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Review Article

Esophageal cancer: Recent advances in screening, targeted therapy, and management

Puja Gaur[1,2,*], Min P. Kim[1,2], Brian J. Dunkin[2]

Departments of [1]Thoracic and [2]General Surgery, Weill Cornell Medical College of Cornell University, Houston Methodist Hospital, 6550 Fannin Street, Suite 1661, Houston, TX 77030, USA

E-mail: pgaur@houstonmethodist.org
*Corresponding author

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Abstract

The incidence of esophageal cancer remains on the rise worldwide and despite aggressive research in the field of gastrointestinal oncology, the survival remains poor. Much remains to be defined in esophageal cancer, including the development of an effective screening tool, identifying a good tumor marker for surveillance purposes, ways to target esophageal cancer stem cells as well as circulating tumor cells, and developing minimally invasive protocols to treat early-stage disease. The goal of this chapter is to highlight some of the recent advances and ongoing research in the field of esophageal cancer.

Keywords: Barrett's, cancer stem cells, carcinogenesis/tumorigenesis, dysplasia, esophageal cancer, targeted therapy

INTRODUCTION

Esophageal cancer remains one of the most fatal cancers worldwide with its incidence on the rise. In 2014 alone, esophageal cancer will affect over 18,000 people across the United States and almost 15,500 will succumb to this disease.[1] Despite clinical advances in the field of oncology, esophageal cancer remains one of the leading causes of cancer-associated mortality. The overall 5-year survival rate for all patients with esophageal cancer is no better than a mere 20%.[2] Understanding and identifying risk factors of esophageal cancer along with the development of improved screening and early detection techniques can potentially impact its diagnosis and therefore allow early intervention. However, due to its aggressive nature and poor response to chemotherapy, esophageal cancer remains a challenging disease to treat. Diagnosing esophageal cancer at an early stage would indeed yield a higher resectability rate due to earlier diagnosis and improved overall disease-specific survival. The goal of this chapter is to highlight pathogenesis of esophageal cancer and the recent advances in screening, diagnosis, and management of esophageal cancer.

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SCREENING ESOPHAGEAL CANCER

Currently, there is no standard for screening patients with esophageal cancer. Like annual mammograms and frequent colonoscopies have made a considerable difference in earlier detection of breast and colorectal cancer respectively, a screening esophageal test could potentially impact esophageal cancer. Screening endoscopies (i.e., esophagogastroduodenoscopy) and endoscopic ultrasound (EUS) have been proposed by clinicians numerous times in addition to Seattle protocol to serve as screening tools;[3,4] however, these have yet to become

standard of care. Additionally, the cost of healthcare to screen every patient with gastroesophageal reflux (GERD) and/or dysphagia would not be cost-effective given the incidence of the disease and the number of patients needed to be screened to diagnose one patient with esophageal cancer; although no study has ever been published on this very subject.

Since adenocarcinoma is known to primarily affect patients with GERD resulting in intestinal metaplasia and squamous cell carcinoma (SCC) is known to primarily affect patients with achalasia, victims of caustic ingestion, diet rich in processed foods, and smokers especially in the setting of alcohol consumption, it may indeed be prudent to target this cohort of patients and subject them to undergo routine surveillance endoscopies. However, the risk of developing esophageal cancer *de novo* without evidence of Barrett's remains as high as 90%, thus questioning how to identify the bulk of the patients with adenocarcinoma.[5,6] Additionally, recent studies have demonstrated that while screening endoscopy can be performed on patients with GERD, the risk of developing adenocarcinoma in a patient with negative screening endoscopy is very low, such that routine follow up endoscopies is not necessary.[7,8] Nonetheless, there is a reported 7.8% inaccuracy rate of endoscopy missing esophageal cancer during endoscopy.[9] Thus, no routine endoscopic surveillance strategy has been established for esophageal cancer.

Multiple studies have now demonstrated other endoscopic modalities such as the use of narrow band imaging and chromoendoscopy to be very effective in detecting these preneoplastic lesions with a higher diagnostic yield of 34% or more compared to standard white-light endoscopy.[10,11] Other features of endoscopy such as chromoendoscopy (where use of various contrast agents including methylene blue, acetic acid, Lugol solution, and indigo carmine), autofluorescence, and confocal laser endomicroscopy have been popularized to be complementary tools to identify early mucosal dysplastic changes.[12-14] Despite all these studies, no cost-effective screening method has been proposed to make the diagnosis of dysplastic changes early.

PATHOGENESIS OF ESOPHAGEAL CANCER

There are two main types of esophageal cancer, adenocarcinoma and SCC. The most common type of esophageal cancer in United States is adenocarcinoma which typically develops in the lower esophagus evolving along a spectrum of metaplasia (Barrett's) whereby esophageal squamous cells undergo metaplasia and degenerate into columnar epithelium, eventually progressing to low-grade dysplasia to high-grade dysplasia and eventually to invasive cancer. This progression is thought to be due to either acid or bile exposure of the lower esophagus due to reflux. However, routine use of proton-pump inhibitors (PPIs) and antireflux surgery for patients with GERD have not been reported to decrease the incidence of esophageal cancer either,[15] and likewise no real preventive measures can be proposed to reduce the incidence of esophageal cancer besides avoiding alcohol, tobacco, and GERD/obesity.[16] Although the pathogenesis of esophageal adenocarcinoma is better understood, the pathogenesis of SCC is less understood and less clearly defined. Hypothesis exists regarding exposure to tobacco and alcohol leading to malignant changes of SCC. The role of human papilloma virus has been questioned,[17] but so far has been demonstrated to be less likely. And for these reasons and unclear etiology, it has been difficult to target tumor progression.

Several agents have been proposed to affect the incidence of developing esophageal cancer. A recent study by Singh *et al*. proposed the use of statin to result in a 28% risk reduction for developing esophageal cancer.[18] Indeed, several medical cocktails involving a concoction of cyclooxygenase (COX) inhibitors, statins, and PPIs (albeit controversial) have been published demonstrating a significant relative-risk reduction of up to 0.64.[19] Unfortunately, since the mechanism of developing esophageal SCC is less clearly defined, that field of tumor progression remains unchartered ground.

BIOLOGICAL PATHWAYS AND TUMOR MARKERS

There have been significant advancements in unraveling the molecular pathogenesis of Barrett's dysplasia, such as the role of bile acids in the induction of several cellular signaling pathways (COX-2, Wnt, Notch, transforming growth factor-β, Sonic hedgehog, and bone morphogenetic protein) and the involvement of transcription factor CDX-2 leading to columnar differentiation.[20-22] Both receptor tyrosine kinase and nontyrosine kinase signaling pathways have been implicated to play a role in Barrett's esophagus and development of esophageal cancer. For example, the Sonic Hedgehog pathway is known to be upregulated in esophagus exposed to gastric acid and bile and is associated with chemoresistance,[23,24] thus making it a promising target for the future. Similarly, the Wnt signaling pathway, which comprises of multiple extracellular ligands that trigger a cascade resulting in activation of beta-catenin, which then translocates into the nucleus and activates transcription of growth-promoting genes, is known to play an active role in Barrett's esophagus.[25] While different strategies have been proposed to deactivate the Wnt pathway (such as administering excess ligand binding domain Frizzled or Dickkopf protein) and a small molecular Wnt inhibitor named pyrivinium has been approved by the Federal Drug

Administration (FDA) for cardiac remodeling, it has not been approved for targeting tumor progression.[26]

Despite aggressive attempts at identifying tumor marker specific to esophageal cancer, no marker has been identified that can be used universally to monitor tumor recurrence. Several studies have explored and suggested circulating IgG antibody levels to p16 protein,[27] CD25,[28] and FOXP3[29] to serve as biomarkers for early diagnosis of esophageal cancer. Historically, p53 antibody level, SCC-antigen, CYFRA21-1, and carcinoembryonic antigen (CEA) have been proposed to be potential tumor markers,[30,31] however none of them have panned out to be as good markers as CEA is to colorectal cancer, CA19-9 to pancreatic cancer, and prostate-specific antigen to prostate cancer.

TARGETED THERAPY FOR ESOPHAGEAL CANCER

At the current time, there are only a handful of FDA-approved biological agents that are used to treat esophageal cancer, albeit with limited response. Human epidermal growth factor receptor 2 (HER 2) pathway has been implicated to play a role in advanced gastric or gastroesophageal cancer, and although a randomized study did show a significant tumor response with trastuzumab, a monoclonal antibody against HER 2 ($P = 0.0046$), the survival was only improved by 2.7 months in the trastuzumab plus chemotherapy arm compared to the chemotherapy alone arm.[32]

Another recent randomized, international, multicenter phase III study (REGARD) has proposed ramucirumab (anti-vascular endothelial growth factor [VEGF] receptor 2) to be a potential biological agent used to treat advanced gastric or gastroesophageal junction adenocarcinomas; however, when looked closely, the study concludes the median overall survival to improve by a mere 1.4 months (5.2 vs. 3.8 months in the ramucirumab vs. placebo group; P 0.047).[33] This suggests that esophageal cancer remains one of the most chemo and biological therapy resistant cancers. Targeting the various proto-oncogenic pathways, tumor suppressor genes, mismatch repair genes, and mitotic checkpoints can all hypothetically halt tumor progression. However, inhibition of neither the epidermal growth factor receptor, VEGF, or mammalian target of rapamycin (mTOR) pathway have made a significant clinical impact in the field of esophageal cancer.[34] Continued research is warranted.

IMMUNOBIOLOGY/THERAPY

For years, scientists have questioned how and why does cancer evade the immune system. Extensive research in melanoma has demonstrated the role of T-cell signaling and how tumor cells have multiple mechanisms to turn the immune system off. Therapies targeting the immune system to turn it back on have now shed a new light on treating patients with melanoma, whereby long-term remission is gained in patients with response. Ground-breaking research at MD Anderson has now demonstrated how inhibition of anticytotoxic T-lymphocyte antigen 4 receptor can allow the immune system to evade cancer, thus resulting in establishing a "vaccine against melanoma".[35] A similar search in other solid organ cancers such as the esophagus is much needed and timely warranted.

CANCER STEM CELLS AND CIRCULATING TUMOR CELLS

Extensive research suggests that unlike most cancer cells within a tumor, cancer stem cells (CSCs) are a fraction of cells that harbor potential to regenerate tumors (i.e., tumorigenicity), develop chemoresistance, and migrate. Research continues to target this CSC population specific to each type of cancer in order to make them more chemo and radiosensitive and inhibit their potential to undergo proliferation, epithelial-mesenchymal transition (EMT) thus decreasing the incidence of metastases, and develop chemoresistance.[36] Targeted therapy against CSCs can inhibit tumor proliferation, migration and therefore development of metastases (EMT pathway). While this research has shed light on different pathways that are differentially regulated on stem cell population versus nonstem cell population, it is much limited on esophageal cancer. Metformin, antidiabetic medication, targets mitogen-activated protein kinase pathway and sensitizes the CSCs and mTOR pathway in esophageal cancer, therefore offering new class of biological agents.[37] Skinner *et al*. suggested that patients with esophageal adenocarcinoma and on metformin had a better response to chemoradiation therapy than those who were not on metformin.[38]

In esophageal cancer, most patients succumb to the disease not due to localized tumor burden, but instead to metastatic disease. The role of circulating tumor cells and circulating endothelial cells has, therefore, been questioned and is currently being explored in esophageal cancer.[39]

MANAGEMENT OF ESOPHAGEAL CANCER

Once the diagnosis of esophageal cancer is made, patient needs to be staged to determine the next step of treatment. The tumor (T), node (N), and metastasis (M) staging system as established by the American Joint Committee on Cancer in 2010 is the universally used system whereby the T-stage of the esophageal tumor is determined by esophageal wall invasion, N is determined by number of regional lymph

nodes involved, and M is dependent on distant metastasis. Once a suspicious nodule is diagnosed to have any invasive cancer, it is screened for depth of invasion to determine the T-stage of the tumor. EUS has become the most commonly used modality to determine the T- and N-stage of an esophageal lesion most accurately,[40] compared with computed tomography and positron-emission tomography scans which are better modalities to evaluate distant extent of metastases and regional invasion.[41,42] This preclinical staging allows the oncologist as well as the surgeon to guide their individualized plan of action for each patient.

Endoscopic therapy for early stage cancer: T1a

While the use of thoracoscopy and laparoscopic instruments have allowed esophagectomy to now become a minimally invasive surgery, endoscopy, and endoscopic instruments have offered a different armamentarium to attack esophageal cancer. Endoscopic resection is quickly becoming a universally-accepted strategy for early stage esophageal lesions. Patients with focal Barrett's, localized dysplasia, and/or T1a cancers can be treated with endoscopic mucosal resection (EMR), which involves saline injection into the submucosal layer thus allowing the mucosa to get lifted away and then removed using an endoluminal band.[43,44] Endoscopic submucosal dissection is essentially an extension of EMR that involves a larger field of en-bloc resection thus resulting in a higher proportion of patients with complete resection and negative margins.[45] It avoids piecemeal resection of EMR that can result in gaps and potential for leaving neoplastic tissue behind. Perforations, subsequent stricture development, risk of tumor recurrence, and the establishment of surveillance protocols are some of the issues that have risen from these lesser interventional procedures.[44,45] Radiofrequency HALO treatment (with the BARRx device, BARRX Medical, Sunnyvale, CA, USA) is also another endoscopic option for patients with long-segment Barrett's or low-grade dysplasia where ablative energy is delivered to the esophageal mucosa thus eradicating the atypical cells up to the muscularis mucosa.[46] However, patients with high-grade dysplasia and/or invasive carcinoma involving the submucosa or beyond are not candidates for BARRX as they have a high reported failure rate given the risk of lymphatic spread and nodal involvement.

Management of advanced disease: T1b-T4, nodal disease

Surgical resection for T1b and some T2 lesions remains the standard of care. On the other hand, advanced cancer patients with T2-T4 tumors or nodal positivity are first treated with induction therapy followed by surgical resection if the tumor demonstrates a favorable response. Treatment of T2 lesion remains controversial amongst clinicians.

CONCLUSION

Despite all these advancements, clinical management of esophageal cancer remains challenging. From identifying tumor markers to defining a standard screening protocol to formulating an effective neoadjuvant or adjuvant chemoradiation/biological therapy regimen – all remains yet unestablished. However, with little known, much remains unknown and thus there remains a vast potential for research.

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AUTHOR'S PROFILE

Dr. Puja Gaur: Departments of Thoracic and General Surgery, Houston Methodist Hospital, 6550 Fannin Street, Smith Tower, Suite 1661, Houston, TX 77030, USA

Dr. Min P. Kim: Interim Head of Thoracic Surgery, Assistant Professor of Surgery, Departments of Thoracic and General Surgery, Weill Cornell Medical College, Houston Methodist Hospital, 6550 Fannin Street, Suite 1661, Houston, TX 77030, USA.

Dr. Brian J. Dunkin: Department of Surgery, Weill Cornell Medical College, Houston Methodist Hospital, 6550 Fannin Street, Suite 1661, Houston, TX 77030, USA.