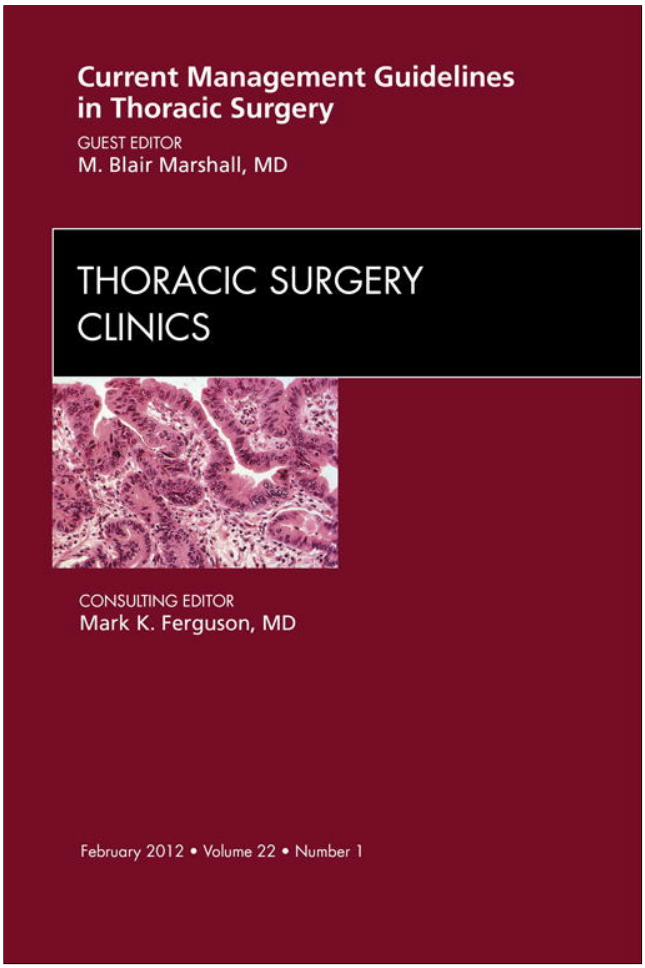
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# Evidence-Based Review of the Management of Cancers of the Gastroesophageal Junction

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**KEYWORDS**

• Esophageal cancer • Gastroesophageal junction cancer
• Cardia tumor • Esophageal adenocarcinoma
• Neoadjuvant chemotherapy
• Neoadjuvant chemoradiotherapy • Mucosal ablation

The management of esophageal cancer continues to be a challenging problem for surgeons and oncologists. Despite improvements in surgical outcomes and techniques, survival for patients with evidence of nodal involvement remains poor. For this reason, neoadjuvant chemotherapy, with or without radiation, is often used, although not in a consistent fashion. Several randomized trials have been performed, but the results are difficult to interpret because of differences in the methods of preoperative staging, inclusion and exclusion criteria used in those trials, and type of esophagectomy performed.

Results are generally better for patients with an early-stage cancer. However, increased use of endoscopic therapies that allow for preservation of the esophagus are being reported for these patients.

In this article, we review the currently available evidence supporting the use of neoadjuvant and adjuvant therapies for esophageal cancer. Additionally, we review the evidence supporting the role of endoscopic therapies for early-stage esophageal cancer. For this article, we performed a search of the PubMed database for English-language articles using the following terms: early-stage esophageal cancer, T2N0 esophageal cancer, neoadjuvant chemotherapy, neoadjuvant chemoradiotherapy, and definitive chemoradiation for esophageal cancer. From this search, we selected 46 articles for inclusion in this article. This included 12 randomized trials, of which 10 were multicenter studies. The randomized trials were limited to the studies evaluating the role of neoadjuvant therapy. Recommendations were graded as indicated in Appendix 1.

## STAGE I ESOPHAGEAL CANCER

### Class I Recommendations

- It is reasonable to use esophagectomy to treat intramucosal (T1aN0) cancers of the esophagus. *Level of Evidence: B*

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- Esophagectomy is the preferred treatment for submucosal (T1bN0) cancers. *Level of Evidence: B*

Class IIb Recommendations

- Endoscopic therapy for superficial esophageal cancer, limited to the mucosa, may be reasonable when performed in experienced centers and in patients who will agree to undergo long-term surveillance endoscopy. In addition, intramucosal cancers treated endoscopically should meet the following criteria: size of 2 cm or smaller, well-differentiated or moderately differentiated pathology, no lymphatic or vascular invasion, and lateral and deep margins free of cancer after endoscopic mucosal resection. *Level of Evidence: B*

Endoscopic therapies are becoming increasingly popular for patients with high-grade dysplasia and superficial esophageal cancers. In part, this is related to concerns about excessive morbidity and mortality as high as 10% after esophagectomy.[1] More recent studies, however, such as a report using the Society of Thoracic Surgeons database, demonstrated a mortality of only 2.7% from a total of 2,315 esophagectomies performed in 73 centers.[2]

Investigators from the Cleveland Clinic previously reported a series of 122 patients with superficial esophageal cancer who underwent esophagectomy.[3] In this series, operative mortality was 2.5%, and 1-year, 5-year, and 10-year survival rates were 89%, 77%, and 68%, respectively. Eight (7%) patients had N1 disease, which was significantly associated with poorer survival. A more recent study from the University of Pittsburgh included 100 patients with T1 esophageal cancers who underwent esophagectomy.[4] Within this series, there were 29 intramucosal (T1a) cancers and 71 submucosal (T1b) cancers. N1 disease was identified in 21 patients. This occurred in 2 (7%) of the T1a patients and 19 (27%) of the T1b cancers. There were no 30-day mortalities. The overall 5-year survival for the entire cohort was 62%. For patients with N0 disease, this was 70% and for patients with N1 disease, this was 35%. Multivariate analysis also demonstrated that long tumor length ($\geq$2 cm) was a significant predictor of poor disease-free survival.

With the increasing use of endoscopic therapies for high-grade dysplasia, an alternative approach for superficial adenocarcinoma has been to combine endoscopic mucosal resection (EMR) with mucosal ablation. This approach was reported in a Dutch study involving 33 patients.[5] Patients with Barrett's esophagus and neoplastic lesions smaller than 2 cm in diameter, without evidence of lymph node involvement or submucosal involvement on endoscopic ultrasound (EUS), underwent EMR. Patients found to have T1b tumors were referred for resection, and patients with T1a tumors underwent follow-up with mucosal ablation for any remaining Barrett's esophagus. Twenty-eight patients were entered into the follow-up protocol after EMR. At a median follow-up of 19 months, 5 out of 26 patients had a recurrence of high-grade dysplasia, which was treated with repeat EMR.

A few centers have also described the use of endoscopic submucosal dissection for esophageal cancer.[6] One report involved 24 patients treated over 5 years. In this study, a curative resection was defined as occurring when the lateral and vertical margins of the tumor were free of cancer, there was no submucosal invasion deeper than 500 $\mu$m from the muscularis mucosa, and lymphatic or vascular invasion was absent. Additionally, any poorly differentiated adenocarcinoma or tumor with signet-ring cells was considered to have a noncurative resection. Using these very strict criteria, 72% of patients had curative resections. At a median follow-up of 30.1 months, there was no local or distant recurrence.

Probably the largest reported experience of endoscopic therapy for superficial adenocarcinoma of the esophagus is that of the group from Wiesbaden, Germany.[7] This center previously reported a series of 144 resections in 100 patients. Each tumor was assessed according to the Japanese classification of early stomach cancers.[8] This classification is as follows: Type I (polypoid), Type IIa (flat and slightly elevated), Type IIb (flat and level), Type IIc (flat and depressed), and Type III (ulcerated). Patients with types I, IIa, IIb, and IIc tumors up to 20 mm were eligible for local therapy, which included EMR followed by mucosal ablation for the remaining non-neoplastic Barrett esophagus. Patients had to have an R0 resection, with one normal endoscopic examination to be considered a complete remission, before undergoing surveillance or mucosal ablation. Additionally, tumors with submucosal invasion or lymphatic or vascular invasion, and poorly differentiated tumors after EMR were not considered eligible for this protocol. At a mean follow-up of 36.7 months, recurrent or metachronous cancers occurred in 11% of patients. All were treated successfully with repeat EMR, with a calculated 5-year survival rate of 98%.

These studies suggest that an endoscopic approach may be reasonable for highly selected patients with superficial adenocarcinoma. However, it should be emphasized that these studies

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were performed in specialized centers where there was commitment, by patients and their treating physicians, to the rigorous long-term follow-up that is required to identify and treat any recurrent cancer that may occur. Additionally, the technique of endoscopic submucosal dissection described by the Japanese investigators[6] is challenging technically, and it is unlikely that this will be widely adopted. On the other hand, several centers are currently performing EMR, and as more data become available, endoscopic therapies may become the preferred treatment for low-risk intramucosal adenocarcinoma for appropriate patients.

## CLINICAL T2N0M0 ESOPHAGEAL CANCER

Class IIb Recommendations

- It is reasonable to treat esophageal tumors that are clinically staged at T2N0M0 with either esophagectomy or with neoadjuvant therapy followed by esophagectomy. *Level of Evidence: B*
- Patients who are treated initially with esophagectomy and are found to have higher-stage cancers on pathology should be treated with adjuvant therapy. *Level of Evidence: B*

The literature concerning tumors clinically staged at T2N0M0 is limited. Because these patients clinically have no evidence of nodal disease, they are often treated with esophagectomy, as is similar to other early-stage, node-negative tumors.[9,10] Multimodality therapy for esophageal tumors, however, has become increasingly popular in response to poor outcomes after surgery alone for more advanced disease. Several of the larger randomized trials studying neoadjuvant therapy have included cT2N0M0 in their patient selection, but numbers are often small in this category and subset analyses for this patient group often have not been provided.[11–16] Given the inconclusive and controversial nature of this topic, it seems reasonable to examine whether patients staged at cT2N0M0 should receive neoadjuvant therapy or proceed directly to esophagectomy.

A major concern with cT2N0 disease is the accuracy of clinical staging. Overstaged patients may be subjected unnecessarily to neoadjuvant therapy and understaged patients may get inadequate therapy if proceeding directly to surgery. One study from the Cleveland Clinic found that the positive predictive value for esophageal carcinoma clinically staged at T2 was 23%.[17] The literature describes the percentage of overstaged cT2N0M0 tumors as ranging from 54% to 66%,[17–21] with errors predominantly in tumor depth.[18] On the other hand, a large proportion of cT2N0 tumors are understaged, ranging from 20.1% to 55.0% in different series.[17–22] Staging errors in this category are unfortunately predominantly in nodal involvement,[18,22] a more significant adverse prognostic indicator than T stage. As such, cT2N0M0 cancers have a worse prognosis than pT2N0M0, simply by virtue of the large portion of understaged tumors.

On the basis of this large proportion of occult, node-positive cancers, many centers advocate induction therapy for cT2N0M0.[16,22,23] A retrospective study from the M. D. Anderson Cancer Center suggested that neoadjuvant therapy effectively downstages a significant number of patients, as their results demonstrated only 10% of patients with pathologic stage greater than T2N0M0,[23] in comparison with the expected percentage of 20.1% to 55.0% from the literature.[17–19,21,22] Although this may support the role of neoadjuvant therapy, this may also have significant negative implications for patients with overstaged tumors. Advocates of the surgery-first approach argue that tumors found to be node positive on pathology may be treated with adjuvant chemoradiation with good results, thereby sparing patients with overstaged cancers from unnecessary chemotherapy and radiation therapy.[18] Adjuvant therapy for node-positive disease, although common practice, is also a subject of debate as to actual effectiveness in prolonging survival.[18,24–28]

There are currently only 2 studies specifically addressing the management of cT2N0M0 esophageal cancer, both of which are single institution and retrospective in design. The first study, by Rice and colleagues,[18] was undertaken at the Cleveland Clinic, and the second was reported by Kountourakis and colleagues,[23] at the M. D. Anderson Cancer Center. In both studies, patients with cT2N0M0 were a relatively small proportion of their total esophageal cancer populations. Rice and colleagues[18] identified 61 patients with this stage over 18 years, and Kountourakis and colleagues[23] identified only 49 patients over 12 years, although the latter report was restricted to cT2N0M0 patients treated with neoadjuvant therapy followed by surgery.

The Cleveland Clinic study reviewed 61 patients with clinically staged T2N0M0 by computed tomography (CT) and endoscopic ultrasonography. Rice and colleagues[18] analyzed patients who had surgery alone (n = 45), surgery first followed by chemoradiation for pathologically more advanced disease (n = 8), and surgery preceded by induction chemoradiation therapy (n = 8).

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Only 7 patients of the 53 who underwent surgery first were found to have pathologic T2N0M0 (13.2%); 17 patients (32.1%) were understaged and 29 patients (54.7%) were overstaged. Overall survival at 10 years for overstaged cT2N0M0 treated with surgery alone was approximately 50%, which was found to be similar to propensity-matched surgery-alone patients (non-cT2N0M0 patients with less than pT2N0M0). Overall survival for correctly staged pT2N0M0 was similar to patients with overstaged T2N0M0 treated with surgery alone. For clinically understaged patients, survival was poor unless followed by adjuvant therapy: 10% at 5 years versus 43% at 5 years ($P$ = .17). The induction therapy group (n = 8) had poor outcomes; of the 7 deaths at 10 years, 5 were cancer related. Patients who had induction therapy also had a poorer 5-year survival compared with the other treatment strategies used, at 13% versus 52% ($P$ = .05). From these results, the investigators concluded that cT2N0M0 esophageal cancers should be treated with surgery first, followed by adjuvant therapy if they are found to be of a pathologically higher stage; otherwise, surgery alone was sufficient. They did not recommend induction therapy for cT2N0M0, although they acknowledged the limitations of that recommendation because of the small number of patients treated with induction therapy in their study.

In the M. D. Anderson Cancer Center study, a retrospective review of 49 patients with cT2N0M0 esophageal carcinoma who were treated with neoadjuvant therapy followed by surgery was undertaken. Clinical staging was done by endoscopic ultrasonography as well as CT imaging. A mean overall survival of 92.6 months and 5-year survival of 64.1% was demonstrated at a median follow-up of 28.4 months (range, 1.60–141.07 months). Five patients (10%) had a pathologic stage higher than T2N0M0. Fifteen of 44 patients with adenocarcinoma, and 3 of 5 patients with squamous cell carcinoma ($P$ = .342), had a pathologic complete response to induction therapy. Although this was a single-arm study, the overall survival is promising compared not only with the 51% survival for cT2N0M0 patients treated with surgery first in the Cleveland Clinic study but also compared with the 50% 5-year survival specifically for pT2N0M0 patients reported in another study by the Cleveland Clinic group.[29]

In summary, there is limited evidence supporting an "induction therapy first" strategy versus an "esophagectomy first" strategy for clinically staged T2N0M0 esophageal tumors. We believe there would be equipoise for a randomized study of this patient group, but this may not be feasible because of the relative scarcity of cT2N0M0 tumors.

## CLINICAL N1 OR T3N0 ESOPHAGEAL CANCER

Class I Recommendations

- It is reasonable to use neoadjuvant chemotherapy with or without radiation to treat locally advanced esophageal cancer, before esophagectomy. *Level of Evidence: A*

Class IIb Recommendations

- There is no evidence that the addition of radiation is superior to chemotherapy alone with respect to survival, when used as neoadjuvant therapy for esophageal cancer. *Level of Evidence: B*
- Definitive radiation and chemotherapy for locally advanced esophageal cancer is reasonable, but should reserved for the high-risk surgical patient, or patients with resectable disease who refuse resection. *Level of Evidence: B*

For this discussion, patients with locally advanced esophageal cancer are defined as those with resectable tumors that are clinically staged as T3N0 or any T stage with N1 disease.

Management of locally advanced esophageal cancer has traditionally been by surgical resection alone. However, survival is poor with patients often succumbing to metastatic disease. In an effort to improve the outcomes, many investigators have studied the use of both preoperative chemotherapy and preoperative chemoradiotherapy and its impact on overall survival, disease-free survival, and R0 resection rate. An issue when interpreting many of these reports is that they are not always restricted to locally advanced disease, staging is not uniformly undertaken, and the type of esophagectomy used also is not uniform.[11,12,30–37] Another issue is that each series may include both mid and lower esophageal tumors, requiring extrapolation of the results for gastroesophageal junction and cardia cancers specifically.

On the other hand, because of the relatively larger number of patients presenting with locally advanced esophageal cancer, and the poorer survival associated with these tumors, many of the reports are from multicenter phase III trials.

### *Neoadjuvant Chemotherapy Followed by Surgery for Locally Advanced Esophageal Cancer*

In 1998, the North American Intergroup trial by Kelsen and colleagues[30] compared 213 patients

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who were randomized to undergo neoadjuvant chemotherapy with cisplatin and fluorouracil followed by surgery with 227 who were randomized to undergo surgery alone for esophageal adenocarcinoma or squamous cell carcinoma. Staging involved chest x-ray, barium esophagram, and CT of the chest and abdomen; importantly, endoscopic ultrasonography was not required. Eligible patients had resectable tumors defined as T1-3, any nodal stage, and M0. Adenocarcinoma was seen in 121 (53%) of 227 patients in the surgery group and 115 (54%) of 233 patients who received preoperative chemotherapy. Interestingly, although chemotherapy did not affect operative mortality, which was 6% for each arm, it did not significantly affect R0 resection rates either (62% of the preoperative chemotherapy group vs 59% in the surgery-only group). Moreover, although there were more patients with R1 resections in the surgery group compared with the preoperative chemotherapy group (15% vs 4%, $P = .001$), there was no difference in overall survival, median survival, or disease-free survival (**Tables 1** and **2**). Therefore, in this Intergroup trial, the use of preoperative chemotherapy did not lead to a survival benefit.

In a subsequent multicenter randomized trial[31] by the Medical Research Council in 2002, 400 patients randomized to treatment with neoadjuvant chemotherapy, consisting of cisplatin and fluorouracil followed by surgery, were compared with 402 patients randomized to undergo surgery alone for esophageal adenocarcinoma or squamous cell carcinoma. Patients with resectable disease of all stages were included. Ten percent of the tumors were in the cardia and 64% were in the lower third of the esophagus. Also, 9% of patients in both arms received preoperative radiotherapy at the direction of their clinician. As was the case in the Intergroup trial, the use of preoperative chemotherapy did not lead to an increase in operative mortality, which was 10% for each arm. However, there was a higher rate of R0 resection when preoperative chemotherapy was used (60% vs 54%, $P<.0001$), and this persisted even when patients who did not receive preoperative radiotherapy were considered separately (60% vs 53%, $P<.0001$). With a median follow-up of 36.9 months for the preoperative chemotherapy group and 37.9 months for the surgery group, a benefit was seen in terms of overall survival (at 2 years, 43% vs 34%, $P = .001$) and improved disease-free survival (see **Tables 1** and **2**) favoring the neoadjuvant group. Interestingly, this study was updated in 2009 in a report[32] with a median follow-up of 72 months that demonstrated an absolute 5-year survival of 23.0% for the neoadjuvant arm compared with 17.1% for the surgery arm ($P = .03$).

In 2006, the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial[33] reported on 250 patients randomized to undergo neoadjuvant chemotherapy with 3 cycles of epirubicin, cisplatin, and fluorouracil followed by surgery and 3 more cycles of adjuvant chemotherapy (same regimen), and compared with 253 patients who underwent surgery alone for adenocarcinoma of the stomach, esophagogastric junction, or lower esophagus. Inclusion criteria required that patients have resectable disease that was stage II or higher, with a tumor of either the stomach or lower third of the esophagus. Staging was performed by chest radiography, CT imaging, endoscopic ultrasonography, or laparoscopy. Gastroesophageal junction tumors comprised only 28 (11.2%) of the cases in the perioperative chemotherapy arm and 30 (11.9%) cases in the surgery-alone arm. The use of perioperative chemotherapy did not affect the rate of perioperative complications (45.7% vs 45.3% for the surgery group) or 30-day operative mortality (5.6% vs 5.9% for the surgery group). Moreover, there was a survival benefit seen among the patients treated with perioperative chemotherapy (5-year survival of 36.3% vs 23%, $P = .009$) and there was a higher likelihood of progression-free survival (hazard ratio for progression, 0.66; 95% confidence interval 0.53 to 0.81, $P<.001$).

More recently, Ychou and colleagues[34] reported on 113 patients randomized to treatment with neoadjuvant chemotherapy of fluorouracil and cisplatin followed by surgery and compared with 111 patients treated with surgery alone for gastroesophageal adenocarcinoma. Patients included in the study had a histologically proven resectable tumor in the lower third of the esophagus, the gastroesophageal junction, or the stomach, and cases of in situ carcinoma were excluded from analysis. In this series, 144 (64%) patients had a gastroesophageal junction tumor. The use of preoperative chemotherapy did not affect perioperative morbidity (25.7% vs 19.1% for surgery-only group, $P = .24$) or operative mortality (4.6% vs 4.5% for the surgery group, $P = .76$), but it did improve the R0 resection rate (84% vs 74% in the surgery group, $P = .04$). In addition, the group treated with neoadjuvant chemotherapy had an improved overall survival (5-year rate of 38% vs 24%, $P = .02$) and disease-free survival (5-year rate of 34% vs 19%, $P = .003$).

In summary, preoperative chemotherapy seemed to improve overall and disease-free survival in 3 of the 4 trials described previously, although

**Table 1**
**Prospective randomized trials of preoperative chemotherapy with overall survival**

| Author, Year | Cancer Stages Treated | Median Follow-Up | Groups | Patients Randomized | Operative Mortality | 3-y Overall Survival | 5-y Overall Survival | Median Survival, mo | *P* Value |
|---|---|---|---|---|---|---|---|---|---|
| Kelsen et al,[30] 1998 | T1-3, Any N, M0 | 46.5 months | Neoadj<br>Surgery | 227<br>213 | 6%<br>6% | 23%<br>26% | 20%[a]<br>23%[a] | 14.9<br>16.1 | .53 |
| Medical Research Council,[31] 2002 | NR<br>No locally inoperable disease or mets | 36.9 months<br>37.9 months | Neoadj<br>Surgery | 400<br>402 | 10%<br>10% | 33%[a]<br>24%[a] | 22%[a]<br>13%[a] | 16.8<br>13.3 | .004 |
| MAGIC,[33] 2006 | Stage II or higher<br>No locally inoperable disease or mets | 49 months | Neoadj<br>Surgery | 250<br>253 | 5.6%<br>5.9% | 45%[a]<br>31%[a] | 36.3%<br>23% | 23[a]<br>20[a] | .009 |
| Ychou et al,[34] 2011 | No Stage 0 | 68.4 months | Neoadj<br>Surgery | 113<br>111 | 4.6%<br>4.5% | NR<br>NR | 38%<br>24% | NR<br>NR | .02 |

*Abbreviations:* MAGIC, Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial; mets, metastasis; Neoadj, neoadjuvant chemotherapy; NR, not recorded in report.
[a] Data estimated from survival curves.

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**Table 2**
**Prospective randomized trials of preoperative chemotherapy with disease-free survival**

| Author, Year | Groups | 3-y Disease-Free Survival | 5-y Disease Free Survival | *P* Value |
|---|---|---|---|---|
| Kelsen et al,[30] 1998 | Neoadj | 18%[a] | 16%[a] | .5 |
| | Surgery | 18%[a] | 16%[a] | |
| MRC,[31] 2002 | Neoadj | 24%[a] | 18%[a] | .0014 |
| | Surgery | 17%[a] | 12%[a] | |
| MAGIC,[33] 2006 | Neoadj | 38%[a] | 30%[a] | <.001 |
| | Surgery | 26%[a] | 18%[a] | |
| Ychou et al,[34] 2011 | Neoadj | NR | 34% | .003 |
| | Surgery | NR | 19% | |

*Abbreviations:* MAGIC, Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial; MRC, Medical Research Council; Neoadj, neoadjuvant chemotherapy; NR, not recorded in report.
[a] Data estimated from survival curves.

stage-specific survival information was not provided. Also, the R0 resection rate was increased when preoperative chemotherapy was used in 2 trials. Neoadjuvant chemotherapy does not appear to affect operative mortality significantly.

## NEOADJUVANT CHEMORADIATION FOLLOWED BY SURGERY FOR LOCALLY ADVANCED ESOPHAGEAL CANCER

Many centers favor the inclusion of radiation therapy as part of their neoadjuvant therapy for esophageal cancer. It is believed that the addition of radiation allows a higher complete response rate (which may translate into better survival) and higher R0 resection rates. On the other hand, concerns remain about increased morbidity with the inclusion of radiation. The following describes 6 recent prospective randomized trials addressing the efficacy of preoperative chemoradiation followed by surgery for esophageal carcinoma.

In 1996, Walsh and colleagues[12] reported on a single-center prospective trial that studied 58 patients randomized to treatment with multimodality therapy (specifically fluorouracil, cisplatin, and 40 Gy of radiation followed by surgery) and compared with 55 patients who underwent surgery alone for esophageal adenocarcinoma. For the series, 51.0% of the patients had a tumor of the lower third of the esophagus and 34.5% had a tumor of the cardia. In the multimodality group, 5 patients died (1 of whom died preoperatively owing to hemorrhage from the tumor bed) compared with 2 patients in the surgery-alone group. At the time of surgery, there were more patients with positive nodes in the surgery-alone group than in the multimodality group (82% vs 42%, $P<.001$). The median follow-up for all patients was 10 months (range, 0.1–59.0 months). The median survival for the multimodality group was longer than for the surgery-alone group (16 vs 11 months, $P = .01$), and the 3-year survival rate was higher for the multimodality group compared with the surgery-alone group (32% vs 6%, $P = .01$). One concern with this study is that the 3-year survival in the surgery-only group was significantly lower than other studies using surgery alone. Additionally, staging was not uniformly undertaken even with the use of a CT scan, which was used selectively in patients with equivocal findings on chest radiographs or liver ultrasonograms.

In the following year, Bosset and colleagues[11] reported on a multicenter trial in which 143 patients were randomized to preoperative chemoradiation (consisting of cisplatin and 18.5 Gy) followed by surgery and were compared with 139 patients who underwent surgery alone for squamous cell carcinoma of the esophagus. Endoscopic ultrasonography was not used, and staging was based on chest CT imaging. The following stages were included: T1N0, T1N1, T2N0, T2N1, and T3N0. Tumors staged as T3N0 comprised 29.5% of the surgery group and 32.9% of the multimodality group. The use of multimodality therapy was not associated with a higher rate of perioperative complications (45% vs 36% for the surgery group, $P = .249$), but was associated with a higher operative mortality rate (12.3% vs 3.6% for the surgery group, $P = .012$). At a median follow-up of 55.2 months, there was no significant difference in overall survival, with a median survival of 18.6 months observed for both treatment groups. The group treated with preoperative chemoradiation, however, had a longer disease-free survival (estimated 3-year disease-free survival of 40% for the multimodality group vs 28% for the surgery group, $P = .003$, and 5-year disease-free survival of 32% vs 24%, $P = .003$).

Thereafter, in 2001, the University of Michigan group reported a study of 50 patients randomized to treatment with preoperative chemoradiation (cisplatin, vinblastine, fluorouracil, and 45 Gy of radiation) followed by transhiatal esophagectomy, and compared with 50 patients treated with surgery alone for either squamous cell carcinoma or adenocarcinoma of the esophagus.[38] Patients included in this study had tumors of the esophagus or gastroesophageal junction, and the staging process did not use endoscopic

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ultrasonography. Two patients (4%) died in the surgery arm, and 1 (2.1%) died in the multimodality group. After a median follow-up of 8.2 years, there was no significant difference in 3-year overall survival (30% for the multimodality group vs 16% for the surgery-alone group, $P = .15$) or disease-free survival (28% vs 16%, respectively, $P = .16$) between the groups.

Similarly, Burmeister and colleagues[35] reported on 128 patients randomized to treatment with neoadjuvant chemoradiation (cisplatin, fluorouracil, and 35 Gy of radiation) followed by surgery and compared with 128 patients treated with surgery alone for squamous cell carcinoma or adenocarcinoma of the esophagus. Eligible patients had to have resectable tumors of the esophagus and gastric cardia (as long as the tumor was mainly in the lower esophagus), and included T1-3, N0-1 tumors. Also, as endoscopic ultrasonography was not widely available at the time of the study, its use in staging was not mandatory. Tumors of the lower third of the esophagus comprised 77% of the multimodality group and 81% of the surgery-alone group. Although an increased R0 resection rate was seen in the multimodality group (80% vs 59% for the surgery group, $P = .0002$), there was no significant difference in overall survival or progression-free survival (**Tables 3** and **4**) after a median length of follow-up of 65 months.

In 2008, the CALGB 9781 trial by Tepper and colleagues[36] reported on 30 patients randomized to treatment with neoadjuvant chemoradiation (cisplatin, fluorouracil, and 50.4 Gy of radiation) followed by surgery who were compared with 26 patients treated with surgery alone for squamous cell carcinoma or adenocarcinoma of the esophagus from 1997 to 2000. Eligible patients had either a thoracic esophageal cancer or a gastroesophageal junction tumor with less than 2-cm spread into the cardia, and stages included T1-3, N0-1, and M0. Staging by either EUS or thoracoscopy/laparoscopy was recommended. In all, 17 (56.7%) of 30 patients in the multimodality arm and 20 (77%) of 26 patients in the surgery arm had a clinical stage of T3N0, 75% of all patients had adenocarcinoma, and only 25% had N1 disease. There was only one perioperative mortality, occurring in the surgery arm. This multicenter randomized trial closed early because of poor accrual. With a median follow-up of 6 years, the median survival was 4.48 years for the multimodality group compared with 1.79 years for the surgery-only group ($P = .002$), and 5-year survival was 39% for the multimodality group compared with 16% for the surgery only group ($P = .008$). Survival based on clinical stage was not reported. This study demonstrates a large and significant difference in median survival favoring the use of neoadjuvant chemoradiation. However, there was an unusually high percentage (66%) of patients who were clinically staged as T3N0. Although this group of patients has a high probability of occult nodal disease, their behavior may be more favorable compared with patients with clinically positive nodal disease and may in part explain these results, which are superior to most other randomized trials.

More recently, Gaast and colleagues[37] of the CROSS study group presented the results of 175 patients randomized to treatment with preoperative chemoradiation (paclitaxel, carboplatin, and 41.4 Gy of radiation) followed by surgery and compared with 188 patients treated with surgery alone. Patients included in the study had either esophageal or gastroesophageal tumors, for clinical stages T2-3, N0-1. For all patients, 75.2% of the tumors were adenocarcinomas. There was no difference in the in-hospital mortality, which was 3.8% for the multimodality group and 3.7% for the surgery group. The R0 resection rate favored the multimodality group (92.3% vs 64.9% for the surgery group). With a median follow-up of 32 months, overall survival was significantly better (3-year survival 59% vs 48%, favoring the multimodality group, $P = .011$), and median survival was 49 months in the multimodality group and 26 months in the surgery group.

It is unclear whether there is an advantage of neoadjuvant chemoradiotherapy over neoadjuvant chemotherapy. Two randomized studies have attempted to address this.[39,40] The first study from Germany randomized patients with T3-T4NXM0 disease to chemotherapy (15 weeks) or induction chemotherapy (12 weeks) followed by chemoradiation (3 weeks) before surgery.[39] The study was designed to include 354 patients but closed because of poor accrual at 126 patients. There was no difference in R0 resection rates, but there was a higher complete pathologic response rate in the chemoradiation patients (15.6% vs 2.0%, $P = .03$). Perioperative mortality was higher after neoadjuvant chemoradiation compared with chemotherapy (10.0% vs 3.8%), but this difference was not statistically significant ($P = .26$). There was also a nonsignificant trend ($P = .07$) favoring 3-year survival after neoadjuvant chemoradiotherapy compared with surgery (47.7% vs 27.7%). The second study addressing this issue was an Australian randomized phase II study involving 75 patients.[40] Preoperative chemotherapy was used in 36 patients and preoperative chemoradiotherapy in 39 patients. There was no difference in toxicity. The histopathological complete response rate (31% vs 11%; $P = .01$) was significantly better in the chemoradiation

**Table 3**
**Prospective randomized trials of preoperative chemoradiotherapy with overall survival**

| Author, Year | Cancer Stages Treated | Median Follow-Up | Groups | Patients Randomized | Operative Mortality | 3-y Overall Survival | 5-y Overall Survival | Median Survival, mo | *P* Value |
|---|---|---|---|---|---|---|---|---|---|
| Walsh et al,[12] 1996 | NR | 10 mo | Multimodal | 58 | 12% | 32% | NR | 16 | .01 |
| | | 8 mo | Surgery | 55 | 4% | 6% | NR | 11 | |
| Bosset et al,[11] 1997 | T1-3, N0-1 | 55.2 mo | Multimodal | 143 | 12.3% | 36%[a] | 26%[a] | 18.6 | .78 |
| | | | Surgery | 139 | 3.6% | 34%[a] | 24%[a] | 18.6 | |
| Urba et al,[38] 2001 | NR. (Disease limited to esophagus/GEJ) | 98.4 mo | Multimodal | 50 | 4% | 30% | 20%[a] | 16.9 | .15 |
| | | | Surgery | 50 | 2% | 16% | 10%[a] | 17.6 | |
| Burmeister et al,[35] 2005 | T1-3, N0-1 | 65 mo | Multimodal | 128 | 5% | 36%[a] | 26% | 22.2 | .57 |
| | | | Surgery | 128 | 5% | 31%[a] | 24% | 19.3 | |
| Tepper et al,[36] 2008 | T1-3, N0-1 | 72 mo | Multimodal | 30 | 0% | 66%[a] | 39% | 53.8 | .002 |
| | | | Surgery | 26 | 4% | 20%[a] | 16% | 21.5 | |
| Gaast et al,[37] 2010 | T2-3, N0-1 | 32 mo | Multimodal | 175 | 4% | 59% | NR | 49 | .011 |
| | | | Surgery | 188 | 4% | 48% | NR | 26 | |

*Abbreviations:* GEJ, gastroesophageal junction; NR, not recorded in report.
[a] Data estimated from survival curves.

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**Table 4**
**Prospective randomized trials of preoperative chemoradiotherapy with disease-free survival**

| Author, Year | Groups | 3-y Disease-Free Survival | 5-y Disease-Free Survival | *P* Value |
|---|---|---|---|---|
| Walsh et al,[12] 1996 | Multimodal | NR | NR | NR |
| | Surgery | NR | NR | |
| Bosset et al,[11] 1997 | Multimodal | 40%[a] | 32%[a] | .003 |
| | Surgery | 28%[a] | 24%[a] | |
| Urba et al,[38] 2001 | Multimodal | 28% | 25%[a] | .16 |
| | Surgery | 16% | 12%[a] | |
| Burmeister et al,[35] 2005 | Multimodal | 34%[a] | 31%[a] | .32 |
| | Surgery | 26%[a] | 24%[a] | |
| Tepper et al,[36] 2008 | Multimodal | 60%[a] | 28% | .007 |
| | Surgery | 15%[a] | 15% | |
| Gaast et al,[37] 2010 | Multimodal | NR | NR | NR |
| | Surgery | NR | NR | |

*Abbreviation:* NR, not recorded in report.
[a] Data estimated from survival curves.

group; however, there was no difference in the median overall and progression-free survivals.

In summary, these trials suggest a benefit with respect to overall survival with neoadjuvant chemotherapy and radiation for esophageal or gastroesophageal junction cancer compared with surgery alone. In addition, an increase in both the R0 resection rate and complete pathologic response rate occurs when preoperative radiation is included in the neoadjuvant protocol. The addition of radiation does not appear to improve survival rates, however, and may lead to increased toxicity compared with chemotherapy alone.

## DEFINITIVE CHEMORADIATION FOR LOCALLY ADVANCED ESOPHAGEAL CANCER

A randomized study from France compared chemoradiation followed by resection to chemoradiation alone.[41] This study was limited to squamous cell carcinoma of the esophagus, and only included patients with T3N0-1 cancers. Randomization occurred after therapy was initiated, and evidence of a response to initial chemoradiation was seen. In their study of 444 patients, there was felt to be no benefit by the addition of surgery with similar 2-year survival rates (34% vs 40%, $P = .44$). There was more locoregional relapse ($P = .03$) and a greater need for esophageal stents (5% vs 32%, $P<.001$) in the patients receiving definitive chemoradiation. Another randomized study from Hong Kong compared esophagectomy with definitive chemoradiotherapy for mid and lower squamous esophageal cancers.[42] Salvage esophagectomy was allowed for patients with incomplete response or recurrence. With this approach, the 80-patient study demonstrated no difference in overall or disease-free survival. A follow-up report, from the same study, demonstrated that surgery was associated with a short-term negative impact on quality of life seen at 6 months, which became insignificant by 2 years.[43] On the other hand, chemoradiation was associated with progressive deterioration in pulmonary function with longer follow-up.

The issue of toxicity after chemoradiation is even more relevant in older patients, as demonstrated in a recent retrospective study from the Massachusetts General Hospital.[44] In this study, involving 34 patients aged 75 years or older (median age 75.9 years), only 50% of patients were able to complete planned therapy. Grade 4 or higher toxicity occurred in 38.2% of patients, with 70.6% of patients requiring hospital admission. Overall survival at 2 years was 29.7%. It should be emphasized that the median Eastern Cooperative Oncology Group Performance Status was excellent, at 1 in this group of elderly patients before therapy.

In one recent retrospective analysis,[45] 266 patients had been treated with platinum-based chemotherapy and 50 Gy of radiotherapy. Fifty-three percent of the cancers were adenocarcinomas. Also, tumors of the lower third of the esophagus or the gastroesophageal junction comprised 56% and 5% of all patients, respectively. Additionally, 58% were T3 tumors, 25% were T4 tumors, and 11% had M1a disease. In this series, median survival was 20.6 months, and the 2-year, 3-year, and 5-year survival rates were 43.6%, 32.9%, and 19.5%, respectively.

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Also, Hironaka and colleagues[46] compared 53 patients treated with chemoradiotherapy and 45 patients treated with surgery for T2-3, N-any, M0 squamous cell carcinoma of the esophagus in a retrospective report in 2003. Chemoradiotherapy consisted of 5-fluorouracil, cisplatin, and 60 Gy of radiation. Lower-third esophageal tumors comprised 51.0% of the tumors in the surgery group and 30.2% of the tumors in the chemoradiation group. Additionally, the chemoradiation group had more advanced stage tumors than the surgery group. A pathologic complete response was seen in 70% of the chemoradiotherapy group, and the R0 resection rate was 98% in the surgery group. The perioperative morbidity rate of the esophagectomy group, however, was very high at 64%, and included an anastomotic leak rate of 29%. There was a 4% operative mortality, and no chemoradiotherapy-related deaths. With a median follow-up period of 43 months in both groups, the 5-year survival rates for the chemoradiotherapy and surgery groups were not significantly different (46% vs 51%, respectively, $P = .47$). Locoregional recurrence rates were not addressed in this study.

Although most reports are from retrospective studies, it does appear that the survival after definitive chemoradiation from retrospective studies approaches that of surgery alone, leading some oncologists to advocate this approach particularly for patients with locally advanced cancer and comorbid disease that would increase the risk of resection. On the other hand, studies as described previously have demonstrated poorer local control and swallowing after definitive chemoradiation, and significant morbidity may occur in patients with good performance status who are elderly.[44] For this reason, the authors advocate a neoadjuvant approach, including resection for patients with T3N0-1 disease, but recommend esophagectomy alone for the elderly patient with a high performance status, because of better locoregional control and preservation of swallowing.

## SUMMARY

The successful management of gastroesophageal cancers continues to be a challenge for gastroenterologists, surgeons, and oncologists. Paralleling outcomes in the management of other solid tumors, neoadjuvant therapy before surgical resection seems to offer an improved survival in advanced stages. Because of the rarity of this disease, mixed stages treated, variety of pathologies and locations, and types of surgical resections performed, identifying optimal treatment strategies has been challenging. Given the unfortunate fact that this disease is on the rise, we will be able to add to the growing body of treatment strategies in the future, hopefully leading to improved results in the management of this complex and deadly disease.

## REFERENCES


1. Bailey SH, Bull DA, Harpole DH, et al. Outcomes after esophagectomy: a ten year prospective cohort. Ann Thorac Surg 2003;75:217–22.
2. Wright CD, Kucharczuk JC, O'Brien SM, et al. Predictors of major morbidity and mortality after esophagectomy for esophageal cancer: A Society of Thoracic Surgeons General Thoracic Database Risk Adjustment Model. J Thorac Cardiovasc Surg 2009;137(3):587–95.
3. Rice W, Blackstone EH, Goldblum JR, et al. Superficial adenocarcinoma of the esophagus. J Thorac Cardiovasc Surg 2001;122:1077–90.
4. Pennathur A, Farkas A, Krasinskas AM, et al. Esophagectomy for T1 esophageal cancer: outcomes in 100 patients and implications for endoscopic therapy. Ann Thorac Surg 2009;87:1048–55.
5. Femke PP, Mohammed AK, Wilda D, et al. Endoscopic treatment of high-grade dysplasia and early stage cancer in Barrett's esophagus. Gastrointest Endosc 2005;61:506–14.
6. Yoshinaga S, Gotoda T, Kusano C, et al. Clinical impact of endoscopic submucosal dissection for superficial adenocarcinoma located at the esophagogastric junction. Gastrointest Endosc 2008;67:202–9.
7. Ell C, May A, Pech O, et al. Curative resection of early esophageal adenocarcinomas (Barrett's cancer). Gastrointest Endosc 2007;65:3–10.
8. Nishi M, Omori, Miwa K. Japanese Society for Gastric Cancer. Japanese classification of gastric carcinoma. 1st English edition. Tokyo: Kanehara; 1995.
9. Tougeron D, Richer JP, Silvain C. Management of esophageal adenocarcinoma. J Visc Surg 2011;148(3):e161–70.
10. Mariette C, Piessen G, Triboulet JP. Therapeutic strategies in oesophageal carcinoma: role of surgery and other modalities. Lancet 2007;8:545–53.
11. Bossett JF, Gignoux M, Triboulet JP, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous cell cancer of the esophagus. N Engl J Med 1997;337:161–7.
12. Walsh TN, Noonan N, Hollywood D, et al. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 1996;335:462–7.
13. Nygaard K, Hagen S, Hansen HS, et al. Pre-operative radiotherapy prolongs survival in operable

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esophageal carcinoma: a randomized, multicenter study of pre-operative radiotherapy and chemotherapy—the second Scandinavian trial in esophageal cancer. World J Surg 1992;16:1104–9 [discussion: 1110].
14. Pennathur A, Luketich JD, Landreneau RJ, et al. Long-term results of a phase II trial of neoadjuvant chemotherapy followed by esophagectomy for locally advanced esophageal neoplasm. Ann Thorac Surg 2008;85:1930–6.
15. Le Prise E, Etienne PL, Meunier B, et al. A randomized study of chemotherapy, radiation therapy, and surgery versus surgery for localized squamous cell carcinoma of the esophagus. Cancer 1994;73:1779–84.
16. Schwer AL, Ballonoff A, McCammon R, et al. Survival effect of neoadjuvant radiotherapy before esophagectomy for patients with esophageal cancer: a surveillance, epidemiology, and end-results study. Int J Radiat Oncol Biol Phys 2008;72:449–55.
17. Rice TW, Blackstone EH, Adelstein DJ, et al. Role of clinically determined depth of tumor invasion in the treatment of esophageal carcinoma. J Thorac Cardiovasc Surg 2003;125:1091–102.
18. Rice TW, Mason DP, Murthy SC, et al. T2N0M0 esophageal cancer. J Thorac Cardiovasc Surg 2007;133:317–24.
19. Crabtree TD, Yacoub WN, Puri V, et al. Endoscopic ultrasound for early stage esophageal adenocarcinoma: implications for staging and survival. Ann Thorac Surg 2011;91(5):1509–16.
20. Shimpi RA, George J, Jowell P, et al. Staging of esophageal cancer by EUS: staging accuracy revisited. Gastrointest Endosc 2007;66:475–82.
21. Zuccaro G Jr, Rice TW, Vargo JJ, et al. Endoscopic ultrasound errors in esophageal cancer. Am J Gastroenterol 2005;100:601–6.
22. Stiles BM, Mirza F, Coppolino A, et al. Clinical T2–T3N0M0 esophageal cancer: the risk of node positive disease. Ann Thorac Surg 2011;92(2):491–6.
23. Kountourakis P, Correa AM, Hofstetter WL, et al. Combined modality therapy of cT2N0M0 esophageal cancer: the University of Texas M. D. Anderson Cancer Center experience. Cancer 2011;117:925–30.
24. Rice TW, Adelstein DJ, Chidel MA, et al. Benefit of postoperative adjuvant chemoradiotherapy in locoregionally advanced esophageal carcinoma. J Thorac Cardiovasc Surg 2003;126:1590–6.
25. Armanios M, Xu R, Forastiere AA, et al. Adjuvant chemotherapy for resected adenocarcinoma of the esophagus, gastro-esophageal junction, and cardia: phase II trial (E8296) of the Eastern Cooperative Oncology Group. J Clin Oncol 2004;22:4495–9.
26. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725–30.
27. Power DG, Reynolds JV. Localized adenocarcinoma of the esophagogastric junction—Is there a standard of care? Cancer Treat Rev 2010;36(5):400–9.
28. Xiao ZF, Yang ZY, Liang J, et al. Value of radiotherapy after radical surgery for esophageal carcinoma: a report of 495 patients. Ann Thorac Surg 2003;75:331–6.
29. Killinger WA, Rice TW, Adelstein DJ, et al. Stage II esophageal carcinoma: the significance of T and N. J Thorac Cardiovasc Surg 1996;111:935–40.
30. Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 1998;339:1979–84.
31. Medical Research Council Oesophageal Cancer Working Party. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet 2002;359:1727–33.
32. Allum WH, Stenning SP, Bancewicz J, et al. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol 2009;27:5062–7.
33. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11–20.
34. Ychou M, Boige V, Pignon J, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715–21.
35. Burmeister BH, Smithers BM, Gebski V, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. Lancet Oncol 2005;6:659–68.
36. Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol 2008;26:1086–92.
37. Gaast AV, van Hagen P, Hulshof D, et al. Effect of preoperative concurrent chemoradiotherapy on survival of patients with resectable esophageal or esophagogastric junction cancer: results from a multicenter randomized phase III study [abstract 4004]. J Clin Oncol 2010;28(Suppl):15s.
38. Urba SG, Orringer MG, Turrisi A, et al. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 2001;19:305–13.
39. Stahl M, Walz MK, Stushka M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced

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adenocarcinoma of the esophagogastric junction. J Clin Oncol 2009;27:851–6.
40. Burmeister BH, Thomas JM, Burmeister EA, et al. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomized phase III trial. Eur J Cancer 2011;47:354–60.
41. Bedenne L, Michel P, Bouche O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol 2007;25(10): 1160–8.
42. Chiu PW, Chan AC, Leung SF, et al. Multicenter prospective randomized trial comparing standard esophagectomy with chemoradiotherapy for treatment of squamous esophageal cancer: early results from the Chinese University Research Group for Esophageal Cancer (CURE). J Gastrointest Surg 2005;9:794–802.
43. Teoh AY, Chiu PW, Wong TC, et al. Functional performance and quality of life in patients with squamous esophageal carcinoma receiving surgery or chemoradiation: results from a randomized trial. Ann Surg 2011;253:1–5.
44. Mak RH, Mamon HJ, Ryan DP, et al. Toxicity and outcomes after chemoradiation for esophageal cancer in patients age 75 or older. Dis Esophagus 2010;23:316–23.
45. Gwynne S, Hurt C, Evans M, et al. Definitive chemoradiation for oesophageal cancer: a standard of care in patients with non-metastatic oesophageal cancer. Clin Oncol 2011;23:182–8.
46. Hironaka S, Ohtsu A, Boku N, et al. Nonrandomized comparison between definitive chemotherapy and radical surgery in patients with T2-3NanyM0 squamous cell carcinoma of the esophagus. Int J Radiat Oncol Biol Phys 2003; 57(2):425–33.

## APPENDIX 1

Classification of Recommendation

Class I: Conditions for which there is evidence and/or general agreement that a given procedure is useful and effective.
Class II: Conditions for which there is conflicting evidence or a divergence, or both, of opinion about the usefulness and efficacy of a procedure.
Class IIa: Weight of evidence favors usefulness and efficacy.
Class IIb: Usefulness and efficacy is less well established by evidence.
Class III: Conditions for which there is evidence or general agreement, or both, that the procedure is not useful and effective.

Level of Evidence

Level A: Data derived from multiple randomized clinical trials.
Level B: Data derived from a single randomized trial or from nonrandomized trials.
Level C: Consensus expert opinion.