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ESOPHAGEAL SQUAMOUS CELL CARCINOMA

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Abstract:

The esophageal cancer is one of the fatal malignancies around the world, with a dramatic increase in incidence rates in the Western world occurring over the past few decades. Esophageal cancer is the 8th most common cancer and the 6th most common cause of cancer deaths worldwide despite improvements in the management and the therapeutic approach.

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INTRODUCTION:

Esophageal cancer remains an integral cause of cancer-related death and has shown a drastic increase of more than 6-fold in incidence rates worldwide. [1] Esophageal cancer occupies the 8th most common cancer and the 6th most common cause of deaths due to cancer worldwide. [2] The incidence rate of esophageal cancer varies considerably with location. [3]

Squamous cell carcinoma accounts for 95% of all esophageal carcinomas. Other histologic types, including adenocarcinoma, account for the remaining 5 %. [4] About 90% of all esophageal cancers arise in the thoracic esophagus and middle thoracic esophagus is the most frequent location.

Esophageal squamous cell carcinoma (ESCC) has a high prevalence in East Asia, eastern and southern Africa, and southern Europe. [5,6] However, the incidence rate of ESCC is low in North America and other parts of Europe. [7]

These geographical differences show that ethnicity, genetic factors, and lifestyle all play an important role in the development of ESCC.

The etiology of ESCC is multifactorial and strongly population dependent.

RISK FACTORS:

1. Smoking:

It is a major cause of ESCC, where the occurrence in men was higher than in women. A current smoker has more risk than an ex-smoker. Total packs per year smoked was also associated with increased risk of ESCC. Those who smoked > 30 packs per year had higher occurrence rate. [8]

2. Alcohol consumption

Ethanol is metabolized by alcohol dehydrogenase and forms acetaldehyde. Which interact with DNA, produced DNA adducts to induce gene mutation. That's why alcohol is one of the risk factors for the development of cancer in upper aerodigestive tract. [9]

Other risk factors with low Evidence includes poor oral health, gastric atrophy, reproductive factors, opium, betel quid, pickled food, hot food, fanconi anemia and previous x-ray and gamma irradiation. [10]

GENETICS ASSOCIATED TO ESCC:

1. Genes that regulate the cell cycle of differentiation

Analyses of comprehensive mutational catalogs, using high-throughput sequencing technology, have detected widespread genomic alterations in ESCC. [11-14] The first large-scale comprehensive analysis revealed that more than 83% of ESCCs contained a somatic mutation in TP53. [11] Genes that control the cell cycle mutation (*C*DKN2A, *RB1*, *NFE2L2*, *CHEK1*, and *CHEK2*), or experience differentiation (NOTCH1 and *NOTCH3*), have been found in 2–10% of ESCCs. [11-13] Moreover, a number of genes that control the cell cycle are also overexpressed in ESCCs (*CCND1*, *CDK4/CDK6*, and *MDM2*), that indicates their presence in the development of ESCC. [11]

2. Epidermal growth factor receptor (EGFR) and receptor tyrosine kinase or RAS signaling

EGFR is overexpressed in 59.6–76% of ESCC patients that associates with a poor prognosis. [15,16] Moreover, 78.6% of ESCC patients have mutations and/or amplifications in factors downstream of EGFR, including the receptor tyrosine kinase, RAS, and AKT pathways. Another clinical trial recruited 193 ESCC patients, whose EGFR expression was significantly correlated with clinical stage and lymph node metastasis. [17]

3. Epigenetic factors

Epigenetic alterations such as DNA methylation, histone modification, and loss of genome imprinting are associated in the development of ESCC. [18] Hypermethylation in the promoter regions of APC, RB1, and CDKN2A could be detected in ESCC [19-21] Methylation of CDKN2A, which transcripted p16 and could regulate RB1, is associated with p53 overexpression [22] These cell cycle-regulatory pathways could promote the progress of ESCC. Polymorphisms in genes such as TP53, MDM21, [23] CASP8, [24] and COX2 [25] are reported to be associated with increased risk of developing ESCC. Recent genome-wide association study-based analyses of patients with ESCC detected several single-nucleotide polymorphisms, and among them were five candidate genes (TDG, MBL2, CASP8, PLCE1, and UCP3) that were strongly correlated with enhancing the risk of ESCC. [26]

PREVALENCE:

In the United States the Incident rates in Black men was significantly increased compared with Black

women (15.8 per 100,000 person-years versus 4.7 per 100,000 person-years). White men also had a higher incident rate than White women (7.1 per 100,000 person-years versus 2.0 per 100,000 person-years). The male/female incidence rate (IR) ratio for ESCC were 1.8 among Whites, 2.9 among Blacks, and > 4 among Hispanics, American Indians/Alaska Natives, and Asians/Pacific Islanders. ESCC accounted for 87% of all esophageal cancer in Blacks but only for 45% in Whites. [27]

The IR significantly upregulated in Black and men was correlated with their lifestyle like smoking and alcohol consumption. The geographical distribution varies greatly, with more than tenfold differences between countries. The highest IR stretch from central to eastern Asia, with another band running along the Indian Ocean coast of Africa along the Great Rift Valley. The 3rd area with higher incidence was around Uruguay in South America and encompassed the entire gaucho region, but lately the rates in Uruguay have decreased. [10]

CLINICAL DESCRIPTION:

Average age of onset of symptoms is mostly between the ages of 60-70 years. Horizontal and longitudinal spread are facilitated by rich lymphovascular network. The esophagus lacks a serosal covering and thus early tumor growth causes the smooth muscles to dilate readily. During the early period of slow tumor growth, the patient generally is asymptomatic.
When the tumor infiltrate more than half of the esophageal circumference, dysphagia develops. The most common presenting symptom and is dysphagia often heralds advanced disease due to local spread with insidious onset. Other, less likely presenting symptoms include coughing or choking, hoarseness, or, more rarely, shock (due to hemorrhage secondary to invasion of the aorta). The physical examination of patients with ESCC often reveals weight loss and dehydration. Mostly anorexia and weight loss usually precede the onset of dysphagia. In metastatic disease palpable nodes are occasionally noted, hepatomegaly or jaundice and pneumonia when it erodes the respiratory tree.

Lymph node metastases vary by region. The upper third to cervical nodes, the middle third to mediastinal, paratracheal and tracheobronchial node, the lower third to gastric and celiac nodes. May be associated with other malignancies of the upper GI tract. Rarely to have multiple focuses in esophagus. Mostly metastasizes to the lungs, liver, bones, adrenal glands, kidneys and the central nervous system. Recurrences are common. [28]

DIAGNOSES:

When complaining of dysphagia, the patients need at least one of two diagnostic tests: an upper gastrointestinal (GI) barium contrast study or a flexible esophagogastroduodenoscopy (EGD) and multiple biopsies should be taken for histopathology examination. EGD is the preferred approach in most centers because the ability to directly visualize the lesion. [29]
Contrast-enhanced CT is very important for the staging of ESCC, with attention to the extent of the local tumor; invasion of mediastinal structures; involvement of supraclavicular, mediastinal, or upper abdominal lymph nodes; and distant metastases.
Magnetic Resonance Imaging (MRI) presents the advantage of direct multiplanar imaging capabilities. Currently, MRI has no other significant advantages when compared with CT. [30]

Ultrasonography, (EUS) allows visualization of the distinct layers within the esophageal wall. Esophageal carcinoma appears as a hypoechoic lesion disrupting the normal circumferential layers. EUS also demonstrates the LN. They are considered to be malignant if they are round, hypoechoic, have well-defined borders.

Nuclear Imaging (PET) is now a standard oncologic imaging modality. It is not only useful for the primary detection of tumor and metastases but also for the further characterization of abnormalities discovered by using other imaging modalities and also for detecting recurrent esophageal cancer after treatment [31-33]

STAGING:

American Joint Committee on Cancer (AJCC) tumor node metastasis (TNM) classification system for esophageal cancer with histologic as below: (34)

Primary tumor (T): (TX) cannot assess the primary tumor , (T0)there is no evidence of primary tumor, (Tis)High-grade dysplasia (HGD), (T1)Tumor invades lamina propria, muscularis mucosae, or Submucosa, (T1a)Tumor invades lamina propria or muscularis mucosal, (T1b)Tumor invades Submucosa, (T2) Tumor invades muscularis propria, (T3)Tumor invades adventitial, (T4)Tumor invades the adjacent structures, (T4a) resectable tumor invading pericardium, pleura, azygos vein, diaphragm, or peritoneum.(T4b) unresectable tumor invading the other adjacent structures(aorta,

vertebral body, trachea).

Regional lymph nodes (N): (NX) can't be assessed, (N0) no LN involvement, (N1) 1-2 LN, (N2) 3-4 LN, (N3) 7 or more regional LN.

Distant metastasis (M): (M0) no metastasis, (M1) metastasis.

Histologic grade (G): (GX) can't be assessed, (G1) well differentiated, (G2): moderately differentiated, (G3) poorly differentiated.

PROGNOSIS:

ESCC is diagnosed mostly at advanced stage with poor prognosis and often refractory to therapeutic approaches, with an overall 5-year survival of between 10-20% and the cure rate currently reaches 40% Surgical resection offers a greater chance for cure if done early.

When the neoplasm involves the submucosal layer, growth became rapid [29]. The disease often metastasizes to the LN and hematogeneously at the same time.

SCREENING AND PROTECTION:

Screening protocols for the high-risk patients are done in Japan and China but not in the United States. The early detection improves survival to 75%, versus 25% for curative resection for patients at advanced stage.
In China "the early diagnosis and treatment of cancer" program include endoscopic iodine staining and biopsy. For patients (40–60 years old) the screening and treatment of early abnormal lesions prevent progression to esophageal cancer [35]

TREATMENT:

The treatment varies according to the stage (stages I-III) versus metastatic cancer (stage IV).
National Comprehensive Cancer Network (NCCN) recommends treatment for ESCC as below: [36]

- Endoscopic therapy (endoscopic mucosal resection(ER), endoscopic submucosal dissection and/orablation) is preferred for HGD or T1a tumors ≤2 cm. Only ablation is a primary treatment option for patients with HGD.
- pT1a or pT1b tumors could be treated with ER.
- Multiple ablation may be needed after ER if multifocal HGD is present elsewhere in the esophagus.
- Patients with extensive HGD are indicated for Esophagectomy. A transhiatal or transthoracic approach may be used; gastric reconstruction preferred; for postoperative nutritional support, feeding jejunostomy or gastrostomy.
- ForT1b, N+ tumors and locally advanced respectable tumors (T2-T4a, any regional N) include preoperative chemoradiotherapy (CRT) (for non-cervical esophagus tumors), definitive CRT (recommended for cervical esophageal tumors) or esophagectomy (for non-cervical esophageal tumors).
- Tumors in the submucosa (T1b) or deeper could be treated with esophagectomy.
- Postoperative treatment is not indicated if no residual disease at surgical margins (R0 resection).
- CRT offered to all patients with residual disease at surgical margins (R1 and R2 resections).
- Definitive CRT is preferred for all T4b (unresectable) tumors.
- Fluoropyrimidine or taxane based regimens are indicated for preoperative and definitive CRT.

Surgical Indications and Contraindications
Surgery remains the cornerstone of treatment. It is indicated for the following:

- In a patient who is candidate for the surgery.
- HGD in patient who can't be adequately endoscopically treated.

Contraindications to surgery include the following:

- Metastasis to N2 nodes [37]
- Invasion of adjacent structures.

The presence of severe, associated comorbid conditions (cardiovascular disease, respiratory disease) decrease a patient's chances of surviving an esophageal resection.
Relative contraindications are forced expiratory volume in 1 second less than 1.2 L and a left ventricular ejection fraction less than 0.4.

Esophagectomy is still a critical component of multimodality therapy. But not for palliation any more.

An esophagectomy can be performed by using a transhiatal esophagectomy (THE) approach or by using a transthoracic esophagectomy [TTE)

approach. The continuity of the GI tract is reestablished using the stomach.
Many retrospective and prospective studies have shown no difference in survival between the operations, the factor which influence survival is not the type of operation but the tumor stage at the operation. [38-41]

Complications occur from esophagectomy in approximately 40% of patients including the following:

- Respiratory complications (15-20%) Include atelectasis, pleural effusion, and pneumonia
- Cardiac complications (15-20%) Include cardiac arrhythmias and myocardial infarction
- Septic complications (10%) Include wound infection, anastomotic leak and pneumonia
  Intrathoracic leak following esophagectomy may lead to sepsis and death. Leaks could be treated with endoscopic placement of self-expanding or removable plastic stents. [42]

As with other complex operations the lowest mortality rate with esophagectomy is achieved when the procedure is performed in high-volume centers by high-volume multidisciplinary team formed of sturgeons intensivists, cardiologists, pulmonologists, and radiologists.

Salvage endoscopic resection
In patients with local failure after definitive CRT for ESCC, salvage endoscopic treatment (SET) may be a viable option.
The predictive factors of improved survival were:

- absence of LN metastasis before CRT
- Time of 6 months or more between the initiation of CRT and the performance of SET. [43]

Chemoradiotherapy (CRT)
Chemotherapy and radiotherapy for ESCC are delivered preoperatively (neoadjuvant). No survival benefit is obtained when CRT is administered postoperatively; however, postoperative continuance of chemotherapy started preoperatively may be beneficial. [44] The aims of neoadjuvant CRT is to reduce the bulk of the tumor before surgery for better curative resection rates and to eliminate or delay the distant metastases.

Chemotherapeutic agents which is currently used for the treatment of ESSC, as alkylating, antimicrotubular, anthracycline and antimetabolite agents, are not approved by the FDA for this indication. Chemotherapy for ESCC is based on cisplatin.

Neoadjuvant chemotherapy alone offers a limited benefit.
Preoperative CRT plus surgery was superior to surgery alone in preventing local, regional, and distant recurrence, particularly hematogenous metastasis and peritoneal carcinomatosis. [45 -47]

Neoadjuvant therapy is a combination of radiotherapy (approximately 45 Gy) and chemotherapy (cisplatin and 5-fluorouracil). The radiotherapy acts at the tumor site locally and the chemotherapy acts on tumor cells that have already spread. This combination therapy is administered over a 45-day period; esophageal resection is performed after an interval of approximately 4 weeks.

PALLIATIVE CARE:

In patients who are not ongoing surgery, as they are not fit for surgery or have advanced disease, treatment focuses on control of dysphagia and other symptoms and to improve quality of life for patients and their caregivers.
Available palliative methods include the following:

- Endoscopic lumen restoration or enhancement
- Temporary self-expanding metal stents (SEMS)
- External beam radiation therapy (EBRT)
- Brachytherapy
- Chemotherapy
- Laser
- Surgery

NCCN guidelines for best supportive/palliative care

For patients with complete esophageal obstruction: [36]

- Endoscopic lumen restoration
- EBRT
- Chemotherapy
- Surgery

Placement of jejunostomy or gastronomy surgically or radiologically tubes is necessary to provide adequate nutrition, if unsuccessful endoscopic lumen restoration is occurred Brachytherapy could be considered instead of EBRT. [48]

STENTS:

Palliation of dysphagia for long-term can be achieved with endoscopic, radiographic-assisted insertion of expandable metal or plastic stents. [49] Temporary placement of SEMS with concurrent EBRT was found to increase survival rates compared with

permanent stent placement. [51] SEMS is the preferred for patients with tracheoesophageal fistful or who are not candidates for CRT are or who failed to achieve adequate palliation with such therapy. Membrane-covered stents have better palliation significantly rather than conventional bare metal stents. [50]

RADIOTHERAPY:

RT is successful in relieving dysphagia in approximately 50% of patients. The preoperative CRT has shown good results.

CHEMOTHERAPY:

Using chemotherapy as a single modality is limited. Only a few numbers of patients achieve a modest and short-lived response.

LASER THERAPY:

Laser therapy (Nd:YAG laser) could help to achieve temporary relief of dysphagia in many patients. Usually multiple sessions are required to keep the esophageal lumen patent.
The FDA approved the photosensitizer porfimer (Photofrin) for palliation of completely obstructing or partially obstructing tumor that cannot be treated with Nd:YAG laser therapy satisfactorily. [51]

POSTOPERATIVE CARE:

Postoperative length of stay is about 9-14 days. Patients spend the first postoperative night in the intensive care unit.
Patients could be extubated immediately after the operation if there is no respiratory distress.

On day 1 postoperative feeding is started through the feeding jejunostomy. On day 5 postoperative, a swallow study is performed for fear of anastomotic leakage. If ok, patients start oral feedings but if a leak is found, the drainage tubes are not removed, and nutrition is provided entirely through the feeding jejunostomy till the leak closes spontaneously.
Most of patients went home after discharge. The patients who may need additional time stay in a skilled nursing facility if they cannot take care of themselves.
Patients are seen by the surgeon after 2weeks then after 4 weeks from discharge from the hospital and then every 6 months by an oncologist. Most of the patients return to their normal life activities within 2 months.

CONCLUSION:

ESCC is a fatal disease, with rising incidence over the past decades. Management needs multidisciplinary team to reach good outcome and improve quality of life for the patients and caregivers. Effective preventive actions, such as health education, nutritional intervention, and screening, should be enhanced, especially in high-risk areas. More future researches for new biomarkers that predict the response to the neoadjuvant chemotherapy is needed.

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