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## Retention Esophagitis in Patients with Achalasia Requires Cancer Surveillance

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See “Retention Esophagitis as a Significant Clinical Predictor of Progression to Esophageal Cancer in Achalasia” by Haewon Kim, Hyojin Park, HeeSeung Choi, et al., on page 161-166.

Achalasia is an uncommon esophageal motility disorder with an estimated incidence of 1.6/100,000 and prevalence of 10.8/100,000 according to a population-based study.<sup>1</sup> Patients with achalasia have a higher risk of developing esophageal cancer.<sup>2,3</sup> The reported incidence of concomitant esophageal cancer and achalasia has varied widely, with an estimated risk 14.5- to 33-fold higher than that in the general population.<sup>2-4</sup> A large-scale, long-term prospective study showed that the relative hazard ratio of esophageal cancer was 28 in patients with achalasia compared to that in controls.<sup>3</sup> Persistent stasis of foods and fluids with resultant chemical irritation and bacterial overgrowth could induce chronic inflammation, squamous epithelial hyperplasia, and subsequent dysplasia and carcinoma.<sup>5</sup>

Despite these risks, the role of cancer surveillance in patients with achalasia remains unclear. The current American Society of Gastrointestinal Endoscopy and American College of Gastroenterology (ACG) practice guidelines do not recommend routine endoscopic surveillance in patients with achalasia.<sup>6,7</sup> Per ACG guidelines, surveillance beyond early detection of cancer such as the detection of late complications of achalasia

has potential advantages, but more evidence is needed to determine whether the advantages of surveillance practices outweigh the costs.<sup>7</sup> In addition, it is unclear whether surveillance can improve the patients' survival. Some have advocated periodic endoscopic surveillance after 15–20 years of symptoms, as esophageal cancer tends to occur no sooner than 20 years after achalasia symptom onset or in those with end-stage disease.<sup>3,5,8</sup> However, the optimal surveillance interval has not yet been determined.

The purpose of surveillance is to detect neoplastic lesions at an early stage to facilitate curative treatment. Therefore, it is important to identify patients at risk who can benefit from the surveillance strategy. In addition, effective modalities are needed to identify neoplastic change. The entire esophagus is at risk in patients with achalasia; thus, the entire length should be carefully inspected and sampled. However, endoscopic examination of the esophagus may be difficult in achalasia because the mucosa is often covered with food and saliva, which compromises meticulous inspection. Few studies have evaluated the efficacy of Lugol's staining in patients with achalasia but have showed unsatisfactory results.<sup>9</sup> Moreover, histological evaluation and assessment of biopsy samples may be challenging because of the presence of chronic inflammatory changes. Identification of morphologic findings or predictive biomarkers that precede the appearance of esophageal cancer may be helpful for a surveillance strategy in patients with achalasia.

In this issue of *Clinical Endoscopy*, the endoscopic and histological features of retention esophagitis in patients with achalasia was reported and the authors suggested the clinical

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implications of retention esophagitis as a precancerous lesion.<sup>10</sup> Retention esophagitis was defined as the endoscopic finding of stasis or thickened and whitish mucosal changes with the presence of histologically confirmed squamous hyperplasia. Among 37 patients with untreated achalasia, 21 showed both endoscopic and histological findings of retention esophagitis. Patients with retention esophagitis had longer duration of symptoms and showed higher frequency of liquid or food retention in the esophageal lumen than those without retention esophagitis.

In immunohistochemical analyses of two tumor suppressor genes, p53 and p16, and a proliferation marker, Ki-67, p53 expression was found to be more frequent in patients with retention esophagitis than in controls or those without retention esophagitis, whereas Ki-67 expression did not differ among the three groups.<sup>10</sup> A previous study reported that 82% of patients with high-grade dysplasia or cancer showed overexpression of p53 in surveillance biopsies before the development of carcinoma.<sup>11</sup> In addition, overexpression of p53 was more frequently observed in patients with achalasia who developed esophageal cancer. Meanwhile, esophageal epithelial cells in lesions with esophagitis, regardless of the presence of dysplasia or carcinoma, showed more Ki-67-positive cells than normal epithelial cells, suggesting that this marker does not discriminate between patients with and without neoplastic change.<sup>12</sup> A longitudinal cohort study also showed that p53 but not Ki-67 could be used to identify patients with achalasia who are at risk of developing malignancy.<sup>11</sup> Accordingly, it was suggested that patients with achalasia and retention esophagitis may benefit from surveillance endoscopy to detect neoplastic changes.

In this study, expression of these markers showed no statistically significant differences between patients without retention esophagitis and controls.<sup>10</sup> Further studies are warranted to confirm whether the presence of retention esophagitis itself, rather than the occurrence of achalasia, is associated with the potential for malignant transformation. In addition, the difference between patients with both endoscopic and histological findings of retention esophagitis and those with endoscopic findings alone should be clarified.

Peroral endoscopic myotomy (POEM) is a new, widely accepted option for the treatment of achalasia.<sup>13</sup> A recent study showed that the expression of p53 and Ki-67 decreased after POEM, suggesting that POEM could decrease the potential risk of esophageal squamous cell carcinoma.<sup>14</sup> However, the potential for malignant transformation seems to persist to some degree, even after treatment.<sup>15,16</sup> Therefore, monitoring should be performed after treatment and symptom resolution in patients with achalasia, particularly in those with other risk factors for the development of esophageal cancer such as smoking and alcohol consumption.

In summary, retention esophagitis was associated with high-

er expression of p53 in patients with achalasia compared to controls or those without retention esophagitis. Patients with achalasia and associated retention esophagitis may be suitable candidates for surveillance endoscopy. Further studies related to the pathogenesis of esophageal cancer in patients with achalasia and the development of effective modalities for surveillance may help in establishing clinical practice guidelines.

#### Conflicts of Interest

The authors have no financial conflicts of interest.

#### REFERENCES

- Sadowski DC, Ackah F, Jiang B, Svenson LW. Achalasia: incidence, prevalence and survival. A population-based study. *Neurogastroenterol Motil* 2010;22:e256-e261.
- Meijssen MA, Tilanus HW, van Blankenstein M, Hop WC, Ong GL. Achalasia complicated by oesophageal squamous cell carcinoma: a prospective study in 195 patients. *Gut* 1992;33:155-158.
- Leeuwenburgh I, Scholten P, Alderliesten J, et al. Long-term esophageal cancer risk in patients with primary achalasia: a prospective study. *Am J Gastroenterol* 2010;105:2144-2149.
- Streitz JM Jr, Ellis FH Jr, Gibb SP, Heatley GM. Achalasia and squamous cell carcinoma of the esophagus: analysis of 241 patients. *Ann Thorac Surg* 1995;59:1604-1609.
- Chino O, Kijima H, Shimada H, et al. Clinicopathological studies of esophageal carcinoma in achalasia: analyses of carcinogenesis using histological and immunohistochemical procedures. *Anticancer Res* 2000;20:3717-3722.
- Hirota WK, Zuckerman MJ, Adler DG, et al. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. *Gastrointest Endosc* 2006;63:570-580.
- Vaezi MF, Pandolfino JE, Vela MF. ACG clinical guideline: diagnosis and management of achalasia. *Am J Gastroenterol* 2013;108:1238-1249; quiz 1250.
- Eckardt VF, Hoischen T, Bernhard G. Life expectancy, complications, and causes of death in patients with achalasia: results of a 33-year follow-up investigation. *Eur J Gastroenterol Hepatol* 2008;20:956-960.
- Loviscek LF, Cenoz MC, Badaloni AE, Agarinakazato O. Early cancer in achalasia. *Dis Esophagus* 1998;11:239-247.
- Kim H, Park H, Choi HS, et al. Retention esophagitis as a significant clinical predictor of progression to esophageal cancer in achalasia. *Clin Endosc* 2018;51:161-166.
- Leeuwenburgh I, Gerrits MM, Capello A, et al. Expression of p53 as predictor for the development of esophageal cancer in achalasia patients. *Dis Esophagus* 2010;23:506-511.
- Fujii T, Yamana H, Sueyoshi S, et al. Histopathological analysis of non-malignant and malignant epithelium in achalasia of the esophagus. *Dis Esophagus* 2000;13:110-116.
- Inoue H, Minami H, Kobayashi Y, et al. Peroral endoscopic myotomy (POEM) for esophageal achalasia. *Endoscopy* 2010;42:265-271.
- Minami H, Yamaguchi N, Matsushima K, et al. Improvement of endoscopic findings after per oral endoscopic myotomy (POEM) in esophageal achalasia; does POEM reduce the risk of developing esophageal carcinoma? Per oral endoscopic myotomy, endocytoscopy and carcinogenesis. *BMC Gastroenterol* 2013;13:22.
- Leeuwenburgh I, Van Dekken H, Scholten P, et al. Oesophagitis is common in patients with achalasia after pneumatic dilatation. *Aliment Pharmacol Ther* 2006;23:1197-1203.
- Ota M, Narumiya K, Kudo K, et al. Incidence of esophageal carcinomas after surgery for achalasia: usefulness of long-term and periodic follow-up. *Am J Case Rep* 2016;17:845-849.