Recurrent Barrett's esophagus and adenocarcinoma after esophagectomy
Herbert C Wolfsen*†, Lois L Hemminger† and Kenneth R DeVault†

Address: Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, Florida, USA
Email: Herbert C Wolfsen* - pdt@mayo.edu; Lois L Hemminger - hemminger.lois@mayo.edu; Kenneth R DeVault - devault.kenneth@mayo.edu
* Corresponding author    †Equal contributors

Abstract
Background: Esophagectomy is considered the gold standard for the treatment of high-grade dysplasia in Barrett's esophagus (BE) and for noninvasive adenocarcinoma (ACA) of the distal esophagus. If all of the metaplastic epithelium is removed, the patient is considered "cured". Despite this, BE has been reported in patients who have previously undergone esophagectomy. It is often debated whether this is "new" BE or the result of an esophagectomy that did not include a sufficiently proximal margin. Our aim was to determine if BE recurred in esophagectomy patients where the entire segment of BE had been removed.

Methods: Records were searched for patients who had undergone esophagectomy for cure at our institution. Records were reviewed for surgical, endoscopic, and histopathologic findings. The patients in whom we have endoscopic follow-up are the subjects of this report.

Results: Since 1995, 45 patients have undergone esophagectomy for cure for Barrett's dysplasia or localized ACA. Thirty-six of these 45 patients underwent endoscopy after surgery including 8/45 patients (18%) with recurrent Barrett's metaplasia or neoplasia after curative resection.

Conclusion: Recurrent Barrett's esophagus or adenocarcinoma after esophagectomy was common in our patients who underwent at least one endoscopy after surgery. This appears to represent the development of metachronous disease after complete resection of esophageal disease. Half of these patients have required subsequent treatment thus far, either repeat surgery or photodynamic therapy. These results support the use of endoscopic surveillance in patients who have undergone "curative" esophagectomy for Barrett's dysplasia or localized cancer.

Background
The incidence of esophageal adenocarcinoma has increased more rapidly than any other form of cancer since the 1970s and now represents the majority of esophageal neoplasms in the West [1]. Barrett's esophagus is the replacement of native squamous mucosa by specialized intestinal metaplasia and is known to be the major risk factor for the development of adenocarcinoma via the metaplasia-dysplasia-neoplasia sequence [2]. Other risk factors for the development of esophageal adenocarcinoma include a lengthy and severe history of gastroesophageal reflux disease (GERD), increased body mass index, male gender and Caucasian race [3-5]. Recent studies, however, have detected Barrett's esophagus in nearly
equal numbers of older white men whether or not they reported GERD symptoms [6,7]. Recommendations, therefore, regarding screening and surveillance of patients at risk for esophageal adenocarcinoma are controversial [2,8].

Detection of dysplastic Barrett’s esophagus or mucosal adenocarcinoma is important because it allows the opportunity to intervene prior to the development of invasive neoplasia. Unfortunately, no medical or surgical GERD treatment has been consistently and convincingly demonstrated to prevent the development of adenocarcinoma [5]. Traditionally, high grade Barrett’s dysplasia and mucosal adenocarcinoma are treated by surgical resection of the esophagus [9]. As endoscopic methods of screening and surveillance have become more widely applied, curative esophagectomy has produced increasing numbers of long-term survivors [10,11]. Coincident with this trend has been the appearance of several reports describing the development of metachronous esophageal adenocarcinoma after undergoing curative esophagectomy for the primary tumor [12,13]. These reports raise questions regarding the role of endoscopic surveillance in these patients. The aim of the current study was to evaluate patients who had undergone complete, presumably curative, esophageal resection for early Barrett’s adenocarcinoma or high grade dysplasia in order to determine how frequently, and over what time period, they developed recurrent Barrett’s esophagus or adenocarcinoma.

Methods
After approval by the Mayo Foundation’s Institutional Review Board for Research, the electronic medical records of Mayo Clinic patients in Jacksonville, Florida, were searched to find all patients who had undergone esophagectomy for cure at the Mayo Clinic surgical facility, St. Luke’s Hospital, Jacksonville, Florida, since 1995. This time period was chosen to coincide with the routine availability and clinical use of pre-operative staging with endosonography in our institution. The records of these patients were reviewed for pre-operative and post-operative staging results including computed tomography and endosonography studies. In addition, endoscopic, surgical studies and histopathological studies were studied. Specifically, the surgical specimens were reviewed to ensure that the esophagectomy specimen, including lymph node sampling, was adequate and the proximal margin was completely free of Barrett’s metaplasia, dysplasia or carcinoma. The patients, in whom we have at least one follow-up endoscopy study, with biopsies obtained for histologic confirmation of mucosal disease, are the subjects of this report. Esophageal disease was staged according to the Tumor-Lymph node-Metastasis (TNM) criteria [14].

Results
Since 1995, 45 patients have undergone esophagectomy for Barrett’s dysplasia or localized adenocarcinoma with curative intent in our institution. At operation, none of these patients were found to have extension of malignant disease to paraesophageal lymph nodes and all esophageal glandular mucosa was resected with only normal squamous mucosa remaining at the proximal surgical margin. Subsequently, 36 of these patients (80%) have undergone endoscopy after surgery including 8/45 patients (18%) who were found to have recurrent Barrett’s glandular mucosa after curative resection and are described in the table.

Open transthoracic esophagectomy (Ivor Lewis procedure) with pyloroplasty was performed in most patients (39/45) including the patients diagnosed with recurrent Barrett’s disease. Five different surgeons performed these operations. Most patients had evidence of gastric stasis (retained food) at endoscopy (30/36; 83%). Anastomotic dilation was performed at endoscopy in 16/36 patients (range of dilation procedures 1–10; median 3). It is possible that patients with anastomotic strictures may be at increased risk of recurrent Barrett’s esophagus because of worse reflux although their swallowing symptoms may, alternatively, be related to other factors such as anastomotic ischemia or surgical sutures. Patients frequently used aspirin (42%) or COX-2 specific non-steroidal anti-inflammatory agents (25%). Twice-daily proton pump inhibitors were routinely prescribed for these patients although patient compliance is difficult to assess because of high drug costs and limited symptomatic improvement. While the small number of patients limits our analysis, these factors were found to occur in a proportional number of patients with Barrett’s disease and no clear trends could be identified.

Five of these patients have been diagnosed with Barrett’s metaplasia or low-grade dysplasia have been followed for more than 12 months in surveillance endoscopy programs monitoring the stability of the glandular epithelium. Two of these 5 patients have been found to have short segment Barrett’s metaplasia with lengths of 10 mm and 15 mm, after complete esophageal resection for Barrett’s high-grade dysplasia in a 72-year-old man and Barrett’s adenocarcinoma $T_3N_0M_0$ in a 78-year-old man. This metaplastic glandular epithelium was detected at a follow up of 90 months and 17 months, respectively. In the other 3 patients, short segment Barrett’s low-grade dysplasia has been found in lengths between 10–25 mm after complete resection of the esophagus for Barrett’s high-grade dysplasia (1 patient) and Barrett’s $T_1N_0M_0$ carcinoma (2 patients). This recurrent Barrett’s glandular dysplasia was detected at a follow up of 42–47 months. Erosive esophagitis was also noted in 4 of 5 patients indicating...
uncontrolled reflux disease. Subsequently all patients have been treated with high doses of proton pump inhibitors (such as esomeprazole 80 mg twice a day or 40 mg three or four times per day) in an attempt to maximally control reflux of acid and digestive juices from the stomach into the cervical esophagus.

Three other patients developed recurrent Barrett’s disease after curative resection of esophageal T2 or T3N0M0 adenocarcinoma. These patients varied in age from 58–80 years of age. These patients were found to have more severe erosive esophagitis suggesting worse acid reflux and mucosal injury compared to the non-carcinoma recurrent Barrett’s patients. Recurrent Barrett’s multi-focal high-grade dysplasia, over a 10 mm segment length was detected 88 months after esophagectomy in one patient and was successfully ablated with porfimer sodium photodynamic therapy using the methods described elsewhere [15]. High-grade dysplasia with features of invasive adenocarcinoma was noted in a 20 mm Barrett’s segment diagnosed 18 months after esophageal resection in another patient. Endosonography detected focal mucosal expansion and the Barrett’s mucosal adenocarcinoma T1N0M0 was confirmed at repeat esophagectomy. Finally, a diminutive polypoid mass proximal to the surgical anastomosis was found in a 58-year-old woman who had 7 months previously undergone esophagectomy for Barrett’s mucosal adenocarcinoma. Computed tomography with contrast enhancement noted esophageal wall thickening and suspicious lymphadenopathy. Repeat resection confirmed the tumor histologic grade of T1N0M0 adenocarcinoma.

**Discussion**

Over the past four decades, the incidence of esophageal adenocarcinoma has risen dramatically, particularly in older white men [16]. Previous studies have documented the association of esophageal cancer with the severity and duration of gastroesophageal reflux [3]. The most important risk factor for the development of esophageal adenocarcinoma, however, is the development of specialized intestinal metaplasia in the lower esophagus (Barrett’s esophagus) [5]. It is recommended that patients with Barrett’s mucosa undergo periodic surveillance endoscopy with systematic biopsies to detect the presence of cancerous or pre-cancerous changes (dysplasia or neoplasia) [2]. In these patients, especially, Barrett’s adenocarcinoma or high-grade dysplasia is found at an early stage when it is increasingly possible to undergo esophagectomy with curative intent [17].

After undergoing esophageal resection, the native squamous mucosa of the cervical esophagus will be brought into contact with the acid-secreting mucosa of the gastric body. This reconstruction allows acid and duodenal juice to reflux from the gastric conduit to the remaining cervical esophagus. Reflux of gastric and duodenal content is an important factor in the pathogenesis of Barrett’s metaplasia, dysplasia and esophageal adenocarcinoma [18-20]. It is well known that recurrent Barrett’s glandular mucosa is frequently found in the cervical esophagus after esophageal resection [21-23]. Recently, Oberg et al performed endoscopy, esophageal manometry and ambulatory pH studies in 32 patients who had undergone esophagectomy for a variety of diagnoses including 16 patients (50%) with adenocarcinoma associated with Barrett’s metaplasia [24]. These studies were performed between 3–10 years after the surgery and most of the patients (70%) were receiving at least once daily proton pump inhibitor therapy for chronic reflux symptoms. At endoscopy, Barrett’s glandular mucosa was histologically documented in 15 patients (47%) ranging in segment lengths from 0.5–4.0 cm. Importantly, recurrent Barrett’s glandular mucosa was significantly more likely to occur in patients with a preoperative diagnosis of Barrett’s epithelium suggesting that

---

Table 1: Recurrent Barrett’s Disease after Esophagectomy with Curative Intent

| Pre-operative diagnosis | Sex | Age | F/u diagnosis | Time to F/U | Tx          |
|-------------------------|-----|-----|--------------|------------|-------------|
| Barrett’s T3 N0 ACA    | F   | 58  | Barrett’s T1 | 7 mos      | Surgery     |
| Barrett’s T3 N0 ACA    | F   | 64  | Barrett’s LGD| 42 mos     | PPI         |
| Barrett’s T3 N0 ACA    | F   | 64  | Barrett’s LGD| 42 mos     | PPI         |
| Barrett’s HGD          | M   | 64  | Barrett’s LGD| 47 mos     | PPI         |
| Barrett’s HGD          | M   | 72  | Barrett’s Mecaplasia | 90 mos | PPI         |
| Barrett’s T3 N0 ACA    | M   | 69  | Barrett’s T1 N0 | 18 mos | Surgery     |
| Barrett’s T2 N0 ACA    | M   | 78  | Barrett’s mecaplasia | 17 mos | PPI         |
| Barrett’s T2 N0 ACA    | M   | 80  | BE+HGD       | 88 mos     | PDT         |

ACA = Adenocarcinoma  
HGD = High-grade dysplasia  
LGD = Low-grade dysplasia  
PDT = Photodynamic therapy  
PPI = Proton pump inhibitor medical therapy
the esophageal mucosa of these patients may be pathoge-
netically predisposed to develop metaplastic changes in
response to gastroesophageal reflux.

In the study of Oberg et al, despite the use of potent acid-
suppressing medications, severe esophageal acid exposure
was noted in most patients. Patients with recurrent Bar-
rett's epithelium were found to have significantly more
severe acid exposure that occurred predominantly in the
supine position [25]. There was also a direct correlation
between the length of the metaplastic segment and the
severity of acid reflux. Similar findings were reported by
da Rocha et al., who studied 48 patients after esophagec-
tomy where 4 of these patients (8%) were found to have
pathological changes of Barrett's metaplasia in the cervical
esophageal stump [26]. In both of these studies, the
authors concluded that the finding of recurrent Barrett's
esophagus was related to reflux esophagitis that resulted
from the action of acid-peptic and biliary secretions. These
studies, however, did not detect dysplasia or neo-
plasia and did not address the issue of metachronous can-
cers and the role of endoscopic surveillance for these
patients.

Murata and colleagues recently reported the diagnosis of
metachronous squamous cell carcinomas in five of 253
patients (2%) who had undergone esophagectomy for
thoracic esophageal squamous cell carcinoma more than
two years previously. These superficial carcinomas (T1n or
T1) were detected at surveillance endoscopy and were
treated with endoscopic laser ablation, mucosal resection
or surgical resection. While squamous cell carcinomas are
not related to gastrointestinal reflux, this paper also sug-
gests that esophageal cancer patients (squamous or aden-
ocarcinoma) are predisposed to the development of
metachronous cancers in the remnant cervical esophagus. This is consistent with DeMeester's experi-
mental model of Barrett's dysplasia and adenocarcinoma
occurring after complete gastrectomy with esophago-jeju-
nostomy and reflux of bile and digestive enzymes into the
cervical esophagus [27]. Also, it is likely that these patients
had other important risk factors, such as tobacco and alco-
hol use, that predispose to both squamous and adenocar-
cinomas [5].

Konishi et al reported finding an adenocarcinoma in Bar-
rett's esophagus following a total resection of the gastric
remnant in a 52-year-old man who had undergone distal
gastrectomy for gastric cancer nearly twenty years previ-
ously [28]. The Barrett's mucosa associated with the aden-
ocarcinoma contained high grade dysplasia supporting
the acquired theory of pathogenesis for Barrett's esopha-
gus that suggests that reflux esophagitis after gastrectomy
may result in the dysplasia-carcinoma sequence. In addi-
tion, Streitz et al retrospectively reviewed long-term survi-
vors after esophagectomy for adenocarcinoma [13]. With
a follow-up as long as 14 years, they found 4 patients who
subsequently were diagnosed with esophageal adenocar-
cinoma. However, the time period between the develop-
ment of the first and second tumors was not specified
making it not possible to determine if these were recurrent
tumors or new, metachronous lesions. Finally, Riben et al
have reported the development of a secondary Barrett's
adenocarcinoma in a patient who had 19 years previously
undergone esophagectomy for a stage IIB Barrett's adeno-
carcinoma [12].

These studies have demonstrated that the cervical esopha-
gus is exposed to high amounts of acid and refluxate
despite the use of proton inhibitor medications and often
in the absence of severe reflux symptoms. Although our
group of patients has been observed for only a median of
2 years after esophagectomy, our study confirms that the
development of metaplastic columnar mucosa in the cer-
vical esophagus is a common complication related to
reflux associated injury to the squamous epithelium. Fur-
ther, our findings suggest that this recurrent glandular
mucosa is unstable and predisposed to the development
doysplasia and invasive carcinoma, as has already devel-
oped in most of patients.

The early detection of this recurrent disease remains
vitally important to preserve all possible treatment
options including surveillance endoscopy follow-up,
endoscopic ablation with porfimer sodium photody-
namic therapy, and if necessary repeat esophagus resec-
tion surgery. Our specific recommendations include
surveillance endoscopy every 6–12 months for patients
who have undergone "curative" esophagectomy for Bar-
rett's dysplasia or adenocarcinoma. In addition, we also
routinely recommend indefinite use of proton pump
inhibitors, regardless of symptom status, starting at twice
daily dosing and increasing as necessary to control reflux
symptoms and mucosal damage due to acid, bile and
gastrointestinal enzymes. Whether these drug doses should
be titrated based on ambulatory pH and impedance test
results remains to be determined. We have generally been
disappointed by prokinetic agents such as metoclopro-
mide in improving reflux symptoms in these patients. For
esophagectomy patients who develop recurrent Barrett's
metaplasia we recommend the use of COX-2 inhibitors or
aspirin chemoprevention to protect against the develop-
ment of metachronous Barrett's carcinoma. [29,30].

**Competing interests**
None declared.

**Author's contributions**
All authors participated in the study design and coordina-
tion as well as case collection and review of histopatho-
logic and endoscopic results. All authors read and approved the final manuscript.

References

1. Shaheen N, Ransohoff DF: Gastroesophageal reflux, Barrett esophagus, and esophageal cancer: scientific review. JAMA 2002, 287:1972-1981.

2. Sampliner RE: Updated guidelines for the diagnosis, surveillance, and therapy of Barrett’s esophagus. Am J Gastroenterol 2002, 97:1888-1899.

3. Lagergren J, Bergstrom R, Lindgren A, Nyren O: Symptomatic gastroesophageal reflux as a risk factor for symptomatic adenocarcinoma. N Engl J Med 1999, 340:825-831.

4. Lagergren J, Sampliner R, Adams HO, Nyren O: Association between medications that relax the lower esophageal sphincter and risk for esophageal adenocarcinoma. Ann Intern Med 2000, 133:165-175.

5. Spechler SJ: Clinical practice. Barrett’s Esophagus. N Engl J Med 2002, 346:836-842.

6. Germon LB, Shetler K, Triadafilopoulos G: Prevalence of Barrett’s esophagus in asymptomatic individuals. Gastroenterology 2002, 123:461-467.

7. Ward EM, Devault KR, Wolfsen HC, Loeb DS, Krishna M, Woodward TA, Hemminger LL, Cayer FK, Achem SR: Barrett’s esophagus in unscreened, older patients undergoing screening or follow-up colonoscopy [Abstract]. Gastroenterology 2003, 124:A-642.

8. Inadomi JM, Sampliner R, Lagergren J, Lieberman D, Hendrick AM, Vakil N: Screening and surveillance for Barrett esophagus in high-risk groups: a cost-utility analysis. Ann Intern Med 2003, 138:176-186.

9. Edwards MJ, Gable DR, Lentsch AB, Richardson JD: The rationale for endoscopy as the optimal therapy for Barrett’s esophagus with high-grade dysplasia. Ann Surg 1996, 223:585-589, discussion 589-591.

10. 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, 122:1077-1090.

11. Ormsby AH, Petras RE, Henricks WH, Rice TW, Rybicki LA, Richter JE, Goldblum JR: Observer variation in the diagnosis of superficial oesophageal adenocarcinoma. Gut 2002, 51:671-676.

12. Ikem M, Ilves R, McKenna BJ: Second primary Barrett’s adenocarcinoma after 19 years. Ann Thorac Surg 1999, 67:1796-1798.

13. Streitz JM Jr, Ellis FH Jr, Gibb SP, Baloqh K, Watkins E Jr: Adenocarcinoma in Barrett’s esophagus. A clinicopathologic study of 65 cases. Ann Surg 1991, 213:122-125.

14. Rice TW, Blackstone EH, Rybicki LA, Adelstein DJ, Murthy SC, DeCamp MM, Goldblum JR: Refining esophageal cancer staging. J Thorac Cardiovasc Surg 2003, 125:110-1113.

15. Wolfsen HC, Woodward TA, Raimondo M: Photodynamic therapy for dysplastic Barrett esophagus and early esophageal adenocarcinoma. Mayo Clin Proc 2002, 77:1176-1181.

16. Devesa SS, Bove WL, Fraumeni Jr: Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer 1998, 83:2049-2053.

17. Schroder W, Gutschow C, Holshcer A: Limited resection for early esophageal cancer? Langenbecks Arch Surg 2003, 388:88-94.

18. Oberg S, Peters JH, DeMeester TR, Lord RV, Johansson J, DeMeester SR, Hagen JA: Determinants of intestinal metaplasia within the columnar-lined esophagus. Arch Surg 2000, 135:651-655, discussion 655-656.

19. Weston AP, Krmposich P, Maldisi WF, Cherian R, Dixon A, McGregor DH, Banerjee SK: Short segment Barrett’s esophagus: clinical and histological features, associated endoscopic findings, and association with gastric intestinal metaplasia. Am J Gastroenterol 1996, 91:981-986.

20. Vazir MF, Richter JE: Role of acid and duodenogastroesophageal reflux in gastroesophageal reflux disease. Gastroenterology 1996, 111:1192-1199.

21. Hamilton SR, Yardley JH: Regenerative of cardiac type mucosa and acquisition of Barrett’s mucosa after esophagogastronomy. Gastroenterology 1977, 72:659-675.

22. Lindahl H, Rintala R, Sariola H, Louhimo I: Barrett’s esophagus: a common complication of gastric tube reconstruction. J Pediatr Surg 1990, 25:446-448.

23. Gutschow C, Collard JM, Romagnoli R, Salizzoni M, Holshcer A: Denovivo stomach as an esophageal substitute recovers intra-luminal acidity with time. Ann Surg 2001, 233:509-514.

24. Oberg S, Johansson J, Vennner J, Walther B: Metaplastic columnar mucosa in the cervical esophagus after esophagectomy. Ann Surg 2002, 235:338-345.

25. Oberg S, DeMeester TR, Peters JH, Hagen JA, Nigro JJ, DeMeester SR, Thiesen J, Campos GM, Crookes PF: The extent of Barrett’s esophagus depends on the status of the lower esophageal sphincter and the degree of esophageal acid exposure. J Thorac Cardiovasc Surg 1999, 117:572-580.

26. de Rocha JR, Cecconello I, Zilberstein B, Sallum RA, Sakai P, Ishioka S, Pinotti HW: Barrett esophagus in the esophageal stump after subtotal esophagectomy with cervical esophagogastroplasty. Rev Hosp Clin Fac Med Sao Paulo 1992, 47:69-70.

27. Campos GM, DeMeester SR, Peters JH, Oberg S, Crookes PF, Hagen JA, Brenner CG, Sillin LF 3rd, Mason R, DeMeester TR: Predictive factors of Barrett esophagus: multivariate analysis of 502 patients with gastroesophageal reflux disease. Arch Surg 2001, 136:1267-1273.

28. Konishi M, Kato M, Tachimori Y, Watanabe H, Yamaguchi H, Ishikawa T, Itabashi M, Hirota T: Adenocarcinoma in Barrett’s esophagus following total resection of the gastric remnant: a case report. Jpn J Clin Oncol 1992, 22:292-296.

29. Bosetti C, Talamini R, Franceschi S, Negri E, Garavello W, La Vecchia C: Aspirin use and cancers of the upper aerodigestive tract. Br J Cancer 2003, 88:672-674.

30. Corley DA, Kerlikowske K, Verma R, Bufler P: Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis. Gastroenterology 2003, 124:47-56.

Pre-publication history

The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/1471-230X/4/18/prepub

Publish with BioMed Central and every scientist can read your work free of charge

*BioMed Central will be the most significant development for disseminating the results of biomedical research in our lifetime.*
Sir Paul Nurse, Cancer Research UK

Your research papers will be:
- available free of charge to the entire biomedical community
- peer reviewed and published immediately upon acceptance
- cited in PubMed and archived on PubMed Central
- yours — you keep the copyright

Submit your manuscript here:
http://www.biomedcentral.com/info/publishing_adv.asp