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REVIEW ARTICLE

Management of Barrett's esophageal carcinoma

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Abstract Barrett's esophagus (BE) is the premalignant lesion from which esophageal adenocarcinoma near the esophagogastric junction arises. The management of BE and the treatment of Barrett's esophageal adenocarcinoma (BEA) are important clinical issues in Europe and the United States. As the *Helicobacter pylori* infection rate in Japan is decreasing in the younger population, the incidence of BE and adenocarcinoma arising from BE may start increasing. Thus, we review the current status of BEA and its management. Magnifying endoscopy with narrow-band imaging is important for diagnosing dysplasia arising from BE. In Japan, adenocarcinoma arising from BE is managed the same way as squamous cell carcinoma in the same location. Strategies to prevent BEA may include medication such as non-steroidal anti-inflammatory drugs and proton pump inhibitors, and anti-reflux surgery. Understanding the pathophysiology of BE will help to reduce the incidence of BEA.

Keywords Barrett's esophagus · GERD · Esophageal adenocarcinoma

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Introduction

Barrett's esophagus (BE) is an important precursor of Barrett's esophageal adenocarcinoma (BEA) via a metaplasia–dysplasia–carcinoma sequence and is the final stage of gastroesophageal reflux disease (GERD). The incidence of BEA has increased remarkably in Europe and the United States, and currently accounts for approximately half of all esophageal cancers in those regions [1, 2]. However, there are many controversial issues regarding the management of BE and BEA. The objective of this article is to review the current status of BEA and its management.

Definitions

Definition of esophagogastric junction (EGJ)

There are some differences in definitions, which must be considered when reviewing BE. In Japan, the esophagogastric junction (EGJ) is defined as the distal limit of the lower esophageal longitudinal or palisade vessels (Hoshihara's proposal) [3], but in other countries, the EGJ is defined as the proximal margin or upper end of the gastric folds (Prague C&M criteria) [4]. This difference in definition results in different measurements of the length of Barrett's epithelium. In the Japanese classification, the EGJ is defined as the lower margin of the palisading small vessels in the lower esophagus on endoscopy, the horizontal level of the angle of His in an upper gastrointestinal series, the oral margin of the longitudinal folds of the greater curvature of the stomach by endoscopy or upper gastrointestinal series, or obvious macroscopic caliber change of the resected esophagus and stomach [5]. The distal limit of the lower esophageal longitudinal or palisade

vessels was not adopted as part of the Prague criteria, because the palisade vessels may not be uniformly visible on standard endoscopy in patients with GERD. A large difference in results was reported when these methods of defining the EGJ were compared [6].

Definition of Barrett's esophagus

BE was first described by Norman Barrett in 1950 as gastric epithelium lining the lower esophagus [7], which he attributed to a congenital anomaly. Allison and Johnstone [8] subsequently described the columnar epithelium-lined part of the esophagus as follows: "(1) the esophagus below this, which is lined by gastric mucosa, retains its tubular contour, although it may be a little dilated; (2) esophageal mucus glands are present in the submucosa; and (3) in its upper part, islands of squamous epithelium remain, and esophageal mucus glands and ducts are prominent in the ulcer floor". Barrett studied Allison's findings and assumed that the BE developed as a repair process for esophagitis [9]. The guidelines of the American College of Gastroenterology define BE as a change in the distal esophageal epithelium of any length, which can be recognized as columnar type mucosa at endoscopy and confirmed by biopsy to have intestinal metaplasia [10].

In the Japanese classification of esophageal cancer [5], BE is defined when at least one of the following conditions is satisfied: esophageal glands in the area of columnar epithelium, squamous islands in the columnar epithelium, or double-layered structure of the muscularis mucosa. BE is classified as long segment BE (LSBE) if the Barrett's mucosa is circumferential and extends longitudinally for 3 cm or more, and as short segment BE (SSBE) if the Barrett's mucosa is not circumferential or it extends for less than 3 cm.

In Europe and the United States, a diagnosis of BE requires observation of columnar type mucosa in the esophagus at endoscopy with confirmed intestinal metaplasia on histological examination [10]. In Japan, the diagnosis of BE does not necessarily require identification of specialized columnar epithelium on biopsy specimens. Specialized columnar epithelium may be present, even if it is not seen in the biopsy specimens. It is difficult to differentiate histologically between BE and the gastric fundus or intestinal metaplasia with atrophy of the cardia of the stomach. Takubo attached great importance to the detection of paneth cells and esophageal gland ducts for the diagnosis [11, 12]. This subtle difference between the way in which BE is diagnosed in Japan versus Europe and the United States makes the clinicopathological study of BE and BEA difficult unless we clarify the definition of BE.

Definition of Barrett's esophageal adenocarcinoma

In the Japanese classification, BEA is defined as adenocarcinoma arising from Barrett's mucosa [5]. Adenocarcinoma arising from the gastric mucosa at the squamocolumnar junction and BEA each have a different pathogenesis, but it is often impossible to differentiate between them when the lesions are advanced.

Epidemiology

BE is an acquired precursor of esophageal adenocarcinoma and the incidence of the two conditions has risen in parallel [13]. The incidence of BEA is approximately 0.5 % per year in Europe and the United States [14], accounting for about half of all esophageal cancers in those regions [1, 2]. The incidence of BEA has risen more than sixfold over the past 25 years [15], but it now seems to have plateaued [16].

In Japan, squamous cell carcinoma accounts for approximately 90 % of esophageal cancers [17], and there have been differences of opinion regarding the incidence of BEA [18, 19]. According to the national statistics on esophageal cancer, published by the Japan Esophageal

Table 1 Rates of different forms of carcinoma of the esophagus in Japan

Years	Total cases	Adenocarcinoma	(%)	Barrett's cancer	(%)	Total adenocarcinoma	(%)
1988–1994	9821	137	1.4	N.D.		137	1.4
1995	1757	25	1.4	4	0.2	29	1.7
1996	1923	25	1.3	3	0.2	28	1.5
1997	1948	31	1.6	6	0.3	37	1.9
1998	1883	29	1.5	9	0.5	38	2.0
1999	1817	29	1.6	9	0.5	38	2.1
2000	N.C.	N.C.	N.C.	N.C.	N.C.	N.C.	N.C.
2001	2093	40	1.9	18	0.9	58	2.8
2002	1821	32	1.8	23	1.3	55	3.0
2003	2233	73	3.3	37	1.7	110	4.9

Citation from comprehensive registry of esophageal cancer in Japan [17, 20–25]

N.D. not described, *N.C.* not conducted

Table 2 Rates of different forms of adenocarcinoma of the esophagus in Japan

Years	Total cases	Adenocarcinoma	(%)	Barrett's cancer	(%)	Total adenocarcinoma	(%)
2003	7510	109	1.5	128	1.7	237	3.2
2004	8260	115	1.4	130	1.6	245	3.0
2005	9436	144	1.5	147	1.6	291	3.1
2006	9225	133	1.4	209	2.3	342	3.7
2007	9390	155	1.7	188	2.0	343	3.7
2008	9775	138	1.4	249	2.5	387	4.0
2009	9839	181	1.8	207	2.1	389	4.0

Citation from Thoracic and cardiovascular surgery in Japan [26–32]

Society, the rate of cancer arising from BE increased from 0.2 % in 1995 to 1.7 % in 2003 (Table 1) [17, 20–25]. Data of the Japanese Association for Thoracic Surgery indicated a smaller change in the rate of cancer arising from BE, from approximately 1.7 % in 2003 to 2 % in 2009 (Table 2) [26–32]. Even though the incidence of BEA appears to have increased from 1995 to 2009, the increase has not been as dramatic as in Europe and the United States. This apparent increase could be attributed to the increased recognition of BE and BEA as well as the more frequent pathological diagnosis of adenocarcinoma, enabled by the early endoscopic detection of cancer, before it becomes too large for BEA to be diagnosed.

Etiology

BE is associated with chronic GERD and has been linked to the frequent symptoms of GERD, the presence of typical GERD symptoms, and reflux episodes lasting longer than 5 min [33]. The risk of cancer developing from BE appears to vary with the extent of esophageal metaplasia; therefore, patients with LSBE may have a higher incidence of adenocarcinoma than those with SSBE [34].

Studies investigating the relationship between BE and *Helicobacter pylori* infection have shown that *H. pylori* infection inhibits the onset of BE [35]. It has been reported that BE with high-grade dysplasia and adenocarcinoma are significantly more prevalent in patients who are not infected with *H. pylori* than in those who are [36, 37]. Thus, *H. pylori* may protect against the development of BEA [36, 37] and as the *H. pylori* infection rate decreases in the younger population, the prevalence of BE and BEA may increase in Japan. This reinforces that we should screen carefully for adenocarcinoma arising from BE.

It has been reported that duodenal content induces esophageal adenocarcinoma similar to BEA in rats [38]. There may be a relationship between BEA and the Cdx2 gene, which induces intestinal metaplasia [39, 40], and many reports describe relationships between BEA and molecular abnormalities such as Cyclin D1 [41], Cyclin A [42], Rb [43], p16 [44], p53 [45, 46], NFκB [47], COX-2 [48], β-Catenin [49, 50], E-Cadherin [50], Ploidy [51], AMACR [52], and others [53]. Clinically, BE is sometimes detected after total gastrectomy and esophagectomy [54]; however, the incidences of BE and BEA do not increase after gastrectomy even in patients with bile reflux [55, 56]. This lack of association between gastric surgery and BE suggests that the reflux of bile without acid is not sufficient to damage the esophageal mucosa [55, 56].

Pathology

Paull et al. [57] described three pathological characteristics of BE: atrophic gastric fundus-type epithelium with parietal and chief cells; junctional-type epithelium with cardiac mucus glands; and distinctive specialized columnar epithelium with a villiform surface, mucus glands, and intestinal-type goblet cells [57]. Specialized columnar epithelium is not morphologically different to incomplete gastric intestinal metaplasia, and distinction between the two is difficult. Specialized columnar epithelium is most commonly located at the proximal end of BE, gastric fundus-type epithelium is most commonly located at the gastric end, and junctional-type epithelium is most commonly located in the middle. Atrophic gastritis with gastric intestinal metaplasia may give rise to well-differentiated adenocarcinoma, whereas specialized columnar epithelium may give rise to differentiated type carcinoma. Even gastric fundus-type or junctional-type mucosa has a greater tendency than normal gastric mucosa to become cancerous. Most BEA is well-differentiated type adenocarcinoma, which tends to become poorly differentiated as the cancer progresses.

Diagnosis

It is difficult to diagnose BEA at an early stage and to differentiate between borderline BEA and squamous cell carcinoma. In the United States, endoscopists carry out surveillance of BE by such methods as random biopsy to detect BEA early [58, 59]. Biopsies taken from each of the

four quadrants at every 2 cm of Barrett's epithelium only sample a small fraction of the lining, but offer the possibility of recognizing dysplasia. Many reports also describe the use of dye to evaluate BEA and dysplasia. Methylene blue selectively dyes Barrett's epithelium without atypia, but it does not dye dysplasia or BEA. Moreover, although methylene blue improves the effectiveness of biopsy sampling [60, 61], it is not always available. Magnifying endoscopy with indigo carmine [62], crystal violet staining [63], and acetic acid [64] enables evaluation of the mucosal pit pattern, while several organizations recommend esophagogastroduodenoscopy as a screening method for BE [65–67]. However, it is not known if endoscopic screening reduces mortality from BEA and this is important for determining cost-effectiveness. Recent trials have been conducted to evaluate the usefulness of methods to screen for BE such as autofluorescence imaging [68–70], nasal endoscopy [71], and capsule endoscopy [72, 73]. It has been reported that the results of screening for BE with conventional esophagogastroduodenoscopy versus esophageal capsule endoscopy are similar. Esophagogastroduodenoscopy is currently the preferred modality. Although it is currently too expensive, esophageal capsule endoscopy has the potential to provide a noninvasive diagnosis for cases of suspected BE in the near future. Capsule endoscopy requires no sedation and is painless; however, it is not currently recommended in the American College of Gastroenterology guidelines [10]. Dysplasia observed by a combination of narrow-band imaging endoscopy [69, 70, 74, 75] and magnifying endoscopy enables a detailed diagnosis to be made. Some reports have described the usefulness of narrow-band imaging targeted biopsies for the diagnosis of abnormal vascular patterns, irregular mucosal patterns, high-grade dysplasia, and BEA [70, 74, 76].

Treatment

The treatment of BEA is often based on the depth of invasion, similar to the treatment of gastric cancer; however, BEA is located in the mediastinum, with different lymphatic and vascular networks to the stomach, resulting in a different pattern of lymph node metastasis. BE also has different pathological features to the stomach such as a double-layered muscularis mucosa and no serosa. According to some reports from Europe and the United States, lymph node metastasis was not found in operative specimens of BEA limited to the mucosal layer [77, 78]. In one report, patients with BEA limited to the mucosal layer had a node metastasis rate of 7.1 % [78]. In Japan, BEA is managed the same way as squamous cell carcinoma of the esophagus [5].

Endoscopic treatment

Endoscopic mucosal resection and submucosal dissection are used to resect BEA, while other endoscopic treatments include argon plasma coagulation, laser treatment, photodynamic therapy, and microwave coagulation therapy. The Japanese guidelines do not provide precise indications for the endoscopic treatment of BEA; however, the indications for endoscopic mucosal resection [79, 80], submucosal dissection [81], argon plasma coagulation [82], photodynamic therapy [83], laser treatment [84], and microwave coagulation therapy are generally restricted to the treatment of BEA limited to the mucosal layer, which has a low possibility of lymph node metastasis and vascular invasion.

Surgical treatment

There is currently no consensus regarding the ideal operative procedure or extent of lymph node dissection for BEA, because of the small number of cases in Japan. According to some reports, the frequency of lymph node metastasis is the same for both esophageal squamous cell carcinoma and adenocarcinoma in same tumor location [85, 86]. However, it has been found to be higher in T1 esophageal squamous cell carcinoma [87, 88], indicating that squamous cell carcinoma is more aggressive than adenocarcinoma. Radical esophagectomy and regional lymph node dissection should be performed for esophageal adenocarcinoma that has invaded the submucosal layer. The surgical treatment of BEA is determined by the location of the tumor, its depth of invasion, and sometimes the experience of the surgeon. For Siewert's type I cancer, esophagectomy and mediastinal lymph node dissection can be performed via thoracotomy. A Dutch study proved the safety and radicality of transhiatal esophagectomy [89], but transhiatal esophagectomy had a worse outcome than thoracotomy for those patients with lymph node metastasis [90]. There is controversy about the choice of right or left thoracotomy, although it has been established that right thoracotomy is better for upper mediastinal lymph node dissection. For Siewert's type II or III cancer, the surgical approach should be decided according to the depth of invasion, location of lymph node metastases, and location of BE. For example, transhiatal esophagectomy should be chosen for superficial carcinoma arising from SSBE without lymph node metastasis, because mid-mediastinal lymph node dissection is not needed. Moreover, the Barrett's epithelium from which the carcinoma arose should be removed because BE is a precursor of esophageal adenocarcinoma and the margin of cancer is unclear.

Chemotherapy

Chemotherapy is indicated as primary treatment for inoperable BEA with distant metastasis, or as adjuvant therapy combined with surgery for patients with multiple lymph node metastases. Chemoradiotherapy without surgery is also an acceptable radical therapy. A meta-analysis of studies provides strong evidence of the survival benefit of neoadjuvant chemoradiotherapy or chemotherapy over surgery alone for patients with BEA [91]. The National Comprehensive Cancer Network Guidelines, version 2.2011, recommend preoperative chemoradiotherapy, definitive chemoradiotherapy, or preoperative chemotherapy for any T2 or higher adenocarcinoma of the distal esophagus or EGJ with nodal metastasis [92]. The decision to administer postoperative radiotherapy is based on the pathological diagnosis and other factors such as performance status, medical comorbidities, toxicity profile, and HER2-neu expression. In Japan, the chemotherapy protocol for adenocarcinoma of the EGJ tends to be the same as for gastric cancer, using S-1.

Radiation therapy

There is little evidence to support the use of radiotherapy for BEA in Japan, because BEA is uncommon and most lesions are resectable without damaging the aorta. Moreover, Japanese surgical oncologists have a preference for surgical therapy over radiotherapy. On the other hand, definitive chemoradiotherapy is standard in the United States (see "Chemotherapy", "Chemoradiotherapy").

Chemoradiotherapy

Combined chemotherapy and radiotherapy is given as definitive therapy and as adjuvant therapy to patients with esophageal adenocarcinoma. A recent meta-analysis found strong evidence of a survival benefit for patients undergoing neoadjuvant chemoradiotherapy or chemotherapy versus those undergoing surgery alone [91]. The survival benefits of neoadjuvant chemoradiotherapy were found to be similar in squamous cell carcinoma (hazard ratio 0.80, 95 % confidence interval 0.68–0.93; $P = 0.004$) and adenocarcinoma (hazard ratio 0.75, 95 % confidence interval 0.59–0.95; $P = 0.02$) [91]. Definitive chemoradiotherapy is also an effective treatment for esophageal adenocarcinoma or BEA in patients who refuse surgery. A prospective randomized trial found no difference in long-term outcomes after definitive chemoradiotherapy for adenocarcinoma and squamous cell carcinoma [93].

Prognosis

Early detection by endoscopic surveillance programs accounts for the good outcome of patients with BEA reported in many series [94, 95]. However, adenocarcinoma has been reported to have a similarly good outcome if detected early 96–98]. This good prognosis may be due to the site of the adenocarcinoma and the surgical techniques employed. As most BEAs are well-differentiated, a good outcome should be expected. On the other hand, advanced BEA has a worse outcome because of the increased rate of lymph node metastasis and the development of a poorly differentiated component as the tumor progresses.

Prevention

Medication and anti-reflux surgery are used to prevent the progression of BE to BEA [10]. The best evidence for chemoprevention supports non-steroidal anti-inflammatory agents [99]. Moreover, data from two retrospective cohort studies suggest that proton pump inhibitors significantly reduce the likelihood of dysplasia developing [100, 101]. Fundoplication provides excellent long-lasting relief of symptoms in patients with BE and may promote the regression of metaplasia and dysplasia [102, 103]. The long-term results of fundoplication are good [102, 103]. One study showed that fundoplication prevented progression to high-grade dysplasia and adenocarcinoma [102]. However, as BEA has been reported to occur after anti-reflux surgery [104], pH monitoring is important in the follow-up of surgically treated patients.

Conclusion

The increasing number of cases of BE and BEA, attributed to the Westernization of lifestyle and a decreasing incidence of *H. pylori* infection, is a serious problem in Japan. The key to reducing the incidence of BEA in Japan is a better understanding of the pathogenesis of BE.

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