

# Epidemiology and Biology of Esophageal Cancer

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## ABSTRACT

In the United States and other Western countries, there has been a remarkable change in the epidemiology of esophageal cancer over the past 50 years. Adenocarcinoma of the esophagus and gastroesophageal junction has replaced squamous cell as the most common type of esophageal cancer in the United States, and the incidence of esophageal adenocarcinoma is increasing faster than that of any other malignancy. Risk factors include gastroesophageal reflux disease and obesity. The increasing incidence of esophageal adenocarcinoma and a greater understanding of its underlying biology provide opportunities to devise treatment strategies that maximize survival and minimize morbidity. However, rational use of available endoscopic procedures, esophagectomy, and chemotherapy and radiotherapy requires a comprehensive understanding of the disease.

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## OVERVIEW OF THE SCOPE OF THE PROBLEM

Worldwide, esophageal cancer is a significant and increasing health problem. In 2005, there were 497,700 new cases, and the prevalence is expected to increase by approximately 140% by 2025.<sup>1</sup> It also remains a deadly disease, with 416,500 people estimated to have died from esophageal cancer in 2005. Of the two major types, squamous cell is most common worldwide, but in the United States and many Western countries, adenocarcinoma has surpassed squamous cell to become the most prevalent form of esophageal cancer. In one of the most dramatic epidemiologic shifts ever recorded, esophageal adenocarcinoma has gone from a disease that was not thought to exist until the 1950s, to the fastest increasing cancer in America in the 2000s.<sup>2–4</sup> From 1975 to 2000, the relative rates of most common cancers including breast, colon, and lung remained stable or decreased in the United States. There were increases in both prostate cancer and melanoma, but these pale in comparison to the six-fold increase in esophageal adenocarcinoma incidence during that same period.<sup>5</sup> The latest Surveillance Epidemiology and End Results (SEER) statistics indicate that this alarming increase is continuing in the United States, with a more than 460% increase in incidence in white

males from 1975 to 2004.<sup>4</sup> The increase has been noted in white females also—at a rate of 335% over the same period.<sup>4</sup> The rising incidence is occurring across all disease stages and all age groups, but the greatest increase (> 600%) is in men over 65 years old. Most cases are diagnosed in white males, but Hispanic, Japanese, Chinese, and African-American people also get esophageal cancer.<sup>1</sup> In the US in 2008, it is projected that 16,470 new patients will be diagnosed with esophageal cancer, and more than 50% of cases will be adenocarcinoma.<sup>4</sup> A similar trend has been reported in other Western countries including the Netherlands.<sup>6</sup> The United Kingdom has the highest incidence of esophageal adenocarcinoma globally, at 7 cases per 100,000 population.<sup>7,8</sup> By comparison, the average incidence in the US is 2.5 per 100,000, although in some regions the incidence in white males is as high as 5.3 per 100,000.<sup>7,9,10</sup> These numbers do not include adenocarcinoma of the gastroesophageal junction (GEJ), which many believe represents esophageal cancer in most patients.

## ADENOCARCINOMA OF THE DISTAL ESOPHAGUS VS. GE JUNCTION

The incidence of adenocarcinoma of the cardia or GEJ has also increased signifi-

cantly since the mid 1970s.<sup>11</sup> However, the average rate stabilized in the US after the late 1980s and perhaps is beginning to decline slightly.<sup>9</sup> The incidence of adenocarcinoma of the GEJ is greatest in white males, as seen in esophageal adenocarcinoma; but unlike esophageal adenocarcinoma, the incidence does not differ significantly between white and African American females and is similar in African Americans and Asians. Further, the rate of adenocarcinoma of the GEJ is double that of esophageal adenocarcinoma in these groups.<sup>10,12</sup> The overall incidence of adenocarcinoma of the GEJ (3.1 per 100,000) previously exceeded that of esophageal adenocarcinoma in the US, but the most recent data indicate that esophageal adenocarcinoma incidence has surpassed that of adenocarcinoma of the cardia.<sup>5,9</sup>

## ETIOLOGY OF ESOPHAGEAL AND GEJ ADENOCARCINOMA

The etiologies of adenocarcinoma of the esophagus and squamous cell cancer are different. While squamous cancer is associated with alcohol and tobacco use,

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esophageal adenocarcinoma develops as a consequence of gastroesophageal reflux disease.<sup>13</sup> There is some association with the use of medications that reduce the lower esophageal sphincter pressure (and worsen reflux), use of acid suppression medications, and obesity, but gastroesophageal reflux remains the major culprit.<sup>13-18</sup> The etiology of adenocarcinoma of the GEJ, or cardia, has been investigated as well. Evidence shows that GEJ adenocarcinoma develops from gastroesophageal reflux in some patients and secondary to *Helicobacter pylori* and gastric intestinal metaplasia in others.<sup>19-21</sup> Although Siewert and Stein suggested a classification system that distinguished between adenocarcinoma of the distal esophagus and the gastroesophageal junction,<sup>22</sup> we have shown that the biologic behavior of these tumors is similar and esophagectomy is appropriate therapy for tumors at both locations (S. DeMeester, et al, unpublished data, 2009).

The increasing incidence of esophageal adenocarcinoma in combination with routine endoscopic surveillance in patients with the precursor lesion for this cancer, Barrett's esophagus, has led to the detection of high-grade dysplasia and early-stage adenocarcinoma in an increasing number of patients. The progression of Barrett's esophagus through dysplasia to invasive adenocarcinoma is a complex process that even today remains incompletely understood. Despite years of investigation and the investment of large sums of research dollars, we remain unable to predict with certainty which patients are most likely to progress to cancer. The best studied and validated markers are the presence and degree of histologic dysplasia and aneuploidy or abnormal cell DNA, yet even these are imperfect. Dysplasia, particularly low-grade dysplasia, is subject to substantial intra- and inter-observer variation among pathologists. While there is less variation in the pathologic interpretation of high-grade dysplasia, Schnell et al and others have suggested a low rate of progression to cancer once an incident cancer has been carefully excluded, while others report progression to cancer in approximately 10% of patients a year.<sup>23,24</sup> In surgical series, intramucosal cancers have been reported in approximately 30% of

resected esophagi thought to have only high-grade dysplasia based on thorough preoperative endoscopic biopsies.<sup>25,26</sup> Additional factors that participate in the complexity of this condition include whether the dysplasia is unifocal or multifocal and the length of the Barrett's.

### **BIOLOGY OF ESOPHAGEAL ADENOCARCINOMA**

Recently, the biology of esophageal adenocarcinoma has become better understood. Once believed to be systemic at the time of diagnosis, it is now clear that esophageal cancer follows a pattern more consistent with other gastrointestinal cancers where lymphatic metastases precede systemic disease in most patients. Clear evidence for this comes from studies demonstrating that intramucosal cancer is curable in nearly all patients and is associated with a low prevalence of lymph node metastases.<sup>27-29</sup> We recently showed that survival was excellent and equivalent for patients with intramucosal adenocarcinoma whether they were treated with an esophagectomy with extensive lymphadenectomy or a less morbid vagal-sparing procedure in which no or few lymph nodes were resected.<sup>30</sup> Until recently, cure of these lesions was reliably accomplished only with esophagectomy, but new technologies now allow endoscopic therapy with esophageal preservation in appropriate patients. Data from Pech and colleagues show excellent survival for patients with intramucosal adenocarcinoma treated with endoscopic resection and/or mucosal ablation without esophagectomy.<sup>31</sup>

### **STAGING ESOPHAGEAL CANCER**

Endoscopic ultrasound (EUS) is the best method for local/regional staging of esophageal adenocarcinoma. Standard 7.5 and 12 MHz endoscopic ultrasound probes can accurately assess the depth of invasion once the tumor has gone through the submucosa, and also provide information on the presence of abnormal or enlarged lymph nodes. However, neither the standard probes nor newer high-resolution 20 MHz probes are able to accurately distinguish intramucosal from submucosal tumor invasion.<sup>32</sup> Currently, endoscopic

mucosal resection (EMR) is the only method that accurately and reliably determines the depth of invasion of a small visible lesion. EMR excises a disc of esophageal (or gastric) wall down to the muscularis propria and provides a specimen for histologic review that includes both mucosa and submucosa. In this way, EMR can reliably determine the "T" stage of early esophageal lesions.<sup>33</sup> Other standard staging studies include computed tomography (CT) scans of the chest and abdomen; positron emission tomography (PET) scans are increasingly being used, although the added value over CT and EUS remains unclear.<sup>34-36</sup>

### **LYMPH NODES AND TYPE OF RESECTION FOR ESOPHAGEAL ADENOCARCINOMA**

Evidence clearly shows that the depth of tumor invasion predicts the risk of lymph node metastases, but the presence and extent of lymph node involvement is the major determinant of survival in patients with esophageal adenocarcinoma. The risk of lymph node involvement increases from a low 2% to 4% for intramucosal tumors to 30% for submucosal tumor invasion and more than 80% with intramural and transmural invasion.<sup>29,37-39</sup> While systemic disease is rare in patients without an involved lymph node, it becomes nearly universal once more than eight lymph nodes are involved.<sup>40</sup> Consequently, an extensive lymphadenectomy as part of esophagectomy for patients with adenocarcinoma is only useful in the subgroup with  $\leq 8$  involved nodes. On the other hand, data from both retrospective and prospective studies have shown that survival in these patients is improved with the systematic lymphadenectomy that accompanies an en bloc resection compared to a transhiatal esophagectomy.<sup>40,41</sup> Further, single-center and multi-center Surveillance Epidemiology and End Results (SEER) data analysis has shown that survival improves with increasing numbers of resected nodes, even in node-negative patients.<sup>42-44</sup> These studies support the use of an en bloc esophagectomy as the preferred surgical therapy for esophageal adenocarcinoma, and numerous series have shown 40% to 50% rates of overall long-term survival for

patients undergoing this procedure.<sup>45-47</sup>

## NEOADJUVANT THERAPY FOR ESOPHAGEAL ADENOCARCINOMA

In an attempt to improve survival for patients with esophageal cancer, Walsh and colleagues studied use of preoperative chemoradiotherapy, results of which, published in 1996, showed a survival advantage for neoadjuvant treatment.<sup>48</sup> These findings changed the management approach for many esophageal cancer patients. While the trial has been criticized for poor staging, unusual exclusions in the multimodal therapy arm, and very poor survival in the surgery arm, the biggest concern is the inaccurate survival curves from which the improved survival was calculated.<sup>19,49</sup> Further, every other randomized trial, with the exception of a recently reported trial that closed prematurely due to poor recruitment, found no survival difference for patients treated with surgery alone vs. neoadjuvant chemoradiotherapy followed by surgery.<sup>19,50</sup> What was demonstrated is that use of neoadjuvant therapy reduced risk of local-regional recurrence; however, this applied primarily to patients who had an inferior transhiatal resection, which is associated with higher local-regional recurrence rates than en bloc resection.<sup>46,47,51-55</sup>

The benefit of an en bloc resection is also seen after neoadjuvant therapy, even in patients with residual disease, a group often dismissed as being incurable. We reported absolute 5-year survival rates of 35% for those undergoing en bloc resection vs. no survivors with transhiatal resection for patients with residual disease after neoadjuvant treatment.<sup>56</sup> These results support the use of an en bloc esophagectomy after neoadjuvant therapy, even in the setting of residual disease.

The application of neoadjuvant chemoradiotherapy has not been associated with a reduction in systemic disease.<sup>51</sup> Improvements in chemotherapy are sorely needed to control the systemic component of disease in patients treated optimally for their local-regional disease by en bloc esophagectomy.

## CONCLUSIONS

There has been an alarming increase in

the incidence of esophageal adenocarcinoma. Reasons for this increase are unclear, but it is related to gastroesophageal reflux disease and Barrett's esophagus. Through careful surveillance endoscopy, an increasing number of patients are being diagnosed with high-grade dysplasia or intramucosal adenocarcinoma, which are potentially curable in the majority of patients. The major determinant of survival in patients diagnosed with esophageal cancer is the presence and number of lymph node metastases. Patients with more than nine involved nodes almost always have systemic disease, and there is limited evidence for efficacy of chemotherapy in reducing risk of death in these patients. The increasing incidence of esophageal cancer should lead to more studies of optimal management strategies. Prevention should also be a focus of research and educational efforts. It is also hoped that the application of ablation techniques for dysplastic Barrett's mucosa will alter the natural history of this disease.

## REFERENCES

- Lambert R, Hainaut P: The multidisciplinary management of gastrointestinal cancer. *Epidemiology of oesophagogastric cancer. Baillieres Best Pract Res Clin Gastroenterol* 21:921-945, 2007
- Armstrong RA, Blalock JB, Carrera G: Adenocarcinoma of the middle third of the esophagus arising from ectopic gastric mucosa. *J Thoracic Surg* 37:398-403, 1959
- Hewlett A: The superficial glands of the esophagus. *J Exp Med* 5:319-331, 1900
- Brown LM, Devesa SS, Chow W-H: Incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, and age. *J Natl Cancer Inst* 100:1184-1187, 2008
- Pohl H, Welch HG: The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst* 97:142-146, 2005
- Crane LM, Schaapveld M, Visser O, et al: Oesophageal cancer in the Netherlands: Increasing incidence and mortality but improving survival. *Eur J Cancer* 43:1445-1451, 2007
- Bollschweiler E, Wolfgarten E, Gutschow C, et al: Demographic variations in the rising incidence of esophageal adenocarcinoma in white males. *Cancer* 92:549-555, 2001
- Botterweck AA, Schouten LJ, Volovics A, et al: Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries. *Int J Epidemiol* 29:645-654, 2000
- El-Serag HB, Mason AC, Petersen N, et al: Epidemiological differences between adenocarcinoma of the oesophagus and adenocarcinoma of the gastric cardia in the USA. *Gut* 50:368-372, 2002

- Kubo A, Corley DA: Marked regional variation in adenocarcinomas of the esophagus and the gastric cardia in the United States. *Cancer* 95:2096-2102, 2002
- Cameron AJ: Epidemiology of Barrett's esophagus and adenocarcinoma. *Dis of Esoph* 15: 106-108, 2002
- Kubo A, Corley DA: Marked multi-ethnic variation of esophageal and gastric cardia carcinomas within the United States. *Am J Gastroenterol* 99:582-588, 2004
- Lagergren J, Bergstrom R, Lindgren A, et al: Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 340:825-831, 1999
- Lagergren J, Bergstrom R, Adami HO, et al: Association between medications that relax the lower esophageal sphincter and risk for esophageal adenocarcinoma. *Ann Intern Med* 133:165-175, 2000
- Garcia Rodriguez LA, Lagergren J, Lindblad M: Gastric acid suppression and risk of oesophageal and gastric adenocarcinoma: a nested case control study in the UK. *Gut* 55:1538-1544, 2006
- Lagergren J, Bergstrom R, Lindgren A, et al: The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia. *Int J Cancer* 85:340-346, 2000
- Nilsson M, Johnsen R, Ye W, et al: Obesity and estrogen as risk factors for gastroesophageal reflux symptoms. *J Am Med Assoc* 290:66-72, 2003
- Merry AH, Schouten LJ, Goldbohm RA, et al: Body mass index, height and risk of adenocarcinoma of the oesophagus and gastric cardia: a prospective cohort study. *Gut* 56:1503-1511, 2007
- DeMeester SR: Adenocarcinoma of the esophagus and cardia: a review of the disease and its treatment. *Ann Surg Oncol* 13:12-30, 2006
- Balaji NS, DeMeester SR, Wickramasinghe K, et al: Etiology of intestinal metaplasia at the gastroesophageal junction: reflux, *H. pylori* infection, or both? *Surg Endosc* 17:43-48, 2003
- Derakhshan MH, Malekzadeh R, Watabe H, et al: Combination of gastric atrophy, reflux symptoms and histologic subtype indicates two distinct aetiologies of gastric cardia cancer. *Gut* 57:298-305, 2008
- Siewert JR, Stein HJ: Classification of adenocarcinoma of the esophagogastric junction. *Br J Surg* 85:1457-1459, 1998
- Schnell TG, Sontag SJ, Chejfec G, et al: Long-term nonsurgical management of Barrett's esophagus with high-grade dysplasia. *Gastroenterology* 120:1607-1619, 2001
- Reid BJ, Haggitt RC, Rubin CE, et al: Barrett's esophagus. Correlation between flow cytometry and histology in detection of patients at risk for adenocarcinoma. *Gastroenterology* 93:1-11, 1987
- Nigro JJ, Hagen JA, DeMeester TR, et al: Occult esophageal adenocarcinoma: extent of disease and implications for effective therapy. *Ann Surg* 230:433-440, 1999
- Dar MS, Goldblum JR, Rice TW, et al: Can extent of high grade dysplasia in Barrett's oesophagus predict the presence of adenocarcinoma at oesophagectomy? *Gut* 52:486-489, 2003

27. Oh DS, Hagen JA, Chandrasoma PT, et al: Clinical biology and surgical therapy of intramucosal adenocarcinoma of the esophagus. *J Am Coll Surg* 203:152–161, 2006
28. Rice TW, Blackstone EH, Goldblum JR, et al: Superficial adenocarcinoma of the esophagus. *J Thorac Cardiovasc Surg* 122:1077–1090, 2001
29. Stein HJ, Feith M, Bruecher BL, et al: Early esophageal cancer: pattern of lymphatic spread and prognostic factors for long-term survival after surgical resection. *Ann Surg* 242:566–573; discussion 573–575, 2005
30. Peyre CG, DeMeester SR, Rizzetto, C, et al: Vagal-sparing esophagectomy: The ideal operation for intramucosal adenocarcinoma and Barrett with high-grade dysplasia. *Ann Surg* 246:665–674, 2007
31. Pech O, Behrens A, May A, et al: Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. *Gut* 57:1200–1206, 2008
32. May A, Gunter E, Roth F, et al: Accuracy of staging in early esophageal cancer using high resolution endoscopy and high resolution endosonography: a comparative, prospective, and blinded trial. *Gut* 53:634–640, 2004
33. Maish MS, DeMeester SR: Endoscopic mucosal resection as a staging technique to determine the depth of invasion of esophageal adenocarcinoma. *Ann Thorac Surg* 78:1777–1782, 2004
34. Wallace MB, Nietert PJ, Earle C, et al: An analysis of multiple staging management strategies for carcinoma of the esophagus: computed tomography, endoscopic ultrasound, positron emission tomography, and thoracoscopy/laparoscopy. *Ann Thorac Surg* 74:1026–1032, 2002
35. Flamen P, Lerut A, Van Cutsem E, et al: Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. *J Clin Oncol* 18:3202–3210, 2000
36. 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* 133:738–745, 2007
37. Nigro JJ, Hagen JA, DeMeester TR, et al: Prevalence and location of nodal metastases in distal esophageal adenocarcinoma confined to the wall: implications for therapy. *J Thorac Cardiovasc Surg* 117:16–23; discussion 25, 1999
38. Nigro JJ, DeMeester SR, Hagen JA, et al: Node status in transmural esophageal adenocarcinoma and outcome after en bloc esophagectomy. *J Thorac Cardiovasc Surg* 117:960–968, 1999
39. Rice TW, Zuccaro G Jr, Adelstein DJ, et al: Esophageal carcinoma: depth of tumor invasion is predictive of regional lymph node status. *Ann Thoracic Surg* 65:787–792, 1998
40. Johansson J, DeMeester TR, Hagen JA, et al: En bloc vs transhiatal esophagectomy for stage T3 N1 adenocarcinoma of the distal esophagus. *Arch Surg* 139:627–631; discussion 31–33, 2004
41. Omloo JMT, Lagarde SM, Hulscher JB, et al: Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. *Ann Surg* 246:992–1000, 2007
42. Altorki NK, Zhou XK, Stiles B: Total number of resected lymph nodes predicts survival in esophageal cancer. *Ann Surg* 248:221–226, 2008
43. Schwarz RE, Smith DD: Clinical impact of lymphadenectomy extent in resectable esophageal cancer. *J Gastrointest Surg* 11:1384–1393, 2007
44. Greenstein AJ, Little VR, Swanson SJ, et al: Effect of the number of lymph nodes sampled on postoperative survival of lymph node-negative esophageal cancer. *Cancer* 112:1239–1246, 2008
45. Hagen JA, DeMeester SR, Peters JH, et al: Curative resection for esophageal adenocarcinoma: analysis of 100 en bloc esophagectomies. *Ann Surg* 234:520–530; discussion 30–31, 2001
46. Altorki NK, Girardi L, Skinner DB: En bloc esophagectomy improves survival for stage III esophageal cancer. *J Thorac Cardiovasc Surg* 114:948–955; discussion 55–56, 1997
47. Lerut T, Coosemans W, Decker G, et al: Extended surgery for cancer of the esophagus and gastroesophageal junction. *J Surg Res* 117:58–63, 2004
48. Walsh TN, Noonan N, Hollywood D, et al: A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. [Erratum appears in *N Engl J Med* 341:384, 1999]. *N Engl J Med* 335:462–427, 1996
49. Walsh T: Correction to a comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med* 341:384, 1999
50. 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* 26:1086–1092, 2008
51. Urba S, Orringer M, Turisi A, et al: Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *J Clin Oncol* 19:305–313, 2001
52. Hulscher JB, van Sandick JW, Tijssen JG, et al: The recurrence pattern of esophageal carcinoma after transhiatal resection. *J Am Coll Surg* 191:143–148, 2000
53. van Sandick JW, van Lanschot JJB, Ten Kate FJ, et al: Indicators of prognosis after transhiatal esophageal resection without thoracotomy for cancer. *J Am Coll Surg* 194:28–36, 2002
54. Collard JM: Exclusive radical surgery for esophageal adenocarcinoma. *Cancer* 91:1098–1104, 2001
55. Altorki N, Skinner D: Should en bloc esophagectomy be the standard of care for esophageal carcinoma? *Ann Surg* 234:581–587, 2001
56. Rizzetto C, DeMeester SR, Hagen JA, et al: En bloc esophagectomy reduces local recurrence and improves survival compared with transhiatal resection after neoadjuvant therapy for esophageal adenocarcinoma. *J Thorac Cardiovasc Surg* 135:1228–1236, 2008

#### Disclosures of Potential Conflicts of Interest

Dr. DeMeester indicated no potential conflicts of interest.