Complete Summary

GUIDELINE TITLE

The role of endoscopy in the assessment and treatment of esophageal cancer.

BIBLIOGRAPHIC SOURCE(S)

Jacobson BC, Hirota W, Baron TH, Leighton JA, Faigel DO. The role of endoscopy in the assessment and treatment of esophageal cancer. Gastrointest Endosc 2003 Jun;57(7):817-22. [76 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Esophageal cancer including esophageal adenocarcinoma and squamous cell carcinoma

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management

CLINICAL SPECIALTY

Gastroenterology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide an updated, practical strategy for the use of endoscopy in the diagnosis, staging, and therapy of esophageal cancer

TARGET POPULATION

Patients with suspected or confirmed esophageal cancer

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Evaluation

1. Upper endoscopy
2. Chromoendoscopy
3. Biopsy
4. Brush cytology
5. Endoscopic ultrasound (EUS) with or without fine-needle aspiration (FNA), including surveillance EUS to detect recurrence
6. Primary **T**umor, Regional Lymph **N**ode, Distant **M**etastasis (TNM) staging
7. Computed tomography (CT)

Palliation

1. Bougienage
2. Stent placement
    - Proton pump inhibitor
    - Raising the head of the bed 30 degrees
    - Lifestyle modifications:
        - Avoidance of dense and fibrous foods
        - Emphasizing liquid and soft mechanical diets
        - Taking all food while sitting fully upright
3. Electrocautery and laser
    - Monopolar electrocautery
    - Bipolar electrocautery
    - Argon plasma coagulation
    - Neodymium-yttrium aluminum garnet (Nd:YAG) laser
4. Chemical debulking using absolute alcohol
5. Photodynamic therapy (PDT) using parenteral porfimer sodium
6. Endoscopic mucosal resection (EMR)

Other Treatments

1. Surgical resection for operable cancers
2. Chemotherapy and radiation therapy (CRT)

MAJOR OUTCOMES CONSIDERED

- Sensitivity of diagnostic tests
- Predictive value of diagnostic tests
- Recurrence
- Survival rate
- Morbidity and mortality
- Clinical remission rate
- Incidence of dysphagia
- Incidence of treatment-related complications
- Length of hospital stay

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

In preparing this guideline, a MEDLINE literature search was performed, and additional references were obtained from the bibliographies of the identified articles and from recommendations of expert consultants.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Guidelines for appropriate utilization of endoscopy are based on a critical review of the available data and expert consensus.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

The guideline developers reviewed published cost analyses in the preparation of the guideline recommendations.

METHOD OF GUIDELINE VALIDATION

Not stated

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not applicable

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Recommendations are followed by evidence grades (A-C) identifying the type of supporting evidence. Definitions of the evidence grades are presented at the end of the "Major Recommendations" field.

Diagnosis

Endoscopy

Standard upper endoscopy remains the primary method for visualizing esophageal masses and for directing biopsies. If a high-grade malignant stricture precludes the passage of a standard endoscope, an ultrathin endoscope with an insertion tube diameter of 5.3 to 6 mm may traverse the stricture and allow complete examination of the esophagus and stomach in up to 75% of cases. Chromoendoscopy with Lugol's iodine or methylene blue may highlight pathology otherwise difficult to visualize by standard endoscopy.

Biopsy and Cytology

Any suspicious lesion should be sampled during diagnostic endoscopy. Standard biopsies are 66 to 96% sensitive for detecting cancers of the esophagus or gastroesophageal junction. Although a single biopsy may be adequate, maximum yields require 7 to 10 biopsies. Larger size "jumbo" biopsy forceps may provide larger specimens, but this does not necessarily mean samples will be more diagnostic. The addition of brush cytology may improve the diagnostic yield and is recommended for sampling tight malignant strictures. In cases where there is a high clinical suspicion but nondiagnostic biopsy and/or brush cytology, endoscopic

ultrasound (EUS) with or without fine-needle aspiration (FNA) may provide a definitive diagnosis.

Staging by EUS

Both esophageal adenocarcinoma and squamous cell carcinoma are staged according to the Primary **T**umor, Regional Lymph **N**ode, Distant **M**etastasis (TNM) system established by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) (see the table below titled "TNM staging classification of esophageal carcinomas"). Accurate staging is important for prognostication and therapeutic decision-making, and may reduce the costs of care. The accuracy of EUS for T staging is 85% and for N staging is 75 to 80%, exceeding the accuracy of computed tomography. EUS staging is more accurate for T3 and T4 tumors (>90%) than for T1 and T2 tumors (65%). The use of high-frequency (15-30 MHz) ultrasound (US) catheter probes for staging small T1 and T2 tumors improves this accuracy to 83 to 92%. When examining lymph nodes by EUS, particular findings may predict malignant nodal involvement, including a hypoechoic echotexture, a sharply demarcated border, a rounded contour, and a size greater than 1 cm. Although these individual findings are predictive, accuracy exceeds 80% when all 4 are present, although this occurs in the minority of cases. FNA of nodes improves the accuracy of EUS for determining N stage. To maximize sensitivity, at least 3 FNA passes should be made.

EUS assessment may be incomplete in the setting of esophageal obstruction. A stricture that restricts passage of an echoendoscope is present in 29% of cases and indicates a lesion with advanced T stage. Failure to traverse a malignant stricture results in significantly decreased accuracy for both T and N staging. When available, catheter ultrasound probes or a 7.5 MHz non-optical wire-guided esophagoprobe may be used to traverse the stricture and attempt complete T and N staging. Alternatively, dilation of the stricture may permit passage of a standard echoendoscope. This approach has been associated with a risk of perforation of 0 to 24% but permits passage of the echoendoscope in the majority of cases.

Residual inflammation and fibrosis after chemotherapy and radiation therapy (CRT) makes EUS too inaccurate to be recommended as a tool for post-therapy restaging. One promising method for detecting adequate response to therapy is the measurement of a tumor's maximal transverse cross-sectional area both before and after chemotherapy and radiation therapy. A $\geq$50% reduction in the tumor's maximal transverse cross-sectional area has been shown to correlate with both a pathologic tumor regression (as determined after resection) and with improved clinical outcomes.

Table: TNM staging classification of esophageal carcinomas

T: Primary tumor	
Tx	The tumor cannot be assessed
T0	No evidence of a primary tumor
Tis	Carcinoma in situ
T1	The tumor invades the lamina propria or submucosa but does not invade the muscularis propria
T2	The tumor invades, but does not extend beyond, the muscularis propria

T: Primary tumor	
T3	The tumor invades the periesophageal tissues but does not invade adjacent organs
T4	The tumor invades adjacent structures
N: Regional lymph nodes	
Nx	Regional lymph nodes cannot be assessed
NO	No regional lymph node metastases
N1	Regional lymph node metastases
M: Distant metastasis	
Mx	Presence of distant metastases cannot be assessed
M0	No distant metastases
M1a	Metastasis to cervical or celiac lymph nodes
M1b	Other distant metastasis

Detecting Recurrence

Any patient presenting with signs or symptoms of locoregional recurrence after resection of esophageal cancer should undergo endoscopy as part of their evaluation. In this setting, standard endoscopy can yield a diagnosis of recurrent disease in 40% of patients. However, recurrence is often extramucosal and therefore missed with standard endoscopy. EUS has been shown to detect cancer with a positive predictive value of 75 to 100%. Although surveillance EUS after cancer resection may detect recurrent cancer, it remains unproven whether this practice has any impact on survival.

Therapy

Surgical resection is indicated for all operable candidates who are considered curable (T1N0 or T2N0). Patients with loco-regionally advanced disease (T3 or N1), should be offered induction chemoradiotherapy followed by surgical resection. A suggested treatment algorithm is shown in Figure 1 of the original guideline document. Although adenocarcinoma of the esophagus is less sensitive to chemoradiotherapy than squamous cell cancer, patients with adenocarcinoma experience a greater survival benefit with multimodal therapy before surgical intervention. Unfortunately, patients with esophageal cancer often present with dysphagia, advanced stage disease, and subsequent poor outcome with an overall 5-year survival rate of less than 20%.

Palliation is indicated in most cases to relieve dysphagia, control pain, and assist in nutrition. There have been few randomized controlled trials or comparative treatment studies to delineate the best possible palliative therapy, and therefore the best modality should be based on tumor characteristics, patient preferences, and local expertise.

Bougienage

Dilation of a malignant stricture can be accomplished using either a through-the-scope balloon or wire-guided polyvinyl bougies with or without fluoroscopic guidance. Although a majority of patients can be dilated to the point at which a standard forward-viewing scope can be passed through the tumor, the clinical

benefits of dilation are brief and not durable. Blind Maloney dilation of complex esophageal strictures has been associated with a higher perforation rate and is not recommended.

Stent Placement

The placement of an expandable metal stent for the purpose of maintaining a patent lumen and to relieve dysphagia has evolved into a mainstay of palliative therapy. Initial material designs which used plastic were associated with a 6 to 8% risk of acute complications during insertion, particularly esophageal perforation. Expandable metal stents, an alternative to the plastic design, are inserted in a preloaded constrained position using endoscopic and fluoroscopic control. The constrained mechanism minimizes or eliminates the need for stricture dilation. Once placed across the tumor, the constraining device is released deploying the stent. The rate of successful deployment is over 90% among experienced operators. Although more expensive than the plastic predecessor, the use of the metal stent is associated with a much lower acute complication and mortality rate.

The incidence of late complications of esophageal metal stent deployment is reported to be as high as 20 to 40%. These complications include chest pain, migration, hemorrhage, and fistulization. Patients who have undergone prior radiation and chemotherapy may be at greater risk of serious complications.

The most proximal and distal esophagus are problematic areas for stent deployment. Stents placed proximally may lead to a foreign body sensation or airway compromise. Stents placed at the esophagogastric junction may lead to intractable reflux symptoms and are prone to migration, ulceration, and food impaction. A recent variant of the Z-stent with a windsock-like antireflux valve on the distal end may successfully reduce severe reflux symptoms. Patients with stents placed beyond the cardia will require acid suppression with a proton pump inhibitor and should maintain an upright or semi-upright position at all times, including raising the head of the bed to approximately 30 degrees. Additional lifestyle modifications for patients with stents include avoidance of dense and fibrous foods, emphasizing liquid and soft mechanical diets, and taking all food while sitting fully upright.

Tracheoesophageal fistulization is a very serious complication of esophageal cancer that leads to aspiration and respiratory insufficiency. Use of a covered stent is the treatment of choice in these patients with closure of the fistula achieved in 70 to 100% of patients.

Electrocautery and Laser

Thermal debulking techniques are optimally used for the palliation of short, exophytic obstructive tumors. The modalities demonstrating clinical efficacy include monopolar and bipolar electrocautery, argon plasma coagulation, and neodymium-yttrium aluminum garnet (Nd:YAG) laser.

Although inexpensive to use, monopolar and bipolar electrocautery have been limited by inadequate control of the treatment delivery. Argon plasma coagulation is a noncontact method that uses ionized argon gas to perform electrocautery.

Unfortunately, the ablation is too superficial (approximately 2 mm) to achieve a durable response in treating bulky obstructing tumors.

High-power Nd:YAG laser can provide deep tissue penetration and palliation from bulky esophageal tumors. The laser is capable of coagulating and vaporizing malignant tissue with endoscopic control. Unfortunately, lasers are expensive and their use technically demanding.

Chemical Debulking

Chemical ablation with absolute alcohol is inexpensive and easy to perform. This is injected into an esophageal cancer with a sclerotherapy needle in a free-hand technique as used in hemostasis of bleeding esophageal varices. The subsequent tissue necrosis may lead to temporary relief of dysphagia. The dose required to accomplish therapy has not been standardized, and it is difficult to target the sclerosant to diseased tissue alone. Post-treatment chest pain is common; palliation tends to be brief and requires repeat endoscopies.

Photodynamic Therapy (PDT)

PDT uses a light sensitizing drug, porfimer sodium. This is injected parenterally and concentrates in tumor tissue. An endoscopically guided low-power laser diffuser exposes the tumor to red light. The light initiates a photochemical reaction in the sensitized tissue producing cytotoxic singlet oxygen, with resultant tumor necrosis. Red light is used to achieve the greatest tissue penetration.

PDT is technically easy to perform and, because of selective tumor tissue destruction, it can be used to treat cancers that nearly obstruct the esophageal lumen. Neoadjuvant PDT has also been used before or after chemotherapy and radiation. It has been used to limit tumor growth reobstructing the ends of previously placed esophageal stents.

The major limiting factors for PDT are the long half-life of porfimer sodium and the expense required for the multiple treatment sessions needed to achieve palliation. Porfimer sodium is retained in the skin for up to 6 weeks after infusion, and patients need to avoid sun exposure or risk the likelihood of sustaining severe sunburn. Other complications of PDT include substernal chest pain, odynophagia, fever, pleural effusion, and the development of tracheoesophageal fistulae.

Endoscopic Mucosal Resection (EMR)

Few patients present with early stage esophageal cancer, however the surveillance of Barrett's esophagus may lead to earlier detection. Mortality rates from esophagectomy performed in experienced centers is as high as 3 to 5%. Morbidity rates are up to 18 to 48%. EMR of well- or moderately differentiated adenocarcinoma limited to the mucosa, with a specific diameter (e.g., <2 cm) and appropriate endoscopic morphology, has been associated with a low morbidity and mortality. In one study, 97% of patients with early stage esophageal cancer were found to be in clinical remission after EMR. However, during a mean follow-up of 12 months, there was a 14% rate of recurrence or metachronous carcinoma. In a

recent nonrandomized study of patients with squamous cell carcinoma, 5-year survival rates after EMR or surgery were 77.4% and 84.5%, respectively.

Additional comparative studies with long-term follow-up are needed before this technique can be routinely recommended. Most studies have used EUS to select patients for EMR.

Comparative Treatment Trials

A randomized trial of thermal ablative therapy with predominantly Nd:YAG laser versus expandable metal stents yielded no clear-cut superiority of one modality over the other. Median survival was superior in patients treated with thermal ablation; however, relief of dysphagia was poor in both groups. There were significant treatment-related complications in both groups, and the median length of hospital stay and total cost was greater in patients receiving thermal therapy. PDT provides similar relief of dysphagia as Nd:YAG laser but is easier to perform and more comfortable for the patient. Alcohol injection was found to have similar efficacy to Nd:YAG laser.

Other studies have demonstrated a superiority of metal stents to thermal ablative therapy. In a prospective randomized study comparing stents (both covered and uncovered) versus Nd:YAG, the technical success rate and improvement in dysphagia was greater in the group receiving primary stent palliation.

Summary

Esophageal cancer carries significant morbidity and mortality. Endoscopy is pivotal in the diagnosis and management of this malignancy. Multiple biopsies and brushings should be obtained from suspicious lesions **(B)**. EUS provides accurate staging that is superior to computed tomography scanning **(A)** and allows for stage-directed therapy **(C)**, which may improve outcome and reduce costs **(B)**. The majority of patients will not be cured and will require palliation. Endoscopic palliation of dysphagia may be achieved with bougienage, tumor ablation, or placement of a stent. Bougienage results in short-lived palliation **(B)**. Tumor ablation can be achieved with alcohol injection, laser, or PDT, with similar efficacy among these techniques **(A)**. Expandable metal stents are superior to plastic stents **(A)**. Choice among the palliative techniques will be determined by tumor characteristics, patient preferences, and local expertise.

Definitions:

A. Prospective controlled trials
B. Observational studies
C. Expert opinion

CLINICAL ALGORITHM(S)

A clinical algorithm is provided in the original guideline document for the staging and treatment of esophageal cancer.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and classified for the recommendations using the following scheme:

A. Prospective controlled trials
B. Observational studies
C. Expert opinion

When little or no data exist from well-designed prospective trials, emphasis is given to results from large series and reports from recognized experts. Guidelines for appropriate utilization of endoscopy are based on a critical review of the available data and expert consensus.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of upper endoscopy for the assessment and treatment of esophageal cancer

POTENTIAL HARMS

- The incidence of late complications of esophageal metal stent deployment is reported to be as high as 20 to 40%. These complications include chest pain, migration, hemorrhage, and fistulization. Patients who have undergone prior radiation and chemotherapy may be at greater risk of serious complications.
- Stents placed at the esophagogastric junction may lead to intractable reflux symptoms, and are prone to migration, ulceration, and food impaction.
- Porfimer sodium is retained in the skin for up to 6 weeks after infusion, and patients need to avoid sun exposure or risk the likelihood of sustaining severe sunburn. Other complications of photodynamic therapy (PDT) include substernal chest pain, odynophagia, fever, pleural effusion, and the development of tracheoesophageal fistulae.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Further controlled clinical studies are needed to clarify aspects of this statement, and revision may be necessary as new data appear. Clinical consideration may justify a course of action at variance to these recommendations.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

End of Life Care
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Jacobson BC, Hirota W, Baron TH, Leighton JA, Faigel DO. The role of endoscopy in the assessment and treatment of esophageal cancer. Gastrointest Endosc 2003 Jun;57(7):817-22. [76 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Jun

GUIDELINE DEVELOPER(S)

American Society for Gastrointestinal Endoscopy - Medical Specialty Society

SOURCE(S) OF FUNDING

American Society for Gastrointestinal Endoscopy

GUIDELINE COMMITTEE

Standards of Practice Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Committee Members: Douglas O. Faigel, MD (*Chair*); Brian C. Jacobson MD, MPH; William Hirota, MD; Todd H. Baron, MD; Jonathan A. Leighton, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American Society for Gastrointestinal Endoscopy (ASGE) Web site.

Print copies: Available from the American Society for Gastrointestinal Endoscopy, 1520 Kensington Road, Suite 202, Oak Brook, IL 60523

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on March 23, 2005. The information was verified by the guideline developer on March 31, 2005.

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Date Modified: 11/3/2008