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A BRIEF REVIEW ON ESOPHAGEAL CANCER

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ABSTRACT

Esophageal cancer is a malignant tumor that originates in the internal layers of the mucosal lining of the esophagus. There are two leading types of esophageal cancer, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). ESCC can arise in any part of the esophagus. EAC, usually found in the lower part of the esophagus near the stomach, forms in glandular cells that replace a section of squamous cells, a condition called Barrett's esophagus (BE). Esophageal cancer is one of the deadliest cancers worldwide. Recent advances in the diagnosis, staging, and management of this neoplastic condition have led to small but remarkable improvements in survival. For mucosal cancer, endoscopic mucosal resection and endoscopic submucosal dissection are standard, while for locally advanced cancer, esophagectomy remains the mainstay. Chemoradiotherapy is the standard for unresectable esophageal cancer and could also be considered as a choice for resectable tumors. For medically or technically inoperable patients, chemoradiotherapy should be the standard of care. Most esophageal cancers are detected at an advanced stage (requiring surgical resection, chemotherapy, and radiation). Early-stage mucosal lesions can be observed through Barrett's surveillance programs or by diagnostic upper endoscopies. Early stage cancers are frequently amenable to endoscopic therapies, including mucosal resection, ablation, and cryotherapy. Studies suggest equal survival rates and reduced morbidity but higher recurrence rates with endoscopic removal of early stage cancers compared to surgical resection.

INTRODUCTION

Esophageal cancer is one of the deadliest cancers worldwide because of its extremely aggressive nature and poor survival rate. Esophageal cancer including squamous cell carcinoma and adenocarcinoma is considered as a serious malignancy. Cancer of the esophagus typically occurs in one of two forms, ESCCs arising from the stratified squamous epithelial lining of the organ, and adenocarcinomas affecting columnar glandular cells that replace the squamous epithelium [1]. In recent studies, tobacco, smoking, hot tea drinking, alcohol, red meat consumption, poor oral health, obesity, dietary deficiencies, gastrointestinal reflux disease, hereditary factors and certain drugs have been associated with a higher risk of esophageal squamous cell carcinoma. The best currently available risk marker is the degree of dysplasia in endoscopic biopsies from the esophagus; however, this marker is suboptimal for a variety of reasons. Dysplasia is the only factor useful for identifying patients at increased risk [2]. The aim of this review is to study various risk factors and feasibility of treatment options for esophageal cancer. The established or suspected risk factors for ESCC and EAC are explained in greater detail below:

Barrett's esophagus

Barrett's esophagus, which is defined as the metaplastic replacement of normal squamous epithelium by columnar epithelium in the distal esophagus, is the most well-studied risk factor for esophageal adenocarcinoma [3]. It a complication of gastroesophageal reflux disease [4]. It is an acquired condition resulting from severe esophageal mucosal injury. Esophagogastroduodenoscopy with biopsy is the current gold standard for the diagnosis and surveillance of BE.

Tobacco

The incidence of squamous cell carcinoma is higher in males than females. Tobacco is a well-known carcinogen responsible for multiple cancers due to its tar fraction. The primary initiators are presumably the polynuclear aromatic hydrocarbons and volatile nitrosamines [5]. Both current and former smokers had an increased risk of developing adenocarcinoma compared with individuals who had never smoked**.** Evaluation of 554 patients with adenocarcinoma suggested that, compared with controls, the risk of cancer among current smokers was twice as high and increased as the number of packs per year increased. Smoking is a major risk factor for esophageal and gastric cardia adenocarcinomas, accounting for approximately 40 % of cases and is only related to adenocarcinomas in the lower stomach [6].

Alcohol

Studies suggested that among alcohol drinkers, those in the highest category of alcohol intake (>3 drinks per day) were at increased risk of developing esophageal squamous cell carcinoma, compared with moderate drinkers who drank up to one drink per day [7]. Consumption of alcohol and tobacco, separately or jointly, can increase the risk of oesophageal squamous cell carcinoma. Both non-drinkers who smoked tobacco and non-smokers who drank heavy alcohol (>30 g/day) were observed to have elevated cancer risks. Both light to moderate and heavy alcohol intake interact separately with tobacco in differently synergistic processes [8].

Obesity

Obesity also increases the risk of Barrett's esphagus- the primary risk factor for esophageal adenocarcinoma- independent of acid reflux. The risk of BE seems to correlate most markedly with measures of central adiposity, such as waist:hip ratio and waist circumference, than body mass index alone. Visceral fat is more metabolically active than subcutaneous fat, producing more hormones and higher concentrations of pro-inflammatory cytokines [9].

Diet

Dietary deficiencies and diets contaminated with carcinogenic compounds have been implicated as factors contributing to a higher risk for esophageal cancer. Nutritional deficiencies have been suspected as risk factors for squamous cell oesophageal cancer for many years. Red meat, stewed meat and salted meat were associated with moderate to strong effects on the risk of squamous cell oesophageal carcinoma. On the other hand, white meat, poultry and fish displayed moderate inverse associations with oesophageal cancer. Among plant foods, total vegetables were weakly associated with this disease, whereas raw vegetables were strongly protective. Citrus fruits are the most protective food groups with reductions in risk close to 80 % [10]. The analysis of consumption of very hot drinks, such as mate, tea, porridge, coffee and coffee with milk, provide the evidence for a carcinogenic effect of chronic thermal injury in the esophagus. Studies further confirms the protective effect of a dietary pattern characterized by daily consumption of fruits and vegetables and low consumption of meat and animal fats [11].

Olive oil intake showed a significant reduction of esophageal cancer risk. Butter consumption was directly associated with the negative effects [12]. Suspected risk factors for ESCC include foods that are sources of heterocyclic amines formed during cooking (e.g., barbecued or fried meats, especially red meat). Higher intake of carotenoids (beta-carotene, alpha-carotene,

lycopene, beta-cryptoxanthin, lutein, and zeaxanthin) is associated with lower risk of esophageal cancer. In human cells carotenoids act as oxidants, which are capable to scavenge free radical and prevent oxidative damage [13].

Zinc is required for the activity of many enzymes, for proper immune function and for the conformation of many transcription factors that control cell proliferation, apoptosis and signaling pathways. Dietary zinc deficiency increases the risk of ESCC**.** Zn replenishment reversed this inflammatory signature at both the dysplastic and neoplastic stages of ESCC development, and prevents cancer formation [14].

Gastroesophageal reflux disease (GERD)

The reflux of gastric acid into the esophagus, which commonly causes chronic heartburn, in gastroesophageal reflux disease may stimulate the esophageal mucosa to develop metaplastic columnar epithelium, which is characteristic of the EAC precursor lesion, Barrett's esophagus, found in almost all patients with EAC. No clear association has been found between drugs used to treat GERD and the risk of EAC.

Hereditary factors

Tylosis is a rare disorder associated with hyperkeratosis of the palms of the hands and soles of the feet and a high rate of squamous cell carcinoma of the esophagus. The inherited type of tylosis (Howell-Evans syndrome) is an autosomal dominant disease. Familial aggregation of esophageal cancer has been described in high-incidence regions such as China [15]. Preclinical studies have demonstrated that estrogens could inhibit squamous cell tumor growth [16].

Use of drugs decreasing lower esophageal sphincter (LES) tone

Past use of LES relaxing drugs was positively associated with risk for esophageal adenocarcinoma. Drugs of all classes contributed to the increased risk, but the association was particularly strong for anticholinergics. Assuming a causal relation, about 10 % of the esophageal adenocarcinomas occurring in the population may be attributable to intake of LES-relaxing drugs [17].

Signs and Symptoms

Symptoms of esophageal cancer generally do not appear until the tumor has grown large enough to obstruct part of the esophagus. 74 % patients with esophageal cancer have dysphagia and 17 % report odynophagia (pain on swallowing food and liquids) at the time of diagnosis. As the tumor grows and becomes locally invasive, additional symptoms may include: regurgitation of

food, indigestion and heartburn, weight loss (more than 10 % of body mass), chest pain behind the breastbone, upper abdominal pain, hoarseness, coughing (with or without blood) and vomiting.

Diagnosis Tests

Tests to rule out esophageal cancer include:

a) A barium-swallow examination (also called an upper GI series or esophagogram): The patient drinks a barium solution, which coats the surface of the esophagus so that any irregularities on the lining of the esophagus show up when a series of X-rays are taken. A computed tomographic (CT) scan of the chest, abdomen, and pelvi with intravenous contrast medium should be obtained to detect metastatic disease.

b) Upper endoscopy (also called esophagoscopy): A thin, flexible, lighted tube (called an endoscope or esophagoscope) with a camera on the end is passed through the mouth or nose and down the esophagus to look for abnormal areas. If an abnormal area is found, a biopsy specimen will be taken and examined for signs of cancer [18].

c) Endoscopic ultrasonography: It is useful for determining the correct stage (prognosis) and accurately identify superficial lesions, which are best treated with surgery alone.

d) Positron-emission tomography (PET) with fludeoxyglucose F 18 is increasingly being used to identify disease that has spread to regional lymph nodes or to sites that are undetectable by CT or endoscopic ultrasonography [19].

Treatment Strategies

Endoscopic treatment

There are two established methods that aim to cure mucosal cancers: endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). EMR and ESD are indicated for lesions that do not infiltrate beyond the mucosal layer, or those confined to the epithelium or the lamina propria mucosae, as it is very unusual for there to be lymph node metastasis in these circumstances. Endoscopic ultrasound (EUS) is used to assess the depth of invasion. This technique uses high frequency ultrasound and is more accurate than conventional ultrasound in the evaluation of the depth of invasion of early esophageal tumors.

Endoscopic mucosal resection was developed for minimally invasive, organ-sparing endoscopic removal of benign and early malignant lesions in the gastrointestinal tract. Injection-assisted EMR is also often called saline solution lift–assisted polypectomy. The procedure starts with

injection of solution into the submucosal space under the lesion creating a safety cushion. The cushion lifts the lesion, facilitating capture and removal. Cap-assisted EMR uses submucosal injection to lift the target mucosal lesion. Dedicated mucosectomy devices have been developed that use a cap affixed to the tip of the endoscope. In ligation-assisted EMR, a band ligation device (Duette Multi-Band Mucosectomy device, Cook Medical Inc., Winston-Salem, NC) is attached to the endoscope, and the banding cap is positioned over the target lesion with or without previous submucosal injection. Suction is applied to retract the lesion into the banding cap, and a band is deployed to capture the lesion [20].

Endoscopic mucosal resection provides few benefits like less time for resection and complications related to the procedure is rare (e.g., perforation, mediastinal emphysema, and structure). Few limitations are also there, like range of resection is small and pathological evaluation is difficult when the tumor is resected piecemeal. Endoscopic submucosal dissection have features like time required for dissection is longer than EMR. The range of en bloc dissection is large (no obvious restriction). Accurate pathological evaluation is possible by ESD [21]. Receipt of either endoscopic ultrasound or CT-PET alone in esophageal cancer patients was associated with improved 1-, 3-, and 5-year survival [22]. Baseline abnormalities in motility can occur in patients with Barrett's high-grade dysplasia or mucosal carcinoma. Changes in esophageal function also may occur following photodynamic therapy, but usually are not clinically significant. Worsening in function was more likely to occur in patients with longer segment Barrett's esophagus [23]. The rates of accurate evaluation of the depth of invasion by endoscopic ultrasound using high-frequency ultrasound probes were 70-88 % for intramucosal cancer, and 83-94 % for submucosal invasive cancer [24].

Surgical treatment

Esophagectomy followed by reconstructive surgery has been the most reliable means of curing patients in whom there is no evidence of invasion to the adjacent organs or distant metastasis. The three most common techniques for thoracic esophagectomy are the transhiatal approach, Ivor Lewis esophagectomy (right thoracotomy and laparotomy), and the McKeown technique (right thoracotomy followed by laparotomy and neck incision with cervical anastomosis) [25, 26].The 5-year survival was approximately 20 % after both transthoracic and transhiatal resections, although transthoracic resection was associated with significantly higher early morbidity and mortality [27].

When comparing transthoracic esophagectomy with transhiatal esophagectomy, there was no difference in the incidence of respiratory failure, renal failure, bleeding, infection, sepsis, anastomotic complications, or mediastinitis [28]. Compared with limited transhiatal resection extended transthoracic esophagectomy for type I esophageal adenocarcinoma shows an ongoing trend towards better 5-year survival. Moreover, patients with a limited number of positive lymph nodes in the resection specimen seem to benefit from an extended transthoracic esophagectomy [29].

Because surgery for esophagogastric junctional cancer occasionally requires a thoracotomy in addition to a laparotomy, surgery is associated with high mortality and morbidity rates. Therefore, minimally invasive surgery should be developed as an alternative to conventional open surgery [30]. Data of 58 patients with cervical esophageal cancer who underwent limited resection and free jejunal graft with or without laryngeal preservation was reviewed. Among them, 45 patients received neoadjuvant treatment. Limited resection with free jejunal graft and laryngeal preservation is a promising treatment strategy for cervical esophageal cancer [31].

The jejunal artery and vein were anastomosed to the neck vessels in an end-to-side fashion without microvascular anastomosis. Pharyngo-jejunostomy with extended end-to-end anastomosis was performed to reduce size mismatch. This technique is simple and safe [32]. Pharyngoesophageal reconstruction using the free vascularized jejunal graft sometimes results in dysphagia and this may be caused by anastomotic stenosis at either the distal or proximal anastomotic site, graft contractility and the entrapment of food in the blind loop after an end-to-side pharyngojejunostomy [33].

Chemotherapy

Chemotherapy plays important roles in adjuvant surgical therapy and amplifies the effect of radiation therapy in patients with esophageal cancer**.** Cisplatin and 5-fluorouracil therapy is a standard protocol for patients with unresectable esophageal cancer. Nedaplatin is a second-generation platinum complex that was shown to have pronounced activity against solid tumors but less nephrotoxicity than cisplatin in preclinical and clinical studies [34]. Neoadjuvant and perioperative platinum fluoropyrimidine-based combination chemotherapy has now an established role in the treatment of stage II and stage III esophageal adenocarcinoma and cancer of the esophago-gastric junction [35].

Long-term follow-up confirms that preoperative chemotherapy improves survival in operable esophageal cancer and should be considered as a standard of care [36]. Postoperative adjuvant chemotherapy with cisplatin and fluorouracil is better able to prevent relapse in patients with esophageal cancer than surgery alone [37]. Capecitabine and oxaliplatin are as effective as fluorouracil and cisplatin, respectively, in patients with previously untreated esophagogastric cancer [38]. Patients were prospectively randomized into two groups (100 patients underwent surgery alone and 105 patients had additional two courses of combination chemotherapy with cisplatin (70 mg/m2) and vindesine (3 mg/m2). Postoperative adjuvant chemotherapy with cisplatin and vindesine has no additive effect on survival in patients with esophageal cancer compared with surgery alone [39].

Chemoradiotherapy

Chemoradiotherapy is the standard therapy for unresectable esophageal cancer and should be considered as an option for resectable esophageal cancer. For patients who are medically or technically inoperable, concurrent chemoradiotherapy should be the standard of care. Preoperative chemoradiotherapy improved survival among patients with potentially curable esophageal or esophagogastric-junction cancer. The regimen was associated with acceptable adverse-event rates [40].

Studies were included to compare preoperative chemoradiotherapy plus surgery with surgery alone. Chemoradiotherapy plus surgery significantly reduces three year mortality compared with surgery alone. However, postoperative mortality was significantly increased by neoadjuvant chemoradiotherapy. Further large scale multicentre randomized controlled trials may prove useful to substantiate the benefit on overall survival [41]. 59 consecutive patients with thoracic esophageal squamous cell carcinoma who underwent salvage esophagectomy after definitive chemoradiotherapy were reviewed. All patients received more than 60 Gy of radiation plus concurrent chemotherapy for curative intent. The data were compared with those of patients who received esophagectomy without preoperative therapy. Patients who underwent salvage esophagectomy after definitive high-dose chemoradiotherapy had increased morbidity and mortality. Nevertheless, this is acceptable in view of the potential long-term survival after salvage esophagectomy [42]. Salvage indications of recurrence, earlier disease, and complete tumor resection are related to longer survival. The total area of mediastinal

dissection with a sufficient number of dissected mediastinal lymph nodes improves survival. Additional neck dissection does not add benefit [43].

Photodynamic therapy

Photodynamic therapy (PDT) is a treatment that uses a photosensitizing drug that is administered to the patient, localized to a tumor, and then activated with a laser to induce a photochemical reaction to destroy the cell. Endoscopic submucosal dissection is currently more popular for esophageal cancer, there is evidence to support PDT as an alternative treatment and as a salvage treatment for local failure after chemoradiotherapy [44].

Photodynamic therapy is a less-invasive salvage treatment option for local failure at the primary site after chemoradiotherapy for esophageal squamous cell carcinoma. PDT may be associated with a longer survival period [45]. Feasibility and safety of photodynamic therapy as a curative treatment option or as palliative therapy for esophageal squamous cell carcinoma were evaluated. Data suggested that photodynamic therapy is a reasonable palliative treatment option with acceptable complication rates for esophageal cancer and could be performed for therapeutic purposes in cases of early esophageal cancer [46].

Vascular targeted photodynamic therapy (VTP) procedures on healthy esophageal tissues have shown a confined destruction only at the illuminated zone while collateral damage to neighboring tissues was not observed. The impact runs as deep as the muscularis propria without signs of perforation or death as a result of the procedure. The VTP protocol was able to ablate implanted and established tumors as opposed to the control group with light illumination alone without the sensitizer. VTP could be safely applied to treat esophageal tumors, with transient and mild adverse effects. Importantly, VTP effectively eradicated established esophageal tumors in tested set up that could be translated into a clinical treatment protocol [47].

Cryotherapy

Endoscopic cryotherapy (Cryo) or local application of cryogen to the gastrointestinal mucosa is a thermal ablative treatment that has been used for Barrett's esophagus and high grade dysplasia, as well as for palliative use in esophageal adenocarcinoma. Cryo using liquid nitrogen or compressed carbon dioxide or nitrogen gas is delivered via an endoscopic spray catheter resulting in tissue destruction without direct contact. Compared to alternative endoscopic cancer palliative therapies for EAC such as photodynamic therapy (that results in extreme photosensitivity, greater pain and more frequent esophageal strictures) and esophageal stenting

(which causes chest pain and does not treat the primary tumor), Cryo is an attractive viable palliative treatment option [48].

Cryotherapy has also been used in combination with resection to treat high-grade dysplasia and intramucosal carcinoma in 27 patients, with a 90 % rate of elimination of the lesion or downgrading of disease stage. Cryotherapy is reported to cause chest pain, dysphagia, and perforation in rare cases [49]. Cryotherapy is currently used for dysplastic and neoplastic esophageal lesions. This procedure has been successful in both squamous cell esophageal cancer and adenocarcinoma of the esophagus [50].

Argon plasma coagulation (APC)

APC is a widely available, alternative way to ablate dysplastic tissue in the esophagus. APC uses a probe device that has a constant flow of ionized argon gas that transmits high-frequency current to tissue to cause superficial cautery effect and tissue destruction. Efficacy of APC varies in studies with 66-100 % of complete eradication of BE and relapse rates of 3-11 % per year. Complications have been reported with APC including strictures, pleural effusions, and perforations. Given this mixed profile, APC for BE is less routinely performed in favour of techniques such as radiofrequency ablation [51].

CONCLUSION

Esophageal cancer is a comparatively rare malignant condition with a low probability to cure. More accurate, data-driven referral regarding the value of endoscopic surveillance in patients with Barrett's esophagus is also needed. A series of cautiousy designed controlled, randomized trials will most likely be required to address the issues related to choice of therapy. Treatment modalities for esophageal cancer have now become subdivided. For early stage cancer, endoscopic treatments are now well recognised as beneficial techniques. Surgical treatment still plays a central role to cure locally advanced cancer. For advanced cancer, neoadjuvant or adjuvant therapy is added. Concurrent chemoradiotherapy is the standardised therapy for unresectable esophageal cancer and could also be considered as an option for resectable esophageal cancer. EMR and ablation offer possibilities for cost-effective, curative treatment of earlystage esophageal cancer. Accurate staging with endoscopic ultrasound and fine needle aspiration (when indicated) is necessary to determine whether a lesion can be considered for endoscopic treatment. EMR can be used for curative treatment of lesions confined to the mucosa; lesions invading the submucosa may require ESD or more radical resection. Ablative methods

such as APC, cryotherapy, or radiotherapy ablation are generally not effective for cure when used as monotherapy; however, they may have a role in ablation of residual high-risk tissue when combined with mucosal resection. Further research exploring specific combinations of ablative modalities with mucosal resection may shed light on the most effective treatment plan.

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