What is Barrett's esophagus?

The normal esophagus (swallowing tube) is lined by a pinkish-white tissue called squamous epithelium. Some people also have red stomach tissue (normal appearing columnar epithelium) present in the bottom part of the esophagus. Barrett's esophagus is a condition in which the normal squamous epithelium of the esophagus has been replaced by an abnormal red columnar epithelium called specialized intestinal metaplasia. Specialized intestinal metaplasia is red, like normal stomach tissue, but does not look like stomach tissue under the microscope. Therefore, a biopsy (a piece of tissue taken from the esophagus) is needed to diagnose Barrett's esophagus.

Normal esophagus and stomach

The esophagus passes through a hole in the diaphragm (breathing muscle) where it joins the stomach. The entire stomach is within the abdominal cavity, below the diaphragm.

Inside the normal esophagus and stomach

The entire esophagus is lined by normal squamous (shown here as light pink). The stomach is lined by normal columnar lining (shown here as dark pink). The region where the normal squamous esophageal lining joins the normal columnar stomach lining is called the squamocolumnar junction.

Hiatal hernia

Most people with Barrett's esophagus have a hiatal hernia. However, hiatal hernias are very common and most people who have a hiatal hernia do not have Barrett's esophagus.
Hiatal hernia

The diaphragm (breathing muscle) separates the abdominal cavity from the chest cavity. Normally the entire stomach lies within the abdominal cavity. In this illustration, a small portion of the stomach has moved backwards through the opening in the diaphragm and into the chest cavity. This small portion of stomach above the diaphragm is referred to as a hiatal hernia.

Inside the normal esophagus with hiatal hernia

The entire esophagus is lined by normal squamous (shown here as light pink). The stomach is lined by normal columnar lining (shown here as dark pink). The region where the normal squamous esophageal lining joins the normal columnar stomach lining is called the squamocolumnar junction. In this case, the squamocolumnar junction has moved up and away from the diaphragm because of the hiatal hernia.

Inside a short segment Barrett's esophagus

A short length of Barrett's esophagus is seen between the top of the hiatal hernia and the normal squamous esophagus. In this case, the squamocolumnar junction is made up of normal squamous esophageal lining on one side and Barrett's esophagus (specialized intestinal metaplasia) on the other side. The Barrett's esophagus must be confirmed by biopsy.

Inside a long segment Barrett's esophagus

A long length of Barrett's esophagus is seen between the top of the hiatal hernia and the normal squamous esophagus. The squamocolumnar junction has moved a great distance up and away from the diaphragm due to the long segment of Barrett's esophagus (specialized intestinal metaplasia). The Barrett's esophagus must be confirmed by biopsy.

Barrett's esophagus and cancer

Barrett's esophagus is a pre-malignant (precancerous) condition. This means that the Barrett's lining is more prone to developing cancer than other normal tissues of the body. The type of cancer that develops in Barrett's esophagus is called esophageal adenocarcinoma. Since the 1970's, this cancer has been rapidly increasing in Western Europe and the United States. Esophageal adenocarcinoma now accounts for 60% of all esophageal cancers in the U.S. with an estimated 8,000 new cases diagnosed per year.

**Important Tip: Diagnosis of Barrett's esophagus**

At the present time, only specialized intestinal metaplasia of the esophagus is classified as Barrett's esophagus. Currently, it is recommended that only patients with this diagnosis undergo periodic cancer surveillance.

People who have Barrett's esophagus have a 30 to 40 fold increased risk of developing esophageal adenocarcinoma as compared to the general population. Still, the overall cancer risk in patients who have Barrett's esophagus is low. The results of multiple studies of patients who are being followed by a doctor for their Barrett's esophagus indicate that most patients with Barrett's esophagus (90-95%) DO NOT develop cancer during long-term follow-up. In addition, autopsy studies have shown that most patients who have Barrett's esophagus live their lives without ever developing Barrett's associated cancer and die of other causes.

**The changing definition of Barrett's esophagus**

The definition of Barrett's esophagus has changed since the condition was first described in 1950 by the British surgeon, Norman Barrett. Dr. Barrett proposed that the red-colored esophagus seen in some patients was actually part of the stomach and that these patients were probably born with a short esophagus (due to the short length of the white squamous esophageal lining). Later, Barrett's esophagus was defined as any red esophageal lining (columnar epithelium), including normal stomach lining, of 3 cm or greater in length.

We now have evidence that most esophageal adenocarcinomas develop in an abnormal columnar lining in the esophagus called specialized intestinal metaplasia. There is little evidence, thus far, that esophageal adenocarcinomas develop in the columnar stomach lining that can sometimes be present in the esophagus. Both types of these columnar linings look red by upper endoscopy, a procedure performed by a gastrointestinal doctor to examine the esophagus. To confirm that a red lining in the esophagus is indeed specialized intestinal metaplasia, the doctor must take multiple biopsies to obtain pieces of tissue from the lining and send it to the pathology lab for histologic analysis (examination of the tissue under a microscope).

According to the American College of Gastroenterology guidelines, Barrett's esophagus should now be defined as "a change in the ESOPHAGEAL epithelium (lining) of ANY LENGTH that can be recognized at upper endoscopy and is confirmed to have intestinal metaplasia by biopsy." This definition makes the distinction between the stomach lining that can be present in the esophagus and the abnormal specialized intestinal metaplasia. The new definition also emphasizes that the intestinal metaplasia must be esophageal in location. Many patients have intestinal metaplasia at the very top of the stomach, just below where the esophagus ends (intestinal metaplasia of the gastric cardia). Intestinal metaplasia in this location is NOT classified as Barrett's esophagus. At the present time, because specialized intestinal metaplasia is the only lining known to have an increased risk of developing esophageal cancer, it is recommended that only patients who have specialized intestinal metaplasia of the esophagus need to undergo endoscopic biopsy surveillance (cancer surveillance procedure) to detect esophageal adenocarcinoma, if it develops, at an early and curable stage.

**What causes Barrett's esophagus?**

Barrett's esophagus is caused by years of chronic heartburn (gastroesophageal reflux disease - GERD). When the esophagus (swallowing tube) is exposed to stomach acid and bile backwashing into it, these substances can cause injury to the normal squamous lining of the esophagus. Esophageal injury with inflammation is called esophagitis. In about 10% of those who have severe GERD, if acid injury to the esophagus continues over many years, the injured normal squamous lining of the esophagus does not grow back. Instead, it is replaced by a new abnormal lining called Barrett's esophagus (specialized intestinal
metaplasia of the esophagus).

No one knows why Barrett's esophagus develops in response to acid injury to the esophagus. Barrett's esophagus produces mucus, like normal stomach lining, and therefore may resist acid injury better than the normal squamous lining of the esophagus. It may be the body's attempt to protect the esophagus against continued injury by chronic GERD. In fact, some people who have Barrett's esophagus report a past history of heartburn but none in recent years. This has led some researchers to believe that the development of Barrett's esophagus may relieve GERD (heartburn) symptoms in some people. No one knows why some people who have severe GERD develop Barrett's esophagus and why others do not.

What is gastroesophageal reflux disease (GERD)?

It is estimated that more than one third of the US population experiences heartburn at least once per month, 20% at least weekly and around 7% daily. Gastroesophageal reflux disease (GERD) is referred to as "heartburn" because the most common symptom is a burning discomfort in the chest under the breast bone. In fact, a burning discomfort in the chest or upper abdomen that is relieved with acid reducing medication, such as Tums® and regurgitation (burping up) of sour tasting gastric juice into the mouth are classic symptoms of GERD, which are easily recognized by physicians. However, there are many other patient symptoms that may be due to GERD, but not so easily recognized as GERD by physicians. The following topics will be discussed in this section:

- The Causes of GERD (pathogenesis of the disease)
- Complications of GERD (side-effects)
- How GERD is diagnosed?
- How GERD is treated?

Causes of GERD (heartburn)

GERD (backwashing of stomach acid and bile into the esophagus or swallowing tube) occurs as a result of the failure of the various mechanisms designed to keep stomach contents (acid and digestive juices) out of the esophagus. The lower esophageal sphincter (LES), is a muscle or valve located at the bottom of the esophagus where the esophagus joins the stomach. The LES normally maintains a higher pressure than the pressure of the stomach to keep stomach contents out of the esophagus. Transient or brief LES relaxations (intermittent lowering of LES pressure) may lead to backwashing of stomach contents into the esophagus. These transient LES relaxations account for most of the gastroesophageal reflux episodes in people, including the occasional symptoms in normal people and in most people who have GERD. However, in some people who have severe GERD, including those who have Barrett's esophagus, the LES has an abnormally low pressure, allowing stomach contents to more readily bathe the esophagus.

The ability to clear the esophagus of refluxed acid also plays a very important role in GERD and in the development of esophagitis (inflammation of the esophagus from acid and bile injury). Although most people who have mild to moderate GERD have normal esophageal contractions that clear the esophagus of refluxed acid, about half of those who have severe GERD, including many of those who have Barrett's esophagus, have weak esophageal contractions. Their esophageal contractions are not strong enough to adequately "strip" stomach contents out of the esophagus, leading to prolonged acid and bile exposure to the esophagus. This prolonged exposure allows injury to the normal squamous lining of the esophagus to occur, resulting in esophagitis and in some people, healing of the esophagus with the development a new lining, Barrett's esophagus.

Other factors that play a role in some people who have GERD include hiatal hernia, delayed gastric emptying, overproduction of acid, a bacterium called H. pylori and bile reflux. Decreased saliva production and protective mucosal factors play a role in GERD but may be less important in the vast majority of patients.

Complications of GERD (side-effects)
Most people who have GERD do not experience complications. For some who have severe GERD, complications do develop. Esophagitis (inflammation of the esophagus) with erosions and ulcerations (breaks in the lining of the esophagus) can occur from repeated and prolonged acid exposure. If these breaks are deep, bleeding or scarring of the esophagus with formation of a stricture (narrowing of the esophagus) can occur. If the esophagus narrows significantly, then food sticks in the esophagus and the symptom is known as dysphagia.

![Normal squamous esophagus](Image)

**Normal squamous esophagus**

*Photo courtesy of the Seattle Barrett's Esophagus Research Program*

![Erosive esophagitis with stricture](Image)

**Erosive esophagitis with stricture**

The squamous esophagus has a narrowed opening (lumen) due to chronic GERD with inflammation and scarring. This narrowed opening is called a stricture. The surrounding esophageal lining has ulcerations and erosions (mucosal breaks) from chronic acid injury to the esophagus.

*Photo courtesy of Joel E Richter MD - Temple University*

GERD has been shown to be one of the most important risk factors for the development of esophageal adenocarcinoma. In a subset of people who have severe GERD (approximately 10%), if acid exposure continues, the injured squamous lining is replaced by Barrett's metaplasia, a precancerous lining in which esophageal adenocarcinoma can develop. No one knows what causes Barrett's esophagus.

Finally, other complications of GERD may not appear to be related to esophageal disease at all. Some people with GERD may develop recurrent pneumonia (lung infection), asthma (wheezing), or a chronic cough from acid backing up into the esophagus and all the way up through the upper esophageal sphincter into the lungs. In many instances, this occurs at night, while the person is sleeping. Occasionally, a person with severe GERD will be awakened from sleep with a choking sensation. Hoarseness can also occur due to acid reaching the vocal cords, causing chronic inflammation or injury.

**Diagnosis of GERD**

**GERD symptoms**

Most people who have GERD can be diagnosed based on their symptoms alone. Typically, these symptoms include a burning pain in the high abdomen or chest that typically moves upward toward the mouth and is relieved by acid reducing medication, such as Tums®. It usually occurs after eating or is related to body position, such as bending over or lying down. It is not uncommon for gastroesophageal reflux to occur at night while lying down with resulting regurgitation of acid into the throat and sometimes the mouth. Many patients with GERD will also have the sensation of fullness in the neck when swallowing, difficulty swallowing, or excess mucous production in the throat. When the typical symptoms are present, no further testing is needed to make a diagnosis of GERD. Many patients are prescribed a course of acid suppressing (acid decreasing) drugs and if symptoms greatly improve or disappear, GERD has been successfully diagnosed and treated. However, if no further work up is done, Barrett's esophagus, if present, will be missed.
Printable List of GERD symptoms

Many people do not have the typical symptoms of GERD and may have vague or atypical symptoms due to GERD. Some of these people may have chest pain without a burning component. In some cases this chest pain due to GERD may radiate down the arms, into the jaw, ear or neck and mimic heart disease. Other people with GERD have vague abdominal pain or burning abdominal pain, bloating and belching and may take a lot of antacids for these symptoms. Sometimes these symptoms are confused with gallbladder disease or peptic ulcer disease. In patients who have atypical symptoms of GERD, it may become necessary to perform tests to distinguish GERD from heart disease, gallbladder disease or peptic ulcer disease. Even more challenging for the physician, it is not rare for patients to have more than one of these diseases, making it extremely important to sort out the cause of a patient's symptoms. In the case of atypical chest pain that could be indicative of heart disease, it is wise practice to have the patient evaluated for heart disease prior to evaluation for GERD.

Unfortunately, a large number of people who have significant complications of GERD will go undiagnosed, many of them with resultant lung disease or Barrett's esophagus. Most of these people never seek medical attention for their symptoms and some self medicate with over-the-counter acid reducing medications such as Tums®, Maalox™, Pepcid® AC or Prilosec OTC. Others have symptoms that do not involve the digestive tract, such as asthma, cough or hoarseness, that may not be recognized as GERD by their physician. Still in others with severe GERD, their symptoms have disappeared after years of chronic heartburn.

A small number of people who have severe GERD will be prompted to see a doctor because they are vomiting blood, passing black or bloody bowel movements, or getting food stuck in their esophagus. These symptoms are serious and need immediate medical attention.

Diagnostic tests for GERD

Most patients who have typical GERD symptoms can be diagnosed based on symptoms alone and if they respond favorably to medical therapy, may need no further tests to diagnose GERD. In fact, if a patient is treated with a high-dose of a medication called a proton pump inhibitor, and their symptoms go away, this confirms that the patient's symptoms are caused by GERD and other more expensive tests to diagnose GERD may not be needed. Diagnostic testing may be necessary to determine whether a patient's atypical heartburn symptoms are due to GERD, and is necessary to diagnose Barrett's esophagus, or as part of an evaluation for anti-reflux surgery.

The initial test may be a barium esophagram (an esophageal x-ray study) that can detect large defects in the esophageal lining, such as some ulcers or strictures or tumors, but cannot reliably diagnose GERD or Barrett's esophagus. Esophagogastroduodenoscopy (EGD or upper endoscopy with biopsy) is the most sensitive test for esophageal injury (esophagitis) and the only test to confirm the presence of Barrett's esophagus.

Endoscopic diagnosis of esophagitis or Barrett's esophagus confirms that the patient has GERD and no further testing is necessary. However, upper endoscopy does not detect those GERD patients who do not have esophagitis or Barrett's esophagus. To confirm the diagnosis of GERD, these patients may need pH monitoring. This test measures the number of acid reflux episodes and is also used to tell whether the patient's symptoms are caused by acid reflux. Patients who are considering anti-reflux surgery also undergo pH monitoring and esophageal manometry in addition to upper endoscopy.

Treatment of GERD

For patients with GERD, with or without Barrett's esophagus, the goal of therapy is to achieve relief of heartburn symptoms as well as to prevent the complications or adverse side-effects of GERD. Treatment of GERD includes life-style changes to lessen the opportunity for acid reflux, medical therapy and anti-reflux surgical therapy. Recently, endoscopic therapies for the treatment of GERD are being offered to patients who have mild or uncomplicated GERD, as an alternative to medical or surgical therapies. However, the long-term outcome of these therapies is unknown and have not been evaluated in patients who have Barrett's esophagus. Most experts agree that these therapies should only be offered in the setting of a clinical trial.

Medical therapy involves the use of acid suppressive drugs, the most potent of which belong to the class of
proton pump inhibitors or PPIs. Examples of these drugs are esomeprazole (Nexium®), lansoprazole (Prevacid®), omeprazole (Prilosec® and Zegerid and now available without a prescription as Prilosec OTC), pantoprazole (Protonix®) and rabeprazole (Aciphex®). These drugs have become the mainstay of treatment of GERD and have an excellent safety record. Anti-reflux surgery, particularly laparoscopic surgery, has an important role in the treatment of GERD, especially in patients who continue to have complications of GERD despite medical therapy. Herbal remedies for the treatment of GERD are beyond the scope of this site.

**Important Tip: Symptom Warnings**

If a patient's GERD symptoms are poorly controlled on proton pump inhibitors (a type of medicine for heartburn), then this may be a warning sign that anti-reflux surgery will also fail to control a patient's symptoms. The warning sign is that the patient's symptoms may not be caused by GERD in the first place.

---

**Expanded Information**

**Acid hypersecretion**

GERD (backwashing of gastric acid and bile into the esophagus) plays a large role in the damage of the normal esophageal lining. In most people who have GERD, including severe GERD, their acid production (the amount of acid that they make is normal). However, many people who have Barrett's esophagus have been shown to make an excessive amount of acid.

---

**Expanded Information**

**Bile reflux**

Reflex of bile acids into the esophagus may contribute to injury of the esophageal lining. Bile is a component of digestive juices normally present in the small intestine. Bile can reflux from the small intestine into the stomach and does so normally. However, in a subset of people who have severe GERD (backwashing of acid and bile into the esophagus), including in those who have Barrett's esophagus, there is an increase in the amount of bile back-washing into the esophagus. Although acid reflux is increased in patients who have Barrett's esophagus and plays a primary role in the development of Barrett's esophagus, there is evidence that bile reflux is also increased in patients who have Barrett's esophagus. Bile and acid reflux occur together in these patients. Bile reflux may increase the effect of acid injury to the esophagus and therefore may contribute to the development of Barrett's esophagus and possibly esophageal adenocarcinoma (cancer).
Esophageal contractions

Several research studies have shown that poor esophageal clearing of refluxed stomach contents (diminished or ineffective esophageal contractions that usually force acid back down into the stomach) is an important factor in causing **GERD** symptoms and esophageal injury from acid. In people who have severe GERD (backwashing of acid and bile into the esophagus), including those with Barrett's esophagus, about half have weak esophageal contractions that fail to adequately clear the esophagus of refluxed acid. In this group, acid and other stomach juices are allowed to remain in the esophagus for a much longer period of time than in people without GERD or those with mild GERD. The result can be esophagitis (inflammation of the esophagus caused by acid exposure) with injury to the esophageal squamous lining and, in some patients, the development of a new lining called **Barrett's esophagus** (specialized intestinal metaplasia) that increases the risk of developing esophageal cancer.

Delayed gastric emptying

Failure of the stomach to empty in a timely manner (delayed gastric emptying), may contribute to **GERD** (backwashing of acid and bile into the esophagus) in some people. Some studies have shown that this may be due to an increase in stomach pressure which can then overcome the pressure of the lower esophageal sphincter (the valve at the bottom of the esophagus that keeps stomach contents out of the esophagus). Transient lower esophageal sphincter relaxations (opening of the lower esophageal valve) also increase in frequency in response to gastric distention (stretching) and this allows more opportunity for stomach contents to backwash into the esophagus. Still other studies have not found that delayed gastric emptying plays a
significant role in GERD in the majority of patients.

---

**Expanded Information**

**Hiatal hernia**

There is an opening in the diaphragm (breathing muscle between the chest and the abdomen) through which the esophagus passes from the chest cavity into the abdominal cavity where it connects to the stomach. Normally, the stomach is entirely within the abdominal cavity, below the diaphragm. In some people the top part of the stomach may pass backwards through this opening in the diaphragm and into the chest cavity. This portion of the stomach which has moved into the chest cavity is called a hiatal hernia.

A hiatal hernia may be important as a cause of GERD (backwashing of stomach acid and bile into the esophagus) but its role is uncertain. It is believed that a hiatal hernia weakens the lower esophageal sphincter (the valve at the bottom of the esophagus that keeps stomach contents out of the esophagus). This is because in patients who have a hiatal hernia, the lower esophageal sphincter (LES) has moved away from the diaphragm that provides part of its surrounding muscular function and support. Also, acid may become trapped in the hiatal hernia and continue to wash back into the esophagus.

The chance of having a hiatal hernia increases with age, as does GERD. Most people with GERD have a hiatal hernia, but, most people who have a hiatal hernia do not have symptoms of GERD. People who have Barrett's esophagus tend to have larger hiatal hernias than people with less severe GERD or people who don't have GERD at all.
**H. pylori**

The role of *H. pylori*, a small bacterium found in association with stomach and duodenal (small intestine) ulcers, is uncertain in **GERD** (backwashing of acid reflux and bile into the esophagus). Recent studies suggest that *H. pylori* might be protective in GERD and some strains of the bacterium may even decrease the risk of esophageal adenocarcinoma (cancer). The mechanism by which *H. pylori* may decrease reflux of acid and the risk of esophageal adenocarcinoma in patients is uncertain. It may be due to *H. pylori* induced inflammation of the stomach (gastritis) with injury to the acid producing stomach cells. These injured cells eventually die, resulting in a decrease in acid production and therefore less acid reflux into the esophagus.

---

**Expanded Information**

**Lower esophageal sphincter (LES) function**

The esophagus is a tube that connects the mouth to the stomach. It is simply a conduit for food and does not aid in digestion. However, the esophagus does have another important job. It keeps stomach contents, (food, acid and bile) in the stomach, out of the esophagus and away from the airway (breathing tube). It does so by the aid of two muscles or valves called the upper and lower esophageal sphincters. The most important valve for keeping stomach contents out of the esophagus and airway is the lower esophageal sphincter, referred to as the LES.

The LES is located at the very bottom of the esophagus where the esophagus joins the top of the stomach. The LES is a high pressure zone between the esophagus and stomach. The LES is made up of muscles at the bottom of the esophagus as well as the muscles of the diaphragm (breathing muscle) that surround the bottom of the esophagus. When it is closed, the LES maintains a higher pressure than that of the stomach so that food and digestive juices cannot wash back into the esophagus.

The LES normally opens or relaxes (lowers its pressure) as food is moved down the esophagus by esophageal contractions. These esophageal contractions are started by swallowing. As soon as swallowing stops, the LES closes to keep the food in the stomach. A normally functioning LES prevents food and stomach acid from backing up into the esophagus and ultimately into the trachea or "windpipe".

In addition to the LES, the gastroesophageal flap valve may close when the stomach is full. The flap valve is an area in the top of the stomach into which the bottom of the esophagus and surrounding stomach tissue protrudes (extends into). The gastroesophageal flap valve can be seen on upper endoscopy.

---

**Normal flap valve**

The endoscope can be seen at the top of the stomach. The stomach folds seen around the endoscope make up the flap valve. Normally, on endoscopic examination, the flap valve appears to "hug" the endoscope as seen here.

*Photo courtesy of the Seattle Barrett's Esophagus Research Program*

---

**Open flap valve**
The endoscope can be seen at the top of the stomach. The stomach folds seen around the endoscope make up the flap valve. The flap valve, which normally appears to "hug" the endoscope, is seen here to be lax creating an opening between the endoscope and the surrounding stomach folds. This opening leads to the hiatal hernia.

*Photo courtesy of the Seattle Barrett's Esophagus Research Program*

---

**Transient LES relaxations**

It is normal for the LES to open occasionally when there is no swallowing. These spontaneous LES openings are called transient LES relaxations and usually occur after a meal when the stomach is full and distended with food and swallowed air. Many of these transient LES relaxations occur to let air out of the stomach and result in "belching or burping". A backwashing of food and stomach acid into the esophagus can occur at this time. Normally, transient LES relaxations do not occur while lying down.

In the normal esophagus, in response to transient LES relaxations and the backwash of gastric contents into the esophagus, strong esophageal contractions are initiated to force refluxed stomach contents back down into the stomach and clear the esophagus of acid. In addition, saliva neutralizes any remaining gastric acid so that it is less likely to injure the lining of the esophagus. As a result of these backup mechanisms, most transient LES relaxations do not cause heartburn symptoms.

Many people have occasional heartburn, but those who have frequent heartburn symptoms have more frequent transient LES relaxations as compared to those who have infrequent or no heartburn symptoms. In addition to increased transient LES relaxations, some people who have severe GERD, including those with Barrett's esophagus, may have a LES that has an abnormally low pressure. This constant low pressure allows free backwash of stomach contents, including acid, that far exceeds that of the normal transient LES relaxations. In many of these people, the gastroesophageal flap valve is open or lax as seen by upper endoscopy, rather than closed. Reflux in these people occurs not only after a meal or with burping, but also at night, and can be easily brought on by coughing, bending over, lying down, or wearing a tight-waisted garment.

---

**Expanded Information**

**Saliva**

Because saliva neutralizes acid, it might be that a decrease in production of saliva could contribute to acid injury of the esophagus in gastroesophageal reflux disease (GERD). No difference has been shown in the saliva production in people without GERD as compared to those with GERD; however, saliva production normally decreases at night while asleep and also with aging. In the setting of decreased esophageal contractions and night-time GE reflux, this decrease in saliva production may contribute to esophageal injury by inadequately neutralizing the refluxed acid that is not effectively cleared from the esophagus. In addition, in the saliva of patients who have erosive esophagitis (severe inflammation of the esophagus from acid injury) there is a decrease in the normal esophageal protective mucosal factors as compared to people without erosive esophagitis.
Barium esophagram

This test is done in radiology (x-ray department) and involves drinking a chalky substance called barium that can be seen on x-ray. The radiologist (physician) has the patient drink the barium and observes by x-ray how the barium moves through the esophagus and into the stomach. If GE reflux (backwashing of stomach contents into the esophagus) occurs during the test, it can be seen as barium backing up from the stomach into the esophagus. Esophageal narrowing (strictures) can also be seen as well as some ulcers and tumors. The problem with this test is that it can miss small abnormalities in the esophagus such as small erosions or ulcers. Another problem is that GE reflux may occur in normal individuals but not necessarily in GERD patients at the time of the barium test. Although there can be some findings on barium esophagram to suggest the presence of Barrett's esophagus, the diagnosis of Barrett's esophagus cannot be confirmed with this test. The advantage of this test is that it can be ordered by a primary care physician and if erosions, strictures, ulcers or tumors are seen, these are highly specific for esophageal disease.

Esophageal manometry

This test involves placing a tube into the esophagus to measure esophageal contractions and LES (valve at the bottom of the esophagus) pressures. A new type of tube can now be placed for 24 hours along with the pH probe to further sort out the exact events associated with reflux of acid into the esophagus, including LES pressure at the time of reflux and esophageal clearing of acid or contractions during the episode. This test is usually obtained along with the esophageal pH as part of an evaluation for anti-reflux surgery. If esophageal contractions are abnormal, then this may influence the type of anti-reflux surgery performed.

Intraesophageal pH monitoring

This test uses a probe to detect a low pH (acidity) in the esophagus. The probe is at the end of a very thin tube that is passed through one side of the nose, swallowed and is advanced to a given location in the bottom of the esophagus. The patient then goes home, participates in his or her usual activities, and the number of GE reflux (backwashing of acid into the esophagus) episodes and length of each episode is recorded by the recording device attached to the probe. The patient also keeps a diary of any symptoms and the times that they occur. The probe is usually worn for 18 to 24 hours so that there is adequate opportunity to detect both daytime and nighttime GE reflux episodes.

Interpretation of results

The physician interpreting the test looks at the number of reflux episodes (esophageal pH below 4.0), how long each lasts, the total percentage of time that the patient has a pH below 4.0 and compares the results to normal values. Using the patient diary, patient symptoms are correlated with the reflux episodes detected by the pH probe. The diary is very important in confirming GERD (gastroesophageal reflux disease) as the cause of a patient's symptoms. It is also important in detecting patients who may not have an increased number of
reflux episodes but who have symptoms during their episodes of reflux and therefore have symptomatic
GERD.

Most of the time this test is used in conjunction with upper endoscopy in the diagnosis of GERD. It is
frequently requested as part of the preoperative (before surgery) work-up for anti-reflux surgery to document
abnormal acid reflux. It is sometimes used to determine whether a medication is controlling acid. Disadvantages of this test include patient inconvenience, overlap in test results between normal persons and
those with real GERD and difficulty standardizing the test from center to center.

There is now a new tubeless device called the Bravo pH probe. It is about the size of a vitamin and is
attached to the lower esophagus with an upper endoscope. The device does not cause pain, does not
interfere with the patient's activities, and records the patient's esophageal pH for about 2 days. The
information from the probe is sent to a small recording device that is worn by the patient during the first 2
days after the probe is placed in the esophagus. Within 10 days to two weeks the device drops off the
esophagus and harmlessly passes out of the body into the feces. Early studies look good for device in its
ability to identify those patients who have GERD.

Symptoms of Gastroesophageal Reflux Disease (GERD)

Typical symptoms:

1. Burning sensation in chest or upper abdomen (heartburn) related to meals or body position and relieved with
acid reducing medications such as Tums®
2. Regurgitation of acid (sour or salty fluid backwashing into the esophagus or into the mouth)

Symptoms that may be due to GERD:

1. Feeling of fullness in the throat
2. Mucous in the back of the throat
3. Vague abdominal pain, usually upper stomach area (indigestion) *COULD INDICATE A HEART
PROBLEM
4. Chest discomfort without burning *COULD INDICATE A HEART PROBLEM
5. Abdominal bloating or belching
6. Hoarseness of the voice
7. Chronic cough or wheezing/asthma
8. Waking up at night with a choking sensation
9. Using a lot of antacids for "indigestion" *COULD INDICATE A HEART PROBLEM

Warning signs of severe GERD or esophageal cancer

1. Bloody, red or black bowel movements
2. Vomiting blood or coffee ground looking material
3. Food getting stuck in the esophagus
4. Anemia (low blood count)
5. Unexplained weight loss

Return to GERD Section
Natural or life-style changes

Lifestyle changes should be made that lessen the opportunity for acid to reflux into the esophagus. Sometimes these changes allow the patient to get relief of their heartburn symptoms on less medication or, less commonly, to avoid the use of medication all together.

Although there are no specific dietary restrictions, any food or substance that causes heartburn symptoms should be avoided. Examples of such foods are: chocolate, peppermint, tomato or citrus fruits. The head of the bed should be elevated using 6 inch blocks or a full-length foam wedge in order to make use of gravity to keep stomach contents below the chest and out of the esophagus at night. Using pillows to elevate the upper body is not sufficient. The evening meal should be small and no food or drink (except water) should be consumed for at least three hours before bedtime. A low fat diet may enhance gastric emptying and decrease the opportunity for food and gastric acid to bathe the esophagus, especially at night. It may also result in modest weight loss which could lessen reflux. All medications should be taken with a full glass of water -- some pills, if they remain in the esophagus, can themselves cause injury to the esophagus.

Since heartburn (gastroesophageal reflux disease - GERD) is a risk factor for esophageal adenocarcinoma (Barrett's esophagus cancer), it is also prudent to advise patients to adopt life-style changes that are believed to lessen the risk of cancer. Patients should stop smoking. Patients should be encouraged to eat a low-fat diet high in fruits and vegetables. This diet may not only lessen GERD, but is believed to decrease the risk of developing many types of human cancers.

Medical treatment of GERD

Histamine receptor antagonists (H2 blockers)

In the past, for GERD symptoms and mild esophagitis (inflammation of the esophagus due to acid and bile backwashing into the esophagus), the mainstay of therapy has been a class of drugs known as histamine receptor antagonists (H2 blockers). These drugs work by blocking the histamine receptors on the acid producing cells in the stomach, blocking one of the mechanisms by which acid is secreted. These drugs decrease acid production, but since other mechanisms can stimulate gastric cells to secrete acid, the production of acid continues. Still, for many patients who have GERD, these drugs result in much improvement in their symptoms, especially when combined with lifestyle changes that limit reflux of stomach contents into the esophagus.

The H2 blockers have been in use since the 1970's and have no known serious side-effects. Many can now be purchased over-the-counter. Some examples of these drugs are cimetidine (Tagamet®), famotidine (Pepcid®), nizatidine (Axid®), and ranitidine (Zantac®). If a patient's symptoms are relieved with these medications, they are much less expensive than the more potent acid inhibitors, a class of drugs known as proton pump inhibitors. However about 50% of patients with erosive esophagitis will not get relief of their symptoms or healing of their esophagus on the usual doses of these drugs. Higher doses of these drugs may be used with some success, but the expense of the drugs goes up with the dose. Some of the H2 blockers interact with...
other medications that a patient might be taking. Anyone taking prescription medication should always ask their doctor about any possible drug interactions, including interactions with any over-the-counter drugs that are taken.

**Proton pump inhibitors (PPIs)**

For many patients who have GERD, especially those with severe GERD and complications - including Barrett's esophagus, use of a class of drugs known as proton pump inhibitors (PPIs) is indicated. These drugs have been in use for more than a decade and have an excellent safety profile. Examples of these drugs are esomeprazole (Nexium®), lansoprazole (Prevacid®), omeprazole (Prilosec® and Zegerid), pantoprazole (Protonix®) and rabeprazole (Aciphex®). Prilosec can now be purchased over-the-counter without a prescription (Prilosec OTC). The PPIs disable the acid pump of the acid producing stomach cell, such that it cannot pump the acid out of the cell. Therefore, the majority of acid secretion is stopped. These medications also lessen bile reflux into the esophagus. Although proton pump inhibitors stop acid secretion, they do not cause problems with digestion of food. This may be due to the fact that bile and pancreatic enzymes are largely responsible for the digestion of food. As acid inhibits bacterial growth in the upper GI tract, there are greater numbers of bacteria in the upper GI tract of patients on these drugs but this does not appear to cause problems.

PPIs are more effective in healing erosive esophagitis as compared to the H2 blockers. They are much more effective in controlling reflux symptoms in patients who have severe GERD, including patients who have Barrett's esophagus. They also have the advantage of once a day dosing as compared to two to four times per day dosing of the H2 blockers. They are, however, more expensive when compared to standard doses of H2 blockers.

In some patients who have severe GERD, including Barrett's esophagus, the standard dose of a PPI does not adequately control symptoms or heal injury to the lining of the esophagus. In many of these instances, breakthrough heartburn occurs at night. Some formal pH studies of acid reflux in patients who are on these medications have shown that up to 78% of symptomatic patients still have significant reflux of acid at night. Either taking these drugs in the morning on an empty stomach, higher doses of the drugs, or twice a day dosing may be necessary to better control acid secretion and heartburn symptoms.

In the past, the main concern with long-term use of PPIs was the possible development of a rare stomach tumor called a carcinoid that occurred in rats given high doses of these drugs. During early use of these drugs, physicians placed patients on a temporary (a short six to eight week) course to heal esophagitis, stopped the drug, and prescribed H2 blockers as maintenance therapy. However, in most cases of severe GERD, including Barrett's esophagus, patients' symptoms and esophagitis recurred after PPIs were discontinued. Fortunately, after more than a decade and a half of clinical use, these drugs have an excellent safety profile and in the mid-1990's, the cancer warning was removed by the US Food and Drug Administration (FDA). Recently, observational studies have raised concerns about the possibility of an increased risk of community acquired pneumonia and Clostridium difficile infections (causes colon inflammation and diarrhea) in patients on long-term PPI therapy. Additional studies are needed. However, because serious side-effects are rare and the complications or adverse side-effects of GERD can be serious, PPIs are considered safe for long-term use in patients who have GERD.

For patients who have Barrett's esophagus, it is unknown whether PPIs prevent cancer. Despite the widespread use of PPIs during the past 15 years, Barrett's cancers have continued to increase in the US and in Western Europe at about the same rate as before PPI therapy. There are some recent studies that report that dysplasia (pre-cancerous changes in the Barrett's tissue as seen by the pathologist under the microscope) is decreased in patients who use PPIs, but little evidence that these medications prevent cancer. Because many patients who have dysplasia, especially low-grade dysplasia, do not develop cancer during long-term follow-up, prevention of cancer is the important goal. At the present time, PPIs are prescribed to Barrett's patients for treatment of GERD symptoms.

**Pro-kinetic agents**

Pro-kinetic agents, another class of drugs, increase the ability of the stomach to empty its contents, including acid and bile, into the intestine. In the past, before widespread use of PPIs, these drugs were used together with H2 blockers to relieve GERD symptoms in patients who did not get relief of their symptoms on H2 blockers alone. Since the most widely used pro-kinetic drug, cisapride, has been withdrawn from the US drug
market due to cardiac (heart) side-effects, and PPIs have been safe and effective in controlling GERD long-term, prokinetic agents are not used much today for the treatment of GERD.

**Endoscopic therapies for GERD**

Endoscopic therapies are the newest treatment for GERD and became available for clinical use in 2000. These therapies all attempt to tighten or thicken the area near the gastroesophageal junction (where the esophagus joins the top part of the stomach) to keep acid and bile out of the esophagus and into the stomach. The FDA (The Food and Drug Administration) approved therapies are: EndoCinch® which involves endoscopic suturing (sewing) of the gastroesophageal junction; the Stretta™ procedure which involves delivery of radiofrequency energy to the gastroesophageal junction and ENTERYX® which involves injection of a substance into the gastroesophageal junction. Recently, the manufacturer of the ENTERYX® procedure kit voluntarily recalled the ENTERYX® kit due to problems with some injections going through the wall of the esophagus into the chest cavity. Some serious complications have occurred, even death. The recall is indefinite and at the present time, physicians have been advised to immediately stop using ENTERYX®

Multiple other endoscopic GERD therapies are also under investigation. They are all performed through an upper endoscope and the experience for the patient is similar to having an upper endoscopy. So far these therapies have been reported to be relatively safe with few serious complications, although serious complications have been reported, including, rarely, patient deaths.

Overall, it is reported that 6 months after one of these therapies, 58% to 85% of patients no longer need their acid controlling medication (one study reported that 100% are off their medications after the Stretta procedure). Most patients say that their heartburn is improved. Most studies reported that esophageal acid exposure (as measured by the esophageal pH probe) is not reduced in most patients. Some studies reported that esophagitis was not improved in patients who had esophagitis prior to the procedure.

Although large numbers of patients have undergone endoscopic therapies, there are very few formal publications of how well patients do. Furthermore, most of the published studies have been open-label, meaning that all patients in these studies have undergone the procedure and both physician and patient know that a procedure has been performed. Only one study of 64 patients using the Stretta™ procedure was double-blinded and included a sham procedure arm. This means that half the patients underwent upper endoscopy but did NOT have the Stretta procedure and half underwent upper endoscopy with the Stretta procedure. The patients did not know whether their procedure had been the real or sham (fake) procedure. Then the patients were all followed off their acid-controlling medication by another doctor who did not know which patients had received the real therapy and which the sham or fake therapy. Surprisingly, at 6 months, there was no difference between the treatment and sham group in the number of patients off their medication, 58% and 57%, respectively. The esophageal pH (acid) measurements did not change in either group. Of course this is one small study but it raises the question of how much of the early positive effects of these treatments are influenced by positive thinking on the part of the patient (placebo response) and their physician as compared to a real improvement in GERD.

Another problem with the studies that have been performed in patients so far, is that they have not included patients with severe esophagitis (severe inflammation of the esophagus from acid and bile), patients who still have heartburn on their acid-controlling therapy, Barrett's esophagus, patients who have medium or large hiatal hernias, or obese patients. Therefore, there is virtually no information concerning how well these therapies work in these patients.

At the present time, patients who desire to try one of these therapies should still consider it experimental. Some have recommended that these procedures only be performed at medical centers with very experienced staff and as part of a good study. Most experts agree that although these and other future endoscopic therapies hold promise as alternative treatments for GERD, it is still too early to answer some important questions: Who will benefit from these therapies? When should they be performed in patients? Will there be long-term problems in some patients caused by these procedures? Many experts agree that better clinical trials are needed comparing these new endoscopic therapies to conventional medical and surgical therapies for GERD before these questions can be answered.
Surgical therapy for GERD

Anti-reflux surgery

Surgical therapy may be indicated in some patients with GERD. Since the advent of proton pump inhibitors (PPIs), surgical therapy has declined in its use as more effective medical therapy emerged. In addition, the risk of life-threatening side-effects from proton pump inhibitors is lower as compared to anti-reflux surgery. However, there are patients in whom surgical therapy is indicated. These patients usually have severe GERD, poorly controlled on standard dose or even high-dose proton pump inhibitors (although poor control on proton pump inhibitors may be a warning sign that anti-reflux surgery may also fail to control the patient's symptoms). They may be relatively young patients who are wary of continuing high doses of a medication long-term. In some instances, surgical treatment as a potential "cure" is more appealing than medical therapy to patients in whom medical therapy is successful in relieving symptoms.

Laparoscopic anti-reflux surgery has made surgery a much more desirable option than the open procedure (the abdomen cut open to expose the esophagus and stomach). The laparoscopic procedure can be performed through a telescope-like instrument called a laparoscope. Using this technique, there are only a few small incisions made and the hospital stay is one to two days. As with most surgical techniques to control GERD, the top part of the stomach (the hiatal hernia) is pulled back down into the abdomen so that there is no longer a hiatal hernia. The top part of the stomach is then wrapped around the bottom of the esophagus to reinforce the weak valve. A successful anti-reflux surgery leads to the disappearance of reflux symptoms and healing of erosive esophagitis with long-term effects.


Laparoscopic anti-reflux surgery has been in use for only about a decade and long-term results are not known. The disadvantages of this treatment are that; 1) the anti-reflux surgery can fail resulting in recurrent GERD. 2) Occasionally, the laparoscopic technique cannot be used in a patient and the surgeon must switch to the open procedure during the operation. 3) In some patients, dysphagia (problems swallowing) after the surgery can be significant and gas bloat can occur due to decreased ability to belch swallowed air, and 4) Even though laparoscopic surgery is usually safe, all surgical procedures carry with them a risk of injury or death. It is generally recommended that any surgery be performed only by a surgeon who is experienced in doing that particular surgery.

The advantage of anti-reflux surgery is that it can afford complete relief of heartburn symptoms without long-
term use of medication. The argument can also be made that a successful anti-reflux surgery keeps bile as well as acid out of the esophagus, thus preventing reflux of any substance that could injure the esophagus and lead to the development of Barrett's esophagus or esophageal adenocarcinoma (cancer). Similarly, proton pump inhibitors also decrease both acid and bile reflux into the esophagus. Although there is a small body of surgical literature suggesting that anti-reflux surgery prevents the development of Barrett's esophagus in GERD patients and prevents the development of dysplasia and cancer in Barrett's esophagus, there are no large, convincing studies. As with the proton pump inhibitors, anti-reflux surgery is unsuccessful in controlling GE reflux in many patients who have a history of severe GERD, such as those who have Barrett's esophagus.

Descriptions of the various anti-reflux surgical techniques are beyond the scope of this site and should be discussed with the surgeon who will be performing the operation.

Who gets Barrett's esophagus and could I have it?

Although anyone can have Barrett's esophagus, the typical patient with Barrett's esophagus is a middle-aged or elderly Caucasian (white) man who has a long history of heartburn. Women also develop Barrett's esophagus but men outnumber women by a ratio of around 4 to 1. Up to 8 times as many men develop esophageal adenocarcinoma (Barrett's associated cancer) as women. Barrett's esophagus and esophageal adenocarcinoma are much less common in minority populations. No one knows why Caucasian men are the largest group which develops Barrett's esophagus and thus are the group at greatest risk for developing esophageal adenocarcinoma.

Heartburn (gastroesophageal reflux disease)

Heartburn, or gastroesophageal reflux disease (GERD) is the most important risk factor for Barrett's esophagus. Heartburn is a very common problem in the United States and in other parts of the Western world. Some studies and polls have suggested that anywhere between 38-44% of people have heartburn symptoms at least once per month. It is believed that up to 20% of people have heartburn symptoms at least once per week and that about 7% of people have heartburn at least once per day. Of the 7-20% of people who have more frequent heartburn, it is estimated that about 10% to 15% have Barrett's esophagus and autopsy studies have reported that up to 1 in 80 to 1 in 60 persons may have Barrett's esophagus.

Typical heartburn symptoms include burning in the chest or high abdomen that can move up the chest towards the mouth. This pain usually occurs after meals, at night while in bed, or can be associated with body position, such as bending over. Regurgitation (burping up) of acid (sour tasting liquid) into the mouth is also a typical GERD symptom. Whether or not your heartburn symptoms get better on medication or even if you had heartburn in the past but none in recent years, you can still have Barrett's esophagus. In one recent Swedish study, 44% of patients who had Barrett's esophagus had no heartburn symptoms during the past 3 months. Surprisingly, as many as 40% of patients who are diagnosed with an esophageal adenocarcinoma (Barrett's associated cancer) deny ever having typical heartburn or GERD symptoms, such as burning chest pain or regurgitation of acid.

Many patients who are diagnosed with Barrett's esophagus have esophageal injury from acid and bile with associated inflammation called esophagitis. Often, a complication or symptom of severe esophagitis, such as vomiting blood, passing black bowel movements, or a stricture (narrowing of the esophagus) with dysphagia (food sticking in the esophagus) leads to the diagnosis of Barrett's esophagus. These are very serious warning signs and anyone who has these signs should see a doctor immediately.

Obesity

Obesity or excess weight gain appears to be a strong risk factor for esophageal adenocarcinoma (Barrett's associated cancer) and therefore may be a risk factor for Barrett's esophagus. In men, there is evidence that the risk of developing esophageal adenocarcinoma increases with increasing weight. One recent study also reports that among male veterans studied at a VA hospital, being overweight is associated with a 2.5 times increased risk of having Barrett's esophagus compared to veterans who are not overweight. Although no one
knows why increased weight is a risk factor, some have thought that fat deposited around the abdominal area increases pressure on the stomach, especially when lying down. This increased pressure may increase the frequency or number of heartburn episodes. It has been proposed that the trend of increasing weight in the general population, especially in men who tend to deposit fat around the abdominal area, may be one of the reasons why esophageal adenocarcinoma has increased in this country during the past three decades.

**Age**

Another risk factor for Barrett's esophagus is age. In one study, Barrett's esophagus was detected more often in older patients, the average age was 63. In this study, Barrett's esophagus was two times as likely to be present in a patient in his seventies compared to a patient 40 years of age or less. Others have also reported that age is a risk factor for Barrett's esophagus.

**Family history**

Not much is known about the influence of family history on the development of Barrett's esophagus. It has been shown that heartburn symptoms and esophagitis (inflammation of the esophagus from reflux of stomach acid and bile) are more common in relatives of patients who have Barrett's esophagus as compared to relatives of patients without Barrett's esophagus. There are a few families reported to have some family members with Barrett's esophagus. It is not clear whether it is the tendency to develop GERD or Barrett's esophagus or both that is passed down in these families. One recent study reported that both members of an identical twin pair were more likely to have GERD than both members of a non-identical twin pair. This study supports that GERD is inherited because only identical twins share exactly the same genes (genetic material passed down to them from their mother and father).

Some researchers are trying to answer the question of whether Barrett's esophagus is inherited or passed down in families. One group of researchers performed upper endoscopy to look for Barrett's esophagus in patients who had heartburn and who also had a family member with Barrett's esophagus and then in patients who had heartburn but who did NOT have a family member with Barrett's esophagus. These researchers reported that so far, they have found no significant difference between these two groups of patients. About the same number in each group had Barrett's esophagus detected on upper endoscopy regardless of whether they had family members with Barrett's esophagus. Another group of researchers reported that family members of patients who had Barrett's esophagus or esophageal adenocarcinoma (Barrett's associated cancer) were more likely to have Barrett's esophagus or esophageal adenocarcinoma compared to family members of patients who had GERD but no Barrett's esophagus. However, as of yet, there is not a large body of evidence that Barrett's esophagus is inherited and most patients who have Barrett's esophagus do not have a known relative with Barrett's esophagus. Certainly, anyone who has chronic heartburn symptoms, whether or not they have a close relative with Barrett's esophagus or esophageal adenocarcinoma, could have Barrett's esophagus.

In summary, the typical patient who has Barrett's esophagus is a middle-aged to elderly Caucasian (white) man, mildly to moderately overweight, who has a history of longstanding heartburn. Although esophageal adenocarcinoma has also dramatically increased in white women over the past three decades, the absolute number of women who have Barrett's esophagus and develops esophageal adenocarcinoma remains low. Although this disease occurs much less often in minority populations, it has increased in the African American population during the past three decades. Barrett's esophagus and Barrett's associated cancer may be inherited in some families, but most patients who have Barrett's esophagus or a Barrett's associated cancer have no known relative with Barrett's esophagus. ANYONE, regardless of race, gender, or family history who has a problem with heartburn now or in the past could have Barrett's esophagus.

**How do I know for sure if I have Barrett's esophagus?**

There are no heartburn symptoms specific for or diagnostic of Barrett's esophagus. A procedure called esophagogastroduodenoscopy (EGD or upper endoscopy) with biopsy is the ONLY way to know for
sure whether you have Barrett's esophagus. If you have specialized intestinal metaplasia of the esophagus based on histologic analysis of an ESOPHAGEAL biopsy, you are at increased risk for the development of a type of esophageal cancer called esophageal adenocarcinoma. It is recommended that you undergo periodic endoscopic biopsy surveillance (cancer surveillance) to be able to detect a cancer when it is early and curable.

Unfortunately, most patients who have Barrett's esophagus never see a doctor for their heartburn symptoms. The vast majority of patients who develop an advanced (large) esophageal cancer are unaware that they have Barrett's esophagus.

Barrett's esophagus is commonly diagnosed because of another complication of heartburn (GERD), such as bleeding or dysphagia due to a stricture (food getting stuck in the esophagus due to esophageal narrowing). Sometimes doctors refer patients for upper endoscopy to check for Barrett's esophagus because the patient still has heartburn symptoms on medication. However, even if your heartburn symptoms go away on medication or without any treatment, you can have still Barrett's esophagus or esophageal adenocarcinoma.

As patients and physicians become more aware of Barrett's esophagus as a complication of GERD, more patients may seek medical attention for their heartburn and be referred by their physician for upper endoscopy to look for Barrett's esophagus. It has been recommended that patients who have a history of GERD for at least five years and are age 50 or older should undergo upper endoscopy to look for Barrett's esophagus. Barrett's esophagus should always be suspected in a Caucasian (white) man who has a longstanding problem with heartburn. However, ANYONE of any age, gender or race who has a chronic problem with heartburn could have Barrett's esophagus.

What is EGD (upper endoscopy) with biopsy?

Esophagogastroduodenoscopy (EGD) with biopsy, also known as upper endoscopy, is a procedure usually performed by a gastroenterologist (GI or intestinal doctor). This test involves passing an endoscope, a long, flexible black tube with a light and video camera on one end, through the mouth to examine the esophagus, stomach and the first part of the small intestine called the duodenum. The advantages of this test over the barium esophagram (x-ray test) are that the lining of the upper digestive tract can be directly viewed by the doctor and very small abnormalities seen. Endoscopic therapies (treatments) can be performed at the time of the procedure. Examples of such therapies include dilation of an esophageal stricture (stretching an esophageal narrowing with a tube) or treating a bleeding ulcer to stop the bleeding. Biopsies (taking small pieces of tissue) of any abnormality may also be done directly through the endoscope including biopsy of suspected Barrett's esophagus or duodenal and stomach ulcers.

EGD (upper endoscopy) may be performed in patients as part of a heartburn or GERD evaluation. It is indicated in patients who have bleeding from the upper GI tract or dysphagia (food sticking in the esophagus, sometimes caused by a stricture or tumor). If reflux esophagitis (inflammation of the esophagus from acid and bile), peptic stricture (a type of esophageal narrowing caused by GERD), or Barrett's esophagus is found, these are diagnostic of GERD and no further testing for the diagnosis per se is needed. However, less than 50% of patients who are referred for endoscopy for symptoms of GERD have esophagitis and even fewer have a stricture or Barrett's esophagus. Patients who have mild to moderate GERD can have symptoms of heartburn but no evidence of esophagitis or esophageal injury that can be seen by the doctor at upper endoscopy. If the patient's symptoms are typical for GERD, these patients may be treated with medications to decrease acid reflux. If they get better on these medications, then no further testing may be necessary. However, some patients may need to undergo intraesophageal pH testing to demonstrate that their symptoms are due to GERD and in some cases undergo esophageal manometry if anti-reflux surgery is anticipated.

What to expect during a typical EGD

An EGD is performed in a hospital or a special treatment center called a GI endoscopy unit. You will be asked not to
eat or drink anything for six to eight hours prior to the test, just like before a surgery. In the endoscopy unit, an intravenous (IV) line will be started in your arm. Because you will receive medication through the IV to make you sleepy, you will be placed on a monitor that checks your heart rate, blood pressure and oxygen level. The medication that you will get is called conscious sedation because it is not general anesthesia. The main goal of this sedation is to make you comfortable, less anxious, and diminish gagging. As a result of the sedation you may be asleep and not remember the procedure or you may be partially awake but comfortable.

After sedation, the doctor will pass the endoscope through your mouth into the back of your throat and ask you to swallow. Most people spontaneously swallow and the scope is easily passed into the esophagus. Using the endoscope, the doctor can see a magnified picture of the lining of the upper intestinal tract on a video monitor. Air, water and suction can be used through the scope so that the doctor can look very carefully at the upper GI tract lining.

If the exam is normal, your esophagus will look white and your stomach will look red. If you have Barrett's esophagus, the doctor will see a red lining in the esophagus, always beginning at the bottom of the esophagus and extending a varying distance up the esophagus toward your mouth. Some patients have only a small portion or very bottom of their esophagus lined with Barrett's and some have a large portion. In some cases, almost the entire esophagus is lined with Barrett's. Most patients with Barrett's esophagus have a hiatal hernia.

Normally, stomach tissue can grow in the bottom of the esophagus and looks red through the endoscope just like Barrett's esophagus. To confirm that the red lining in the esophagus is Barrett's esophagus and not stomach tissue, the doctor will take biopsies through the endoscope. The biopsy device is called a forceps. It is a long wire with a biopsy device at one end of the wire. Many commonly used biopsy devices have a small metal spike in the middle and two cups on either side of the spike to spike, grab and pull off tissue. The doctor places the forceps through the biopsy channel in the endoscope, opens the forceps, spikes a piece of tissue, closes the forceps grasping the tissue and pulls the forceps, containing the biopsy, out of the endoscope. There is not much bleeding and most patients do not feel the biopsy. The biopsy is small, about the size of a grain of cooked rice. It is placed in a tissue preservative, called a fixative, and sent to the pathology lab for histologic analysis to identify Barrett's tissue if present.
Normal squamous esophagus

Upper endoscopic view of the normal squamous esophagus. In the illustration, the tip of the endoscope is just above the bottom of the esophagus where it joins the stomach.

Short segment Barrett's esophagus

The short segment of Barrett's esophagus is seen here as a strip or "tongue" of red lining surrounded by normal pinkish-white squamous lining. There is a small island of Barrett's esophagus, surrounded by normal squamous lining, next to the tongue of Barrett's esophagus.
Long segment Barrett's esophagus

The squamocolumnar junction, where the Barrett's esophagus joins the normal squamous esophagus, is a great distance from the bottom of the esophagus due to the long segment of Barrett's esophagus.

Upper endoscope with biopsy forceps in the biopsy channel

During the endoscopy, the doctor passes the biopsy forceps through a channel in the endoscope. After the biopsy is taken, the forceps and the biopsy are pulled back and out of the biopsy channel.

Upper endoscope with biopsy forceps open and ready to take a biopsy
Endoscopic photo of a closed biopsy forceps "grasping" the esophageal lining

After the forceps is closed, the forceps is pulled out of the biopsy channel, opened and the biopsy is removed. Photo courtesy of the Seattle Barrett's Esophagus Research Program

An endoscopic biopsy

The biopsy is small, seen here to measure about one-half centimeter or one-quarter inch.

The typical EGD procedure lasts about 15 to 20 minutes, depending upon whether there are any abnormalities, biopsies taken or therapy given. If you do have Barrett's esophagus, endoscopic biopsy surveillance (cancer surveillance) will be performed in you periodically. It is identical to the EGD procedure but involves taking more biopsies of the esophagus and thus, usually lasts longer, up to one hour in patients whose Barrett's esophagus is very long.

After the EGD procedure is over, you will stay in the endoscopy unit until you are fully awake. You will be told about your exam but will have to wait on biopsy results until the histologic analysis is completed. Because of the sedation, you will need someone to drive you home after the procedure.

EGD safety

EGD is very safe and one of the most frequently performed endoscopic procedures. One possible severe complication that is rare, less than a 1 in 1000 chance of occurring, is accidentally making a hole or tear in the esophagus, stomach or small bowel that would likely require surgery to repair it. Other, possible but usually less severe complications include significant bleeding from the biopsies; pneumonia from getting stomach fluid or saliva into the lungs, and a bad reaction to the sedation medications.

Endoscopic biopsies are very superficial, taking only the very top layer of the esophagus. Therefore, significant bleeding from the biopsies is rare and the biopsies do not scar the esophagus. A serious medication reaction is unusual and now reversal drugs are widely used to reverse or stop the sedation if complications occur. The usual complications of sedation are a low blood pressure and abnormally slowed breathing.

In summary, the EGD is one of the most commonly performed GI procedures and is very safe. It is the most sensitive test for detection of abnormalities of the upper GI tract lining and the ONLY test that confirms the
What is histology?

Histology is the microscopic study of tissue, which is an organized collection of cells and their supporting structures. In Barrett's esophagus, biopsy with histology preserves the normal architecture of the tissue such that not only can the individual Barrett's cells be seen, but also their relationship to other Barrett's cells or “growth pattern” can be seen. In Barrett's esophagus, the growth pattern of cells is in the form of glands.

Biopsy collection and preparation

At the time of EGD (upper endoscopy), biopsies are taken from the esophagus and placed in a fixative (a chemical mixture) that preserves the biopsies so cells don't start breaking apart and the basic tissue architecture is preserved. A few hours in fixative is usually sufficient for GI biopsies, then the biopsies are embedded in paraffin (wax) to support the tissue so that thin sections or slices can be cut and placed on a microscope slide. The tissue can then be stained with any variety of stains which are used to identify important structures in the tissue.

Endoscopic biopsy

The biopsy is ready to be placed into the fixative for processing.

Cutting the paraffin block

The biopsy is embedded in a paraffin (wax) block so that thin slices of the biopsy can be made. The long paraffin slice is referred to as a "ribbon."
This paraffin ribbon was cut from a paraffin block that contained four biopsies. Each of the gray strips is a thin slice of a biopsy.

The paraffin ribbon containing the thinly sliced biopsies is placed on a microscope slide, stained, and is ready for reading by the pathologist.

Endoscopic biopsies only reach the top layer of esophageal tissue called the mucosa. This top layer is made up of surface cells, the basement membrane (the supporting foundation of the cells), the lamina propria (contains small blood vessels and glands), and a thin muscle layer called the muscularis mucosa. Other deeper layers of the esophagus not reached by the forceps include the submucosa, muscularis propria and adventia.
Histologic definition of Barrett's esophagus

The normal esophagus is lined by squamous cells. In Barrett's esophagus, the normal lining is replaced by an abnormal lining called specialized intestinal metaplasia. Metaplasia is a term used for a tissue that is not normally found in the body. Barrett's metaplasia has characteristics of both stomach tissue and intestinal tissue. Barrett's metaplasia, like stomach and intestinal tissue, produces mucous. The mucous producing cells (goblet cells) stain blue with a special stain (Alcian blue). The Alcian blue stain can be used to differentiate Barrett's tissue from normal stomach tissue that does not have Alcian blue staining goblet cells.
**Esophagus**

Photo courtesy of Robert Odze - Brigham & Women's Hospital - Boston

---

**Microscopic Photo of the Normal Columnar Lining of the Stomach**

Photo courtesy of Robert Odze - Brigham & Women's Hospital - Boston

---

**Microscopic Photo of the Normal Gastric Cardia**

Photo courtesy of Robert Odze - Brigham & Women's Hospital - Boston
Microscopic photo of Barrett's esophagus

Shown is specialized intestinal metaplasia stained with Alcian blue. The goblet cells stain dark blue with this stain. Barrett's cells grow in the form of glands.

Photo courtesy of Robert Odze - Brigham & Women's Hospital - Boston

Misdiagnosis of Barrett's esophagus

Occasionally, patients who have stomach-type lining in the bottom of their esophagus and NOT specialized intestinal metaplasia will be given a diagnosis of Barrett's esophagus. Unfortunately, this causes unnecessary anxiety on the part of patients who now believe that they have a pre-malignant condition. A misdiagnosis of Barrett's esophagus can also lead to unwarranted loss of medical insurance benefits or increase in the cost of medical or life insurance premiums. Based on our present level of knowledge, specialized intestinal metaplasia of the esophagus is the only known columnar esophageal lining at risk for developing esophageal adenocarcinoma (cancer). It is also the only lining for which periodic endoscopic biopsy surveillance is currently recommended.

Under certain conditions, stomach tissue just below the bottom of the esophagus, in the top part of the hiatal hernia (gastric cardia), can have intestinal metaplasia that looks very similar to Barrett's esophagus when the pathologist examines it under the microscope. Intestinal metaplasia of the gastric cardia is very common in the general population and in persons who do not have GERD. At our present level of knowledge, it is not believed to be related to Barrett's esophagus or to the development of esophageal adenocarcinoma. That is why it is important that the gastroenterologist, performing the biopsies, precisely identifies where the bottom of the esophagus begins. This can sometimes be a challenge as the transition from upper stomach (or hiatal hernia) to the lower end of the esophagus can be indistinct and difficult to identify. The problem of accurately and consistently identifying the lower end of the esophagus in every patient is a subject that is quite controversial among Barrett's esophagus experts. This issue is important because it is currently recommended that ONLY specialized intestinalized metaplasia of the esophagus be referred to as Barrett's esophagus and warrants endoscopic cancer surveillance.

The gastroesophageal junction (GE junction) and gastric cardia

The GE junction is the region where the esophagus joins the stomach (or hiatal hernia if a hiatal hernia is present). The gastric cardia is located at the top of the...
stomach or hiatal hernia if present. Specialized intestinal metaplasia in biopsies from the esophageal side of the gastroesophageal junction is Barrett's esophagus. However, intestinal metaplasia in biopsies from the gastric side of the GE junction is intestinal metaplasia of the gastric cardia and NOT Barrett's esophagus.

---

**What if Barrett's esophagus is identified?**

If Barrett's esophagus is identified in biopsies examined by the pathologist, then an EGD procedure with multiple systematically obtained biopsies (endoscopic biopsy surveillance) is needed to look for atypical or abnormal changes in the Barrett's tissue that cannot be seen by the GI doctor directly through the endoscope. These atypical changes are collectively known as **dysplasia** and are used to determine whether a patient is at increased risk for the development of cancer.

---

**What is dysplasia?**

If histologic analyses of biopsies obtained from the esophagus are interpreted or read by the pathologist as **Barrett's esophagus (specialized intestinal metaplasia of the esophagus)**, the pathologist then looks for changes in the Barrett's tissue referred to collectively as dysplasia. Dysplasia, or dysplastic changes, are atypical changes in the nuclei of cells (the inside of the cell that contains DNA), the cytoplasm (the portion of the cell surrounding the nuclei), or in the growth pattern of cells. These changes can be subtle or very pronounced. They are considered pre-cancerous changes (increases the risk of developing cancer). Barrett's biopsies are usually reported with readings of "negative for dysplasia", "indefinite for dysplasia", "low-grade dysplasia" and "high-grade dysplasia". Sometimes terms such as "mild dysplasia" or "severe dysplasia" are used, but these terms are no longer widely accepted by expert gastrointestinal pathologists.

---

**Negative for dysplasia**
This means that there are no atypical changes in the Barrett's tissue. The growth pattern of the cells is very even with the cells lined up in a neat row. The nuclei (center of the cell) are not large and do not have prominent nucleoli (dark spots in the nucleus). The cytoplasm appears normal.

![Microscopic photo: Barrett's esophagus, negative for dysplasia](image)

Microscopic photo: Barrett's esophagus, negative for dysplasia
The surface cells are lined up in an even row. The nuclei of the cells are normal appearing and neatly lined up along the basement membrane. The dark blue cells are Alcian blue staining goblet cells.

Photo courtesy of Robert Odze - Brigham & Women's Hospital - Boston

**Indefinite for dysplasia**
This is an intermediate reading between negative and low-grade dysplasia. It simply means that the pathologist is not certain whether changes seen in the tissue are due to dysplasia. For example, esophagitis (inflammation of the lining of the esophagus from acid injury) can make cells look atypical so that they resemble dysplastic cells although they are not dysplastic. The pathologist may see other signs of inflammation in the biopsy to help distinguish between inflammatory changes in the tissue and true dysplasia. Sometimes a pathologist may determine that dysplasia is difficult to grade due to inflammation.

**Low-grade dysplasia**
This means that there are some atypical changes but these changes do not involve most of the cells, and the growth pattern of the glands is still normal. In "low-grade dysplasia" some of the nuclei, less than 50%, are large and have dark spots but the cells are still growing in an even row. Some cells are dividing (a process called mitosis which usually indicates increased growth rate), but very few.

**High-grade dysplasia**
This is considered the most advanced dysplasia with atypical changes in many of the cells and a very abnormal growth pattern of the glands. In high-grade dysplasia, the growth pattern of the glands, or rows of cells, are distorted or very irregular. Some of the glands are branching or budding. More than 50% of the cells have large spotted nuclei and are frequently dividing. The number of Alcian blue staining goblet cells is reduced. The cellular cytoplasm is reduced and looks abnormal.
Microscopic photo: Barrett's esophagus, high-grade dysplasia
The surface cells are NOT in neat, even rows. The nuclei are large and the glands are distorted. None of the Barrett's cells are in the lamina propria and therefore this is not cancer. The small cells seen in the lamina propria are inflammatory cells and normal stromal cells.

Photo courtesy of Robert Odze - Brigham & Women's Hospital - Boston

Some pathologists call high-grade dysplasia "carcinoma in situ" because the changes in the cells and growth pattern of the cells resemble those of cancer cells. The difference between "carcinoma in situ" and cancer is that, in "carcinoma in situ", the pathologist has made the judgment that all of the cells are still confined to the basement membrane and have not migrated into or invaded the lamina propria. In the diagnosis of early cancer, the pathologist has made the judgment that cells have migrated below their basement membrane and into the lamina propria.

Important Tip: Carcinoma In Situ

CARCINOMA IN SITU IS INCLUDED WITHIN THE SAME DIAGNOSTIC CATEGORY AS HIGH-GRADE DYSPLASIA AND IS NOT A DIAGNOSIS OF CANCER.
Microscopic photo: A Barrett's associated cancer (lamina propria)

This is a magnified view of the lamina propria in a biopsy from Barrett's esophagus. Cancer cells can be seen scattered within the lamina propria, below the normal boundary of their basement membrane.

Photo courtesy of Robert Odze - Brigham & Women's Hospital - Boston

Variation in the interpretation of dysplasia

There are problems with the consistency of readings of dysplasia and therefore, problems determining a patient's risk of developing cancer based on these readings. Ideally, all pathologists viewing the same slide would grade the dysplastic changes exactly the same. Unfortunately, this is not the case. Although there is good agreement in the interpretation of high-grade dysplasia and cancer among EXPERT GI pathologists, there is much less agreement in the interpretation of the other categories of dysplasia.

Dysplasia and cancer risk

At the present time, the clinical management of patients who have Barrett's esophagus is based almost solely on the histologic readings of their endoscopic surveillance biopsies. Patients who have readings of "negative for dysplasia" are considered to be at low-risk for developing cancer.

"High-grade dysplasia" is the diagnosis most widely used to identify a group of Barrett's patients who are at increased risk of developing adenocarcinoma of the esophagus, but not all patients who have high-grade dysplasia develop cancer. There have been two large studies of patients with high-grade dysplasia followed for many years. One study followed more than 1,000 patients who had Barrett's esophagus over a course of 20 years. Patients who were diagnosed with high-grade dysplasia and followed by the researchers for more than a year before developing cancer, had only a 15% chance of developing cancer over an 8 year period. Another study of more than 300 patients reported that the chance of developing cancer over a 5 year period was 59% in patients who already had high-grade dysplasia when they entered the study and 31% in those patients who developed high-grade dysplasia after they entered the study. Smaller studies have also reported cancer developing in a variable number of patients with high-grade dysplasia, ranging from 14-56%. The reasons these numbers are so variable are unknown but may be related to differences in patients. One of these differences may be that patients who enter a study with a diagnosis of high-grade dysplasia may be further along in their time course to the development of cancer and therefore may develop cancer sooner than patients who developed high-grade dysplasia later during a study. It also may be due to differences in how the pathologists at these various medical centers read dysplasia. There may be other factors as well. One study reported that patients who had only a small area of high-grade dysplasia in one biopsy had much less of a chance of developing cancer compared to those who had a greater area of dysplasia or dysplasia in multiple
biopsies, but these findings were not confirmed by another study. Although the numbers of patients with high-grade dysplasia who eventually develop cancer varies among medical centers, what is important to know is that MANY PATIENTS WHO HAVE HIGH-GRADE DYSPLASIA DO NOT PROGRESS TO CANCER DURING LONG-TERM FOLLOW-UP and the numbers of those who do may be much lower than originally thought.

Agreement in the diagnosis of high-grade dysplasia and cancer is good among experienced GI pathologists, but it may not be as good in the hands of pathologists less experienced in reading Barrett's biopsies. Many pathologists do not get much experience reading these biopsies because high-grade dysplasia is not a common diagnosis and there is not the opportunity to see many cases. It is widely recommended that Barrett's biopsy readings of high-grade dysplasia be confirmed by an experienced GI pathologist and that the patient undergo a second endoscopy with biopsy before any treatment of high-grade dysplasia is recommended. Also, because most gastroenterologists do not have the opportunity to take care of many Barrett's patients with high-grade dysplasia, it is preferable that these patients be referred to a large specialty center with esophageal surgeons and gastroenterologists experienced in the management of high-grade dysplasia.

Although it is well accepted that readings of high-grade dysplasia does identify a group of patients with Barrett's esophagus who are at increased risk for cancer, readings of low-grade dysplasia have been much less useful in the prediction of who will develop cancer. In part, this may be due to the disagreement among pathologists in the interpretation of low-grade dysplasia.

Other tests, in addition to histology, are needed to better separate those patients who will go on to develop cancer from those who will not. There are many studies looking at different tests to determine who with Barrett's esophagus will, or will not, go on to get cancer. Some studies have shown that one test, called flow cytometry, can be combined with histology to better separate Barrett's esophagus patients into those who are at increased risk of developing cancer from those who are not.

---

**Is there a cure for my Barrett's esophagus?**

No heartburn medication or anti-reflux surgery has been proven to make Barrett's esophagus completely disappear or decrease the risk of developing esophageal adenocarcinoma. The only therapy proven to completely remove the entire Barrett's esophagus is esophagectomy (surgical removal of the esophagus). Esophagectomy is a surgical procedure that is typically reserved for patients who have high-grade dysplasia or cancer and is not recommended for patients who have Barrett's esophagus alone. This is because esophagectomy has a much higher rate of death or serious complications as compared to other, more commonly performed, gastrointestinal tract surgeries. In addition, studies indicate that most patients who have Barrett's esophagus do not develop cancer during follow-up. It is therefore recommended that periodic endoscopic biopsy surveillance be performed to detect patients who are at high risk for cancer rather than removing the esophagus of all Barrett's patients.

**Ablation therapy** is a relatively new option for the treatment of Barrett's esophagus. This therapy involves destruction of the Barrett's lining with replacement by the normal squamous esophageal lining. This therapy is usually reserved for patients who have high-grade dysplasia or early cancers. An FDA approved therapy, porfimer sodium photodynamic therapy (PDT) has been reported to cause disappearance of high-grade dysplasia in twice as many treated as compared to untreated patients and reduce the cancer rate in half in patients who have high-grade dysplasia. However, because this therapy reduces, but does not eliminate the cancer risk, experts agree that endoscopic biopsy surveillance should be continued indefinitely, until we can better determine who is still at risk for developing cancer after treatment, long-term.

**Goal of therapy for Barrett's esophagus**

At the present time, the main goal of therapy for patients who have Barrett's esophagus is to control heartburn symptoms and heal esophageal injury caused by GE reflux of acid. It is basically the same therapy as for patients who have gastroesophageal reflux disease (GERD) without Barrett's esophagus. There are three main ways to lessen GERD: medical treatment with acid-suppressive agents, anti-reflux surgery.
and life-style changes without the use of surgery or medicines. In patients who have Barrett's esophagus, life-style changes alone are rarely effective in completely relieving heartburn symptoms, but can enhance the effects of medical or surgical GERD therapies.

Both successful medical and surgical treatments of GERD control patient symptoms of heartburn and heal esophageal injury and inflammation from acid (esophagitis). Some of the more potent acid-suppressive drugs, such as proton pump inhibitors, as well as anti-reflux surgery, can cause some of the normal squamous esophageal lining to partially grow back inside of the Barrett's esophagus lining. In some patients who have a short segment of Barrett's esophagus, the Barrett's esophagus may appear to be completely replaced by normal squamous lining. It is unknown whether those patients whose Barrett's esophagus has apparently disappeared will have Barrett's tissue detected at a future endoscopy or whether they are safe from ever developing cancer. There are some recent reports that the use of proton pump inhibitors decreases the development of dysplasia, but because many patients with dysplasia, especially low-grade dysplasia do not develop cancer during long-term follow-up, what is important is whether these drugs prevent the development of cancer. At the present time, there is little evidence that proton pump inhibitors prevent cancer in Barrett's esophagus.

Barrett's esophagus with a single small squamous island

Photo courtesy of the Seattle Barrett's Esophagus Research Program

Squamous esophageal lining concealing Barrett's esophagus

In some cases, endoscopically normal appearing squamous lining may grow on top of Barrett's lining, as seen in biopsies when they are examined under the microscope by the pathologist. Unfortunately, when this occurs, the Barrett's lining is not only still there, but looks like normal squamous lining through the endoscope. This leads the gastrointestinal (GI) doctor to think that the Barrett's is gone when it is simply buried beneath normal appearing squamous lining. Squamous over Barrett's can be seen commonly in patients on PPI therapy alone and in those patients who have undergone ablation therapy. Recently, more GI doctors who take care of Barrett's patients know about this and take biopsies from both the new squamous lining and the Barrett's lining during endoscopic biopsy surveillance.

Microscopic photo of squamous lining growing on top of the Barrett's lining

A gland of Barrett's esophagus is seen below the normal squamous epithelium in this biopsy. This particular biopsy is not stained with Alcian blue, so the Barrett's goblet cells appear clear rather than dark blue.

Photo courtesy of the late Rodger C. Haggitt MD
Anti-reflux surgery versus medical therapy?

The choice between medical and anti-reflux surgical therapy should be individualized, based on patient preference for one over the other, or chosen because the other has failed to control the patient's GERD. Much larger studies with longer patient follow-up are needed to prove an advantage of one therapy over another in the reversal of Barrett's esophagus or prevention of Barrett's associated cancers. Thus far, most Barrett's experts agree that patients who have Barrett's esophagus should not view anti-reflux surgery as a cancer prevention therapy but rather as a GERD therapy.

Do we know how cancer develops in Barrett's esophagus?

The normal cell cycle

In most tissues of the body, cells multiply through a process known as the cell cycle. Before cells can multiply and divide into other cells, they have to make exact copies of their DNA. DNA is the genetic code that is in all the cells of our bodies and is exactly the same code in each cell no matter what tissue the cell is from. Chromosomes are made up of the genes of our cells and our genes are made up of strands of DNA. Each cell of our body has two copies of each gene, one inherited from our mother and one from our father. The nucleus of the cell houses our chromosomes and genes.

Normally, most cells are not actively growing and dividing and are in the G0 or resting phase of the cell cycle and have a diploid or 2N DNA content. Cells in the G1 phase are actively cycling but like G0 cells have a "diploid" or 2N DNA content. A small percentage of cells in normal tissues are undergoing DNA synthesis (making a copy of their DNA) and are in the S phase of the cell cycle (have a DNA content between 2N and 4N). A few cells have completed their DNA synthesis and doubled their amount of DNA and are in the G2 phase of the cell cycle (have a 4N or tetraploid DNA content). After cells double their DNA, they undergo mitosis (M phase) dividing into two daughter cells that are exact genetic copies of each other and have a DNA content of 2N.
The cell cycle

Resting G0 cells receive a signal to replicate and enter the cell cycle at G1 with a 2N DNA content (46 total chromosomes). The G1 Phase prepares the cell for duplication. When those preparations are complete AND no genetic mistakes are detected, the cell enters S Phase (DNA synthesis). During S Phase, all DNA in the cell is duplicated. Upon completion of S Phase, there are a total of 92 chromosomes and the cell has a 4N DNA content. Following S Phase, cells move into G2 Phase where the duplicated DNA is checked for errors. G2 cells then undergo cell division (mitosis - M Phase) and divide into two daughter cells, each with a normal DNA content of 2N. These daughter cells can then undergo DNA synthesis and multiply again or can enter G0 (the resting phase) of the cell cycle.
**Nowell's hypothesis**

There are many events or steps that occur in Barrett's esophagus that lead to the development of cancer. A few of these events are known but most are not. Most of the known events appear to occur early, before **high-grade dysplasia** or cancer actually develops. No one knows what the late events are that give cells the ability to leave their normal growth boundaries and become a cancer.

It is now widely accepted that the development of most cancers is due to something called genomic or genetic instability. This theory was first proposed by Dr. Peter Nowell in 1976. The theory is that for some unknown reason, perhaps due to environmental factors or inherited factors, some cells in the body develop genetic abnormalities that give them the ability to outgrow genetically normal cells. These abnormal cells grow and expand into a clone of cells (a group of cells having the same genetic make-up) and may replace their neighboring normal cells. Eventually one of the abnormal clones may undergo another genetic change that leads to the development of a sub-clonal population with the expansion of this cell line into its own large clone of cells. As multiple genetic abnormalities occur, multiple sub-clones develop or evolve. Eventually, one of these sub-clones may acquire the necessary combination of genetic abnormalities to become a cancer.

![Ball diagram of Nowell's hypothesis](image)

**Ball diagram of Nowell’s hypothesis**

The green balls represent cells that have developed a genetic abnormality and are expanding or growing into a clone of cells. One of these cells develops a second genetic abnormality, illustrated by a blue ball, seen to expand into its own clone of cells or subclones of the green population. A third genetic mistake is made, illustrated by a dark red ball, with clonal expansion of this cell population. Eventually, another genetic mistake is made in one of the cells of the dark red population that allows that cell to become a cancer.

**Cell cycle checkpoint genes**

Incredibly, genetic mistakes are rarely made in the duplication of a cell's DNA. If a genetic mistake is made, for example - caused by exposure of a cell to radiation, there are genes (called cell cycle checkpoint genes) that control the cell cycle and prevent cells from dividing into two daughter cells. These cell cycle checkpoint genes insure that abnormal clones of cells will not be produced by the tissues of our bodies under normal circumstances.

**The p53 gene**

The p53 gene was the first cell cycle checkpoint gene to be discovered in humans. It is referred to as a tumor suppressor gene because its normal function is to suppress the development of tumors by detecting genetic mistakes in G1 cells resulting in arrested cell growth (cell cycle arrest) or destruction (programmed cell death) of the cells with the mistake. When genetic abnormalities develop in the p53 gene leading to loss of its normal function, tumors more readily develop because cells with genetic mistakes are allowed to divide and pass the mistake on to daughter cells.

![Site of p53 action on the cell cycle](image)
If a G1 cell makes a genetic mistake, the protein made by the p53 gene does not allow that cell to enter S phase and copy its DNA. The abnormal G1 cell will usually undergo programmed cell death. This prevents cells with genetic abnormalities from dividing and undergoing clonal expansion and evolution.

p53 gene abnormalities are detected in up to 95% of Barrett's associated cancers indicating that loss of function of the p53 gene is a necessary step in the progression to cancer in Barrett's esophagus. Loss of function of the p53 gene in Barrett's esophagus is one of the earliest known genetic events in the development of cancer and it is closely tied to abnormalities that develop in the cell cycle of Barrett's cells. These abnormalities can be detected by a test called flow cytometry (a test that measures the amount of DNA in a cell).

**Important Tip: Somatic Abnormalities**

In most people, genetic abnormalities in the p53 gene develop only in cells of a particular tissue, such as in Barrett's cells, and do not occur in other cells of the body. These types of genetic abnormalities are referred to as somatic genetic abnormalities because you are not born with them and cannot pass them on to your children. Somatic genetic abnormalities may occur through environmental exposure, such as tobacco use, for example.

**Increased 4N fraction**

The earliest abnormality in the cell cycle of Barrett's cells that can be detected by flow cytometry is an increase in the percentage of cells that have doubled their amount of DNA (4N cells). It has been shown that this increase in percentage of 4N cells corresponds to loss of function of the p53 gene. These 4N cells appear to be unstable and lead to the development of aneuploid cells, cells that have multiple genetic errors or mistakes. Frequently in Barrett's high-grade dysplasia and cancer, multiple different aneuploid cell populations representing multiple sub-clones can be detected. There is evidence that these populations develop by clonal evolution and expansion similar to that proposed by Nowell.

Increased numbers of 4N cells and abnormalities in the p53 gene are some of the earliest abnormalities detected in the Barrett's lining and can be detected BEFORE high-grade dysplasia or cancer develops. In fact, abnormalities in the p53 gene can be detected in some apparently normal diploid (2N) Barrett's cells prior to the development of increased 4N cells, aneuploidy or high-grade dysplasia in Barrett's esophagus. One large study that followed Barrett's patients with and without a p53 gene abnormality reported that patients with a p53 gene abnormality had a significantly increased chance of developing cancer as compared to Barrett's patients who did NOT have a p53 gene abnormality. In this study, patients with a p53 gene abnormality also developed increased numbers of 4N cells, aneuploidy, and high-grade dysplasia much more frequently than patients without a p53 gene abnormality.

**The p16 gene**

In addition to the p53 gene, other genes are inactivated, or their functions lost, in the progression to cancer in Barrett's esophagus. Another gene, called p16, is frequently abnormal in Barrett's esophagus. p16 is also a tumor suppressor gene and, like p53, inhibits the transition of cells from G1 to S phase. Abnormalities in the p16 gene are the earliest known genetic abnormalities in Barrett's esophagus and can be detected prior to the development of p53 gene abnormalities, increased 4N cells, aneuploid cells, or high-grade dysplasia. Recently, it has been shown that there are several types of p16 gene abnormalities that can affect one or both copies of the p16 gene. What was surprising about this study, was that more than 85% of all Barrett's linings have at least one of these abnormalities in their p16 gene. In fact, the number of abnormalities in the p16 gene increases with the increase in the length of the Barrett's lining. Very short Barrett's linings tend NOT to have p16 gene abnormalities, intermediate length Barrett's linings tend to have only one abnormality in the p16 gene, and very long Barrett's linings tend to have 2 abnormalities. This has led investigators to hypothesize that the Barrett's lining starts out as a single clone of cells that develops p16 gene abnormalities very early on, causing the Barrett's to spread along the esophagus. The greater the number of p16 gene abnormalities, the greater the ability of these cells to spread and grow and extend the length of the Barrett's segment. In addition to causing spread of the Barrett's lining, p16 gene abnormalities may make it easier for other gene abnormalities to develop.
in the Barrett's lining or for these other gene abnormalities to spread over wide areas of the Barrett's lining. However, as most patients' Barrett's linings have at least one p16 gene abnormality and most patients with Barrett's do NOT develop cancer during their lifetime, including most people with long Barrett's linings, many more genetic errors must take place before a cancer can develop.

**Other genes**
Other genes that tend to develop abnormalities in the progression to cancer include genes on chromosome 5, 13 and 18. Clearly, there are many other genes involved in the progression to cancer in Barrett's esophagus that are yet to be identified and their roles characterized.

**Summary**
Cancer in Barrett's esophagus develops in a step-wise fashion from metaplasia to dysplasia to cancer. This step-wise progression occurs through clonal evolution similar to that proposed by Nowell, but has been shown to be more complex, with multiple subclones developing in the Barrett's tissue prior to the development of cancer. Flow cytometric abnormalities can be detected early in Barrett's esophagus and before the development of high-grade dysplasia and cancer. These abnormalities include increased 4N and aneuploid cell populations. Genetic abnormalities in the p53 and p16 genes with loss of function in these genes, occur even earlier than flow cytometric abnormalities. Previously it was known that p53 gene and p16 gene abnormalities are present in the vast majority of patients with a Barrett's associated cancer. It has recently been confirmed that having a p53 gene abnormality greatly increases the risk of developing cancer in Barrett's esophagus. We now also know that p16 gene abnormalities are the earliest gene abnormalities yet detected in Barrett's esophagus, present in more than 85% of Barrett's linings. It is hypothesized that p16 abnormalities contribute to the expansion of Barrett's cells along the surface of the esophagus, as well as to the expansion or spread of additional gene abnormalities that occur during progression to cancer in Barrett's esophagus.

Other genes develop abnormalities in the progression to Barrett's esophagus but their relationship to flow cytometric abnormalities or the development of cancer is less clear than those of p53 and p16. Identification of additional genes will lead to a better understanding of how cancer develops, tests to determine who is at risk for developing cancer, and better therapy in the treatment of cancer and Barrett's esophagus.

**Important Tip: Genetic Testing**

At the present time, checking a patient's Barrett's cells for genetic abnormalities is not routinely done for clinical care. No therapy should be recommended to a patient based on the results of any genetic test. Currently, it is not known which genetic tests or panel of tests will reliably be useful in predicting who will develop cancer in Barrett's esophagus and therefore, at the present time, no therapy should be recommended to a patient based on the results of any genetic test.

**If I have Barrett's esophagus will I get cancer?**

Fortunately, the results of multiple studies of patients followed for many years, indicate that about 90-95% of patients who have Barrett's esophagus DO NOT develop cancer. It is not known why some people who have Barrett's esophagus get cancer, while the majority do not.

**Chronic heartburn (GERD)**

Chronic heartburn (or GERD - gastroesophageal reflux disease) is the most important risk factor for the development of adenocarcinoma of the esophagus (Barrett's associated cancer). It has been shown that the risk of cancer increases in proportion to how often you get heartburn symptoms and the length of time that you had a problem with heartburn. In other words, the more frequent your heartburn symptoms and the greater the number of years you have had heartburn, the greater your risk of cancer. In one large study of
heartburn and the development of adenocarcinoma of the esophagus, the majority of patients who had esophageal adenocarcinoma also had Barrett's esophagus. Others have shown that the majority of patients who have chronic GERD and develop esophageal adenocarcinoma also have Barrett's esophagus. What this probably means is that the more heartburn you have, the more likely you are to develop Barrett's and it is the Barrett's esophagus that increases the risk of developing cancer. No one knows whether Barrett's esophagus patients who continue to have GERD have a higher risk of developing cancer as compared to Barrett's esophagus patients whose GERD is controlled with medication or anti-reflux surgery. There is certainly no convincing evidence that controlling heartburn symptoms with medication or anti-reflux surgery prevents the development of cancer in Barrett's esophagus.

**Family history**

There is no strong evidence that having a close relative with esophageal adenocarcinoma significantly increases your risk of developing esophageal adenocarcinoma. There are at least four recent studies looking at relatives of patients who developed esophageal adenocarcinoma. Three of these studies reported that having a close relative with esophageal adenocarcinoma did not increase the risk of developing esophageal adenocarcinoma. The fourth study reported that patients who had Barrett's esophagus or esophageal adenocarcinoma were more likely to have a relative with Barrett's esophagus or esophageal adenocarcinoma compared to patients who had GERD but no Barrett's esophagus. However, most patients who have an esophageal adenocarcinoma do not have a known family history of esophageal adenocarcinoma.

**Length of Barrett's esophagus**

The length of your Barrett's esophagus segment may be a risk factor in the development of esophageal adenocarcinoma. Longer segments may be at increased risk, however, some studies have not shown this increase to be significant and short segments can also progress to cancer.

**Diet**

A diet high in fat and low in fruits and vegetables has been associated with the development of esophageal adenocarcinoma. Alternatively, a diet high in vegetable fiber may be protective.

**Asthma, smoking and obesity**

There are other factors that may increase the risk of esophageal adenocarcinoma. Asthma and the use of asthma medications may also be associated with an increased risk of esophageal adenocarcinoma. Cigarette smoking has been shown to be a significant risk factor for the development of esophageal adenocarcinoma. Obesity also appears to be a strong risk factor for esophageal adenocarcinoma, especially in non-smokers and in younger patients. One recent study suggests that it is actually the amount of fat around the abdominal area (between the hips and chest) and not how fat you are in general, that increases the risk of developing esophageal adenocarcinoma in Barrett's esophagus. This study found that in Barrett's esophagus patients, the greater the size of the abdominal area compared to the size of the hips, the greater the chance of having genetic abnormalities and flow cytometric abnormalities in the Barrett's cells that are associated with an increased risk of developing esophageal adenocarcinoma.

**Alcohol consumption**

Alcohol consumption does not appear to increase the risk of adenocarcinoma of the esophagus. Consumption of wine, aspirin (NSAIDs), and the presence of certain strains of the bacterium H. pylori, may be protective and lessen the risk of esophageal adenocarcinoma. Heavy alcohol use is NOT recommended and increases the risk of developing another type of esophageal cancer called squamous cell carcinoma of the esophagus.

Whether or not you have any of the above suspected risk or protective factors for esophageal adenocarcinoma, if you have Barrett's esophagus, the ONLY way to know if you are at increased risk of developing cancer is to undergo periodic endoscopic biopsy surveillance.
Alcohol consumption and the risk of esophageal adenocarcinoma

Some studies have looked at consumption of alcohol and risk of developing esophageal adenocarcinoma (Barrett's esophagus associated cancer). Drinking beer and liquor does not appear to increase the risk of esophageal adenocarcinoma as compared to non-drinkers. Of interest, wine appears to decrease the risk of developing adenocarcinoma of the esophagus. Heavy alcohol use, however, increases the risk of developing another type of esophageal cancer called squamous cell carcinoma.

Asthma and the risk of esophageal adenocarcinoma

In many patients, asthma may be related to GERD (backwashing of acid and bile into the esophagus). It has been estimated that more than 80% of adult asthmatics have GERD. Many of the medications for asthma can relax the LES (lower esophageal sphincter at the bottom of the esophagus where it joins the stomach), thereby increasing the backwashing of stomach contents into the esophagus and ultimately into the airways of the lungs of the patients who use them. At least one study has shown that risk of esophageal adenocarcinoma (cancer) is increased two to three times in patients who use asthma medications. Of course, if you have asthma, you may need these medications to help you breathe and should not stop using them without getting the advice of your doctor. You should, however, discuss with your doctor any heartburn symptoms or regurgitation (backwashing of acid into the esophagus, sometimes leading to a choking or coughing sensation at night), indigestion or other abdominal pain, bloating, hoarseness of your voice or problems with food sticking in the esophagus.

Cigarette smoking and the risk of esophageal adenocarcinoma

According to one large recently published study, a significant risk factor for the development of adenocarcinoma (Barrett's esophagus associated cancer) of the esophagus is cigarette smoking. This study reported that smokers had more than two times the risk of esophageal adenocarcinoma as compared to non-smokers. For heavier and longer use of cigarettes, this risk increased. Surprisingly, in this study, smoking was a risk factor for the development of esophageal adenocarcinoma for up to 30 years after smoking was stopped, although somewhat less of a risk than for current smokers. The results of this large study implicating the use of cigarettes as a significant risk factor for the development of esophageal adenocarcinoma is supportive of the results of other similar population-based studies.
NSAIDS and the risk of esophageal adenocarcinoma

Use of NSAIDS (drugs commonly used for the treatment of arthritis or headache, such as aspirin or ibuprofen) has been shown to lower the risk of colon cancer and the formation of colon polyps. One study has looked at the use of these drugs and the risk of developing upper GI tract tumors, including adenocarcinoma (Barrett’s esophagus associated cancer) of the esophagus. The researchers in this study concluded that the use of aspirin or other NSAIDs, at least once a week for six months or more, lowered the risk of esophageal adenocarcinoma. The risk was lowered even more in patients who were on these medications at the time of the study (current users). Other studies have supported these findings while some have not. There are side-effects with the use of these drugs and most can cause ulcers or bleeding in the esophagus, stomach or intestine. You should always discuss the use of these drugs with your doctor before starting them.

What is endoscopic biopsy surveillance?

If you have Barrett's esophagus, periodic endoscopic biopsy surveillance (EGD with biopsy of the Barrett's esophagus lining to check for cancer) is the ONLY way to know for sure whether you are at increased risk for developing cancer. It can also detect an early cancer that has not yet grown large enough to cause symptoms, such as bleeding, food sticking in the esophagus or weight loss. Endoscopic biopsy surveillance instead of esophagectomy (surgical removal of the esophagus) is recommended for most patients who have Barrett's esophagus. This is because most patients who have Barrett's esophagus do not develop cancer. Also, esophagectomy is a surgery that has a much higher rate of complications and mortality (death) as compared to most gastrointestinal surgeries. Therefore, esophagectomy is typically performed only in those Barrett's esophagus patients who have high-grade dysplasia or cancer.

Periodic endoscopic biopsy surveillance has been shown to be safe and there is evidence that it is successful in the detection of esophageal adenocarcinoma when the cancer is early and curable with surgery. Unfortunately, because most patients who develop esophageal adenocarcinoma are not in a cancer surveillance program, endoscopic biopsy surveillance has not favorably impacted the mortality (rate of death) of this disease. Esophageal adenocarcinoma must be detected early, before the patient develops symptoms, for the patient to have a high likelihood of a cure.

Endoscopic biopsy surveillance is just like having an EGD with biopsy except that many more biopsies are taken from the Barrett's lining, in a systematic manner, to screen for dysplasia (atypical or abnormal changes in the Barrett's tissue) and cancer. Although many more biopsies are taken compared to a standard EGD with biopsy, this practice has been shown to be safe. In the past, there have been no standardized guidelines for how biopsies are taken. It is now widely recommended that the patient with Barrett's esophagus have four quadrant biopsies at every two centimeter intervals along the entire length of the Barrett's lining. A jumbo forceps may be useful in obtaining larger biopsies. The reason for taking four quadrant biopsies is that sampling all four walls of the esophagus decreases the odds of missing a small area of abnormal cells that can only be seen by histologic analysis (examination of tissue under the microscope) and not through the endoscope. Because high-grade dysplasia and early cancer can be invisible to the doctor performing the endoscopy and seen only under a microscope, biopsies taken in a systematic manner may increase the odds of hitting an endoscopically invisible abnormality. Small abnormalities that CAN be seen through the endoscope, such as nodules, polyps, ulcers, reddened areas and erosions are sometimes the only areas in which there is high-grade dysplasia or cancer so these should have additional biopsies. Future endoscopic technologies, including increasing the resolution of the endoscopic image (Like high definition TV) offers the possibility of endoscopic detection of areas of high-grade dysplasia and early cancer that cannot be currently seen with the current endoscopic technology.
The four quadrant biopsy pattern as seen through the endoscope

Illustration of an every two centimeter endoscopic biopsy surveillance protocol

The "x" marks represent the positions of the biopsies obtained in a four quadrant biopsy pattern

Photo courtesy of the Seattle Barrett’s Esophagus Research Program

Four quadrant biopsies are taken at two centimeter intervals throughout the entire length of the Barrett’s esophagus segment.

Problems with endoscopic biopsy surveillance

There are problems with endoscopic biopsy surveillance. The main problem is sampling error. Sampling error means that there can be abnormal areas in the esophagus that are so small that they cannot be seen through the endoscope and therefore missed with the biopsy forceps even when a systematic biopsy protocol is used. Presumably, the sampling error gets lower when the doctor takes more biopsies and follows a systematic protocol, but sampling error is never completely eliminated.

There are studies looking at different ways to minimize sampling error. One group of investigators has shown that brush cytology (collecting cells that are brushed off the surface of the Barrett’s lining), when combined with endoscopic biopsy, improves the detection of dysplasia and cancer as compared to biopsy alone.

Some studies have looked at applying stains or dyes to the Barrett’s lining, or investigated new endoscopic technologies that direct the doctor to the abnormal areas in the esophagus that need to be biopsied. Some of these studies show the results to be good while others do not. Because it remains unclear whether any of these techniques improve surveillance, brush cytology, stains and dyes are not routinely used in most medical centers in the cancer surveillance of patients who have Barrett’s esophagus. New endoscopic technologies to enhance the detection of dysplasia such as narrow band imaging, autofluorescence endoscopy, optical coherence tomography, magnification endoscopy and confocal microscopy are currently under study in an effort to enhance the detection of dysplasia. However, none are as yet ready for routine clinical practice.

How often do patients with Barrett’s esophagus need to have endoscopic biopsy surveillance?

Biopsies obtained during endoscopic biopsy surveillance are sent to a pathology lab for histologic analysis. How often a patient returns for endoscopy is usually based on their histologic grade of dysplasia. Although high-grade dysplasia identifies patients who are at increased risk for cancer, readings of low-grade dysplasia are much less useful in predicting who will develop cancer. Other tests, such as flow cytometry, genetic, and protein markers, are being investigated to better separate patients into low-risk and high-risk groups for the development of cancer. None of these other tests are routinely used, in most medical centers, in the clinical care of patients who have Barrett’s esophagus.
American College of Gastroenterology (ACG) Guidelines

In most medical centers, how often a patient returns for endoscopic biopsy surveillance is based solely on the biopsy readings of dysplasia. The American College of Gastroenterology (ACG) has developed guidelines for physicians on how often a patient with Barrett's esophagus should undergo endoscopic biopsy surveillance based on readings of dysplasia. The current recommendation for patients who have a stable diagnosis of negative for dysplasia, confirmed by two endoscopic biopsy surveillance procedures, is that they come back every 3 years for follow-up endoscopic biopsy surveillance. For patients who have a stable diagnosis of low-grade dysplasia, confirmed by two endoscopic biopsy surveillance procedures, it is recommended that they return yearly for endoscopic biopsy surveillance until they have a set of biopsies in which no dysplasia is detected. **Endoscopic biopsy surveillance of high-grade dysplasia** should be individualized in each patient who has that diagnosis and who elects to continue in a cancer surveillance program or have an endoscopic therapy rather than undergoing esophagectomy as treatment for their high-grade dysplasia.

The most recent ACG guidelines recommend that patients who have a diagnosis of high-grade dysplasia undergo a second endoscopic biopsy surveillance procedure to increase the chance of detecting an early cancer if it is already there, and that all biopsies be reviewed by a second expert GI pathologist. If no cancer is detected, then patients have several options including: remaining in endoscopic biopsy surveillance and returning every few months for their procedures; esophagectomy (surgical removal of the esophagus); or endoscopic therapy followed by endoscopic biopsy surveillance, indefinitely. These ACG guidelines are based on the use of a four-quadrant every two centimeter biopsy protocol with additional biopsies of any abnormality in the Barrett's lining seen through the endoscope. Several centers now perform (and some Barrett's experts recommend) four-quadrant biopsies every one centimeter in patients who have high-grade dysplasia to further decrease the chances of missing a very small cancer if present.

The current guidelines for how often a patient should return for endoscopic biopsy surveillance are based on readings of dysplasia and the hypothesis that cancer develops in Barrett's esophagus in an orderly fashion from metaplasia (no dysplasia) to dysplasia to cancer. The current endoscopic biopsy surveillance guidelines have not been tested in patient studies or in the community practice. This is an area of active research. However, it is important to note that your physician may recommend different endoscopic biopsy surveillance intervals for you, depending on a variety of factors. The ACG guidelines emphasize that "physicians must always choose the course best suited to the individual patient". At this point in time, it is impossible to adequately address the management of each individual patient who has Barrett's esophagus in a set of published guidelines.

For most patients who have Barrett's esophagus and who will never develop cancer, endoscopies are performed more frequently than necessary. Some guidelines are even suggesting that most patients who have Barrett's esophagus can safely go up to five years between endoscopies. The patient's risk of developing cancer must be weighed against the cost of endoscopic biopsy surveillance as well as the risk of complications from EGD and discomfort to the patient. In the future, endoscopic surveillance intervals will likely be lengthened out for most patients who have Barrett's esophagus, but to do this safely, we must be able to better predict who will and won't develop cancer in Barrett's esophagus.

**Endoscopic biopsy surveillance of high-grade dysplasia**

A standard recommendation for the treatment of high-grade dysplasia in Barrett's esophagus is esophagectomy, surgical removal of the esophagus. This recommendation has been largely based on studies showing that 30-50% or more of patients who had a diagnosis of high-grade dysplasia and then underwent esophagectomy for high-grade dysplasia, actually had cancer in their esophagectomy specimen (surgically removed esophagus). In other words, endoscopic biopsy surveillance missed a cancer that was already present in their esophagus. The problem with most of these studies is that they did not report if a systematic biopsy protocol was used, the number of endoscopic biopsies taken from the Barrett's lining, how many endoscopies were preformed prior to the surgery or whether there was an abnormality in the Barrett's lining, such as an ulcer or nodule, that could be seen endoscopically prior to surgery.

Three recent studies performed endoscopic biopsy surveillance in patients who had a diagnosis of high-grade dysplasia to determine how many cancers would be missed using a jumbo forceps and a four-quadrant, two centimeter protocol. Endoscopic biopsy evaluation was performed once in each patient, prior to surgery. The patients then underwent esophagectomy and their esophageal specimens were checked for cancer. In the largest study, two of 19 patients had cancer in their esophagectomy specimens (10.5%). In the two other studies, four of 12 (33%) patients and 5 of 9 (56%) patients had cancer in their esophagectomy specimens.
The argument for continuing endoscopic biopsy in patients who have high-grade dysplasia is that a substantial number of patients who have high-grade dysplasia (range 40% to 85%) do not progress to cancer during long-term follow-up. Also it has been reported that in some patients who have a diagnosis of high-grade dysplasia, the high-grade dysplasia is not detected in follow-up endoscopies. At the present time, it is unclear whether the high-grade dysplasia truly goes away in some patients, whether it is not detected due to sampling error (missing a small area of high-grade dysplasia in the set of biopsies taken) or the initial diagnosis of high-grade dysplasia was incorrect. Therefore, some patients may elect to remain in surveillance, unless cancer is detected.

It has been recommended that sampling error can be greatly minimized and cancer detected when it is still early and curable if patients who have high-grade dysplasia return for three consecutive (back-to-back) and closely spaced endoscopies to detect cancer that may already be there. This allows a diagnosis to be made based on many more biopsies obtained in a short period of time as compared to declaring the patient free of cancer based on one endoscopic surveillance procedure. The American College of Gastroenterology (ACG) guidelines now include a recommendation that patients with a diagnosis of high-grade dysplasia undergo repeat EGD with biopsy to minimize sampling error and maximize detection of cancer, if present. If no cancer is detected and the patient elects to remain in endoscopic biopsy surveillance, then it is recommended that the patient undergo endoscopic biopsy surveillance every 3 months.

In patients with high-grade dysplasia, it is also recommended by one Barrett's research center that four quadrant biopsies be taken, using a jumbo forceps, at every one centimeter interval rather than every two centimeters. At this center, if no cancer is detected, the patient returns in one month for repeat endoscopic biopsy surveillance. If again no cancer is detected, the patient returns in three months for their next surveillance procedure. If after three closely spaced procedures, no cancer is detected, the patient undergoes endoscopic biopsy surveillance at least every 6 months to detect cancer, if it develops, when it is early and curable with surgery. The basis for the recommendation of a one centimeter biopsy protocol in patients who have high-grade dysplasia is a study that demonstrated that half of all cancers detected using the 1 centimeter protocol would be missed using a 2 centimeter protocol. This biopsy protocol is not in widespread use at the present time and even though cancers are typically detected early in experienced centers, cancers can still be missed until they are larger and less curable, even when such a rigorous protocol is used.

Sampling error, and the concern that a patient who has a diagnosis of high-grade dysplasia already has a cancer that will not be detected until it is advanced and incurable with surgery, remains a big concern. As with any medical practice, the recommendation of endoscopic biopsy surveillance or endoscopic therapies versus surgery in the management of high-grade dysplasia must be weighed with respect to the risk of developing advanced and incurable cancer while in surveillance versus the mortality (rate of death) from the surgery. Because high-grade dysplasia is rare in patients who have Barrett's esophagus, many gastroenterologists do not have the opportunity to care for many of these patients or have routine access to an expert GI pathologist. Further, intensive and frequent endoscopic biopsy surveillance of patients with high-grade dysplasia, using a one centimeter biopsy protocol, may require increased staffing and advanced planning in the endoscopy unit and the cost of such a complex procedure may not be fully reimbursed by insurance companies. For these reasons, and because the mortality (rate of death) of esophagectomy is lower in institutions where a high number of esophagectomies are performed, consideration should be given to referral of these patients to specialty centers that follow large numbers of patients with high-grade dysplasia.

Care of the patient who has high-grade dysplasia should be individualized, taking into account the patient's desires, medical fitness to undergo esophagectomy, and willingness to come back for frequent endoscopies. Any patient who will NOT return at the recommended endoscopic intervals and who has a diagnosis of high-grade dysplasia, CONFIRMED by an expert GI pathologist and a repeat endoscopic biopsy surveillance procedure, should undergo esophagectomy, performed by an experienced esophageal surgeon. Esophagectomy is the ONLY treatment that allows a patient to safely stop periodic endoscopic biopsy surveillance. Even the patient who chooses endoscopic therapy, must be willing to undergo endoscopic biopsy surveillance indefinitely, even if it appears that the high-grade dysplasia has disappeared. A recent randomized controlled trial of photodynamic ablation therapy in patients who had high-grade dysplasia, reported that although the numbers of cancers were cut in half as compared to those patients who did not have ablation, it did not completely eliminate the cancer risk.
What is flow cytometry?

Flow Cytometry is a test that can be used to measure the amount of DNA in cells. By measuring the amount of DNA in cells, this test is able to identify the proportions of cells in different parts of the cell cycle (the growth cycle of a cell). It can also detect populations of cells that have abnormal amounts of DNA (cells that have a lot of gene abnormalities). In the past, flow cytometry has primarily been a research tool in the study of cancer and other conditions including Barrett’s esophagus. This test is now widely used in the characterization of many different human cancers, with the information used by physicians to determine how well a cancer may respond to a particular therapy. At the present time, flow cytometry is not widely used to clinically manage patients with Barrett's esophagus.

To perform flow cytometry on an endoscopic biopsy, when the biopsy is removed from the esophagus it needs to be placed immediately into a special solution that protects the cells from breaking apart, and then frozen. What happens to the biopsy next depends on the type of flow cytometry performed. DNA content flow cytometry is the most commonly performed test in characterizing cancers and has been the test most commonly used in Barrett's esophagus.

DNA content flow cytometry

When DNA content flow cytometry is performed, the frozen biopsy is thawed and placed in a solution that ruptures the cells, leaving only the nuclei (the component of the cell that contains the DNA). The nuclei are stained with a fluorescent dye that binds to the DNA of the nuclei. The solution of stained nuclei is placed into a machine called a flow cytometer that has a focused light source, typically a laser, that excites the fluorescent dye bound to the nuclear DNA causing it to fluoresce (emit visible light). Because the fluorescent dye is bound to the DNA in the nucleus of the cell, the intensity or brightness of the cell’s fluorescence is proportional to the amount of DNA in the cell (the greater the amount of DNA, the greater the intensity of the fluorescence). Because cells contain different amounts of DNA depending on where they are in the cell cycle, it can thus be determined what percentage of cells are in the different parts of the cell cycle based on the intensity of fluorescence of the nuclei. The data are expressed as a flow cytometric histogram.

A typical flow cytometric histogram in Barrett’s esophagus

Most of the cells have a DNA content of 2N, seen here as a large peak on the flow histogram. The 4N peak is much smaller and in this case makes up only 3.4% of the cell cycle.

Normally, in a biopsy from Barrett’s tissue, most of the cells are in the G0/G1 phase of the cell cycle and have a 2N DNA content, the content of most of the normal cells of our bodies. Normally, in a biopsy from Barrett's tissue, 6% or less of the cells have a 4N DNA content (twice the DNA of the G0/G1 cells).

Flow cytometric abnormalities

In Barrett's esophagus, flow cytometry can be used to identify patients who are at low- or high-risk for
progression to high-grade dysplasia or cancer. Several studies have shown that in Barrett's esophagus, flow cytometric abnormalities can occur in patients BEFORE high-grade dysplasia or cancer develops. One study showed that patients who had 4N populations greater than 6% of the total cell cycle, or aneuploid cell populations (abnormal populations of cells with DNA content between 2N and 4N), were at increased risk of developing high-grade dysplasia or cancer. Another study in which patients were followed for a long time showed similar results. In this study, patients who did not have aneuploidy were in a low-risk group compared to those who had aneuploidy.

The most recent, and largest, flow cytometry study is one of more than 300 patients who had Barrett's esophagus followed for up to 13 years. In this study, patients had both flow cytometry and histology performed on their endoscopic biopsies and then were followed in the study. The chance of developing cancer over a 5 year period was 0% in patients who had biopsy results of negative, indefinite or low-grade dysplasia and normal flow cytometry upon entry into the study. However, the chance of developing cancer over a 5 year period was 28% in patients who had biopsy results of negative, indefinite or low-grade dysplasia and increased 4N fractions or aneuploid cells by flow cytometry at the time of entry into the study. In the group of patients with high-grade dysplasia, when they entered the study, the chance of developing cancer over a 5-year period was 59% regardless of their flow cytometry result, so having a diagnosis of high-grade dysplasia was an independent risk factor for developing cancer in this particular study. Based on these study results, for patients who DO NOT have high-grade dysplasia, flow cytometry is more useful than histologic analysis in separating those patients who have a low-risk of progression to cancer from those who have a much higher risk of progressing to cancer. Because not all patients who have high-grade dysplasia or flow cytometric abnormalities develop cancer, other biologic measurements or biomarkers are needed to better predict which patients in these groups will ultimately develop cancer.

Another, more recent, flow cytometry study of the same Barrett's esophagus study group above further characterized flow cytometric abnormalities and looked at the percentage of cells in the S phase fraction of the cell cycle as a predictor of who will get cancer in Barrett's esophagus. What this study found is that increased S phase fraction is NOT an independent predictor of who will develop cancer in Barrett's esophagus so is not helpful in determining patient risk. This study also divided aneuploid cell populations by DNA content and found that, of the 11 patients who had what is called a "near-diploid aneuploid cell population (a DNA content of less than 2.7N), the 5-year cancer risk was zero (none of these patients developed cancer). The numbers of patients who had aneuploid cell populations with DNA contents of less than 2.7N are too small to draw any definite conclusions and many more patients will need to be followed to confirm whether these patients' risk of cancer is much lower compared to those who have aneuploid cell populations with DNA contents of greater than 2.7N. Most patients who have Barrett's esophagus and who develop aneuploid cell populations have populations of greater than 2.7N DNA content.

Increased 4N cells in Barrett's esophagus

There is an increased percentage (16.7%) of cells in this biopsy with a DNA content of 4N.
Aneuploidy in Barrett's esophagus

A large aneuploid (cells with abnormal DNA content) peak with a DNA content of 2.8N can be seen just to the right of the diploid (2N) peak. The aneuploid cell population makes up 78% of the cells in this Barrett's biopsy.

Clinical use of flow cytometry

Clinical guidelines have been developed for DNA content flow cytometric analysis. There is extensive literature on decreasing the causes of variation (disagreement in the analysis of results) among laboratories that perform flow cytometry. Recent studies have shown flow cytometry to be consistent from laboratory to laboratory when the guidelines are followed. For example, one large study found 94% agreement among laboratories in the interpretation of DNA content flow cytometry. There is now good evidence that flow cytometry is a more objective test than histologic analysis of biopsies. However, flow cytometry should be performed in a reference laboratory or at a center experienced in DNA content flow cytometry.

At the present time, treatment is not recommended based solely on flow cytometric abnormalities as many patients who have flow cytometric abnormalities DO NOT progress to high-grade dysplasia or cancer during long-term follow-up. However, flow cytometry may be clinically useful in separating patients who do NOT have a diagnosis of high-grade dysplasia into those who need more frequent endoscopic biopsy surveillance from those who need much less frequent surveillance.

What are the treatment options for high-grade dysplasia in Barrett's esophagus?

The management of patients who have high-grade dysplasia (severe, precancerous tissue changes) in Barrett's esophagus is controversial. This is because there is no firm evidence supporting one way to manage these patients, safely, over another. This has led experts in Barrett's esophagus to come to different conclusions about how patients who have high-grade dysplasia should be managed.

At the present time, options for the treatment of high-grade dysplasia are esophagectomy (surgical removal of the esophagus) and endoscopic therapies. A significant number of patients who have high-grade dysplasia do not develop cancer when followed for many years by endoscopic biopsy surveillance. Therefore, an option, other than treatment for these patients, is to remain in close endoscopic biopsy surveillance of high-grade dysplasia, reserving esophagectomy or endoscopic therapy for cancer if it develops.

The controversy in the management of patients who have high-grade dysplasia

High-grade dysplasia is not the same as cancer because the dysplastic Barrett's cells can not invade or grow
into other tissues and they can not metastasize (spread) throughout the body. However, esophagectomy has been a standard recommended treatment for high-grade dysplasia in Barrett's esophagus for two main reasons. First, there are surgical studies reporting that a significant number of patients who were diagnosed with high-grade dysplasia and then had esophagectomy actually had cancer in their esophagus that was missed by upper endoscopy with biopsy. Second, esophageal cancer is highly curable with esophagectomy if detected early, but is much less curable if detected when it is deeper and larger. For these reasons, experts who are advocates of esophagectomy as a treatment for high-grade dysplasia argue that if the esophagus is not removed, the patient may already have a cancer that was missed by endoscopy and that cancer may become larger and incurable by the time it is finally diagnosed. Esophagectomy is the only treatment for high-grade dysplasia in which complete removal of the Barrett's lining can be confirmed with certainty by examination of the esophagus when it is out of the body. Because complete removal of the entire Barrett's lining can be confirmed, advocates of esophagectomy argue that the risk of developing an incurable cancer is eliminated, along with the need for continued endoscopic biopsy surveillance.

The main problem with recommending esophagectomy for all patients who have high-grade dysplasia is that a significant number of these patients do NOT develop cancer. In one large study, patients who had a diagnosis of high-grade dysplasia had a 31% to 59% chance of developing cancer over a 5-year period. In a second large study, patients who had a diagnosis of high-grade dysplasia had only a 15% chance of developing cancer over an 8-year period, with 85% all patients remaining cancer free. In addition, the mortality associated with esophagectomy (risk of death) and the rate of significant complications are much greater as compared to most other gastrointestinal surgeries. These problems are magnified in centers performing low volumes of esophagectomies. Many patients are elderly and have other medical problems, which may further increase their risk of having significant surgical complications.

### Endoscopic therapies

Many Barrett's experts are now recommending endoscopic therapies for patients who have high-grade dysplasia. All of these therapies involve destruction of the Barrett's lining or cutting out the portion of the Barrett's lining that has high-grade dysplasia. Following the treatment, gastroesophageal reflux is controlled, usually with medication, to encourage the normal squamous esophageal lining to grow into the esophagus, replacing the destroyed Barrett's lining. All of these procedures are performed through the endoscope. Advocates of these therapies argue that they may successfully rid the patient of the high-grade dysplasia and thus the risk of developing cancer, without removing the patient's esophagus. This allows the patient to avoid the risk of death or complications associated with esophagectomy.

One of these endoscopic therapies, porfimer sodium photodynamic therapy (PDT) is FDA approved for the treatment of high-grade dysplasia based on the results of a recently published multi-center study (follow link to endoscopic therapies for details of this study). This study reported that PDT caused high-grade dysplasia to regress or disappear in twice as many patients as compared to endoscopic biopsy surveillance without treatment and PDT treated patients had half the cancer rate compared to that of untreated patients. However, PDT did not eliminate the cancer risk.

The main disadvantage of endoscopic therapy is that unlike surgery, in which complete removal of the Barrett’s lining can be confirmed by analysis of the entire surgically removed esophagus, some of the Barrett's lining can still be present even after several treatments. In some cases, the area of Barrett's lining that remains after treatment is so small that it cannot be seen through the endoscope and it appears, endoscopically, that the esophagus is completely lined by the normal white lining. Because there is a possibility that very small areas of the Barrett’s lining remain after treatment, experts performing endoscopic therapies recommend that endoscopic biopsy surveillance be continued after treatment to periodically check the patient for recurrence of high-grade dysplasia and the development of cancer.

### Endoscopic biopsy surveillance

A significant number of patients who have high-grade dysplasia, 40% to 85%, do not develop cancer during long-term follow-up. Furthermore, a significant number of these patients have regression or disappearance of their high-grade dysplasia without treatment. Barrett's experts who are advocates of endoscopic biopsy surveillance for patients who have high-grade dysplasia, argue that many patients who have high-grade dysplasia are unnecessarily subjected to treatments that can have severe complications, even cause unnecessary death and that for many patients, endoscopic biopsy surveillance, reserving esophagectomy or an endoscopic therapy as a treatment for cancer if it develops, is the best management strategy.
There are studies reporting that upper endoscopy with biopsy frequently misses cancers in patients who have been diagnosed with high-grade dysplasia because a large number of these patients had unsuspected cancer in their surgically removed esophagus. However, advocates of endoscopic biopsy surveillance argue that most of these studies failed to give details of what was seen through the endoscope, how the patients were biopsied or if a biopsy protocol was used, that only one endoscopy was performed prior to the esophagectomy. Therefore, cancer was missed in the majority of these cases because the patients were not screened carefully for co-existing cancer.

Some centers have reported that endoscopic biopsy surveillance of high-grade dysplasia is successful in detecting cancer when it is early and curable if a systematic biopsy protocol (consistent method of taking the biopsies) is used and the patient is seen back frequently to have the biopsies performed. There are two published studies reporting that using a more intensive biopsy protocol (taking more biopsies) combined with performing several closely spaced endoscopic biopsy procedures is highly successful in separating those patients who have early cancer from those patients who have only high-grade dysplasia, minimizing the risk that the patient already has an undiagnosed cancer.

Additional evidence that cancer can be detected early, when careful biopsy surveillance is performed, comes from the multi-center photodynamic therapy (PDT) trial. As part of this trial, a standard systematic biopsy protocol was performed in patients who had high-grade dysplasia, both in PDT treated and untreated patients, every three months for two years. This same protocol was performed in 30 different centers as part of this trial and reportedly the great majority of cancers were diagnosed at an early stage. Although not an endpoint of this study, it was the first study to demonstrate that a systematic biopsy protocol could be performed successfully across multiple centers in patients who had high-grade dysplasia, detecting cancer at an early stage in most patients.

Although there is evidence that the use of an intensive biopsy protocol and seeing the patient back frequently for endoscopic biopsy surveillance decreases the risk of missing a cancer, it doesn't eliminate the risk. The disadvantage of endoscopic biopsy surveillance for high-grade dysplasia remains that a cancer can be missed during surveillance and become incurable by the time it is finally detected.

**Referral to specialty centers**

Because high-grade dysplasia is uncommon in patients who have Barrett’s esophagus, most gastroenterologists and general surgeons do not have the opportunity to see many of these patients in their medical practice. Therefore, consideration should be given to referral of these patients to large volume specialty centers that have expert pathologists, esophageal surgeons and gastroenterologists who are experienced in the care and counseling of patients who have high-grade dysplasia. Because there are no clinical trials directly comparing esophagectomy, endoscopic therapies and surveillance in the prevention of death from esophageal cancer, management of the patient who has high-grade dysplasia should include in-depth patient counseling with regard to the risks and benefits of each option for management of their high-grade dysplasia. Ultimately, the management of the patient who has high-grade dysplasia should be individualized, based on the patient’s desire for a particular course of action as well as their medical fitness to undergo a particular procedure.

---

**What are the treatment options for cancer in Barrett's esophagus?**

**Cancer staging**

After the diagnosis of cancer is confirmed by upper endoscopy with biopsy, the patient goes through tests to stage the tumor (determine as best as possible how much cancer is present). The staging tests used give a very good estimate of how deep the tumor is growing into the esophageal wall, whether it involves other chest structures (such as blood vessels or the lungs), whether it has spread to lymph nodes and whether it
has spread to other organs (metastasized). Accurate staging of a tumor is important because decisions concerning how to best treat the patient's cancer will be made based on the stage of the tumor, the medical fitness of the patient as well as the patient's preference for a particular therapy, especially in the treatment of very early stage cancer.

The main tests used to stage a tumor are computerized tomography (CT) scan, positron emission tomography (PET scanning), and endoscopic ultrasound (EUS). These tests are complimentary. A CT scan is a computer enhanced x-ray and the best test to determine whether a tumor has spread to other organs. PET scans are sometimes done in cases where the CT scan is unclear. PET scans utilize radioactive tracer material which concentrates in tumors and can help identify tumor spread which is not evident on CT scans. Endoscopic ultrasound is the best test to estimate how deep the cancer is growing into the wall of the esophagus and to check the lymph nodes in the chest and upper abdomen for cancer. An endoscopic ultrasound is just like having upper endoscopy but the endoscope has an ultrasound probe in it that sends sound waves into the esophagus. These sound waves allow the doctor to make images of the layers of the esophageal wall as well as to visualize surrounding structures. From how the sound waves bounce off the wall of the esophagus, each individual layer of the esophagus can be seen.

**Stage of the cancer and likelihood of cure**

Early cancers, growing no deeper than into the submucosal layer of the esophagus have a high cure rate with esophagectomy, surgical removal of the esophagus, especially those growing only into the very top layer of the esophagus called the mucosal layer. Non-surgical endoscopic therapies are now also available for the treatment of early cancers, but how the cure-rate for the earliest stage cancers compares to esophagectomy long-term is unknown.

The deeper a cancer invades into the esophageal wall, or if lymph nodes are positive for cancer, the less likely the patient will be cured by esophagectomy. Large or deeply invasive cancers and cancers with positive lymph nodes cannot be cured by endoscopic therapies. Patients who have cancers growing deep into the wall of the esophagus may also be offered chemotherapy and radiation therapy either alone or in combination with esophagectomy.

**How will my doctor develop a cancer treatment plan for me?**

After an esophageal cancer has been diagnosed and staged, a treatment plan will be developed. If the cancer seems to be very superficial (very early stage) based on EUS and CT scan criteria, you can consider a non-surgical endoscopic therapy such as endoscopic mucosal resection, photodynamic therapy or a combination of these two therapies performed by an experienced gastroenterologist (GI doctor). You should also see an experienced esophageal surgeon who operates at a large volume specialty center to hear about the risks and benefits of esophagectomy (surgical removal of the esophagus) as treatment for an early stage cancer. Which of these treatments your doctor recommends and you decide to undergo will depend on your overall medical health and your personal desire for a particular therapy after hearing about the risks and benefits of both endoscopic therapy and surgery.

If staging tests show that the cancer is deeper than early stage or that there may be positive lymph nodes but no spread of the cancer to other organs such as the liver or lungs, then esophagectomy is the usual recommended therapy for patients in otherwise good medical health. There are several types of surgeries which can be performed and what type of surgery is performed depends on the location of the cancer and the experience of the surgeon in performing that surgery. If the cancer is too large for immediate surgery, but is still considered potentially curable, your doctor may recommend the use of neoadjuvant therapy. Neoadjuvant therapy is when chemotherapy and/or radiation therapy is given before surgery in an attempt to make the tumor smaller and allow the surgeon to completely remove it. The best approach to neoadjuvant therapy is not currently known and is a source of ongoing studies.

If a very large cancer is diagnosed, it has spread to other organs or based on a medical health assessment, it is considered too dangerous to do the surgery, palliative therapy (treatment not intended to cure but rather to improve symptoms such as difficulty in swallowing) may be recommended. Palliative options include stents (hollow pipes which open up the food passage way), photodynamic or other ablative therapy. Radiation and chemotherapy may also be recommended. Chemotherapy can sometimes shrink tumors even if they have spread to organs such as the liver. Cancer specialists called oncologists, especially one who specializes in esophageal cancer, can help design treatment plans which are of the most potential benefit to you and take
into account your health, the stage of your disease and your own preference for treatment choices.

---

**Expanded Information**

### Endoscopic treatments for large esophageal cancers

Many patients who are diagnosed with a large esophageal adenocarcinoma (Barrett's esophagus associated cancer) have problems swallowing as their main symptom. In these cases, especially if the patient is not a good candidate for esophagectomy (surgical removal of the esophagus), an endoscopic treatment may be recommended. Endoscopic treatments are performed through a long black tube with a light on the end called an endoscope which is passed through the mouth into the esophagus by a stomach and intestines doctor (a gastroenterologist). Endoscopic treatments allow food and saliva to pass by the tumor into the stomach. Endoscopic treatments may be combined with chemotherapy and radiation therapy to try and shrink a large tumor, but endoscopic treatments usually do not cure the cancer if the cancer is large and advanced. Two examples of endoscopic therapies are ablation therapy and esophageal dilation.

**Esophageal dilation**

One endoscopic treatment commonly performed is esophageal dilation (stretching the esophagus to open the area narrowed by the tumor). In order to keep the area opened, an esophageal stent or tube may be inserted into the esophagus. The stent is usually made of plastic or metal and is placed through the endoscope into the esophagus in the area of the tumor. The stent is opened at both ends so that food and liquid can pass through the stent and the area of the tumor into the stomach. One main problem with stents is that they can become clogged and stop working after a while. Other endoscopic treatments such as ablation treatments, aim to destroy much of the tumor so that the patient can swallow. Two types of ablation treatments are laser and photodynamic therapies which have been used to shrink esophageal tumors and work well in some patients. Complications can be severe, and include making a hole in the esophagus, making a fistula (connection) between the esophagus and airways of the lung, bleeding, and rarely death.

---

### What is esophagectomy?

Esophagectomy (surgical removal of the esophagus) is typically **ONLY** recommended as a treatment for high-grade dysplasia or cancer in Barrett's esophagus. This is because most patients who have Barrett's esophagus never develop cancer and the risk of complications from the surgery is too great to justify removing the esophagus of all patients who have Barrett's esophagus.

In patients who have high-grade dysplasia, the goal of surgery is to remove all of the Barrett's lining to completely eliminate the risk of developing a large and incurable esophageal adenocarcinoma (Barrett's associated cancer). Additionally, if the patient is found at surgery to have an unsuspected cancer, early surgical treatment gives the patient the best chance for cure and the only treatment that allows patients to safely stop endoscopic biopsy surveillance because all of the Barrett's lining at risk for cancer is removed along with the esophagus. **The diagnosis of high-grade dysplasia should always be confirmed by an experienced GI pathologist prior to recommending esophagectomy as treatment for high-grade dysplasia.**

Because not all patients who have high-grade dysplasia develop cancer when followed for many years by endoscopic biopsy surveillance, other options for these patients include ablation therapies or remaining in endoscopic biopsy surveillance without treatment. All patients who elect either of these options should undergo frequent endoscopic biopsy surveillance and if cancer is detected, esophagectomy is usually recommended. Strong consideration should be given to referring all patients with a diagnosis of high-grade
dysplasia to a large specialty center that has esophageal surgeons and gastroenterologists experienced in the management of these patients.

In patients who have esophageal cancer without metastatic disease (spread of cancer to other organs) and who are good surgical candidates, surgery is performed with the intention of a possible cure and to allow the patient to swallow. In some patients, chemotherapy and radiation therapy may also be recommended. Most patients who have developed esophageal cancer come to the doctor because they are having problems swallowing food. Very few patients who develop esophageal cancer were in an endoscopic surveillance program and had their cancer detected early. Patients who have surgery for a cancer found in Barrett's esophagus have all of the Barrett's lining removed as well as the cancer to eliminate the risk of developing another cancer in the future or missing an unsuspected second cancer that can also be present in the Barrett's tissue.

**Surgical techniques**

Two commonly performed surgical techniques are the “transhiatal esophagectomy” and the “transthoracic esophagectomy” (Ivor-Lewis Procedure). Both of these surgeries involve removing the patient's esophagus and top part of the stomach. A portion of the stomach is then pulled up into the chest and connected to the remaining normal portion of the esophagus. The patient then has a "new" esophagus made up of the normal portion of the esophagus not removed at surgery connected to a portion of the stomach pulled up into the chest.

Both of these esophagectomy surgeries have similar cure rates and complication rates and these should be discussed with the surgeon prior to the operation. There are advantages and disadvantages in using either surgical technique. In general, the type of surgery performed depends on many factors. Some of these factors are: age of the patient; size and location of the cancer; whether the cancer has grown into other structures in the chest, such as the lungs or large blood vessels; overall health of the patient, and even the experience of the surgeon in performing a particular surgical technique. Therefore, the type of surgery chosen should be individualized to meet the needs of the patient being treated. It is desirable for the surgeon to be flexible and experienced with both techniques.

Some centers are now performing minimally invasive esophageal surgery. Minimally invasive esophageal surgery may offer the advantage of a quicker recovery and fewer complications, but , how it compares to conventional surgical techniques is unknown. The experience in performing this procedure is limited to very few specialty centers. Studies comparing minimally invasive surgery to conventional esophagectomy with longer follow-up are needed to confirm that there are advantages of minimally invasive esophagectomy as compared to conventional esophagectomy. At the present time, conventional surgical approaches remain the standard operations in most specialty centers.

**Surgeon experience and rate of mortality**

Several large studies now confirm that whether a patient has a good result from the esophagectomy surgery is highly dependent on the number of esophagectomies performed at the medical center where the surgeon operates. In the hands of an experienced esophageal surgeon who performs these surgeries in a center experienced in the care of patients who undergo esophagectomy, the mortality (rate of death) is around 3-8%. On the other hand, the surgical mortality in low volume centers is in the range of 16-23%. Because esophagectomy is a technically difficult surgery, the surgeon needs to be a specialist in esophageal surgery and be regularly performing these procedures in a medical center with experience in the care of these patients. Therefore, one should undergo esophagectomy only in the hands of an EXPERIENCED esophageal surgeon who has a surgical mortality of no greater than 5% and who is regularly performing these procedures in a large specialty center.

---

**Are there any non-surgical treatments for high-grade dysplasia and cancer in Barrett's esophagus?**
There are three main types of non-surgical or endoscopic therapies used in the treatment of Barrett's high-grade dysplasia and early cancer. These are photodynamic therapy, thermal ablation and endoscopic mucosal resection. Other non-surgical therapies are also being developed.

### Porfimer sodium photodynamic therapy (PDT)

Porfimer sodium photodynamic therapy (PDT) has been approved by the US Food and Drug Administration (FDA) for treatment of high-grade dysplasia in Barrett's esophagus. Porfimer sodium PDT is performed by first injecting a drug called porfimer sodium, (Photofrin®) intravenously (into a vein). This drug makes all the tissues in the body, including the Barrett's esophagus tissue, light sensitive. About 48 hours after the porfimer sodium is given, the patient returns for upper endoscopy. During the endoscopy, a red, non-heat producing laser light is passed through the endoscope and directed onto the Barrett's esophagus. The laser light activates the porfimer sodium in the Barrett's tissue which causes the Barrett's tissue to be destroyed by a photochemical reaction. Patients are also given strong anti-acid medications called proton-pump inhibitors to control their gastroesophageal reflux disease (GERD) so that the normal white squamous esophageal lining is encouraged to grow back inside the esophagus, replacing the destroyed red Barrett's lining.

There have been single center studies reporting the effectiveness of porfimer sodium PDT in the treatment of high-grade dysplasia as well as early cancer in Barrett's esophagus. One single center study by Overholt, et al, reported the results of treatment of 103 patients who had dysplasia or early stage cancer with porfimer sodium PDT combined with Nd:Yag laser therapy to get rid of small areas of Barrett's esophagus that remained after treatment with PDT. These patients were followed an average of 4.2 years. In this study, 77.5% of patients who had high-grade dysplasia were successfully treated (did not have high-grade dysplasia detected in biopsies after treatment) and 44.4% of patients who had early stage cancer were successfully treated (did not have cancer detected in biopsies after treatment).

Porfimer sodium PDT was approved by the FDA for the treatment of high-grade dysplasia in Barrett's esophagus in 2003, based on the results of a recently published multi-center clinical trial in patients who had high-grade dysplasia (Gastrointestinal Endoscopy, 2005,62(4);488-498). In this trial, one group of patients with high-grade dysplasia was treated with PDT and compared to a control group who did not have PDT. Both groups were given a proton pump inhibitor (omeprazole) and followed with endoscopic biopsy surveillance for 24 months.

In this trial, patients with Barrett's high-grade dysplasia, from 30 international centers, were randomly assigned in a 2:1 fashion to the PDT treatment group (138 patients) or to the omeprazole only group (70 patients). The primary goal of this trial was to determine whether PDT could cause more regression or disappearance of high-grade dysplasia compared to patients who had not received PDT. This study differed from previous single center studies in its use of a balloon system to help smooth out the folds of the esophagus as well as its use of a significantly lower light dose.

The results were that significantly more patients who were treated with PDT (77%) had complete disappearance of their high-grade dysplasia as compared to those patients who were in endoscopic biopsy surveillance on omeprazole alone (39%). Although not a primary goal of the study, cancer developed in 13% who had PDT as compared to 28% of those who were on omeprazole alone. This means that there was a 50% reduction in the development of cancer in those who received PDT. The majority of patients treated with PDT required more than one treatment.

This study is a very important one because it is the first prospective randomized multi-center clinical trial testing the effectiveness of endoscopic ablation therapy in the treatment of high-grade dysplasia. During the study follow-up period, investigators demonstrated complete regression of high-grade dysplasia in almost twice as many PDT treated patients as compared to those not treated with PDT and the reduction of cancer development in PDT treated patients to half that of patients who were not treated with PDT.

This multi-center clinical trial is also important because it underscores three other important points. First, of the 435 patients who referred to the study because of a diagnosis of high-grade dysplasia, less than half (208) actually had high-grade dysplasia based on the opinion of an EXPERT gastrointestinal pathologist. Second, untreated patients on proton pump inhibitors alone can have regression of their high-grade dysplasia (39%) or remain stable without progressing to cancer (72%), at least during a relatively short, 24 month, follow-up period. Third, patients who have had PDT need to continue endoscopic biopsy surveillance after treatment.
even those patients who have achieved complete regression or disappearance of their high grade dysplasia. In the PDT multi-center trial, 48% of patients who received PDT still had Barrett's esophagus after treatment, 23% still had high-grade dysplasia after treatment, around 35% of patients who had complete disappearance of their high-grade dysplasia after PDT re-developed high-grade dysplasia by one year after treatment, and 50% re-developed high-grade dysplasia by 2.7 years after PDT treatment. Finally, 13% of patients treated with porfimer sodium PDT developed cancer during the study follow-up period. **Although PDT significantly reduced the rate of re-development of high-grade dysplasia and the development of cancer as compared to omeprazole alone, in this trial, the risk of cancer was not eliminated by profimer sodium PDT.**

The side effects of porfimer sodium PDT reported in the multi-center PDT trial are very similar to those reported by single centers performing PDT. The side effects include chest pain within 24 hours that can be severe and require narcotics (strong pain killers). Nausea is also very common. A stricture (narrowing of the esophagus due to scar tissue formation) can occur and requires dilation (stretching the esophagus) in around one-quarter to one-third of patients. Strictures may occur more often at higher laser light doses and with multiple treatments. These strictures can be persistent and require many dilations. Rarely esophageal perforation (poking a hole in the esophagus) has occurred. Other reported problems after photodynamic therapy include fluid surrounding the lungs, irregular heart rhythms, and severe skin burns from light exposure. Porfimer sodium makes skin cells sensitive to light and skin sensitivity to light and the risk of burn may last 4-6 weeks or longer after treatment. Sunscreen provides no protection so the patient must completely cover-up (including using a ski mask and gloves).

In Europe, there have been clinical trials of PDT using a different photosensitizing agent called 5-ALA. One recent study from Germany reported the results of a 3-year follow-up of patients who had high-grade dysplasia and early cancer and who were treated with 5 ALA. Thirty-five patients had high-grade dysplasia and 31 patients had early cancer. Almost all patients had a good initial response to treatment. During follow-up, 11% of patients whose high-grade dysplasia had been treated with 5-ALA PDT, redeveloped high-grade dysplasia or cancer (2 patients or 6% of those treated developed cancer). Of the 31 patients who underwent this treatment for cancer, and who had a good response to treatment, 32% re-developed cancer during follow-up. This drug is given orally and causes less problems with light sensitivity of the skin and fewer esophageal strictures. However, this drug can cause heart and commonly blood pressure problems during the procedure that can be significant.

Most photodynamic therapy studies have also reported that a few patients have a situation in which the Barrett's lining doesn't completely go away but is still there underneath the new normal appearing squamous lining. In other words, when their esophagus is examined with the endoscope, it looks like the Barrett's is completely gone but some biopsies (small pieces of tissue taken during endoscopy to look for Barrett's lining under the microscope) show that small areas of Barrett's lining are still there underneath the new squamous lining. Rarely, patients have developed cancer under what appeared to be normal squamous lining after photodynamic therapy. However, in the porfimer sodium PDT multi-center trial, most cancers that developed in the PDT treatment group as well as the omeprazole only group, were detected at an early stage, suggesting, that an intensive and careful endoscopic biopsy surveillance program can detect cancers when they are early, whether or not the patient has received prior PDT.

At the present time, we do not know who will have the best results with porfimer sodium PDT. We do know that in some PDT treated patients, Barrett's esophagus has grown back, high-grade dysplasia has developed and cancer has developed. Some studies have reported that genetic abnormalities in the Barrett's lining did not go away with the endoscopic ablation therapy and may be a risk factor for the re-development of high-grade dysplasia or the development of cancer after what appears to be a successful treatment.

Based on the positive results of the multi-center trial, porfimer sodium PDT offers patients who have high-grade dysplasia another viable alternative to esophagectomy or endoscopic biopsy surveillance alone. Although the long-term effectiveness of porfimer sodium PDT is not known at this point, for many patients, especially the elderly with multiple medical problems, even a significant delay in the development of cancer may allow these patients to keep their esophagus, avoiding esophagectomy for the remainder of their life-time. Patients who have an **EARLY** cancer, including those who are not good surgical candidates due to their health, may now choose PDT or another endoscopic therapy such as endoscopic mucosal resection as the most appropriate alternative to esophagectomy.

All patients who have high-grade dysplasia or cancer should receive in-depth counseling concerning the risks and benefits associated with all of their options for management of their condition. At the present time,
photodynamic therapy as well as endoscopic biopsy surveillance of patients who have high-grade dysplasia, is best performed at a large specialty center with expertise in performing PDT and in the endoscopic biopsy surveillance of these patients. PDT is not appropriate as an intended cure for patients who have large cancers because it cannot treat deep cancers or lymph nodes. However, it is FDA approved to help patients who have large cancers get relief from their swallowing difficulties (palliative therapy).

Endoscopic Mucosal Resection (EMR)

Endoscopic mucosal resection (EMR) is an endoscopic procedure that is now used most often to remove an area of high grade dysplasia or a small, early cancer. The FDA has approved two devices for EMR; the Olympus EMR cap and the Wilson-Cook Duette.

Endoscopic Mucosal Resection (EMR) is performed through the endoscope and involves lifting up the Barrett's lining to be removed by injecting a solution under it or applying suction to it and then cutting it off, much like colon polyp removal. The lining containing the early cancer or high-grade dysplasia is taken out through the endoscope and sent for histologic analysis (analysis under the microscope) to check if the margins are free of cancer or high-grade dysplasia. This procedure, unlike esophagectomy (surgical removal of the esophagus), usually does not remove all of the Barrett's lining but can be successful in removing a small cancer; or a localized area of high-grade dysplasia. A major advantage to endoscopic mucosal resection is the ability to remove a large piece of tissue and examined it for evidence of cancer or depth of cancer invasion which has previously not been available. Because it does not remove all of the Barrett's lining, the Barrett's lining left behind can develop other areas of high-grade dysplasia or cancer. EMR has been combined with photodynamic therapy in an attempt to get rid of remaining Barrett's tissue at risk for developing high-grade dysplasia or other cancers. More recently there are published reports of patients with high grade dysplasia or early stage cancer undergoing multiple endoscopic mucosal resections in an attempt to remove the entire Barrett's lining. A reasonable success rate in removing all of the Barrett's lining has been reported but the length of time these patients have been followed after treatment is very short and the numbers of patients who have had this procedure are small. At the present time, it is unknown whether some patients will re-develop their Barrett's lining, high-grade dysplasia or cancer. More studies with longer patient follow-up are needed.

If EMR is used to treat an early cancer, before the EMR procedure is performed another procedure, called endoscopic ultrasound, is often performed to make certain that the cancer involves only the very top layer of cells and is therefore an intramucosal cancer. An average 3-year survival rate of more than 80% has been reported for intramucosal cancers treated by EMR. The rate of severe complications, (bleeding or perforation) as high as 6.8% have been reported. Bleeding can be controlled at the time of the procedure and rarely requires transfusion. Other studies have reported no significant side-effects.

EMR is unproven to have a long-term cure rate for early stage cancers but the short-term follow-up of patients who have early cancer looks promising. Patients who have early cancers and who are not good surgical candidates or who want to avoid esophagectomy may undergo this therapy as potentially curative. Again, if this therapy is chosen instead of esophagectomy, the patient needs to remember that close endoscopic biopsy surveillance must be continued in order to have the opportunity to diagnose a cancer at an early stage if it develops because cancers can develop in the Barrett's lining that remains after endoscopic mucosal resection. As with any endoscopic therapy, it should be performed at a specialty center with expertise in performing this procedure and, ideally, as part of a study. Cancers that are deeper than intramucosal (submucosal or deeper) are not as likely to be cured with this treatment.

Thermal ablation

Like photodynamic therapy, thermal ablation is performed with the goal of destroying the Barrett's lining. This therapy uses heat (electrical probes, lasers, or an electrically conducting gas) to directly burn the Barrett's lining off. The re-growth of normal squamous lining is then encouraged by the use of proton-pump inhibitors to control gastroesophageal reflux. Some of these therapies, based on the names of the more commonly used devices, are: multipolar electrocoagulation (MPEC); argon plasma coagulation (APC); and laser ablation (KTP:YAG laser, Nd:YAG laser, argon laser). There are advantages and disadvantages with each of these therapies.

MPEC studies are small, but report a high rate of complete disappearance of the Barrett's lining and no significant complications. The therapy is low-cost. However, multiple treatments are frequently required.
Many studies have reported the use of argon plasma coagulation (APC) in the treatment of Barrett's patients, including those who have high-grade dysplasia. There have been different success rates reported in different studies with Barrett's lining still detected in up to one-third of patients treated. In more recent studies, however, ablation of Barrett's esophagus with APC appears to be more successful using a higher energy setting and higher doses of proton pump inhibitors. As with other therapies, there have been complications including perforations (making a hole in the esophagus), bleeding, strictures, and a reported death.

Laser ablation therapies (KTP:YAG laser, Nd:YAG laser, argon laser) have various success rates in destroying the Barrett's lining. Laser ablation in combination with MPEC has been reported to be very successful in treating a small number of patients who had an early cancer (intramucosal carcinoma) in Barrett's esophagus, but longer follow-up of these patients are needed.

For thermal ablation, there are no long-term follow-up studies of large numbers of patients to know whether treated patients are safe from developing cancer. Very few clinical trials have been performed. Like photodynamic therapy, Barrett's lining can be buried under what appears through the endoscope to be normal squamous lining and this appears likely to occur in certain forms of thermal therapy. Most thermal ablation therapies are reported to have fewer side-effects as compared to photodynamic therapy, however, at least one patient death, as a direct result of APC therapy, has been reported. Thermal ablation therapies generally require more treatment sessions as compared to photodynamic therapy. Thermal ablation is experimental, and if undertaken, the patient must be followed in periodic endoscopic biopsy surveillance indefinitely at a specialty center experienced in the surveillance of patients who have undergone thermal ablation.

**Other endoscopic therapies**

At the present time, photodynamic therapy, thermal ablation therapy and endoscopic mucosal resection or a combination of these, remain the most widely available non-surgical, endoscopic therapies in the treatment of Barrett's high-grade dysplasia and early cancer. Recently, radiofrequency ablation therapies which are those that use sound waves (ultrasonic therapy), such as the BarRX device has been developed. The BarRX uses a balloon device to apply radiofrequency energy to the Barrett's lining. The treatment can be used on up to three centimeters of lining at a time. The radiofrequency device is designed to treat only the very superficial or top layers of the esophagus. A recent study reported that BarRX was successful in removing all of the Barrett's esophagus lining in the large majority of patients who had Barrett's esophagus without dysplasia. Some Barrett's experts are questioning the benefit of treating patients who have Barrett's esophagus without dysplasia because most of these patients will never develop cancer and the procedure can have complications. Also, it is recommended that endoscopic biopsy surveillance be continued indefinitely in all patients, even those who appear not to have any Barrett's lining in biopsies after treatment, as it is unknown whether this treatment reduces the cancer risk long-term. Most experts are recommending that all ablation therapies be reserved for patients who have high-grade dysplasia as these are the patients who have the highest cancer risk and who are most likely to benefit from these therapies.

Freezing (cryotherapies) to destroy the Barrett's lining are also being tested for their effectiveness in getting rid of the Barrett's lining and dysplasia. Freezing therapies use devices that are like those used by dermatologists to treat skin growths, but instead, these esophageal cryotherapy devices help deliver liquid nitrogen onto the esophagus. It is also hoped that there will be drug therapies to prevent cancer from developing in Barrett's esophagus. One class of drugs that has received recent attention for its possible cancer prevention qualities are Cox inhibitors (a class of arthritis drugs called NSAIDS). Recently, there have been concerns about the use of Cox 2 inhibitors and their effects on the cardiovascular system. One such drug, Vioxx was pulled from the drug market by its manufacturer after a study showed that it raised the risk of heart attacks and stroke. Based on the analysis of some population and cohort studies of aspirin and cancer prevention, there is evidence that aspirin, a Cox 1 and Cox 2 inhibitor may also be effective in reducing the rate of esophageal adenocarcinoma, but to date, there have been no published clinical trial results of aspirin or other Cox inhibitors as esophageal cancer prevention agents.