Clinical Study

Dilation of Malignant Strictures in Endoscopic Ultrasound Staging of Esophageal Cancer and Metastatic Spread of Disease

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Background. Dilation of malignant strictures in endoscopic ultrasound (EUS) staging of esophageal cancer is safe, but no data exists regarding the subsequent development of metastases. Aim. Compare the rates of metastases in esophageal cancer patients undergoing EUS staging who require esophageal dilation in order to pass the echoendoscope versus those who do not. Methods. We reviewed consecutive patients referred for EUS staging of esophageal cancer. We evaluated whether dilation was necessary in order to pass the echoendoscope, and for the subsequent development of metastases after EUS at various time intervals. Results. Among all patients with similar stage (locally advanced disease, defined as T3, N0, M0 or T1-3, N1, M0), there was no difference between the dilated and nondilated groups in the rates of metastases at 3 months (14% versus 10%, \( P = 1.0 \)), 6 months (28% versus 20%, \( P = 0.69 \)), 12 months (43% versus 40%), \( P = 1.0 \), or ever during a mean followup of 15 months (71% versus 55%), \( P = 0.48 \). Conclusions. Dilation of malignant strictures for EUS staging of esophageal cancer does not appear to lead to higher rates of distant metastases.

1. Introduction

Endoscopic ultrasound (EUS) is an important part of staging for esophageal cancer. It provides key information regarding local tumor invasion, locoregional, and celiac lymph node involvement. This information is essential to guide future treatment decisions [1–9]. Often a malignant stricture is present that prohibits passage of the echoendoscope for complete EUS staging. Earlier studies showed that dilating these malignant strictures led to high complication rates [1, 10]. More recently, the safety of dilating malignant strictures for passage of an echoendoscope for esophageal cancer staging has been well established [2–4, 11]. Safety data in previous studies primarily focused on rates of perforation. Currently there are no data available on whether dilating malignant strictures may precipitate metastatic spread of cancer.

At our institution, it was noted by our thoracic surgery and oncology section that there were a high number of distant metastases in unusual locations shortly after surgery in patients who had been dilated at the time of pretreatment EUS staging. This led to a request by the thoracic surgery section to limit dilation for the performance of EUS in the staging of esophageal cancer patients.

Numerous reports of iatrogenic periprocedural spread of cancer cells in many other procedures exist, including seeding needle tracts in breast biopsies [12–14], diagnostic and therapeutic procedures for hepatocellular carcinoma [15–17], cutaneous seeding in laparoscopic cholecystectomy [18–21], and seeding tracts with fine needle aspiration (FNA) in pancreatic, esophageal, and thyroid lesions [22–26]. It is also well known that dilation of esophageal strictures carries a high rate of transient bacteremia [27–30], presumably through the breakdown of tissue planes and bacteria seeding the bloodstream. In theory, a similar mechanism could occur with cancer cells seeding the bloodstream during dilation of a malignant stricture, but this has not been previously documented or noted. The goal of our study is to ascertain if dilating malignant strictures in EUS esophageal cancer staging lead to higher rates of metastases.
2. Methods

Our institution uses a multimodality staging regimen for esophageal cancer including EUS, CT scan, positron emission tomography (PET) scan, or combined CT-PET scan. There was no predetermined order of the various staging tests. We reviewed 55 consecutive patients referred for EUS for the purpose of staging esophageal cancer. All patients had biopsy-proven esophageal cancer. EUS was performed by 3 endoscopic ultrasonographers (D. V. Gopal, T. J. Frick, and P. R. Pfau) with experience ranging from 5 to 10 years with an average of 200 EUS exams per year per endoscopist, using an Olympus GF-UM130 or GF-UM160 radial array echoendoscope (Olympus America, Melville, NY, USA) with both 7.5 and 12.0 mHz frequencies. Malignant strictures were only dilated if the stricture prevented passage of the echoendoscope. Dilation was performed sequentially with either wire-guided dilation or a through-the-scope balloon. No strictures were dilated beyond 15 mm. EUS staging was done immediately after dilation using the American Joint Committee on Cancer (AJCC) Tumor, Node, Metastasis (TNM) staging system, 6th edition.

Patients’ electronic medical records were reviewed to obtain all data. We collected data on the patients age, gender, histology of cancer, location of malignant stricture (cervical esophagus, thoracic esophagus, or gastroesophageal junction) if dilation was required to pass the echoendoscope, TNM stage at the time of EUS, and whether or not distant metastases had been identified at certain time intervals—0 (the time of original EUS staging), 1, 3, 6, and 12 months following EUS, or at any time beyond 12 months if applicable. Survival data was also collected using the Social Security Death Index. Patients who had evidence of distant metastases on the pretreatment staging were not included in the analysis. Ascertainment of the presence of distant metastases at the chosen time intervals was done by reviewing all imaging studies and clinic notes through the given time interval on each patient. This study was approved by the University of Wisconsin Health Sciences Institutional Review Board.

Two groups of patients were compared, those who required dilation in order to pass the echoendoscope and those who did not. Patients with locally advanced disease (defined as T3, N0, M0 or T1-3, N1, M0) were identified in both the dilated and nondilated group and compared with each other in order to attempt to match the patients in the two groups for similar stage at the time of EUS.

Statistical analysis comparing the dilated group and nondilated group was performed with Chi-square test or Fisher’s exact test where appropriate.

3. Results

55 consecutive patients were identified. 23 patients required dilation in order to pass the echoendoscope, 32 did not. The echoendoscope was successfully passed through the malignant stricture following dilation allowing full staging in 21 of the 23 patients in the dilated group. There was no difference between the two groups with respect to age, sex, location of stricture, or histology of cancer (Table 1). There were no procedure-related complications in either group.

15 of the 55 patients had distant metastases present at the time of EUS, 9 in the dilated group and 6 in the nondilated group (P = 0.13). In these 15 patients, EUS was done on the same day or within the same week as the CT or PET that detected the distant metastases. The remaining 40 patients had no distant metastases at the time of the pretreatment staging EUS. Of these 40 remaining patients, 14 required dilation at the time of the staging EUS and 26 did not undergo dilation at the time of staging EUS. These 40 patients formed the basis for the study’s comparison.

Of these 40 patients who had no evidence of metastatic disease at the time of original staging, 10 of 14 (71%) in the dilated group and 11 of 26 (46%) in the nondilated group went on to develop metastases at any point during a mean followup of 20 months (range 1–125) (P = 0.19) (Figure 1). Metastases were detected at a median of 10 months (range 1–54) after EUS in the dilated group and 10 months after EUS in the nondilated group (range 1–125). Metastases were identified in a variety of locations in both the nondilated group and the dilated group (Table 2).

Patients from the dilated and nondilated groups were further compared to account for similar stage at the time of EUS. All 14 patients in the dilated group and 20 out of 26 patients in the nondilated group had locally advanced disease (defined as T3, N0, M0 or T1-3, N1, M0). Excluding all patients with distant metastases at initial staging, the exact dilated group stages were as follows: T3N1 (N = 8), T2N1 (N = 1), and T3N0 (N = 5); the exact nondilated group stages were as follows: T3N1 (N = 8), T2N1 (N = 5), T1N1 (N = 1), T3N0 (N = 6), T2N0 (N = 1), and T1N0 (N = 5). Among these patients with locally advanced disease, the results were as follows: at both 1 and 3 months after EUS, 2 of

Table 1: Demographics of patients with esophageal cancer who did and did not undergo dilation at the time of staging EUS.

|                      | Dilated group | Nondilated group | P value |
|----------------------|---------------|------------------|---------|
| Total patients       | 23            | 32               |         |
| Men                  | 18            | 29               | 0.26    |
| Women                | 5             | 3                | 0.26    |
| Mean age             | 63            | 64               |         |
| Adenocarcinoma       | 16            | 27               | 0.21    |
| Squamous cell carcinoma | 7           | 5                | 0.21    |
| Cervical esophagus stricture | 2   | 2 | 0.99 |
| Thoracic esophagus stricture | 6   | 10               | 0.77    |
| Gastroesophageal junction stricture | 15 | 20 | 1.0 |
| Metastases present at time of EUS | 9 | 6 | 0.13 |
| Locally advanced disease at time of EUS | 14 | 20 | 1.0 |
Table 2: Location of metastases by time from staging EUS in patients who did and did not undergo dilation at the time of staging EUS.

|                      | Dilated group | Nondilated group |
|----------------------|---------------|------------------|
|                      | 4 patients    | 4 patients       |
| Location of metastases detected at <6 months (total number of occurrences) | Mediastinal lymph nodes (2) | Liver (2) |
|                      |               | Pleural effusion (1) | Peritoneum (2) |
|                      |               | Axillary lymph nodes (1) | Back (1) |
|                      |               | Adrenal gland (1) | |
|                      |               | Gastric lymph nodes (1) | |
|                      | 2 patients    | 5 patients       |
| Location of metastases detected at 6–12 months (total number of occurrences) | Recurrence at GE junction (2) | Liver (3) |
|                      |               | Diffuse bony metastases (1) | Lungs (2) |
|                      |               | Mediastinal lymph nodes (1) | Pleural effusion (2) |
|                      |               | | Peritoneum (1) |
|                      |               | | Recurrence at GE junction (1) |
|                      | 4 patients    | 3 patients       |
| Location of metastases detected at >12 months (total number of occurrences) | Recurrence at GE junction (1) | Liver (1) |
|                      |               | Axillary lymph nodes (1) | Lungs (1) |
|                      |               | Cervical lymph nodes (1) | Abdominal mass (1) |
|                      |               | Neck (1) | |
|                      |               | Mediastinum (1) | |
|                      | 10 patients   | 10 patients      |
| Median time to detection of metastases (range) | (1–54 months) | (1–125 months) |

Figure 1: Development of metastases at any time during a mean followup of 20 months among all patients without metastases present at the time of staging EUS.

14 (14%) in the dilated group had metastases present compared to 2 of 20 (10%) in the nondilated group ($P = 0.19$); at 6 months after EUS, 4 of 14 (28%) in the dilated group and 4 of 20 (20%) in the nondilated group had metastases present ($P = 0.69$); at 12 months after EUS, 6 of 14 (43%) in the dilated group and 8 of 20 (40%) in the nondilated group had metastases present ($P = 1.0$); 10 of 14 (71%) in the dilated group versus 11 of 20 (55%) in the nondilated group went on to develop metastases at any time during a mean followup of 20 months ($P = 0.48$) (Figure 2).

Five-year survival data among all patients, regardless of initial stage, reveal that 1 of 22 patients (4%) in the dilated group was alive at 5-years, compared to 6 of 32 (19%) in the nondilated group ($P = 0.22$). When those with metastases present at initial staging are excluded, the 5-year survival data is 1 of 14 (7%) in the dilated group, compared to 6 of 26 (23%) in the nondilated group ($P = 0.39$). Among those who had locally advanced disease, the 5-year survival rate is 1 of 14 (7%) in the dilated group, compared to 1 of 20 (5%) in the nondilated group ($P = 1.0$).

4. Discussion

EUS is an essential part of a comprehensive staging workup for esophageal cancer and, when used appropriately in conjunction with CT and/or PET scan, is generally considered
the need for dilation may be a marker for more advanced or aggressive disease. Thus, these patients may be more likely to develop metastases at an earlier time regardless of dilation.

Because of this observation, we evaluated patients in the dilated and nondilated groups to match those with similar staging—locally advanced disease. When these groups were analyzed, we saw no difference in the rates of metastases at any time interval studied (Figure 2). Furthermore, there is no distinct pattern of metastatic spread unique to either group, and no distinct pattern of location of metastases based on the time frame they were detected. There is also no difference in the median time to detection of metastases in either group (Table 2).

Survival data show a nonsignificant trend towards lower survival in the dilated group when we look at all patients regardless of initial staging. A similar nonsignificant trend is also seen among those without distant metastases at initial staging. However, when the dilated and nondilated groups were matched for similar initial staging, locally advanced disease, five-year survival rates were similar.

The possibility remains that dilation results in seeding the bloodstream and metastatic spread of disease in a small number of cases. However, this theory has not been proven in any previous model or study in this particular clinical setting. While limited by the total number of patients, our study appears to refute that dilation of malignant strictures leads to increased rates of metastases. A more likely explanation is simply that the cases of early metastases in each group represent metastases that were present but not detectable at the time of initial staging.

Our study was limited by a small sample size, retrospective nature of the study, and being a single-center experience. The small sample size makes it difficult to draw any definitive conclusions; however, our study provides valuable information about the natural progression of metastases in patients who undergo EUS for staging of esophageal cancer.

EUS provides the most accurate locoregional staging for esophageal cancer, and dilation may often be necessary to complete EUS staging. Dilating malignant strictures in order to complete EUS staging does not clearly lead to a higher rate of metastases.

Conflict of Interests

None of the authors have received funding for this study or have conflict of interests to disclose.

References

[1] J. van Dam, T. W. Rice, M. F. Catalano, T. Kirby, and M. V. Sivak, “High-grade malignant stricture is predictive of esophageal tumor stage: risks of endosonographic evaluation,” *Cancer*, vol. 71, no. 10, pp. 2910–2917, 1993.

[2] G. E. Kallimanis, P. K. Gupta, F. H. Al-Kawas et al., “Endoscopic ultrasound for staging esophageal cancer, with or without dilation, is clinically important and safe,” *Gastrointestinal Endoscopy*, vol. 41, no. 6, pp. 540–546, 1995.
A. Stolier, J. Skinner, and E. A. Levine, "A prospective study of malignant esophageal strictures is safe and effective," *American Journal of Gastroenterology*, vol. 95, no. 10, pp. 2813–2815, 2000.

M. B. Wallace, R. H. Hawes, A. V. Sahai, A. van Velse, and B. J. Hoffman, "Dilation of malignant esophageal stenosis to allow EUS guided fine-needle aspiration: safety and effect on patient management," *Gastrointestinal Endoscopy*, vol. 51, no. 3, pp. 309–313, 2000.

P. R. Pfau, S. B. Perlman, P. Stanko et al., "The role and clinical value of EUS in a multimodality esophageal carcinoma staging program with CT and positron emission tomography," *Gastrointestinal Endoscopy*, vol. 65, no. 3, pp. 377–384, 2007.

G. Blackshaw, W. G. Lewis, A. N. Hopper et al., "Prospective comparison of endosonography, computed tomography, and histopathological stage of junctional oesophagogastric cancer," *Clinical Radiology*, vol. 63, no. 10, pp. 1092–1098, 2008.

M. A. Morgan, C. P. Twine, W. G. Lewis et al., "Prognostic significance of failure to cross esophageal tumors by endoluminal ultrasound," *Diseases of the Esophagus*, vol. 21, no. 6, pp. 508–513, 2008.

P. R. Pfau, G. G. Ginsberg, R. J. Lew, C. M. Brensinger, and M. L. Kochman, "EUS predictors of long-term survival in esophageal carcinoma," *Gastrointestinal Endoscopy*, vol. 53, no. 4, pp. 463–469, 2001.

S. Mallery and J. van Dam, "EUS in the evaluation of esophageal carcinoma," *Gastrointestinal Endoscopy*, vol. 52, no. 6, pp. S6–S11, 2000.

M. F. Catalano, J. van Dam, and M. V. Sivak, "Malignant esophageal strictures: staging accuracy of endoscopic ultrasonography," *Gastrointestinal Endoscopy*, vol. 41, no. 6, pp. 535–539, 1995.

B. C. Jacobson, V. M. Shami, D. O. Faigel et al., "Through-the-scope balloon dilation for endoscopic ultrasound staging of stenosing esophageal cancer," *Digestive Diseases and Sciences*, vol. 52, no. 3, pp. 817–822, 2007.

A. Stolier, J. Skinner, and E. A. Levine, "A prospective study of seeding of the skin after core biopsy of the breast," *American Journal of Surgery*, vol. 180, no. 2, pp. 104–107, 2000.

C. Chao, M. H. Torosian, M. C. Boraas et al., "Local recurrence in the diagnosis of hepatocellular cancer: a systematic review and meta-analysis," *Gut*, vol. 57, no. 11, pp. 1592–1596, 2008.

D. G. Clair, D. B. Lautz, and D. C. Brooks, "Rapid development of umbilical metastases after laparoscopic cholecystectomy for unsuspected gallbladder carcinoma," *Surgery*, vol. 113, no. 3, pp. 355–358, 1993.

C. A. Jacobi, H. Keller, S. Möning, and S. Said, "Implantation metastasis of unsuspected gallbladder carcinoma after laparoscopy," *Surgical Endoscopy*, vol. 9, no. 3, pp. 351–352, 1995.

N. Sakata, M. Suzuki, K. Shibuya, K. Takeda, and S. Matsuno, "Unexpected bile duct carcinoma presenting with port-site metastasis after laparoscopic cholecystectomy for cholecystolithiasis," *Journal of Hepato-Biliary-Pancreatic Surgery*, vol. 9, no. 4, pp. 511–514, 2002.

A. Polychronidis, A. K. Tsaroucha, S. Perente, A. Giatromanolaki, M. Koukourakis, and C. Simopoulos, "Port-site metastasis of extraperitoneal bile duct carcinoma after laparoscopic cholecystectomy without evidence of a primary tumour," *Acta Chirurgica Belgica*, vol. 108, no. 6, pp. 768–770, 2008.

J. K. Karwowski, K. W. Nowels, I. R. McDougall, and R. J. Weigel, "Needle track seeding of papillary thyroid carcinoma from fine needle aspiration biopsy: a case report," *Acta Cytologica*, vol. 46, no. 3, pp. 591–595, 2002.

C. Micames, P. S. Jowell, R. White et al., "Lower frequency of peritoneal carcinomatosis in patients with pancreatic cancer diagnosed by EUS-guided FNA vs. percutaneous FNA," *Gastrointestinal Endoscopy*, vol. 58, no. 5, pp. 690–695, 2003.

S. C. Paquin, G. Gariépy, L. Lepanto, R. Bourdages, G. Raymond, and A. V. Sahai, "A first report of tumor seeding because of EUS-guided FNA of a pancreatic adenocarcinoma," *Gastrointestinal Endoscopy*, vol. 61, no. 4, pp. 610–611, 2005.

A. Basu, S. C. Sistla, N. Siddaraju, S. K. Verma, K. R. Iyengar, and S. Jagdish, "Needle tract sinus following aspiration biopsy of papillary thyroid carcinoma: a case report," *Acta Cytologica*, vol. 52, no. 2, pp. 211–214, 2008.

S. Doi, I. Yasuda, T. Iwashita et al., "Needle tract implantation on the esophageal wall after EUS-guided FNA of metastatic mediastinal lymphadenopathy," *Gastrointestinal Endoscopy*, vol. 67, no. 6, pp. 988–990, 2008.

D. B. Nelson, S. J. Sanderson, and M. M. Azar, "Bacteremia with esophageal dilation," *Gastrointestinal Endoscopy*, vol. 48, no. 6, pp. 563–567, 1998.

G. Zuccaro Jr., J. E. Richter, T. W. Rice et al., "Viridans streptococcal bacteremia after esophageal stricture dilation," *Gastrointestinal Endoscopy*, vol. 48, no. 6, pp. 568–573, 1998.

W. K. Hirotta, G. W. Wortmann, C. L. Maydonovitch et al., "The effect of oral decontamination with clindamycin palmitate on the incidence of bacteremia after esophageal dilation: a prospective trial," *Gastrointestinal Endoscopy*, vol. 50, no. 4, pp. 475–479, 1999.

S. Banerjee, B. Shen, T. H. Baron et al., "Antibiotic prophylaxis for GI endoscopy," *Gastrointestinal Endoscopy*, vol. 67, no. 6, pp. 791–798, 2008.

G. E. Ginsberg and D. E. Fleischer, "Tumors of the esophagus," in Sleisenger & Fordtran’s Gastrointestinal and Liver Disease, M. Feldman, L. S. Friedman, and L. J. Brandt, Eds., pp. 956–961, Saunders Elsevier, Philadelphia, Pa, USA, 8th edition, 2006.

S. R. Puliti, J. B. K. Reddy, M. L. Bechtold, M. R. Antillon, and J. A. Ilbdah, "Accuracy of endoscopic ultrasonography in the diagnosis of distal and celiac axis lymph node metastasis in esophageal cancer: a meta-analysis and systematic review," *Digestive Diseases and Sciences*, vol. 53, no. 9, pp. 2405–2414, 2008.
[33] J. G. Moreno, S. M. O’Hara, J. P. Long et al., “Transrectal ultrasound-guided biopsy causes hematogenous dissemination of prostate cells as determined by RT-PCR,” *Urology*, vol. 49, no. 4, pp. 515–520, 1997.

[34] M. Louha, K. Poussin, N. Ganne et al., “Spontaneous and iatrogenic spreading of liver-derived cells into peripheral blood of patients with primary liver cancer,” *Hepatology*, vol. 26, no. 4, pp. 998–1005, 1997.