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Radiation Therapy for Locally Advanced Esophageal Cancer

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KEYWORDS

Esophageal cancer • Radiation • Chemotherapy • IMRT • Dose-escalation

KEY POINTS

- General guidelines for treatment of locally advanced esophageal cancer include both preoperative and nonoperative approaches, predicated upon resectability, histology, and location.
- In patients with resectable disease who are medically fit for this procedure, pre-operative chemoradiation to 50.4 Gy, with consideration of a lower dose (41.4 Gy) based on the CROSS trial, is recommended.
- In non-operative patients, definitive chemoradiation to 50.4 Gy is standard; however, enrollment of these patients on dose-escalation or other protocols is encouraged.
- Clinicians should make use of all available imaging and diagnostic modalities to delineate tumor and involved lymphadenopathy.

OVERVIEW

Locally-advanced esophageal cancer (LAEC) is broadly defined as American Joint Commission on Cancer, version 7, clinical stage III or IVA (T3-4 and/or N+) disease. Therapeutic approaches commonly include preoperative concurrent chemotherapy plus radiation (chemoradiation) or definitive chemoradiation alone. There is controversy regarding the ideal therapeutic approach to this disease. The US Patterns of Care Study offers a historical perspective. A total of 414 patients (51%: adenocarcinoma and 49%: squamous cell carcinoma [SCC]) received radiation therapy as part of definitive or adjuvant management at 59 institutions from 1996 to 1999. 1.2 Overall, patients who received chemoradiation followed by surgery had a significant decrease in locoregional recurrence (hazard ratio [HR], 0.40, *P*<.0001) and survival improvement

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Surg Oncol Clin N Am ■ (2016) ■-■ http://dx.doi.org/10.1016/j.soc.2016.10.006 1055-3207/16/© 2016 Elsevier Inc. All rights reserved. (HR, 0.32, P<.001) compared with those who did not undergo surgery. A similar significant decrease in locoregional recurrence (HR, 1.36, P = .01) and survival (HR 1.32, P<.03) was seen in those patients who received their care at large radiation oncology centers (treating \geq 500 new patients with cancer per year) compared with small centers (treating <500 new patients with cancer per year).

In the current review, the authors discuss the management of inoperable esophageal cancer and review neoadjuvant chemoradiation, perioperative chemotherapy, and radiotherapy techniques.

DEFINITIVE THERAPY IN UNRESECTABLE LOCALLY ADVANCED ESOPHAGEAL CANCER Radiation Monotherapy

In LAEC, radiation therapy alone should be reserved for palliation or for patients who are medically unfit to receive concurrent chemotherapy. The 5-year survival rate for patients treated with conventional doses of radiation therapy alone is suboptimal. ^{3–5} In the landmark Radiation Therapy Oncology Group (RTOG) 85-01 trial in which patients were randomized to receive either 64 Gy at 2 Gy/d or chemoradiation, all patients who received radiation alone were all dead of disease by 3 years. ^{6,7} Shi and colleagues reported a 33% 5-year survival rate with the use of late course accelerated fractionation to a total dose of 68.4 Gy.

Primary radiation is more successful in patients with cT1N0 disease. Sai and colleagues⁹ from Kyoto University treated 34 patients who were either medically inoperable or refused surgery with either external beam alone (64 Gy) or external beam (52 Gy) plus 8 to 12 Gy with brachytherapy. The 5-year results included 59% overall survival, 68% local relapse-free survival, and 80% cause-specific survival. Yamada and colleagues¹⁰ reported the results in a similar group of 63 patients treated with chemoradiation plus brachytherapy. The 5-year results included 66% overall survival, 64% disease-free survival, and 76% cause-specific survival.

Brachytherapy Boost

Brachytherapy can be delivered by low- or high-dose rates and has previously been used as a boost following external beam radiation therapy or chemoradiation. 11–16 This technique is limited by the effective treatment distance. The primary isotope is Iridium 192 (Ir-192), which is usually prescribed to treat to a distance of 1 cm from the source. Therefore, as confirmed by pathologic analysis of treated specimens, any portion of the tumor that is greater than 1 cm from the source will receive a suboptimal radiation dose. 17

There does not appear to be an advantage of adding brachytherapy to external beam radiation. One series reported a local failure rate of 57% and a 5-year actuarial survival of 28% in 46 patients with stage T2-3N0-1M0 disease. ¹⁸ Even in patients with earlier stage disease (clinical T1-2), brachytherapy likely does not offer an advantage. Yorozu and colleagues ¹⁹ reported a local failure rate of 44% and a 5-year survival of 26%, and Pasquier and associates ²⁰ reported local failure of 23% and the 5-year survival of 36%. However, in an updated series by Ishikawa and colleagues, ²¹ 59 patients with submucosal esophageal cancer received external beam followed by brachytherapy in a subset of 36 patients with either low-dose-rate Caesium 137 (17 patients) or high-dose-rate Ir-192 (19 patients). Patients selected to receive a brachytherapy boost had a significantly higher 5-year cause-specific survival (86% vs 62%, P = .04).

Chemoradiation plus brachytherapy was tested prospectively by the RTOG Trial 9207. A total of 75 patients with cancers of the thoracic esophagus (92% squamous cell, 8% adenocarcinoma) received the RTOG 8501 50-Gy chemoradiation regimen

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