autores também terão a oportunidade de retirar a sua submissão.

d) Para manuscritos que são aceites para avaliação

fast-track, a decisão Editorial será feita no prazo de 5 dias úteis.

e) Se o manuscrito for aceite para publicação, o objectivo será publicá-lo, online, no prazo máximo de 3 semanas após a aceitação.

12. REGRAS DE OURO ACTA MÉDICA PORTUGUESA

a) O editor é responsável por garantir a qualidade da revista e que o que publica é ético, actual e relevante para os leitores.

b) A gestão de reclamações passa obrigatoriamente pelo editor-chefe e não pelo bastonário.

c) O peer review deve envolver a avaliação de revisores externos.

d) A submissão do manuscrito e todos os detalhes associados são mantidos confidenciais pelo corpo editorial e por todas as pessoas envolvidas no processo de peer-review.

e) A identidade dos revisores é confidencial.

f) Os revisores aconselham e fazem recomendações; o editor toma decisões.

g) O editor-chefe tem total independência editorial.

h) A Ordem dos Médicos não interfere directamente na avaliação, selecção e edição de artigos específicos, nem directamente nem por influência indirecta nas decisões editoriais.

i) As decisões editoriais são baseadas no mérito de trabalho submetido e adequação à revista.

j) As decisões do editor-chefe não são influenciadas pela origem do manuscrito nem determinadas por agentes exteriores.

k) As razões para rejeição imediata sem peer review externo são: falta de originalidade; interesse limitado para os leitores da Acta Médica Portuguesa; conter graves falhas científicas ou metodológicas; o tópico não é coberto com a profundidade necessária; é preliminar de mais e/ou especulativo; informação desactualizada.

l) Todos os elementos envolvidos no processo de peer review devem actuar de acordo com os mais elevados padrões éticos.

m) Todas as partes envolvidas no processo de peer review devem declarar qualquer potencial conflito de interesses e solicitar escusa de rever manuscritos que sintam que não conseguirão rever objectivamente.

13. NORMAS GERAIS

ESTILO

Todos os manuscritos devem ser preparados de acordo com o "AMA Manual of Style", 10th ed. e/ou "Uniform Requirements for Manuscripts Submitted to Biomedical Journals".

Escreva num estilo claro, directo e activo. Geralmente, escreva usando a primeira pessoa, voz activa, por exemplo, "Analisámos dados", e não "Os dados foram analisados". Os agradecimentos são as excepções a essa directriz, e deve ser escrito na terceira pessoa, voz activa; "Os autores gostariam de agradecer". Palavras em latim ou noutra língua que não seja a do texto deverão ser colocadas em itálico.

Os componentes do manuscrito são: Página de Título, Resumo, Texto, Referências, e se apropriado, legendas de figuras. Inicie cada uma dessas secções em uma nova página, numeradas consecutivamente, começando com a página de título.

Os formatos de arquivo dos manuscritos autorizados incluem o *Word* e o *WordPerfect*. Não submeta o manuscrito em formato PDF.

SUBMISSÃO

Os manuscritos devem ser submetidos online, via "Submissão Online" da Acta Médica Portuguesa http://www.actamedicaportuguesa.com/revista/index.php/amp/about/submissions#onlineSubmissions.

Todos os campos solicitados no sistema de submissão *online* terão de ser respondidos.

Após submissão do manuscrito o autor receberá a confirmação de recepção e um número para o manuscrito.

Na primeira página/ página de título:

a) Título em **português** e **inglês**, conciso e descritivo

b) Na linha da autoria, liste o Nome de todos os Autores (primeiro e último nome) com os títulos académicos e/ou profissionais e respectiva afiliação (departamento, instituição, cidade, país)

c) Subsídio(s) ou bolsa(s) que contribuíram para a realização do trabalho

d) Morada e *e-mail* do Autor responsável pela correspondência relativa ao manuscrito

e) Título breve para cabeçalho

Na segunda página

a) Título (sem autores)

b) Resumo em **português** e **inglês**. Nenhuma informação que não conste no manuscrito pode ser mencionada no resumo. Os resumos não podem remeter para o texto, não podendo conter citações nem referencias a figuras.

c) Palavras-chave (*Keywords*). Um máximo de 5 *Keywords* em inglês utilizando a terminologia que consta no Medical Subject Headings (MeSH), http://www.nlm.nih.gov/mesh/MBrowser.html, devem seguir-se ao resumo.

Na terceira página e seguintes:

Editoriais:

Os Editoriais serão apenas submetidos por convite do Editor. Serão comentários sobre tópicos actuais. Não devem exceder as 1.200 palavras nem conter tabelas/figuras e terão um máximo de 5 referências bibliográficas. Não precisam de resumo.

Perspectiva:

Artigos elaborados apenas por convite do Conselho Editorial. Podem cobrir grande diversidade de temas com interesse nos cuidados de saúde: problemas actuais ou emergentes, gestão e política de saúde, história da medicina, ligação à sociedade, epidemiologia, etc.

Um Autor que deseje propor um artigo desta categoria

deverá remeter previamente ao Editor-Chefe o respectivo resumo, indicação dos autores e título do artigo para avaliação.

Deve conter no máximo 1200 palavras (excluindo as referências e as legendas) e até 10 referências bibliográficas. Só pode conter uma tabela ou uma figura. Não precisa de resumo.

Artigos Originais:

O texto deve ser apresentado com as seguintes secções: Introdução (incluindo Objectivos), Material e Métodos, Resultados, Discussão, Conclusão, Agradecimentos (se aplicável), Referências, Tabelas e Figuras.

Os Artigos Originais não deverão exceder as 4.000 palavras, excluindo referências e ilustrações. Deve ser acompanhado de ilustrações, com um máximo de 6 figuras/tabelas e 60 referências bibliográficas**.**

O resumo dos artigos originais não deve exceder as 250 palavras e serão estruturados (com cabeçalhos: Introdução, Materiais e Métodos, Resultados, Discussão e Conclusão).

A Acta Médica Portuguesa, como membro do ICMJE, exige como condição para publicação, o registo de todos os ensaios num registo público de ensaios aceite pelo ICMJE (ou seja, propriedade de uma instituição sem fins lucrativos e publicamente acessível, por ex. clinicaltrials.gov). Todos os manuscritos reportando ensaios clínicos têm de seguir o CONSORT *Statement* http://www.consort-statement.org/.

Numa revisão sistemática ou meta-análise siga as PRISMA *guidelines*.

Numa meta-análise de estudos observacionais, siga as MOOSE *guidelines* e apresente como um ficheiro complementar o protocolo do estudo, se houver um.

Num estudo de precisão de diagnóstico, siga as STARD *guidelines*.

Num estudo observacional, siga as STROBE *guidelines.*

Num *Guideline* clínico incentivamos os autores a seguir a GRADE *guidance* para classificar a evidência.

Artigos de Revisão:

Destinam-se a abordar de forma aprofundada, o estado actual do conhecimento referente a temas de importância. Estes artigos serão elaborados a convite da equipa editorial, contudo, a título excepcional, será possível a submissão, por autores não convidados (com ampla experiência no tema) de projectos de artigo de revisão que, julgados relevantes e aprovados pelo editor, poderão ser desenvolvidos e submetidos às normas de publicação.

Comprimento máximo: 3500 palavras de texto (não incluindo resumo, legendas e referências). Não pode ter mais do que um total de 4 tabelas e / ou figuras, e não mais de 50-75 referências.

O resumo dos artigos de revisão não deve exceder as 250 palavras e serão estruturados (com cabeçalhos: Introdução, Materiais e Métodos, Resultados, Discussão, Conclusão.

Caso Clínico:

O relato de um caso clínico com justificada razão de publicação (raridade, aspectos inusitados, evoluções atípicas, inovações terapêuticas e de diagnóstico, entre outras). As secções serão: Introdução, Caso Clínico, Discussão, Referências.

A linha de autoria deste tipo de artigos não deverá exceder quatro autores. Outros contributos poderão ser reconhecidos no final do texto, sob o parágrafo “Agradecimentos”.

O texto não deve exceder as 1.000 palavras e 15 referências bibliográficas. Deve ser acompanhado de figuras ilustrativas. O número de tabelas/figuras não deve ser superior a 5**.**

Inclua um resumo não estruturado que não exceda 150 palavras, que sumarie o objectivo, pontos principais e conclusões do artigo.

Imagens em Medicina (Imagem Médica):

A Imagem em Medicina é um contributo importante da aprendizagem e da prática médica. Poderão ser aceites imagens clínicas, de imagiologia, histopatologia, cirurgia, etc. Podem ser enviadas até duas imagens por caso.

Deve incluir um título com um máximo de oito palavras e um texto com um máximo de 150 palavras onde se dê informação clínica relevante, incluindo um breve resumo do historial do doente, dados laboratoriais, terapêutica e condição actual. Não pode ter mais do que três autores e cinco referências bibliográficas. Não precisa de resumo.

Só são aceites fotografias originais, de alta qualidade, que não tenham sido submetidas a prévia publicação. Para informação sobre o envio de imagens digitais, consulte as «Normas técnicas para a submissão de figuras, tabelas ou fotografias».

***Guidelines* / Normas de orientação:**

As sociedades médicas, os colégios das especialidades, as entidades oficiais e / ou grupos de médicos que desejem publicar na Acta Médica Portuguesa recomendações de prática clínica, deverão contactar previamente o Conselho Editorial e submeter o texto completo e a versão para ser publicada. O Editor-Chefe poderá colocar como exigência a publicação exclusiva das recomendações na Acta Médica Portuguesa.

Poderá ser acordada a publicação de uma versão resumida na edição impressa cumulativamente à publicação da versão completa no *site* da Acta Médica Portuguesa.

Cartas ao Editor:

Devem constituir um comentário a um artigo da Acta Med Port ou uma pequena nota sobre um tema ou caso clínico. Não devem exceder as 400 palavras, nem conter mais de uma ilustração e ter um máximo de 5 referências bibliográficas. Não precisam de resumo.

Deve seguir a seguinte estrutura geral: Identificar o artigo (torna-se a referência 1); Dizer porque está a escrever; fornecer evidência (a partir da literatura ou a partir de uma

experiência pessoal) fornecer uma súmula; citar referências.

A(s) resposta(s) do(s) Autor(es) devem observar as mesmas características.

Uma Carta ao editor discutindo um artigo recente da Acta Med Port terá maior probabilidade de aceitação se for submetida quatro semanas após a publicação do artigo.

Abreviaturas: Não use abreviaturas ou acrónimos no título nem no resumo, e limite o seu uso no texto. O uso de acrónimos deve ser evitado, assim como o uso excessivo e desnecessário de abreviaturas. Se for imprescindível recorrer a abreviaturas não consagradas, devem ser definidas na primeira utilização, por extenso, logo seguido pela abreviatura entre parenteses. Não coloque pontos finais nas abreviaturas.

Unidades de Medida: As medidas de comprimento, altura, peso e volume devem ser expressas em unidades do sistema métrico (metro, quilograma ou litro) ou seus múltiplos decimais.

As temperaturas devem ser dadas em graus Celsius (ºC) e a pressão arterial em milímetros de mercúrio (mm Hg).

Para mais informação consulte a tabela de conversão "Units of Measure" no *website* da AMA Manual Style.

Nomes de Medicamentos, Dispositivos ou outros Produtos: Use o nome não comercial de medicamentos, dispositivos ou de outros produtos, a menos que o nome comercial seja essencial para a discussão.

IMAGENS

Numere todas as imagens (figuras, gráficos, tabelas, fotografias, ilustrações) pela ordem de citação no texto.

Inclua um título/legenda para cada imagem (uma frase breve, de preferência com não mais do que 10 a 15 palavras).

A publicação de imagens a cores é gratuita.

No manuscrito, são aceitáveis os seguintes formatos: BMP, EPS, JPG, PDF e TIF, com 300 dpis de resolução, pelo menos 1200 *pixeis* de largura e altura proporcional.

As Tabelas/Figuras devem ser numeradas na ordem em que são citadas no texto e assinaladas em numeração árabe e com identificação, figura/tabela. Tabelas e figuras devem ter numeração árabe e legenda. Cada Figura e Tabela incluídas no trabalho têm de ser referidas no texto, da forma que passamos a exemplificar:

Estes são alguns exemplos de como uma resposta imunitária anormal pode estar na origem dos sintomas da doença de Behçet (Fig. 4).

Esta associa-se a outras duas lesões cutâneas (Tabela 1).

Figura: Quando referida no texto é abreviada para Fig., enquanto a palavra Tabela não é abreviada. Nas legendas ambas as palavras são escritas por extenso.

Figuras e tabelas serão numeradas com numeração árabe independentemente e na sequência em que são referidas no texto.

Exemplo: Fig. 1, Fig. 2, Tabela 1

Legendas: Após as referências bibliográficas, ainda no ficheiro de texto do manuscrito, deverá ser enviada legenda detalhada (sem abreviaturas) para cada imagem. A imagem tem que ser referenciada no texto e indicada a sua localização aproximada com o comentário "Inserir Figura nº 1… aqui".

Tabelas: É obrigatório o envio das tabelas a preto e branco no final do ficheiro. As tabelas devem ser elaboradas e submetidas em documento *word*, em formato de tabela simples (*simple grid*), sem utilização de tabuladores, nem modificações tipográficas. Todas as tabelas devem ser mencionadas no texto do artigo e numeradas pela ordem que surgem no texto. Indique a sua localização aproximada no corpo do texto com o comentário "Inserir Tabela nº 1… aqui". Neste caso os autores autorizam uma reorganização das tabelas caso seja necessário.

Quaisquer tabelas submetidas que sejam mais longas/largas do que duas páginas A4 serão publicadas como Apêndice ao artigo.

As tabelas devem ser acompanhadas da respectiva legenda/título, elaborada de forma sucinta e clara.

Legendas devem ser auto-explicativas (sem necessidade de recorrer ao texto) – é uma declaração descritiva.

Legenda/Título das Tabelas*:* Colocada por cima do corpo da tabela e justificada à esquerda. Tabelas são lidas de cima para baixo. Na parte inferior serão colocadas todas as notas informativas – notas de rodapé (abreviaturas, significado estatístico, etc.) As notas de rodapé para conteúdo que não caiba no título ou nas células de dados devem conter estes símbolos *, †, ‡, §, ||, ¶, **, ††, ‡‡, §§, ||||, ¶¶,

Figuras: Os ficheiros «figura» podem ser tantos quantas imagens tiver o artigo. Cada um destes elementos deverá ser submetido em ficheiro separado, obrigatoriamente em versão electrónica, pronto para publicação. As figuras (fotografias, desenhos e gráficos) não são aceites em ficheiros *word*.

Em formato TIF, JPG, BMP, EPS e PDF com 300 *dpis* de resolução, pelo menos 1200 *pixeis* de largura e altura proporcional.

As legendas têm que ser colocadas no ficheiro de texto do manuscrito.

Caso a figura esteja sujeita a direitos de autor, é responsabilidade dos autores do artigo adquirir esses direitos antes do envio do ficheiro à Acta Médica Portuguesa.

Legenda das Figuras: Colocada por baixo da figura, gráfico e justificada à esquerda. Gráficos e outras figuras são habitualmente lidos de baixo para cima.

Só são aceites imagens de doentes quando necessárias para a compreensão do artigo. Se for usada uma figura em que o doente seja identificável deve ser obtida e remetida à Acta Médica Portuguesa a devida autorização. Se a fotografia permitir de forma óbvia a identificação do doente, esta poderá não ser aceite. Em caso de dúvida, a decisão final será do Editor-Chefe.

- **Fotografias**: Em formato TIF, JPG, BMP e PDF com 300 *dpis* de resolução, pelo menos 1200 *pixeis* de largura e altura proporcional.
- **Desenhos e gráficos**: Os desenhos e gráficos devem ser enviados em formato vectorial (AI, EPS) ou em ficheiro bitmap com uma resolução mínima de 600 dpi. A fonte a utilizar em desenhos e gráficos será obrigatoriamente Arial.

As imagens devem ser apresentadas em ficheiros separados submetidos como documentos suplementares, em condições de reprodução, de acordo com a ordem em que são discutidas no texto. As imagens devem ser fornecidas independentemente do texto.

AGRADECIMENTOS (facultativo)

Devem vir após o texto, tendo como objectivo agradecer a todos os que contribuíram para o estudo mas não têm peso de autoria. Nesta secção é possível agradecer a todas as fontes de apoio, quer financeiro, quer tecnológico ou de consultoria, assim como contribuições individuais. Cada pessoa citada nesta secção de agradecimentos deve enviar uma carta autorizando a inclusão do seu nome.

REFERÊNCIAS

Os autores são responsáveis pela exactidão e rigor das suas referências e pela sua correcta citação no texto.

As referências bibliográficas devem ser citadas numericamente (algarismos árabes formatados sobrescritos) por ordem de entrada no texto e ser identificadas no texto com algarismos árabes. **Exemplo: "**Dimethylfumarate has also been a systemic therapeutic option in moderate to severe psoriasis since 1994[13] and in multiple sclerosis.[14]"

Se forem citados mais de duas referências em sequência, apenas a primeira e a última devem ser indicadas, sendo separadas por traço.[5-9]

Em caso de citação alternada, todas as referências devem ser digitadas, separadas por vírgula.[12,15,18]

As referências são alinhadas à esquerda.

Não deverão ser incluídos na lista de referências quaisquer artigos ainda em preparação ou observações não publicadas, comunicações pessoais, etc. Tais inclusões só são permitidas no corpo do manuscrito (ex: P. Andrade, comunicação pessoal).

As abreviaturas usadas na nomeação das revistas devem ser as utilizadas pelo National Library of Medicine (NLM) *Title Journals Abbreviations* http://www.ncbi.nlm.nih.gov/nlmcatalog/journals

Notas: Não indicar mês da publicação.

Nas referências com 6 ou menos Autores devem ser nomeados todos. Nas referências com 7 ou mais autores devem ser nomeados os 6 primeiros seguidos de "et al".

Seguem-se alguns exemplos de como devem constar os vários tipos de referências.

Artigo:

Apelido Iniciais do(s) Autor(es). Título do artigo. Título das revistas [abreviado]. Ano de publicação;Volume: páginas.

1. Com menos de 6 autores

Miguel C, Mediavilla MJ. Abordagem actual da gota. Acta Med Port. 2011;24:791-8.

2. Com mais de 6 autores

Norte A, Santos C, Gamboa F, Ferreira AJ, Marques A, Leite C, et al. Pneumonia Necrotizante: uma complicação rara. Acta Med Port. 2012;25:51-5.

Monografia:

Autor/Editor AA. Título: completo. Edição (se não for a primeira). Vol.(se for trabalho em vários volumes). Local de publicação: Editor comercial; ano.

1. Com Autores:

Moore, K. Essential Clinical Anatomy. 4th ed. Philadelphia: Wolters Kluwer Lippincott Williams & Wilkins; 2011.

2. Com editor:

Gilstrap LC 3rd, Cunningham FG, VanDorsten JP, editors. Operative obstetrics. 2nd ed. New York: McGraw-Hill; 2002.

Capítulo de monografia:

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113.

Relatório Científico/Técnico:

Lugg DJ. Physiological adaptation and health of an expedition in Antarctica: with comment on behavioural adaptation. Canberra: A.G.P.S.; 1977. Australian Government Department of Science, Antarctic Division. ANARE scientific reports. Series B(4), Medical science No. 0126

Documento electrónico:

1.CD-ROM

Anderson SC, Poulsen KB. Anderson's electronic atlas of hematology [CD-ROM]. Philadelphia: Lippincott Williams & Wilkins; 2002.

2. Monografia da Internet

Van Belle G, Fisher LD, Heagerty PJ, Lumley TS. Biostatistics: a methodology for the health sciences [e-book]. 2nd ed. Somerset: Wiley InterScience; 2003 [consultado 2005 Jun 30]. Disponível em: Wiley InterScience electronic collection

3. Homepage/Website

Cancer-Pain.org [homepage na Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01; [consultado 2002 Jul 9].Disponível em: http://www.cancer-pain.org/.

PROVAS TIPOGRÁFICAS

Serão da responsabilidade do Conselho Editorial, se os Autores não indicarem o contrário. Neste caso elas deverão ser feitas no prazo determinado pelo Conselho Editorial, em função das necessidades editoriais da Revista. Os autores receberão as provas para publicação em formato PDF para correcção e deverão devolvê-las num prazo de 48 horas.

ERRATA E RETRACÇÕES

A Acta Médica Portuguesa publica alterações, emendas ou retracções a um artigo anteriormente publicado. Alterações posteriores à publicação assumirão a forma de errata.

NOTA FINAL

Para um mais completo esclarecimento sobre este assunto aconselha-se a leitura do *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* do International Commitee of Medical Journal Editors), disponível em http://www.ICMJE.org.

Scale for the Assessment of Narrative Review Articles – SANRA

Please rate the quality of the narrative review article in question, using categories 0–2 on the following scale. For each aspect of quality, please choose the option which best fits your evaluation, using categories 0 and 2 freely to imply general low and high quality. These are not intended to imply the worst or best imaginable quality.

Nota: Para a UC de Dissertação/Projecto, todos os seis items devem ser cumpridos em nível 2.

1) Justification of the article's importance for the readership

The importance is not justified. — 0
The importance is alluded to, but not explicitly justified. — 1
The importance is explicitly justified. — 2

2

2) Statement of concrete aims or formulation of questions

No aims or questions are formulated. — 0
Aims are formulated generally but not concretely or in terms of clear questions. — 1
One or more concrete aims or questions are formulated. — 2

2

3) Description of the literature search

The search strategy is not presented. — 0
The literature search is described briefly. — 1
The literature search is described in detail, including search terms and inclusion criteria. — 2

2

4) Referencing

Key statements are not supported by references. — 0
The referencing of key statements is inconsistent. — 1
Key statements are supported by references. — 2

2

5) Scientific reasoning

(e.g., incorporation of appropriate evidence, such as RCTs in clinical medicine)

The article's point is not based on appropriate arguments. — 0
Appropriate evidence is introduced selectively. — 1
Appropriate evidence is generally present. — 2

2

6) Appropriate presentation of data

(e.g., absolute vs relative risk; effect sizes without confidence intervals)

Data are presented inadequately. — 0
Data are often not presented in the most appropriate way. — 1
Relevant outcome data are generally presented appropriately. — 2

2

Sumscore 12

Fig. 1 SANRA - Scale

Nota 1: O ponto 5 diz respeito à contextualização da evidência científica em relação ao tipo de estudo(s) que a produziu (e, idealmente, à qualidade do(s) mesmo(s)). O ponto 6 diz respeito a sustentar as afirmações com os dados quantitativos mais apropriado. A título de exemplo, para cumprir o ponto 5 e o ponto 6, ao invés de afirmar "já foi evidenciado que os testes de alergia às penicilinas apresentam alta especificidade e moderada sensibilidade", dever-se-á indicar "uma revisão sistemática com meta-análise de acuidade diagnóstica evidenciou que os testes de alergia às penicilinas apresentam alta especificidade (valor meta-analítico: 97%; IC95%=94-98%) e moderada sensibilidade (valor meta-analítico: 31%; IC95%=19-46%).

SANRA – explanations and instructions

This scale is intended to help editors assess the quality of a narrative review article based on formal criteria accessible to the reader. It cannot cover other elements of editorial decision making such as degree of originality, topicality, conflicts of interest or the plausibility, correctness or completeness of the content itself. SANRA is an instrument for editors, authors, and reviewers evaluating individual manuscripts. It may also help editors to document average manuscript quality within their journal and researchers to document the manuscript quality, for example in peer review research. Using only three scoring options, 0, 1 and 2, SANRA is intended to provide a swift and pragmatic sum score for quality, for everyday use with real manuscripts, in a field where established quality standards have previously been lacking. It is not designed as an exact measurement of the quality of all theoretically possible manuscripts. For this reason, the extreme values (0 and 2) should be used relatively freely and not reserved only for perfect or hopeless articles.

We recommend that users test-rate a few manuscripts to familiarize themselves with the scale, before using it on the intended group of manuscripts. Ratings should assess the totality of a manuscript, including the abstract. The following comments clarify how each question is designed to be used.

Item 1 – Justification of the article's importance for the readership

Justification of importance for the readership must be seen in the context of each journal's readership.
Consider how well the manuscript outlines the clinical problem and highlights unanswered questions or evidence gaps – thoroughly (2), superficially (1), or not at all (0).

Item 2 – Statement of concrete/specific aims or formulation of questions

A good paper will propose one or more specific aims or questions which will be dealt with or topics which will be reviewed.
Please rate whether this has been done thoroughly and clearly (2), vaguely or unclearly (1), or not at all (0).

Item 3 – Description of the literature search

A convincing narrative review will be transparent about the sources of information on which the text is based. Please rate the degree to which you think this has been achieved. To achieve a rating of 2, it is not necessary to describe the literature search in as much detail as for a systematic review (searching multiple databases, including exact descriptions of search history, flowcharts, etc.), but it is necessary to specify search terms, and the types of literature included. A manuscript which only refers briefly to its literature search would score 1, while one not mentioning its methods would score 0.

Item 4 – Referencing

No manuscript references all statements. However, those that are essential for the arguments of the manuscript – "key statements" – should be backed by references in all or almost all cases. Exceptions could reasonably be made for rating purposes where a key statement has uncontroversial face-validity, such as "Diabetes is among the commonest causes of chronic morbidity worldwide."
Please rate the completeness of referencing: for most or all relevant key statements (2), inconsistently (1), sporadically (0).

Item 5 – Scientific reasoning

The item describes the quality of the scientific point made. A convincing narrative review presents evidence for key arguments. It should mention study design (randomized controlled trial, qualitative study, etc), and where available, levels of evidence.
Please rate whether you feel this has been done thoroughly (2), superficially (1), or hardly at all (0). Unlike item 6, which is concerned with the selection and presentation of concrete outcome data, this item relates to the use of evidence and of types of evidence in the manuscript's arguments.

Item 6 – Appropriate presentation of data:

This item describes the correct presentation of data central to the article's argument. Which data are considered relevant varies from field to field. In some areas relevant data would be absolute rather than relative risks or clinical versus surrogate or intermediate endpoints. These outcomes must be presented correctly. For example, it is appropriate that effect sizes are accompanied by confidence intervals. Please rate how far the paper achieves this – thoroughgoingly (2), partially (1), or hardly at all (0). Unlike item 5, which relates to the use of evidence and of types of evidence in the manuscript's arguments, this item is concerned with the selection and presentation of concrete outcome data.

Fig. 2 SANRA—explanations and instructions document