Impact of Pretreatment Imaging on Survival of Esophagectomy After Induction Therapy for Esophageal Cancer: Who Should be Given the Benefit of the Doubt?

Esophagectomy Outcomes of Patients with Suspicious Metastatic Lesions

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ABSTRACT

Purpose. We examined survival of patients who underwent esophagectomy for locally advanced esophageal cancer with foci that were suspicious for metastatic disease on initial imaging but whose disease did not progress after induction chemoradiation treatment (CRT).

Methods. The impact of pre- and posttherapy staging characteristics on survival of patients who underwent esophagectomy after CRT between 2003 and 2009 was evaluated using multivariable logistic regression. Survival of patients with and without possible metastatic disease on initial imaging was compared with the log-rank test.

Results. During the study period, 71 (32 %) of 220 patients who underwent CRT followed by esophagectomy had possible distant metastatic disease on initial imaging. Patients with initial suspicion of metastases had a 5-year survival of 24.8 %. Overall survival of patients with and without possible metastatic disease on initial imaging was not significantly different ($p = 0.4$), but pretreatment positron emission tomography (PET) suggesting a liver lesion (hazard ratio [HR] 3.2, $p = 0.003$) predicted worse survival. Additional predictors of worse survival were clinical T4 status (HR 3.1, $p = 0.001$), post-CRT pathologic nodal status (HR 1.6, $p = 0.04$), and pathologically confirmed metastatic disease at or before resection (HR 3.1, $p = 0.01$). None of 10 patients with pathologic metastatic disease at resection lived longer than 2.5 years.

Conclusions. Patients with possible liver metastases on pretreatment PET and patients with confirmed metastatic disease at the time of surgery do not benefit from resection. However, patients with pretreatment imaging that shows possible metastatic disease in sites other than the liver still have reasonable long-term survival after resection.

The incidence of esophageal cancer is increasing, with an estimated 17,460 new cases in the United States in 2012.¹ Overall 5-year survival for patients with esophageal cancer remains poor, although some improvement has been achieved with an increase from 5 % to 17–19 % over the past four decades.^{1–3} Approximately 32 % of esophageal cancer patients have regional disease at the time of diagnosis, with a 5-year survival of only 10–30 %.^{4–6} Recent evidence suggests that induction chemoradiation treatment (CRT) followed by surgical resection is the optimal treatment for patients with locally advanced disease.^{7–13} Treatment guidelines for locally advanced esophageal cancer therefore typically involve induction CRT followed by esophagectomy for patients considered resection candidates.¹⁴ However, obtaining accurate pretreatment staging and then subsequently providing stage-appropriate treatment is crucial in optimizing esophageal cancer outcomes to avoid both inadequate and unnecessary treatment.

Unfortunately, pretherapy imaging has many limitations.^{15–17} Liberale et al. found that the sensitivity, specificity, and accuracy of positron emission tomography (PET) scanning was 38, 81, and 67 %, respectively, for lymph node involvement detection and 88, 88, and 88 %, respectively, for distant metastasis detection in patients with esophageal cancer.¹⁵ Van Vliet et al. found similar

results in a meta-analysis that looked at imaging techniques used to evaluate esophageal cancer.¹⁶ Thus, imaging remains imperfect despite its crucial role in determining esophageal cancer treatment.

One particularly difficult clinical scenario is when initial imaging shows possible distant metastatic disease that would be difficult to pathologically confirm and is no longer present or is unchanged after CRT. One management option is to give the patients the benefit of doubt in regards to whether metastatic disease is present and perform esophagectomy. The major downside to this strategy is that patients who may not gain survival benefit from esophagectomy are still exposed to potential peri-operative morbidity and mortality, which unfortunately remains considerable despite improvements over time and the development of minimally invasive techniques.^{18–24} This study was performed to characterize outcomes after surgery in this situation and provide data to assist treatment decisions. Specifically, we evaluated outcomes based on pretreatment imaging, other preoperative staging characteristics, and posttherapy pathological staging.

METHODS

We performed an institutional review board–approved retrospective review of a prospectively collected database of 220 patients with esophageal cancer who underwent induction CRT followed by esophagectomy between 2003 and 2009. We included patients who had adenocarcinoma or squamous cell carcinoma of the thoracic esophagus with or without involvement of the gastroesophageal junction. The data collected included patient demographics, comorbid status, tumor histologic type and location, locations of suspicious metastases on CT and PET scan, pathologic T and N stage, surgical approach, and treatment effect, including whether or not there was complete response, as well as whether and where there was recurrence.

The algorithm for treatment of fit esophageal cancer patients with locally advanced disease (typically defined as disease that is T2 or higher or positive for the presence of nodal disease) at our institution begins with CRT.¹⁴ The patients then undergo follow-up imaging with CT or PET/CT at the completion of this therapy. Patients who do not have worsening of disease on this imaging will undergo an esophagectomy about 6 weeks later. The resection technique is based on surgeon preference as well as the location of the tumor. Although our treatment algorithm is quite selective, occasionally patients being referred for surgery present with evidence of suspicious metastatic disease considered somewhat ambiguous and not readily suitable for biopsy. In addition, patients are sometimes referred for surgery with a suspicious lesion at presentation that was

not pathologically confirmed before CRT. Patients who are physically fit and have had a response to induction therapy, especially in the setting of an ambiguous mass, may be given the benefit of the doubt and move forward with surgery after evaluation by both surgical and medical oncology.

A Cox proportional hazards model was performed for evaluation of overall survival. A multivariable logistic regression model was developed to predict the impact of preoperative staging characteristics and posttherapy pathological staging on survival. Survival time was measured from the date of surgery to the date of death or last follow-up. Survival curves were estimated by the Kaplan–Meier method. Survival of patients with and without possible metastatic disease on initial imaging was compared with the log-rank test.

Continuous data are presented as median and interquartile range (IQR). Categorical variables are presented as frequency and percentages. Multivariate regression results are presented as hazard ratios and 95 % confidence intervals (CI). Comparisons of patient characteristics were performed using the Pearson's χ^2 test or Fisher's exact test for categorical variables, as appropriate. The two-sample unpaired t test was used to compare normally distributed continuous variables, and the Kruskal–Wallis test was used for nonnormally distributed data. A two-tailed *p* value of less than 0.05 was considered significant. The SAS 9.2 statistical package (SAS Institute, Cary, NC) and R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) software were used for statistical analyses.

RESULTS

Preoperative Characteristics

In our cohort, 220 patients underwent CRT followed by esophagectomy; 72 % of the patients were staged via CT, 73 % by EUS, and 80 % with PET. During the study period, 71 patients (32 %) had initial imaging that officially reported a total of 110 areas considered to be suspicious for metastatic disease: lungs (*n* = 38, 34 %), liver (*n* = 16, 14 %), kidneys (*n* = 11, 3 %), adrenals (*n* = 8, 7.2 %), pleura (*n* = 5, 4.5 %), spleen (*n* = 5, 4.5 %), bone (*n* = 5, 3.6 %), prostate (*n* = 4, 3.6 %), colon (*n* = 4, 3.6 %), pancreas (*n* = 3, 2.7 %), heart (*n* = 3, 2.7 %), thyroid (*n* = 2, 1.8 %), stomach (*n* = 2, 1.8 %), cervix (*n* = 1, 0.9 %), bladder (*n* = 1, 0.9 %), paraaortic (*n* = 1, 0.9 %), and breast (*n* = 1, 0.9 %). There was no difference seen in the group without suspicion of metastatic disease and the group with suspicion of metastatic disease in regards to the demographic parameters age, gender, race or smoking history. Neither was there

TABLE 1 Patient demographics according to suspicion of metastatic disease at pretherapy imaging

Characteristic	No suspicion of metastatic disease	Suspicion of metastatic disease	<i>p</i>
No. of patients	149 (67.7 %)	71 (32.3 %)	
Age, years	62 (54, 69)	60 (54, 65)	0.43
Female	27 (18.1 %)	11 (15.5 %)	0.63
Race			0.746
White	135 (90.6 %)	63 (88.7 %)	
Black	13 (8.7 %)	8 (11.3 %)	
Other	1 (0.7 %)	0 (0 %)	
Zubrod score			0.113
0	33 (22.6 %)	9 (12.7 %)	
1	104 (71.2 %)	60 (84.5 %)	
≥2	9 (6.2 %)	2 (2.8 %)	
History of tobacco use	108 (73 %)	50 (70.4 %)	0.694
Pack-years of smoking	40 (20, 50)	40 (25, 58)	0.504
CAD	22 (14.9 %)	13 (18.3 %)	0.515
Hypertension	71 (48 %)	28 (39.4 %)	0.235
Diabetes	18 (12.2 %)	12 (16.9 %)	0.34
Renal insufficiency	9 (6.1 %)	2 (2.8 %)	0.51
Chronic obstructive pulmonary disease	17 (11.5 %)	4 (5.6 %)	0.223
Previous thoracic surgery	16 (10.8 %)	12 (16.9 %)	0.206
ASA			0.391
≤2	40 (29.2 %)	16 (23.5 %)	
≥3	97 (70.8 %)	52 (76.5 %)	
CAD coronary artery disease, ASA American Society of Anesthesiologists			

any difference between the two groups in regards to the comorbid states as measured by the Zubord performance score or American Society of Anesthesiologists class. History of CAD, hypertension, diabetes, renal insufficiency, chronic obstructive pulmonary disease, and thoracic surgery were the same in both groups as well (Table 1).

Pathology and Perioperative Outcomes

Both the group with suspicion of metastatic disease and the group without had similar tumor characteristics (Table 2). Adenocarcinoma of the esophagus predominated in both groups and the tumor was located in the lower third of the esophagus over 80 % of the time in both groups. T and N stage were also similar, as were the median lymph nodes collected, the percentage of R0, R1 and R2 resections and the percentage of radial margin positivity in both groups. Of note there were 11 patients who had clinical T4 tumors. The reason for the T4 status was: 7 (64 %) pleural invasion, 1 (9 %) lung, 1 (9 %) aortic, 1 (9 %) tracheal,

TABLE 2 Tumor characteristics in those with suspicion of metastatic disease and in those without on pre-therapy imaging

Variable	No suspicion of metastatic disease	Suspicion of metastatic disease	<i>p</i>
Tumor characteristics			
Histologic type			0.451
Adenocarcinoma	117 (81.8 %)	61 (85.9 %)	
Squamous cell carcinoma	26 (18.2 %)	10 (14.1 %)	
Tumor location			0.421
Lower third	120 (82.2 %)	59 (83.1 %)	
Middle third	25 (17.1 %)	10 (14.1 %)	
Upper third	1 (0.7 %)	2 (2.8 %)	
T stage			0.843
1	6 (6.1 %)	2 (3.7 %)	
2	13 (13.1 %)	6 (11.1 %)	
3	72 (72.7 %)	43 (79.6 %)	
4	8 (8.1 %)	3 (5.6 %)	
N stage			0.355
0	19 (20 %)	11 (22.9 %)	
1	76 (80 %)	36 (75 %)	
2	0 (0 %)	1 (2.1 %)	
Median lymph nodes harvested	9 (6, 14)	9 (5, 13)	0.781
Completeness of resection			0.999
R0	140 (94 %)	67 (94.4 %)	
R1	9 (6 %)	4 (5.6 %)	
R2	0 (0 %)	0 (0 %)	
Radial margin			0.51
Positive	9 (6 %)	2 (2.8 %)	
Negative	140 (94 %)	69 (97.2 %)	
Short-term outcomes			
Complete response			0.778
No	100 (67.1 %)	49 (69 %)	
Yes	49 (32.9 %)	22 (31 %)	
Length of stay	10 (8, 14)	11 (9, 16)	0.12
Esophagectomy technique			0.09
Transhiatal	55 (37.2 %)	29 (40.8 %)	
Three incision	52 (35.1 %)	30 (42.3 %)	
Ivor-Lewis	31 (20.9 %)	12 (16.9 %)	
Left thoracotomy	10 (6.8 %)	0 (0 %)	
Perioperative mortality	11 (7.5 %)	6 (8.5 %)	0.803

and 1 (9 %) with direct extension into the liver. Overall, 71 patients (32.3 %) had complete pathologic response after induction treatment; 22 (31 %) of the complete response were in patients who had suspicion of metastatic disease on pretherapy imaging. The length of stay after esophagectomy was similar between both groups, as was the perioperative mortality. In our cohort, transhiatal and

FIG. 1 Survival of esophageal cancer patients with and without suspicion for metastatic disease on pretherapy imaging

TABLE 3 Multivariable survival analysis

Characteristic	Hazard ratio	95 % confidence interval	<i>p</i>
Pretreatment PET evidence of a liver lesion	3.2	1.5–6.8	0.003
Clinical T4 stage	3.1	1.6–6.1	0.001
Posttreatment pathologic nodal stage	1.6	1.0–2.4	0.04
Pathologic metastatic disease	3.1	1.3–7.4	0.01

three-incision esophagectomies were performed at near-equal rates—approximately 40 % for each procedure. The Ivor-Lewis esophagectomy was performed next frequently, followed by left thoracotomy. There was no difference in the two groups in regard to the surgical approach used. There were some differences in short-term outcomes between patients who had an approach that involved a chest incision (three incision with thoracotomy or thoracoscopy, left thoracotomy, and Ivor-Lewis with thoracotomy or thoracoscopy) and patients whose approach did not involve a chest incision (transhiatal). Compared to the transhiatal patients ($n = 84$), patients who had a chest incision ($n = 135$) had a longer median length of stay (11 [9,17] vs. 8 [7,12] days, $p < 0.0001$), but they also had a higher median number of collected lymph nodes (10 [6,16] vs. 8 [4,11] lymph nodes, $p < 0.0001$). There was no statistically significant difference in 30-day mortality between the transhiatal patients and the patients who had a chest approach (2.4 % [2 of 84] vs. 6.7 % [9 of 135], $p = 0.17$).

Long-Term Outcomes and Multivariable Analysis

Mean follow-up was 24 months for all patients. Survival of patients with and without possible metastatic disease was similar. The group with suspicion of metastases had a 5-year survival of 24.8 %. The group without suspicion of metastatic disease had a 5-year survival of 25.4 %

FIG. 2 Survival of patients with suspicion of liver metastasis versus those without suspicion of liver metastasis on pretherapy imaging

($p = 0.368$) (Fig. 1). Multivariable analysis was performed and revealed that pretreatment PET evidence of a liver lesion, clinical T4 stage, posttreatment pathologic nodal stage, and pathologic metastatic disease predicted worse survival (Table 3).

Subgroup Analysis

None of the 10 patients who we found with pathologic confirmation of metastatic disease at resection survived longer than 2.5 years. Although there was no difference in survival between patients with suspicion of metastatic disease on pretreatment imaging and those without, those with suspicion of liver metastases did statistically significantly worse when compared to those with other suspicious metastases or those with no metastases at all. As seen in Fig. 2, the 5-year survival for those patients with no suspicion of metastases or those with suspicion of metastases to nonliver sites was 26.1 %. The 5-year survival for those with suspicion of liver metastases was only 9.9 %, however. The difference between both groups is statistically significant ($p = 0.014$). For the 71 patients who had findings suspicious for metastatic disease before treatment, there was not a statistically significant difference in survival ($p = 0.561$) between 45 patients who had only one suspicious site (5-year survival 27.5 %) and 26 patients who had more than one suspicious site (5-year survival 21.4 %).

DISCUSSION

We set out to determine whether isolated foci suspicious for metastatic disease on pretherapy imaging, which is known to have limitations, should preclude a patient from esophagectomy, and whether one should proceed if the patient with the suspicious disease undergoes treatment with no progression or with actual regression of the

suspicious site. In this cohort of 220 patients who underwent CRT followed by esophagectomy, 71 patients (32.3 %) had possible metastatic disease on initial CT or PET imaging. The survival of the patients with suspicious metastatic disease on pretherapy imaging was similar to that of those who had no suspicion of metastases. Considering that survival of patients with metastatic esophageal cancer is clearly far inferior to that of patients with esophageal cancer who have no evidence of disease spread, these results suggest that many patients have false-positive findings of distant metastatic disease on pretreatment imaging.^{1,25} Frequently staging studies show ambiguous findings that are interpreted as possibly representing metastatic disease but are not easily amenable to biopsy for pathologic confirmation. Our results suggest that in this situation, using a strategy of giving the benefit of doubt and proceeding with aggressive therapy that includes resection may be appropriate. This strategy can also be utilized when patients have a suspicious finding on pretreatment imaging that is no longer present after CRT.

In our subgroup analysis we did note that those with suspicion of liver metastases did statistically significantly worse than those with suspicious nonliver metastases or than those with no suspicion of metastases at all. Therefore, it appears that suspicious liver lesions in the setting of esophageal cancer may be more likely to represent metastatic disease than abnormalities in other locations. Our results suggest that nonliver lesions found on pretherapy imaging frequently represent benign disease and thus would not negatively impact survival like true metastases would. Other studies have had similar findings. Malik and colleagues found that PET imaging had a high false-positive rate in regard to detection of metastatic disease in patients with esophageal cancer.²⁶ Meyers and colleagues of the ACOSOG (American College of Surgeons Oncology Group) Z0060 trial evaluated 189 patients with resectable esophageal cancer and studied the impact that PET had on these patients. Overall, the authors found that PET usage was clearly favorable but that of the 35 lesions found to be suspicious for metastatic disease on PET (2 M1a, 33 M1b), 7 (20 %) were found to be falsely positive by biopsy. The authors wrote that “the risks and costs that characterize the burden of false positive results are likely underestimated here.”²⁷

Because patients with suspicion of nonliver metastases have the same survival as those with no suspicion of metastases in our study, we feel that aggressive treatment strategies are appropriate in many situations. Possible life-preserving measures, like esophagectomy should not be withheld because of ambiguous, possibly benign, findings on pretherapy imaging in patients who are fit and otherwise good surgical candidates. A more aggressive approach at either biopsy of these lesions preoperatively or

intraoperatively is warranted before a patient is denied surgical resection. If the biopsy of an ambiguous lesion is either technically difficult or involves risk of patient morbidity, the lesion can be evaluated on imaging before and after CRT. If there is no worsening of disease and certainly if there is resolution of the lesion and the patient is otherwise a good operative candidate, operative management should be considered. In some cases, additional imaging modalities can be considered in the evaluation for metastatic disease, i.e. bone scan for suspicious bony lesions.

Even with the use of PET/CT, whose main incremental value over PET is in the identification of unsuspected metastatic disease, current imaging is still limited.^{28,29} As clinicians, we must understand this and assure that our patients are not being denied therapy based on inaccurate imaging. Our study does have limitations, which include its small size and the fact that it is performed solely at a single institution. It is also retrospective and evaluates highly selected patients. Applying these findings to patients must therefore be done very carefully, as the results are not necessarily generalizable to all patients. The study does have clinical merit as the results suggest that suspicion of nonliver metastatic disease on pretherapy imaging should not necessarily preclude a patient from esophagectomy after induction therapy. Selection certainly is key, but some patients with these findings will benefit from aggressive surgical management. The results of our study suggest, that if, however, at the time of surgery or after induction therapy, biopsy reveals residual pathologic metastatic disease, esophagectomy likely does not imply potential cure and should only be considered for palliative purposes. In conclusion, patients with pretreatment staging studies that suggest T4 disease or liver metastases and patients with unexpected metastatic disease found at the time of surgery do not likely benefit from resection. Resection may, however, confer a survival benefit to patients with pretreatment imaging that shows possible distant metastatic disease not involving the liver.

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REFERENCES

1. Seigel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin*. 2013;63:11–30.
2. Dubecz A, Gall I, Solymosi N, et al. Temporal trends in long-term survival and cure rates in esophageal cancer: a SEER database analysis. *J Thorac Oncol*. 2012;7:443–7.
3. Horner M, Ries L, Krapcho M, et al. SEER cancer statistics review, 1975–2006. Bethesda: National Cancer Institute. <http://>

- seer.cancer.gov/csr/1975_2006/, based on November 2008 SEER data submission, posted to the SEER Web site; 2009.
4. Howlader N, Noone AM, Krapcho M, et al. SEER cancer statistics review, 1975–2008, Bethesda: National Cancer Institute. http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER Web site, 2011; 2011.
 5. Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med*. 2003;349:2241–52.
 6. Rice TW, Rusch VW, Ishwaran H, et al. Cancer of the esophagus and esophagogastric junction: data-driven staging for the seventh edition of the American Joint Committee on Cancer/International Union Against Cancer Staging Manuals. *Cancer*. 2010;116:3763–73.
 7. Worni M, Castleberry AW, Gloor B, et al. Trends and outcomes in the use of surgery and radiation for the treatment of locally advanced esophageal cancer: a propensity score adjusted analysis of the surveillance, epidemiology, and end results registry from 1998 to 2008. *Dis Esophagus*. 2014;27:662–9.
 8. 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.
 9. 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.
 10. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol*. 2011;12:681–92.
 11. Schwer AL, Ballonoff A, McCammon R, Rusthoven K, D'Agostino RB, Schefter TE. 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*. 2009;73:449–55.
 12. Solomon N, Zhuge Y, Cheung M, Franceschi D, Koniaris LG. The roles of neoadjuvant radiotherapy and lymphadenectomy in the treatment of esophageal adenocarcinoma. *Ann Surg Oncol*. 2010;17:791–803.
 13. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012;366:2074–84.
 14. National Comprehensive Cancer Network. Esophageal and esophagogastric junction cancer. Version 2.2013. Available at: http://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Accessed May 6, 2014.
 15. Libérale G, Van Laethem JL, Gay F, et al. The role of PET scan in the preoperative management of oesophageal cancer. *Eur J Surg Oncol*. 2004;30:942–7.
 16. van Vliet EPM, Heijenbrok-Kal MH, Hunink MGM, Kuipers EJ, Siersema PD. Staging investigations for oesophageal cancer: a meta-analysis. *Br J Cancer*. 2008;98:547–57.
 17. Strauss LG. Fluorine-18 deoxyglucose and false-positive results: a major problem in the diagnostics of oncological patients. *Eur J Nucl Med*. 1996;23:1409–15.
 18. Bailey SH, Bull DA, Harpole DH, et al. Outcomes after esophagectomy: a ten-year prospective cohort. *Ann Thorac Surg*. 2003;75:217–22.
 19. Chang AC, Ji H, Birkmeyer NJ, Orringer MB, Birkmeyer JD. Outcomes after transhiatal and transthoracic esophagectomy for cancer. *Ann Thorac Surg*. 2008;85:424–9.
 20. Rentz J, Bull D, Harpole D, et al. Transthoracic versus transhiatal esophagectomy: a prospective study of 945 patients. *J Thorac Cardiovasc Surg*. 2003;125:1114–20.
 21. Connors RC, Reuben BC, Neumayer LA, Bull DA. Comparing outcomes after transthoracic and transhiatal esophagectomy: a 5-year prospective cohort of 17,395 patients. *J Am Coll Surg*. 2007;205:735–40.
 22. Dimick JB, Wainess RM, Upchurch GR, Iannettoni MD, Orringer MB. National trends in outcomes for esophageal resection. *Ann Thorac Surg*. 2005;79:212–6.
 23. Ra J, Paulson EC, Kucharczuk J, et al. Postoperative mortality after esophagectomy for cancer: development of a preoperative risk prediction model. *Ann Surg Oncol*. 2008;15:1577–84.
 24. Berry MF, Atkins BZ, Tong BC, Harpole DH, D'Amico TA, Onaitis MW. A comprehensive evaluation for aspiration after esophagectomy reduces the incidence of postoperative pneumonia. *J Thorac Cardiovasc Surg*. 2010;140:1266–71.
 25. Rice TW, Blackstone EH, Rusch VW. 7th edition of the AJCC Cancer Staging Manual: esophagus and esophagogastric junction. *Ann Surg Oncol*. 2010;17:1721–4.
 26. Malik V, Keogan M, Gilham C, Duffy G, Ravi N, Reynolds JV. FDG-PET scanning in the management of cancer of the oesophagus and oesophagogastric junction: early experience with 100 consecutive cases. *Ir J Med Sci*. 2006;174:48–54.
 27. Meyers BF, Downey RJ, Decker PA, et al. The utility of positron emission tomography in staging of potentially operable carcinoma of the thoracic esophagus: results of the American College of Surgeons Oncology Group Z0060 trial. *J Thorac Cardiovasc Surg*. 2007;133:738–45.
 28. Kato H, Miyazaki T, Nakajima M, et al. The incremental effect of positron emission tomography on diagnostic accuracy in the initial staging of esophageal carcinoma. *Cancer*. 2005;103:148–56.
 29. Chowdhury FU, Bradley KM, Gleeson FV. The role of F18-FDG PET/CT in the evaluation of oesophageal carcinoma. *Clin Radiol*. 2008;63:1297–309.