Review Article

Esophageal cancer risk in achalasia

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Abstract: Observational data consistently suggests that achalasia is associated with a moderately increased risk of developing esophageal cancer. Squamous cell carcinomas predominate but adenocarcinomas also occur in the setting of Barrett's metaplasia. This review will (I) explore the pathophysiology associated with this malignant transformation, (II) appraise contemporary epidemiological evidence to understand the magnitude of the risk, (III) describe experience with endoscopic surveillance including the role of Lugol chromoendoscopy and (IV) summarize the recommendations of current international guidelines. This data will help inform discussions in the outpatient setting. In essence, patients should be aware that the risk of esophageal cancer is moderately increased compared to the general population but that the overall incidence remains low. Surveillance endoscopy is not an efficacious screening tool as it cannot reliably detect premalignant lesions and is not associated with a survival benefit in those who develop esophageal cancer. Instead, clinicians should aggressively investigate deteriorating symptoms to exclude malignant transformation, particularly in older male patients with a dilated esophagus.

Keywords: Achalasia; cancer; squamous cell carcinoma; adenocarcinoma; Barrett's metaplasia

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Introduction

Since its first description in the 1870s, observational studies have suggested that the risk of developing esophageal cancer in patients with long-standing achalasia is up to 50 times greater than the risk in the general population (1). However, previous international guidelines have fallen short of recommending screening for esophageal malignancy in patients with achalasia due to a lack of robust epidemiological evidence and a failure to demonstrate that regular endoscopic surveillance strategies improve survival (1-3). This review will explore the pathophysiology of the proposed association and review the most contemporary epidemiological evidence in an attempt to clarify the risk and facilitate decision making in the clinical setting.

Pathophysiology

Achalasia is predominantly associated with the risk of developing esophageal squamous cell carcinoma against a background of chronic esophagitis. It is also associated with Barrett's metaplasia and esophageal adenocarcinoma, albeit to a lesser extent (4). The pathophysiology of the transition to malignancy is likely to be multifactorial and there is overlap between the two histological subtypes (5,6).

First, stasis of food and saliva in the esophagus can lead to bacterial overgrowth, fermentation and chemical irritation of esophageal epithelial cells. Second, this inflammatory process precipitates chronic hyperplastic esophagitis and predisposes to dysplasia and ultimately esophageal squamous cell carcinoma (5-7). The prevalence of such chronic esophagitis in patients with long-standing achalasia has been shown to be high with one group reporting histological confirmation in 83% of patients attending for endoscopic assessment five or more years after a Heller's myotomy (8).

Chronic esophageal inflammation may also occur in the setting of treated achalasia whereby therapy targeting the lower esophageal sphincter mechanism predisposes to gastro-esophageal reflux disease and Barrett's metaplasia (6).

Indeed, long-term follow-up of patients in the European Achalasia Trial demonstrated abnormal gastric acid exposure, defined as a pH of less than 4 for more than 4.5% of the time, in 34% of patients in the laparoscopic Heller's myotomy arm of the trial (9). In a single-center cohort study of 331 achalasia patients treated with pneumatic dilatation in the Netherlands, 28 (8.4%) patients were diagnosed with Barrett's metaplasia after a follow-up of almost 9 years (10). Post-treatment lower esophageal sphincter pressures were lower in patients with Barrett's than in those without (13.9 *vs.* 17.4 mmHg; P=0.03), highlighting the predisposition to gastro-esophageal reflux and Barrett's metaplasia in successfully treated patients. Interestingly, patients with an associated hiatal hernia were eight times as likely to develop Barrett's esophagus compared to those without [HR =8.04, 95% confidence interval (CI): 3.5–18.1] (10).

Epidemiology

Meta-analyses of observational studies

Over 40 observational studies have reported the association between esophageal cancer and achalasia (4). In a 2019 meta-analysis of 16 studies that included length of follow-up and duration of achalasia, Gillies et al. reported that the incidence rate of esophageal cancer in achalasia patients was 1.36 (95% CI: 0.56–2.51) per 1,000 person-years. This is over 10 times higher than the general population incidence rate reported by the International Agency for Research on Cancer (11). In 2017, Tustumi et al. stratified their meta-analysis based on histological subtype and reported incidence rates of 312.4 and 21.23 cases per 100,000 patient-years at risk, equivalent to risk ratios of 72.65 and 6.63, for squamous cell carcinoma and adenocarcinoma respectively (4). The variation between the independent pooled analyses is apparent. The latter meta-analysis only included 13 studies and two of these studies were excluded from the former analysis on the basis of duplication of the cohorts. However, both meta-analyses remain limited by the inclusion of data from historical retrospective cohort studies. More specifically, the data was often from single institutions with relatively short follow-up, the potential for selection bias, and high numbers of cases lost to follow-up (12).

Contemporary population-based cohort studies

More recently a population-based cohort study involving 2,369 achalasia cases and 3,865 controls within The Health Improvement Network (THIN) database in the United Kingdom (UK) estimated the risk of esophageal cancer to be 1.0 per 1,000 person-years (13). This was equivalent to an incidence rate ratio of 5.22 compared to the control population. Data within THIN is truly representative and population-based, as it comprises data from a group of primary care practices that cover 6% of the UK population. On this basis, the higher risk of esophageal cancer in patients with achalasia is a robust finding however, the actual risk ratio may be higher as (I) the duration of follow-up was short (mean 6.1 person-years) considering the median time from achalasia diagnosis to esophageal cancer was over 15 years and (II) the rate of esophageal cancer in the general UK population is higher than that seen in other countries.

Another recent population-based cohort study from the UK interrogated the Hospital Episode Statistics (HES) database. A total of 7,487 patients were identified within HES as having both a diagnosis and receiving a treatment for achalasia between 2002 and 2012 (14). This database utilizes administrative data to capture all hospital events, public and private, in England. Within this cohort, 101 patients (1.3%) developed esophageal cancer. The incidence of esophageal cancer was 205 cases per 100,000 patient-years at risk, equivalent to a 15.19 incidence rate ratio. The median time to develop cancer from primary treatment was only 3 years (range, 1–11 years). A subsequent case-control analysis within this achalasia cohort demonstrated that patients who developed esophageal cancer were older (>80 *vs.* <40 years, HR =18.71, 95% CI: 4.30–81.44) and more commonly primarily treated with pneumatic dilation (82.2% *vs.* 60.3%; HR =2.27, 95% CI: 1.03–5.03) (14). It is important to highlight though that the latter association may be confounded by age, as a greater proportion of patients will be treated with pneumatic dilatation rather than a Heller's myotomy with increasing age (15).

The final large-scale population-based cohort study to consider included 2,896 patients with a discharge diagnosis of achalasia in the Swedish Inpatient Register between 1965 and 2003 (16). Unlike the previous two studies, data from this population-based cohort was included in the meta-analyses described above. The cohort has complete registers of cancer, causes of death, and migration. After excluding the first year of follow-up to exclude prevalent esophageal cancer cases, the standardised incidence ratio (SIR, compared to age-, sex-, and calendar period-matched Swedish population controls) for squamous cell carcinoma was 11.0 (95% CI: 6.0–18.4) and for adenocarcinoma was 10.4 (95% CI 3.8–22.6). The number of cancers in this

Table 1 Pros and cons associated with routine endoscopic surveillance in achalasia

Pros	Cons
Contemporary epidemiological studies estimate the risk of esophageal cancer is 5–15 times greater than the general population	Lack of evidence confirming clinical efficacy
Esophageal cancer is usually diagnosed late in achalasia patients and the prognosis is poor	Prevalence of esophageal cancer remains low
Up to 8% of patients will develop Barrett's metaplasia	Not cost-effective
Management of patient expectations	No agreed evidenced-based surveillance protocol
	Endoscopic assessment can be technically challenging due to food residue
	Unlike Barrett's metaplasia, the whole esophagus is at risk and a well defined endoscopically visible precursor lesion has not been identified

cohort was small (n=22) and any stratified analysis should be interpreted with caution. However, the esophageal cancer cases occurred predominantly in males (n=20) with no evidence of higher incidence rates for squamous cell carcinoma as the duration of follow-up increased (2–9 years SIR =11.1, 95% CI: 5.1–21.1 *vs.* 10–38 years SIR =10.8, 95% CI: 3.5–25.1) (16).

Presentation and prognosis

The diagnosis of esophageal cancer is often delayed as worsening dysphagia is often attributed to recurrent or deteriorating achalasia (17). Ultimately the tumor has to be large enough to obstruct a dilated esophagus or present with an upper gastrointestinal bleed to facilitate diagnosis (18,19). Tumors therefore present at a more advanced stage and the prognosis is poorer. It has previously been estimated that up to 80% of patients with achalasia and esophageal cancer are not candidates for definitive management (18). Only 4.54% of these patients survived longer than five years with a mean survival of 12.7 months in the meta-analysis by Tustumi *et al.* (4). By comparison, global five-year survival rates for esophageal cancer range between 15–25% (20).

Endoscopic surveillance

Argument for and against

The role of surveillance endoscopy in patients with achalasia remains controversial and no consensus exists (17). On the one hand, the population-based observational data described above suggests the risk of developing esophageal cancer is 5–15 times higher in patients with achalasia compared to the general population (13,14,16). Poor prognosis secondary to delayed presentation strengthens the argument for regular surveillance in an effort to diagnose esophageal malignancy at an earlier stage. However, amongst 448 achalasia patients enrolled in an institutional surveillance program (white light endoscopy) in the Netherlands, the death rate from esophageal cancer was similar to what would be expected in the general population (21). It should be noted that endoscopic surveillance can be difficult in patients with long-standing or incompletely treated achalasia because, unlike Barrett's metaplasia, the whole esophagus is at risk, the mucosa is often covered with food debris, and random biopsies might not be representative (17). The final issue to consider is that the incidence of esophageal cancer is low. The cost-effectiveness of a surveillance strategy that incorporates all achalasia patients would therefore be questionable (17). The pros and cons for endoscopic surveillance are summarized in *Table 1*.

Efficacy of white light endoscopy and Lugol chromoendoscopy

To enhance the efficacy of surveillance, some authors have suggested a role for screening for dysplasia with Lugol chromoendoscopy. In this technique, normal glycogen containing esophageal mucosa yields a brown-green color. Dysplastic lesions lack glycogen and do not stain, which allows them to be visualized more efficiently (5). In a cohort of 230 achalasia patients being treated at two tertiary

referral centers in Europe, this technique tripled the detection rate of suspected lesions (111 lesions white light *vs.* 329 lesions Lugol). However only 8% of these lesions were histopathologically confirmed as esophageal squamous cell carcinoma or low-grade dysplasia (5). Achalasia patients within this cohort underwent surveillance endoscopy with both white light and Lugol chromoendoscopy every three years. Only three patients developed a squamous cell cancer after a median follow-up of 12 years and none of these patients had preceding dysplasia. Similarly, four patients were diagnosed with low-grade dysplasia and did not progress to high-grade dysplasia or invasive malignancy after a median follow-up of 9 years (5). On the basis of these findings, white light and Lugol chromoendoscopy cannot be systematically recommended for esophageal cancer surveillance in achalasia patients as neither method can accurately identify precursor lesions.

Data from a cross-sectional study in Adelaide also strengthens the argument that routine surveillance endoscopy in all achalasia patients is probably unnecessary (8). In this study 68 patients within a prospectively maintained database of 171 patients treated with a Heller's myotomy were recruited for a one-off endoscopic assessment. While 83% had histological evidence of esophagitis and 7% had Barrett's metaplasia, no patients had dysplasia or invasive malignancy after at least five years of follow-up (8). In the primary cohort of 171 patients, two patients died from esophageal squamous cell carcinoma, which were diagnosed eight and 10 years after the surgical myotomy. Based on individual studies demonstrating that the risk of esophageal cancer appears to be apparent after an excess of 10 years of symptoms, or five years from myotomy, many authors suggest surveillance could be more effective if implemented after these times (5,8,17). Such thresholds should be interpreted cautiously, particularly in light of new population-based data from the UK demonstrating an excess cancer risk only 3 years from the time of primary treatment (14).

Targeted surveillance of higher-risk patients

As previously described, older patients (14) and men (16) represent subgroups that could potentially benefit from more targeted surveillance. Patients with a dilated esophagus may also represent a higher risk group due to the assumed burden of food stasis in the immotile esophagus. Indeed, the risk of esophageal cancer in an Italian cohort of 583 achalasia patients was higher for patients with either a dilated esophagus prior to treatment (esophageal diameter at diagnosis >71 mm, risk ratio =21.07, 95% CI: 9.29–47.82) or end-stage achalasia and a sigmoid esophagus (risk ratio =17.64, 95% CI: 4.13–75.43) (19). To date though, there is a paucity of data in relation to more targeted screening in these patients and it cannot be widely recommended.

Cost-effectiveness

Finally, the cost-effectiveness of any surveillance program should be carefully considered. Surveillance for malignant transformation in patients with Barrett's metaplasia is generally accepted but only cost-effective for non-dysplastic Barrett's every five years when the cancer incidence is 0.5% (22). When the incidence of cancer is lower, the usefulness of surveillance is questioned further. Despite the increased risk of esophageal cancer in patients with achalasia, the overall risk remains low (17). In one cohort of achalasia patients (n=448) the annual incidence rate for malignant transformation was 0.34%. This figure has been used to advocate surveillance as it is only slightly lower than the rate of 0.5–1.0% for adenocarcinoma in patients with Barrett's metaplasia (21). However, in a much larger and more contemporary population-based study (n=7,487), the equivalent annual incidence rate for malignant progression in achalasia patients was only 0.21% (14). Given this lower incidence rate, the cost-effectiveness of routine surveillance for all patients remains questionable (12). It is further impeded by the lack of data confirming the efficacy of endoscopic surveillance (23).

International guidelines and lack of consensus

For these reasons, current guidance from the International Society for Diseases of the Esophagus (ISDE) (1), the American Society of Gastrointestinal Endoscopy (ASGE) (2), and the American College of Gastroenterology (ACG) (3) do not recommend routine surveillance endoscopy in achalasia patients. The notable exception is the European Society of Gastrointestinal Endoscopy (ESGE) Position Statement but it does not give details on the timing or frequency of such surveillance (22). The ISDE 2018 guidance recommends that it is good practice to inform achalasia patients of the moderately increased risk of esophageal cancer, particularly in males after at least 10 years from the initial treatment. No recommendation is made with respect to routine endoscopic surveillance or endoscopy intervals after any treatment (1). However, it should be stressed that it is important to remind patients

that the overall risk remains low.

The ISDE guidelines accept that endoscopy can be recommended on an individual patient basis while ASGE suggests, "*if surveillance were to be considered, it would be reasonable to initiate it 15 years after onset of symptoms*." (2). Therefore, while most guidelines do not recommend surveillance, the potential for ambivalence with regard to these recommendations exists (12). Indeed, a novel global survey involving 16 achalasia experts identified discordant practices with regards to the perceived cancer risk and the subsequent screening practices (23). More specifically, three experts reported no increased risk compared with the general population, eight experts a lifetime risk of 0.1–0.5%, three experts a 0.5–1% risk, two experts a 1–2% risk, and one expert a 3–5% risk. Screening practices also varied commencing at or within one year (n=2), five years (n=3), or 10 years (n=3) of diagnosis. Surveillance intervals also varied between two and five years.

Summary

Epidemiological evidence confirms that the increased risk of esophageal cancer in patients with achalasia is real and modern estimates of the incidence risk ratio suggest it ranges between 5 and 15. Unfortunately the prognosis for esophageal cancer in achalasia patients is poor and may be secondary to delayed presentation in patients with a chronically dilated esophagus. Current clinical practices are discordant but the risk of malignant transformation in population-based cohort studies appears to be less than that observed in Barrett's metaplasia. Taken together with the lack of efficacy associated with routine endoscopic assessment, most guidelines do not advocate endoscopic surveillance. However, numerous studies have suggested certain groups are at higher risk such as males, older patients, those with a dilated esophagus, and those with prolonged symptoms. To date though, there is a paucity of data in relation to more targeted screening in these patients and it cannot be widely recommended. In publicly-funded health care systems, routine endoscopic surveillance cannot be recommended. Individual clinicians should remain vigilant to deteriorating symptoms and investigate with prompt endoscopy in an attempt to facilitate earlier diagnosis of any malignant transformation (14).

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