

Optimal Use of Combined Modality Therapy in the Treatment of Esophageal Cancer

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KEYWORDS

• Esophageal cancer • Chemoradiation • Trimodality • IMRT • Esophagectomy

KEY POINTS

- Esophageal cancer continues to be associated with poor treatment outcomes despite significant advances in treatment technique.
- There has been an increasing incidence of esophageal adenocarcinoma and decreasing esophageal squamous cell carcinoma owing to changes in diet and lifestyle factors.
- Owing to the adoption of endoscopic surveillance, there has been an increasing incidence of early stage esophageal cancer with potential treatment options including endomucosal therapy, esophagectomy, or chemoradiation.
- Trimodality therapy consisting of neoadjuvant chemoradiation followed by esophagectomy is the preferred treatment option for patients with locally advanced esophageal cancer.

EPIDEMIOLOGY

Esophageal cancer is the sixth most common cancer diagnosis in the world with more than 450,000 patients diagnosed each year.¹ Although squamous cell carcinoma is the most common histology globally, adenocarcinoma is the most common histologic diagnosis in the United States. Despite significant advances in treatment techniques as well as the introduction of newer chemotherapy and targeted biologic agents, prognosis remains poor with 5-year survival rates of approximately 15% to 20%.^{2,3} When examining outcomes according to stage, patients with clinically localized disease have a 5-year survival of nearly 40% versus only 4% in patients with metastatic disease. Over the past decade, the use of endoscopic screening has increased the number of early stage cancers diagnosed each year, yet approximately one-third of patients are still diagnosed with advanced disease.³

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RISK FACTORS

Risk factors for the development of esophageal cancer are provided in **Table 1**. Esophageal cancer peaks in late adulthood (60–70 years of age), and the incidence varies greatly according to gender, geography, and ethnicity. In general, esophageal cancer is diagnosed more commonly in males, although the patterns in diagnosis vary by geographic area. When examining histology, squamous cell carcinoma is far more common in black patients, and adenocarcinomas are more commonly seen in white patients.

The incidence of esophageal adenocarcinoma has increased dramatically in the United States over the past several decades, while the incidence of squamous cell carcinoma has been decreasing (**Fig. 1**).^{4–6} The increase in esophageal adenocarcinoma has been attributed to changes in diet, with increased intake of high-fat foods and a decrease in fruit and vegetable consumption.⁷ Gastroesophageal reflux disease has been linked to esophageal adenocarcinoma (but not esophageal squamous cell carcinoma) in multiple population-based series.^{8,9} A large metaanalysis suggested that weekly symptoms of gastroesophageal reflux disease resulted in a dramatic increase in the risk for esophageal adenocarcinoma (odds ratio, 4.92; 95% confidence interval, 3.90–6.22) compared with asymptomatic controls.¹⁰ The decrease in squamous cell carcinoma incidence is likely owing to decreasing rates of smoking and alcohol use.

Barrett's esophagus is defined as a change in the normal squamous epithelium of the distal esophagus to a columnar type, with the classic appearance of a salmon-colored mucosa and the presence of goblet cells. These changes are thought to occur owing to a chronic inflammatory state that increases the risk for the development of esophageal adenocarcinoma. Patients diagnosed with Barrett's esophagus have 11 times the risk of developing esophageal cancer versus those without Barrett's. A large series from the Netherlands examined a cohort of 42,207 patients and found a risk of 0.4% of developing esophageal cancer with a history of Barrett's.¹¹ This study clearly illustrates that, although the risk of esophageal cancer in patients with Barrett's is high relative to the general population, it is still relatively low.

Patients found to have Barrett's esophagus typically undergo surveillance esophagogastroduodenoscopy owing to the increased risk of esophageal cancer. Typically, it is recommended that patients with Barrett's undergo esophagogastroduodenoscopy every 3 to 5 years with standardized sampling and methodological documentation of the extent of disease. When a high-grade dysplastic lesion is identified, patients may undergo either endoscopic mucosal resection (EMR) or surgical resection. There is wide variation in the incidence of esophageal adenocarcinoma in this setting, ranging from 0% to 3.5% per year.¹²

Table 1
Risk factors associated with development esophageal cancer

Adenocarcinoma	Squamous Cell Carcinoma
Obesity	Socioeconomic class
Smoking	Nitrosamine
Gastroesophageal reflux disease	Polyaromatic hydrocarbons
Barrett's esophagus	Tobacco smoking
Family history	Poor oral hygiene
	Family history
	Alcohol

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