Published in final edited form as:

Gastroenterology. 2012 September ; 143(3): 564–566.e1. doi:10.1053/j.gastro.2012.04.051.

Development of Subsquamous High-Grade Dysplasia and Adenocarcinoma After Successful Radiofrequency Ablation of Barrett's Esophagus

Mohammad Titi^{*,‡}, Andrew Overhiser^{*,‡}, Ozlem Ulusarac^{*,‡}, Gary W. Falk[§], Amitabh Chak^{||}, Kenneth Wang^{||}, and Prateek Sharma^{*,‡}

^{*}Veterans Affairs Medical Center, Kansas City, Missouri

[‡]University of Kansas School of Medicine, Kansas City, Kansas

[§]University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania

^{||}Case Western Reserve University School of Medicine, Cleveland, Ohio

^{||}Mayo Graduate School of Medicine, College of Medicine, Mayo Clinic, Rochester, Minnesota

Abstract

Patients with Barrett's esophagus are frequently treated with radiofrequency ablation (RFA). Those that undergo this procedure have a low risk of developing subsquamous intestinal metaplasia, and none have been reported to develop subsquamous dysplasia or cancer. We report the development of subsquamous neoplasia in 3 patients who were treated with RFA for Barrett's esophagus (2 developed adenocarcinoma and 1 developed high-grade dysplasia). The identification of these cases indicates the need for continued surveillance following RFA, even after complete eradication of intestinal metaplasia, and caution for widespread use of ablation, especially in patients with low-risk Barrett's esophagus.

Keywords

Therapy; Cancer Risk; Esophageal Adenocarcinoma; Biopsy

Barrett's esophagus is the only known precursor to esophageal adenocarcinoma, a cancer that continues to increase in incidence.^{1,2} Progression to adenocarcinoma may involve progressive histologic changes from intestinal metaplasia to low-grade dysplasia to high-grade dysplasia to adenocarcinoma.^{3–5} Neither medical nor surgical therapy has yet shown a major impact on cancer risk in Barrett's esophagus. In contrast, there has been much interest in techniques for Barrett's ablation in an effort to decrease or even eliminate cancer risk.

Reprint requests. Address requests for reprints to: Prateek Sharma, MD, Division of Gastroenterology, Veterans Affairs Medical Center, University of Kansas School of Medicine, 4801 East Linwood Boulevard, Kansas City, Missouri 64128. psharma@kumc.edu.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at <http://dx.doi.org/10.1053/j.gastro.2012.04.051>.

Conflicts of interest

The authors disclose no conflicts.

Increasing research is being directed to radiofrequency ablation (RFA) as an ideal ablation technique.^{6,7} However, one of the concerns after any ablation technique is development of subsquamous intestinal metaplasia, which could have the potential to progress to neoplasia.^{8–14} Thirty-four cases with subsquamous neoplasia have been described in the literature, with the majority occurring after photodynamic therapy (31 cases); the other 3 cases were after argon plasma coagulation or laser ablation.⁸ To date, no cases of subsquamous neoplasia have been reported after RFA.

We report 3 cases of subsquamous neoplasia: 2 with adenocarcinoma and 1 with high-grade dysplasia detected after apparently successful RFA. The reporting centers have been performing RFA for several years (approximately 215 cases total). All procedures in these cases were performed by the respective investigators at each center. All patients were being treated with a twice-daily dose of a proton pump inhibitor at the time of neoplasia occurrence; proton pump inhibitor therapy was initiated and continued during the ablation period. These patients had undergone surveillance biopsies per the Seattle protocol before undergoing endoscopic therapy. Finally, postablation biopsy specimens were obtained only when the investigator observed neosquamous mucosa without any evidence of columnar lining in the distal esophagus (Supplementary Materials and Methods).

Case 1

A 65-year-old patient with Barrett's esophagus had been undergoing surveillance for 2 years when an intramucosal adenocarcinoma was detected and distal esophagectomy was performed. Margins were positive for high-grade dysplasia. Endoscopy showed residual segment of Barrett's esophagus (C0M3). Endoscopic mucosal resection (EMR) was performed at the surgical anastomosis using the cap technique (EMR-001; Olympus, Center Valley, PA) and confirmed high-grade dysplasia. No post-EMR esophageal stenosis was seen. The patient underwent RFA (HALO⁹⁰; Bârrx Medical, Sunnyvale, CA) in 3 sessions, leading to complete eradication of dysplasia and intestinal metaplasia. Over the next 2 years, 5 surveillance endoscopies were performed with no endoscopic or histologic evidence of intestinal metaplasia. Finally, almost 2 years after RFA, surveillance biopsy specimens from the neosquamous epithelium 2 cm above the surgical anastomosis showed subsquamous intestinal metaplasia with high-grade dysplasia (Figure 1A and B).

Case 2

A 59-year-old patient with a 10-year history of Barrett's esophagus (C0M2) was found to have focal high-grade dysplasia. He underwent 2 sessions of RFA (HALO⁹⁰) with complete eradication of dysplasia and intestinal metaplasia. Surveillance endoscopy at 3 months after RFA showed normal neosquamous epithelium with no intestinal metaplasia on biopsy specimens. Surveillance endoscopy at 6 months after RFA showed normal neosquamous epithelium; however, biopsy specimens 1 cm above the gastroesophageal junction revealed subsquamous adenocarcinoma (Figure 2A and B). EMR showed moderately differentiated adenocarcinoma. The patient underwent esophagectomy, where residual subsquamous carcinoma was found and negative lymph nodes.

Case 3

A 76-year-old patient with Barrett's esophagus (C7M7) and focal high-grade dysplasia was initially treated with EMR. There was no post-EMR esophageal stenosis. This was followed by 4 sessions of RFA (2 sessions with HALO³⁶⁰ and then 2 sessions with HALO⁹⁰) with complete ablation of dysplasia and intestinal meta-plasia. Two surveillance endoscopies at 3-month intervals showed no evidence for intestinal metaplasia. The third surveillance endoscopy per protocol was at 9 months after RFA and showed a nodular area in the neosquamous epithelium above the gastroesophageal junction, 1 cm distal to the site of previous EMR. Biopsy specimens showed subsquamous adenocarcinoma. The patient underwent esophagectomy, confirming a T1N0 adenocarcinoma.

Discussion

This report illustrates an important fact that must be remembered about any ablative therapy, including RFA: high-grade dysplasia or cancer can develop in some patients even after apparently successful eradication of neoplasia and intestinal metaplasia. Reported patients had complete eradication of intestinal metaplasia for at least 6 months after RFA before the development of subsquamous neoplasia, and the patient in case 1 had almost 2 years of normal endoscopic surveillance. Two patients underwent EMR before RFA, but the subsquamous neoplasia occurred away from the original EMR site. It is possible that anatomic characteristics such as a tortuous distal esophagus, large hiatus hernia, or presence of a surgical anastomosis may interfere with complete energy delivery via RFA.

Reported rates of subsquamous intestinal metaplasia vary from 0 to 30%, which can be secondary to lack of a standardized definition, sampling protocol, inadequate biopsy depth, and different ablative techniques.^{8,10,13} In 22 reports describing results of photodynamic therapy in 953 patients, subsquamous intestinal metaplasia was found in 135 (14.2%). In contrast, 18 reports described results of RFA in 1004 patients and found subsquamous intestinal metaplasia in only 9 patients (0.9%).⁸

In conclusion, although ablation can eradicate intestinal metaplasia, the risk of developing future cancer is unknown. Recurrences of Barrett's esophagus have been reported and we now report 3 cases of subsquamous neoplasia, including 2 developing adenocarcinoma. These findings have significant implications because they highlight the need for continued meticulous surveillance with biopsies of neosquamous epithelium even after apparently successful eradication of intestinal metaplasia. In the absence of definitive guidelines, the appropriate surveillance intervals after ablation are not currently clear. A prudent approach is to perform surveillance every 3 months for the first year after ablation, every 6 months for the next year, and then annually. This surveillance program is used in the centers reporting current cases. The group's practice is to perform detailed inspection of the esophagus, obtain a biopsy specimen of any visible lesions, and then obtain a biopsy specimen every 1 cm, as per the Seattle protocol, from the neosquamous epithelium in the previously ablated segment. These reports should also temper our enthusiasm to apply ablation to all patients with Barrett's esophagus.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations used in this paper

EMR	endoscopic mucosal resection
RFA	radiofrequency ablation.

References

1. Blot WJ, et al. *Semin Oncol.* 1999; 26:2–8.
2. Brown LM, et al. *Surg Oncol Clin North Am.* 2002; 11:235–256.
3. Rastogi A, et al. *Gastrointest Endosc.* 2008; 67:394–399. [PubMed: 18045592]
4. Sharma P, et al. *Clin Gastroenterol Hepatol.* 2006; 4:566–572. [PubMed: 16630761]
5. Birkmeyer JD, et al. *N Engl J Med.* 2003; 349:2117–2127. [PubMed: 14645640]
6. Shaheen NJ, et al. *N Engl J Med.* 2009; 360:2277–2288. [PubMed: 19474425]
7. Shaheen NJ, et al. *Gastroenterology.* 2011; 141:460–468. [PubMed: 21679712]
8. Gray NA, et al. *Am J Gastroenterol.* 2011; 106:1899–1908. [PubMed: 21826111]
9. Hernandez JC, et al. *Endoscopy.* 2008; 40:388–392. [PubMed: 18459075]
10. Gupta N, et al. *Gastrointest Endosc.* 2012; 75:11–18. [PubMed: 21907985]
11. Van Laethem JL, et al. *Gut.* 2000; 46:574–577. [PubMed: 10716690]
12. Lyday WD, et al. *Endoscopy.* 2010; 42:272–278. [PubMed: 20146164]
13. Wani S, et al. *Gastrointest Endosc.* 2010; 71:147–166. [PubMed: 19879565]
14. Wani S, et al. *Am J Gastroenterol.* 2009; 104:502–513. [PubMed: 19174812]

Figure 1.
(A) Alcian blue stain shows subsquamous intestinal metaplasia. (B) Subsquamous high-grade dysplasia (case 1).

Figure 2.
(A) Low and (B) high power showing subsquamous adenocarcinoma (case 2).