Management of locally advanced, unresectable and inoperable esophageal cancer

AUTHORS: Dwight E Heron, MD, MBA, FACRO, FACR, Michael K Gibson, MD, PhD, FACP
SECTION EDITORS: Richard M Goldberg, MD, Kenneth K Tanabe, MD
DEPUTY EDITOR: Sonali M Shah, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Sep 2023.**
This topic last updated: **Nov 01, 2022.**

INTRODUCTION

Management of patients with unresectable or inoperable but non-metastatic esophageal cancer is challenging and requires a multimodality approach. This is a heterogeneous group that includes patients with potentially resectable (T4a (table 1)) and unresectable (T4b) primary disease, poor surgical candidates, and those who decline surgery. (See "Clinical manifestations, diagnosis, and staging of esophageal cancer", section on 'TNM staging criteria'.)

Prolonged progression-free survival (PFS) is possible in a minority of these patients; however, control (which we herein label as "palliation," or "palliative" modalities) rather than cure of the cancer is the treatment goal for the majority, and quality of life (QOL) issues generally take precedence. Major goals of therapy are restoration and/or maintenance of the ability to swallow, management of pain, and prevention of bleeding. To achieve these goals, a variety of therapies may be used, including external beam radiation therapy with or without chemotherapy, esophageal dilatation and/or stenting, photodynamic therapy (PDT), laser ablation, chemical ablation, and palliative surgery.

Optimal palliation usually requires the integration of two or more of these modalities, either concurrently or sequentially. While combined modality therapy offers a small but real chance of prolonged PFS and, potentially, prolonged overall survival, improvement in QOL and sustained relief of dysphagia can be achieved in the majority of patients. However, the durability of symptom palliation is variable.

This topic focuses on locoregional therapy for locally advanced, inoperable, but non-metastatic esophageal cancer. The roles of palliative surgery and radiation therapy without or with concurrent chemotherapy will be covered, as well as an overview of endoscopic procedures for palliation of swallowing (dilation, stenting, PDT, and laser ablation). Other approaches to localized esophageal cancer and metastatic disease, as well as a more detailed discussion of endoscopic palliation, are provided in other topic reviews. (See "Surgical management of resectable esophageal and esophagogastric junction cancers" and "Radiation therapy, chemoradiotherapy, neoadjuvant approaches, and postoperative adjuvant therapy for localized cancers of the esophagus" and "Multimodality approaches to potentially resectable esophagogastric junction and gastric cardia adenocarcinomas" and "Initial systemic therapy for locally advanced unresectable and metastatic esophageal and gastric cancer" and "Endoscopic palliation of esophageal cancer" and "Endoscopic stenting for palliation of malignant esophageal obstruction", section on 'Efficacy'.)

GRADING THE SEVERITY OF DYSPHAGIA

Dysphagia is a subjective term that encompasses any difficulty in swallowing food, liquids, or oral secretions [1]. Dysphagia can be caused by benign or malignant disorders of the oral cavity, oropharynx, or esophagus. (See "Oropharyngeal dysphagia: Etiology and pathogenesis" and "Approach to the evaluation of dysphagia in adults".)

Due to the lack of standardization for grading the severity of dysphagia, published reports vary in how they quantify or characterize dysphagia. The Radiation Therapy Oncology Group (RTOG) and the European Organisation for Research and Treatment of Cancer (EORTC) developed a grading scale for late effects of radiation therapy, which helps standardize the evaluation of dysphagia (table 2) [2]. These criteria are especially useful for radiation-induced benign strictures. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) provides separate grading scales for dysphagia (table 3) and long-term stricture/stenosis.

STAGING EVALUATION

The Tumor, Node, Metastasis (TNM) staging system of the combined American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) is used universally. Regardless of histology, esophageal tumors arising in the cervical, thoracic, or abdominal esophagus, and those involving the esophagogastric junction (EGJ) that have an epicenter within 2 cm of the EGJ (table 4) share the same criteria for T stage, N stage, and M stage

designation (table 1). By contrast, EGJ tumors with their epicenter located more than 2 cm into the proximal stomach are staged as stomach cancers, as are all cardia cancers not involving the EGJ, even if they are within 2 cm of the EGJ (table 5).

Staging and evaluation for resectability require endoscopic ultrasound (EUS) for T staging (focusing on the possibility of T4 disease) and for staging and evaluation of lymph nodes, computed tomography (CT), and fluorodeoxyglucose positron emission tomography (FDG-PET), which is often integrated with CT (PET/CT). For squamous cell cancers (SCCs) located at or above the carina, bronchoscopy is indicated to rule out tracheoesophageal fistula. For cervical SCCs, flexible laryngoscopy to assess local disease spread and exclude a synchronous malignancy of the head and neck is generally recommended. (See "Clinical manifestations, diagnosis, and staging of esophageal cancer".)

Criteria for unresectability — Although criteria vary according to institution and individual surgeon, the presence of any of the following is generally considered to preclude resection:

Distant metastases — The presence of peritoneal, lung, bone, adrenal, brain, or liver metastases or extraregional lymph node spread (eg, paraaortic or mesenteric lymphadenopathy) precludes an attempt at resection.

The finding of a malignant node in the celiac area remote from the primary tumor (eg, for a SCC in the upper or middle thoracic esophagus) was previously thought to be a sign of unresectability and was considered metastatic disease [3]. However, celiac nodal metastases are scored as **regional nodal disease** in the current TNM staging system, regardless of the primary tumor location or histology, and they no longer carry the connotation of distant metastatic disease [4].

Nevertheless, prognosis is poor in such cases, even if the primary tumor is located in the distal esophagus or EGJ [5,6]. In one series, the two-year survival rate of patients with celiac node involvement who underwent surgery as a component of therapy was approximately 10 percent [6].

Unresectable primary disease

Thoracic or abdominal esophagus — In the current TNM staging criteria, invasion of the pleura, pericardium, azygos vein, peritoneum, or diaphragm is classified as T4a disease and considered potentially resectable [4]. By contrast, invasion of other adjacent structures, including the aorta, trachea, or vertebral body, constitutes unresectable (T4b) disease (table 1 and image 1).

A thorough evaluation of the airway is mandatory for all esophageal cancers at or above the carina, including those involving the middle third of the esophagus (figure 1). Meticulous attention should be paid to the preservation or obliteration of fat planes between the esophagus and adjacent structures on chest CT. In general, preservation of fat planes implies no direct tumor invasion and suggests potential resectability.

On the other hand, obliteration of the fat plane does not necessarily indicate direct tumor invasion and unresectability. In normal patients, fat may be absent between an esophageal carcinoma and the aorta, trachea, left main bronchus, or pericardium, thus complicating the differentiation between an abutting tumor and true invasion. Fat planes may also be absent in cachectic patients who do not have evidence of tumor invasion.

If the tumor abuts the aorta with obliteration of the normal adventitial plane, there will likely be a positive radial margin, but this finding does not preclude exploration if there are no other findings to indicate unresectability [7,8]. Invasion of the aorta (and thus, unresectable disease) is suggested by an arc of contact between the tumor and the aorta that is more than 90 degrees, although this is not absolute confirmation of an unresectable T4b tumor.

Cervical esophageal tumors — For tumors of the cervical esophagus (which extends from the hypopharynx to the sternal notch (figure 1)), infiltration into the prevertebral fascia or posterior larynx, invasion of the membranous trachea to the level of the carina, or significant bilateral encasement of major neurovascular structures precludes surgical resection. Regardless of apparent resectability, however, tumors of the cervical esophagus are rarely resected, due to the resultant functional deficits and impairment of quality of life. They are more often treated in a similar manner to head and neck SCCs. (See 'Treatment of cervical tumors' below.)

TREATMENT OF THORACOABDOMINAL TUMORS

External beam radiation therapy (RT) with concurrent chemotherapy is a standard approach for patients with locally advanced, unresectable or inoperable, thoracic and abdominal esophageal cancer who are medically able to tolerate chemotherapy and radiation. The optimal type, dose, combination, and schedule of drugs have not been definitively established. In general, similar chemotherapy regimens are used for squamous cell cancers (SCCs) and adenocarcinomas. (See 'Conventional chemoradiotherapy' below.)

Patients who are fit for combined modality therapy — For inoperable or unresectable esophageal SCC or adenocarcinoma, we recommend concurrent chemoradiotherapy (CRT)

rather than RT alone for patients who are able to tolerate this approach and who have an estimated life expectancy of greater than a few weeks.

Choice of treatment — The optimal type, dose, combination, and schedule of drugs have not been definitively established. For patients with categorically inoperable esophageal SCC who are planned for definitive CRT, we suggest the concurrent CRT regimen that was used in the Radiation Therapy Oncology Group (RTOG) 85-01 and the US Intergroup 0123 trials [9,10] (see 'Impact on survival' below):

- Infusional fluorouracil (FU) 1000 mg/m^2 per day for 96 hours during weeks 1 and 5 of external beam RT
- Cisplatin 75 mg/m^2 on day 1 during weeks 1 and 5 of external beam RT

For other patients, including those with inoperable adenocarcinomas, we suggest CRT as was used in the Dutch CROSS trial [11], rather than cisplatin plus FU (see 'Impact on survival' below). The chemotherapy regimen during RT consists of:

- Carboplatin dosed at an area under the curve of concentration X time (AUC) 2, weekly for five weeks
- Paclitaxel 50 mg/m^2 weekly for five weeks

The great majority of patients treated with palliative CRT will not benefit from post-CRT esophagectomy. Rarely, patients with initially unresectable disease will have a sufficient disease response to warrant subsequent surgical consideration. However, particularly for SCCs, the benefit of post-CRT surgery is debated, even in those with initially localized potentially resectable disease. In our view, definitive CRT is appropriate for patients with locoregionally advanced esophageal SCC. For patients with adenocarcinoma, the role of nonoperative treatment remains poorly defined. (See 'Role of postchemoradiotherapy surgery' below.)

Historically, external beam RT played an important role in the management of unresectable esophageal cancer, both for palliation of dysphagia and for maintenance of long-term locoregional disease control. Although RT alone may successfully palliate dysphagia, sustained remission and long-term survival are rarely achieved [9,12-16]. Most experts consider combined CRT to provide superior palliation and the potential for long-term progression-free survival (PFS). It is the preferred approach for patients who are suitably fit for combined therapy.

Conventional chemoradiotherapy

Impact on survival — Many randomized controlled trials have compared CRT with RT alone for definitive treatment of esophageal cancer. Some show a significant survival advantage for the addition of chemotherapy to RT [9,14,16], but results are not consistent [17]. Most of these studies were flawed because of suboptimal doses of RT or chemotherapy, or the sequential, rather than concurrent, delivery of chemotherapy and RT. Sequential administration is now recognized as inferior to concurrent use of chemotherapy and RT. (See "Radiation therapy, chemoradiotherapy, neoadjuvant approaches, and postoperative adjuvant therapy for localized cancers of the esophagus", section on 'Sequential chemoradiotherapy'.)

- **Chemoradiotherapy versus RT alone: RTOG 85-01** – The only randomized trial that used adequate RT doses and modern concurrent chemotherapy, the landmark RTOG 85-01 trial, demonstrated that the addition of concurrent cisplatin-based chemotherapy to conventional fractionation RT provided a significant survival benefit compared with treatment with RT alone [9,14]. Patients with locoregional (T1 to 3, N0 to 1, M0) esophageal cancer were randomly assigned to CRT (two cycles of infusional FU [1000 mg/m^2 per day, days 1 to 4, weeks 1 and 5] plus cisplatin [75 mg/m^2 on day 1 of weeks 1 and 5] plus RT [50 Gy in 25 fractions over five weeks]) or RT alone (64 Gy). CRT was associated with significantly better median survival (14 versus 9 months) and five-year survival (27 versus 0 percent). These data resulted in the widespread adoption of CRT, rather than RT alone, as the definitive nonoperative treatment of locoregional esophageal cancer.

  Patients with T4 disease and high nodal burden were not included in this study. Because the inclusion criteria did not require surgical unresectability or initial endoscopic ultrasound (EUS) to assess local tumor extent, the study group likely represents, on average, a prognostically more favorable population than those with unresectable, locally advanced disease. Furthermore, 85 percent of the study group had SCC. Nevertheless, these data are widely considered to provide support for the superiority of CRT over RT in patients with unresectable, locally advanced esophageal SCC or adenocarcinoma.

- **Dutch CROSS trial** – An alternative regimen to that used in RTOG 85-01 was used in the Dutch CROSS trial, in which 363 patients with potentially resectable esophageal or esophagogastric junction (EGJ) cancer (273 adenocarcinoma, the majority distal esophageal) were randomly assigned to preoperative CRT using weekly paclitaxel 50 mg/m^2 plus carboplatin (area under the curve of concentration X time [AUC] of 2) plus concurrent RT (41.4 Gy over five weeks) or to surgery alone [11]. As with RTOG 85-01, patients with T4 disease were not included in this study.

Preoperative CRT was well tolerated, with grade 3 or worse hematologic toxicity in 7 percent and grade 3 or higher nonhematologic toxicity in <13 percent. The complete (R0) resection rate was higher with CRT (92 versus 69 percent), and 29 percent of those treated with CRT had a pathologic complete response (pCR). Median overall survival was significantly better with CRT (median 49.4 versus 24 months, hazard ratio 0.657, 95% CI 0.495-0.871) [11].

In the latest report with long-term follow-up, preoperative CRT achieved a median overall survival of 48.6 months, versus 24 months for surgery alone. Patients with SCCs had a median overall survival of 81.6 months, while those with adenocarcinoma had a median overall survival of 43.2 months when treated with preoperative CRT, as compared with 21.1 and 27.1 months in the surgery-alone arms, respectively [18].

Palliation of dysphagia — Combined CRT provides long-lasting palliation of dysphagia in most patients with unresectable disease [19-22]. As an example, one report described post-treatment swallowing function in 120 patients who were treated with different combination regimens [19]. The majority of evaluable patients (88 percent) noted improvement in dysphagia within an average of two weeks. Benefit was maximal by four weeks in 86 percent of responding patients. At this time point, all but two could swallow at least soft or solid food without dysphagia. Two-thirds of the patients treated with palliative intent had no significant dysphagia until death or last follow-up examination.

Alternative methods for palliation of dysphagia in patients with esophageal cancer, including the use of expandable stents, are summarized below and discussed in detail elsewhere. (See 'Endoscopic interventions' below and "Endoscopic palliation of esophageal cancer" and "Endoscopic stenting for palliation of malignant esophageal obstruction".)

Complications — Patients who undergo RT are at risk for an esophagorespiratory fistula (eg, a tracheoesophageal [TE] fistula) and postradiotherapy esophageal strictures.

- **TE fistula** – A TE fistula may develop in the setting of a locally advanced tumor or as a complication of RT or CRT (image 1). Combined modality therapy for patients who present with a TE fistula in the setting of locally advanced disease is addressed below. (See 'Patients presenting with a malignant fistula' below.)

  TE fistulas are uncommon during RT or CRT for esophageal cancer. The incidence of a TE fistula during CRT was 6 percent in one series and accounted for one-half of all fistulas that developed in patients with esophageal cancer [23]. The others presented before the initiation of therapy; in this cohort, spontaneous closure of the fistula after completion of CRT was noted in 70 percent.

Esophageal stenting is a risk factor for a post-RT TE fistula. In a report of 208 patients who underwent stent placement with or without palliative RT for inoperable, locally advanced esophageal cancer, 18 developed a TE fistula, 17 of whom had received RT [24]. The risk of a TE fistula was higher among patients who received RT after stent placement compared with those who received it beforehand. In our own experience, TE fistulas occur more often with SCC than with adenocarcinoma due to proximity to the airways.

For patients with a persistent TE fistula after the completion of treatment, options for symptomatic management include airway stents, esophageal stents (picture 1), or surgery. In most cases, symptomatic treatment and closure of the fistula are achieved with stenting; dual stenting appears to work better than single prosthesis, both for palliation and safety [25]. (See "Airway stents" and "Endoscopic stenting for palliation of malignant esophageal obstruction".)

Alternatives to stenting include esophageal exclusion with cervical esophagostomy, gastrostomy, and placement of a jejunostomy feeding tube. Surgical intervention (eg, esophageal bypass, palliative resection) is justified in very few cases and carries very high morbidity and mortality [26].

- **Strictures** – Post-RT strictures may be either benign or malignant and may lead to recurrent dysphagia. The prevalence of malignant and non-malignant post-RT strictures was approximately equal in one series [27]. The majority of patients with benign strictures were successfully dilated and had a 12-month survival rate of 88 percent, compared with 19 percent for those with malignant strictures [27].

Patients presenting with a malignant fistula — The presence of a malignant TE fistula in patients with locoregionally advanced esophageal cancer was historically considered a relative contraindication for RT or CRT because of the high rate of perforation [28]. However, at least some data support the view that selected patients who have a previously unirradiated T4 lesion with a malignant fistula can be safely treated with CRT, with some achieving at least transient closure of the fistula and, occasionally, long-term survival [5,29]. Toxicity may be prominent, and most patients fail to achieve long-term local control. The best way to select those patients who might benefit from CRT versus placement of stents is uncertain.

Treatment intensification — Intensification of the different components of the CRT regimen has been explored in an attempt to improve outcomes in patients with unresectable or inoperable esophageal cancer. However, to date, none has been shown to definitively improve outcomes, and toxicity may be worse. None of these approaches can be recommended outside of the context of a clinical trial.

RTOG protocol 85-01 clearly demonstrated that patients with locally advanced esophageal cancer (mostly SCC) can be cured without surgery [9,14]. However, the local failure rate (persistent and recurrent disease) of approximately 45 percent in patients treated with definitive CRT (as has been seen in other trials as well [10,30]) leaves much room for improvement. (See 'Impact on survival' above.)

Radiation therapy dose intensification — The available options for intensification of RT include higher radiation doses, accelerated fractionation RT, and the addition of brachytherapy to RT. At present, none of these approaches has been shown to improve outcomes, and none can be recommended over standard fractionation RT (50.4 to 54 Gy total dose in daily 1.8 to 2 Gy fractions) for patients with locally advanced esophageal cancers.

Several trials have explored RT dose escalation as a means of improving outcomes, none of which have demonstrated improved cancer outcomes from this approach, and most show prohibitive toxicity. As examples:

- US Intergroup trial 0123 compared high-dose external beam RT (64.8 Gy) with the previous standard (50.4 Gy), with both schedules being administered with concurrent chemotherapy (cisplatin plus infusional FU) in 236 patients with clinical stage T1 to 4, NX, M0 (table 1) esophageal cancer [10]. Two additional chemotherapy courses were repeated four weeks after the completion of RT. The trial was closed early because there was no demonstrable survival or local control advantage from higher-dose RT, although most of the deaths occurred before reaching escalated doses. Furthermore, there was a higher rate of toxic deaths (9 versus 2 percent) with the higher RT dose. One- and two-year survival rates were 66 and 40 percent, respectively.

  A similar negative result was obtained in the ARTDECO study in which 260 patients with locally advanced unresectable esophageal cancer (adenocarcinoma or SCC) were randomly assigned to RT at 50.4 Gy (SD) or up to 61.6 Gy (HD) concurrent with weekly carboplatin plus paclitaxel (the CROSS CRT regimen) [31], and in a Chinese study comparing 60 Gy versus 50 Gy concurrent with weekly cisplatin and docetaxel for inoperable SCC [32]. (See "Multimodality approaches to potentially resectable esophagogastric junction and gastric cardia adenocarcinomas", section on 'CROSS trial'.)

- Another approach to RT dose intensification is the addition of brachytherapy to external beam RT and chemotherapy. Brachytherapy permits treatment of a localized area of the esophagus to high radiation doses with relative sparing of surrounding structures. It can be administered using two general methods: low dose rate brachytherapy (LDRB) and high dose rate brachytherapy (HDRB). Modern HDRB equipment delivers radiation at a high

dose rate, permitting the delivery of a planned dose within minutes, compared with LDRB sources, which require many hours or days. Because of this high dose rate, fractionation is necessary; typically, two to four fractions are administered for treatment of esophageal cancer. (See "Radiation therapy techniques in cancer treatment", section on 'Brachytherapy'.)

The combination of CRT with a brachytherapy boost has been investigated in patients ineligible for surgical resection. However, randomized trials comparing this approach with CRT alone are not currently available, and the results of uncontrolled trials are mixed. While encouraging results are reported by some [33-36], others demonstrate prohibitive toxicity [37-39].

Consensus guidelines for brachytherapy in the treatment of esophageal cancer from the American Brachytherapy Society are presented in the tables (table 6A-B) [40]. However, given the potential for treatment-related toxicity, we recommend that if brachytherapy is given as a component of treatment for locally advanced esophageal cancer, chemotherapy not be administered concurrently with brachytherapy. Furthermore, brachytherapy should be used with extreme caution in the setting of a local recurrence after prior CRT because of the risk of fistula formation.

Chemotherapy intensification — Others have explored the use of novel combinations, targeted agents, or alternative radiation sensitizers (eg, taxanes, oxaliplatin) during RT [41-52]. Although results from phase II trials are encouraging, particularly for adenocarcinomas [50], at least one randomized phase II/III trial conducted in 134 patients who were "unsuitable for surgery" failed to show improved outcomes from the use of oxaliplatin plus short-term infusional FU and leucovorin (the FOLFOX regimen) during definitive concurrent CRT compared with conventional concurrent cisplatin and FU both during and following RT [49]. Approximately 85 percent of the enrolled patients had SCCs. Benefit has also not been shown for the addition of cetuximab, an inhibitor of the epidermal growth factor receptor (EGFR), to standard cytotoxic chemotherapy [48,51,52].

Other studies are evaluating combinations of cytotoxic chemotherapy with agents targeting the human epidermal growth factor receptor 2 (HER2) for HER2-overexpressing esophageal adenocarcinomas. These trials are addressed in detail elsewhere. (See "Multimodality approaches to potentially resectable esophagogastric junction and gastric cardia adenocarcinomas", section on 'HER2-targeted therapy for HER2+ adenocarcinomas'.)

These and other approaches to chemotherapy intensification are discussed in more detail elsewhere. (See "Radiation therapy, chemoradiotherapy, neoadjuvant approaches, and

postoperative adjuvant therapy for localized cancers of the esophagus".)

Induction plus concurrent chemoradiotherapy — Up to 75 percent of patients diagnosed with locally advanced disease will ultimately develop distant metastases, providing the rationale for studying induction systemic chemotherapy prior to CRT. While phase I/II studies have shown that this approach is feasible and provides significant relief of dysphagia in up to 90 percent of patients, no trials have compared this approach with concurrent CRT alone, and it remains uncertain whether induction chemotherapy followed by concurrent CRT is superior to concurrent CRT alone for locally advanced esophageal cancer.

Most of the trials evaluating this approach have been conducted in patients with locally advanced but potentially resectable disease, and are described elsewhere. (See "Radiation therapy, chemoradiotherapy, neoadjuvant approaches, and postoperative adjuvant therapy for localized cancers of the esophagus".)

Two of the only trials to include patients with T4 disease are described below:

- One randomized trial included 172 patients with T3 to 4, N0 to 1, M0 SCC (29 with EUS-staged T4 disease) [30]. The treatment groups were induction chemotherapy (three 21-day courses of bolus FU, leucovorin, etoposide, and cisplatin on days 1 to 3) followed by CRT (40 Gy RT with concurrent cisplatin and etoposide on days 2 through 8) and then surgery, or the same induction chemotherapy followed by CRT (RT dose at least 65 Gy) without surgery.

  Only 62 of the 86 patients in the surgery arm underwent surgery, and this number was not broken down according to the initial EUS T stage. Overall survival was similar in both groups, although two-year PFS significantly favored the surgery arm (64 versus 41 percent). Treatment-related mortality was also significantly higher in this group (13 versus 4 percent). Tumor response to induction chemotherapy identified a prognostically favorable group within both treatment arms. The major criticisms of this study were its small size and the relatively low RT dose in the surgery arm.

- The RTOG conducted a multi-institutional phase II randomized trial of two nonoperative regimens of induction chemotherapy followed by CRT in patients with non-metastatic esophageal cancer (25 SCC, 47 adenocarcinoma) who were technically unresectable or unwilling/medically unfit for surgery [53]. One group received FU-based induction chemotherapy (FU, cisplatin, and paclitaxel followed by RT [50.4 Gy] concurrent with paclitaxel and FU; arm A), while the other received non-fluoropyrimidine-based therapy (induction paclitaxel plus cisplatin followed by the same regimen concurrent with 50.4 Gy RT; arm B).

Treatment-related morbidity was prominent in both groups; grade 3 toxicity developed in 54 and 40 percent of patients in arms A and B, respectively, while the corresponding rates of grade 4 toxicity were 27 and 40 percent, respectively. The rate of gastrointestinal grade 3 or 4 toxicity was similar in both groups (54 and 60 percent in arms A and B). There was one treatment-related death in arm A and two in arm B.

At one and two years, 76 and 56 percent of the patients in arm A were alive, respectively, while the corresponding rates in arm B were 69 and 37 percent, respectively. The authors concluded that both approaches were toxic and neither was sufficiently superior to historical results from Intergroup 0123/RTOG 94-05 (one- and two-year survival of 66 and 40 percent in the standard RT dose arm) to justify their selection over standard cisplatin and FU-based CRT. (See 'Radiation therapy dose intensification' above.)

Role of postchemoradiotherapy surgery — The great majority of patients treated with palliative CRT will not benefit from esophagectomy following CRT. However, some patients with initially unresectable or borderline resectable limited disease (ie, limited T4 tumors) might achieve a sufficient response from preoperative CRT such that potentially curative resection becomes feasible [54,55]. This decision must be individualized and made on a case-by-case basis.

The benefit of surgery following CRT among patients who present with locoregionally advanced esophageal cancer is an area of major controversy, even among those who present with potentially resectable disease. (See "Radiation therapy, chemoradiotherapy, neoadjuvant approaches, and postoperative adjuvant therapy for localized cancers of the esophagus", section on 'Necessity for surgery'.)

The key question for locally advanced, unresectable or borderline resectable disease is whether neoadjuvant concurrent CRT can successfully downstage these patients to the point where they are potentially resectable. There are no randomized trials that included patients with initially unresectable or borderline resectable disease. The only two randomized trials to address the benefit of post-CRT surgery were conducted predominantly in patients with T3, N0 to 1, M0 SCC, and both concluded that definitive CRT alone and CRT followed by surgery were equivalent in terms of two-year survival and quality of life [30,56]. CRT alone, however, was associated with more local failures (40 to 50 percent) and a greater need for later endoscopic intervention for relief of dysphagia. (See "Radiation therapy, chemoradiotherapy, neoadjuvant approaches, and postoperative adjuvant therapy for localized cancers of the esophagus", section on 'Necessity for surgery'.)

These data have led some to conclude that definitive CRT is a reasonable option for patients with locoregionally advanced, potentially resectable esophageal SCC who respond to initial therapy; others disagree, arguing that successful downstaging that leads to an R0 resection improves overall and disease-free survival, especially for those who achieve a pCR from neoadjuvant therapy [57,58]. The role of nonoperative treatment for adenocarcinomas remains poorly defined. These issues are discussed in detail elsewhere. (See "Radiation therapy, chemoradiotherapy, neoadjuvant approaches, and postoperative adjuvant therapy for localized cancers of the esophagus", section on 'Necessity for surgery'.)

An important point is that if post-CRT surgery is considered, a through restaging to include positron emission tomography (PET) prior to planned esophagectomy is useful to detect interval metastases (which were found in 8 percent of such patients in one study [59]) and, thus, avoid an unnecessary operation.

Salvage esophagectomy for locoregionally recurrent or persistent disease — Although rarely used, salvage esophagectomy is a feasible therapeutic option for carefully selected patients who have a limited volume of recurrent disease following definitive CRT. Surgery should only be attempted if an R0 resection is technically feasible and after distant metastatic disease has been carefully ruled out. Although there is no consensus as to which patients are appropriate candidates, we typically reserve salvage esophagectomy for patients with early stage recurrent disease (ie, node negative, T1 to 2 disease) (table 1).

A decision to pursue salvage surgery for patients with disease persistence after definitive CRT, particularly with adenocarcinomas, is more difficult. Persistent disease likely represents a more aggressive phenotype than recurrent disease, and outcomes with salvage surgery are poorer [60]. Distant metastatic disease is the cause of death in the majority of such patients, and esophagectomy is unlikely to improve survival.

While long-term disease control has been achieved in a few patients (particularly those with SCC [61,62]), there is little doubt that salvage esophagectomy is a more morbid operation than either primary esophagectomy or planned esophagectomy after neoadjuvant CRT [61,63-71].

The feasibility of salvage esophagectomy for persistent or recurrent disease following definitive CRT relates to two major issues: meticulous selection of candidates who are appropriate for salvage surgery (true local failures without metastatic disease), and experienced surgical skills in performing esophagectomy with measured and acceptable operative mortality.

A major problem is the difficulty in diagnosing recurrent or persistent local disease. In contrast to the primary diagnosis of esophageal cancer, which is usually straightforward, EUS and CT are of limited utility for assessing locoregional therapeutic response; furthermore, endoscopic

biopsies are sometimes negative despite the presence of viable tumor in deeper layers of the esophagus [59]. PET-CT may offer some advantages over conventional anatomic imaging; however, it too suffers from false-positive and false-negative results in patients with prior interventions such as stent placement. (See "Clinical manifestations, diagnosis, and staging of esophageal cancer", section on 'PET restaging after induction therapy' and "Clinical manifestations, diagnosis, and staging of esophageal cancer", section on 'CT, PET, and integrated PET/CT'.)

A persistent stricture may be the only clue that malignant disease is present; confirmation is often difficult, but it is essential if salvage esophagectomy is being considered. A lack of tumor in the resected esophagectomy specimen represents a diagnostic failure and a particularly difficult situation should the patient die (disease free) after surgery. Conclusive evidence of a local failure on a biopsy specimen and absence of metastases (distant failure) on a restaging PET scan should be obtained before embarking on salvage esophagectomy for locally recurrent disease.

A locoregional failure following CRT may manifest as persistent disease at the completion of the planned definitive therapy (primary failure) or as recurrent disease months later (secondary failure). Although surgery may be easier to perform in the setting of a primary failure, these patients are CRT nonresponders, and their anticipated survival is poor. As a group, they are more likely to die from metastatic than locoregionally recurrent disease. On the other hand, a carefully selected patient with a late recurrence may have a better cancer prognosis, but the potential for long-term survival must be balanced against the technical difficulty and greater morbidity of salvage esophagectomy in this setting.

Thus, salvage esophagectomy can be performed with acceptable mortality in selected patients in the hands of experienced surgeons [72]. The best way to select patients for this approach is not established.

A substantial number of patients, particularly those with SCC, have a pCR after CRT (eg, in the CROSS trial, 49 percent of patients with SCC and 23 percent of patients with adenocarcinoma achieved pCRs [11]), and these patients may not benefit from surgery. A clinical complete response has been associated with rates of pCR in up to 73 percent [73]. Clinically complete responses have been identified as being more likely in women, squamous cell tumors, and tumors with lower T stages and poor differentiation [74]. A multicenter trial is planned to evaluate a "surgery as needed" protocol with active surveillance following the completion of CRT for patients with both SCC and adenocarcinoma who have a clinical complete response to CRT [75].

Patients who are unable to tolerate initial chemoradiotherapy — For patients who are unable to tolerate initial CRT or who have a short estimated life expectancy (ie, six months or less), we suggest alternative approaches to palliation of dysphagia, such as endoscopic therapy (stenting, laser resection, photodynamic therapy, etc) or brachytherapy, rather than concurrent CRT.

Endoscopic interventions — Endoscopic interventions may be appropriate for palliation of dysphagia in patients who have advanced esophageal cancer in the following settings:

- Patients for whom definitive management is planned, but who have severe dysphagia at presentation requiring intervention prior to therapy
- Failure to achieve adequate palliation of dysphagia with initial therapy
- Recurrent dysphagia due to locoregional failure
- Recurrent dysphagia due to benign strictures in patients who are successfully treated with RT
- Patients are poor candidates for either chemotherapy or RT

In addition to brachytherapy, which doesn't require endoscopic guidance, there are several endoscopic approaches to providing palliation from malignant dysphagia:

- Placement of a prosthetic self-expanding metal stent (SEMS)
- Dilation
- Endoscopic mucosal resection
- Photodynamic therapy

Stenting is preferred for patients with a malignant stricture and/or fistula (image 1). In the absence of a fistula, optimal therapy remains controversial. A systematic review of interventions for palliation of dysphagia associated with locally advanced esophageal cancer concluded that insertion of an SEMS is safe and provides rapid relief of dysphagia, while thermal and chemical ablative therapy provided comparable dysphagia palliation but with an increased requirement for reintervention and adverse effects [76]. Brachytherapy is a suitable alternative that may be associated with improved survival and quality of life.

Endoscopic approaches to palliation in esophageal cancer are discussed in detail elsewhere. (See "Endoscopic palliation of esophageal cancer" and "Endoscopic stenting for palliation of malignant esophageal obstruction".)

Brachytherapy — Brachytherapy permits treatment of a localized area of the esophagus with high radiation doses with relative sparing of surrounding structures. It should be considered an alternative to stent placement for palliation of dysphagia, particularly when the extent of extraluminal disease is limited, and long-term palliation is likely. Although stenting has the advantage of palliating dysphagia immediately, the palliative effect of brachytherapy is frequently more durable.

Consensus guidelines for brachytherapy in the treatment of esophageal cancer from the American Brachytherapy Society are presented in the tables (table 6A-B) [40]. However:

- Although brachytherapy can successfully palliate dysphagia, as monotherapy, its use should be restricted to patients with a short life expectancy (less than six months). For patients who are expected to live less than three months, short-term palliation of swallowing may be better achieved with endoscopic stent placement. (See 'Endoscopic interventions' above and "Endoscopic palliation of esophageal cancer" and "Endoscopic stenting for palliation of malignant esophageal obstruction", section on 'Efficacy'.)

  A simple score to identify patients with a poor prognosis in whom stent placement may be preferable to brachytherapy has been developed [77]. However, this prognostic model has not been independently validated, and further study, particularly of long-term outcomes, is needed.

- Brachytherapy should be used with extreme caution in the setting of a local recurrence after prior CRT because of the risk of fistula formation.

Brachytherapy alone can provide successful long-term palliation of dysphagia in patients with unresectable and/or advanced esophageal cancer [78-82]. In a trial in which 209 patients with obstruction from esophageal or gastroesophageal junction tumors were randomly assigned to brachytherapy alone (12 Gy) or to endoscopic placement of a metal stent, the stented group had more rapid improvement within 30 days of the procedure [81]. However, at later time points, brachytherapy was associated with significantly lower dysphagia severity scores and a significantly greater number of days with almost no dysphagia (115 versus 82 days). The brachytherapy group also had a significantly lower complication rate, as well as better quality of life scores, and they were no more likely to require retreatment for recurrent or persistent dysphagia than the stented group.

Surgical palliation — Palliative resection is usually not considered for patients with locally advanced disease and distant metastases due to their short life expectancy (usually less than six months). Palliative resection is also no longer considered a valid concept for patients with locally advanced non-metastatic esophageal cancer. Perioperative morbidity and mortality rates

are high, and the opportunity for potentially curative alternatives, such as definitive CRT, may be lost. Furthermore, although palliative resection can relieve dysphagia, restoration of the ability to swallow can now be accomplished successfully nonsurgically in the majority of patients and is most commonly achieved by the placement of an endoluminal stent. (See 'Endoscopic interventions' above and "Endoscopic palliation of esophageal cancer".)

Like palliative esophagectomy, surgical bypass provides limited benefit and is associated with substantial morbidity in patients with clearly unresectable disease [7,8,83-85]. Although these palliative bypasses relieve symptoms, complication rates usually exceed 50 to 60 percent, and mortality rates are between 5 and 10 percent [8,83-85]. As a result, these procedures are now rarely attempted. Instead, the recommended treatment for inoperable patients with local tumor invasion of the airway or aorta, or extraregional abdominal metastases, is endoscopic therapy, stent placement, RT, or combined chemotherapy and radiation. (See 'Palliation of dysphagia' above.)

TREATMENT OF CERVICAL TUMORS

We suggest radiation therapy (RT) combined with concurrent chemotherapy rather than surgery for most patients with locally advanced tumors of the cervical esophagus.

Between 5 and 6 percent of esophageal cancers arise in the cervical portion of the esophagus, which is 6 to 8 cm long and extends from the hypopharynx to the thoracic inlet (suprasternal notch) (figure 1) [86]. Locally advanced disease is usually present at the time of diagnosis [87].

Cervical esophageal squamous cell cancers (SCCs) present a unique management challenge. Surgery is usually not possible or highly morbid due to the very close relationship to other organs, such as the larynx and trachea. As such, treatment is more closely related to SCC of the head and neck than to thoracic esophageal cancer [88].

As with SCCs of the oropharynx, hypopharynx, and larynx, RT combined with chemotherapy is preferred over initial surgery because it contributes to organ preservation; overall survival, local failure-free survival (FFS), and distant FFS are the same; major morbidity is avoided in most [88-97]:

- The largest retrospective series included 224 patients with cervical esophageal cancer, 161 treated with RT (either RT alone or concomitant chemoradiotherapy) with or without subsequent surgery and 63 with primary surgery with or without subsequent RT [93]. At a median follow-up of 15.1 months, rates of overall two-year local FFS, distant FFS, and

overall survival for patients undergoing primary RT versus primary surgery were 69.9 versus 68.6, 74.3 versus 62.5, and 49.3 versus 50.7 percent, respectively (all with p values >0.05). Treatment-related mortality was significantly greater in the surgery group (12.8 versus 3.5 percent).

- The best data on oncologic outcomes of definitive chemoradiotherapy come from a systematic review and meta-analysis of 1222 patients derived from 22 retrospective studies [97]. Estimated pooled overall survival rates at one, three, and five years were 78, 48, and 35 percent, respectively, and the corresponding PFS rates were 64, 38, and 30 percent, respectively.

Cisplatin-based chemotherapy concurrent with RT is usually chosen. Specific regimens as are appropriate for patients with head and neck cancer are discussed in detail elsewhere. (See "Overview of treatment for head and neck cancer", section on 'Locoregionally advanced disease'.)

Surgery may be considered for selected patients, mainly those with earlier stage disease. If surgery is performed, it usually requires removal of portions of the pharynx, the larynx, the thyroid gland, and the proximal esophagus or the entire esophagus (pharyngo-laryngo-esophagectomy [PLE]). This one-stage, three-phase operation requires cervical, abdominal, and thoracic incisions and a permanent terminal tracheostomy. Restoration of gastrointestinal tract continuity can be accomplished with a gastric pull-up and anastomosis to the pharynx. (See "Surgical management of resectable esophageal and esophagogastric junction cancers", section on 'Cervical esophageal cancer resection'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Esophageal cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading

level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Esophageal cancer (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Pretreatment considerations**
  - Locally advanced, unresectable or inoperable esophageal cancer is incurable in the majority of patients. A major goal of treatment is improvement in quality of life by restoring and/or maintaining the ability to swallow. (See 'Introduction' above.)
  - Evaluation for resectability requires endoscopic ultrasound (EUS), computed tomography (CT), and integrated fluorodeoxyglucose positron emission tomography (FDG-PET)/CT. For squamous cell cancers (SCCs) located at or above the carina, bronchoscopy is indicated to rule out tracheoesophageal fistula. For cervical SCCs, flexible laryngoscopy to assess local disease spread and exclude a synchronous malignancy of the head and neck is generally recommended. (See 'Staging evaluation' above.)

    In general, the finding of unresectable T4b disease (table 1), the presence of a tracheoesophageal fistula (image 1), or distant metastases precludes curative surgical resection. (See 'Criteria for unresectability' above.)
- **Treatment for thoracoabdominal tumors**
  - For most patients with non-metastatic, inoperable or unresectable esophageal SCC or adenocarcinoma who are able to tolerate it and have an estimated life expectancy of greater than a few weeks, we recommend concurrent chemoradiotherapy (CRT) rather than radiation therapy (RT) alone (**Grade 1B**). (See 'Patients who are fit for combined modality therapy' above.)
  - For most patients with SCC who are undergoing definitive CRT, we suggest concurrent cisplatin and fluorouracil (FU) during RT, as was used in the Radiation Therapy

Oncology Group (RTOG) 85-01 and the US Intergroup 0123 trials rather than a different regimen (**Grade 2B**). (See 'Impact on survival' above.)

For patients with adenocarcinoma, we suggest the low-dose weekly carboplatin plus paclitaxel regimen (table 7) concurrent with RT, as was used in the Dutch CROSS trial, rather cisplatin plus FU (**Grade 2B**). (See 'Impact on survival' above and "Treatment protocols for esophagogastric cancer" and "Radiation therapy, chemoradiotherapy, neoadjuvant approaches, and postoperative adjuvant therapy for localized cancers of the esophagus", section on 'Concurrent chemoradiotherapy'.)

Modern three-dimensional (3-D) conformal techniques should be used for treatment planning to minimize toxicities to adjacent vital organs. Even though the Dutch CROSS trial used a lower dose (41.4 Gy), the standard dose of RT for patients treated with concurrent CRT for esophageal cancer remains 50.4 Gy administered in 28 daily fractions, as was used in RTOG 85-01. (See 'Impact on survival' above and "Radiation therapy, chemoradiotherapy, neoadjuvant approaches, and postoperative adjuvant therapy for localized cancers of the esophagus", section on 'Technique for preoperative RT'.)

- The great majority of patients will not benefit from esophagectomy following CRT. However, selected patients with initially unresectable or borderline resectable disease (ie, limited T4 disease) might achieve a sufficient response from preoperative CRT such that potentially curative resection becomes feasible. (See 'Role of postchemoradiotherapy surgery' above.)

  For patients whose disease recurs after initial definitive CRT, the decision to pursue salvage esophagectomy must be made on a case-by-case basis. The best candidates are those who have early stage (ie, node negative, T1 to 2 tumors (table 1)) recurrent, rather than persistent, disease. Definitive pathologic evidence of an isolated local failure with the absence of metastatic disease should be established using integrated PET/CT and diagnostic laparoscopy (for distal adenocarcinomas) prior to salvage esophagectomy. (See 'Salvage esophagectomy for locoregionally recurrent or persistent disease' above.)

- For patients who are unable to tolerate initial CRT or who have a short estimated life expectancy, we suggest alternative approaches to palliation of swallowing, such as endoscopic therapy or brachytherapy, rather than concurrent CRT (**Grade 2C**). (See 'Endoscopic interventions' above and 'Brachytherapy' above.)

Endoscopic interventions (dilation, placement of an endoluminal stent, laser and photodynamic therapy) are appropriate for palliation of dysphagia in the following settings (see "Endoscopic palliation of esophageal cancer" and "Endoscopic interventions for nonmalignant esophageal strictures in adults" and "Endoscopic stenting for palliation of malignant esophageal obstruction", section on 'Efficacy'):

- Patients for whom definitive management with CRT is planned, but who have severe dysphagia at presentation requiring intervention prior to therapy
- A failure to achieve adequate palliation of dysphagia with initial therapy
- Recurrent dysphagia due to locoregional failure
- Recurrent dysphagia due to benign strictures in patients who are successfully treated with RT
- Patients who are poor candidates for either chemotherapy or RT
- Dysphagia associated with a tracheoesophageal fistula

Brachytherapy is an alternative to endoscopic therapy for palliation of dysphagia, particularly when the extent of extraluminal disease is limited, and long-term palliation is likely to be needed. Although stenting has the advantage of immediate palliation of dysphagia, the benefit of brachytherapy is frequently more durable. (See 'Brachytherapy' above.)

- The preferred treatment for inoperable patients with local tumor invasion of the airway or aorta, or extraregional abdominal metastases, is endoscopic therapy, stent placement, RT, or concurrent CRT rather than surgical palliation. (See 'Surgical palliation' above.)

- **Cervical tumors** – We suggest RT combined with concurrent chemotherapy rather than RT alone or surgery for most patients with locally advanced tumors of the cervical esophagus (**Grade 2C**). (See 'Treatment of cervical tumors' above.)

REFERENCES

1. Ilson DH, Saltz L, Enzinger P, et al. Phase II trial of weekly irinotecan plus cisplatin in advanced esophageal cancer. J Clin Oncol 1999; 17:3270.

2. Coia LR, Myerson RJ, Tepper JE. Late effects of radiation therapy on the gastrointestinal tract. Int J Radiat Oncol Biol Phys 1995; 31:1213.
3. American Joint Committee on Cancer Staging Manual, 6th ed, Greene FL, Page DL, Fleming ID, et al (Eds), Springer Verlag, New York 2001. p.91.
4. Rice TW, Kelsen D, Blackstone EH, et al. Esophagus and esophagogastric junction. In: AJCC Cancer Staging Manual, 8th ed, Amin MB (Ed), AJCC, Chicago 2017. p.185. Corrected at 4th printing, 2018.
5. Koike R, Nishimura Y, Nakamatsu K, et al. Concurrent chemoradiotherapy for esophageal cancer with malignant fistula. Int J Radiat Oncol Biol Phys 2008; 70:1418.
6. Eloubeidi MA, Wallace MB, Hoffman BJ, et al. Predictors of survival for esophageal cancer patients with and without celiac axis lymphadenopathy: impact of staging endosonography. Ann Thorac Surg 2001; 72:212.
7. Bolton JS, Fuhrman GM, Richardson WS. Esophageal resection for cancer. Surg Clin North Am 1998; 78:773.
8. Mannell A, Becker PJ, Nissenbaum M. Bypass surgery for unresectable oesophageal cancer: early and late results in 124 cases. Br J Surg 1988; 75:283.
9. al-Sarraf M, Martz K, Herskovic A, et al. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. J Clin Oncol 1997; 15:277.
10. Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002; 20:1167.
11. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012; 366:2074.
12. van Andel JG, Dees J, Dijkhuis CM, et al. Carcinoma of the esophagus: results of treatment. Ann Surg 1979; 190:684.
13. Petrovich Z, Langholz B, Formenti S, et al. Management of carcinoma of the esophagus: the role of radiotherapy. Am J Clin Oncol 1991; 14:80.
14. Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 1992; 326:1593.
15. Caspers RJ, Welvaart K, Verkes RJ, et al. The effect of radiotherapy on dysphagia and survival in patients with esophageal cancer. Radiother Oncol 1988; 12:15.

16. Wobbes T, Baron B, Paillot B, et al. Prospective randomised study of split-course radiotherapy versus cisplatin plus split-course radiotherapy in inoperable squamous cell carcinoma of the oesophagus. Eur J Cancer 2001; 37:470.
17. Penniment MG, Harvey JA, Wong R, et al. A randomized phase III study in advanced esophageal cancer (OC) to compare the quality of life (QoL) and palliation of dysphagia in patients treated with radiotherapy (RT) or chemoradiotherapy (CRT) TROG 03.01 NCIC CTG ES.2. J Clin Oncol 2014; 32S: ASCO #4009.
18. Shapiro J, van Lanschot JJ, Hulshof MC, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 2015; 16:1090.
19. Coia LR, Soffen EM, Schultheiss TE, et al. Swallowing function in patients with esophageal cancer treated with concurrent radiation and chemotherapy. Cancer 1993; 71:281.
20. Gill PG, Denham JW, Jamieson GG, et al. Patterns of treatment failure and prognostic factors associated with the treatment of esophageal carcinoma with chemotherapy and radiotherapy either as sole treatment or followed by surgery. J Clin Oncol 1992; 10:1037.
21. Wong SK, Chiu PW, Leung SF, et al. Concurrent chemoradiotherapy or endoscopic stenting for advanced squamous cell carcinoma of esophagus: a case-control study. Ann Surg Oncol 2008; 15:576.
22. Ikeda E, Kojima T, Kaneko K, et al. Efficacy of concurrent chemoradiotherapy as a palliative treatment in stage IVB esophageal cancer patients with dysphagia. Jpn J Clin Oncol 2011; 41:964.
23. Muto M, Ohtsu A, Miyamoto S, et al. Concurrent chemoradiotherapy for esophageal carcinoma patients with malignant fistulae. Cancer 1999; 86:1406.
24. Park JY, Shin JH, Song HY, et al. Airway complications after covered stent placement for malignant esophageal stricture: special reference to radiation therapy. AJR Am J Roentgenol 2012; 198:453.
25. van den Bongard HJ, Boot H, Baas P, Taal BG. The role of parallel stent insertion in patients with esophagorespiratory fistulas. Gastrointest Endosc 2002; 55:110.
26. Hürtgen M, Herber SC. Treatment of malignant tracheoesophageal fistula. Thorac Surg Clin 2014; 24:117.
27. O'Rourke IC, Tiver K, Bull C, et al. Swallowing performance after radiation therapy for carcinoma of the esophagus. Cancer 1988; 61:2022.
28. Ishida K, Iizuka T, Ando N, Ide H. Phase II study of chemoradiotherapy for advanced squamous cell carcinoma of the thoracic esophagus: nine Japanese institutions trial. Jpn J

Clin Oncol 1996; 26:310.

29. Ohtsu A, Boku N, Muro K, et al. Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. J Clin Oncol 1999; 17:2915.
30. Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol 2005; 23:2310.
31. Hulshof MCCM, Geijsen ED, Rozema T, et al. Randomized Study on Dose Escalation in Definitive Chemoradiation for Patients With Locally Advanced Esophageal Cancer (ARTDECO Study). J Clin Oncol 2021; 39:2816.
32. Xu Y, Dong B, Zhu W, et al. A Phase III Multicenter Randomized Clinical Trial of 60 Gy versus 50 Gy Radiation Dose in Concurrent Chemoradiotherapy for Inoperable Esophageal Squamous Cell Carcinoma. Clin Cancer Res 2022; 28:1792.
33. Yin W. Radiotherapy of carcinoma of oesophagus in China. Chin Med J (Engl) 1997; 110:289.
34. Sur RK, Singh DP, Sharma SC, et al. Radiation therapy of esophageal cancer: role of high dose rate brachytherapy. Int J Radiat Oncol Biol Phys 1992; 22:1043.
35. Calais G, Dorval E, Louisot P, et al. Radiotherapy with high dose rate brachytherapy boost and concomitant chemotherapy for Stages IIB and III esophageal carcinoma: results of a pilot study. Int J Radiat Oncol Biol Phys 1997; 38:769.
36. Iwasa M, Ohmori Y, Iwasa Y, et al. Effect of multidisciplinary treatment with high dose rate intraluminal brachytherapy on survival in patients with unresectable esophageal cancer. Dig Surg 1998; 15:227.
37. Chiarion-Sileni V, Corti L, Ruol A, et al. Phase II trial of docetaxel, cisplatin and fluorouracil followed by carboplatin and radiotherapy in locally advanced oesophageal cancer. Br J Cancer 2007; 96:432.
38. Ishikawa H, Sakurai H, Tamaki Y, et al. Radiation therapy alone for stage I (UICC T1N0M0) squamous cell carcinoma of the esophagus: indications for surgery or combined chemoradiotherapy. J Gastroenterol Hepatol 2006; 21:1290.
39. Gaspar LE, Qian C, Kocha WI, et al. A phase I/II study of external beam radiation, brachytherapy and concurrent chemotherapy in localized cancer of the esophagus (RTOG 92-07): preliminary toxicity report. Int J Radiat Oncol Biol Phys 1997; 37:593.
40. Gaspar LE, Nag S, Herskovic A, et al. American Brachytherapy Society (ABS) consensus guidelines for brachytherapy of esophageal cancer. Clinical Research Committee, American Brachytherapy Society, Philadelphia, PA. Int J Radiat Oncol Biol Phys 1997; 38:127.

41. Blanke CD, Choy H, Teng M, et al. Concurrent paclitaxel and thoracic irradiation for locally advanced esophageal cancer. Semin Radiat Oncol 1999; 9:43.
42. Adelstein DJ, Rice TW, Rybicki LA, et al. Does paclitaxel improve the chemoradiotherapy of locoregionally advanced esophageal cancer? A nonrandomized comparison with fluorouracil-based therapy. J Clin Oncol 2000; 18:2032.
43. Kim DW, Blanke CD, Wu H, et al. Phase II study of preoperative paclitaxel/cisplatin with radiotherapy in locally advanced esophageal cancer. Int J Radiat Oncol Biol Phys 2007; 67:397.
44. Chiarion-Sileni V, Innocente R, Cavina R, et al. Multi-center phase II trial of chemo-radiotherapy with 5-fluorouracil, leucovorin and oxaliplatin in locally advanced esophageal cancer. Cancer Chemother Pharmacol 2009; 63:1111.
45. Ruppert BN, Watkins JM, Shirai K, et al. Cisplatin/Irinotecan versus carboplatin/paclitaxel as definitive chemoradiotherapy for locoregionally advanced esophageal cancer. Am J Clin Oncol 2010; 33:346.
46. Zhao T, Chen H, Zhang T. Docetaxel and cisplatin concurrent with radiotherapy versus 5-fluorouracil and cisplatin concurrent with radiotherapy in treatment for locally advanced oesophageal squamous cell carcinoma: a randomized clinical study. Med Oncol 2012; 29:3017.
47. Conroy T, Yataghène Y, Etienne PL, et al. Phase II randomised trial of chemoradiotherapy with FOLFOX4 or cisplatin plus fluorouracil in oesophageal cancer. Br J Cancer 2010; 103:1349.
48. Tomblyn MB, Goldman BH, Thomas CR Jr, et al. Cetuximab plus cisplatin, irinotecan, and thoracic radiotherapy as definitive treatment for locally advanced, unresectable esophageal cancer: a phase-II study of the SWOG (S0414). J Thorac Oncol 2012; 7:906.
49. Conroy T, Galais MP, Raoul JL, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. Lancet Oncol 2014; 15:305.
50. Khushalani NI, Leichman CG, Proulx G, et al. Oxaliplatin in combination with protracted-infusion fluorouracil and radiation: report of a clinical trial for patients with esophageal cancer. J Clin Oncol 2002; 20:2844.
51. Suntharalingam M, Winter K, Ilson D, et al. Effect of the Addition of Cetuximab to Paclitaxel, Cisplatin, and Radiation Therapy for Patients With Esophageal Cancer: The NRG Oncology RTOG 0436 Phase 3 Randomized Clinical Trial. JAMA Oncol 2017; 3:1520.

52. Stahl M, Maderer A, Lordick F, et al. Perioperative chemotherapy with or without epidermal growth factor receptor blockade in unselected patients with locally advanced oesophagogastric adenocarcinoma: Randomized phase II study with advanced biomarker program of the German Cancer Society (AIO/CAO STO-0801). Eur J Cancer 2018; 93:119.
53. Ajani JA, Winter K, Komaki R, et al. Phase II randomized trial of two nonoperative regimens of induction chemotherapy followed by chemoradiation in patients with localized carcinoma of the esophagus: RTOG 0113. J Clin Oncol 2008; 26:4551.
54. Forshaw MJ, Gossage JA, Chrystal K, et al. Neoadjuvant chemotherapy for locally advanced carcinoma of the lower oesophagus and oesophago-gastric junction. Eur J Surg Oncol 2006; 32:1114.
55. Defize IL, van der Horst S, Bülbul M, et al. Salvage Robot-Assisted Minimally Invasive Esophagectomy (RAMIE) for T4b Esophageal Cancer After Definitive Chemoradiotherapy. Ann Surg Oncol 2021; 28:2730.
56. Bedenne L, Michel P, Bouché O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol 2007; 25:1160.
57. Morita M, Toh Y, Saeki H, et al. Clinical significance of chemoradiotherapy and surgical resection for cT4 esophageal cancer. Anticancer Res 2012; 32:3275.
58. Pimiento JM, Weber J, Hoffe SE, et al. Outcomes associated with surgery for T4 esophageal cancer. Ann Surg Oncol 2013; 20:2706.
59. Bruzzi JF, Swisher SG, Truong MT, et al. Detection of interval distant metastases: clinical utility of integrated CT-PET imaging in patients with esophageal carcinoma after neoadjuvant therapy. Cancer 2007; 109:125.
60. Markar S, Gronnier C, Duhamel A, et al. Salvage Surgery After Chemoradiotherapy in the Management of Esophageal Cancer: Is It a Viable Therapeutic Option? J Clin Oncol 2015; 33:3866.
61. Nishimura M, Daiko H, Yoshida J, Nagai K. Salvage esophagectomy following definitive chemoradiotherapy. Gen Thorac Cardiovasc Surg 2007; 55:461.
62. Booka E, Haneda R, Ishii K, et al. Appropriate Candidates for Salvage Esophagectomy of Initially Unresectable Locally Advanced T4 Esophageal Squamous Cell Carcinoma. Ann Surg Oncol 2020; 27:3163.
63. Swisher SG, Wynn P, Putnam JB, et al. Salvage esophagectomy for recurrent tumors after definitive chemotherapy and radiotherapy. J Thorac Cardiovasc Surg 2002; 123:175.

64. Borghesi S, Hawkins MA, Tait D. Oesophagectomy after definitive chemoradiation in patients with locally advanced oesophageal cancer. Clin Oncol (R Coll Radiol) 2008; 20:221.

65. Gardner-Thorpe J, Hardwick RH, Dwerryhouse SJ. Salvage oesophagectomy after local failure of definitive chemoradiotherapy. Br J Surg 2007; 94:1059.

66. Piessen G, Briez N, Triboulet JP, Mariette C. Patients with locally advanced esophageal carcinoma nonresponder to radiochemotherapy: who will benefit from surgery? Ann Surg Oncol 2007; 14:2036.

67. D'Journo XB, Michelet P, Dahan L, et al. Indications and outcome of salvage surgery for oesophageal cancer. Eur J Cardiothorac Surg 2008; 33:1117.

68. Urschel JD, Ashiku S, Thurer R, Sellke FW. Salvage or planned esophagectomy after chemoradiation therapy for locally advanced esophageal cancer--a review. Dis Esophagus 2003; 16:60.

69. Hofstetter WL, Maru DM, Correa A, et al. Salvage resection for esophageal adenocarcinoma after failed definitive chemoradiation (abstract). Data presented at the 2009 ASCO Gastroint estinal Cancer Symposium, San Francisco, CA, January 16, 2009.

70. Miyata H, Yamasaki M, Takiguchi S, et al. Salvage esophagectomy after definitive chemoradiotherapy for thoracic esophageal cancer. J Surg Oncol 2009; 100:442.

71. Farinella E, Safar A, Nasser HA, et al. Salvage esophagectomy after failure of definitive radiochemotherapy for esophageal cancer. J Surg Oncol 2016; 114:833.

72. Watanabe M, Mine S, Nishida K, et al. Salvage Esophagectomy After Definitive Chemoradiotherapy for Patients with Esophageal Squamous Cell Carcinoma: Who Really Benefits from this High-Risk Surgery? Ann Surg Oncol 2015; 22:4438.

73. Liu SL, Xi M, Yang H, et al. Is There a Correlation Between Clinical Complete Response and Pathological Complete Response After Neoadjuvant Chemoradiotherapy for Esophageal Squamous Cell Cancer? Ann Surg Oncol 2016; 23:273.

74. Toxopeus EL, Nieboer D, Shapiro J, et al. Nomogram for predicting pathologically complete response after neoadjuvant chemoradiotherapy for oesophageal cancer. Radiother Oncol 2015; 115:392.

75. Noordman BJ, Shapiro J, Spaander MC, et al. Accuracy of Detecting Residual Disease After Cross Neoadjuvant Chemoradiotherapy for Esophageal Cancer (preSANO Trial): Rationale and Protocol. JMIR Res Protoc 2015; 4:e79.

76. Sreedharan A, Harris K, Crellin A, et al. Interventions for dysphagia in oesophageal cancer. Cochrane Database Syst Rev 2009; :CD005048.

77. Steyerberg EW, Homs MY, Stokvis A, et al. Stent placement or brachytherapy for palliation of dysphagia from esophageal cancer: a prognostic model to guide treatment selection. Gastrointest Endosc 2005; 62:333.

78. Fleischman EH, Kagan AR, Bellotti JE, et al. Effective palliation for inoperable esophageal cancer using intensive intracavitary radiation. J Surg Oncol 1990; 44:234.

79. Jager JJ, Pannebakker M, Rijken J, et al. Palliation in esophageal cancer with a single session of intraluminal irradiation. Radiother Oncol 1992; 25:134.

80. Sur RK, Levin CV, Donde B, et al. Prospective randomized trial of HDR brachytherapy as a sole modality in palliation of advanced esophageal carcinoma--an International Atomic Energy Agency study. Int J Radiat Oncol Biol Phys 2002; 53:127.

81. Homs MY, Steyerberg EW, Eijkenboom WM, et al. Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: multicentre randomised trial. Lancet 2004; 364:1497.

82. Bergquist H, Wenger U, Johnsson E, et al. Stent insertion or endoluminal brachytherapy as palliation of patients with advanced cancer of the esophagus and gastroesophageal junction. Results of a randomized, controlled clinical trial. Dis Esophagus 2005; 18:131.

83. Segalin A, Little AG, Ruol A, et al. Surgical and endoscopic palliation of esophageal carcinoma. Ann Thorac Surg 1989; 48:267.

84. Orringer MB. Substernal gastric bypass of the excluded esophagus--results of an ill-advised operation. Surgery 1984; 96:467.

85. Hirai T, Yamashita Y, Mukaida H, et al. Bypass operation for advanced esophageal cancer--an analysis of 93 cases. Jpn J Surg 1989; 19:182.

86. Mendenhall WM, Sombeck MD, Parsons JT, et al. Management of Cervical Esophageal Carcinoma. Semin Radiat Oncol 1994; 4:179.

87. Collin CF, Spiro RH. Carcinoma of the cervical esophagus: changing therapeutic trends. Am J Surg 1984; 148:460.

88. Hoeben A, Polak J, Van De Voorde L, et al. Cervical esophageal cancer: a gap in cancer knowledge. Ann Oncol 2016; 27:1664.

89. Bidoli P, Bajetta E, Stani SC, et al. Ten-year survival with chemotherapy and radiotherapy in patients with squamous cell carcinoma of the esophagus. Cancer 2002; 94:352.

90. Wang HW, Chu PY, Kuo KT, et al. A reappraisal of surgical management for squamous cell carcinoma in the pharyngoesophageal junction. J Surg Oncol 2006; 93:468.

91. Huang SH, Lockwood G, Brierley J, et al. Effect of concurrent high-dose cisplatin chemotherapy and conformal radiotherapy on cervical esophageal cancer survival. Int J

Radiat Oncol Biol Phys 2008; 71:735.

92. Tong DK, Law S, Kwong DL, et al. Current management of cervical esophageal cancer. World J Surg 2011; 35:600.
93. Cao CN, Luo JW, Gao L, et al. Primary radiotherapy compared with primary surgery in cervical esophageal cancer. JAMA Otolaryngol Head Neck Surg 2014; 140:918.
94. Cao C, Luo J, Gao L, et al. Definitive radiotherapy for cervical esophageal cancer. Head Neck 2015; 37:151.
95. Zhang P, Xi M, Zhao L, et al. Clinical efficacy and failure pattern in patients with cervical esophageal cancer treated with definitive chemoradiotherapy. Radiother Oncol 2015; 116:257.
96. Valmasoni M, Pierobon ES, Zanchettin G, et al. Cervical Esophageal Cancer Treatment Strategies: A Cohort Study Appraising the Debated Role of Surgery. Ann Surg Oncol 2018; 25:2747.
97. De Virgilio A, Costantino A, Festa BM, et al. Oncological outcomes of squamous cell carcinoma of the cervical esophagus treated with definitive (chemo-)radiotherapy: a systematic review and meta-analysis. J Cancer Res Clin Oncol 2023; 149:1029.

Topic 2472 Version 61.0

GRAPHICS

Esophagus and esophagogastric junction cancers TNM staging AJCC UICC 8th edition

Primary tumor (T), squamous cell carcinoma and adenocarcinoma	
T category	**T criteria**
TX	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined to the epithelium by the basement membrane
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades the lamina propria or muscularis mucosae
T1b	Tumor invades the submucosa
T2	Tumor invades the muscularis propria

T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b	Tumor invades other adjacent structures, such as the aorta, vertebral body, or airway

Regional lymph nodes (N), squamous cell carcinoma and adenocarcinoma

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases in 1 or 2 regional lymph nodes
N2	Metastases in 3 to 6 regional lymph nodes
N3	Metastases in 7 or more regional lymph nodes

Distant metastasis (M), squamous cell carcinoma and adenocarcinoma

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

Histologic grade (G), squamous cell carcinoma and adenocarcinoma

G	G definition
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated, undifferentiated

Location, squamous cell carcinoma

Location plays a role in the stage grouping of esophageal squamous cancers.

Location category	Location criteria
X	Location unknown
Upper	Cervical esophagus to lower border of azygos vein
Middle	Lower border of azygos vein to lower border of inferior pulmonary vein
Lower	Lower border of inferior pulmonary vein to stomach, including gastroesophageal junction

NOTE: Location is defined by the position of the epicenter of the tumor in the esophagus.

Prognostic stage groups, squamous cell carcinoma

Clinical (cTNM)

When cT is…	And cN is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1	N0-1	M0	I
T2	N0-1	M0	II
T3	N0	M0	II
T3	N1	M0	III
T1-3	N2	M0	III
T4	N0-2	M0	IVA
Any T	N3	M0	IVA
Any T	Any N	M1	IVB

Pathological (pTNM)

When pT is…	And pN is…	And M is…	And G is…	And location is…	Then the stage group is…
Tis	N0	M0	N/A	Any	0
T1a	N0	M0	G1	Any	IA
T1a	N0	M0	G2-3	Any	IB
T1a	N0	M0	GX	Any	IA
T1b	N0	M0	G1-3	Any	IB
T1b	N0	M0	GX	Any	IB
T2	N0	M0	G1	Any	IB
T2	N0	M0	G2-3	Any	IIA
T2	N0	M0	GX	Any	IIA
T3	N0	M0	Any	Lower	IIA
T3	N0	M0	G1	Upper/middle	IIA
T3	N0	M0	G2-3	Upper/middle	IIB
T3	N0	M0	GX	Any	IIB
T3	N0	M0	Any	Location X	IIB
T1	N1	M0	Any	Any	IIB

T1	N2	M0	Any	Any	IIIA
T2	N1	M0	Any	Any	IIIA
T2	N2	M0	Any	Any	IIIB
T3	N1-2	M0	Any	Any	IIIB
T4a	N0-1	M0	Any	Any	IIIB
T4a	N2	M0	Any	Any	IVA
T4b	N0-2	M0	Any	Any	IVA
Any T	N3	M0	Any	Any	IVA
Any T	Any N	M1	Any	Any	IVB

Post-neoadjuvant therapy (ypTNM)

When ypT is…	And ypN is…	And M is…	Then the stage group is…
T0-2	N0	M0	I
T3	N0	M0	II
T0-2	N1	M0	IIIA
T3	N1	M0	IIIB
T0-3	N2	M0	IIIB
T4a	N0	M0	IIIB
T4a	N1-2	M0	IVA
T4a	NX	M0	IVA
T4b	N0-2	M0	IVA
Any T	N3	M0	IVA
Any T	Any N	M1	IVB

Prognostic stage groups, adenocarcinoma

Clinical (cTNM)

When cT is…	And cN is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1	N0	M0	I
T1	N1	M0	IIA
T2	N0	M0	IIB
T2	N1	M0	III

T3	N0-1	M0	III
T4a	N0-1	M0	III
T1-4a	N2	M0	IVA
T4b	N0-2	M0	IVA
Any T	N3	M0	IVA
Any T	Any N	M1	IVB

Pathological (pTNM)

When pT is…	And pN is…	And M is…	And G is…	Then the stage group is…
Tis	N0	M0	N/A	0
T1a	N0	M0	G1	IA
T1a	N0	M0	GX	IA
T1a	N0	M0	G2	IB
T1b	N0	M0	G1-2	IB
T1b	N0	M0	GX	IB
T1	N0	M0	G3	IC
T2	N0	M0	G1-2	IC
T2	N0	M0	G3	IIA
T2	N0	M0	GX	IIA
T1	N1	M0	Any	IIB
T3	N0	M0	Any	IIB
T1	N2	M0	Any	IIIA
T2	N1	M0	Any	IIIA
T2	N2	M0	Any	IIIB
T3	N1-2	M0	Any	IIIB
T4a	N0-1	M0	Any	IIIB
T4a	N2	M0	Any	IVA
T4b	N0-2	M0	Any	IVA
Any T	N3	M0	Any	IVA
Any T	Any N	M1	Any	IVB

Post-neoadjuvant therapy (ypTNM)

When ypT is...	And ypN is...	And M is...	Then the stage group is...
T0-2	N0	M0	I
T3	N0	M0	II
T0-2	N1	M0	IIIA
T3	N1	M0	IIIB
T0-3	N2	M0	IIIB
T4a	N0	M0	IIIB
T4a	N1-2	M0	IVA
T4a	NX	M0	IVA
T4b	N0-2	M0	IVA
Any T	N3	M0	IVA
Any T	Any N	M1	IVB

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control; N/A: not applicable.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

Graphic 111221 Version 9.0

Dysphagia grading system

Dysphagia	Symptom
Grade 0	Able to swallow all solid foods without difficulty
Grade 1	Able to swallow solid foods with some difficulty
Grade 2	Able to swallow soft or semi solid foods only
Grade 3	Able to swallow liquefied foods and liquids only
Grade 4	Unable to swallow liquids/saliva

Coia LR, Myerson RJ, Tepper JE. Late effects of radiation therapy on the gastrointestinal tract. Int J Radiat Oncol Biol Phys 1995; 31:1213.

Graphic 70813 Version 2.0

NCI CTCAE v5.0 dysphagia

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death

Dysphagia is characterized by difficulty in swallowing.

NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; TPN: total parenteral nutrition.

Reproduced from: Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, November 2017, National Institutes of Health, National Cancer Institute. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf (Accessed March 27, 2018).

Graphic 91245 Version 4.0

Anatomy of esophageal cancer primary site by ICD-O-3 topography codes

Anatomic name	Compartment ICD-O-3	Esophageal location		Anatomic boundaries	Typical esophagectomy (cm)
		ICD-O-3	Name		
Cervical	C15.0	C15.3	Upper	Hypopharynx to sternal notch	15 to <20
Thoracic	C15.1	C15.3	Upper	Sternal notch to azygos vein	20 to <25
		C15.4	Middle	Lower border of azygos vein to inferior pulmonary vein	25 to <30
		C15.5	Lower	Lower border of inferior pulmonary vein to esophagogastric junction	30 to <40
Abdominal	C15.2	C15.5	Lower	Esophagogastric junction to 2 cm below esophagogastric junction	40 to 45
		C16.0	Esophagogastric junction/cardia	Esophagogastric junction to 2 cm below esophagogastric junction	40 to 45

ICD-O-3: International Classification of Diseases for Oncology, 3rd Edition.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. Corrected at 4th printing, 2018.

Graphic 111351 Version 7.0

Stomach cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*: Intraepithelial tumor without invasion of the lamina propria, high-grade dysplasia
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades the lamina propria or muscularis mucosae
T1b	Tumor invades the submucosa
T2	Tumor invades the muscularis propria*
T3	Tumor penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures¶ Δ
T4	Tumor invades the serosa (visceral peritoneum) or adjacent structures¶ Δ
T4a	Tumor invades the serosa (visceral peritoneum)
T4b	Tumor invades adjacent structures/organs
* A tumor may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case, the tumor is classified as T3. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified as T4. ¶ The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum. Δ Intramural extension to the duodenum or esophagus is not considered invasion of an adjacent structure, but is classified using the depth of the greatest invasion in any of these sites.	
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases in 1 or 2 regional lymph nodes
N2	Metastases in 3 to 6 regional lymph nodes
N3	Metastases in 7 or more regional lymph nodes
N3a	Metastases in 7 to 15 regional lymph nodes
N3b	Metastases in 16 or more regional lymph nodes

Distant metastasis (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

Prognostic stage groups

Clinical (cTNM)

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	I
T1	N1, N2, or N3	M0	IIA
T2	N1, N2, or N3	M0	IIA
T3	N0	M0	IIB
T4a	N0	M0	IIB
T3	N1, N2, or N3	M0	III
T4a	N1, N2, or N3	M0	III
T4b	Any N	M0	IVA
Any T	Any N	M1	IVB

Pathological (pTNM)

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1	N0	M0	IA
T1	N1	M0	IB
T2	N0	M0	IB
T1	N2	M0	IIA
T2	N1	M0	IIA
T3	N0	M0	IIA
T1	N3a	M0	IIB
T2	N2	M0	IIB
T3	N1	M0	IIB

T4a	N0	M0	IIB
T2	N3a	M0	IIIA
T3	N2	M0	IIIA
T4a	N1	M0	IIIA
T4a	N2	M0	IIIA
T4b	N0	M0	IIIA
T1	N3b	M0	IIIB
T2	N3b	M0	IIIB
T3	N3a	M0	IIIB
T4a	N3a	M0	IIIB
T4b	N1	M0	IIIB
T4b	N2	M0	IIIB
T3	N3b	M0	IIIC
T4a	N3b	M0	IIIC
T4b	N3a	M0	IIIC
T4b	N3b	M0	IIIC
Any T	Any N	M1	IV

Post-neoadjuvant therapy (ypTNM)

When T is...	And N is...	And M is...	Then the stage group is...
T1	N0	M0	I
T2	N0	M0	I
T1	N1	M0	I
T3	N0	M0	II
T2	N1	M0	II
T1	N2	M0	II
T4a	N0	M0	II
T3	N1	M0	II
T2	N2	M0	II
T1	N3	M0	II
T4a	N1	M0	III
T3	N2	M0	III

T2	N3	M0	III
T4b	N0	M0	III
T4b	N1	M0	III
T4a	N2	M0	III
T3	N3	M0	III
T4b	N2	M0	III
T4b	N3	M0	III
T4a	N3	M0	III
Any T	Any N	M1	IV

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

Graphic 111190 Version 8.0

Carcinoma of esophagus complicated by TE fistula on barium swallow and CT

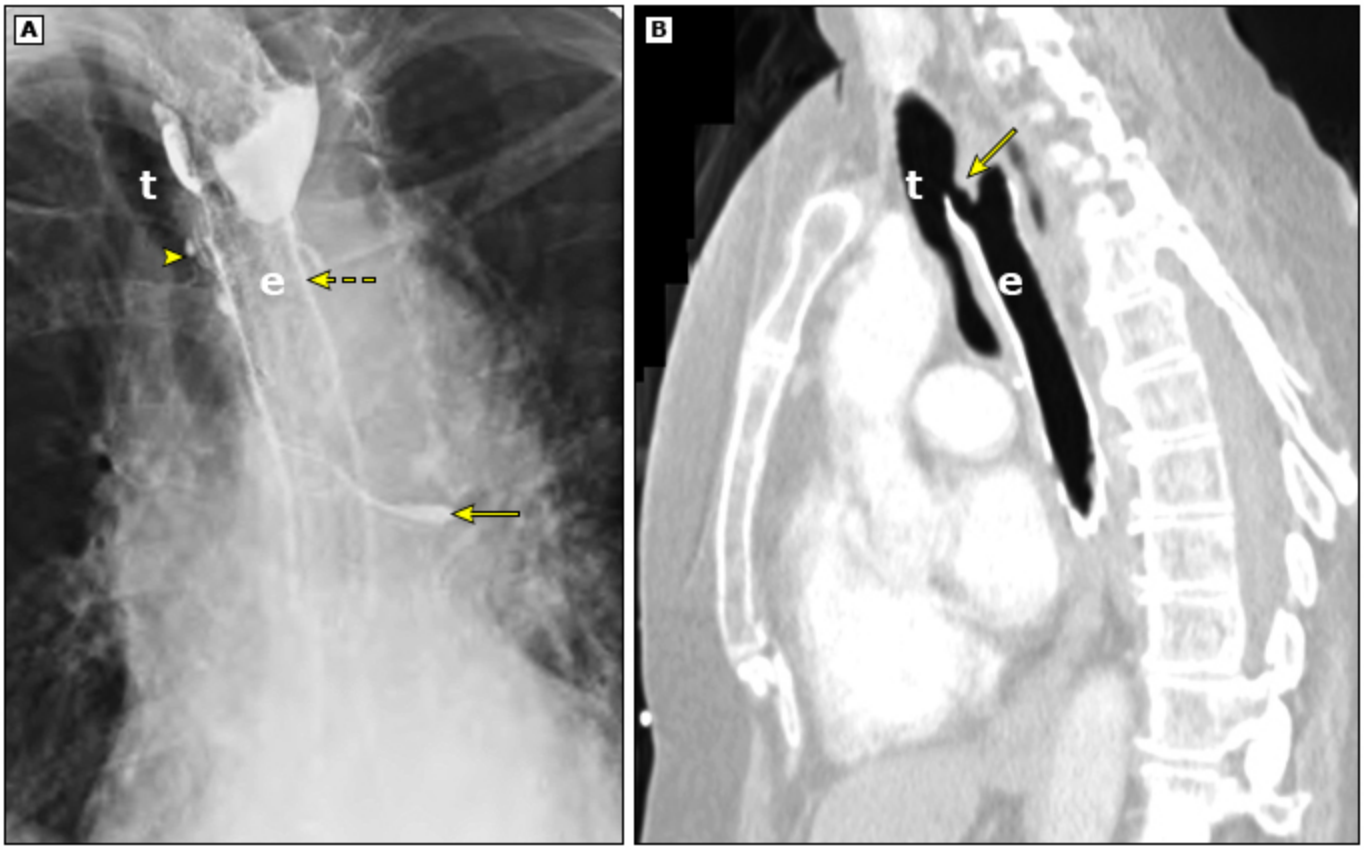
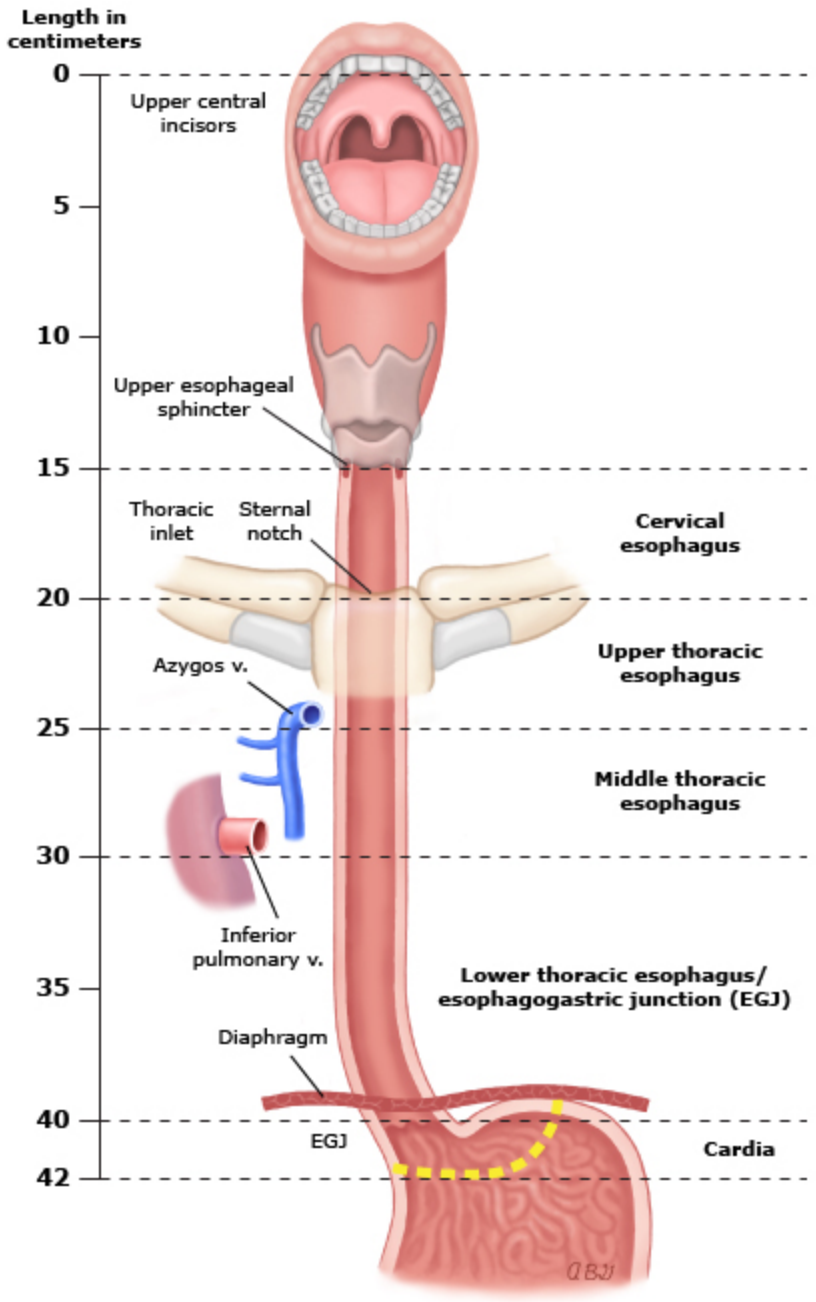


Image A of a barium swallow in a patient with esophageal carcinoma and an esophageal stent (dashed arrow) shows a fistulous tract (arrow head) from the esophagus (e) to the trachea (t) and spillage of the contrast into the left mainstem bronchus (arrow). Image B is a sagittal reconstruction of a chest CT and shows an air-filled fistulous tract (arrow) between the esophagus (e) and trachea (t).

TE: tracheo-esophageal; CT: computed tomography.

Graphic 101702 Version 2.0

AJCC 8th edition regions of the esophagus



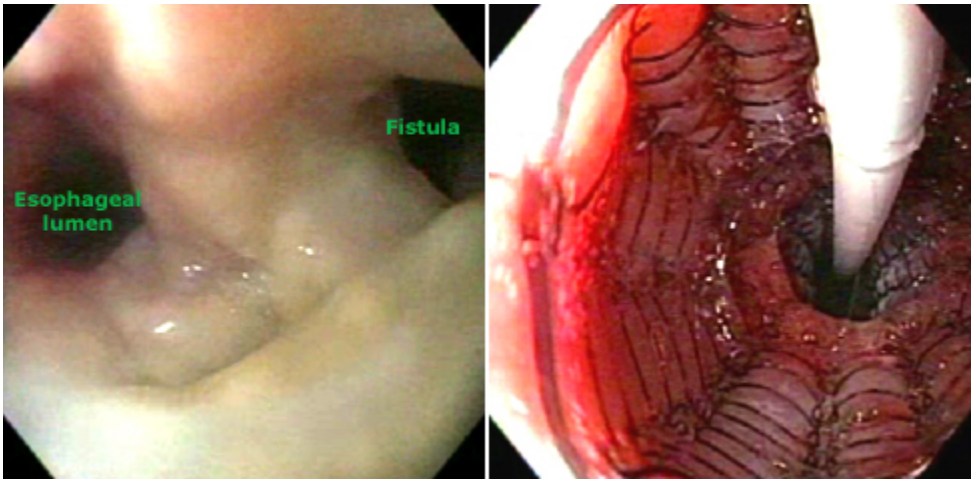
Anatomy of esophageal cancer primary site, including typical endoscopic measurements of each region measured from the incisors. Exact measurements depend on body size and height. For tumors of the EGJ and cardia, location of cancer primary site (ie, esophagus, stomach) is defined by cancer epicenter.

AJCC: American Joint Committee on Cancer; v: vein.

Modified from: Rice TW, Kelsen D, Blackstone EH, et al. Esophagus and esophagogastric junction. In: AJCC Cancer Staging Manual, 8th Ed, Amin MB (ed), Springer Science+Business Media, LLC, New York, 2017.

Graphic 111260 Version 8.0

Tracheoesophageal fistula



Left panel shows a view into the esophagus during endoscopy revealing a tracheoesophageal fistula. A covered, self-expanding metal stent has been deployed covering the fistula (right panel).

Courtesy of Todd H Baron, MD.

Graphic 60771 Version 1.0

Selection criteria for definitive and palliative brachytherapy for esophageal cancer

Definitive treatment
Good candidates
Unifocal thoracic esophageal cancer ≤10 cm
No extraesophageal extension
No nodal disease or metastatic disease
Poor candidates
Tumor >10 cm in length
Extraesophageal extension
Regional lymphadenopathy
Tumor involving GE junction or cardia
Contraindications
Esophageal fistula
Cervical esophageal location
Stenosis that cannot be bypassed

Palliative treatment
Thoracic esophageal lesions with distant metastases
Unresectable local disease progression
Recurrence after definitive EBRT

GE: gastroesophageal; EBRT: external beam radiation therapy.

Adapted from Gaspar LE, Nag S, Herskovic A, et al. American Brachytherapy Society (ABS) consensus guidelines for brachytherapy of esophageal cancer. Int J Radiat Oncol Biol Phys 1997; 38:127.

Graphic 73664 Version 5.0

Schema for definitive and palliative treatment for esophageal cancer

Suggested scheme for definitive treatment
External beam radiotherapy (EBRT)
45 to 50 Gy in 1.8 to 2.0 Gy fractions, five times a week with concurrent chemotherapy followed by brachytherapy
Brachytherapy after EBRT and not concurrent with chemotherapy
HDR: total dose of 10 Gy, 5 Gy fractions, one fraction per week starting two to three weeks following completion of EBRT
LDR: total dose of 20 Gy single course, 0.4 to 1.0 Gy per hour starting two to three weeks after completion of EBRT

Suggested scheme for palliative treatment
Recurrence after EBRT or short life expectancy
Brachytherapy* (HDR: 10 to 14 Gy in one to two fractions or LDR: 20 to 40 Gy in one to two fractions at 0.4 to 1.0 Gy per hour)
No previous EBRT
EBRT 30 to 40 Gy in two to three Gy fractions followed by brachytherapy* (HDR: 10 to 14 Gy in one to two fractions or LDR: 20 to 25 Gy in a single course at 0.4 to 1.0 Gy per hour)
No previous EBRT and life expectancy >6 months
Guidelines similar to those for definitive therapy above

Gy: gray; HDR: high-dose rate; LDR: low-dose rate.

* All brachytherapy doses specified 1 cm from midsource/mid-dwell position. Applicator diameter of 6 to 10 mm is recommended.

Adapted from Gaspar LE, Nag S, Herskovic,A, et al. American Brachytherapy Society (ABS) consensus guidelines for brachytherapy of esophageal cancer. Int J Radiat Oncol Biol Phys 1997; 38:127.

Graphic 80000 Version 5.0

Weekly carboplatin and paclitaxel chemotherapy with concurrent radiotherapy for esophageal and esophagogastric junction (EGJ) cancer[1]

Cycle length: Carboplatin and paclitaxel are each given weekly for five weeks with concurrent RT followed by surgery.

Drug	Dose and route	Administration	Given on days
Paclitaxel	50 mg/m^2 IV	Dilute in 250 mL NS* and administer over one hour; special tubing needed.¶	Days 1, 8, 15, 22, and 29
Carboplatin	AUC$^\Delta$ = 2 mg/mL × min IV	Dilute in 250 mL NS* and administer over 30 minutes after paclitaxel.	Days 1, 8, 15, 22, and 29

Pretreatment considerations:

Emesis risk	▪ MODERATE (30 to 90% frequency of emesis). We recommend prophylaxis with a combination of a 5-HT3 receptor antagonist plus dexamethasone on days 1, 8, 15, 22, and 29, and with a 5-HT3 antagonist on days when radiation alone is given. ▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults and radiotherapy-induced nausea and vomiting, prophylaxis and treatment.
Prophylaxis for infusion reactions	▪ Premedicate with dexamethasone plus both an H1 and an H2 receptor antagonist prior to paclitaxel administration. ▪ Refer to UpToDate topics on infusion reactions to systemic chemotherapy.
Vesicant/irritant properties	▪ Carboplatin is an irritant. Paclitaxel can cause significant tissue damage; avoid extravasation. ▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants.
Infection prophylaxis	▪ Primary prophylaxis with G-CSF is not justified (incidence of neutropenic fever <1%[1]). ▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation.
Dose adjustment for baseline liver or renal dysfunction	▪ A lower starting dose of paclitaxel may be needed for liver impairment.[2] Carboplatin dose is calculated based upon renal function by use of the Calvert formula.$^\Delta$[3]

	▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents; chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents; and dosing of anticancer agents in adults.
Monitoring parameters:	
▪ CBC with differential and platelet count weekly during treatment.	
▪ Assess electrolytes, renal, and liver function weekly during treatment.	
▪ Assess changes in neurologic function weekly during treatment.	
Suggested dose modifications for toxicity:	
Myelotoxicity/neurologic toxicity	▪ Weekly doses of paclitaxel and carboplatin should not be repeated unless the ANC is at least 1500/microL and the platelet count is at least 100,000/microL. Reduce paclitaxel dose by 20% for ANC <500/microL for a week or longer, or severe peripheral neuropathy.[2]
Renal toxicity	▪ Alterations in renal function during therapy require a recalculation of the carboplatin dose. ▪ Refer to UpToDate topics on dosing of anticancer agents in adults.
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

RT: radiotherapy; IV: intravenous; NS: normal saline; AUC: area under the concentration × time curve; G-CSF: granulocyte colony stimulating factor; CBC: complete blood count; ANC: absolute neutrophil count; GFR: glomerular filtration rate; NCCN: National Comprehensive Cancer Network.

* Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

¶ Paclitaxel can be administered in NS, D5W, or NS/D5W* at varying concentrations between 0.3 to 1.2 mg/mL. Use glass or polypropylene bottles or polypropylene or polyolefin plastic bags, and administer through a polyethylene-lined administration sets with a microporous membrane 0.22 microns or less.

Δ AUC is converted to a patient-specific carboplatin dose (in mg) according to renal function by using the Calvert formula: Total dose (mg) = (target AUC) × (GFR + 25). If using measured creatinine, limit the maximal GFR for the calculation to 125 mL/min. Refer to UpToDate topic on "Dosing of anticancer agents in adults".

References:

1. *Gaast AV, et al. Effect of preoperative concurrent chemoradiotherapy on survival of patients with resectable esophageal or esophagogastric cancer: Results from a multinational randomized phase III study (abstract 4004). J Clin Oncol 2010; 28:302s.*
2. *Paclitaxel injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on October 29, 2019).*
3. *Carboplatin injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on October 29, 2019).*

Graphic 68266 Version 18.0

Contributor Disclosures

Dwight E Heron, MD, MBA, FACRO, FACR No relevant financial relationship(s) with ineligible companies to disclose. **Michael K Gibson, MD, PhD, FACP** Grant/Research/Clinical Trial Support: Natera [ECOG project]; National Cancer Institute [Head and neck cancer and UGI cancer]; Papivax [IIT clinical trial]. Consultant/Advisory Boards: Amgen [Gastric cancer]; BMS [Immunotherapy]; Regeneron [Skin cancer]. Speaker's Bureau: Bristol-Myers Squibb [Immuno-oncology, not disease specific]. Other Financial Interest: AbbVie Data and Safety Monitoring Board [Phase 1 solid tumors]; Soligenix Data and Safety Monitoring Board [Head and neck cancer]. All of the relevant financial relationships listed have been mitigated. **Richard M Goldberg, MD** Equity Ownership/Stock Options: Advanced Chemotec Inc [Pancreatic cancer]; Compass Therapeutics [Biliary tract and colorectal cancer]. Consultant/Advisory Boards: AbbVie [GI cancers]; Advanced Chemotherapy Technologies [GI cancer]; AstraZeneca [GI cancer]; Bayer [GI cancer]; Compass Therapeutics [GI cancer]; Eisai [GI cancer]; G1 Therapeutics [GI cancer]; GSK [Colorectal cancer]; Innovative Cellular Therapeutics [Colorectal cancer]; Inspirna [Colorectal cancer]; Merck [GI cancer]; Modulation Therapeutics [Lymphoma]; Novartis [GI cancer]; Sorrento Therapeutics [GI cancer]; Taiho [GI cancer]. Other Financial Interest: Taiho [Expert testimony GI cancer]. All of the relevant financial relationships listed have been mitigated. **Kenneth K Tanabe, MD** Patent Holder: EGF SNP to determine risk for HCC [Cirrhosis, hepatocellular carcinoma]; Use of EGFR inhibitors to prevent HCC [Cirrhosis, hepatocellular carcinoma]. Consultant/Advisory Boards: Cancer Expert Now [GI cancers, melanoma]; GSK [GI Cancers]; Imvax [GI cancers]; Leidos [Melanoma, GI cancers]; Teledoc [GI cancers, melanoma]. Other Financial Interest: American Cancer Society [Honoraria as editor of Cancer]. All of the relevant financial relationships listed have been mitigated. **Sonali M Shah, MD** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

→