

## STOMACH CANCER

### Stomach cancer can cause the following signs and symptoms:

#### Stage 1 (Early)

- Indigestion or a burning sensation (heartburn)
- Loss of appetite, especially for meat
- Abdominal discomfort or irritation

#### Stage 2 (Middle)

- Weakness and fatigue
- Bloating of the stomach, usually after meals

#### Stage 3 (Late)

- Abdominal pain in the upper abdomen
- Nausea and occasional vomiting
- Diarrhea or constipation
- Weight loss
- Bleeding (vomiting blood or having blood in the stool) which will appear as black. This can lead to anemia.
- Dysphagia; this feature suggests a tumor in the cardia or extension of the gastric tumor in to the esophagus.
- Note that these can be symptoms of other problems such as a stomach virus, gastric ulcer or tropical sprue.

### Causes:

Infection by *Helicobacter pylori* is believed to be the cause of most stomach cancer while autoimmune atrophic gastritis, intestinal metaplasia and various genetic factors are associated with increased risk levels. The *Merck Manual* states that diet plays no role in the genesis of stomach cancer. However, the American Cancer Society lists the following dietary risks, and protective factors, for stomach cancer: "smoked foods, salted fish and meat, and pickled vegetables (appear to increase the risk of stomach cancer) Nitrates and nitrites are substances commonly found in cured meats.

They can be converted by certain bacteria, such as *H. pylori*, into compounds that have been found to cause stomach cancer in animals. On the other hand, eating fresh fruits and vegetables that contain antioxidant vitamins (such as A and C) appears to lower the risk of stomach cancer. A December 2009 article in American Journal of Clinical Nutrition found a statistically significant inverse correlation between higher adherence to a Mediterranean Dietary Pattern and stomach cancer.

In more detail, *H. pylori* is the main risk factor in 65–80% of gastric cancers, but in only 2% of such infections. The mechanism by which *H. pylori* induces stomach cancer potentially involves chronic inflammation, or the action of *H. pylori* virulence factors such as CagA. Approximately ten percent of cases show a genetic component. Some studies indicate that bracken consumption and spores are correlated with incidence of stomach cancer, though causality has yet to be established.

A very important but preventable cause of gastric cancer is tobacco smoking. Smoking considerably increases the risk of developing gastric cancer considerably: from 40% increased risk for current smokers to 82% increase for heavy smokers. Gastric cancers due to smoking mostly occur in the upper part of the stomach near the esophagus.

Studies are variable with respect to stomach cancer and alcohol consumption. For example, one recent Japanese study has shown a positive correlation and another, insufficient evidence to render a conclusion. There does seem to be a stronger correlation, however, with combined use of alcohol and tobacco.

Gastric cancer shows a male predominance in its incidence as up to three males are affected for every female. Estrogen may protect women against the development of this cancer form. A very small percentage of diffuse-type gastric cancers (see Histopathology below) are thought to be genetic. Hereditary Diffuse Gastric Cancer (HDGC) has recently been identified and research is ongoing. However, genetic testing and treatment options are already available for families at risk.

#### Diagnosis:

To find the cause of symptoms, the doctor asks about the patient's medical history, does a physical exam, and may order laboratory studies. The patient may also have one or all of the following exams:

- Gastroscopic exam is the diagnostic method of choice. This involves insertion of a fiber optic camera into the stomach to visualize it.
- Upper GI series (may be called barium roentgenogram)
- Computed tomography or CT scanning of the abdomen may reveal gastric cancer, but is more useful to determine invasion into adjacent tissues, or the presence of spread to local lymph nodes.

Abnormal tissue seen in a gastroscopy examination will be biopsied by the surgeon or gastroenterologist. This tissue is then sent to a pathologist for histological examination under a microscope to check for the presence of cancerous cells. A biopsy, with subsequent histological analysis, is the only sure way to confirm the presence of cancer cells.

Various gastroscopic modalities have been developed to increase yield of detected mucosa with a dye that accentuates the cell structure and can identify areas of dysplasia. *Endocytoscopy* involves ultra-high magnification to visualize cellular structure to better determine areas of dysplasia. Other gastroscopic modalities such as optical coherence tomography are also being tested investigationaly for similar applications.

A number of cutaneous conditions are associated with gastric cancer. A condition of hyperplasia of the skin, frequently of the axilla and groin, known as acanthosis nigricans, is associated with intra-abdominal cancers such as gastric cancer. Other cutaneous manifestations of gastric cancer include *tripe palms* (a similar darkening hyperplasia of the skin of the palms) and the Leser-Trelat sign, which is the rapid development of skin lesions known as seborrheic keratoses.

Various blood tests may be done, including: Complete Blood Count (CBC) to check for anemia. Also, a stool test may be performed to check for blood in the stool.

#### Staging

If cancer cells are found in the tissue sample, the next step is to stage, or find out the extent of the disease. Various tests determine whether the cancer has spread and, if so, what parts of the body are affected.

Because stomach cancer can spread to the liver, the pancreas, and other organs near the stomach as well as to the lungs, the doctor may order a CT scan, a PET scan, an endoscopic ultrasound exam, or other tests to check these areas.

Blood tests for tumor markers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) may be ordered, as their levels correlate to extent of metastasis, especially to the liver, and the cure rate.

Staging may not be complete until after surgery. The surgeon removes nearby lymph nodes and possibly samples of tissue from other areas in the abdomen for examination by a pathologist.

The clinical stages of stomach cancer are:

- Stage 0. Limited to the inner lining of the stomach. Treatable by endoscopic mucosal resection when found very early (in routine screenings); otherwise by gastrectomy and lymphadenectomy without need for chemotherapy or radiation.
- Stage I. Penetration to the second or third layers of the stomach (Stage 1A) or to the second layer and nearby lymph nodes (Stage 1B). Stage 1A is treated by surgery, including removal of the omentum. Stage 1B may be treated with chemotherapy (5-fluorouracil) and radiation therapy.
- Stage II. Penetration to the second layer and more distant lymph nodes, or the third layer and only nearby lymph nodes, or all four layers but not the lymph nodes. Treated as for Stage I, sometimes with additional neoadjuvant chemotherapy.
- Stage III. Penetration to the third layer and more distant lymph nodes, or penetration to the fourth layer and either nearby tissues or nearby or more distant lymph nodes. Treated as for Stage II; a cure is still possible in some cases.
- Stage IV. Cancer has spread to nearby tissues and more distant lymph nodes, or has metastasized to other organs. A cure is very rarely possible at this stage. Some other techniques to prolong life or improve symptoms are used, including laser treatment, surgery, and/or stents to keep the digestive tract open, and chemotherapy by drugs such as 5-fluorouracil, cisplatin, epirubicin, etoposide, docetaxel, oxaliplatin, capecitabine, or irinotecan.

The TNM staging system is also used.

## Treatment

As with any cancer, treatment is adapted to fit each person's individual needs and depends on the size, location, and extent of the tumor, the stage of the disease, and general health. Cancer of the stomach is difficult to cure unless it is found in an early stage (before it has begun to spread). Unfortunately, because early stomach cancer causes few symptoms, the disease is usually advanced when the diagnosis is made. Treatment for stomach cancer may include surgery, chemotherapy, and/or radiation therapy. New treatment approaches such as biological therapy and improved ways of using current methods are being studied in clinical trials. An antibody-drug conjugate IMG242 is in phase II clinical trials.

## Surgery

Surgery is the most common treatment. The surgeon removes part or all of the stomach, as well as the surrounding lymph nodes, with the basic goal of removing all cancer and a margin of normal tissue. Depending on the extent of invasion and the location of the tumor, surgery may also include removal of part of the intestine or pancreas. Tumors in the lower part of the stomach may call for a Billroth I or Billroth II procedure.

Endoscopic mucosal resection (EMR) is a treatment for early gastric cancer (tumor only involves the mucosa) that has been pioneered in Japan, but is also available in the United States at some

centers. In this procedure, the tumor, together with the inner lining of stomach (mucosa), is removed from the wall of the stomach using an electrical wire loop through the endoscope.

The advantage is that it is a much smaller operation than removing the stomach. Endoscopic submucosal dissection (ESD) is a similar technique pioneered in Japan, used to resect a large area of mucosa in one piece. If the pathologic examination of the resected specimen shows incomplete resection or deep invasion by tumor, the patient would need a formal stomach resection. Surgical interventions are currently curative in less than 40% of cases, and, in cases of metastasis, may only be palliative.

## **Chemotherapy**

The use of chemotherapy to treat stomach cancer has no firmly established standard of care. Unfortunately, stomach cancer has not been particularly sensitive to these drugs, and chemotherapy, if used, has usually served to palliatively reduce the size of the tumor, relieve symptoms of the disease and increase survival time. Some drugs used in stomach cancer treatment have included: 5-FU (fluorouracil) or its analog capecitabine, BCNU (carmustine), methyl-CCNU (Semustine), and doxorubicin (Adriamycin), as well as Mitomycin C, and more recently cisplatin and taxotere, often using drugs in various combinations.

The relative benefits of these different drugs, alone and in combination, are unclear. Clinical researchers have explored the benefits of giving chemotherapy before surgery to shrink the tumor, or as adjuvant therapy after surgery to destroy remaining cancer cells. Combination treatment with chemotherapy and radiation therapy has some activity in selected post surgical settings.

For patients who have HER2 overexpressing metastatic gastric or gastroesophageal (GE) junction adenocarcinoma, who have not received prior treatment for their metastatic disease, the US Food and Drug Administration granted approval (2010 October) for trastuzumab (Herceptin, Genentech, Inc.) in combination with cisplatin and a fluoropyrimidine (capecitabine or 5-fluorouracil). This was based on an improvement of the median overall survival (OS) of 2.5 months with trastuzumab plus chemotherapy treatment compared to chemotherapy alone (BO18255 ToGA trial). The combination of Herceptin with chemotherapy for treating metastatic gastric cancer was also sanctioned by the European regulatory authorities (2010 January). Doctors have also tested putting the anticancer drugs directly into the abdomen, often with warmed solutions of the medication (intraperitoneal hyperthermic chemoperfusion).

## **Radiation**

Radiation therapy (also called radiotherapy) is the use of high-energy rays to damage cancer cells and stop them from growing. When used, it is generally in combination with surgery and chemotherapy, or used only with chemotherapy in cases where the individual is unable to undergo surgery. Radiation therapy may be used to relieve pain or blockage by shrinking the tumor for palliation of incurable disease.

## **Multimodality therapy**

While previous studies of multimodality therapy (combinations of surgery, chemotherapy and radiation therapy) gave mixed results, the Intergroup 0116 (SWOG 9008) study showed a survival benefit to the combination of chemotherapy and radiation therapy in patients with nonmetastatic, completely resected gastric cancer. Patients were randomized after surgery to the standard group of observation alone, or the study arm of combination chemotherapy and radiation therapy. Those in the study arm receiving chemotherapy and radiation therapy survived on average 36 months; compared to 27 months with observation.