

UNIT NO. 3

GASTRIC CANCER, BARRETT'S ESOPHAGUS AND ESOPHAGEAL ADENOCARCINOMA

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ABSTRACT

Over the past decades, the epidemiology of gastric cancer, Barrett's esophagus and esophageal adenocarcinoma have shifted dramatically, with some populations in the West reporting several folds increase in the incidence of Barrett's esophagus and esophageal adenocarcinoma. In Asia, rising incidence in esophageal adenocarcinoma has been reported in Singapore. Although the overall incidence of gastric cancer has decreased in many regions, gastric cancer remains one of the top killers worldwide, and is particularly prevalent in developing countries. The incidences of gastric cancer, Barrett's esophagus and esophageal adenocarcinoma vary widely from region to region, and are dependent on genetic, economic and socio-environmental factors. Among them, dietary factors and *Helicobacter pylori* infection are two major determinants of gastric cancer, while gastroesophageal reflux and obesity have been linked to Barrett's esophagus, a known precursor of esophageal adenocarcinoma. The use of high-tech diagnostic methods developed in recent years has made screening and diagnosis of these diseases easier. These technologies, together with strategic screening of high-risk populations have enabled earlier detection of neoplastic lesions to allow more timely intervention of the disease process. On the other hand, newer, less invasive endoscopic and surgical intervention techniques are making radical changes towards better management of the diseases, right from pre-neoplasia stage. This article will review the diagnosis and management of these diseases in the light of current clinical practices.

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INTRODUCTION

The recent decade has seen marked changes in the epidemiology of gastric cancer, Barrett's esophagus and esophageal adenocarcinoma. While the overall incidence of gastric cancer has been on the down trend, tumors in the lower third of the esophagus and in areas just adjacent to the gastroesophageal junction are increasingly seen. Many Western nations have witnessed dramatic increases (up to more than 300%) in the

incidence of esophageal adenocarcinoma, a malignancy which is associated with longstanding Barrett's esophagus¹.

The incidence of Barrett's esophagus has also been rising gradually, a trend believed to be associated with the growing obesity epidemic in many populations, and the increasing prevalence of gastroesophageal reflux disease in many urbanized regions². Both increase in gastroesophageal reflux disease and decrease in gastric cancer have been attributed to the recent reduction or eradication of *Helicobacter pylori* in populations, a theory that is supported by several observational studies but remains scientifically controversial^{3,4}.

Both gastroesophageal reflux disease and Barrett's Esophagus are more prevalent in the West than in the East, where prevalence remains low but is reported to be on the gradual rise^{4,5}. Other than genetics and environment, dietary factors and habitual smoking and alcoholism have been associated with gastric cancer⁶.

DIAGNOSIS AND TREATMENT

Symptomatic presentation per se is often a poor indicator of presence of Barrett's esophagus, and early stage gastric cancer and esophageal adenocarcinoma. In early stage gastric cancer or esophageal adenocarcinoma, patients may present with upper abdominal symptoms which may be vague and not particularly distinctive of the disease they are suffering from. More specific symptoms only come with advancing cancer development. Cancer should be suspected if patient present with any alarm symptom (e.g., dysphagia, vomiting, weight loss, anaemia); in which case, a prompt referral to a gastrointestinal specialist for further investigation is in the order.

These days, although barium radiology and other laboratory investigations are still being used in the diagnostic work-up, investigations of suspected Barrett's esophagus, gastric cancer or esophageal adenocarcinoma are primarily conducted via an upper endoscopy, with biopsy of endoscopically suspected areas, and histopathologic examinations of the specimens acquired. The histology of specimen remains the gold standard for confirmative diagnosis.

Gastric Cancer

Gastric cancer is the second leading cause of cancer death worldwide, accounting for 700,349 deaths per year⁷. Most gastric cancers are adenocarcinomas (90-95%). Patients with early stage gastric cancer typically present with mild upper abdominal symptoms such as the ones listed in Table I. As the

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Table 1. Symptoms of Early Gastric Cancer

| | |
|------|-----------------------|
| i. | Abdominal discomfort |
| ii. | Postprandial fullness |
| iii. | Loss of appetite |
| iv. | Heartburn |
| v. | Nausea |

Table 2. Symptoms of Advanced Gastric Cancer

| | |
|------|---------------------------|
| i. | Vomiting |
| ii. | Dysphagia |
| iii. | Fecal occult blood |
| iv. | Unintentional weight loss |
| v. | Pain in the stomach |
| vi. | Ascites |
| vii. | Jaundice |

cancer advances, patient may feel an insidious upper abdominal pain or discomfort and may complain of postprandial fullness, with or without nausea, vomiting and anorexia. The patient may also experience weight loss and symptoms such as the ones listed in Table 2 may surface as the cancer progresses. Dysphagia may be a main symptom if lesion grows in the cardia region. A palpable abdominal mass generally indicates a long-standing tumor growth. At more advanced stages of the disease, hematology/biochemistry tests may show hypoproteinemia, anemia, and abnormal liver function. An increase in carcino-embryonic antigen (CEA) may be observed in 45-50% of gastric cancer cases. The cancer antigen (CA) 19-9 may be elevated in about 20% of the cases.

Endoscopy with histopathologic examination of biopsied specimens is the preferred examination tool because of its high diagnostic accuracy (>95%) and ability to identify even diminutive lesions. For preoperative staging of gastric cancer, endoscopic ultrasound (EUS) is currently the modality of choice; it is most accurate among available diagnostic modalities in determining the depth of tumor penetration, and in assessment of cancer spread to adjacent structures and nodes. Computed tomography (CT) scan and magnetic resonance imaging (MRI) of the abdomen, chest and pelvis may be more useful for delineating the extent of the tumor and metastases.

Treatment for gastric cancer is dependent on the location, type and stage of the cancer, and the overall health of the patient. The aim in all treatments is to eliminate the cancer, although this is not always possible. Surgical resection is usually recommended for patients amenable to surgery, while chemotherapy, radiotherapy and palliative treatment are options for patients unfit to undergo surgical procedures. Gastrectomy may be partial, sub-total or total, depending on the location and extent of the cancer, and may be performed with regional lymphadenectomy. An esophagogastrectomy may be performed in cases of tumors residing at the cardia and gastroesophageal junction. A subtotal gastrectomy is recommended if tumor is

located at the distal stomach. Post-operative chemoradiotherapy may be adjuvant treatment for stage I cancer with node-positive and muscle-invasive disease. For stage II, III and IV cancer, both perioperative and postoperative chemoradiotherapy are recommended. The stage of the cancer and the completeness of surgical resection is main determinant of prognosis. At stage 0, more than 90% of patients treated by curative gastrectomy with lymphadenectomy could survive beyond 5 years. Survival generally decreases with advancing stage of the disease, with 5-year survival rate post-surgical resection down to 60-90% for stage I, 30-50% for stage II, and 10-25% for stage III disease.

Barrett's Esophagus

Barrett's Esophagus is a premalignant condition. It usually presents with no specific symptom, but patients with Barrett's Esophagus would typically have experienced symptoms associated with gastroesophageal reflux disease. Approximately 10% of patients with chronic GERD develops Barrett's esophagus. Diagnosis of Barrett's esophagus is based on initial endoscopic investigation and histopathologic examination of specimens obtained from biopsy of the endoscopically visible Barrett's segment. On endoscopy, Barrett's esophagus usually appears as a well-defined salmon-pink area of velvety mucosa at the esophagogastric junction. The affected segment may extend to variable lengths, but amongst Asians, short-segment (< 3 cm) Barrett's esophagus is more commonly seen, as opposed to the long segment (> 3 cm) type seen most often in Western populations. Diagnosis is confirmed only if histologic examination of biopsied specimens shows the presence of intestinal metaplasia (columnar epithelium with goblet cells). Treatment and management of Barrett's Esophagus is based on histologic findings; in other words, the presence or absence of intraepithelial neoplasia and the degree of the neoplasia, if present. The degree of intraepithelial neoplasia determines the malignant potential of the lesion. Patients with Barrett's esophagus with no intraepithelial neoplasia may need no specific treatment, although if they have gastroesophageal reflux disease, it may be controlled with antisecretory drugs such as proton pump inhibitors (see Table 3), as per regular treatment. Patient may also opt for antireflux procedures such as fundoplication, if suitable. But therapies such as these ones have not been proven to cause substantial regression of metaplastic tissue nor avert progression of Barrett esophagus to adenocarcinoma.

Table 3. Common Anti-Secretory Drugs Used for Treatment of Gastroesophageal Reflux

| |
|--------------------------------|
| lansoprazole (Prevacid) |
| omeprazole (Prilosec, Zegerid) |
| pantoprazole (Protonix) |
| rabeprazole (Aciphex) |

If intraepithelial neoplasia is found in the Barrett's epithelium, appropriate intervention, with follow-up surveillance at appropriate time-intervals is generally recommended⁸. There is presently no consensus on the optimal frequency of endoscopic surveillance for Barrett's esophagus. But generally, a repeat endoscopy at 3-year interval is deemed adequate for cases with no evidence of intraepithelial neoplasia. The finding of low grade neoplasia would warrant a follow-up endoscopy within six months, followed by yearly endoscopy if no sign of neoplasia is found on two consecutive annual endoscopies. In case of advanced neoplasia, a repeat endoscopy 3 months after the initial one, followed by intervention and/or further 3-monthly surveillance is recommended. In all cases, confirmation of diagnosis by a gastrointestinal pathologist is called for.

Cases with confirmed advanced intraepithelial neoplasia should be intervened. Current intervention methods include endoscopic submucosal dissection or ablation of the Barrett's segment using photodynamic therapy. Other available ablative methods include multipolar electrocautery, laser therapy, radiofrequency ablation, cryotherapy, and argon plasma coagulation. The aim of all treatment methods is to eliminate the Barrett's epithelium to let normal esophageal epithelium grow over and replace it. But whether ablated Barrett esophagus could still develop into cancer is not certain; many of the ablative techniques are still experimental at this point in time. Esophagectomy is usually reserved for Barrett's segment with extensive neoplastic development.

Esophageal Adenocarcinoma

Adenocarcinomas represent about 50% of esophageal cancer and the majority of esophageal adenocarcinoma occurs in the distal end of the esophagus. It often arises in the setting of pre-existent Barrett's esophagus. Under the endoscopic view, esophageal cancer appears as thickened plaque-like white mucosa. Larger lesions may appear as white exophytic polypoid masses with well demarcated margins. Patients with esophageal cancer, and unintentional loss of body weight (approximately 10%) which occurs over a short span of time (< 6 months). Patient may have anemia from chronic gastrointestinal bleeding, but melena or acute upper gastrointestinal bleeding is rare. Intractable coughing may occur if patient develops a tracheoesophageal fistula. Sudden onset of hiccups, and episodes of regurgitation and aspiration pneumonia may indicate possible transmural disease that involves either the mediastinum or the diaphragm. Prognosis is dismal in such cases. Although contrast barium radiology is still being used for initial screening of esophageal cancer, upper endoscopy is now the preferred modality. Diagnosis of esophageal adenocarcinoma is always confirmed by histopathologic report.

Treatment option is fundamentally based on the stage of the disease, which is also the main determinant of clinical

outcome and survival. Usually, a CT, MRI or positron emission tomography (PET) scan of the abdomen, chest and pelvis would serve to evaluate the presence and extent of metastases. While contrast-enhanced CT is most accurate for detecting distant metastasis, EUS is most accurate for locoregional staging, and is the modality of choice to evaluate the depth of tumor's invasion. Management and treatment of esophageal adenocarcinoma depends on the stage of the tumor at diagnosis. Lymph node involvement is associated with poor prognosis. Surgical resection is the mainstay treatment for all patients fit enough to undergo surgery, but multi-modality treatment may be recommended⁹. Ablative treatments such as photodynamic therapy and laser therapy may be employed for local destruction of the tumor. Complete tumor removal with histologically confirmed tumor free margins may be curative for stage 0 and stage I tumors. Patients with dysphagia (usually in stage II and III) are best managed with surgery and/or chemoradiotherapy. Median survival after surgery alone is approximately 12 months. Chemoradiotherapy with palliative treatment is recommended for patients with metastatic stage III and stage IV cancer. The main goal here is to palliate symptoms and improve survival of patient.

CONCLUSION

Gastric cancer, Barrett's esophagus and esophageal adenocarcinoma represent three upper gastrointestinal diseases that are undergoing epidemiologic shifts. Despite the low prevalence of Barrett's esophagus and esophageal adenocarcinoma, the overall disease burden is considerable. As curability of the disease at late stage is extremely remote, and treatment options are limited, early detection and intervention is key to better clinical outcomes. This might improve with availability of newer, more powerful diagnostic imaging modalities such as high-resolution confocal endomicroscopy, Raman spectroscopic imaging, narrow-band and autofluorescence imaging, as well as emerging highly specific and sensitive molecular diagnostic techniques, which are all set to make early diagnosis of the diseases easier and faster. But more strategic management of the diseases needs await a better understanding of the changing epidemiology and etiology of these diseases, and identification of the population at risk of these diseases.

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LEARNING POINTS

- **Gastric cancer, Barrett's esophagus and esophageal adenocarcinoma represent three upper gastrointestinal diseases that are undergoing epidemiologic shifts.**
 - **As curability of the disease at late stage is extremely remote, and treatment options are limited, early detection and intervention is key to better clinical outcomes.**
 - **Availability of newer, more powerful diagnostic imaging modalities such as high-resolution confocal endomicroscopy, Raman spectroscopic imaging, and narrow-band and autofluorescence imaging help to make early diagnosis of the diseases easier and faster.**
 - **A CT, MRI or positron emission tomography (PET) scan of the abdomen, chest and pelvis would serve to evaluate the presence and extent of metastases. EUS is most accurate for locoregional staging, and is the modality of choice to evaluate the depth of tumor's invasion.**
 - **Treatment option is fundamentally based on the stage of the disease, which is also the main determinant of clinical outcome and survival.**
 - **Surgical resection is the mainstay treatment for all patients fit enough to undergo surgery, but multi-modality treatment may be recommended.**
 - **Ablative treatments such as photodynamic therapy and laser therapy may be employed for local destruction of the tumor.**
 - **Complete tumor removal with histologically confirmed tumor free margins may be curative for stage 0 and stage I tumors. Patients with dysphagia (usually in stage II and III) are best managed with surgery and/or chemoradiotherapy.**
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