ANTICANCER FUND

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

STOMACH CANCER: A GUIDE FOR PATIENTS

PATIENT INFORMATION BASED ON ESMO CLINICAL PRACTICE GUIDELINES

This guide for patients has been prepared by the Anticancer Fund as a service to patients, to help patients and their relatives better understand the nature of stomach cancer and appreciate the best treatment choices available according to the subtype of stomach cancer. We recommend that patients ask their doctors about what tests or types of treatments are needed for their type and stage of disease. The medical information described in this document is

based on the clinical practice guidelines of the European Society for Medical Oncology (ESMO) for the management of stomach cancer. This guide for patients has been produced in collaboration with ESMO and is disseminated with the permission of ESMO. It has been written by a medical doctor and reviewed by two oncologists from ESMO including the lead author of the clinical practice guidelines for professionals. It has also been reviewed by patients' representatives from ESMO's Cancer Patient Working Group.

More information about the Anticancer Fund: www.anticancerfund.org

More information about the European Society for Medical Oncology: www.esmo.org

For words marked with an asterisk, a definition is provided at the end of the document.

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This text was written by Dr Annemie Michiels (RCT) and reviewed by Dr. Gauthier Bouche (RCT), Dr. Svetlana Jezdic (ESMO), Dr. Alicia Okines (ESMO), Prof. David Cunningham (ESMO), Dr. William Allum (ESMO) and Pr. Lorenz Jost (ESMO's Cancer Patient Working Group).

DEFINITION OF STOMACH CANCER

This definition is adapted from and is used with the permission of the National Cancer Institute (NCI) of the United States of America.

Stomach cancer is a cancer that forms in tissues lining the stomach. Most stomach cancers start from cells in the inner layer of the stomach (the mucosa) which normally make and release mucus* and other fluids. These cancers are called adenocarcinomas and represent about 90% of stomach cancers.

Important note regarding other types of stomach cancer

The information provided in this Guide for Patients does not apply to other types of stomach cancers. The main other types of stomach cancer include:

- **Gastric lymphomas**, which are cancers originating from cells of the immune system found in the wall of the stomach. Most gastric

lymphomas are non-Hodgkin lymphomas. More information on non-Hodgkin lymphoma can be found here.

- **Gastro-intestinal stromal tumors** or GIST, which are rare tumors that are believed to originate from cells in the wall of the stomach called interstitial cells of Cajal. Information on gastro-intestinal stromal tumor can be found here.
- **Neuroendocrine tumors** which are tumors originating from nervous or endocrine cells of the stomach. Information on gastric neuroendocrine tumors can be found here.

Diagnosis and treatment of these types of cancer are different from those for gastric adenocarcinoma.

IS STOMACH CANCER FREQUENT?

Worldwide, stomach cancer is most common in East Asia, South America and Eastern Europe. It is less common in Western Europe even though stomach cancer is the fifth most frequent cancer in Europe. It is approximately twice as frequent in men as it is in women. It is most often diagnosed between the age of 60 and 80. In Europe, about 150,000 people developed stomach cancer in 2008.
The marked variation in the frequency of stomach cancer between continents and countries is mainly due to differences in diet and to genetic factors.

In Europe, an average of 1 or 2 in every 100 men and 0.5 to 1 in every 100 women will develop stomach cancer at some point in their lifetime. There are marked geographic variations between countries worldwide but also within Europe. Stomach cancer is

more frequent in countries of Eastern Europe and in Portugal where up to 4 in every 100 men and 2 in every 100 women will develop the disease at some point in their lifetime.

WHAT CAUSES STOMACH CANCER?

Today, it is not clear why stomach cancer occurs. Some risk factors* have been identified. A risk factor* increases the risk of cancer occurring, but is neither sufficient nor necessary to cause cancer. It is not a cause in itself. **Most people with these risk factors* will never develop stomach cancer and some people without any of these risk factors will nonetheless develop stomach cancer.**

The main risk factors* of stomach cancer are:

Environmental factors: Helicobacter pylori or H. pylori is a bacteria and can reside in the stomach and cause chronic inflammation or stomach ulcers*. If this situation persists for a few decades, it can evolve into cancer. However, the infection will first go through a number of pre-cancerous stages (like atrophic gastritis, metaplasia and dysplasia) that could, but do not

systematically turn into cancer. These stages can already be detected and treated before they could evolve to cancer. If left untreated, 1% of all patients with H. pylori will eventually develop stomach cancer. About 50% of the world's population is infected with H. pylori. Transmission occurs through stools and saliva and is strongly related to poor socio-economic status and poor living conditions. Treatment of this infection consists of a cure with antibiotics. Infection with H. pylori is the most important and at the same time, one of the most treatable risk factors for stomach cancer.

Lifestyle:

Nutrition:

A high dietary intake of salt, including salt-preserved (e.g. smoked or pickled with salt) food, strongly increases the risk of developing stomach cancer. The presence of salt makes an infection with H. pylori more likely to occur and also seems to aggravate the effect of an infection. Besides that, it damages the mucosa*

of the stomach and can in this way directly contribute to the development of stomach cancer.
A high intake of food containing nitrates* or nitrites*, like preserved meat, can increase the risk of developing stomach cancer.
Eating fruit and vegetables that contain vitamins A and C has proven to protect significantly against the development of stomach cancer.
Smoking: The rate of stomach cancer is about doubled in smokers.
Occupation: Workers in the coal, metal, and rubber industries seem to have a slightly higher risk of developing stomach cancer.
Some studies have shown that people who do a great deal of physical activity can reduce their risk of developing stomach cancer by up to a half.

Factors that cannot be modified:

Some inherited conditions may increase the risk of developing stomach cancer

A rare hereditary mutation* in the gene that codes for a protein* called E-cadherin, leads to a very high risk of developing stomach cancer. The type of stomach cancer due to this mutation* is called *hereditary diffuse stomach cancer* and has a bad prognosis*. Individuals with this mutation* might therefore consider close surveillance, or discuss a preventative removal of the stomach.

Some hereditary mutations which are predisposed to cancer in other parts of the body seem to slightly increase the risk of developing stomach cancer. Examples of these are mutations* in the BRCA1 and BRCA2-gene, which are known to increase the risk of developing breast and ovarian cancer, and two conditions increasing the risk for colorectal cancer, called *Hereditary non-polyposis colorectal cancer* or *Lynch Syndrome* and *Familial Adenomatous Polyposis*.

A history of stomach cancer in first-degree relatives (parents, siblings or children) increases one's own risk of developing the disease.
For unknown reasons, people with type A blood are at a greater risk of developing stomach cancer.
Gender: Stomach cancer is more frequent in men than in women. Reasons for this difference are unclear, but the female sex hormone estrogen may have a protective effect.

Medical conditions:
People who have been treated for another type of stomach cancer, known as *mucosa-associated lymphoid tissue (MALT) lymphoma,* are at an increased risk of getting adenocarcinoma of the stomach. This is probably because MALT lymphoma of the stomach is caused by infection with H pylori bacteria.
Gastro-esophageal reflux, a common condition where stomach acid comes up from the stomach into the esophagus increases the risk of cancer at the junction

of the stomach and the gullet (the oesophago-gastric junction or OGJ).

Previous stomach surgery: when a part of the stomach has been removed, e.g. because of a stomach ulcer, there is a higher chance of developing cancer in the remaining part. This may be because less stomach acid is produced. The reduced acid level may allow more bacteria to grow and the bacteria may help to produce more chemicals that may increase stomach cancer risk.

Gastric polyps are benign growths on the inner lining of the stomach. One type of polyp, called adenoma, can sometimes develop into cancer. Adenomas can be detected and removed during a gastroscopy, an examination of the stomach in which the doctor passes a thin, flexible, light-emitting tube, called an endoscope, downthe patient's throat and into the stomach.

Pernicious anemia is a condition in which patients fail to absorb enough vitamin B12 from their food, which is needed to make new red blood cells. Along with

anemia (low red blood cell counts), the risk of stomach cancer is also increased for these patients.

Other factors have been suspected to be associated with an increased risk of stomach cancer, like obesity, infection with the Epstein-Barr virus* (causing infectious mononucleosis) and a rare medical condition called Ménétrier's disease*. However, the evidence is inconsistent and the mechanism remains unclear.

HOW IS STOMACH CANCER DIAGNOSED?

Stomach cancer can be suspected in different circumstances. Unfortunately, these signals are often vague and quite common, and they can also point to many other medical conditions. In the early phase, most stomach cancers do not even cause any symptoms. Therefore a stomach tumor is often not suspected. In case of a combination of the following complaints, and especially if persistent, further examinations should be considered:

- abdominal discomfort or pain
- a sense of fullness, even after eating a small meal
- heartburn, indigestion, acidity and burping
- nausea and/or vomiting, especially including blood.

- swelling or fluid build-up in the abdomen
- poor appetite
- unexplained extreme weight loss

Unnoticeable blood loss from the stomach may also cause anemia*, leading to tiredness and breathlessness in the long term.

In Japan and Korea, where there is a high number of new cases of stomach cancer, a screening is proposed to every individual at the age of 50 and with a follow-up according to the result of the screening exam.
In Europe, no such screening is proposed because the number of new cases of stomach cancer is not considered to be sufficient for screening to be efficient[1]. The diagnosis of stomach cancer is based on the following examinations.

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[1] Screening consists of performing an exam in order to detect cancer at an early stage, before any sign of the cancer appears. A screening is proposed if a safe and acceptable exam can be

1. **Clinical examination.** The doctor will examine the abdomen to identify any abnormal swelling or pain. He will also check for any abnormal swelling above the left collar bone, which may be caused by a spread of the cancer to the lymph nodes* that are situated there.

2. **Endoscopic examination.** During an endoscopic examination of the upper digestive tract or the gastroscopy, the doctor passes a thin, flexible, light-emitting tube called an endoscope down the patient's throat and into the stomach. This allows the doctor to see the lining of the

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performed and if this exam is able to detect cancer in the majority of cases. It should also be proved that treating screened cancers is more effective than treating cancers diagnosed because signs of cancer were present.

esophagus, stomach, and the first part of the small intestine. If abnormal areas are noted, biopsies* (tissue samples) can be taken using instruments passed through the endoscope. These tissue samples are examined by a specialist in the laboratory (see histopathological* examination).

During the gastroscopy, an **endoscopic ultrasound** can be performed at the same time. An ultrasound probe is introduced down the throat and into the stomach. It provides images of the different layers of the stomach wall, as well as the nearby lymph nodes* and other structures. This technique is used to see how far a cancer has spread in the stomach wall, into nearby tissues or to nearby lymph nodes*. It can also guide the doctor in removing a small sample (biopsy*) of a suspicious lesion during the gastroscopy.

3. **Radiological examination.** A CT-scan shows how far the cancer has spread, both locally and to other parts of the body. It can also be used to guide a biopsy*. Additional investigations such as a chest X-ray and a PETscan may be performed to exclude distant spread of the disease, called metastasis*.

4. **Histopathological* examination.** The biopsy* specimen (the tissue sample that has been taken during the gastroscopy) will be examined in the laboratory by a pathologist*. This is called a histopathological* examination. Using the microscope and several other tests, the pathologist* will confirm the diagnosis of cancer and will give more information on the characteristics of the cancer.

   The histopathological* examination can also be performed on samples obtained during either a

laparoscopy*, or on the liquid used for peritoneal washing*, or on the tumor removed during surgery.

A laparoscopy* is usually performed when the stomach cancer has already been found and when an operation is foreseen. It helps to confirm that the cancer is still only in the stomach and thus can be completely removed by surgery. During this intervention a thin flexible tube is inserted through a small surgical opening in the patient's tummy. It has a small camera on its end, through which doctors can look closely at the surfaces of the organs and nearby lymph nodes*, and take small samples of tissue, to check for possible metastases*. Sometimes surgeons also pour liquid in the abdominal cavity, remove it by suction and send it to the laboratory to check for cancer cells. This is called peritoneal washing*.

When surgery is performed to remove a tumor, the tumor and the lymph nodes* will also be examined in the lab. This is very important to confirm the results of the biopsy* and to provide more information on the cancer.

WHAT IT IS IMPORTANT TO KNOW TO GET THE OPTIMAL TREATMENT?

Doctors will need to consider many aspects of both the patient and the cancer in order to decide on the best treatment.

Relevant information about the patient

- personal medical history
- results of the physical examination
- general well-being
- results of the blood examination performed, including a blood count to check for anemia*, and liver and renal function tests
- results of a CTscan of the chest, the abdomen and the pelvis

Relevant information about the cancer

- **Staging**

Doctors use staging to assess the extent of the cancer and the prognosis* of the patient. The TNM staging system is commonly used. The combination of size of the tumor and invasion of nearby tissue (T), involvement of lymph nodes* (N), and metastasis* or spread of the cancer to other organs of the body (M), will classify the cancer as being at one of the following stages.

The stage is fundamental in order to make the right decision about the treatment. The less advanced the stage, the better the prognosis*. Staging is usually performed twice: after clinical and radiological examination and after surgery. This is because if surgery is performed, staging may be influenced by the

results of the laboratory examination of the removed tumor and lymph nodes*.

The table below presents the different stages of stomach cancer. The definitions are sometimes technical, so it is recommended that you ask your doctor for more detailed explanations.

Stage	Definition
Stage 0	*The abnormal cells are only found in the inner layer of the mucosa* of the stomach, called the epithelium. This stage is also called carcinoma in situ.*
Stage I	*The tumor invades the complete mucosa with or without affecting lymph nodes*, or invades the muscle layer or the subserosa* without affecting any of the lymph nodes*. Stage I is divided into stages IA and IB.*
Stage IA	*The abnormal cells are found in the deepest layer of the mucosa* (called lamina propria) or in the submucosa*, but no lymph nodes* are affected.*
Stage IB	– *The abnormal cells are found in the deepest layer of the mucosa* (called lamina propria) or in the submucosa* and in 1 to 6 lymph nodes* OR* – *The abnormal cells are found in the muscle layer or the subserosa* of the stomach, but no lymph nodes* are affected.*
Stage II	*Stage II groups various combinations of depth of tumor invasion and number of lymph nodes* involved.* – *Either the abnormal cells are found in the deepest layer of the mucosa* (called lamina propria) or in the submucosa* and in 7 to 15 lymph nodes* OR* – *the abnormal cells are found in the muscle layer or in the subserosa* of the stomach and in 1 to 6 lymph nodes* OR* – *the abnormal cells are found in the serosa*, but no lymph nodes* are affected.*

Stage	Definition
Stage III	*The tumor has spread to the muscle layer, the subserosa*or the serosa* and to up to 15 lymph nodes*, or has invaded the structures that surround the stomach without affecting any lymph nodes*. The tumor has not spread to distant organs such as liver, lungs or lymph nodes* in other parts of the body. Stage III is divided in stage IIIA and IIIB.*
Stage IIIA	– *The abnormal cells are found in the muscle layer or the subserosa* of the stomach and in 7 to 15 lymph nodes* OR* – *The abnormal cells are found in the serosa* and in 1 to 6 lymph nodes* OR* – *The tumor has invaded the structures that surround the stomach, but no lymph nodes* are affected.*
Stage IIIB	*The abnormal cells are found in the serosa* and in 7 to 15 lymph nodes*.*
Stage IV	*More than 15 lymph nodes* are involved or the tumor has spread to structures surrounding the stomach or to other parts of the body:* - *The tumor has invaded the structures that surround the stomach and there are lymph nodes* involved OR* - *The tumor has not invaded structures that surround the stomach but more than 15 lymph nodes* are affected OR* - *Distant metastasis* is to be found, meaning the cancer has spread to other parts of the body.*

- **Results of the biopsy***

The biopsy* will be examined in the laboratory. This examination is called a histopathology*. The second histopathological* examination involves the examination of the tumor and the lymph nodes* after surgical removal. This is very important to confirm the results of the biopsy* and to provide more information on the cancer. Results of the examination of the biopsy* should include:

- **Histological* type**
  The histological type describes the characteristics of the cells that make up the tumor. Most stomach cancers are from the adenocarcinoma histological type, meaning that tumor cells resemble, to some extent, cells of the inner layer of the stomach (the

mucosa). Adenocarcinomas can then be divided into so-called *diffuse* or *undifferentiated*, and *intestinal* or *well-differentiated* types. Differentiation is the biological process in which a less specialized cell turns into a more specialized cell type. Differentiated tumor cells look more like normal stomach cells and grow more slowly than undifferentiated or poorly differentiated cells that look completely different and grow quickly. The diffuse or undifferentiated type of stomach cancer may be harder to treat.

- **Presence of ulceration***
  Ulceration* is a break in the inner lining of the stomach, caused by the inflammation and death of the cells in

this layer. Cancer with ulceration* may be harder to treat than cancer without ulceration*.

Besides investigating the biopsy* under the microscope, the pathologist* will perform certain tests that provide information about the genes of the tumor cells. These tests include FISH* or immunohistochemistry*.

- **HER2-status**
  Some cells have an overexpression of a gene called HER2, meaning that there are too many copies of it in one of the cell's chromosomes*. The HER2 gene is responsible for the production of a protein* that influences its growth and migration. Therefore it is an important element in defining the treatment options in patients with advanced,

unresectable (inoperable) gastric cancer. When there are too many copies of HER2, we speak of a HER2-positive stomach cancer or HER2 overexpression. Otherwise, the HER2 status is negative.

WHAT ARE THE TREATMENT OPTIONS?

Planning of the treatment involves an inter-disciplinary team of medical professionals. This usually implies a meeting of different specialists, called multidisciplinary opinion or tumor board review. In this meeting, the planning of treatment will be discussed according to the relevant information mentioned previously. A multidisciplinary opinion will preferably include that of a medical oncologist (who provides cancer treatment with drugs), a surgical oncologist (who provides cancer treatment with surgery), a radiation oncologist (who provides cancer treatment with radiation), a gastroenterologist (specialist in diseases of stomach and intestines), a radiologist* and a pathologist*.

They will, as a first step, judge the cancer as operable (or resectable), meaning that it is possible to remove the complete tumor in an operation, or as not

operable (or unresectable), meaning that this is not possible. In a tumor judged operable, the tumor may also have invaded structures surrounding the stomach but these can be removed without complication. A tumor can be unresectable because it has grown too close to nearby organs or lymph nodes*, because it has grown too close to major blood vessels, or because it has spread to distant parts of the body. There is no distinct dividing line between resectable and unresectable in terms of the TNM stage of the cancer, but earlier stage cancers are more likely to be resectable.

Surgery is the only treatment that is performed with the purpose of curing the cancer. If this is not possible, the other treatments are done with the purpose of relieving symptoms and prolonging the patient's lifespan.

The treatments listed below have their benefits, their risks and their contraindications. It is recommended to

ask oncologists about the expected benefits and risks of every treatment in order to be informed of all the possible consequences. For some treatments, several possibilities are available and the choice should be discussed based on weighing up their respective benefits and risks.

Treatment plan for localized disease (Stage 0 to III and resectable)

Endoscopic Treatment

Endoscopic Mucosal Resection or EMR can be done for cancers limited to the inner layer of the stomach or mucosa*, usually for small (<2cm) cancers without ulceration*. The doctor will pass a small tube down the throat and into the stomach (as is done during a gastroscopy) and remove the tumor. Recently, larger tumors could be removed by Endoscopic Submucosal Dissection (ESD). Endoscopic Submucosal Dissection

also use a small tube passed down the throat and in the stomach, but the technique is different and allows for the removal of larger tumors. This technique should normally only be proposed to patients in a clinical trial*.

Surgery

During an operation surgeons will remove the tumor with part or all of the stomach. The amount of tissue to be removed depends on the stage. It is important to remove the tumor with a clear margin of healthy stomach and the lymph nodes* close to the stomach.

Removal of the Stomach

- A part of the stomach, or the entire stomach, is surgically removed in cases of stage Ib to III stomach cancer. The medical term for this removal is gastrectomy. If the tumor is located

far enough away from the upper opening of the stomach, the upper part of the stomach can be saved. This is called a **subtotal gastrectomy**. If the tumor is located in the upper part of the stomach, the surgeon can save the lowest part and remove the upper part of the stomach along with the lowest part of the esophagus. The lowest third of the stomach will be joined to the remaining end of the esophagus in order to create a new smaller stomach.

- If the tumor has spread throughout the stomach, and also if it is located in the upper part of the stomach, a **total gastrectomy** or complete removal of the stomach is performed. In this case, the esophagus is subsequently attached again to the small intestine creating a small new pouch replacing the stomach, where food can be stored before moving down the intestinal tract.

Removal of the Lymph Nodes*

In the case of a partial or total gastrectomy, at least 15 lymph nodes* around the stomach are also removed. These very small organs, that filter liquid coming from the stomach, are then examined by the pathologist*, to refine the staging. He will check if he can find tumor cells in the lymph nodes*, indicating spread of the tumor from the stomach. When more lymph nodes* are removed, studies have shown a better rate of survival, but there are also more side effects, therefore this procedure is only advised in fit patients.

Removal of other Organs

- If other nearby organs like the pancreas, are invaded by tumor cells and if the patient is fit enough, these organs can be removed as well. The spleen, located on the left side of the stomach, should be removed in the case of a

tumor on this side of the stomach. This is because some lymph nodes* lie very close to the spleen and in this way the doctors can make sure that all the lymph nodes* between the stomach and the spleen are removed.

- Surgery for stomach cancer is commonly done by opening the abdomen. Laparoscopy* can be used for these interventions, but the advantages have not yet been proven. During this type of surgery the surgeon works with a small camera and a few instruments that are inserted through small incisions in the abdomen. Because a big incision is avoided, the patient recovery time might be shorter. Research is trying to establish that laparoscopic surgery is as effective as open surgery, particularly in determining if enough lymph nodes* are removed.

Complications of Surgery

Possible complications of surgery include bleeding, blood clots and damage to nearby organs. Later on, the patient might suffer from heartburn, abdominal pain and some deficiencies for vitamins that are normally absorbed in the stomach. Vitamin supplements are prescribed to patients for this reason. After gastrectomy the patient will, at least for a while, also have to eat smaller quantities of food, more frequently. A nutritionist can help the patient to adjust to new eating habits. It is common to have diarrhea for some months after stomach surgery.

Removal of the spleen may lead to a reduced immunity, therefore the patient will receive several vaccinations, before and after the removal of the spleen and take antibiotics daily. It is also important to be aware of the fact that there is a greater risk of

infection and should be a reason to see a doctor and often to start antibiotics.

Overall, the experience of the surgeon in these specific interventions plays a big role in the success of the treatment. It is important to ask the surgeon about his or her experience beforehand.

Adjuvant therapy

An adjuvant therapy is a therapy given in addition to surgery. This may take the form of chemotherapy either on its own or in combination with radiotherapy. Adjuvant therapies can be started before (neoadjuvant) or after surgery. The goal of adjuvant therapies is to reduce the size of the tumor and make its removal by surgery easier when given before surgery and to eliminate the remaining cancer cells left after surgery either in the stomach or lymph nodes*.

The option that is currently most widely used in Europe is pre- and postoperative chemotherapy.

Pre- and post-operative (peri-operative) chemotherapy

The goal of chemotherapy is the use of medication to kill tumor cells or limit their growth.
There is no single drug, or combination of drugs, which is known to work best for all patients. The choice should be discussed during the multidisciplinary consultation, taking into account the relevant information described above.
A combination of three drugs (epirubicin* or 'E', cisplatin* or 'C' and 5-fluorouracil* or 'F'), abbreviated to ECF, is often used. These drugs are given before and after surgery. Another common combination includes E, C and capecitabine* ('X') and is abbreviated to ECX. It gives comparable results to the ECF combination.

Other adjuvant therapies

The following options have also shown some good results, but more evidence is needed to compare them to peri-operative chemotherapy. Therefore they are currently being investigated further.

- **Chemoradiation:** Chemoradiation is the combination of chemotherapy and radiation therapy. Radiation therapy is a cancer treatment that kills cancer cells using radiation, directed specifically to the area of the cancer.
    1. **Adjuvant chemoradiation:** Chemoradiation can be given after surgery to reduce the chance of the cancer coming back. Two chemotherapies, 5-fluorouracil* and leucovorin*, will be given before, during and after a series of 5 weeks of radiotherapy. This intervention currently appears to be most useful if too few lymph nodes* were removed during surgery,

although improving techniques of this chemoradiation are also likely to improve results in other situations.

2. **Neo-adjuvant chemoradiation:** Chemoradiation that is given only before surgery remains in an experimental stage and should therefore only take place in the context of a clinical trial*.

- **Adjuvant chemotherapy:** This is chemotherapy that is given only after surgery. Studies in Asia suggest that patients receiving chemotherapy after surgery lived longer, but more research is needed to confirm this result in European patients.

Treatment plan for locally advanced inoperable disease (stage III and IV that are unresectable)

A tumor can be unresectable because it has invaded structures around the stomach (like main blood vessels), because it has spread to other parts of the body, or because the patient is not fit enough for such major surgery.

For patients with locally advanced inoperable disease, chemotherapy* is recommended to relieve symptoms. Afterwards, the patients can be reassessed for surgery, if they respond well to the chemotherapy. Chemotherapy* targets cancer cells all over the body and is given in order to kill tumor cells or limit their growth. The types of chemotherapy* for inoperable disease are discussed in the next section (treatment plan for stage IV).

Some patients may be reassessed for surgery, and they might also receive neo-adjuvant chemoradiation (chemoradiation before undergoing surgery), although this strategy remains investigational.

Treatment plan for advanced and metastatic* disease (stage IV)

In these cases, the tumor has invaded the structures that surround the stomach, or more than 15 lymph nodes are affected, or the cancer has spread to other parts of the body.*

For the treatment of patients with advanced or metastatic* stomach cancer:

- The main treatment goal is to maintain, or improve, quality of life. Patients should be offered personalized appropriate supportive care.
- The realistic treatment goals should be discussed with the patient and their family and the patient should be encouraged to actively participate in all decisions. The patient's

preferences should always be taken into account.

- Some patients are advised against or choose not to have chemotherapy* and are treated with supportive care (symptom control) only.

Treatment of patients with stage IV stomach cancer can rely on:

- Systemic therapies that target cancer cells all over the body, like chemotherapy* and targeted therapies.
- Therapies that target cancer cells locally, like surgery and radiotherapy.

Systemic therapy

At this stage, the use of chemotherapy* and targeted therapies can improve survival. They are given in order to kill tumor cells, or limit their growth, resulting in a reduction of symptoms and a prolongation of survival.

Chemotherapy

Drugs used for chemotherapy* are categorized and named based on their chemical structure and mechanism of action. The main categories of drugs used in the treatment of stomach cancer are: platinum agents, anthracyclines*, pyrimidines and taxanes. These drugs are usually given in combination with each other to increase the expected efficacy.

There are different combinations of types of drugs than can be used, each with their advantages and side effects. The choice will be made according to the specific state of a patient and the possible side effects of each regimen. Possible combinations include the following:

- The combination of a drug containing platinum, such as cisplatin*, with a fluoropyrimidine*, such as 5-fluorouracil*, are most commonly used.

- An anthracycline*, such as epirubicin*, can be added to a platinum agent and a fluoropyrimidine* to increase the anti-tumor activity. An example of this is the ECF-regimen mentioned previously (epirubicin* or ‘E’, cisplatin* or ‘C’ and 5-fluorouracil* or ‘F’). However, recent studies suggest that in the ECF-regimen, 5-fluorouracil* (‘F’) can be substituted with capecitabine* (‘X’), and cisplatin* (‘C’) by oxaliplatin* (‘O’). In this way, new combinations are possible, known as ECX and EOX. An advantage of substituting F with X is that there is no more need for a port or port-a-cath, which is a temporary access device for administration of the chemotherapy*. A port is a tube that goes into the main vein in the neck, and is attached to a small reservoir placed under the skin of the chest through which the drug is administered. It stays there for as long as the chemotherapy* is given, which can be up

to six months. The goal of this device is to avoid repeated injections at each administration, which is uncomfortable for patients and can result in local tissue damage.

- Alternatively, docetaxel* can be added to the combination of cisplatin* and 5-fluorouracil* or capecitabine* to increase the anti-tumor effect. Although this combination prolongs disease control and survival, it may give more unwanted effects, such as a shortage of a type of white blood cells protecting the body against and fighting infections, which is called *neutropenia*.
- Irinotecan*, 5-fluorouracil* and leucovorin*, when combined, act in a similar way to cisplatin* and 5-fluorouracil* and can therefore be administered in patients, but this is not commonly used as the first treatment with chemotherapy*.

Platinum agents, (fluoro)pyrimidines*, taxanes and anthracyclines* are different families of chemotherapies* which have different side-effects, although all of them can affect the body's immune system and increase the risk of serious infection.

If the cancer progresses despite the first chemotherapy*, a new drug or combination of drugs can be administered in patients who are well enough to tolerate more chemotherapy*. This strategy is called second-line chemotherapy*. It can also be given to patients who initially responded to the first chemotherapy*, when the cancer starts to progress. Irinotecan is a drug that has shown a prolongation in survival after failure of conventional chemotherapy*.
Another option is to participate in a clinical trial* investigating new treatments.

Alternatively, in patients who relapsed after therapy but relapsed more than 3 months after the first

chemotherapy*, consideration should be given to trying the same chemotherapy* regimen again, since it did have an effect on the tumor and it may be active again.

Targeted therapies

Targeted therapies are drugs that act on specific targets in cancer cells to inhibit cancer cell growth. They can be added to a chemotherapy* regimen to increase its effectiveness. The only targeted therapy available for stomach cancer is trastuzumab*. It is a drug that targets a protein* called HER2, which is excessively present on the surface of cancer cells in certain types of stomach cancers. It is usually administered together with cisplatin and a fluoropyrimidine* in patients with HER2-positive stomach cancer. Therefore, for patients with evidence of HER2 overexpression measured by FISH* and/or immunohistochemistry*, consideration should be

given to treatment with this combination. Other targeted agents include cetuximab*, panitumumab* and bevacizumab*, but their use remains experimental for stomach cancers at the moment and should not be administered outside of clinical trials*.

Surgery and radiotherapy

Surgery and radiotherapy can reduce certain symptoms in patients with stage IV stomach cancer.

Radiotherapy

Patients with locally advanced or recurrent disease whose cancer makes them bleed from the digestive tract or for whom it becomes difficult to eat because of an obstruction due to the tumor, radiotherapy can bring relief. Radiotherapy can also relieve a possible pain in the stomach, or in the bones if the cancer has

spread to them. Radiotherapy aims to kill cancer cells using radiation directed towards the area of the cancer.

Surgery

Resection of the tumor by surgery can sometimes relieve the patient of possible complications of stomach cancer growth including: obstruction in the stomach because of the tumor; bleeding in the stomach; and perforation of the stomach wall. However, a multidisciplinary team should discuss the feasibility and the added value of such a surgical intervention, according to the general condition of each patient.

Side effects of chemo- and targeted therapies

All the drugs that are given to fight the cancer have unwanted effects. The most frequent side-effects of chemo- and targeted therapies are usually reversible after treatment. Some strategies are available to prevent or relieve a certain range of these side-effects. This should be discussed upfront with doctors.

The main side effects of chemotherapy* are:

- fatigue (all drugs)
- hair loss (epirubicin*, docetaxel*)
- nausea and vomiting (all drugs, particularly cisplatin*)
- diarrhea (mostly 5-FU, capecitabine* and oxaliplatin*)
- a sore mouth or mouth ulcers (all drugs)
- low blood cell counts (all drugs). A decrease in white blood cells* will increase the risk of getting infections and make it harder to fight them. A drop in red blood cells* leads to anemia*, which can cause tiredness and

breathlessness. A shortage in blood platelets causes one to bruise easily and bleeding (e.g. nose bleeds or bleeding gums).

- Most chemotherapeutics are dangerous for a developing baby. It is therefore important to use barrier contraception and not to become pregnant during treatment.
- Infertility and premature menopause.
- All chemotherapy* drugs make the blood more sticky and increase the risk of blood clots in the legs and the lungs.

Apart from these, each drug can also give different unwanted effects. The most common ones are listed below, although not everyone will have the same side-effects, or experience them to the same extent.

- 5-fluorouracil* and capecitabine* can cause soreness of the palms of the hands and soles of the feet. This condition is called palmar-plantar syndrome and may cause tingling, numbness,

pain and dryness. It can also (rarely) cause a spasm in the arteries that supply the heart with blood, causing chest pain like angina*. Cisplatin* may lead to hearing loss, and to kidney damage. The kidney function is examined in the blood before starting the treatment. To prevent damage it is very important to drink a lot of water during the treatment.

- Epirubicin* can rarely cause damage to the heart muscle, although usually only when used for many months or in people with heart problems before treatment. If you have heart problems, your doctor will arrange a scan before treatment to see if your heart is strong enough for this treatment. It can make the skin more sensitive to sunlight and cause reddening in areas where the patient has had radiotherapy in the past. The urine may turn red or pink for a few days after treatment. This

is not blood and is only due to the color of the medication.

- Oxaliplatin* can cause temporary or permanent damage to the nerves that affect the fingers and toes, causing numbness or pins and needles.
- Irinotecan* can lead to increased sweating and saliva production, watery eyes, abdominal cramps and sometimes severe diarrhea.
- Docetaxel* sometimes causes fluid retention, temporary nail discoloration and an itchy skin rash. Some people also develop palmar-plantar syndrome mentioned with capecitabine*, or simple numbness and tingling in the hands and feet. About one in four patients will suffer from an allergic reaction during the first or second infusion with docetaxel*.
- Trastuzumab* (Herceptin) often causes allergic reactions ranging from chills, fever and possibly an itchy rash, feeling sick, breathlessness,

wheezing and headaches, to flushes and faintness. Some patients can experience heart problems; these usually get better once the treatment has stopped.

Most side effects can, however, be treated so that patients suffer much less from them. Therefore it is important to talk about everything that is felt to the doctor or nurse.

WHAT HAPPENS AFTER TREATMENT?

It is not unusual to experience treatment-related symptoms once the treatment is over.

- It is not rare that anxiety, sleeping problems or depression are experienced in the post-treatment phase. Patients who experience these symptoms may benefit from psychological support.
- Memory deficiencies and difficulties in concentrating are common side effects of chemotherapy* and are generally reversible within a few months.
- Fatigue can last for months after treatment. Most patients find their energy levels are back to normal within 6 months to a year.

After gastrectomy, the patient has to develop new eating habits. A nutritionist* can help patients adjust to this. Due to the removal of the upper part of the stomach, the body will absorb less vitamin B12 from food. Regular blood tests are advised, and often substitution with vitamin B12 injections is necessary. It is common to have diarrhea for some months after stomach surgery. Some patients also suffer from heartburn and abdominal pain.

Removal of the spleen may lead to a reduced immunity. Therefore the patient will receive several vaccinations, before and after the removal of the spleen and antibiotics to take every day. It is also important to be aware that any infection carries a greater risk and should be a reason to see a doctor and sometimes start taking antibiotics.

Follow-up with doctors

After the treatment has been completed, doctors will propose a follow-up aiming to:

- evaluate adverse effects of the treatment and treat them
- provide psychological support and information to enhance returning to normal life
- detect possible recurrence* as soon as possible

Follow-up visits will be arranged on a regular basis. However, it is even more important is that the patient contacts his or her doctor when experiencing any symptoms that might indicate a recurrence*, such as weight loss, fatigue or tiredness and breathlessness.

During a follow-up visit, the oncologist will:

- take your history
- conduct a physical examination
- perform some blood tests

- if necessary, decide to do a radiological investigation or a new endoscopy (an examination of the stomach in which the doctor passes a thin, flexible, light-emitting tube called an endoscope down the patient's throat and into the stomach) to investigate new symptoms

If the patient has undergone surgery, a follow-up visit with the surgeon might also be arranged, to make sure the wound from the operation and the new junction in the intestines are healing well.

Returning to normal life

It can be hard to live with the idea that the cancer can come back, but from what is known today, no specific way of decreasing the risk of recurrence* can be recommended, although eating enough vitamin-

containing fruit and vegetables may have a beneficial effect.

As a consequence of the cancer itself and of the treatment, the return to normal life may not be easy for some people. Questions related to bodyimage, fatigue, work, emotions or lifestyle may come up. Discussing these questions with relatives, friends or doctors may be helpful. Some people may also want to find support from ex-patients' groups or telephone information lines.

What if the stomach cancer comes back?

If the cancer comes back, it is called a recurrence* and the treatment depends on the extent of the recurrence*. The tumor might come back in the stomach or in another part of the body (a metastasis*).

If the cancer comes back in the stomach or around the area where the cancer occurred the first time, doctors will again evaluate whether the tumor is resectable or unresectable. Treatment options depend on the extent of the recurrence* and will be discussed in a multidisciplinary team. A multidisciplinary opinion will preferably include that of a medical oncologist (who provides cancer treatment with drugs), a surgical oncologist (who provides cancer treatment with surgery), a radiation oncologist (who provides cancer treatment with radiation), a gastro-enterologist (specialist in stomach and intestines), a radiologist* and a pathologist*.

If the cancer comes back in distant organs such as liver or lungs, these tumors are called metastases*. Such a recurrence should be treated as described in the paragraph "Treatment plan for advanced or metastatic* disease (stage IV)" but will also depend on

the therapies that the patients already received to treat the cancer the first time.

In case of a recurrence* it is advised to ask your doctor about the possibility of participating in a clinical trial*. This might give you access to new treatments that are not yet available elsewhere, and also to help test new treatments that may be useful to future patients with gastric cancer.

DEFINITIONS OF DIFFICULT WORDS

5-fluorouracil
A drug used to treat symptoms of cancer of the colon, breast, stomach, and pancreas. It is also used in a cream form to treat certain skin conditions. 5-fluorouracil stops cells from making DNA and it may kill cancer cells. It is a type of antimetabolite. Also called 5-FU and fluorouracil.

Anemia
Condition characterized by the shortage of red blood cells or hemoglobin, the iron that contains the hemoglobin carries oxygen from the lungs to the whole body; this process is diminished in this condition.

Angina
Severe pain in the chest. This condition arose when the heart muscle is not sufficiently supplied with blood, and, hence oxygen.

Anthracycline
Antibiotic drug used in chemotherapy to treat a wide range of cancers.

Bevacizumab
Bevacizumab is a monoclonal antibody that has been designed to recognise and attach itself to a specific structure (called an antigen) that is found in certain cells in the body or is circulating in the body. Bevacizumab has been designed to attach to vascular endothelial growth factor (VEGF), a protein that circulates in the blood and makes blood vessels grow. By attaching to VEGF, bevacizumab stops it having an effect. As a result, the cancer cells cannot develop

their own blood supply and are starved of oxygen and nutrients, helping to slow down the growth of tumors.

Biopsy

The removal of cells or tissues for examination by a pathologist. The pathologist may study the tissue under a microscope or perform other tests on the cells or tissue. There are many different types of biopsy procedures. The most common types include: (1) incisional biopsy, in which only a sample of tissue is removed; (2) excisional biopsy, in which an entire lump or suspicious area is removed; and (3) needle biopsy, in which a sample of tissue or fluid is removed with a needle. When a wide needle is used, the procedure is called a core biopsy. When a thin needle is used, the procedure is called a fine-needle aspiration biopsy.

Capecitabine

Capecitabine is a cytotoxic medicine that belongs to the group antimetabolites. Capecitabine is a 'prodrug'

that is converted to 5-fluorouracil (5-FU) in the body, but more is converted in tumor cells than in normal tissues. It is taken in tablet form, while 5-FU, an analogue of pyrimidine, normally needs to be injected. Pyrimidine is part of the genetic material of cells (DNA and RNA). In the body, 5-FU takes the place of pyrimidine and interferes with the enzymes involved in making new DNA. As a result, it inhibits the growth of tumor cells and eventually kills them.

Cetuximab

Cetuximab is a monoclonal antibody. Cetuximab has been designed to attach to EGFR, which can be found on the surface of some tumor cells. As a result, the tumor cells can no longer receive the messages needed for growth, progression and spreading. Between 79 and 89% of colorectal cancers and more than 90% of squamous cell cancers of the head and neck have EGFR on their cell surfaces.

Chemotherapy

A type of cancer treatment using drugs that kill cancer cells and/or limit their growth. These drugs are usually administered to the patient by slow infusion into a vein but can also be administered orally, by direct infusion to the limb or by infusion to the liver, according to cancer location.

Chromosome

An organized structure which encodes genes which are the body's code for characteristics such as hair color or sex. Human cells have 23 pairs of chromosomes (total of 46 chromosomes).

Cisplatin

A drug used to treat many types of cancer. Cisplatin contains the metal platinum. It kills cancer cells by damaging their DNA and stopping them from dividing. Cisplatin is a type of alkylating agent. Also called Platinol.

Clinical trial

A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical study.

Docetaxel

Docetaxel belongs to the group of anticancer medicines known as the taxanes. Docetaxel prevents cells from destroying the internal 'skeleton' that allows them to divide and multiply. With the skeleton still in place, the cells cannot divide and they eventually die. Docetaxel also affects non-cancer cells such as blood cells, which can cause side-effects.

Endoscopy/endoscopic

A medical procedure where a doctor puts a tube-like instrument into the body to look inside it. There are many types of endoscopy, each of which is designed for looking at a certain part of the body.

Epirubicin

A drug used together with other drugs to treat early breast cancer that has spread to lymph nodes. It is also being studied in the treatment of other types of cancer. Epirubicin is a type of anthracycline antibiotic. Also called Ellence and epirubicin hydrochloride.

Epithelium

The term "epithelium" refers to cells that line hollow organs and glands and those that make up the outer surface of the body. Epithelial cells help to protect or enclose organs. Most produce mucus or other secretions.

Epstein-Barr virus

Epstein-Barr virus, frequently referred to as EBV, is a member of the herpes virus family. Most people become infected with EBV during their lives. Many children become infected with EBV, and these infections usually cause no symptoms or are

indistinguishable from the other mild, brief illnesses of childhood. EBV also establishes a lifelong dormant infection in some cells of the body's immune system, which might increase the risk of developing stomach cancer.

FISH/Fluorescence *in situ* hybridization

A technique used by pathologists to identify changes to genes and chromosomes. Unique changes to genes or chromosomes can be detected by FISH and help a pathologist know what type of cancer a patient has.

Histopathology

The study of diseased cells and tissues using a microscope.

Immunohistochemistry

Immunohistochemistry or IHC refers to the process of detecting antigens (e.g. proteins) in cells of a tissue section by exploiting the principle of antibodies binding specifically to antigens in biological tissues.

These antigens are visualized by a marker such as fluorescent dye, enzyme, or colloidal gold. Immunohistochemical staining is widely used in the diagnosis of abnormal cells such as those found in cancerous tumors.

Irinotecan

The active ingredient in a drug used alone or with other drugs to treat colon cancer or rectal cancer that has spread to other parts of the body, or has come back after treatment with fluorouracil. It is also being studied in the treatment of other types of cancer. Irinotecan blocks certain enzymes needed for cell division and DNA repair, and it may kill cancer cells. It is a type of topoisomerase inhibitor and a type of camptothecin analog.

Lamina propria

The lamina propria is a thin layer of loose connective tissue which lies beneath the epithelium and together

with the epithelium constitutes the mucosa. The term mucosa (or mucous membrane) always refers to the combination of the epithelium plus the lamina propria.

Laparoscopy

An operation where surgical instruments are introduced in the abdomen or in the pelvis through small incisions and with the help of a camera.

Leucovorin

The active ingredient in a drug used to lessen the toxic effects of substances that block the action of folic acid, especially the anti-cancer drug methotrexate. Leucovorin is used to treat some types of anemia and is also used with fluorouracil to treat colorectal cancer. It is also being studied in the treatment of other types of cancer and other conditions. Leucovorin is a form of folic acid. It is a type of chemoprotective agent and also a type of chemosensitizing agent. Also called folinic acid.

Lymph node
A rounded mass of lymphatic tissue that is surrounded by a capsule of connective tissue. Lymph nodes filter lymph and they store lymphocytes. They are located along lymphatic vessels. Also called lymph gland.

Membrane
In biology, a membrane can define (1) a layer within a cell that encloses different internal structures, (2) a layer around a cell that separates the cell from its surrounding, (3) a layer of cells that separate one tissue from another (like basement membrane and mucosa).

Ménétrier's disease
A disorder of the stomach, causing giant folds of tissue to grow in the wall of the stomach. This tissue may be inflamed and may contain ulcers. The disease also causes glands in the stomach to waste away and the body to lose fluid containing protein, causing

abdominal pain, vomiting, and generalized swelling. Ménétrier's disease is a rare disease that most commonly affects adults over the age of 50 years.

Metastasis/metastase(s)/metastatic
The spread of cancer from one part of the body to another. A tumor formed by cells that have spread is called a metastatic tumor or a metastasis. The metastatic tumor contains cells that are like those in the original tumor.

Mucosa
The moist, inner lining of some organs and body cavities. Glands in the mucosa make mucus. Also called mucous membrane.

Mucus
Mucus is a slippery substance secreted by the mucous membranes that line many of the body's inner surfaces. It consists of proteins, antimicrobial enzymes,

antibodies, and salt. Mucus serves to protect cells from the epithelium in the respiratory, gastrointestinal, urinary, genital, visual, and auditory systems.

Mutation

A change in the sequence of base pairs in the DNA that makes up a gene. Mutations in a gene do not necessarily change the gene permanently.

Nitrates

Nitrates are naturally present in soil, water, and food. They are compounds containing nitrogen that can exist in the atmosphere or as a dissolved gas in water and which can have harmful effects on humans and animals. Once taken into the body, nitrates are converted into nitrites.

Nitrites

Nitrites are manufactured mainly for use as a food preservative, and both nitrates and nitrites are used extensively to enhance the color and extend the shelf life of processed meats.

Nutritionist

A nutritionist is a health professional who advises on matters of how food and nutrition impacts health. Some use the terms "dietitian" and "nutritionist" as basically interchangeable terms. However, there are important differences between countries regarding the training needed to be recognized as a nutritionist or as a dietitian. In some countries, any person may call themselves a nutrition expert even if they are wholly self-taught.

Oxaliplatin

A drug used with other drugs to treat colorectal cancer that is advanced or has come back. It is also being

studied in the treatment of other types of cancer. Oxaliplatin attaches to DNA in cells and may kill cancer cells. It is a type of platinum compound. Also called Eloxatin.

Panitumumab

Panitumumab, is a monoclonal antibody. Panitumumab has been designed to attach to the Epidermal Growth Factor Receptor (EGFR), which can be found on the surface of certain cells, including cells in some tumors. As a result, these tumor cells can no longer receive the messages transmitted via EGFR that they need for growth, progression and spreading. Panitumumab does not seem to work in tumor cells that contain a mutated form of the protein KRAS. This is because their growth is not controlled by signals transmitted via EGFR and they continue to grow even when the EGFR is blocked.

Pathologist
A doctor specialized in histopathology; the study of diseased cells and tissues using a microscope.

Peritoneal washing
Procedure performed during surgery where salt solution is introduced into the peritoneal cavity and then removed by suction. The fluid removed is then analyzed in the laboratory to look for cancer cells.

Prognosis
The likely outcome or course of a disease; the chance of recovery or recurrence.

Protein
Essential nutrients that are made of amino acids. They are essential for the functioning of many organisms including the human body. They are responsible for transport and communication between cells, for

chemical changes and they also maintain the structure of cells.

Radiologist
A doctor specialized in the diagnosis of disease and injury with the use of imaging devices such as those used for X-rays, CTscans or MRIs (magnetic resonance imaging).

Recurrence
Cancer or disease (usually auto-immune) that has come back, usually after a period of time during which the cancer or disease was not present or could not be detected. This may happen at the same location as the original (primary) tumor or in another part of the body. Also called recurrent cancer or recurrent disease.

Red blood cells

The most common type of blood cell. It is the substance that makes the blood appear red. The main function is the transport of oxygen.

Risk factor

Something that increases the chance of developing a disease. Some examples of risk factors for cancer are age, a family history of certain cancers, use of tobacco products, being exposed to radiation or certain chemicals, infection with certain viruses or bacteria, and certain genetic changes.

Serosa

Serous membrane (or serosa) is a smooth membrane consisting of a thin layer of cells which secrete serous fluid. Serous membranes line and enclose the heart, the lungs and organs in the abdomen, where they secrete a lubricating fluid which reduces friction from muscle movement.

Submucosa

In the gastrointestinal tract, the submucosa is the layer of dense irregular connective tissue or loose connective tissue that supports the mucosa, as well as joins the mucosa to the bulk of underlying smooth muscle (fibers running circularly within layers of longitudinal muscle).

Subserosa

The subserosa is a layer of tissue between the muscularis and serosa. The term is used in histopathology and is particularly associated with cancer staging (for example, in staging stomach cancer).

Trastuzumab

Trastuzumab is a monoclonal antibody. Trastuzumab has been designed to attach to HER2. By attaching to HER2, trastuzumab activates cells of the immune system, which then kill the tumor cells. Trastuzumab

also stops HER2 producing signals that cause the tumor cells to grow. About a quarter of all breast cancers and a fifth of all gastric cancers overexpress HER2.

Ulcers/ulceration
A break on the skin, in the lining of an organ, or on the surface of a tissue. An ulcer forms when the surface cells become inflamed, die, and are shed. Ulcers may be linked to cancer and other diseases.

White blood cells
Cells of the immune system that are involved in the body's defense against infections.

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