Chemoradiation for Esophageal Cancer

Mariela A. Blum, MD[a], Takashi Taketa, MD[a], Kazuki Sudo, MD[a], Roopma Wadhwa, MD[a], Heath D. Skinner, MD, PhD[b], Jaffer A. Ajani, MD[a,*]

KEYWORDS

• Esophageal carcinoma • Definitive chemoradiation • Radiotherapy • Multimodality therapy

KEY POINTS

- There is a subset of esophageal cancer patients who seem to benefit from definitive chemoradiation. Selection of such patients improves with the multidisciplinary interactions with colleagues of all relevant disciplines on a regular basis.
- Identifying patients with high probability of a complete pathologic response (pathCR) through predictive models that can incorporate clinical parameters and biomarkers is challenging and is an area of active research.
- In the future, better understanding of the molecular biology involved in response should lead to rationally designed clinical trials targeting those patients who are at risk for treatment failure.

INTRODUCTION

Globally, esophageal cancer (EC) is the sixth leading cause of cancer death, with an estimated 482,000 new cases and 407,000 deaths in 2008.[1,2] The diagnosis of EC heralds an ominous prognosis, as more than half of the patients have advanced or inoperable disease. Because screening strategies are not well developed, EC is often diagnosed in symptomatic patients; thus, only 30% of patients will have localized disease at diagnosis,[3] and the overall 5-year survival for those able to undergo resection is approximately 47%, with even worse survival rates in those patients unable to undergo primary resection.[4] The 5-year survival rates for localized EC (LEC) have improved recently, owing to the addition of preoperative treatment and better management of morbidities resulting from surgery.

The 2 most common histologic subtypes of EC are squamous cell carcinoma, most prevalent in the Caspian littoral and China,[5,6] and adenocarcinoma, increasing in incidence in the western countries since 1970.[7,8]

The treatment of LEC is challenging. Factors involved in the treatment decision include baseline clinical stage, location of the primary, and, in some instances, histology. Some geographic variations in approach are evident based on the patterns of practice, and likely reflect bias due to the body habitus of the patient population, age, and the dominant histology. Associated comorbid conditions are often incorporated in the decision-making process for the recommendation of a specific therapy. Among many prognostic factors, lymph node involvement carries the highest impact in prognosticating survival.[9] Historically, surgical resection of LEC has been the most

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[a] Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA; [b] Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA

* Corresponding author. The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 426, Houston, TX 77030.

E-mail address: jajani@mdanderson.org

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common primary approach, but in most patients, primary surgery results in dismal outcomes.[10]

Over the last several years, several clinical trials have been completed in EC. Preoperative chemotherapy and preoperative chemoradiation have been the predominant strategies to improve surgical outcome, while bimodality treatment (definitive chemotherapy and radiation) has been reserved for patients with cervical tumors or patients with LEC who are medically inoperable or have technically unresectable disease.

The purpose of this article is to discuss the representative published data forming the basis of contemporary recommendations for LEC.

Definitive Chemoradiotherapy Versus Radiotherapy Alone

Based on the encouraging data using concurrent chemoradiation in patients with anal cancer,[11] several prospective studies have been carried out in EC.[12–21] Chemotherapeutic agents have often been added to radiotherapy in the preoperative setting with the expectation of improved outcome. However, the addition of chemotherapy increases the toxicity of the treatment. Chemotherapy drugs most commonly used as radiosensitizers include fluoropyrimidines, taxanes, and platinum compounds.[22–25]

One of the first studies by Steiger and colleagues[26] combined 5-fluorouracil (5-FU) and mytomycin C or cisplatin with radiation therapy (50–60 Gy) in the preoperative setting in EC and observed a pathCR rate of 37% and a 2-year survival rate of 30%. Additional similar phase 2 trials followed, confirming the possible benefit to this therapeutic approach.[12–14] Subsequently, randomized trials evaluated the benefit of concurrent and sequential chemoradiation versus radiation alone (**Tables 1–3**), culminating in a prospective randomized phase 3 trial that documented the benefit of chemoradiation over radiation alone. In this study, conducted by the Radiation Therapy Oncology Group (RTOG),[17] 121 patients with EC

Table 1
Randomized trials of definitive chemoradiation versus radiotherapy

Study	Number of Patients	Histology	Treatment	Survival	Survival Difference (*P*)
Andersen et al,[50] 1984	82	SCC	RT (63 Gy) vs CT (Bleomycin) + RT (55 Gy)	2 y 11.9% 12%	.80
Araujo et al,[15] 1991	59	SCC	RT (50 Gy) vs CT (5-FU, MM, Bleomycin) + RT 50 Gy	5 y 6% 16%	NS
Cooper et al,[17] 1999	121	SCC/AC	RT 64 Gy vs CT (5-FU + CDDP) RT (50 Gy)	5 y 0% 26%	*P*<.001
Earle et al,[51] 1980	91	SCC	RT (50 or 60 Gy) vs CT (Bleomycin) + RT 50 Gy	5 y <8%	NS
Kaneta et al,[52] 1997	24	SCC	RT (60 Gy) CT (CDDP) + RT (60 Gy)	NR	NS
Li et al,[53] 2000	96	Ca	RT (60–70 Gy) CT (CDDP + 5-FU) + RT (5–60 Gy)	5 y 4.1% 28.8%	S
Roussel et al,[54] 1994	221	SCC	RT (40 Gy) CT (CDDP) + RT (40 Gy)	NR	*P* = .17
Slabber et al,[55] 1998	70	SCC	RT 40 Gy CT (CDDP + 5-FU) + RT (40 Gy)	NR	NS
Zhang,[56] 1984	99	SCC/AC	CT (Bleomycin 10 mg IM × 2-3/d + RT 39–73 Gy) RT 73 Gy		NS

Abbreviations: 5-FU, 5-Fluourouracil; AC, adenocarcinoma; CDDP, cisplatin; CT, chemotherapy; EB, external beam; HDBT, high-dose brachytherapy; IM, intramuscular; MM, mitomycin; MTX, methrotrexate; NR, nonreported; NS, nonsignificant; RT, radiation therapy; S, significant; SCC, squamous cell carcinoma.
Data from Refs.[15,17,50–56]