

The Role of Induction Therapy for Esophageal Cancer



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KEYWORDS

• Esophageal neoplasms • Induction therapy • Esophagectomy

KEY POINTS

- Induction therapy before esophagectomy has been extensively investigated and increasingly used, and may be partially responsible for the recent improvements noted for the prognosis of esophageal cancer.
- Induction therapy does not seem to have a role for superficial cancers without lymph node involvement, but several randomized trials found a benefit for more locally advanced but resectable tumors.
- Induction chemoradiation is recommended before esophagectomy for locally advanced squamous cell carcinoma.
- Both induction chemotherapy and induction chemoradiation are found to be beneficial for locally advanced adenocarcinoma. Neither strategy has a clear advantage, but consensus-based guidelines currently recommend induction chemoradiation for this clinical scenario.

INTRODUCTION

The incidence of esophageal cancer is increasing, with an estimated 16,980 new cases in the United States in 2012.^{1–4} Esophageal cancer staging is currently defined by the most recent seventh edition American Joint Committee on Cancer (AJCC) TNM Staging System (**Table 1**), which classifies Barrett's esophagus with high-grade dysplasia as T_{is} and also stages esophagogastric junction (EGJ) tumors, defined as those tumors arising at the EGJ or in the cardia of the stomach within 5 cm of the EGJ that extend into the EGJ or esophagus, as esophageal cancers.⁵ Surgery with esophagectomy is considered the standard of care for localized disease and is the best single-modality therapy for potentially resectable disease. Overall 5-year survival for patients with esophageal cancer is generally poor, although improvement has been observed over time with

an increase from 5% to 17% to 19% over the last 4 decades.^{2–4} These survival improvements have likely partly resulted from earlier detection in the setting of Barrett's esophagus and improvements in perioperative care. However, the recently improved prognosis is also likely partially caused by the demonstration of the benefits and the subsequent use of multimodality therapy for specific stages of esophageal cancer.

The poor survival rate after esophagectomy alone for patients with locally advanced but not metastatic disease led to many studies of multimodality therapy in efforts to improve outcomes.⁶ The use of chemotherapy and radiation therapy has been investigated in the preoperative and postoperative settings. Adjuvant therapies, with either chemotherapy or radiotherapy, have not shown survival benefits.⁷ However, induction therapy used before esophagectomy has been

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Table 1
T, N, and M status and histologic grade definitions for esophagus and esophagogastric junction cancer in the seventh edition of the AJCC Cancer Staging Manual

T Status	
T _{is}	High-grade dysplasia
T1	Invasion into the lamina propria, muscularis mucosae, or submucosa
T2	Invasion into muscularis propria
T3	Invasion into adventitia
T4a	Invades resectable adjacent structures (pleura, pericardium, diaphragm)
T4b	Invades unresectable adjacent structures (aorta, vertebral body, trachea)
N status	
N0	No regional lymph node metastases
N1	1–2 positive regional lymph nodes
N2	3–6 positive regional lymph nodes
N3	7 or more positive regional lymph nodes
M status	
M0	No distant metastases
M1	Distant metastases
Histologic grade	
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

hypothesized to potentially downstage and control local and micrometastatic disease and, therefore, be more beneficial than adjuvant therapy. This hypothesis is partly supported by the belief that chemotherapy and radiation are better tolerated before rather than after esophagectomy. In addition, the use of induction therapy may allow potentially morbid surgery to be avoided in patients with unfavorable biology who show progression of disease through induction therapy.

Many studies have investigated the use of induction therapy before esophagectomy for esophageal cancer. Not all of these studies found a benefit to induction therapy, but several did, and induction therapy is currently used in most patients who have locally advanced esophageal cancer.⁸ This article reviews the evidence and guidelines related to the use of either chemotherapy or radiation therapy before esophagectomy for esophageal cancer.

ROLE OF INDUCTION THERAPY

Surgery is considered integral to achieving cure in patients with esophageal cancer.^{9–11} Randomized

trials comparing surgical versus nonsurgical treatment have not been performed, but a study from the linked Surveillance, Epidemiology, and End-Results (SEER)-Medicare database found that 5-year survival rates for patients with stages I through III esophageal cancer treated with and without surgery were 28% and 10%, respectively.¹⁰ Although these data may reflect a selection bias in which surgically treated patients had better survival because they were younger and healthier, definitive chemoradiation is generally reserved for those patients who refuse surgery or are not surgical candidates.¹² The only area of esophageal cancer in which definitive chemoradiation is recommended in place of surgical resection is squamous cell carcinoma of the cervical esophagus.^{12,13} Some data suggest that definitive chemoradiation could be adequate for some patients with squamous cell carcinoma in other esophageal locations, but surgery is considered integral to potential cure for adenocarcinoma in which pathologic complete response rates are generally less common.^{14–16}

However long-term outcomes are generally not considered satisfactory with resection alone, even if microscopically complete (R0), except for early-stage superficial cancers without lymph node involvement.¹⁷ These poor outcomes have fueled many investigations into the use of induction therapy to try and improve survival. As will be discussed in detail later, many studies failed to show a definitive benefit to induction therapy, and the level of evidence supporting the use of induction therapy remains somewhat limited. Despite the limited evidence, the use of induction therapy has been supported by meta-analyses and remained an active area in research, with additional trials being performed, and in clinical practice.^{18,19} The use of induction chemoradiation in the United States steadily increased from 2003 to 2011, which was a period in which published studies supporting the practice were generally limited in number.⁸

A complicating feature of establishing the optimal treatment for esophageal cancer is the heterogeneous nature of this disease. Squamous cell carcinoma was historically the most common histology seen with a location somewhat evenly distributed throughout the distal two-thirds of the esophagus. Epidemiologic shifts in the last few decades have led to adenocarcinomas of the distal esophagus or EGJ to be the most common clinical entity of esophageal cancer seen in the United States.²⁰ Patients with adenocarcinoma and squamous cell carcinoma were observed to have similar long-term survival across major treatment modalities, and treatment guidelines

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