Treatment of Locally Advanced Esophageal Carcinoma: ASCO Guideline

Shah et al.
Introduction

- Within this guideline, the Expert Panel provides a review of recent evidence for these therapy options in locally advanced esophageal cancer and addresses ongoing areas of controversy, including where the addition of radiation to surgery and CT, i.e. trimodality therapy, is appropriate, as well as the addition of surgery to chemoradiation (CRT) in squamous cell carcinoma.

- The overall purpose of this guideline is to provide evidence- and consensus-based recommendations for treatment options for patients with locally advanced esophageal and Siewert I/II gastroesophageal junction adenocarcinoma who are candidates for resection.

- Results and recommendations are provided for specific histological subtype because of the differing risk factors, pathogenesis, prognosis after surgical resection, and pattern of lymph node metastases associated with adenocarcinoma and squamous cell carcinoma, respectively.¹
ASCO Guideline Development Methodology

The ASCO Clinical Practice Guidelines Committee guideline process includes:

• a systematic literature review by ASCO guidelines staff
• an Expert Panel provides critical review and evidence interpretation to inform guideline recommendations
• final guideline approval by ASCO Clinical Practice Guidelines Committee

The full ASCO Guideline methodology manual can be found at:
www.asco.org/guideline-methodology
Clinical Questions

This clinical practice guideline addresses the following clinical questions for patients with locally advanced esophageal cancer (≥T2 or N+, MO):

1. Is neoadjuvant or adjuvant therapy in addition to surgery recommended compared to surgery alone?

2. What is the preferred modality of neoadjuvant or adjuvant therapy for patients with locally advanced esophageal adenocarcinoma?

3. What is the preferred modality of neoadjuvant or adjuvant therapy for patients with locally advanced esophageal squamous cell carcinoma?
Target Population and Audience

**Target Population**
Patients with locally advanced esophageal adenocarcinoma or squamous-cell carcinoma.

**Target Audience**
Medical oncologists, radiation oncologists, surgeons, gastroenterologists.
Summary of Recommendations

CLINICAL QUESTION 1

Is neoadjuvant or adjuvant therapy in addition to surgery recommended compared to surgery alone?

Recommendation 1.

Multimodality therapy should be offered to patients with locally advanced esophageal carcinoma. (Type: Evidence-based; benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Note: Although outside the scope of recommendations for locally advanced esophageal cancer, the Expert Panel recommends that for patients with clinical earlier stage esophageal cancer (T2, N0), surgery alone may be considered after discussion with a multidisciplinary team. Within this group, surgery alone may be more appropriate for patients with low risk cT2NO lesions (i.e. well-differentiated, less than 2cm), and where there is a sufficient degree of confidence in the results of pretreatment staging.
Summary of Recommendations

**CLINICAL QUESTION 2**

What is the preferred modality of neoadjuvant or adjuvant therapy for patients with locally advanced esophageal adenocarcinoma?

*Recommendation 2.*

Preoperative chemoradiotherapy (CRT) or perioperative chemotherapy (CT) should be offered to patients with locally advanced esophageal adenocarcinoma. (Type: Evidence-based; benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

*Subgroup considerations:*

- For the subgroup of patients for whom surgery is not feasible, CRT without surgery is recommended.
- Preoperative CT should be considered for patients who are not candidates for radiation or postoperative chemotherapy.\(^5,6\)
- Postoperative complications may be more severe with CRT as compared to CT.\(^7\) Consider the potential for patient tolerance of the addition of RT based on tumor location and other factors.\(^8\)

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Subgroup considerations (continued):

- The addition of radiotherapy is expected to be more beneficial in the setting of less extensive surgery. Adequate quality and extent of surgery includes clear surgical margins and adequate nodal dissection within appropriate nodal fields, e.g. abdominal and thoracic, with a goal of obtaining at least 16 to 18, and preferably greater than 20 lymph nodes. Lymphadenectomy fields and extent of surgery will be affected by tumor location. Detailed recommendations for surgical approach are beyond the scope of this guideline.

**Note:** While outside the scope of the systematic review, the Expert Panel recognizes FLOT as the standard of care for perioperative chemotherapy in esophageal adenocarcinoma. The FLOT regimen includes four preoperative and four postoperative 2-week cycles of 50 mg/m² docetaxel, 85 mg/m² oxaliplatin, 200 mg/m² leucovorin and 2600 mg/m² fluorouracil as 24-h infusion on day 1. Where the FLOT regimen is not available or feasible, the Expert Panel suggests cisplatin-fluorouracil (CF; two 3-weekly cycles of cisplatin [80 mg/m² intravenously on day 1] and fluorouracil [1 g/m² per day intravenously on days 1–4]), or a similar platinum-based regimen.
Summary of Recommendations

CLINICAL QUESTION 3

What is the preferred modality of neoadjuvant or adjuvant therapy for patients with locally advanced esophageal squamous cell carcinoma?

Recommendation 3.

Preoperative CRT or CRT without surgery (definitive CRT) should be offered to patients with locally advanced esophageal squamous cell carcinoma. (Type: Evidence-based; benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).
Summary of Recommendations

Subgroup considerations:

- Historical studies suggest that in patients who respond completely to CRT, the addition of surgery may offer minimal benefit.\textsuperscript{13,14} In patients with squamous cell carcinoma who appear to have a complete response to CRT, the option of surveillance and salvage surgery upon progression may be considered, where salvage esophagectomy is practiced.\textsuperscript{15} At this time, a randomized controlled trial is exploring the question of surveillance and salvage surgery after CRT compared to planned surgery after CRT\textsuperscript{16} using the clinical assessment criteria established in the pre-SANO trial.\textsuperscript{17}

- In patients for whom radiation is not an option, preoperative CT (without radiation) may be considered.\textsuperscript{6}

- Definitive CRT is recommended for patients with tumors located in the cervical esophagus; surgery should be considered in the event of persistent or recurrent disease.

- While CRT and surgery are preferred, definitive CRT is an option for patients who cannot tolerate or choose not to undergo surgery.
Summary of Recommendations

*Practice Statement.*

For patients with esophageal squamous cell carcinoma, the decision to undertake surgery should be considered in the context of shared decision making, considering age, comorbidities, patient preference, caregiver support, and other factors. (Type: Consensus-based; Strength of recommendation: High).
Patient and Clinician Communication

- Given the number of potential therapeutic options that have been reviewed in this guideline, it is vitally important that the harms and benefits of each option are presented to patients and that patients’ values and preferences for treatment are explored and discussed.

- A practice statement has been provided following Recommendation 3, detailing that for patients with esophageal squamous cell carcinoma, the decision to undertake surgery should be considered in the context of shared decision making, taking into account age, comorbidities, patient preference, caregiver support, and other factors.

- A discussion of these factors also applies to decision-making for the other treatment options included in this guideline.
Discussion

- The management of locally advanced esophageal cancer has evolved with the changing epidemiology of the disease, improvements in staging, surgery, and radiation techniques.

- As a result, the management is often complex and confusing with multiple acceptable treatment strategies.

- Using a more selective evidence base, this systematic review and meta-analyses are supportive of the conclusions of previous reviews\(^1\) showing the significant benefit associated with neoadjuvant and adjuvant therapies; however, some controversy remains regarding the balance of benefits and harms associated with these treatment options.

- Thus, the Expert Panel advocates for an individualized approach to therapy among patients with locally advanced esophageal cancer, taking into consideration factors such as histological type, likelihood of metastatic disease and or nodal involvement, tumor size and location, surgical approach, response to neoadjuvant therapy, and overall health and performance status.
Limitations

- Many included studies have patient populations that were not accrued recently.
- In some studies, since the time of patient staging systems have changed, selection of patients for curative treatments including surgery have improved, and surgical outcomes have improved due to centralization.
- Studies have historically included relatively few older patients or patients with poor performance status.
- Studies with smaller sample sizes lack statistical power to detect differences between treatment & control groups.
Ongoing Research

- There are several ongoing studies exploring research questions of interest, including:
  - The German ESOPEC study of perioperative CT (FLOT regimen\textsuperscript{11}) compared to preoperative CRT (CROSS regimen\textsuperscript{15}) in patients with adenocarcinoma.
  - NeoAEGIS is a study of chemotherapy (FLOT\textsuperscript{11} or MAGIC regimen\textsuperscript{19}) and surgery, compared to chemoradiation and surgery (CROSS regimen\textsuperscript{15}) in gastroesophageal junction adenocarcinoma.\textsuperscript{20,21}
  - The optimal combination of diagnostic modalities to detect locoregional residual disease after CRT is being used in the current SANO trial of active surveillance in high volume centers.\textsuperscript{17} The Esostrate trial is also exploring this comparison.\textsuperscript{22}
  - The Japanese NExT trial (JCOG1109) is a three-arm phase III trial comparing cisplatin plus 5-FU (CF) versus docetaxel and cisplatin plus 5-FU (DCF) versus radiotherapy with CF (CF-RT) as preoperative therapy for locally advanced esophageal cancer.\textsuperscript{23}
Additional Resources

More information, including a supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/gastrointestinal-cancer-guidelines

Patient information is available at www.cancer.net
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References


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References


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