PET/Computed Tomography Scanning and Precision Medicine

Esophageal Cancer

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KEYWORDS

• Esophageal cancer • Esophageal carcinoma • PET • PET/CT • FDG PET/CT

KEY POINTS

- National Comprehensive Cancer Network guidelines recommend PET with fluorine-18 fluoro-2-deoxy-D-glucose/computed tomography (FDG PET/CT) scanning at baseline staging for exclusion of distant metastatic disease to prevent unnecessary interventions.
- FDG PET/CT scanning can predict neoadjuvant chemoradiotherapy assessment and survival outcome of patients who undergo subsequent surgical resection.
- FDG PET/CT scanning is valuable in detecting recurrences and metastases in follow-up.

INTRODUCTION

Esophageal malignancy ranks sixth among cancer deaths worldwide.[1] The 2 major histologic types of esophageal cancer—adenocarcinoma (AC) and squamous cell carcinoma (SCC)—are known to differ greatly in terms of risk factors and epidemiology. In 2012 alone, an estimated 398,000 SCCs and 52,000 ACs of the esophagus were diagnosed, translating to incidence rates of 5.2 and 0.7 per 100,000, respectively.[2] However, over the past 3 decades, the rates of SCC have declined, whereas those of AC have been progressively increasing.[3] There is a significantly high concentration of AC in high-income countries in North America and Europe, with gastroesophageal reflux disease and obesity being the principal risk factors.[2] SCC remains the predominant esophageal cancer in Asia, Africa, and South America as well as among African Americans in North America. Alcohol and tobacco use are the main risk factors, with esophageal squamous dysplasia identified as the precursor lesion.[4] The incidence of esophageal carcinoma increases with age, peaking in the seventh and eighth decades of life. Men are at 3 to 4 times higher risk for AC as compared with women. However, the sex distribution is more similar for SCC. Esophageal malignancies continue to have a particularly poor prognosis because early

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disease typically causes no symptoms and are diagnosed later in their course.[4] More than one-half of cases (ACC or SCC or both) present with distant metastases or unresectable disease. Although the 5-year survival has been increasing over time, it remains at a dismal 18%.[5]

Owing to its poor prognosis, the development of clinically applicable biomarkers for diagnosis, therapy response, and recurrence detection has been the focus of many research studies. Although advances in molecular biology and bioinformatics have led to an improved understanding of esophageal cancer genetics, its in-depth molecular characterization remains an enigma.[6] In today's emerging era of precision medicine, a better understanding of individual variability in environment, lifestyle, and genetics may help in tailoring precise management approaches. Imaging could be a major component of such an assessment technique. This review summarizes the recent molecular advances in esophageal cancer highlighting the role of molecular and functional imaging including PET with ^{18}F-flourodeoxy glucose and computed tomography (FDG PET/CT) scanning and novel PET tracers in characterizing specific molecular mechanisms for therapy selection and its follow-up response assessment.

GENOMICS

Squamous Cell Carcinoma

Tremendous progress has been made in cancer genomics in the recent past with the advent of high-throughput techniques like next-generation sequencing. However, the full repertoire of molecular events detailing the pathogenesis of SCC remains unclear. The genetic landscape of human SCC with whole-genome, exon sequencing and array-based comparative genomic hybridization has been reported.[7,8] These studies found the highest frequency of mutation in TP53, proposing mutation of TP53 as a key factor in the development of SCC. Another common genetic polymorphism noted in SCC is SOX2 polymorphism, which is an amplified lineage-survival oncogene in SCC.[9] This transcription factor is overexpressed and amplified in a subset of squamous epithelial cells of SCC, and is associated with higher histologic grade and poor survival in SCC.[10]

Other tumor-associated genes, such as RB1, CDKN2A, PIK3CA, NOTCH1, NFE2L2, ADAM29, and FAM135B, have been implicated.[8] Notably, FAM135B is identified as a novel cancer-implicated gene as assayed for its ability to promote malignancy of SCC cells. Additionally, MIR548K, a miRNA (microRNA) encoded in the amplified 11q13.3 to 13.4 region, is characterized as a novel oncogene, and functional assays demonstrate that MIR548 K enhances malignant phenotypes of SCC cells.

Epidermal growth factor receptor (EGFR) signaling pathways are also considered to be involved in the development of SCC. It is reported to be overexpressed in 60% to 76% of SCCs and is associated with a poor prognosis.[11,12] Genomic alterations of several important pathways, including Wnt, cell cycle, Notch, RTK–Ras, and AKT pathways are detailed in **Fig. 1**.

Adenocarcinoma

The natural history of AC is poorly understood; however, it is well-known that most of these cases arise on a background of Barrett esophagus. Barrett esophagus is a readily detectable premalignant precursor and occurs when there is metaplastic transformation of stratified squamous esophageal epithelium to the intestinal epithelium, which ultimately turns into AC.[13,14] This unique feature of AC makes it a prime candidate for the exploration of novel approaches to early diagnosis (**Fig. 2**), including a combination of genomics, transcriptomics, and microbiomics, which might lead to a personalized risk stratification approach for each patient, enabling time for early intervention.

Both Barrett esophagus and AC seem to have substantial overlap in the set of genes contributing to risk of each condition.[15,16] However, genetic risk factors contributing specifically to Barrett esophagus or esophageal AC alone might also exist. So far, genome-wide association studies have identified 4 loci within or near MHC, namely, *FOXF1*, *GDF7*, and *TBX5*, associated with the development of Barrett esophagus, and 4 additional loci within or near *CRTC1*, *BARX1*, *FOXP1*, and *ALDH1A2* associated with the development of both Barrett esophagus and AC.[17,18] However, no specific marker for AC has been identified.

Both Barrett esophagus and AC are characterized by loss of heterozygosity, aneuploidy, specific genetic mutations, and clonal diversity. Epigenetic as well as DNA methylation abnormalities are also frequently seen in AC.

Somatic genomic alterations

Somatic genomic alterations in AC, including recurrent amplifications, deletions, and single nucleotide variants, have been demonstrated at the loci of a number of novel as well as established oncogenes involved with cell signaling (*EGFR, ERBB2, KRAS, MET, FGFR2*), the cell cycle (*CCND1, CDK6* and *CCNE1*), and transcription factors (*MYC, GATA4* and *GATA6*).[19–24] Aneuploidy and oncogene activation seem to be