Clinical T2N0M0 carcinoma of thoracic esophagus

Timothy D. Wagner[1], Nikhil Khushalani[2], Gary Y. Yang[3]

[1]*Radiation Oncology Service, Department of Radiology, Brooke Army Medical Center, 3851 Roger Brooke Drive, Fort Sam Houston, TX 78234, United States.*
[2]*Deparment of Medical Oncology, Roswell Park Cancer Institute, Elm & Carlton Streets, Buffalo, NY 14263, United States.*
[3]*Deparment of Radiation Medicine, Roswell Park Cancer Institute, Elm & Carlton Streets, Buffalo, NY 14263, United States.*

ABSTRACT The incidence of esophageal cancer continues to rise. Historically, the majority of patients had been diagnosed with more advanced stages of disease. However, with screening programs, like those in place for patients with Barrett's esophagus, many patients are being diagnosed earlier in their disease course. Results of randomized trials and meta-analyses have led to emerging guidelines advocating for neoadjuvant therapy as part of the treatment algorithm for esophageal cancer, particularly for T3 or greater T-stage and/or node-positive disease. And for those patients that present with disease localized to the esophageal mucosa, endoscopic mucosal resection has proved to be an effective and less morbid alternative to radical resection. However, there is a group of patients that lie between these two extremes for which evidence is sparse and treatment recommendations vary. In this manuscript, recent data regarding work-up and treatment are reviewed along with a closer look at those patients clinically staged with T2N0M0 (Stage IIA) esophageal cancer. Pertinent data in this subset of patients is analyzed as potential treatment algorithms are discussed.

KeyWords: T2 esophageal cancer; endoscopic ultrasound; esophagectomy; radiation therapy; chemotherapy trimodality therapy

J Thorac Dis 2010; 2: 36–42.

Esophageal cancer is one of the ten most common malignancies worldwide, and its incidence is rising in the United States, where there were an estimated 16,470 new cases and 14,530 deaths from esophageal cancer in 2009 (1, 2). While squamous cell carcinoma is the most common histology of esophageal cancer worldwide, there have been substantial increases in the rates of adenocarcinoma in both the United States and Europe over the last several years. Adenocarinoma is now the most common histology in these countries (3). Analysis of this increase of adenocarcinoma has found rising incidence across stages, ages, and gender indicating that it is not artificially increased because of increased surveillance and earlier diagnosis (4). Esophageal cancer is a significant health concern throughout the world not only because of its prevalence but also because of its substantial mortality, with 5-year overall survival rates of <20% overall (5).

Historically, most patients have been diagnosed with locally advanced or metastatic disease, both of which carry a dismal prognosis even with aggressive multimodality therapy. In recent years, screening programs have been developed, particularly for patients with a history of Barrett's esophagus. A recent a recent meta-analysis reported an estimated cancer incidence in Barrett's esophagus of 4.1-6.1/1,000 person-years (6). This screening has led to an increase in early stage esophageal detection and treatment. With many factors to account for, including stage, location, and histology, treatment of esophageal cancer should be individualized for each patient to optimize outcome while minimizing morbidity. In this review, the evolution of esophageal cancer staging and management is examined with special attention to the unique case of clinical (c) T2N0M0 cancer of the thoracic esophagus. This optimal management strategy in lesions felt to be invading into, but not through, the muscle wall of the esophagus (T2) is a topic of debate. In this manuscript, the relevant prospective and retrospective data for treating this stage of esophageal cancer are evaluated in detail as potential management algorithms are discussed.

Work–Up

Differentiating between potentially curable and incurable disease has been difficult historically. Secondary to inaccurate staging and aggressive pathology, local and distant recurrences have been common despite aggressive treatment that often utilizes combinations of surgery, radiation therapy, and chemotherapy. As patterns of disease failure are being better elucidated, accurate staging is critical for both prognosis and for guiding management. Proper staging allows for the selection of patients who can be treated with monotherapy or combined modality therapy, while also identifying those patients with metastatic disease and sparing them from undergoing intensive local therapy (7, 8).

Pre-therapy staging of esophageal cancer should include

Supporting Foundations: None

Correspondence to: Timothy D. Wagner, MD, MBA, Major, Medical Corps, United States Army, Staff Radiation Oncologist, Radiation Oncology Service, Department of Radiology, Brooke Army Medical Center, 3851 Roger Brooke Drive, Fort Sam Houston, TX 78234, United States. Tel: +11-210-9165046; Fax: +11-210-9160330. Email: Timothy.d.wagner@us.army.mil

Submitted Feb 2, 2010. Accepted for publication Feb 14, 2010.
Available at www.jthoracdis.com
ISSN: 2072-1439

esophageal ultrasonograpy (EUS). An echoendoscope is passed into the esophagus where there is direct visualization of the histological layers of the esophagus potentially involved with tumor (9, 10). It has been shown to be relatively accurate in evaluating the depth of tumor invasion and also appears to be useful in assessing involvement of regional lymph nodes (11). There have been several studies completed suggesting that EUS is superior to other imaging modalities, such as computed tomography (CT) and fluorodeoxyglucose positron emission tomography (FDG-PET), for assessing T-stage since these other modalities lack the ability to differentiate between layers of the esophagus (12-17). In addition, EUS has been found to be more accurate and has a higher sensitivity than CT and PET for determining lymph node involvement (17-18). There is however, some discrepancy between studies as to how accurate EUS is in determining depth through the esophagus and lymph node involvement, particularly for early T-stages (9, 19-22). An early meta-analysis found EUS to have 89% accuracy for determining T-stage, and a more recent meta-analysis by Kelly et al. found EUS to have 79% accuracy for determining N-stage (12, 14). Puli et al. also published a meta-analysis that included 49 studies and 2558 patients which showed a pooled sensitivity of EUS to determine T-stage of approximately 81-90%, with a higher sensitivity for advanced (T3-T4) disease (9). In this study, the pooled sensitivity and specificity of EUS was 81.6% (95% Confidence Interval [CI]: 77.8-84.9) and 99.4% (95% CI: 99.0-99.7), respectively for T1 disease, 81.4% (95% CI: 77.5-84.8) and 96.3% (95% CI: 95.4-97.1), respectively for T2 disease, 91.4% (95% CI: 89.5-93.0) and 94.4% (95% CI: 93.1-95.5), respectively for T3 disease, and 92.4% (95% CI: 89.2-95.0) and 97.4% (95% CI: 96.6-98.0), respectively for T4 disease (9). In the same study, the sensitivity and specificity of EUS to diagnose nodal (N) stage disease was 84.7% (95% CI: 82.9-86.4) and 84.6% (95% CI: 83.2-85.9), respectively. These modest numbers for nodal diagnosis were improved with the addition of fine-needle aspiration (FNA), a procedure that allows for tissue diagnosis and carries little additional risk of morbidity or complication (9, 23). With the addition of FNA to EUS, sensitivity improved to 96.7% (95% CI: 92.4-98.9), and specificity improved to 95.5% (95% CI: 91.0-98.2).

In more recent years, FDG-PET has been used increasingly for initial staging in esophageal cancer, as malignant cells have increased uptake of FDG and following phosphorylation are temporarily retained in the cell (7). These areas of increased FDG concentration are then evaluated with PET (24). FDG-PET has been shown to be more specific but often less sensitive than CT for detecting locoregional disease, and both have been found to be less sensitive and accurate that EUS for determining T and N stage (17-18, 25). In initial staging of esophageal cancer, FDG-PET has been found to have the most utility in detecting distant metastases. Lerut et al. compared FDG-PET to the combination of EUS and CT for the detection of distant disease, and found FDG-PET to have superior accuracy 86% versus (vs.) 62% in favor of FDG-PET (26). In the United States, current guidelines recommend FDG-PET or PET/CT, preferably, as part of the initial staging algorithm in esophageal cancer management (27).

Treatment

Endoscopic Mucosal Resection (EMR)

With earlier detection, particularly in patients undergoing screening for Barrett's esophagus, along with improved staging with EUS, there are large populations of esophageal patients with superficial disease (Tis or T1a). In these patients, the risk of lymph node involvement in surgical series is typically on the order of 5% or less (28-29), and EUS has been shown to have an accuracy in detecting T1a disease of over 90% in most series (30-32). Esophagectomy is the standard surgical treatment in esophageal cancer but carries significant morbidity and risk of mortality (29, 33). For these patients with superficial disease, endoscopic therapy, typically in the form of endoscopic mucosal resection (EMR), has been gaining acceptance worldwide. A study evaluating the Surveillance Epidemiology and End Results (SEER) database of the National Cancer Institute (NCI) from 1988-2003 found that for patients with superficial esophageal tumors treated endoscopically or with surgical resection experienced equivalent long-term survival (34). In fact, recent studies have shown 5-year OS rates of over 95% and relatively low recurrence rates for patients treated with EMR (35-36). For those patients treated with EMR found to have T1b or greater depth of invasion on pathological assessment, EMR acts as a diagnostic tool, with further therapy recommended because of the increased risk of lymph node metastases (35, 37-39).

Esophagectomy

While the rate of lymph node metastasis with mucosal cancers is typically 5% or less, submucosal invasion (T1b) carries a much higher risk of LVI and lymph node involvement (28). Kim et al. found that the rate of lymph node involvement increased from 6% (4/64) in mucosal cancers to 29% (39/133) in submucosal cancers ($P = 0.001$), while Cen et al. reported an increase from 4% in T1a patients to 23% in patients with T1b tumors (28-29). Other series have rates of lymph node metastasis as high as 40-50% in patients with submucosal extension of disease and clinical T2 disease can carry an approximately 50% risk of spread to lymph nodes (40-41). For these patients, surgical management should include primary resection and lymph node dissection (41-43). There is some debate over the extent of lymph node dissection that should be undertaken at resection, but there is also data suggesting that the number of nodes removed at resection is associated with survival (44). In addition, at least a 2-field abdominal and thoracic lymphadenectomy has been associated with improved local control (45). Less invasive techniques such as laparoscopic or thoracoscopic approaches

have shown some promise but their routine use is still considered investigational (46).

Neoadjuvant Concurrent Chemotherapy and Radiation Therapy

While neither on its own has been highly efficacious in the neoadjuvant setting, the combination of concurrent chemotherapy and radiation therapy has some theoretical advantages. With approximately one-third of patients recurring distantly after surgical management alone, additional therapy continues to be investigated (47). Microscopic disease outside the typical radiation field or surgical resection can be treated with the systemic therapy. In addition, chemotherapy can sensitize the local-regional disease to the radiation therapy, thus increasing its efficacy. Ideally, increased efficacy would allow for tumor downsizing and allow for a more complete surgical resection (48). And while acute toxicity may potentially be increased, with such poor prognosis for esophageal cancer patients, several studies have been undertaken to evaluate the benefit of neoadjuvant concurrent chemoradiation. While neoadjuvant chemoradiation should be of theoretical benefit, randomized trials evaluating its efficacy have had conflicting results, with very few of the studies reaching target accrual allowing for complete analysis (49-54). The recently published Cancer and Leukemia Group B (CALGB) 9781 trial assessed OS and treatment response of neoadjuvant chemoradiation followed by surgery compared to surgery alone (54). And while the study failed to reach accrual, the results are intriguing. Neoadjuvant therapy consisted of cisplatin 100 mg/m2 and fluorouracil 1,000 mg/m^2/d for 4 days during weeks 1 and 5 concurrent with radiotherapy (50.4 Gray), followed by surgery. Neoadjuvant therapy was well tolerated with no increase in increase in perioperative mortality. Pathologic CR was 40% in the neoadjuvant arm and median survival was 4.48 years vs. 1.79 years (P=0.02) in favor of neoadjuvant chemoradiation. In addition, 5-year OS was 39% for patients receiving neoadjuvant therapy vs. 16% in the surgery alone arm. With so many of the trials having results that are difficult to interpret because of study design flaws or failure to reach targeted accrual, meta-analyses are very important to determine what, if any, role neoadjuvant chemoradiation has in esophageal cancer treatment. In a recent meta-analysis by Gebski et al. 10 randomized trials comparing neoadjuvant chemotherapy and radiation therapy followed by surgery vs. surgery alone are analyzed (55). The hazard ratio (HR) for mortality with neoadjuvant chemoradiation (either sequential or concurrent) vs. surgery alone was found to be 0.81 (95% CI 0.70 – 0.93; P=0.002). This corresponded to a 13% absolute difference in OS at 2 years. The results were similar for both adenocarcinoma and squamous cell carcinoma. Another recent meta-analyses presented by Thirion et al. also demonstrated an OS benefit to neoadjuvant chemoradiation, HR = 0.82 (95% CI: 0.72-0.93, P = 0.002) translating into 2 and 5-year absolute benefits of 7% (from 37% to 44%) and 7% (from 18% to 25%), respectively (56). This study also found a significant disease-free survival (DFS) benefit for neoadjuvant therapy, HR= 0.85 (95% CI: 0.72-0.99, P= 0.036), yielding a 2 and 5-year absolute DFS increase of 6% (from 26% to 32%) and 4% (from 11% to 15%), respectively. R0 resections were also increased by 6% (73% vs. 67%, P=0.03) with the addition of neoadjuvant therapy and there was no difference in perioperative mortality among the two groups.

Clinical T2N0

Based on individual randomized trials and meta-analyses, there is an emerging agreement that either chemoradiation or systemic therapy alone should be considered as part of the treatment algorithm for esophageal cancer, particularly for T3 or greater T-stage and/or node-positive disease (2, 57). And in those patients that present with disease localized to the esophageal mucosa only, EMR is proving to be an efficacious and less morbid alternative to radical resection. But what treatment algorithm should be considered for the medically fit patient with intermediate risk disease, such as clinical T2N0M0 (Stage IIA), who have clinical evidence of disease invading into the muscularis propria after initial staging is complete? Killinger et al. reported on their experience with pathologic T2N0M0 disease treated with esophagectomy alone (58). In this retrospective analysis, patients with pT2N0M0 disease had a survival rate on par with patients treated with pT1N0M0 (approximately 50% at 5-years; P=0.83), and trended toward improved survival over patients with pT3N0M0 disease (p=0.06). Tachibana et al. published their results of patients with squamous cell carcinoma of the esophagus treated with upfront esophagectomy and found to have pT1 or pT2 disease (59). Among patients that were node negative, patients with pT1 and pT2 tumors had similar cancer specific survival (CSS).

Clinical T2N0M0 is a relatively unusual entity, with the majority of esophageal cancers presenting with more advanced disease, and many of those detected as part of screening programs being diagnosed with disease confined to the mucosa (24). In addition, by the time esophageal cancer has extended to the muscularis propria, there is an approximately 50% risk of nodal involvement (41). Despite its relative rarity, consideration should be made for a potential treatment algorithm for this stage of disease. In the United States, the National Comprehensive Cancer Network (NCCN) guidelines advocate for a multimodality approach for any clinical T-stage that is T2 or greater regardless of nodal status (27). For either adenocarcinoma or squamous cell carcinoma, at least concurrent chemoradiation is recommended, and in adenocarcinoma the addition of surgery after concurrent therapy is favored.

Is there a basis for this recommendation, particularly for cT2N0M0 patients, that we can draw from the published randomized trials? As previously described, many of the randomized trials evaluating the role of neoadjuvant chemoradiation are flawed in some way, whether it is due to study design, failure to accrue, or outdated staging techniques and treatment. In reviewing the major randomized phase III studies published over the last 15 years,

cT2N0M0 patients were typically eligible for study but the data for these patients is sparse (49-54). In the study by Burmeister et al., neither EUS nor PET was used for initial staging and the published results did not include stratification according to depth of invasion (53). Similarly, the trial published by Urba et al. did not utilize EUS for initial staging and did not include results based on esophageal invasion (52). Walsh et al. did not employ EUS or PET, and they did not routinely employ CT as part of the initial staging (51). The published results of this study do include some data on pathologic staging, noting that of the 55 patients who underwent surgical resection alone, 8 (15%) had stage IIA (pT2N0 or pT3N0 by current staging) disease. The European Organization for Research and Treatment of Cancer (EORTC) randomized trial relied on CT scan for clinical staging (49). They utilized a clinical staging system where the T stage was defined by the maximal transverse diameter of the esophageal tumor, with < 1 cm being T1, between 1 and 3 cm being T2, and > 3 cm being T3. Lymph nodes were considered involved if the maximal transverse diameter was > 1 cm. While 92/282 (33%) of patients enrolled were cT2N0M0, the positive predictive value (PPV) of the disease-stage classification based on the CT scan for T2 lesions was only 22% and for N0 was 49% (49). Thus, very few of those felt to be cT2N0M0 turned out to be pT2N0M0, and very few of these patients would have been similarly staged with modern staging procedures. The recently published CALGB 9781 study recommended EUS or laparoscopy/thoracoscopy as part of initial staging and one or the other was completed in 43/56 (77%) of patients (54). With these more modern staging techniques, only 3/56 (5%) of enrolled patients were felt to have cT2N0M0 disease, so drawing meaningful conclusions from this trial for these 3 patients is difficult. The EORTC 40001-22001 study comparing neoadjuvant chemoradiation followed by surgery vs. surgery alone for clinical stages I-II closed to accrual in 2004, and may potentially aid in answering this clinical question (60).

With such a dearth of randomized data for these patients, examination of single institution retrospective experiences may be of more value. The M. D. Anderson experience with cT2N0M0 disease was presented at the International Society of Gastrointestinal Oncology 2009 Gastrointestinal Oncology Conference (61). They presented data on 272 patients with cT2N0M0 esophageal cancer, 186 (68%) of which underwent surgery first and 86 (32%) who first underwent neoadjuvant chemoradiation. They found that patients receiving preoperative chemoradiation had superior OS when compared to the group having surgery alone (65.27 months vs. 25.9 months, P=0.006). In addition there was increased time to recurrence (TTR) among the group receiving neoadjuvant chemoradiation (52.87 months vs. 18.67 months, P=0.006). Postoperative complications were more frequently associated with neoadjuvant chemoradiation but this did not impact on treatment-related mortality. Of the 186 patients who underwent surgery upfront, 147 (79%) had a change in their T-stage, 47 (25%) of which were initially overstaged and 100 (54%) of which were understaged. In addition, of the 186 felt to have N0 and M0 disease clinically, 101 (54%) have lymph node involvement and 25 (13%) were found to have M1 disease. They concluded that there is significant stage migration in patients with cT2N0M0 esophageal cancer treated with upfront surgery, and that preoperative neoadjuvant chemoradiation in this population improved outcome (61).

The Cleveland Clinic also recently published their single institution experience with T2N0M0 esophageal cancer treated from1987-2005 (62). Out of 742 patients diagnosed with esophageal cancer during that timeframe, 61 (8%) were determined to have cT2N0M0 disease. Clinical staging for primary and regional nodes was accomplished with EUS and designation of cT2 was invasion into the 4th ultrasound (muscularis propria) layer of the esophagus (62-64), while nodal assessment utilized size, shape, border, and texture to determine involvement. EUS guided FNA of suspected lymph nodes was performed in 58 patients. Metastatic assessment was by CT, with approximately one-third of patients also undergoing FDG-PET. Of the 61 patients with cT2N0M0 disease, 45 underwent surgery alone, 8 had surgery and postoperative adjuvant therapy, and 8 underwent some form of neoadjuvant therapy. Of 53 patients with cT2N0M0 disease who underwent surgery upfront, on 7 (13%) were found to have pT2N0M0 disease, while 29 (55%) were initially overstaged and 17 (32%) were understaged. Of those patients that were overstaged, 3/29 patients (10%) were found to have in situ disease, 11/29 (38%) had invasive disease confined to the mucosa (T1a), and 15/29 (52%) had extension into the submucosa (T1b). Of those patients that were understaged, 13/17 (76%) had lymph node involvement. In fact, EUS was found to have 29% sensitivity and 89% specificity for determining T2N0M0 disease. For those patients overstaged as cT2N0M0 and undergoing surgery alone, their 5-year OS was similar to matched controls (69% vs. 63%, P=0.8). For those patients that were understaged and treated with surgery alone, their survival was similar to matched patients with >pT2N0M0 treated with surgery alone (P=.4). And though the numbers were small, patients understaged as cT2N0M0 had a trend toward improved survival if they received adjuvant therapy when compared to similar pTNM staged patients who underwent surgery alone (43% vs. 10%, P=0.17). For the 8 patients with cT2N0M0 disease receiving induction therapy, they had a decreased 5-year OS compared to the other cT2N0M0 patients (13% vs. 52%, P=0.05). Survival of patients with cT2N0M0 and pT2N0M0 treated with upfront surgery was similar, approximately 50% at 5 years, but the authors were quick to caution that this does not imply that clinical staging accurately reflects pathologic staging (62). In fact, they felt that it was relatively useless and that the relatively high survival in the overstaged group balanced out for the poor survival among the understaged group. The authors recommended that patients with cT2N0M0 tumors should undergo surgical resection with lymphadenectomy upfront. And those patient clinically understaged should go on to receive adjuvant therapy, and for those patients overstaged or appropriately staged, surgery should serve as definitive therapy (62, 65).

Discussion

With evolving diagnostic tools and techniques such as EUS, EUS-guided FNA, and FDG-PET, initial clinical staging for esophageal cancer is becoming increasingly accurate. In recent years, there has been a movement for initial stage to guide management. Those patients with disease clinically confined to the mucosa appear to be adequately treated with EMR or potentially other endoscopic techniques with diminished morbidity when compared to esophagectomy. And in those patients known to have more advanced disease (cT3 and/or N1) multimodality therapy such as neoadjuvant chemoradiation should be strongly considered based meta-analyses of randomized data.

The optimal strategy for cT2N0M0, an intermediate risk group of esophageal cancer patients, remains undefined. As shown, there is very little randomized data evaluating these patients, and single institution retrospective data conflict both in terms of results and treatment recommendations. In evaluating the M. D. Anderson experience, the PPV of their initial staging in predicting final pathologic staging was very poor, with the majority of patients being upstaged both in terms of T-stage and N-stage following surgery. So it is not surprising that they saw an increase in survival with the addition of neoadjuvant chemoradiation since the majority of patients in their analysis likely had T3 and/or N1 at diagnosis. Staging techniques were not fully addressed, and it would be of interest to know if EUS, FNA, and FDG-PET were routinely employed. The group at the Cleveland Clinic had similarly poor PPV for T2N0M0, with the majority of patients being either under- or overstaged. This included 14/53 (26%) patients treated with surgery upfront who had either pTisN0M0 or pT1aN0M0 disease. These patients could have potentially been candidates for less invasive definitive therapy, such as EMR, if they had been staged properly. In addition, another 17/53 (32%) treated with upfront surgery were initially understaged. And while the authors of the study advocated for adjuvant therapy for patients in this population based on their institutional experience, neither adjuvant radiation nor chemotherapy have been shown to definitively improve outcomes in esophageal cancer in the phase III setting (62, 65). And though understaged cT2N0M0 had similar outcomes with correctly staged more advanced patients, ideally these patients should have been considered for neoadjuvant treatment.

The main challenge faced by both of these retrospective series looking at cT2N0M0 disease was the poor PPV of initial staging. Initial staging for this subset of patients was futile as final pathologic stage ran the gamut from in situ to metastatic disease. It is therefore difficult to draw meaningful conclusions from their results. Should all patients staged as cT2N0M0 receive neoadjuvant chemoradiation since there is a substantial risk of understaging? Or should these patients undergo upfront surgery and await final pathologic staging to guide any adjuvant therapy, where data for its utility is limited? Neither strategy seems optimal, and the key may lie in improved initial staging. As previously reviewed EUS continues to evolve as a staging tool and with more recent incorporation of FNA, the accuracy of EUS is improving. This along with advancements such as FDG-PET/CT should allow for more reliable initial staging. That in combination with publication of modern clinical trials, such as the EORTC 40001-22001 study evaluating the utility of neoadjuvant chemoradiation for clinical stages I-II esophageal cancer, may potentially allow for a more universal algorithm for this relatively uncommon but clinically significant group of patients.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer Statistics, 2009. CA Cancer J Clin 2009; 59: 225-49.
2. Yang GY, Ott K. Accomplishments in 2008 in the management of esophageal cancer. Gastrointest Cancer Res 2009;3: S53-7.
3. Trivers KF, Sabatino SA, Stewart SL. Trends in esophageal cancer incidence by histology, United States, 1998-2003. Int J Cancer 2008; 123: 1422-8.
4. Brown LM, Devesa SS, Chow WH. Incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, and age. J Natl Cancer Inst 2008; 100: 1184-7.
5. Fitzgerald RC. Review article: Barrett's oesophagus and associated adenocarcinoma-a UK perspective. Aliment Pharmacol Ther 2004; 20 Suppl 8: 45-9.
6. Yousef F, Cardwell C, Cantwell MM, Galway K, Johnston BT, Murray L. The incidence of esophageal cancer and high-grade dysplasia in Barrett's esophagus: a systematic review and meta-analysis. Am J Epidemiol 2008; 168: 237-49.
7. Yang GY, Wagner TD, Jobe BA, Thomas CR. The role of positron emission tomography in esophageal cancer. Gastrointest Cancer Res 2008; 2: 3-9.
8. Dehdashti F, Siegel BA. Neoplasms of the Esophagus and Stomach. Semin Nucl Med 2004; 34: 198-208.
9. Puli SR, Reddy JB, Bechtold ML, Choudhary A, Antillon MR, Brugge WR. Accuracy of endoscopic ultrasound to diagnose nodal invasion by rectal cancers: a meta-analysis and systematic review. Ann Surg Oncol 2009; 16: 1255-65.
10. Wiersema MJ, Wiersema LM. High-resolution 25-megahertz ultrasonography of the gastrointestinal wall: histologic correlates. Gastrointest Endosc 1993; 39: 499-504.
11. Shimpi RA, George J, Jowell P, Gress FG. Staging of esophageal cancer by EUS: staging accuracy revisited. Gastrointest Endosc 2007; 66: 475-82.
12. Rosch T. Endosonographic staging of esophageal cancer: a review of literature results. Gastrointest Endosc Clin North Am 1995; 5: 537-47.
13. Van Dam J. Endosonographic evaluation of the patient with esophageal cancer. Chest 1997; 112(4 Suppl): 184-90S.
14. Kelly S, Harris KM, Berry E, Hutton J, Roderick P, Cullingworth J, et al. A systematic review of the staging performance of endoscopic ultrasound in gastro-oesophageal carcinoma. Gut 2001; 49: 534-9.
15. Grimm H, Binmoeller KF, Hamper K, Koch J, Henne-Bruns D, Soehendra N. Endosonography for preoperative locoregional staging of esophageal and gastric cancer. Endoscopy 1993; 25: 224-30.
16. Familiari P, Marchese M, Larghi A, Spada C, Costamagna G. Staging of esophageal carcinoma: endoscopic ultrasonography. Rays 2005; 30: 357-62.
17. Rosch T, Lorenz R, Zenker K, von Wichert A, Dancygier H, Hofler H, et al. Local staging and assessment of resectability in carcinoma of the esophagus, stomach, and duodenum by endoscopic ultrasonography. Gastrointest Endosc 1992; 38: 460-7.
18. Pfau PR, Perlman SB, Stanko P, Frick TJ, Gopal DV, Said A, et al. The role and clinical value of EUS in a multimodality esophageal carcinoma staging program with CT and positron emission tomography. Gastrointest Endosc 2007; 65:

377-84.
19. DeWitt J, Kesler K, Brooks JA, LeBlanc J, McHenry L, McGreevy K, et al. Endoscopic ultrasound for esophageal and gastroesophageal junction cancer: Impact of increased use of primary neoadjuvant therapy on preoperative locoregional staging accuracy. Dis Esophagus 2005; 18: 21-7.
20. Nesje LB, Svanes K, Viste A, Laerum OD, Odegaard S. Comparison of a linear miniature ultrasound probe and a radial-scanning echoendoscope in TN staging of esophageal cancer. Scand J Gastroenterol 2000; 35: 997-1002.
21. Vazquez-Sequeiros E, Norton ID, Clain JE, Wang KK, Affi A, Allen M, et al. Impact of EUS-guided fine-needle aspiration on lymph node staging in patients with esophageal carcinoma. Gastrointest Endosc 2001; 53: 751-7.
22. Wakelin SJ, Deans C, Crofts TJ, Allan PL, Plevris JN, Paterson-Brown S. A comparison of computerised tomography, laparoscopic ultrasound and endoscopic ultrasound in the preoperative staging of oesophago-gastric carcinoma. Eur J Radiol 2002; 41: 161-7.
23. Vilmann P. Endoscopic ultrasonography-guided fine-needle aspiration biopsy of lymph nodes. Gastrointest Endosc 1996; 43: S24-S29.
24. Patel M, Ferry K, Franceschi D, Kaklamanos I, Livingstone A, Ardalan B. Esophageal carcinoma: current controversial topics. Cancer Invest 2004; 22: 897-912.
25. Meltzer CC, Luketich JD, Friedman D, Charron M, Strollo D, Meehan M, et al. Whole-body FDG positron emission tomographic imaging for staging esophageal cancer comparison with computed tomography. Clin Nucl Med 2000; 25:882-7.
26. Lerut T, Flamen P, Ectors N, Van Cutsem E, Peeters M, Hiele M, et al. Histopathologic validation of lymph node staging with FDG-PET scan in cancer of the esophagus and gastroesophageal junction: A prospective study based on primary surgery with extensive lymphadenectomy. Ann Surg 2000; 232:743-52.
27. National Comprehensive Cancer Network (2010). Esophagus Cancer, version 1.2010. Available at: http://www.nccn.org/professionals/physician_gls/PDF/esophagus.pdf
28. Cen P, Hofstetter WL, Correa AM, Wu TT, Lee JH, Ross WA, et al. Lymphovascular invasion as a tool to further subclassify T1b esophageal adenocarcinoma. Cancer 2008; 112: 1020-7.
29. Kim DU, Lee JH, Min BH, Shim SG, Chang DK, Kim YH, et al. Risk factors of lymph node metastasis in T1 esophageal squamous cell carcinoma. J Gastroenterol Hepatol 2008; 23: 619-25.
30. May A, Gunter E, Roth F, Gossner L, Stolte M, Vieth M, et al. Accuracy of staging in early oesophageal cancer using high resolution endoscopy and high resolution endosonography: a comparative, prospective, and blinded trial. Gut 2004; 53: 634-40.
31. Pech O, May A, Gunter E, Gossner L, Ell C. The impact of endoscopic ultrasound and computed tomography on the TNM staging of early cancer in Barrett's esophagus. Am J Gastroenterol 2006; 101: 2223-9.
32. Larghi A, Lightdale CJ, Memeo L, Bhagat G, Okpara N, Rotterdam H. EUS followed by EMR for staging of high-grade dysplasia and early cancer in Barrett's esophagus. Gastrointest Endosc 2005; 62: 16-23.
33. Spechler SJ. Dysplasia in Barrett's esophagus: limitations of current management strategies. Am J Gastroenterol 2005; 100: 927-35.
34. Das A, Singh V, Fleischer DE, Sharma VK. A comparison of endoscopic treatment and surgery in early esophageal cancer: an analysis of surveillance epidemiology and end results data. Am J Gastroenterol 2008; 103: 1340-5.
35. Ell C, May A, Pech O, Gossner L, Guenter E, Behrens A, et al. Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). Gastrointest Endosc 2007; 65: 3-10.
36. Katada C, Muto M, Manabe T, Ohtsu A, Yoshida S. Local recurrence of squamous-cell carcinoma of the esophagus after EMR. Gastrointest Endosc 2005; 61: 219-5.
37. Soetikno R, Kaltenbach T, Yeh R, Gotoda T. Endoscopic mucosal resection for early cancers of the upper gastrointestinal tract. J Clin Oncol 2005; 23: 4490-8.
38. Kakushima N, Yahagi N, Fujishiro M, Kodashima S, Nakamura M, Omata M. Efficacy and safety of endoscopic submucosal dissection for tumors of the esophagogastric junction. Endoscopy 2006; 38: 170-4.
39. Eguchi T, Nakanishi Y, Shimoda T, Iwasaki M, Igaki H, Tachimori Y, et al. Histopathological criteria for additional treatment after endoscopic mucosal resection for esophageal cancer: analysis of 464 surgically resected cases. Mod Pathol 2006; 19: 475-80.
40. Endo M, Yoshino K, Kawano T, Nagai K, Inoue H. Clinicopathologic analysis of lymph node metastasis in surgically resected superficial cancer of the thoracic esophagus. Dis Esophagus 2000; 13:125-9.
41. Rice TW, Zuccaro G Jr, Adelstein DJ, Rybicki LA, Blackstone EH, Goldblum JR. Esophageal carcinoma: depth of tumor invasion is predictive of regional lymph node status. Ann Thorac Surg 1998; 65: 787-92.
42. Bollschweiler E, Baldus SE, Schr?der W, Prenzel K, Gutschow C, Schneider PM, et al. High rate of lymph-node metastasis in submucosal esophageal squamous-cell carcinomas and adenocarcinomas. Endoscopy 2006; 38: 149-56.
43. Vieth M, Rosch T. Endoscopic mucosal resection and the risk of lymph-node metastases: indications revisited? Endoscopy 2006; 38: 175-9.
44. Peyre CG, Hagen JA, DeMeester SR, Van Lanschot JJ, H?lscher A, Law S, et al. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. Ann Surg 2008; 248:549-56.
45. Altorki N, Skinner D. Should en bloc esophagectomy be the standard of care for esophageal carcinoma? Ann Surg 2001; 234: 581-87.
46. Nishihira T, Hirayama K, Mori S. A prospective randomized trial of extended cervical and superior mediastinal lymphadenecto my for carcinoma of the thoracic esophagus. Am J Surg 1998; 175: 47-51.
47. Mariette C, Balon JM, Piessen G, Fabre S, Van Seuningen I, Triboulet JP. Pattern of recurrence following complete resection of esophageal carcinoma and factors predictive of recurrent disease. Cancer 2003; 97: 1616-23.
48. Mariette C, Triboulet JP. Is preoperative chemoradiation eff ective in treatment of oesophageal carcinoma? Lancet Oncol 2005; 6: 635-7.
49. Bosset JF, Gignoux M, Triboulet JP, Tiret E, Mantion G, Elias D, 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.
50. Nygaard K, Hagen S, Hansen HS, Hatlevoll R, Hultborn R, Jakobsen A, et al. Pre-operative radiotherapy prolongs survival in operable 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.
51. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 1996; 335: 462-7.
52. Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 2001; 19: 305-13.
53. Burmeister BH, Smithers BM, Gebski V, Fitzgerald L, Simes RJ, Devitt P, 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.
54. Tepper J, Krasna MJ, Niedzwiecki D, Hollis D, Reed CE, Goldberg R, 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.
55. Gebski V, Burmeister B, Smithers BM, Foo K, Zalcberg J, Simes J; Australasian Gastro-Intestinal Trials Group. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. Lancet Oncol 2007; 8: 226-34.
56. Thirion P, Maillard E, Pignon J, MA of Chemo in Oesophagus Cancer Collaborative Group. Individual patient data-based meta-analysis assessing the effect of preoperative chemo-radiotherapy in resectable esophageal carcinoma. Int J Radiat Oncol Biol Phys 2008; 72: S71-S72 (abstract 158).
57. Juergens RA, Forastiere A. Combined modality therapy of esophageal cancer. J

Natl Comp Cancer Network 2008; 6: 851-60.

58. Killinger WA Jr, Rice TW, Adelstein DJ, Medendorp SV, Zuccaro G, Kirby TJ, et al. Stage II esophageal carcinoma: the significance of T and N. J Thorac Cardiovasc Surg 1996; 111: 935-40.
59. Tachibana M, Kinugasa S, Dhar DK, Tabara H, Masunaga R, Kotoh T, et al. Prognostic factors in T1 and T2 squamous cell carcinoma of the thoracic esophagus. Arch Surg 1999; 134: 50-4.
60. FFCD, EORTC, Mariette C, Triboulet JP, Seitz JF (Study Coordinators). Protocol FFCD 9901 - EORTC 22001/40001. Randomized study of preoperative radiochemotherapy versus surgery alone in thoracic esophageal cancer deemed to be resectable. (cited 2010 Jan 31). Available from: http://www.cancer.gov/search/ViewClinicalTrials.aspx? cdrid=257600&version=patient&protocolsearchid=1096015.
61. Kountourakis P, Correa AM, Hayashi Y, Hofstetter WL, Komaki R, Vaporciyan AA, et al. In Patients with Clinical T2N0M0 Esophageal Cancer, Surgery First or Preoperative Chemoradiotherapy? Presented at the 2009 International Society of Gastrointestinal Annual Meeting in Philadelphia, PA.
62. Rice TW, Mason DP, Murthy SC, Zuccaro G Jr, Adelstein DJ, Rybicki LA , et al. T2N0M0 esophageal cancer. J Thorac Cardiovasc Surg 2007;133: 317-24.
63. Rice TW, Blackstone EH, Adelstein DJ, Zuccaro G Jr, Vargo JJ, Goldblum JR, et al. Role of clinically determined depth of tumor invasion in the treatment of esophageal carcinoma. J Thorac Cardiovasc Surg 2003; 125: 1091-102.
64. Zuccaro G Jr, Rice TW, Vargo JJ, Goldblum JR, Rybicki LA, Dumot JA, et al. Endoscopic ultrasound errors in esophageal cancer. Am J Gastroenterol. 2005; 100: 601-6.
65. Rice TW, Adelstein DJ, Chidel MA, Rybicki LA, DeCamp MM, Murthy SC, et al. Benefit of postoperative adjuvant chemoradiotherapy in locoregionally advanced esophageal carcinoma. J Thorac Cardiovasc Surg. 2003;126:1590-6.