Published in final edited form as:

Curr Treat Options Oncol. 2015 July ; 16(7): 35. doi:10.1007/s11864-015-0352-6.

Management of Locally Advanced Adenocarcinoma of the Esophagus and Gastroesophageal Junction: Finally a Consensus

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Keywords

Esophagus; Thoracotomy; Radiotherapy; Chemotherapy; Minimally invasive esophagectomy; Staging; Neoplasm; Adenocarcinoma

Introduction

The incidence of esophageal and gastroesophageal junction adenocarcinoma has been increasing in western nations for several decades, and the prognosis remains poor [1–3]. Historically, adenocarcinoma and squamous cell carcinoma of the esophagus and gastroesophageal junction were considered the single entity of esophageal cancer. These histologies are now considered separately with recognition of important differences in biology and anatomical patterns, and this summary focuses on adenocarcinoma.

Combined modality treatment using systemic therapy and radiotherapy along with surgery, designed to address the high local and systemic failure with surgery alone, is now a standard optimal management to improve survival for patients with locally advanced resectable adenocarcinoma of the esophagus and gastroesophageal junction. Surgery alone, previously the treatment used for most curable patients, is now reserved for early T stage node-negative disease. Randomized trials have confirmed that neoadjuvant chemoradiation and neoadjuvant chemotherapy are effective at improving long-term survival outcome. The use of preoperative therapies had required a shift to an approach using clinical staging to guide

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

Institutional Review Board approval was obtained at all participating institutions and informed consent was obtained from all patients.

Conflict of Interest

Lawrence Kleinberg, Malcolm Brock, and Michael Gibson declare that they have no conflict of interest.

decisions, rather than the official American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) pathologic staging.

There is also an ongoing shift to operative approaches that may reduce the substantial morbidity of standard transthoracic esophagectomy. Transhiatal esophagectomy has been well established for distal and gastroesophageal junction lesions. Newer minimally invasive approaches also appear to improve pulmonary complications but not necessarily other major morbidity and mortality.

Important issues include (1) appropriate pretreatment assessment to guide therapy for an entity where formal staging and earlier approaches to therapy were based on surgical pathology; (2) the benefit of neoadjuvant therapy, including or omitting radiotherapy; (3) optimal systemic therapy selection; (4) the evolving role of minimally invasive surgical approaches; (6) and the alternative of adjuvant (postoperative) therapy or non-operative management. Some ongoing trials that may further optimize treatment selection for future patients will be discussed.

Selecting patients for aggressive local therapy: improving pathologic staging while transitioning to clinical staging

The AJCC/UICC staging system [4] for esophageal adenocarcinoma is based on pathologic findings at the time of surgery, but the increased use of preoperative therapy has required development of an “unofficial” approach to clinical staging that now actually guides treatment. Data from a worldwide collaboration [5, 6•] was utilized to refine pathological staging to provide a more nuanced prediction of outcome that may then better guide therapeutic decision making [4, 7].

Although esophageal cancer has been historically considered one entity and included in the same clinical trials without stratification, squamous cell and adenocarcinoma are now considered separately with differences in stage assignment reflecting differences in anatomy, patterns of spread, etiology, molecular biology, and response to therapeutic agents. In addition, pathologic grade of adenocarcinoma is also now recognized in the staging system as an important prognostic factor.

The nodal staging of esophageal and gastric cancer has been harmonized. Previously, esophageal cancer nodal staging was based stochastically on the presence or absence of regional lymph nodes. Now the staging system is based on the recognition that the quantity of involved lymph nodes provides important prognostic information in esophageal as well as gastric cancer. Five-year survival for NO, N1 (1–2 nodes), N2 (3–6 nodes), and N3 (>6 nodes) disease was 58, 34, 21, and 9 % [8].

The staging system now defines the gastroesophageal junction (GEJ) as a subsite of esophageal cancer. GEJ adenocarcinoma has been, according to individual preference, managed according to the divergent staging and therapeutic algorithms used for esophageal or gastric cancers and therefore previously was included as only a modest subgroup in clinical trials for both entities. Tumors involving the GE junction with epicenter in distal esophagus,

GEJ, or within proximal 5 cm of stomach, are now classified as esophageal cancer in AJCC/UICC 7, and this will guide clinical trial design and result reporting.

The pathologic staging system for adenocarcinoma is summarized in Tables 1 and 2 and outcome by stage in Fig. 1. In applying the literature to current patients, it is important to consider that those patients may have had stage assignments according to a different version of the staging system. In addition, it is important to evaluate the applicability of trial results based on the histology and anatomic location of the enrolled population.

Clinical staging is now used to guide therapy

At the present time, clinical and imaging assessment of the extent of disease (to assess likely pathologic stage) has a major impact on therapeutic decision-making for single modality versus multimodality treatment as well as use of curative versus palliative approaches. This has been driven by trials demonstrating that preoperative therapy improves survival for patients identified as having locally advanced disease.

Although preoperative clinical staging does not have the capacity to predict outcome of staging based on operative and pathologic results, clinical staging achieves the major objective of sufficiently predicting ultimate pathologic stage in order to divide patients into three groups that require differing therapeutic approaches: (1) those with very early tumors, corresponding to pathologic stage T1N0M0, who have a high cure rate with esophagectomy or endoluminal approaches, a situation beyond the scope of this review; (2) those who have localized but more advanced tumors with a prognosis after surgery alone that justifies management with combined modality therapy, including T1N1M0 and T2-T3 NO-1 MO tumors as well as potentially resectable T4a NO-1 MO; and (3) those with metastatic disease who should not undergo aggressive potentially curative local therapies.

In clinical staging, endoscopic ultrasound (EUS) is utilized to assess local and regional disease [9–11]. A pooled analysis of the published literature indicated a sensitivity and specificity respectively for T1 stage 81.6 and 99.4 %, T2 81.4 and 96.3 %, T3 91.4 and 99.4 %, T3 91.4 and 94.4 %, and T4 92.4 and 97.4 %. Therefore, this is successful at identifying patients who may or may not benefit from neoadjuvant therapy based on T stage.

For nodal staging based on morphology (size, shape, border, and echo characteristics), the observed sensitivity and specificity was 81 % (0.76–0.85) and 0.73 (0.63–0.80) in a pooled analysis [12] and was superior for this purpose than CT scan 0.54 (0.48–0.61) and 0.87 (0.79–0.92) and PET scan 0.52 (0.44–0.60) and 0.82 (0.65–0.92). Specificity is greatly improved with availability of fine needle aspiration to confirm presence of malignant cells [13–15]. Management is only affected in the case of a patient with T1 disease, where presence or absence of nodal disease affects use of neoadjuvant therapy.

There exists controversy about whether clinical stage T2N0M0 patients should receive preoperative therapy as approximately 30 % [16, 17] will prove to have T1N0M0 and may have been optimally managed with surgery alone, which must be balanced against the benefit of preoperative therapy for the remainder.

Patients with metastatic disease would not be selected for curative local management, but only for palliative local therapies and systemic therapy that may improve survival. CT imaging is utilized for detecting distant metastasis, and PET scanning may detect distant disease-altering management [18, 19] in approximately 15–20 % of patients otherwise considered to have localized disease (on CT) and thereby alter patient management, i.e., upstaging. As precise assessment of local disease extent is not important if metastasis is identified, it may be most efficient to obtain a CT scan or PET scan prior to EUS and FNA.

Therapy for patients with locally advanced disease

Trimodality therapy: importance of chemotherapy, radiotherapy, and surgery

Neoadjuvant or perioperative therapy has become standard in the management of clinically staged locally advanced esophageal adenocarcinoma with the goal of improving survival as well as local control. The poor 5-year survival outcome with T2-3N0M0 tumors (30–40 %) and node-positive disease (20–30 %) [4] after therapy with surgery alone creates the need for development of more aggressive therapies that will improve both local and systemic control.

The definitively powered Chemoradiotherapy for Esophageal Cancer Followed by Surgery Study (CROSS) [20••] trial published in 2012 confirmed a survival benefit with a well-tolerated preoperative chemoradiation and thus established this approach as a standard of care. Three hundred and sixty-eight patients with stage T1N1M0 and T2-3 N0-1 M0 esophageal and GE junction tumors (82 % distal esophagus/24 % GEJ) patients were randomly assigned to surgery as the only therapy or to neoadjuvant chemotherapy on days 1, 8, 15, 22, and 29 using carboplatin (AUC 2 mg/ml/min) and paclitaxel 50 mg/m² concurrent with 41.4 Gy radiotherapy. Staging required endoscopy with ultrasound and CT scanning, but not PET scan.

The activity of the preoperative therapy was confirmed, including for patients with adenocarcinoma (77 %). Twenty-three percent of the patients with adenocarcinoma had a pathologic complete response. Node-positive disease remained in 31 % after chemoradiation but in 75 % with surgery alone. Disease was T2 or greater in 51 vs 92 %. Gross total resection with negative margins was achieved for 92 vs 69 %.

Survival was meaningfully improved to 49 months median and 47 % at 5 years compared with 24 months and 34 % with surgical therapy alone. Subgroup analysis suggested a survival benefit existed for adenocarcinoma (hazard ratio (HR) 0.741 (0.536–1.024), $p=0.07$). With further follow-up [21], the survival benefit for adenocarcinoma patients is significant.

Pattern of failure data [22••] demonstrated that this therapy achieved the goal of impacting a high rate of both local and distant failure. Overall recurrence was reduced from 58 to 35 %. Locoregional recurrence (LRR) was reduced from 34 to 14 % ($p<0.001$), peritoneal failure from 14 to 4 % ($p<0.001$), and distant failure from 35 to 29 % ($p=0.025$).

Earlier randomized data for adenocarcinoma using fluorouracil- and platinum-containing regimens [23•, 24–26] provides additional support for neoadjuvant CRT. This data has been

analyzed in several recent meta-analyses which confirm that the weight of available data [27•, 28, 29] supports trimodality therapy. Very-long-term results have recently published [30] for adenocarcinoma in the trial reported by Walsh using two courses of chemotherapy in weeks 1 and 6 (fluorouracil, 15 mg/kg daily for 5 days and cisplatin, 75 mg/m² on day 7) and radiotherapy (40 Gy, administered in 15 fractions). The mean overall survival time in the trimodality arm was 75.65 (±11.74, 52.6–98.7) months, compared with 22.97 (±3.94, 15.25–30.89) months in the surgical monotherapy arm ($p < 0.001$, $\chi^2 = 13.336$). The survival benefit appeared to persist through 10 and more years of follow-up.

Drug therapy

Choice of chemotherapy agents with radiotherapy in locally advanced disease

Various single agents and combinations have been combined both sequentially and concurrently with radiotherapy in the setting of locally advanced disease. The two combinations validated with level 1 evidence include paclitaxel/carboplatin and 5-fluorouracil (5-FU)/cisplatin. The paclitaxel and carboplatin regimen used in the CROSS trial [20•, 31,32] and is utilized as a standard both because it has been rigorously validated as having a survival benefit and because it is well tolerated. Seven percent of patients had grade 3 (1% grade 4) hematologic toxicity and 13 % had grade 3 nonhematologic toxicity (1 % esophagitis).

Alternative regimens [33–36] based on cisplatin, 5-FU, oxaliplatin, paclitaxel, and irinotecan appear to be less tolerable and mostly less well validated. Of these, the combination of fluorouracil and cisplatin has a proven survival benefit in randomized trials compared with surgery alone [23•, 25, 30]. Unfortunately, there are no comparative trials to determine which regimen is optimal.

The neoscope trial (NCT01843829) of the British NHS is comparing outcome of paclitaxel/carboplatin or capecitabine/oxaliplatin given along with pre-operative radiotherapy, with a plan to then test the superior chemotherapy regimen with or without radiotherapy.

Neoadjuvant chemotherapy without radiotherapy is also an appropriate alternative

An alternative approach for combined modality therapy versus surgery alone is preoperative or perioperative chemotherapy. Two early large randomized trials testing whether 5-FU and cisplatin-based neoadjuvant chemotherapy improves outcome when compared with surgery alone in esophageal and GEJ cancer had discordant results—leading to uncertainty and regional differences in utilization of neoadjuvant chemotherapy without radiation. The US intergroup trial [37, 38] randomized 467 (55 % adenocarcinoma) patients to three courses of cisplatin 100 mg/m² plus infusional 5-FU 1000 mg/m² days 1–5 followed by surgery followed by two courses of adjuvant chemotherapy with the same agents. No survival benefit was seen. In contrast, the similar UK Medical Research Council (MRC) 0E02 trial [39, 40] randomized 802 (67 % adenocarcinoma) patients to two cycles of cisplatin 80 mg/m² and 5-FU 1000 mg/m²/day continuous infusion (96 h) prior to resection. The median survival was significantly improved from 13.3 to 16.8 months in the chemotherapy arm. Two-year survival improved from 34 to 43 % and 5-year survival from 17 vs 23 %.

The follow-up to the OEO2 study, the UK/MRC MAGIC trial, enrolled 508 patients with gastroesophageal cancer (esophageal 14.5 %, GEJ 11.5 %, gastric 74 %) [41]. to 3 cycles before and after surgery of epirubicin (50 mg/m²) day 1, cisplatin (60 mg/m²) day 1, and 5-fluorouracil (200 mg/m²/day by CI for 21 days). Two- and 5-year survival improved from 31 to 45 % and 23 to 36 %, respectively (p= 0.009). Complementary results in support of perioperative chemotherapy were found in the more recently completed 244 patient (64 % GEJ) FNCLCC/FFCD [42] trial. This trial randomized patients to two or three preoperative cycles of cisplatin (100 mg/m² day 1) and 5-FU (800 mg/m²/day by CI for 5 days on days 1 to 5) given every 28 days followed by three or four postoperative cycles of the same regimen. The 5-year survival improved from 24 to 38 % (p=0.02).

Options to improve upon current multimodality approaches

Adaptive therapy based on response

Ongoing studies aim to determine whether adaptively altering therapy (i.e., during preoperative treatment for those not responding to the selected neoadjuvant therapy may improve outcome. Response to neoadjuvant chemotherapy or CRT may be measured in various ways, including cross-sectional imaging, functional imaging (PET), endoscopic biopsy, and endoscopic ultrasound. However, none of these are currently validated.

Standard imaging with EUS has not been of value in assessing response presumably due to slow reconstitution of tissue planes and inflammatory changes induced by treatment [43–45]. Similarly, biopsy is not accurate in identifying completely responders soon after neoadjuvant therapy [46]

Regarding functional imaging, an aggregate review of the literature [47] that included 1544 patients demonstrated an HR for overall survival of 0.51 (95 % CI 0.4–0.64) and disease-free survival 0.47 (0.38–0.57) in PET responders. There are no standardized criteria for assessing metabolic response by PET as these studies varied in scan technique, timing of scan during or after therapy, and in the criteria of change considered to indicate a favorable response.

The phase II MUNICON studies showed that among patients with adeno-carcinomas of the esophagus or EGJ who underwent PET scanning 2 weeks after beginning neoadjuvant chemotherapy with cisplatin and FU, metabolic responders had a significantly better prognosis than did nonresponders [48, 49]. However, it designed to determine whether aborting neoadjuvant therapy and either proceeding directly to surgery or adding radiotherapy salvage to neoadjuvant chemotherapy for PET nonresponders improved outcome versus continuing with the initial chemotherapy choice.

In follow up to MUNICON, CALGB 80803 (NCT01333033) is exploring whether adaptive alteration of therapy for PET scan nonresponders treated with either induction FOLFOX or carboplatin/paclitaxel, by crossing over to the other regimen during radiotherapy, will result in a pathologic complete response (pCR) rate >20 %.

pCR after neoadjuvant CRT is an important predictor of survival outcome that can be used to advise patients and potentially to select high-risk patients for trials of novel adjuvant

therapies but cannot be used to guide early alteration of therapy as with PET scanning (see MUNICON and CALGB 80803). A meta-analysis exploring association of pCR with overall survival [50], suggested 3- and 5-year survival of 75 and 50 % with pCR vs 29 and 22.6 % without, including patients with adenocarcinoma and squamous cell carcinoma. It is intriguing to consider whether those who do not have a complete response would benefit from postoperative therapy with noncross-resistant agents, but this has not been validated. Furthermore, postoperative therapy with the current standard agents has not been well tolerated after neoadjuvant therapy (generally initiated for only 40–60 % of patients) [35, 37, 41, 51].

Can systemic therapy be optimized through personalized use of targeted agents?

Integration of targeted agents in this disease has been challenging for several reasons. Given the relative rarity of markers for any given tumor, large samples must be screened in phase 3 trials. This is difficult in small subgroups of less common tumors such as gastroesophageal AC. In addition, there is a general dearth of molecular markers (mutations, rearrangements, overexpression, epigenetic alterations) to evaluate. However, HER-2 represents a promising predictive marker for guidance of curative therapy based on data from the metastatic population (ToGA). In this study, patients (n = 594, 80 % gastric) with HER-2 positive (standard IHC and FISH) tumors received 5-FU (or capecitabine) and cisplatin with randomization to receive trastuzumab. Patients in the experimental arm had a median OS of 13.8 months versus 11.1 in the control arm. [52] Based on the benefit of adding trastuzumab that was demonstrated in the ToGA trial, RTOG 1010 (NCI-2011-02601) was designed to assess the potential benefit of adding trastuzumab to preoperative paclitaxel/carboplatin/radiotherapy.

Additional targets are under study in the advanced/metastatic population. The ongoing randomized phase II trial S1201 (NCT01498289) is testing in metastatic esophageal and gastric cancer whether elevated excision repair cross-complementing 1 (ERCC1) mRNA expression, which is associated with platinum resistance, may predict optimal treatment with FOLFOX versus docetaxel/irinotecan. A planned ECOG-ACRIN trial (NCT02344810) will test whether AMG-337, a small molecule c-met tyrosine kinase inhibitor, will improve outcome for c-met overexpressing advanced or metastatic esophagogastric cancer. If either of these trials confirms a benefit in this metastatic population, evaluation in patients with locally advanced disease would be warranted.

Neoadjuvant chemotherapy alone or chemoradiation: which is optimal?

With the availability of the data from the CROSS trial and others, preoperative chemoradiation is now the preferred approach in the US National Comprehensive Cancer Network (NCCN) Guidelines [53] as well as the European Society of Medical Oncology clinical practice guidelines [54]. An aggregate meta-analysis of randomized trials²⁷ including data for adenocarcinoma patients suggests a greater benefit with CRT HR 0.75 (0.59–0.95) than for chemotherapy alone HR 0.83 (0.71–0.95).

Several studies have attempted to compare induction chemotherapy to combined chemoradiation. The German Esophageal Study Group randomized study (POET) [55•]

specifically directed at assessing the value of radiotherapy, including Seiwert I–III adenocarcinoma of the GE junction, randomizing patients to cisplatin/5-FU with or without radiation. The trial dosed due to slow accrual with only 126 of 452 planned patients. Three-year survival improved from 28 to 48 %, median survival from 21 to 33 months ($p=0.07$), pCR was improved from 2.0 to 15.6 % ($p=0.03$), and the rate of node-negative stage was improved from 36.7 to 64.4 % ($p=0.01$). Local progression was reduced from 41 to 23 % ($p=0.06$). Other trials containing radiation showed improved local control. Urba [24] found that local failure was significantly reduced from 52 to 23 % ($p=0.002$) and Oppedijk (CROSS) [22•] from 34 to 14 % ($p<0.001$). In contrast, local failure was not significantly reduced with neoadjuvant chemotherapy alone in randomized trials including the US intergroup [37] and the MRC [39] trials.

It does not appear that preoperative therapy significantly increases operative mortality. A meta-analysis comparing neoadjuvant chemotherapy or neoadjuvant chemoradiation with surgery alone indicated that there was no evidence that either approach increased mortality for adenocarcinoma patients, although there was increased mortality for squamous cell carcinoma treated with radiation (where there may be increased risk from the typically higher thoracic location of the radiation field in combination with cardiac and pulmonary comorbidities in that population) [56]. In the CROSS trial [20•], for example, mortality was 6 % for those receiving preoperative therapy and 7 % after surgery alone.

As the role of radiation remains controversial, there are several randomized trials underway. The All Ireland Cooperative Oncology Research Group (NCT01726452) is randomizing patients to the “Magic” versus “CROSS” regimens. The British NHS Neoscope trial (NCT01843829) is a Randomised Phase II Study of neoadjuvant oxaliplatin and capecitabine followed by either preoperative Chemoradiotherapy with Oxaliplatin/Capecitabine or with Paclitaxel/Carboplatin for Resectable Oesophageal Cancer, which will be followed by a planned phase III study testing the “winner” chemotherapy regimen administered with or without radiotherapy. The trans-Tasmanian TOPGEAR (NCT01924819) trial will randomly assign patients with gastric and GE junction tumors to preoperative therapy with epirubicin + cisplatin + 5-fluorouracil chemotherapy for three cycles or for two cycles followed by radiotherapy and continuous infusion 5-FU or capecitabine.

Surgical approaches

Historically, an open esophagectomy with thoracotomy was not only utilized to resect the esophagus and achieve adequate exposure for lymph node dissection but was also associated with significant morbidity and risk of mortality. Recently, minimally invasive approaches have been developed with the goal of reducing complications and speeding recovery, but equivalent long-term oncologic outcomes have not been confirmed. Without evidence of superiority of any one approach, decisions are currently made based on the experience of the operating surgeon and the location of the tumor.

Standard open approaches have included a transthoracic incision (thoracotomy) for excellent thoracic exposure allowing extended mediastinal and wide circumferential dissections.

The Ivor-Lewis approach achieves access with a right posteriolateral thoracotomy and midline laparotomy, with reconstruction after resection using an intrathoracic anastomosis.

The McKeown approach adds a cervical incision allowing a cervical anastomosis which permits a wider margin for proximal tumors and may be associated with reduced serious complications from anastomotic leaks that may be easier to contain in the neck.

Transhiatal resection is validated and suitable for mid and distal esophageal lesions [57]. A transhiatal resection achieves access by laparotomy and cervical incision allowing reconstruction with a gastric pull-up and a cervical anastomosis. There is access to intraabdominal nodal groups and paraesophageal and proximal lesser curvature and also paraesophageal nodes up to the level of the inferior pulmonary vein.

This approach was assessed in a multiinstitutional randomized trial [58,59], including gastroesophageal junction tumors which compared a transhiatal resection to a right thoracic-abdominal (RTA) approach also using a cervical anastomosis. The 5-year survival outcome did not differ significantly, 39 and 29 %. Perioperative morbidity was substantially less (57 vs 27 %, $p<0.001$) with transhiatal resection, especially pulmonary complications, but in-hospital mortality was similar.

The optimal extent of lymph node dissection remains controversial, with a two-field dissection (thoracic-upper abdominal lymphadenectomy) generally recommended in the USA and three-field (cervical-thoracic-upper abdominal lymphadenectomy) in Japan. As described above, the extent of nodal dissection differed in the two arms of the randomized trial testing transhiatal esophagectomy [58], as the transhiatal approach does not provide adequate exposure for dissection of mediastinal nodal stations from subcarinal extending superiorly. Survival was excellent in both arms for patients confirmed to be NO (86 vs 89 %) and was 0 % for those with more than eight nodes involved with cancer in both arms, but there was a significant benefit to patients who received the more extensive nodal dissection if they had one to eight nodes involved with cancer (23 vs 64 %, $p=0.02$) by subgroup analysis. However, another likely explanation for the observed difference in clinical outcome is stage migration. Some of the patients with one to eight involved nodes resected by transhiatal esophagectomy that may have had additional positive nodes had a more extensive dissection occurred.

In Asia, extended three-field lymph node dissections are frequently performed based on nonrandomized data [60, 61] subject to similar bias resulting from stage migration. A randomized trial [62], albeit conducted in the 1990s, did not confirm a benefit but did demonstrate higher operative complications with the three-field procedure. Another randomized trial of 400 patients randomized to a three-field versus two-field lymphadenectomy with esophagectomy is being carried out in China at Fudan University.

Preoperative chemoradiotherapy causes nodal downstaging as described above and may eliminate any marginal benefit to nodal dissection

Minimally invasive alternatives have been developed with the goal of further decreasing surgical complications. These involve laparoscopic and/or thoroscopic access for resection

and lymph node dissection, with a separate incision being utilized when a cervical anastomosis is performed.

Newly developed robotic techniques, which require further testing for outcome, may allow for improved visualization and greater degree of freedom of instrument manipulation [63]) but may result in longer operative procedures and loss of touch feedback especially important in managing the gastric conduit.

Multiple studies suggest that adequate removal of tumor and lymph nodes can be achieved [64–66], but long-term survival results to validate outcomes are not available.

Recently, reported randomized trials suggest that minimally invasive approaches do reduce the morbidity of esophagectomy and therefore become optimal management for many patients. A randomized trial [67•, 68] of 115 patients compared an open right thoracotomy with minimally invasive procedures using a right thoroscopy and laparoscopy, with cervical incisions utilized if anastomosis was made in that area. In-hospital pulmonary infections were reduced from 34 to 12 % ($p=0.005$) but with no difference in mortality, R0 resection rate, or number of lymph nodes retrieved. The 207 patient MIRO trial [69•], reported in abstract form, tested a hybrid minimally invasive approach using laparoscopic abdominal access with a thoracotomy for chest access (allowing a full thoracic dissection). Compared to an Ivor-Lewis resection, this approach had the benefit of decreased complications, improvement in morbidity with equivalent R0 resection rate, and no difference in lymph nodes harvested. It was superior to the Ivor-Lewis in that the 30-day postoperative grade III–IV morbidity rate was reduced from 64 to 36 % ($p=0.001$) primarily resulting from reduction in pulmonary complications. Mortality was 1–2 % in both arms.

Alternatives

Postoperative therapy

The value of postoperative therapy guided by pathologic findings has not been assessed in randomized trials powered for esophageal and GEJ adenocarcinoma. This may be selected as a preferred management strategy, when surgery must be expedited for symptom relief or when locally advanced disease is unexpectedly encountered. Results achieved with postoperative therapy should be compared with caution to results of neoadjuvant therapy as the population includes only patients who have recovered adequately after surgery and who did not have unexpected findings of metastatic cancer, different than the population selected for up front chemoradiation.

The only randomized prospective data to support chemoradiation following surgery (without neoadjuvant therapy) is the randomized G-I Intergroup trial [70] using fluorouracil for gastric and GEJ adenocarcinoma. Only a modest subgroup of 20 % of the patients had tumor of the GE junction, so the relevance of the data is unknown. Median survival for the entire population in the study was improved from 27 to 36 months ($p=0.005$) Three-year survival was 50 vs 41 %. Further follow-up [71], median 10.3 years, confirmed that a favorable HR for OS was maintained, 1.32 (95 % CI, 1.10 to 1.60; $p=0.0046$).

Definitive chemoradiation as an alternative

While randomized trials have clearly demonstrated that chemoradiation is a curative approach for squamous cell carcinoma, this is not established for adenocarcinoma and the approach should only be recommended when the tumor is unresectable or the patient medically inoperable. Prospective trials evaluating chemoradiation, including RTOG 8501 [51, 72], included few adenocarcinoma patients such that conclusions regarding survival benefit for this histology cannot be made. For example, only 23 patients with adenocarcinoma were enrolled in RTOG 8501 with 5-year survival of 13 % but 95 % confidence interval 0–27 %. In addition, definitive chemoradiotherapy is of limited curative potential for adenocarcinoma of any organ.

The RTOG has since completed a phase III US intergroup trial [73] of nonoperative management, including paclitaxel, carboplatin, and radiation with randomization to receive or not receive cetuximab. Although stopped prematurely for futility in demonstrating a benefit to cetuximab, this trial will provide important prospective information about the use of nonoperative therapy in meaningfully large group of patients with adenocarcinoma.

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Opinion statement

Adenocarcinoma of the esophagus is increasing in incidence in Western nations leading to increased interest in and opportunity to study optimal management. Randomized trials have now robustly demonstrated the preoperative therapy with chemoradiotherapy and chemotherapy alone improves survival outcome for the bulk of curable patients, those with locally advanced T1N1M0 and T2-3 N0-1 M0 disease. Evidence suggests but does not confirm that radiation-containing regimens are more beneficial. Clinical staging is designed to exclude patients with TINOMO disease who may be treated with surgery alone and those with metastatic disease who may not benefit from intensive local therapy. The approach to clinical staging includes endoscopy with ultrasound and fine needle aspirate to assess local and regional disease, supplemented by CT and PET scanning primarily to exclude metastatic disease. Minimally invasive approaches to esophagectomy may be used with the goal of reducing complications, but there is no evidence that mortality or ultimate outcome is improved.

Fig. 1. Survival by AJCC 7.0 staging [5, 6•]. From rice TW, Rusch VW, Ishwaran H, Blackstone EH, Worldwide esophageal cancer collaboration. Cancer of the esophagus and esophagogastric junction: data-driven staging for the seventh edition of the American Joint Committee on Cancer/International Union against cancer staging manuals. *Cancer*. 2010;116(16):3763–3773, with permission from John Wiley and Sons.

Table 1

Stage groupings for AJCC/UICC seventh edition, adenocarcinoma

AJCC/UICC seventh edition stage groupings				
Adenocarcinoma				
Stage	T	N	M	Grade
0	Is or HGD	0	0	1
IA	1	0	0	1–2
	1	0	0	3
IB	2	0	0	1–2
	2	0	0	3
IIA				
IIB	3	0	0	Any
	1–2	1	0	Any
IIIA	1–2	2	0	Any
	3	1	0	Any
	4a	0	0	Any
IIIB	3	2	0	Any
IIIC	4a	1–2	0	Any
	4b	Any	0	Any
	Any	N3	0	Any
IV	Any	Any	1	Any

Table 2

TNM classification [4]

AJCC/UICC seventh edition	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ, high grade dysplasia
T1	Tumor invades lamina propria or submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable cancer invades adjacent structures such as pleura, pericardium, diaphragm
T4b	Unresectable cancer invades adjacent structures such as aorta, vertebral body, trachea
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	1 to 2 positive regional lymph nodes, from cervical to celiac
N2	3 to 6 positive regional lymph nodes, from cervical to celiac
N3	7 positive regional lymph nodes
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Histopathology	
	Adenocarcinoma
	Squamous cell carcinoma
Histologic grade	
	G1: well differentiated
	G2: moderately differentiated
	G3: poorly differentiated
	G4: undifferentiated
Location	
	Upper thoracic: 20–25 cm from incisors
	Middle thoracic: >25–30 cm from incisors
	Lower thoracic: >30–40 cm from incisors
	Esophagogastric junction: now defined as an esophageal cancer subsite (not gastric). See definition below*

* Includes cancer whose epicenter is in the distal thoracic esophagus, esophagogastric junction, or within the proximal 5 cm of the stomach (cardia) that extend into the esophagogastric junction or distal thoracic esophagus