Published in final edited form as:

Clin Gastroenterol Hepatol. 2010 March ; 8(3): 248–253. doi:10.1016/j.cgh.2009.11.016.

Depth of Submucosal Invasion Does Not Predict Lymph Node Metastasis and Survival of Patients with Esophageal Carcinoma

Rami J. Badreddine¹, Ganapathy A. Prasad¹, Jason T. Lewis², Lori S. Lutzke¹, Lynn S. Borkenhagen¹, Kelly T. Dunagan¹, and Kenneth K. Wang¹

¹ Barrett's Esophagus Unit, Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester MN, USA

² Department of Laboratory Medicine and Anatomic Pathology, Mayo Clinic College of Medicine, Rochester MN, USA

Abstract

Background & Aims—There is controversy over the outcomes of esophageal adenocarcinoma with superficial submucosal invasion. We evaluated the impact of depth of submucosal invasion on the presence of metastatic lymphadenopathy and survival in patients with esophageal adenocarcinoma.

Methods—Pathology reports were reviewed of esophagectomy samples collected from 1997 to 2007. Specimens from patients with esophageal adenocarcinoma and submucosal invasion were reviewed and classified as superficial (upper one third, sm1) or deep (middle third, sm2 or deepest third, sm3) invasion. Outcomes studied were presence of metastatic lymphadenopathy and overall survival. Variables of interest were analyzed as factors that affect overall and cancer-free survival using Cox proportional hazards modeling. A multivariate model was constructed to establish independent associations with survival.

Results—The study included 80 patients; 31 (39%) had sm1 carcinoma, 23 (29%) had sm2 carcinoma, and 26 (33%) had sm3 carcinoma. Superficial and deep submucosal invasion were associated with substantial rates of metastatic lymphadenopathy (12.9% and 20.4%, respectively). The mean follow-up time was 40.5±4 months and the mean overall unadjusted survival time was 53.8±4.1 months. Factors significantly associated with reduced survival time included the presence of metastatic lymph nodes (hazard ratio [HR] 2.89, confidence interval [CI] 1.13–6.88) and esophageal cancer recurrence (HR 6.39, CI 2.40–16.14), but not depth of submucosal invasion.

Conclusions—Patients with sm1 esophageal carcinoma have substantial rates of metastatic lymphadenopathy. Endoscopic treatment of superficial submucosal adenocarcinoma is not advised for patients that are candidates for surgery.

INTRODUCTION

Esophageal carcinoma is one of the few gastrointestinal cancers with a steadily rising incidence^{1,2}. Esophagectomy has been the treatment of choice for esophageal adenocarcinoma (EAC).

Corresponding author: Ganapathy Prasad, MD, Alfred Main, St. Mary's Hospital, 200, 1st Street SW, Rochester, MN USA, prasad.ganapathy@mayo.edu, Tel: 507-284-2174, Fax: 507-255-7612.

No disclosures

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Esophagectomy is associated with a major morbidity and nontrivial mortality especially at less experienced centers ³ making endoscopic management of superficially invasive carcinoma a potential option. Over the last few years, endoscopic treatment of early stage esophageal cancer has been increasingly described with excellent results and minimal morbidity ^{4, 5, 6, 7, 8,9}

TNM (Tumor-Node-Metastasis) staging is the system used by the American Joint Committee on Cancer (AJCC) to stage esophageal carcinoma and this has been shown to correlate with patient survival ^{10, 11, 12}. TNM edition 6 was used to stage the tumors in this study. In the TNM staging system, the T1 stage is divided into mucosal (T1a) and submucosal (T1b). The T1a and T1b stages can be further subdivided each into three sublevels depending on the depth of tumor involvement. T1b stage is divided into the upper one third of the submucosa (sm1), middle one third (sm2) or lower one third (sm3). This classification is also used by the Japanese society for Esophageal Diseases ¹³. The depth of tumor invasion has been shown to correlate with the rate of lymph node (LN) involvement in esophageal carcinoma ¹⁴.

Looking at early (T1a) stage esophageal carcinoma, the rate of lymph node metastasis has been reported to be very low in several studies ^{15, 16, 14}. This is not the case with submucosal (T1b) cancers where some studies report low rates of metastasis in the (sm1) stage whereas other studies describe high rates of metastatic lymph nodes in (sm1) stages comparable to (sm2) and (sm3) stages ^{17, 14, 18}. This has potential management implications since endoscopic treatment could be offered if (sm1) lesions behave like mucosal lesions.

We have previously found a significant risk of metastatic lymphadenopathy in patients with submucosal EAC ¹⁹. We hypothesized that the survival and the rate of LN metastasis in patients with sm1 invasion is not different from those patients with deeper submucosal invasion (sm2/sm3) making endoscopic treatment of such tumors problematic. The aim of this study was to evaluate the impact of the depth of submucosal invasion of esophageal cancer on the rate of LN metastasis at esophagectomy since endoscopic assessment of these lesions is difficult without actually removing a portion of the muscularis propria. Overall and disease free survival was also assessed since this is the most important endpoint of any oncological procedure.

PATIENTS AND METHODS

Study Population

Pathology reports of all patients who underwent esophagectomy EAC at our institution between 1997 and 2007 were reviewed. All esophagectomies were performed by expert thoracic surgeons using either a transthoracic or a transhiatal route with lymph node dissection.

Histopathologic slides of patients with submucosal invasion were retrieved and reviewed by an experienced gastrointestinal pathologist (JTL) as described below. Patients who underwent preoperative neoadjuvant treatment with chemotherapy and/or radiotherapy were excluded. Medical records of all these patients were reviewed and the following data was abstracted: gender, date of birth, date of diagnosis, presence and length of Barrett's esophagus (BE), preoperative EUS and CT/PET staging when done, date of last follow up and recurrence date when appropriate. Recurrence was defined as a histologically confirmed site specified recurrence of esophageal carcinoma or the appearance of metastatic LN on subsequent imaging. Survival status was checked using an institutionally approved web based service (www.accurant.com). Patients who had no recent follow up records were contacted using an IRB approved telephone script and asked about the time of last follow up locally, time of last upper endoscopy and whether they had any evidence of cancer recurrence. The cause of death was also abstracted from medical records of those patients who died. Death certificates were requested for those patients whose medical records were not clear on the cause of death.

Pathologic assessment

All histology was reviewed by an experienced gastroenterology pathologist (JTL). These were hematoxylin and eosin (H & E) stained slides that were examined to confirm the diagnosis of malignancy as well as the depth of invasion. The pathologist was blinded to the outcome of the cases. The entire resected tumor was submitted for histopathologic evaluation and was serially sectioned and grossly examined for areas of deepest invasion. Areas of deepest invasion were then histologically examined and depth of invasion was recorded. Tumors invading into the muscularis propria as well as intramucosal tumors were excluded from the study. Intramucosal carcinomas included tumors invading into lamina propria, muscularis mucosae, or the space between duplicated muscularis mucosae, when this was present as this has been reviewed in a prior publication²⁰. Sections with the best orientations were used to determine depth of invasion. Invasion into the upper one-third of the submucosa was considered an SM1 tumor. SM2 carcinomas demonstrated extension into the middle third of the submucosa, while SM3 tumors invaded into the lower third of the submucosa. This method is in accordance with previous studies^{21, 14, 17} (illustrated in Fig. 1a, Fig. 1b, Fig. 1c and Fig. 1d., see online supplement). H&E slides of all sampled regional and distant (e.g. mediastinal) lymph nodes were reviewed. Presence of lymph node metastases were documented in each case. The presence of any tumor (micro or macrometastasis) in the LN was considered positive for metastasis. When small enough (less than 1 cm) one section of each LN was analyzed. For larger LNs, multiple sections were made and each section analyzed separately. In addition the presence or absence of lymphovascular invasion was also assessed on standard H&E sections.

Statistical Analysis

Given the current debate in the literature in terms of the behavior of superficially invasive (sm1) submucosal carcinoma versus that of deeper invasion (sm2 and sm3), we apriori classified tumors into 2 groups: sm1 *versus* sm2/sm3 tumors. Baseline continuous data were compared using the 2-sample *t* test or the Wilcoxon rank sum tests depending on the data normality. Categorical data were compared using Chi square test or Fisher's exact test when cell expected values were too small. Overall survival was defined as the time between esophagectomy and death from any cause for patients who died or time between esophagectomy and the date the survival data was run (11/28/2007). Cancer free survival was defined as the time between esophagectomy and last cancer free follow up or date of death. Survival analysis was done using Kaplan- Meyer product limit model. Variables of interest (age, gender, presence and length of BE, size of tumor, histologic grade, depth of submucosal invasion, lymphovascular invasion and LN status) were analyzed as factors affecting survival using Cox proportional hazards modeling. A multivariate model was then constructed using factors significant on univariate analysis and clinically relevant variables to establish independent associations with survival. Differences in overall survivals and recurrence free survivals were assessed using the log-rank test. A *p* value below 0.05 was considered statistically significant. All statistical analyses were performed using the JMP statistical analysis package (JMP, Version 6, 1989–2002; SAS Institute Inc., Cary, NC-USA).

RESULTS

1260 esophagectomies were performed during the selected study period (1997–2007). After exclusion of patients who underwent preoperative chemoradiotherapy and those with intramucosal disease, slides of 80 patients with submucosal invasion were available for review. 68 patients (85%) were males and 12 were females (15%). 53 patients had BE (66%) with a mean BE length of 5 ± 0.4 cm (0.5cm–13cm).

Preoperative staging

66 patients had endoscopic ultrasound (EUS) done prior to surgery with the following staging results: 3 T0N0 (4%), 39 T1N0 (60%), 2 T1N1 (3%), 18 T2N0 (27%), 3 T2N1 (4%) and 1 T3N0 (2%). Prior to 2001, Positron emission tomography (PET) imaging was not routinely done for preoperative staging at our institution but starting 2002 most patients underwent fusion computed tomography (CT)/PET scans for staging. 34 patients (40%) had fusion CT/PETs for preoperative staging, 49 patients (58%) had only CT scans and 2 patients did not have CT or PET scans (2%). Of those who had CT/PETs, 3/34 (9%) showed evidence of metastasis (2 patients with periesophageal positive LN uptake and 1 patient with minimal uptake in the right upper lobe of the lung along with some calcifications). Histologic LN assessment did not show evidence of metastasis in those patients and the uptake in the right upper lobe was more suggestive of inflammatory uptake so the patient proceeded to esophagectomy. Of the 49 patients who had only CT scanning for preoperative staging, 3 patients (6%) had lesions suspicious for metastasis (2 patients with enlarged periesophageal LN and 1 patient with enlarged axillary LN). Those with enlarged periesophageal LN had negative preoperative EUS FNA of these LN and negative histologic assessment postoperatively. The patient with enlarged axillary LN on CT scan had recurrent lymphoma on further LN biopsy. In patients who had BE (53 patients), preoperative histology was available on 38 patients as follows: No dysplasia 3 patients (8%), LGD 4 patients (10%) and HGD in 31 patients (82%). This was due to some patients being directly referred for esophagectomy without any record of preoperative surveillance being available for review.

Surgical/staging results

The Ivor-Lewis procedure was done in 56 patients (70%) and the transhiatal approach was performed in the remainder. Table 1 summarizes the major clinical variables of patients with superficial (sm1) invasion and those with deeper (sm2+sm3) invasion. The distribution of submucosal invasion in the esophagectomy specimens was: sm1 in 31 patients (39%), sm2 in 23 patients (29%) and sm3 in 26 patients (33%). The mean number of LN that were resected and examined histologically was 15 (SEM 0.8). The mean number of LN examined was not statistically different between the sm1 vs sm2/sm3 group (13 ± 1.4 vs 15 ± 1.0 , $p=0.22$). Mean size of the tumor was 2.8 ± 0.3 cm. This was also not different between the two groups (2.5 ± 0.6 cm vs 2.9 ± 0.3 cm, $p=0.5$). Mean age at esophagectomy was 67 ± 1 years. Table 1 summarizes these results.

Histologic examination revealed metastatic lymphadenopathy in 14/80 patients (17.5%). Distribution of LN metastasis by depth of invasion was as follows: 12.9% (4/31 patients) in the sm1 group, 22% (5/23 patients) in the sm2 group and 19% (5/26 patients) in the sm3 group. Lymphovascular invasion was assessed in all patients: 27 (34%) showed evidence of invasion while the remaining did not. Patients with evidence of LV invasion were more likely to have metastatic lymphadenopathy (8/27, 30%) than those without LV invasion (6/53, 11%). This difference was statistically significant ($p=0.047$). The influence of lymphovascular invasion on metastatic lymphadenopathy in sm1 and sm2/3 EAC is shown in tables 2a and 2b. The proportion of metastatic lymphadenopathy was not statistically different between patients with sm1 and those with deeper invasion (12.9% vs 20.4%, $p=0.38$). There was a total of 4 positive LN in the sm1 group and 10 positive LN in the sm2/sm3 group. Adjuvant combined chemotherapy and radiation treatment was administered in 5 patients with postoperative findings of metastatic LN. Combined chemo/radiotherapy were not given to any of the patients without evidence of metastatic LN.

Follow up and recurrence data

Mean follow up time was 40.5 ± 4 months (express as mean [SEM]). 7 patients (9.0%) had recurrence of esophageal cancer on follow up. Recurrence was at the anastomotic site in 2

patients, appeared as liver metastasis in 1 patient and as LN metastasis in 4 patients. Of the two patients with anastomotic recurrences, one had no BE to start with and the other had no residual BE segment post operatively. All five patients with lymphatic recurrences had negative LN on initial surgical staging.

Presence of metastatic LN on initial presentation was not statistically different between those who recurred and those who did not (3/8 vs 11/77, $p=0.24$). Of those 8 patients who recurred, 3 patients had sm1 lesions (37.5%) and 5 patients had sm2/3 lesions (62.5%). In the sm1 group ($n=31$) there were 3 recurrences (9.7%) whereas in the sm2/3 group ($n=49$) there were 4 recurrences (8.1%) and this was statistically not different ($p=0.82$).

Survival Data

Median overall unadjusted survival for all patients was 46.5 months (IQR 19.98–82.87 months). Cumulative mortality was 39 % during the follow up period. Cumulative mortality in patients with sm1 carcinoma was 32% and 43% in those with deeper invasion. Total in-hospital mortality was 6% (5/80 patients) and this occurred within a range of 7 to 15 days giving a 30-day mortality of 6% as well. Causes of death are summarized in Table 3.

Overall survival in the two groups is displayed in Figure 2. Median overall survival in the sm1 group was 52 months (IQR: 23.6–78.34 months) and in the sm2/3 group was 38 months (IQR: 19.4–95.00 months). Median cancer free survival for all patients was 30 months (IQR: 9–69 months). Cancer free survival in the two groups is displayed in Figure 2. Median cancer free survival in the sm1 group was 35.3 months (IQR: 13–62.40 months) and in the sm2/3 group was 27.8 months (IQR: 7–75.2 months).

Table 4 shows the results of the univariate analysis of the different variables considered. On univariate analysis, the depth of submucosal involvement by cancer was not a significant predictor of survival. We also assessed the degree of differentiation as a marker of metastatic lymphadenopathy and did not find this to be a significant predictor. 10% of well differentiated tumors had metastatic LN compared to 20% of poorly differentiated tumors.

Older age at esophagectomy as well as a history of recurrence of esophageal cancer were associated with a worse survival on univariate analysis.

On multivariate analysis, age, gender, depth of submucosal involvement, presence of metastatic lymph nodes as well as recurrence of esophageal cancer was analyzed. (Table 5). Of these, a history of recurrence as well as the presence of metastatic lymph nodes were significantly associated with a worse survival. Superficial versus deep submucosal invasion was not an independent predictor of survival.

DISCUSSION

We found that superficial (sm1) submucosal invasion in esophageal carcinoma is associated with a substantial rate of LN metastasis (12.9%). Furthermore, the overall survival and cancer free survival of patients with sm1 carcinoma were comparable to those with deeper submucosal lesions (sm2 and sm3). While this maybe due to lack of adequate power to detect a difference given the relatively small sample sizes of the two groups, these results are biologically plausible, given that lymphatics in the esophagus are present in the very superficial submucosa (sm1), making lymphatic dissemination likely with any degree of submucosal invasion. It is well known that the esophagus is unique among viscous hollow organs of the gastrointestinal tract in that lymphatics are even present in the deep mucosa ^{22, 23}.

The TNM system used in the staging of esophageal carcinoma has been a strong predictor of patient survival in several studies in the past 12, 14, 24. Mucosally confined esophageal carcinoma has a very low risk of metastatic lymphadenopathy (1–2%) and consensus appears to be evolving on the feasibility of treating these neoplasms endoscopically. There has been however controversy in the literature regarding the prognosis of patients with superficial submucosal lesions. Superficial submucosal involvement (sm1) was found to behave more like intramucosal lesions by Westerterp et al 17. This paper analyzed the outcome of esophagectomy in 120 patients with Barrett's esophagus and high grade dysplasia or T1 stage adenocarcinoma.. Unlike our results, none of the sm1 lesions in this paper were associated with LN involvement. In addition, sm1 lesions, like their intramucosal counterparts, were associated with a better 5 year recurrence free survival when compared to sm2/3 lesions.. Liu et al 21 found that the rate of LN metastasis in superficial submucosal lesions was very low and actually similar to that of mucosal lesions (36% in deep submucosal invasion vs 8% in superficial submucosal lesions, $p<0.001$). Overall survival however was not statistically different among patients with different depths of tumor invasion which is similar to our findings. In our study the overall rate of LN metastasis in all submucosal lesions was 17.5 % (15/80) which is similar to other series 25, 26. Our results show a substantial rate of metastatic LN in sm1 cancers, which makes endoscopic treatment inadvisable in these patients at this time.

Another recent study by Manner et al showed that endoscopic resection in superficial submucosal lesions is safe and effective on long term follow up ²⁷. This study included 21 patients with low risk sm1 adenocarcinoma of the esophagus. The low risk group was defined as sm1 patients without lymphovascular invasion, grades 1 or 2 and macroscopic type I/II. Interestingly, none of these patients had evidence of LN involvement and their outcome was excellent over the follow up period of about 5 years. Our patient population in this study is different in that we did not a priori exclude high grade tumors or those with lymphovascular invasion. We also did not look at the macroscopic type of the tumor. In addition, the classification of tumors into sm1, 2 and 3 was performed on esophagectomy specimens as opposed to on EMR specimens (which may not be as accurate as esophagectomy specimens). These factors might explain the differences between our results and those in this paper. More importantly; our data is based entirely based on esophagectomy samples as well as histologic examination of sampled LN which is more accurate than endosonographic assessment. This might explain why in our study, 4 out of 32 patients with sm1 invasion had metastatic LN (12.9%) which is different from Manner's paper. In addition, 2 out of 4 patients with sm1 cancers without lymphovascular invasion had metastases to LNs, indicating that the absence of LV invasion does not eliminate the possibility of LN metastasis in submucosal carcinomas (see table 2a).

Older age at esophagectomy was a strong predictor of worse survival on univariate analysis in our study (HR 1.04; 95% CI 1.00, 1.08). The other strong predictor of worse survival on univariate analysis was recurrence of esophageal adenocarcinoma (HR 4.71, 95% CI 1.92–10.49). The depth of submucosal invasion (sm1 vs sm2/3) on the other hand was not a significant predictor of survival on univariate or multivariate analysis. On multivariate analysis when the data was age and gender adjusted, the presence of metastatic LN became a strong predictor of a worse survival (HR 2.89, $p=0.02$). These findings are consistent with other studies in which lymph node status predicted survival 28, 23. A history of recurrence remained a statistically significant predictor of survival on the multivariate model (HR 6.39, $p<0.001$). The rate of recurrence was comparable between patients with sm1 disease and those with sm2/sm3 disease (9.6% vs 8.2%,) reinforcing our hypothesis that these two groups behave similarly.

Based on our results, it appears to be critical to know whether there is submucosal involvement when endoscopic treatment is considered for superficial esophageal carcinoma. In our study,

the accuracy of EUS in LN staging was 79% (54/68). The accuracy of standard EUS (7.5/12MHz) compared to histopathology in detecting T1 lesions ranges from 50–80% in previous studies ^{29,30,31}. Higher frequency EUS probes could be used to improve the accuracy of early T staging ³² but given the limited depth of penetration this would be at the expense of nodal staging. It has been recently reported by our group that frozen section analysis by EMR is an accurate staging modality in esophageal adenocarcinoma when compared to permanent EMR section analysis ³³. If EMR specimens showed submucosal invasion, there was a high rate of lymph node metastasis (31%) and residual disease at surgery (50%) ¹⁹ reinforcing our findings. Another notable point is the high prevalence of HGD in preoperative surveillance biopsies in patients with submucosal EAC in this study (31 of 38 patients where the data was available). This underscores the importance of careful endoscopic assessment to exclude invasive carcinoma (submucosal and deeper invasion) in patients with HGD before consideration of ablative therapy such as radiofrequency ablation, given that identification of advanced neoplasia would change recommended therapy from endoscopic therapy to surgical resection.

Our study has some potential limitations. Classifying submucosal lesions into three categories based on the depth of invasion can be challenging, particularly in EMR specimens where the entire submucosa is not available for assessment. In this study, availability of the entire submucosa as part of the esophagectomy specimen limits this disadvantage. Moreover, we defined submucosal invasion as the presence of adenocarcinoma cells beyond the second layer of duplicated muscularis mucosae to avoid misclassifying deep mucosal invasion as superficial submucosal invasion. Another limitation is the relatively small numbers, especially with the number of LN involvement, which could result in a type 2 error. While we did not perform a formal statistical comparison of the rate of LN involvement in the two groups, given the potential for a type 2 error, we feel that the rate of LN metastasis in the sm1 group is high enough to make a recommendation against endoscopic therapy in this group. This could explain some of the differences between our results and others. The retrospective design and the abstraction of medical records pose another limitation although we tried to limit this by choosing objective outcome criteria (overall survival), validated methods to collect these data and by also collecting additional data on patients prospectively.

Our data suggest that patients with sm1 esophageal carcinoma have a substantial rate of LN involvement and behave similarly to patients with deeper submucosal involvement in terms of cancer recurrence and overall as well as cancer free survival. The absence of lymphovascular invasion does not completely eliminate the possibility of metastatic lymphadenopathy in submucosal carcinoma. Endoscopic treatment of submucosal cancers in patients who are candidates for esophagectomy appears to be inadvisable at this time.

Acknowledgments

Supported by NIH grants (R01 CA111603-01A1 and R01CA097048 to KKW, R03 CA 135991-01 to GAP) and the Miles and Shirley Fiterman Digestive Disease Center, Mayo Clinic College of Medicine.

Glossary

RJB	Data collection, analysis and interpretation of data, drafting and revision of manuscript
GAP	Study concept, critical revision of manuscript, analysis of data
KKW	Critical revision of manuscript
JTL	Data analysis (pathology)

LSB LSL, KTD, Data collection

References

1. Falk GW. Barrett's esophagus. *Gastroenterology* 2002;122:1569–91. [PubMed: 12016424]
2. Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998;83:2049–53. [PubMed: 9827707]
3. van Lanschot JJ, Hulscher JB, Buskens CJ, Tilanus HW, ten Kate FJ, Obertop H. Hospital volume and hospital mortality for esophagectomy. *Cancer* 2001;91:1574–8. [PubMed: 11301408]
4. Pacifico RJ, Wang KK, Wongkeesong LM, Buttar NS, Lutzke LS. Combined endoscopic mucosal resection and photodynamic therapy versus esophagectomy for management of early adenocarcinoma in Barrett's esophagus. *Clin Gastroenterol Hepatol* 2003;1:252–7. [PubMed: 15017665]
5. Buttar NS, Wang KK, Lutzke LS, Krishnadath KK, Anderson MA. Combined endoscopic mucosal resection and photodynamic therapy for esophageal neoplasia within Barrett's esophagus. *Gastrointest Endosc* 2001;54:682–8. [PubMed: 11726842]
6. May A, Gossner L, Pech O, Fritz A, Gunter E, Mayer G, Muller H, Seitz G, Vieth M, Stolte M, Ell C. Local endoscopic therapy for intraepithelial high-grade neoplasia and early adenocarcinoma in Barrett's oesophagus: acute-phase and intermediate results of a new treatment approach. *Eur J Gastroenterol Hepatol* 2002;14:1085–91. [PubMed: 12362099]
7. Overholt BF, Wang KK, Burdick JS, Lightdale CJ, Kimmey M, Nava HR, Sivak MV Jr, Nishioka N, Barr H, Marcon N, Pedrosa M, Bronner MP, Grace M, Depot M. Five-year efficacy and safety of photodynamic therapy with Photofrin in Barrett's high-grade dysplasia. *Gastrointest Endosc* 2007;66:460–8. [PubMed: 17643436]
8. Pohl J, Pech O, May A, Manner H, Ell C. Endoscopic resection of early esophageal and gastric neoplasias. *Dig Dis* 2008;26:285–90. [PubMed: 19188716]
9. Ell C, May A, Pech O, Gossner L, Guenter E, Behrens A, Nachbar L, Huijsmans J, Vieth M, Stolte M. Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). *Gastrointest Endosc* 2007;65:3–10. [PubMed: 17185072]
10. Eloubeidi MA, Desmond R, Arguedas MR, Reed CE, Wilcox CM. Prognostic factors for the survival of patients with esophageal carcinoma in the U.S: the importance of tumor length and lymph node status. *Cancer* 2002;95:1434–43. [PubMed: 12237911]
11. Killinger WA Jr, Rice TW, Adelstein DJ, Medendorp SV, Zuccaro G, Kirby TJ, Goldblum JR. Stage II esophageal carcinoma: the significance of T and N. *J Thorac Cardiovasc Surg* 1996;111:935–40. [PubMed: 8622316]
12. Rice TW, Blackstone EH, Goldblum JR, DeCamp MM, Murthy SC, Falk GW, Ormsby AH, Rybicki LA, Richter JE, Adelstein DJ. Superficial adenocarcinoma of the esophagus. *J Thorac Cardiovasc Surg* 2001;122:1077–90. [PubMed: 11726882]
13. for JSoEDG. the clinical and pathologic studies on carcinoma of the esophagus. 9. Kanehara T;
14. 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. [PubMed: 9527214]
15. Peters JH, Clark GW, Ireland AP, Chandrasoma P, Smyrk TC, DeMeester TR. Outcome of adenocarcinoma arising in Barrett's esophagus in endoscopically surveyed and nonsurveyed patients. *J Thorac Cardiovasc Surg* 1994;108:813–21. discussion 821–2. [PubMed: 7967662]
16. van Sandick JW, van Lanschot JJ, ten Kate FJ, Offerhaus GJ, Fockens P, Tytgat GN, Obertop H. Pathology of early invasive adenocarcinoma of the esophagus or esophagogastric junction: implications for therapeutic decision making. *Cancer* 2000;88:2429–37. [PubMed: 10861416]
17. Westertorp M, Koppert LB, Buskens CJ, Tilanus HW, ten Kate FJ, Bergman JJ, Siersema PD, van Dekken H, van Lanschot JJ. Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. *Virchows Arch* 2005;446:497–504. [PubMed: 15838647]
18. Buskens CJ, Westertorp M, Lagarde SM, Bergman JJ, ten Kate FJ, van Lanschot JJ. Prediction of appropriateness of local endoscopic treatment for high-grade dysplasia and early adenocarcinoma by EUS and histopathologic features. *Gastrointest Endosc* 2004;60:703–10. [PubMed: 15557945]

19. Prasad GA, Buttar NS, Wongkeesong LM, Lewis JT, Sanderson SO, Lutzke LS, Borkenhagen LS, Wang KK. Significance of neoplastic involvement of margins obtained by endoscopic mucosal resection in Barrett's esophagus. *Am J Gastroenterol* 2007;102:2380–6. [PubMed: 17640326]
20. Lewis JT, Wang KK, Abraham SC. Muscularis mucosae duplication and the musculo-fibrous anomaly in endoscopic mucosal resections for barrett esophagus: implications for staging of adenocarcinoma. *Am J Surg Pathol* 2008;32:566–71. [PubMed: 18300796]
21. Liu L, Hofstetter WL, Rashid A, Swisher SG, Correa AM, Ajani JA, Hamilton SR, Wu TT. Significance of the depth of tumor invasion and lymph node metastasis in superficially invasive (T1) esophageal adenocarcinoma. *Am J Surg Pathol* 2005;29:1079–85. [PubMed: 16006804]
22. Sabik JF, Rice TW, Goldblum JR, Koka A, Kirby TJ, Medendorp SV, Adelstein DJ. Superficial esophageal carcinoma. *Ann Thorac Surg* 1995;60:896–901. discussion 902. [PubMed: 7574991]
23. Sugimachi K, Ikebe M, Kitamura K, Toh Y, Matsuda H, Kuwano H. Long-term results of esophagectomy for early esophageal carcinoma. *Hepatogastroenterology* 1993;40:203–6. [PubMed: 8325583]
24. Siewert JR, Stein HJ, Feith M, Bruecher BL, Bartels H, Fink U. Histologic tumor type is an independent prognostic parameter in esophageal cancer: lessons from more than 1,000 consecutive resections at a single center in the Western world. *Ann Surg* 2001;234:360–7. discussion 368–9. [PubMed: 11524589]
25. Ruol A, Merigliano S, Baldan N, Santi S, Petrin GF, Bonavina L, Ancona E, Peracchia A. Prevalence, management and outcome of early adenocarcinoma (pT1) of the esophago-gastric junction. Comparison between early cancer in Barrett's esophagus (type I) and early cancer of the cardia (type II). *Dis Esophagus* 1997;10:190–5. [PubMed: 9280078]
26. Holscher AH, Bollschweiler E, Schneider PM, Siewert JR. Early adenocarcinoma in Barrett's oesophagus. *Br J Surg* 1997;84:1470–3. [PubMed: 9361616]
27. Manner H, May A, Pech O, Gossner L, Rabenstein T, Gunter E, Vieth M, Stolte M, Ell C. Early Barrett's carcinoma with "low-risk" submucosal invasion: long-term results of endoscopic resection with a curative intent. *Am J Gastroenterol* 2008;103:2589–97. [PubMed: 18785950]
28. Kitamura K, Ikebe M, Morita M, Matsuda H, Kuwano H, Sugimachi K. The evaluation of submucosal carcinoma of the esophagus as a more advanced carcinoma. *Hepatogastroenterology* 1993;40:236–9. [PubMed: 8325589]
29. Rosch T. Endosonographic staging of esophageal cancer: a review of literature results. *Gastrointest Endosc Clin N Am* 1995;5:537–47. [PubMed: 7582580]
30. Hasegawa N, Niwa Y, Arisawa T, Hase S, Goto H, Hayakawa T. Preoperative staging of superficial esophageal carcinoma: comparison of an ultrasound probe and standard endoscopic ultrasonography. *Gastrointest Endosc* 1996;44:388–93. [PubMed: 8905355]
31. Zuccaro G Jr, Rice TW, Vargo JJ, Goldblum JR, Rybicki LA, Dumot JA, Adelstein DJ, Trolli PA, Blackstone EH. Endoscopic ultrasound errors in esophageal cancer. *Am J Gastroenterol* 2005;100:601–6. [PubMed: 15743358]
32. Murata Y, Suzuki S, Ohta M, Mitsunaga A, Hayashi K, Yoshida K, Ide H. Small ultrasonic probes for determination of the depth of superficial esophageal cancer. *Gastrointest Endosc* 1996;44:23–8. [PubMed: 8836712]
33. Prasad GA, Wang KK, Lutzke LS, Lewis JT, Sanderson SO, Buttar NS, Wong Kee Song LM, Borkenhagen LS, Burgart LJ. Frozen section analysis of esophageal endoscopic mucosal resection specimens in the real-time management of Barrett's esophagus. *Clin Gastroenterol Hepatol* 2006;4:173–8. [PubMed: 16469677]

Figure 1.

Fig 1a. SM1-High power view. Infiltrating malignant glands extend just through the muscularis mucosae into the loose connective tissue of the submucosa.

Fig. 1b SM2-Low power view. Tumor extends into the middle third of the submucosa. The thick bundles of smooth muscle which compose the muscularis propria are seen at the bottom of the field.

Fig. 1c SM3-Low power. Invasive adenocarcinoma abuts but does not invade the muscularis propria

Fig. 1d Lymph node involved by metastatic adenocarcinoma from an SM3 case.

Fig. 2. Overall unadjusted survival of patients with sm1 submucosal esophageal adenocarcinoma and sm2/sm3 submucosal esophageal adenocarcinoma ($p=0.43$ -Red sm1, Blue sm2/3).

Fig. 3.
Cancer free survival of patients with sm1 submucosal esophageal adenocarcinoma and sm2/
sm3 submucosal esophageal adenocarcinoma ($p=0.48$ -Red sm1, Blue sm2/3).

Table 1

Comparison of patients with superficial (sm1) and deep (sm2+sm3) submucosal invasion

	Sm1 Carcinoma (n=31)	Sm2/3 Carcinoma (n= 49)	p value
Age Years (mean±SEM)	68±1.7	66±1.6	1.0
Gender (M/F)	28/3	42/7	0.55
Size of tumor cm (mean±SEM)	2.4 ± 0.6	2.8 ± 0.3	0.50
Number of LN examined (mean±SEM)	13 ± 1.4	15 ± 1.0	0.22
Metastatic lymphadenopathy	4 (12.9%)	10 (20%)	0.38
Poor differentiation	23 (71.87%)	41 (79.35%)	0.61
Lymphovascular invasion	10 (32%)	17 (35%)	0.82
Recurrent Carcinoma	3 (9.6%)	4 (8.2%)	0.80
Cumulative mortality	10 (32%)	21 (43%)	0.34

Table 2

Influence of lymphovascular invasion on metastatic lymphadenopathy in submucosal adenocarcinoma.

Table 2a: SM1 EAC			
	Metastatic LNs neg	Metastatic LNs pos	Total
Lymphovascular invasion absent	19	2 (9.5 %)	21
Lymphovascular invasion present	8	2 (20 %)	10
	27	4	31

Table 2b: SM2/3 EAC			
	Metastatic LNs neg	Metastatic LNs pos	Total
Lymphovascular invasion absent	28	4 12.9%	32
Lymphovascular invasion present	11	6 35.3%	17
	39	10	49

P=0.42

P=0.06

Table 3

Causes of death in patients with superficial (sm1) and deep (sm2, sm3) submucosal invasion

Cause of death	sm1 carcinoma (n=10)	sm 2/3 carcinoma (n=21)
Recurrence of cancer	3	5
Post op complications	2	5
Cardiac	2	3
Pulmonary	2	5
Lung cancer	0	1
Head and Neck cancer	0	1
Sepsis	1	1

Table 4

Univariate analysis of predictors of overall survival (n=80)

Variable	HR (95% CI)	P value
Age at Esophagectomy	1.04 (1.00–1.08)	0.03
Gender	0.46(0.11–1.31)	0.16
Type of surgery(Ivor-Lewis/Transhiatal)	1.42 (0.63–2.96)	0.37
Presence of BE	0.74 (0.37–1.52)	0.41
Size of tumor (cm)	1.10 (0.97–1.20)	0.10
Differentiation degree	1.23 (0.78–1.95)	0.35
Metastatic lymph nodes	2.09 (0.86–4.54)	0.09
Recurrence of esophageal cancer	4.71 (1.92–10.49)	0.001
Depth of submucosal invasion (sm1 vs sm2/3)	1.33 (0.65–2.96)	0.43
Lymphovascular invasion	1.4 (0.90, 1.50)	0.30

Table 5

Multivariate analysis of predictors of overall survival (n=80)

Variable	HR (95% CI)	P value
Age at esophagectomy	1.02 (1.00–1.07)	0.08
Gender	0.44 (0.10–1.24)	0.13
Depth of submucosal invasion sm1 vs sm2/3	1.52 (0.71–3.45)	0.28
Metastatic Lymph nodes	2.80 (1.13–6.66)	0.023
Recurrence of esophageal cancer	6.12 (2.35–15.30)	0.0008