



Let us answer some of your questions.

# **ESMO Patient Guide Series**

# An ESMO guide for patients

#### Patient information based on ESMO Clinical Practice Guidelines

This guide has been prepared to help you, as well as your friends, family and caregivers, better understand stomach cancer and its treatment. It contains information on the causes of the disease and how it is diagnosed, up-to-date guidance on the types of treatments that may be available and any possible side effects of treatment.

The medical information described in this document is based on the ESMO Clinical Practice Guideline for stomach cancer, which is designed to help clinicians with the diagnosis and management of stomach cancer. All ESMO Clinical Practice Guidelines are prepared and reviewed by leading experts using evidence gained from the latest clinical trials, research and expert opinion.

The information included in this guide is not intended as a replacement for your doctor's advice. Your doctor knows your full medical history and will help guide you regarding the best treatment for you.

Words highlighted in **colour** are defined in the glossary at the end of the document.

This guide has been developed and reviewed by:

Representatives of the European Society for Medical Oncology (ESMO):

Florian Lordick; Radka Obermannová; Elizabeth Smyth; and Svetlana Jezdic

Representative of the European Oncology Nursing Society (EONS):

Tihana Gašpert

Representative of the Digestive Cancers Europe (DiCE):

**7**orana Maravic

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# Stomach cancer: A summary of key information

The following information will be discussed in detail in this guide.

## Introduction to stomach cancer

- Stomach cancer (also known as gastric cancer) forms in the stomach, which is part of the digestive system.
   The most common type of stomach cancer is adenocarcinoma; this guide will focus exclusively on adenocarcinoma.
- There are several known risk factors for stomach cancer, including Helicobacter pylori infection, smoking
  and alcohol consumption. Around 3% of stomach cancers are hereditary; people with a family history of
  stomach cancer may be offered genetic counselling.
- Stomach cancer is the fifth most common cancer worldwide. It is more common in men than women and its incidence increases with age.

# **Diagnosis of stomach cancer**

- Stomach cancer often has no symptoms, especially in its early stages. Symptoms that may occur include problems with swallowing, indigestion, vomiting and weight loss.
- A diagnosis of stomach cancer is usually based on the results of an endoscopy, which can show if there is
  a tumour in the stomach, and a biopsy to confirm the presence of cancer cells.
- Stomach cancer is categorised according to how far it has spread. Early-stage stomach cancer is contained
  within the area it first developed in and has not spread anywhere else in the body. Locally advanced stomach
  cancer has spread to neighbouring areas and may affect nearby lymph nodes. Metastatic stomach cancer
  has spread to another part of the body. This information is used to help decide the best treatment.
- Patients with metastatic stomach cancer may undergo molecular testing for the presence of certain biomarkers, as this can help to decide if certain types of targeted therapy or immunotherapy could be beneficial.

### **Treatment options for stomach cancer**

- Treatment for stomach cancer depends on the size, location and stage of the tumour, and the general health
  of the patient.
- Patients should be fully informed and involved in decisions about treatment options.

# **Early-stage stomach cancer**

- Very early-stage stomach cancer might be removed via endoscopic resection.
- Most early and locally advanced stomach cancers are removed via radical gastrectomy, with the patient
  also receiving neoadjuvant and adjuvant chemotherapy.

#### Metastatic stomach cancer

- The standard first-line treatment for metastatic stomach cancer is chemotherapy. The chemotherapy
  may be combined with targeted therapy or immunotherapy, depending on the results of molecular
  testing.
- Second-line treatment may include a targeted therapy in combination with chemotherapy, a targeted
  therapy alone, chemotherapy alone or immunotherapy, depending on the results of molecular testing,
  the general health of the patient and the patient's preferences.
- Chemotherapy is the typical third-line treatment for stomach cancer.

#### **Additional interventions**

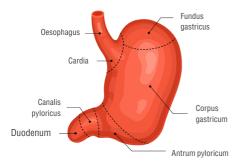
- Stomach cancer, and the treatments for it, can have a long-term impact on quality of life. Gastrectomy can
  cause problems with eating and many patients find it difficult to maintain a healthy weight. Some patients
  will need to have a feeding tube.
- A dietician should provide advice on how and what to eat in order to stay healthy.
- Physical changes may affect self-esteem and can have an impact on relationships and sex. Many patients
  find it helpful to talk to other people about their feelings and experiences; this can include family and
  friends, or a trained professional such as a therapist. Talking to other people who have had treatment for
  stomach cancer can also help, and patient support groups can connect patients with fellow survivors.

## Follow-up during/after treatment

- The timings of follow-up appointments vary between countries and practices. Follow-up appointments may
  include a physical examination, blood tests and/or a computed tomography scan.
- Patients who experience a recurrence of their cancer can usually have further treatment. The treatment will
  depend on the extent of the recurrence, previous treatments received, the overall health of the patient and
  the patient's preferences.
- Support groups can help patients and their families to better understand stomach cancer and to learn how to cope with all aspects of the disease, from diagnosis to long-term effects.
- Digestive Cancers Europe is a community of patient organisations that support people affected by digestive cancers, including stomach cancer: https://digestivecancers.eu/members.

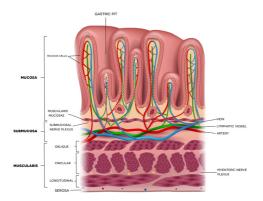
# What is stomach cancer?

Stomach cancer (also known as **gastric** cancer) is a type of cancer that develops in the stomach, which is part of the digestive system. The stomach is connected to the **oesophagus** at the top and the **duodenum** at the bottom, and produces **gastric** juice, which breaks down food so the body can absorb it.



Anatomy of the stomach.

The stomach has several layers, including the inner lining, supportive tissue and muscle layers.



Layers of the stomach wall.

Stomach cancer can develop in any part of the stomach, but most begin in the gland cells of the inner stomach lining. These stomach cancers are called **adenocarcinomas**.

Rarer types of stomach cancer include **squamous cell carcinoma**, which develops in flat cells that cover the lining of the stomach, and **gastrointestinal stromal tumours**, which are a rare type of **sarcoma**.

This guide will focus on adenocarcinomas.

Adenocarcinoma is the most common type of stomach cancer

# What are the symptoms of stomach cancer?

There are often no symptoms of stomach cancer, particularly in the early stages. However, if there are symptoms, they may include (Lordick et al., 2022):

- Problems with swallowing
- Indigestion
- Vomiting
- Weight loss
- Feeling weak
- Feeling full after eating a small amount of food
- Anaemia

You should see your doctor if you experience any of these symptoms. However, it is important to remember that these symptoms can also occur in people who do not have stomach cancer; they may also be caused by other conditions.



Any symptoms of stomach cancer should be checked by a doctor

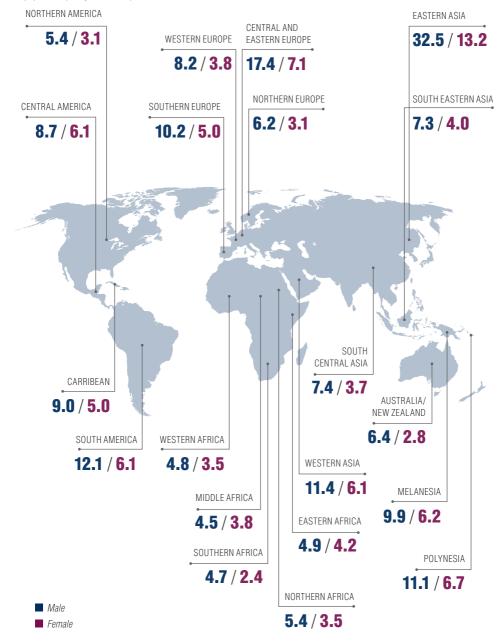
# **How common is stomach cancer?**

Stomach cancer is the fifth most common cancer worldwide, with more than 1 million new cases and 770,000 deaths in 2020. The highest incidence rates are in Eastern Asia, Central and Eastern Europe and South America (Lordick et al., 2022; Ferlay et al., 2020).

Stomach cancer is more common in older people, with around half of cases occurring in people aged 75 years and older. It is two times more common in men than in women (Lordick et al., 2022).

Stomach cancer is the fifth most common cancer worldwide and is more common in men than women

The map shows estimated numbers of new cases of stomach cancer diagnosed in 2020 per 100,000 people of each region's population (Ferlay et al., 2020).



# What causes stomach cancer?

Several **risk factors** for developing stomach cancer have been identified. It is important to remember that having a **risk factor** increases the risk of cancer developing but it does not mean that you will definitely get cancer. Likewise, not having a **risk factor** does not mean that you definitely won't get cancer.

Several risk factors have been identified for stomach cancer



# **FACTORS THAT MAY INCREASE RISK**

Helicobacter pylori infection

Smoking

Alcohol consumption

High salt intake

Low consumption of fruit and vegetables

#### Obesity

### Gastro-oesophageal reflux

There are various **risk factors** associated with developing cancer of the stomach or the junction where the stomach meets the **oesophagus** although each factor may not apply to everyone who develops the disease.

An important **risk factor** for developing stomach cancer is infection with **Helicobacter pylori** (**H. pylori**). **H. pylori** is a type of bacteria that lives in the lining of the stomach and is spread through contaminated food and water. Infection with **H. pylori** does not cause problems for most people, but in some, it can cause inflammation and stomach ulcers, which can lead to cancer. **H. pylori** infection is no longer common in developed countries but is still prevalent in developing countries.

The risk of developing stomach cancer can be reduced by limiting exposure to **risk factors**; for example, reducing alcohol intake, stopping smoking and eating a healthy diet. Treating **H. pylori** with **antibiotics** reduces the risk of stomach cancer developing.

Lifestyle changes can reduce the risk of developing stomach cancer

## **Hereditary stomach cancer**

Around 3% of stomach cancers are **hereditary**. This means that they are caused by genetic changes that have been passed from parent to child. Several **hereditary** syndromes can lead to a high risk of stomach cancer (*Lordick et al., 2022*). You should talk to your doctor if you have a family history of stomach cancer, as you may be offered **genetic counselling**. Some people who are known to be at high risk for developing stomach cancer may be offered regular **endoscopic surveillance** to ensure any signs of cancer are identified early.

# **How is stomach cancer diagnosed?**

A diagnosis of stomach cancer is based on the results of the following examinations and tests:

#### **Clinical examination**

If you have symptoms of stomach cancer, your doctor may carry out a general clinical examination and feel around your stomach for any areas that are swollen or feel unusual. You may have to give a **stool** sample. Your doctor may also listen to your chest and stomach to check if your digestive system sounds normal.



Clinical examination and a stool test can indicate if further tests are needed

# **Endoscopy**

Your doctor may recommend that you have an **endoscopy** (Lordick et al., 2022). This procedure allows doctors to see inside your **oesophagus**, stomach and **duodenum** using a light and camera attached to a thin, flexible tube that is inserted into your stomach via the mouth. You will usually be awake during the **endoscopy**, although your throat will be numbed with a **local anaesthetic** and you may be offered a **sedative** to help you relax.

During the **endoscopy**, your doctor can take samples (**biopsies**) of any areas that look abnormal so they can be examined under a microscope to check for cancer cells. This will also tell the doctors whether you have **adenocarcinoma** or another type of stomach cancer.

Stomach cancer is usually diagnosed by taking biopsies during an endoscopy

# **How will my treatment be determined?**

Your treatment will largely depend on the stage of your cancer.

## **Staging**

Staging is used to describe the extent of the cancer overall; this includes its size and position and whether it has spread from where it started.

If your **endoscopy** and **biopsies** show that you have stomach cancer, you are likely to have a **computed tomography** (CT) scan of your abdomen, chest and pelvis (*Lordick et al., 2022*). CT is a type of **x-ray** technique that lets doctors see your internal organs in detail by showing very thin cross sections of the body.

The CT scan will allow the doctor to assess the location and size of the cancer and to check for any signs that the cancer has spread.



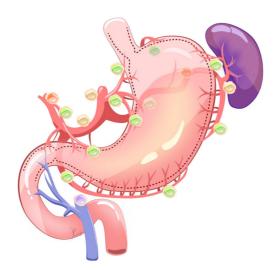
After diagnosis, imaging scans can show if the cancer has spread to other parts of the body

Other techniques that are used to assess the size and position of stomach cancer include **endoscopic ultrasound** (EUS) and **laparoscopy**. EUS is similar to an **endoscopy**, but the **endoscope** also has an **ultrasound** probe at its tip, which produces sound waves to create a picture of the internal organs. **Laparoscopy** is a minor operation in which a thin tube with a light and a camera are inserted through a small cut in the abdomen, allowing the doctor to check around the stomach and take **biopsies**.

The results of your **biopsies** and imaging scans will confirm what type of stomach cancer you have and how far your cancer has spread. Your doctor will categorise your disease as one of the following:

- Early-stage stomach cancer is contained within the area it first developed in and has not spread anywhere
  else in the body.
- Locally advanced stomach cancer has spread to neighbouring areas and may affect nearby lymph nodes.
- Metastatic stomach cancer has spread to another part of the body. Tumours found in other parts of the body away from the original tumour site are called metastases.

Lymph nodes are a small bean-shaped glands that are a part of the lymphatic system. Lymph nodes filter lymph as it passes through them and white blood cells attack any bacteria or viruses in the lymph. When cancer cells break away from a tumour, they can become stuck in nearby lymph nodes, so doctors always check lymph nodes to see if a cancer has spread.



Main lymph nodes and lymph drainage around the stomach.

Adapted by permission from MDPI: [Cancers] (Zhang, et al. Signature and Prediction of Perigastric Lymph Node Metastasis in Patients with Gastric Cancer and Total Gastrectomy: Is Total Gastrectomy Always Necessary?), copyright (2022).

## **TNM** staging

Staging to determine the size and spread of the cancer is described using a sequence of letters and numbers. For stomach cancer, there are five stages designated with Roman numerals 0 to IV. Generally, the lower the stage, the better the **prognosis**. The TNM staging system considers:

- How far the tumour has grown into the stomach wall (T).
- Whether the cancer has spread to nearby lymph nodes (N).
- Whether it has spread to distant sites, or metastases (M).

Staging helps to determine the most appropriate treatment for stomach cancer

he staging system for stomach cancer is described in the table below (Lordick et al., 2022). This may seem complicated, but your doctor will be able to explain which parts of the table correspond to your cancer.

Stage 0. The cancer is only in the	Т	<ul> <li>Intraepithelial tumour without invasion of the lamina propria, high grade dysplasia (Tis)</li> </ul>
surface layer of the stomach	N	No regional lymph node metastasis (NO)
lining (Tis-N0-M0)	M	No distant metastasis (M0)
Stage IA. The cancer has spread into	Т	Tumour invades lamina propria, muscularis mucosae or submucosa (T1)
the supportive layer of the	N	No regional lymph node metastasis (NO)
stomach wall (T1-N0-M0)	M	No distant metastasis (M0)
Stage IB. The cancer has spread into the	T	Tumour invades lamina propria, muscularis mucosae or submucosa (T1)
muscle layer of the stomach		Tumour invades muscularis propria (T2)
wall (T1-N1-M0 or T2-N0-M0)	N	No regional lymph node metastasis (NO)
		Metastasis in 1-2 regional lymph nodes (N1)
	M	No distant metastasis (M0)
Stage IIA.	T	Tumour invades lamina propria, muscularis mucosae or submucosa (T1)
The cancer has grown into the inner, supportive, muscle		Tumour invades muscularis propria (T2)
or outer layer of the stomach		• Tumour invades suberosa (T3)
(T1-N2-M0 or T2-N1-M0 or	N	No regional lymph node metastasis (NO)
T3-N0-M0)		Metastasis in 1-2 regional lymph nodes (N1)
		Metastasis in 3-6 regional lymph nodes (N2)
	M	No distant metastasis (M0)
Stage IIB. The cancer has grown into	T	Tumour invades lamina propria, muscularis mucosae or submucosa (T1)
the inner, supportive, muscle		Tumour invades muscularis propria (T2)
or outer layer of the stomach		• Tumour invades suberosa (T3)
and is in nearby <b>lymph nodes</b> ,		• Tumour perforates serosa (T4a)
or it may have grown through the outer layer of the stomach	N	No regional lymph node metastasis (N0)
(T1-N3a-M0 or T2-N2-M0 or		Metastasis in 1-2 regional lymph nodes (N1)
T3-N1-M0 or T4a-N0-M0)		Metastasis in 3-6 regional lymph nodes (N2)
	M	No distant metastasis (M0)

Stage IIIA.  The cancer has grown into or through the muscle or outer layer of the stomach and there is cancer in nearby lymph nodes, or the cancer has grown through the stomach wall and into nearby organs or tissues (T2-N3a-M0 or T3-N2-M0 or T4a-N1/2-M0 or T4b-N0-M0)	N M	Tumour invades muscularis propria (T2) Tumour invades suberosa (T3) Tumour perforates serosa (T4a) Tumour invades adjacent structures (T4b)  No regional lymph node metastasis (N0) Metastasis in 1-2 regional lymph nodes (N1) Metastasis in 3-6 regional lymph nodes (N2) Metastasis in 7-15 regional lymph nodes (N3a)  No distant metastasis (M0)
Stage IIIB.	T	Tumour invades lamina propria, muscularis mucosae or submucosa
The cancer has grown into or through the inner, supportive, muscle or outer layer of the stomach, or the cancer has grown through the stomach		<ul> <li>(T1)</li> <li>Tumour invades muscularis propria (T2)</li> <li>Tumour invades suberosa (T3)</li> <li>Tumour perforates serosa (T4a)</li> <li>Tumour invades adjacent structures (T4b)</li> </ul>
wall and into nearby organs or tissues. There is cancer in nearby <b>lymph nodes</b> (T1/2-N3b-M0 or T3/4a-N3a-M0 or	N	<ul> <li>Metastasis in 1-2 regional lymph nodes (N1)</li> <li>Metastasis in 3-6 regional lymph nodes (N2)</li> <li>Metastasis in 7-15 regional lymph nodes (N3a)</li> <li>Metastasis in 16 or more regional lymph nodes (N3b)</li> </ul>
T4b-N1/2-M0)	M	No distant metastasis (M0)
Stage IIIC. The cancer has grown into or through the outer layer of the	T	<ul> <li>Tumour invades suberosa (T3)</li> <li>Tumour perforates serosa (T4a)</li> <li>Tumour invades adjacent structures (T4b)</li> </ul>
stomach, or the cancer has grown through the stomach wall and into nearby organs	N	<ul> <li>Metastasis in 7-15 regional lymph nodes (N3a)</li> <li>Metastasis in 16 or more regional lymph nodes (N3b)</li> </ul>
or tissues. There is cancer in nearby <b>lymph nodes</b> (T3/4a-N3b-M0 or T4b-N3a/3b-M0)	M	No distant metastasis (M0)
Stage IV. The cancer has spread to distant body parts (any T-any N-M1)	T	Intraepithelial tumour without invasion of the lamina propria, high grade dysplasia (Tis) Tumour invades lamina propria, muscularis mucosae or submucosa (T1) Tumour invades muscularis propria (T2) Tumour invades suberosa (T3) Tumour perforates serosa (T4a) Tumour invades adjacent structures (T4b)
	N	No regional lymph node metastasis (N0) Metastasis in 1-2 regional lymph nodes (N1) Metastasis in 3-6 regional lymph nodes (N2) Metastasis in 7-15 regional lymph nodes (N3a) Metastasis in 16 or more regional lymph nodes (N3b)  No distant metastasis (M0)

The staging information above is complex, but the most important thing you need to know is the overall stage your cancer, as shown below:

Stage I	The earliest stage, when the cancer is localised to the lining and connective tissues of the stomach
Stage II	The cancer has grown through the lining of the stomach and into the thick inner muscles of the stomach
Stage III	The cancer has spread and grown into or through the layers of your stomach. The cancer may have also spread to nearby <b>lymph nodes</b> , but it has not spread to other organs
Stage IV	The cancer has grown into nearby tissues and organs or has spread across your body

#### Molecular tests

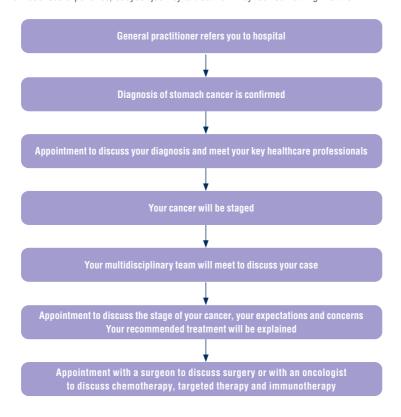
The biopsies taken during your endoscopy may also undergo molecular testing, or you may have further biopsies for molecular testing at a later time (usually if the cancer is metastatic). This type of testing can identify specific biological molecules (biomarkers) in your cancer cells, which can help doctors to decide which type of treatment will be best for you.

If molecular testing shows that your metastatic stomach cancer has a high level of the biomarkers human epidermal growth factor receptor 2 (HER2) or programmed death-ligand 1 (PD-L1) then you may be offered specific treatments for those types of stomach cancers (so-called HER2-positive or PD-L1-positive disease). If your cancer is found to have a high number of mutations within microsatellites (short, repeated sequences of DNA) or changes in certain genes that are involved in correcting mistakes made when DNA is copied in a cell, then you have microsatellite instability-high (MSI-high) or mismatch repair-deficient (MMR-deficient) cancer, which will influence the treatment you receive (Lordick et al., 2022).

**Biomarker** research is evolving quickly, and other **biomarkers** to guide treatment may soon become available (e.g. **fibroblast growth factor receptor 2** and **claudin-18.2**). It is important to understand, however, that **molecular testing** and **biomarker**-based treatment are not available in all countries.

# What are the treatment options for stomach cancer?

Your treatment will depend upon the size, location and stage of your tumour, as well as your general health and level of fitness. The choice of treatments will be discussed with you and your preferences will be taken into account. Your treatment should be discussed by a multidisciplinary team, which means that experts in different areas of cancer treatment (e.g. oncologists, gastroenterologists, surgeons, radiologists, nurses and dieticians) come together to share their expertise in order to provide the best patient care. Every patient will have an individualised experience, but your journey to treatment may look something like this:



It is important for patients to feel fully involved in the treatment decision-making — when there are several treatments available, your doctor should involve you in making decisions about your care so that you can choose the care that meets your needs and reflects what is important to you. This is called 'shared decision-making'.



It is important that patients are fully involved in discussions and decisions about their treatment

Your doctor will be happy to answer any questions you have about your treatment. Five simple questions that may be helpful when talking with your doctor or any healthcare professional involved in your care are shown below.

"What treatment options do I have?"

"What are the possible advantages and disadvantages of these treatment options?"

"How likely am I to experience benefits or side effects?"

"Are there any clinical trial options?"

"How long will my treatment take?"

Your doctor may recommend one or more of the following approaches for treating stomach cancer:

## **Surgical resection**

The aim of **resection** is to remove the cancer along with a healthy **margin** of tissue around the **tumour** to help stop it from coming back. It is important to understand that not all stomach cancers are suitable for surgery; it is not generally recommended for patients with **metastatic** disease. The type of surgical **resection** depends on the stage of the cancer.

Surgery options for stomach cancer include:

- Endoscopic resection in which the tumour is removed from the lining of the stomach via an endoscope. This type of surgery is typically only used to remove early-stage stomach cancer.
- Gastrectomy, in which all of the stomach (radical gastrectomy) or part of the stomach (partial gastrectomy) is removed.



During a **gastrectomy**, nearby **lymph nodes** will also be removed. This is to ensure all of the cancer is removed with a healthy **margin**. After a **gastrectomy**, the surgeon must remodel your digestive syste:

- After a partial **gastrectomy**, the surgeon will join your **duodenum** to the remaining part of the stomach.
- After a radical gastrectomy, the surgeon will join your duodenum to your oesophagus.

Changes in the way you digest food are a significant side effect of **gastrectomy** that can have long-term effects on your physical and emotional wellbeing (see sections 'What are the possible side effects of treatment?' and 'Additional interventions' for more information).



## **Chemotherapy**

**Chemotherapy** destroys cancer cells and is used in the treatment of both early-stage and **metastatic** stomach cancer. In some patients, **chemotherapy** may be given in combination with **radiotherapy**.

**Chemotherapy** agents used in the treatment of oesophageal cancer include:

- 5-fluorouracil (5-FU)
- Capecitabine
- Cisplatin
- Docetaxel
- Irinotecan
- Oxaliplatin
- Paclitaxel
- Trifluridine + tipiracil (TAS-102)



**Chemotherapies** can be used as single agents or in combination with each other; for example, **FLOT** is a combination of **5-FU, folinic acid, oxaliplatin** and **docetaxel** that is used in the treatment of stomach cancer. It is important to understand that not all of these agents are suitable for all patients. Some patients may not be well enough to tolerate treatment with certain **chemotherapy regimens**, so your doctor will take your general health and fitness into consideration when deciding on the best treatment for you.

Chemotherapy is frequently used in the treatment of stomach cancer

Before receiving certain types of **chemotherapy** (including **5-FU** and **capecitabine**), you may be tested for a deficiency in an **enzyme** called dihydropyrimidine dehydrogenase. If you have a deficiency in this **enzyme**, you may be treated with a lower dose of **chemotherapy** than usual, or your doctor might decide to use a difference type of **chemotherapy**.

## **Radiotherapy**

Radiotherapy uses ionising radiation to damage the DNA of cancerous cells, causing them to die. In the treatment of stomach cancer, radiotherapy is most often used in combination with chemotherapy.

## **Targeted therapy**

Targeted therapies are drugs that block specific biological processes in cancer cells that encourage them to grow. Ramucirumab is a monoclonal antibody that attaches to a protein called vascular endothelial growth factor receptor 2 (VEGFR2). By blocking VEGFR2, ramucirumab stops the cancer developing the blood vessels it needs to grow. Trastuzumab is another monoclonal antibody, which attaches to HER2 in cancer cells and kills them. This treatment has also been combined with a chemotherapy agent to produce trastuzumab deruxtecan. Trastuzumab and trastuzumab deruxtecan are only used when molecular testing shows that the cancer is HER2 positive (see section 'Molecular tests' for more information). Ramucirumab, trastuzumab and trastuzumab deruxtecan are used in the treatment of metastatic stomach cancer and are given intravenously.

## **Immunotherapy**

**Immunotherapies** are treatments that block processes which reduce the body's immune response to cancer. The **immunotherapies** thereby help to reactivate the body's immune system to detect and fight the cancer.

Nivolumab and pembrolizumab are intravenous immunotherapies that block the actions of programmed cell death protein-1 (PD-1). PD-1 suppresses the body's immune response to cancer, but when its actions are blocked by immunotherapy, the immune system is reactivated to fight the cancer. Nivolumab and pembrolizumab are used in the treatment of metastatic stomach cancer. Nivolumab is used when molecular testing shows that the cancer is PD-L1-positive and pembrolizumab is used for MSI-high/MMR-deficient tumours and for PD-L1-positive tumours at the junction where the stomach meets the oesophagus (see section 'Molecular tests' for more information).

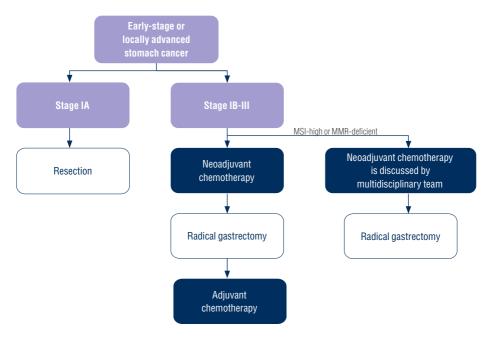
Novel immunotherapies are now available for the treatment of stomach cancer

# What are the treatment options for early-stage and locally advanced stomach cancer?

Very early-stage stomach cancer (stage IA) may be removed via **endoscopic resection** alone, but most early and locally advanced stomach cancers (stages IB-III) require **chemotherapy** in addition to surgical removal (*Lordick et al., 2022*).

Patients with stage IB-III stomach cancers are usually offered **chemotherapy** before surgery to remove the **tumour** — this is called **neoadjuvant chemotherapy**. **FLOT** is often used in these cases, but your doctor will recommend the best **neoadjuvant chemotherapy** for you based on your general health (*Lordick et al., 2022*).

Following **neoadjuvant chemotherapy**, stage IB-III **tumours** are usually removed via radical **gastrectomy** along with removal of nearby **lymph nodes**. After surgery, **adjuvant chemotherapy** is typically recommended (often with **FLOT**) (*Lordick et al.*, 2022). **MSI-high tumours** can have a different level of benefit from **chemotherapy**, so the use of **neoadjuvant chemotherapy** in these patients is discussed on a case-by-case basis within the **multidisciplinary team**.

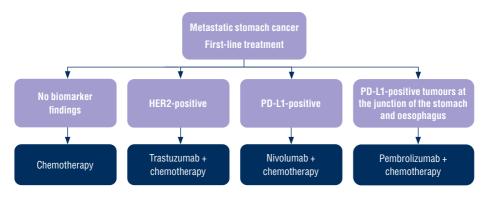


Overview of treatment options for early-stage and locally advanced stomach cancer. MMR, mismatch repair; MSI, microsatellite instability. It is important to understand that your experience may differ from the typical pathway shown above, as your doctor will personalise your treatment to ensure you receive the best possible care.

Some patients may be offered **radiotherapy**, although this is not very common. **Adjuvant radiotherapy** (alone or in combination with **chemotherapy**) may be recommended for patients who did not have **neoadjuvant chemotherapy** and have not had enough **lymph nodes** removed, or in cases where the surgeon was not able to achieve a healthy **margin** of tissue when removing the **tumour** (*Lordick et al.*, 2022).

# What are the treatment options for metastatic stomach cancer?

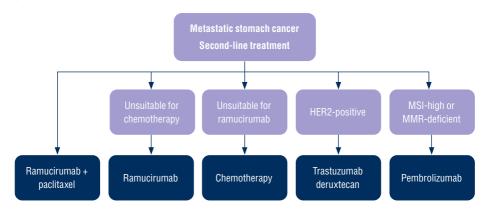
The first-line treatment for metastatic stomach cancer is chemotherapy. The chemotherapy is usually oxaliplatin, cisplatin or irinotecan, combined with either 5-FU or capecitabine. Patients with HER2-positive cancer are usually offered trastuzumab in combination with the chemotherapy, and patients with PD-L1-positive cancer typically receive nivolumab in combination with the chemotherapy (Lordick et al., 2022). Pembrolizumab can be offered to patients who have PD-L1-positive tumours located at the junction where the stomach meets the oesophagus.



Overview of first-line treatment options for metastatic stomach cancer.

HER2, human epidermal growth factor receptor 2; PD-L1, programmed death-ligand 1.

If the cancer progresses after first-line treatment, ramucirumab in combination with the chemotherapy drug paclitaxel is usually recommended as second-line treatment. Ramucirumab can be used alone in patients who are unsuitable for chemotherapy, and patients who are unsuitable for treatment with ramucirumab may receive chemotherapy alone. Patients with HER2-positive disease may be offered trastuzumab deruxtecan, and patients with MSI-high or MMR-deficient disease can be treated with pembrolizumab (Lordick et al., 2022).



Overview of second-line treatment options for metastatic stomach cancer.

HER2, human epidermal growth factor receptor 2; MMR, mismatch repair, MSI, microsatellite instability.

Third-line treatment of stomach cancer is typically chemotherapy with TAS-102, which can be taken orally. In patients who are unable to take oral drugs, intravenous chemotherapy is recommended (Lordick et al., 2022).

# **Clinical trials**

Your doctor may ask whether you would like to take part in a **clinical trial**. This is a research study conducted with patients in order to (ClinicalTrials.gov, 2019):

- Test new treatments.
- Look at new combinations of existing treatments or change the way they are given to make them more effective or reduce side effects
- Compare the effectiveness of drugs used to control symptoms.
- Identify new biomarkers to guide treatment.

Clinical trials help to improve knowledge about cancer and develop new treatments, and there can be many benefits



to taking part. You will have to undergo various tests before entering a trial and be carefully monitored during and after the study. Although the new treatment may offer benefits over existing therapies, it's important to bear in mind that some new treatments are found not to be as good as existing treatments or to have side effects that outweigh the benefits (ClinicalTrials.gov. 2019).

Clinical trials help to improve knowledge about diseases and develop new treatments – there can be many benefits to taking part

You have the right to accept or refuse participation in a **clinical trial** without any consequences for the quality of your treatment. If your doctor does not ask you about taking part in a **clinical trial** and you want to find out more about this option, you can ask your doctor if there is a trial for your type of cancer taking place nearby (ClinicalTrials.gov, 2019).

The European Medicines Agency has a register of all European clinical trials. You can find it here: https://www.clinicaltrialsregister.eu/

# **Additional interventions**

Patients may find that supplementary care helps them to cope with their diagnosis, treatment and the impact of stomach cancer on their quality of life

Your cancer, and the treatment you receive for it, can cause complications that require further interventions. During the course of your cancer, anti-cancer treatments should be supplemented with interventions that aim to prevent the complications of disease and treatment, and to maximise your quality of life. These interventions may include supportive, palliative, survivorship and end-of-life care, which should all be coordinated by a multidisciplinary team (Jordan et al., 2018).

Ask your doctor or nurse about which additional interventions are available; you and your family may receive support from several sources, such as a **dietician**, physiotherapist, social worker, priest or other spiritual advisor, complementary therapist or occupational therapist.

## Supportive care

Supportive care involves the management of cancer symptoms and the side effects of therapy. Stomach cancer, and the treatment you receive for it, can have significant effects on your quality of life, so you will receive supportive care to help you adjust.

Surgery for stomach cancer can cause problems with eating (see section 'What are the possible side effects of treatment?' for more information), but support will be available to help you with this. A **dietician** can provide advice on how and what to eat following your surgery in order to reduce the side effects and ensure you eat enough to stay at a healthy weight. Removal of the stomach may mean you can't absorb enough vitamins and minerals from a normal diet; therefore, you may be advised to take supplemental calcium, vitamin D, iron and vitamin B12. You may also be encouraged to keep a food diary.

Some **tumours** can block the entrance to the stomach or **duodenum**. Your doctor may recommend that a **stent** (a small metal or plastic tube) is inserted to relieve the blockage and allow food to pass through the digestive system. This procedure can be used for symptom relief in **metastatic** stomach cancer, or prior to surgery in early-stage or locally advanced stomach cancer. **Tumours** that are interfering with swallowing may be suitable for **radiotherapy** to reduce the size of the **tumour**.

#### Palliative care

Palliative care is a term used to describe care interventions in advanced disease, including the management of symptoms as well as support for coping with a **prognosis**, making difficult decisions and preparation for end-of-life care. Palliative care in patients with stomach cancer may include treatment for obstructions and bleeding (Harada et al., 2020).

In some cases, tube feeding may be necessary. There are different types of tube feeding, which place liquid food directly into the stomach or intestine. Your doctor and **dietician** will explain which type of tube you need and what type of liquid feed is best for you. Some types of feeding tubes pass directly through the skin and into the stomach or intestine via an opening called a **stoma**. The most common tube feeding procedure used in patients with stomach cancer is a **jejunostomy**, in which a soft plastic feeding tube (called a J-tube) is placed through the skin of the abdomen into the middle section of the small intestine. If you have a **stoma**, you will be taught how to care for it. A specialist nurse will show you how to clean it and how to tackle any problems. These changes can be distressing, and it is important to allow yourself time to adjust. Some patients may feel nervous about coping with these changes when going about their normal life, but you will get used to your new feeding method. If you tell your family and friends how you feel, they can support you. All tube feeding options should be discussed with your doctor in advance and the decision should be made jointly, taking your preferences into account.

## Survivorship care

Support for patients surviving cancer includes social support, education about the disease and rehabilitation. Psychosocial problems impacting on your quality of life may include anxiety around eating, concerns about the physical changes to your body, weight loss, and effects on your relationships. Having a **stoma** can affect the way you feel about yourself and having sex, and you and your partner might need a bit of time to get used to what a **stoma** looks like. It's important for you and your partner to be open about what's worrying you.



Your cancer diagnosis, as well as the treatment and side effects, can affect you emotionally for a long time after your treatment has finished, but there are things you can do to minimise the effects on your mental health. You may find it helpful to educate yourself about all aspects of your cancer and treatment so you can fully understand the changes that you are experiencing. Don't be afraid to ask your doctor to explain things several times to ensure you are fully informed. Having a frank conversation with your surgeon before undergoing surgery can help to prepare you for the physical changes.

Talking to other people about your feelings and experiences can help you to process the changes — some people choose to talk to family and friends, while others prefer to talk to a trained professional such as a cancer nurse or therapist.

Some patients find it helpful to talk to people who have been through a similar experience — your doctor or nurse will be able to tell you if there is a support group in your area (see section *'Support groups'* for more information). Patients often find that social support is essential for coping with the cancer diagnosis, treatment and emotional consequences.

A survivor care plan can help you to recover wellbeing in your personal, professional and social life. For further information and advice on survivorship, see ESMO's patient guide on survivorship

(https://www.esmo.org/for-patients/patient-guides/survivorship).





#### End-of-life care

End-of-life care for patients with incurable cancer primarily focuses on making the patient comfortable and providing adequate relief of physical and psychological symptoms, for example ensuring the appropriate use of painkillers to aid comfort. For further information and advice on the management of cancer-related pain, see ESMO's patient guide on cancer pain (https://www.esmo.org/for-patients/patient-guides/cancer-pain-management).

Discussions about end-of-life care can be upsetting, but support should always be available to you and your family at this time. Your doctor or nurse will help to guide you through the options available.



# What are the possible side effects of treatment?

As with any medical treatment, you may experience side effects from your anti-cancer treatment. The most common side effects for each type of treatment are highlighted below, along with some information on how they can be managed. You may experience side effects other than those discussed here. It is important to talk to your doctor about any potential side effects that are worrying you.

Doctors classify side effects from any cancer therapy by assigning each event a 'grade', on a scale of 1–4, by increasing severity. In general, grade 1 side effects are



considered to be mild, grade 2 moderate, grade 3 severe and grade 4 very severe. However, the precise criteria used to assign a grade to a specific side effect varies depending on which side effect is being considered. The aim is always to identify and address any side effect before it becomes severe, so you should always report any worrying symptoms to your doctor as soon as possible.

It is important to talk to your doctor about any treatment-related side effects that are worrying you

Fatigue is very common in patients undergoing cancer treatment and can result from either the cancer itself or the treatments. Your doctor can provide you with strategies to limit the impact of **fatigue**, including getting enough sleep, eating healthily and staying active (see section 'Looking after your health' for more information) (Cancer.Net. 2020).

#### Surgery

Gastrectomy is a major operation and it will take some time to recover — you will have to stay in hospital for at least a week. It is normal to experience pain for the first week or so and your doctor or nurse will be able to give you painkillers to help keep you feeling comfortable. You may have an intravenous drip to keep you hydrated in the first few days. You will gradually be able to drink and some patients will be able to eat a light diet. You will be encouraged to move around as soon as possible after your operation to speed up your recovery; however, it is normal to feel tired for several weeks after surgery.

If you have a **stoma**, you will be taught how to care for it before going home and you will receive support to ensure you are comfortable with whichever tube feeding system you have. Most patients, however, will be able to eat and drink normally following **gastrectomy**, although it may take some time for your body to adjust to losing part or all of your stomach.

Most patients experience problems with eating following **gastrectomy**. There is a risk that food will move too quickly into the **duodenum**, causing a sudden rush of **hormones** and making your blood sugar drop. This can make you feel dizzy, faint and nauseous. Your **dietician** or doctor can give you advice to avoid this, including eating small amounts regularly (rather than large meals) and avoiding certain types of food.

You may find that your **stools** change, for example you may experience diarrhoea due to the food passing through your digestive system faster than usual. Your **dietician** will be able to look at your diet and provide advice on which foods to avoid to reduce the risk of diarrhoea. You may also be offered anti-diarrhoea medicine. If your **stools** float, look pale or have a very bad smell, it may indicate that you are not digesting fat properly. You may need to take tablets containing digestive **enzymes** to help break down the fat.

Many patients find it difficult to maintain a healthy body weight following **gastrectomy**. This may be due to a loss of appetite and/or the digestive system not absorbing nutrients from food. It is important that you continue to eat the same amount of food that you usually would — your **dietician** will be able to help you adjust your eating habits to ensure you can maintain your weight. You will probably be advised to eat smaller, more regular meals and you will get to know which types of foods you can and can't tolerate (a food diary can help with this). You may be offered high-calorie drinks and/or vitamin supplements. For more information on eating healthily before, during and after treatment for stomach cancer, see Digestive Cancer Europe's dietary advice for patients (https://digestivecancers.eu/publication/dietary-advice-booklet-for-patients-with-oesophageal-or-gastric-cancer/).

Gastrectomy is a major operation and can have long-term health implications

# **Radiotherapy**

Radiotherapy for stomach cancer can cause nausea, vomiting and loss of appetite. The side effects usually start a few days after the radiotherapy begins and should start to get better 1 to 2 weeks after the end of treatment.

Radiotherapy may also cause the skin in the treatment area to become red/dark and sore (like mild sunburn). You may be given cream to soothe the skin, and the soreness usually disappears a few weeks after finishing treatment.

#### Chemotherapy

Side effects from **chemotherapy** vary depending upon the drugs and doses used — you may get some of those listed below but you are very unlikely to get all of them. You may also experience some side effects that are not listed below. The main areas of the body affected by **chemotherapy** are those where new cells are being quickly made and replaced (**bone marrow**, **hair follicles**, the digestive system, the lining of your mouth). Some patients find that their sense of taste is affected — changes in **enzymes** in your mouth can lead to a metallic taste and blisters. Reductions in your levels of **neutrophils** (a type of white blood cell) can lead to **neutropenia**, which can make you more susceptible to infections. Most side effects of **chemotherapy** are temporary and can be controlled with drugs or lifestyle changes — your doctor will help you to manage them (*Macmillan*, 2022). The table below lists the most important side effects of **chemotherapy** drugs that may be used in the treatment of stomach cancer

CHEMOTHERAPY Drug	POSSIBLE SIDE EFFECT	HOW THE SIDE EFFECTS MAY BE MANAGED
5-fluorouracil (5-FU) (SPC, 2022)	Anaemia     Anorexia     Asthenia     Cardiac effects     Diarrhoea     Fatigue     Hand-foot syndrome     Leukopenia     Mucositis     Nausea     Neutropenia     Thrombocytopenia	Your blood cell counts will be monitored frequently throughout your treatment in order to detect any neutropenia, anaemia, leukopenia or thrombocytopenia – your doctor may adjust your treatment according to test results and will advise you on how to prevent infections  Effects on the gastrointestinal system (nausea, diarrhoea) and mucositis may result in loss of appetite (anorexia) or feelings of weakness (asthenia). Your doctor or nurse will be able to help you to prevent or manage these side effects  Very effective drugs are available to prevent nausea  Your treatment schedule may need to be adjusted if you experience severe hand-foot syndrome but in most cases, symptoms will be mild and treatable with creams and ointments and will subside once you have finished treatment  Your cardiac function will be monitored before and during treatment to minimise the risk of cardiac impairment
Capecitabine (SPC, 2022)	<ul> <li>Anaemia</li> <li>Anorexia</li> <li>Asthenia</li> <li>Diarrhoea</li> <li>Fatigue</li> <li>Hand-foot syndrome</li> <li>Leukopenia</li> <li>Mucositis</li> <li>Nausea</li> <li>Neutropenia</li> <li>Thrombocytopenia</li> </ul>	Your blood cell counts will be monitored frequently throughout your treatment in order to detect any neutropenia, anaemia, leukopenia or thrombocytopenia — your doctor may adjust your treatment according to test results and will advise you on how to prevent infections  Fifects on the gastrointestinal system (nausea, diarrhoea) and mucositis may result in loss of appetite (anorexia) or feelings of weakness (asthenia). Your doctor or nurse will be able to help you to prevent or manage these side effects  Very effective drugs are available to prevent nausea  Your treatment schedule may need to be adjusted if you experience severe hand-foot syndrome but in most cases, symptoms will be mild and treatable with creams and ointments and will subside once you have finished treatment
Cisplatin (SPC, 2021)	Anaemia     Changes in blood electrolytes     Kidney disorders: kidney failure, nephrotoxicity     Leukopenia     Nausea     Ototoxicity     Peripheral neuropathy     Thrombocytopenia     Vomiting	<ul> <li>Your blood cell counts will be monitored frequently throughout your treatment in order to detect any anaemia, leukopenia or thrombocytopenia – your doctor may adjust your treatment according to test results, and will advise you on how to prevent infections</li> <li>Very effective drugs are available to prevent nausea and vomiting</li> <li>Report any signs of peripheral neuropathy (tingling or numbness in your hands or feet) to your doctor or nurse, who will help you to manage this side effect</li> <li>You will have tests before and during treatment to check how well your kidneys are functioning. You will be asked to drink plenty of fluids (1.5–2 litres per day) to prevent your kidneys from becoming damaged. You should avoid drinking alcohol, as this can result in dehydration and kidney dysfunction</li> <li>Tell your doctor if you notice any changes in your hearing or experience ringing in your ears (tinnitus). Changes in hearing can occasionally be permanent</li> <li>Changes in blood electrolytes may occur as a result of changes in kidney function or diarrhoea. It is important to drink plenty of fluids and tell your doctor or nurse if you experience any lethargy or confusion</li> </ul>

continued overleaf

CHEMOTHERAPY Drug	POSSIBLE SIDE EFFECT	HOW THE SIDE EFFECTS MAY BE MANAGED
Docetaxel (SPC, 2020)	Alopecia     Anaemia     Anorexia     Asthenia     Diarrhoea     Extravasation-related tissue damage     Increased infections     Mucositis     Nail disorders     Nausea     Neutropenia     Oedema     Peripheral neuropathy     Skin reaction     Thrombocytopenia     Vomiting	<ul> <li>Your blood cell counts will be monitored frequently throughout your treatment in order to detect any neutropenia, anaemia or thrombocytopenia – your doctor may adjust your treatment according to test results and will advise you on how to prevent infections</li> <li>Report any signs of peripheral neuropathy (tingling or numbness in your hands or feet) to your doctor or nurse, who will help you to manage this side effect</li> <li>Effects on the gastrointestinal system (nausea, vomiting, diarrhoea) and mucositis may result in loss of appetite (anorexia) or feelings of weakness (asthenia). Your doctor or nurse will be able to help you to prevent or manage these side effects</li> <li>Very effective drugs are available to prevent nausea and vomiting</li> <li>Let your doctor know if you experience any nail changes, skin reactions or fluid retention/swelling (oedema) – they will help you to manage these side effects</li> <li>Alopecia can be upsetting for many patients; your doctor or nurse will provide you with information on how to cope with this side effect. Some hospitals can provide cold caps to reduce hair loss</li> <li>Let your doctor know if you experience any burning or skin changes at the injection site, so that they can decide how to manage these. Many extravasations cause very little damage, but you may need to be treated with an antidote and apply compresses to the area for a few days (Pérez Fidalgo et al., 2012)</li> </ul>
Irinotecan (SPC, 2022)	<ul> <li>Alopecia</li> <li>Anaemia</li> <li>Diarrhoea</li> <li>Increased infections</li> <li>Increased liver enzymes</li> <li>Mucositis</li> <li>Nausea</li> <li>Neutropenia</li> <li>Thrombocytopenia</li> <li>Vomiting</li> </ul>	Your blood cell counts will be monitored frequently throughout your treatment in order to detect any anaemia, neutropenia or thrombocytopenia — your doctor may adjust your treatment according to test results and will advise you on how to prevent infections     Your doctor or nurse will be able to help you to prevent or manage effects on the gastrointestinal system such as nausea, vomiting and diarrhoea. Very effective drugs are available to prevent nausea and vomiting     Alopecia can be upsetting for many patients; your doctor or nurse will provide you with information on how to cope with this side effect. Some hospitals can provide cold caps to reduce hair loss     Your liver function will be monitored during treatment

CHEMOTHERAPY Drug	POSSIBLE SIDE EFFECT	HOW THE SIDE EFFECTS MAY BE MANAGED
Oxaliplatin (SPC, 2022)	Abdominal pain     Allergic reaction     Alopecia     Anaemia     Anorexia     Asthenia     Fatigue     High blood glucose     Increased liver enzymes     Injection site reactions     Leukopenia     Lymphopenia     Nausea     Neutropenia     Peripheral neuropathy     Taste changes     Thrombocytopenia     Vomiting	Your blood cell counts will be monitored frequently throughout your treatment in order to detect any anaemia, neutropenia, leukopenia, lymphopenia or thrombocytopenia – your doctor may adjust your treatment according to test results and will advise you on how to prevent infections  Effects on the gastrointestinal system (nausea, vomiting, abdominal pain) and taste changes may result in loss of appetite (anorexia) or feelings of weakness (asthenia). Your doctor or nurse will be able to help you to prevent or manage these side effects  Very effective drugs are available to prevent nausea and vomiting Report any signs of peripheral neuropathy (tingling or numbness in your hands or feet) to your doctor or nurse, who will help you to manage this side effect  Let your doctor or nurse know if you experience any burning or skin changes at the injection site so that they can decide how to manage these  Your liver function will be monitored during treatment
Paclitaxel (SPC, 2020)	<ul> <li>Alopecia</li> <li>Anaemia</li> <li>Arthralgia</li> <li>Diarrhoea</li> <li>Hypersensitivity reactions</li> <li>Increased infections</li> <li>Leukopenia</li> <li>Mucositis</li> <li>Myalgia</li> <li>Nail disorders</li> <li>Nausea</li> <li>Neutropenia</li> <li>Nose bleeds</li> <li>Peripheral neuropathy</li> <li>Thrombocytopenia</li> <li>Vomiting</li> </ul>	<ul> <li>Your blood cell counts will be monitored frequently throughout your treatment in order to detect any anaemia, neutropenia, leukopenia or thrombocytopenia – your doctor may adjust your treatment according to test results and will advise you on how to prevent infections</li> <li>Report any effects on the gastrointestinal system (nausea, vomiting, diarrhoea) to your doctor or nurse as they may be able to help you to prevent or manage these side effects. Very effective drugs are available to prevent nausea and vomiting</li> <li>Report any signs of peripheral neuropathy (tingling or numbness in your hands or feet) to your doctor or nurse, who will help you to manage this side effect</li> <li>Let your doctor or nurse know if you experience nose bleeds, nail changes, arthralgia or myalgia, so that they can decide how to manage these</li> <li>Alopecia can be upsetting for many patients; your doctor or nurse will provide you with information on how to cope with this side effect. Some hospitals can provide cold caps to reduce hair loss</li> </ul>
Trifluridine + tipiracil (TAS-102) (SPC, 2021)	<ul> <li>Anaemia</li> <li>Anorexia</li> <li>Diarrhoea</li> <li>Fatigue</li> <li>Leukopenia</li> <li>Nausea</li> <li>Neutropenia</li> <li>Thrombocytopenia</li> </ul>	Your blood cell counts will be monitored frequently throughout your treatment in order to detect any anaemia, leukopenia, neutropenia or thrombocytopenia – your doctor may adjust your treatment according to test results and will advise you on how to prevent infections  Effects on the gastrointestinal system (nausea, diarrhoea) may result in loss of appetite (anorexia). Your doctor or nurse will be able to help you to prevent or manage these side effects  Very effective drugs are available to prevent nausea

Important side effects associated with individual chemotherapy drugs used in the treatment of stomach cancer. The most recent Summary of Product Characteristics (SPC) for any individual drug can be located at: http://www.ema.europa.eu/ema/.

# **Targeted therapies**

Common side effects in patients treated with **targeted therapies** include skin reactions and effects on the **gastrointestinal system** (e.g. nausea, diarrhoea). Many of the side effects from **targeted therapies** can be prevented or managed effectively. Always tell your doctor or nurse as soon as possible if you notice any side effects from taking a **targeted therapy**.

The table below lists the most important specific side effects of **targeted therapies** used in the treatment of stomach cancer.

TARGETED THERAPY	POSSIBLE SIDE EFFECT	HOW THE SIDE EFFECTS MAY BE MANAGED
Ramucirumab (SPC, 2022)	Blood clots Changes in blood electrolytes Diarrhoea Fatigue Headache Hypertension Injection site reactions Nose bleeds Proteinuria	Your blood pressure will be monitored during treatment and anti-hypertensive treatment will be given if necessary  Let your doctor or nurse know if you experience any burning or skin changes at the injection site so that they can decide how to manage these  Changes in blood electrolytes or proteinuria may occur as a result of changes in kidney function or diarrhoea. It is important to drink plenty of fluids and tell your doctor or nurse if you experience any lethargy or confusion  Let your doctor know if you experience headaches or nose bleeds so that they can decide how to manage these
Trastuzumab (SPC, 2021)	Arthralgia     Cardiac disorders     Rash and other skin effects     Respiratory effects including dyspnoea	Your cardiac function will be assessed before starting treatment with trastuzumab and will be monitored every 3-4 months during treatment. If your cardiac function is affected, your doctor may decide to reduce or pause trastuzumab treatment or prescribe you another drug to treat the cardiac side effects (Curigliano et al. 2020)  Let your doctor or nurse know if you experience respiratory problems. Troublesome dyspnoea can be treated with drugs called opioids or benzodiazepines, and in some cases, steroids are used (Kloke and Chemy, 2015)  Let your doctor or nurse know if you experience arthralgia or pain — they will help you to manage these side effects. They can also give you advice on skin reactions

# Stomach cancer

TARGETED THERAPY	POSSIBLE SIDE EFFECT	HOW THE SIDE EFFECTS MAY BE MANAGED
Trastuzumab deruxtecan (SPC, 2022)	Alopecia     Anaemia     Anorexia     Cardiac effects     Diarrhoea     Fatigue     Leukopenia     Liver enzymes increased     Lymphopenia     Nausea     Neutropenia     Respiratory effects including dyspnoea, pneumonitis and interstitial lung disease     Thrombocytopenia     Vomiting	<ul> <li>Your blood cell counts will be monitored frequently throughout your treatment in order to detect any anaemia, leukopenia, lymphopenia, neutropenia or thrombocytopenia – your doctor may adjust your treatment according to test results</li> <li>Effects on the gastrointestinal system (e.g. diarrhoea, nausea, vomiting) may result in loss of appetite (anorexia) and fatigue. Your doctor or nurse will be able to help you to prevent or manage these side effects</li> <li>Your cardiac function will be monitored before and during treatment to minimise the risk of cardiac impairment</li> <li>Your liver function will be monitored before and during treatment – your doctor may adjust your treatment according to test results</li> <li>Let your doctor or nurse know if you experience respiratory problems. Troublesome dyspnoea can be treated with drugs called opioids or benzodiazepines, and in some cases, steroids are used (Kloke and Chemy, 2015)</li> <li>A cough, shortness of breath or other new or worsening breathing problems can be symptoms of interstitial lung disease – tell your doctor immediately if you have these symptoms</li> <li>Alopecia can be upsetting for many patients; your doctor or nurse will provide you with information on how to cope with this side effect</li> </ul>

Important side effects associated with individual targeted therapies used in the treatment of stomach cancer. The most recent Summary of Product Characteristics (SPC) for any individual drug can be located at: http://www.ema.europa.eu/ema/.

# **Immunotherapy**

Common side effects in patients treated with **immunotherapy** include effects on the **gastrointestinal system** and **thyroid** dysfunction. Many of the side effects from **immunotherapy** can be effectively managed if they are recognised and treated early.

It is important to be aware that **immunotherapy** can cause **autoimmunity**, in which the immune system incorrectly identifies its own tissues as foreign bodies and attacks them. **Autoimmunity** can cause inflammation that may affect any organ in the body. In some cases, this side effect can be life-threatening; therefore, it is essential that you alert your doctor or nurse immediately if you notice any side effects or if you feel at all unwell when being treated with an **immunotherapy** drug.

The table below lists the most important specific side effects of the **immunotherapy** drugs used in the treatment of stomach cancer

For further information and advice on **immunotherapy** side effects, see ESMO's patient guide on **immunotherapy**-related side effects and their management (https://www.esmo.org/for-patients/patient-guides/immunotherapy-side-effects).



IMMUNOTHERAPY	POSSIBLE SIDE EFFECT	HOW THE SIDE EFFECTS MAY BE MANAGED
Nivolumab (SPC, 2022) Pembrolizumab (SPC, 2022)	Cardiac effects Colitis Cough Diarrhoea Endocrine disorders Eye problems (e.g. uveitis) Fatigue Headache Hepatitis Kidney disorders Musculoskeletal pain Pneumonitis Rash	<ul> <li>Effects on the gastrointestinal system (e.g. diarrhoea) may result in fatigue. Your doctor or nurse will be able to help you to prevent or manage these side effects</li> <li>Your cardiac function will be monitored before and during treatment to minimise the risk of cardiac impairment</li> <li>Your liver and kidney function will be monitored before and during treatment — your doctor may adjust your treatment according to test results</li> <li>A cough, shortness of breath or other new or worsening breathing problems can be symptoms of pneumonitis — tell your doctor immediately if you have these symptoms</li> <li>Colitis, hepatitis and pneumonitis are immune-related side effects. Your doctor or nurse will be able to help you recognise and manage these side effects</li> <li>Let your doctor or nurse know if you experience eye problems, headaches or rash — they will help you to manage these side effects</li> </ul>

Important side effects associated with immunotherapy drugs used in the treatment of stomach cancer.

The most recent Summary of Product Characteristics (SPC) for any individual drug can be located at: http://www.ema.europa.eu/ema/.

# What happens next?

# Follow-up appointments

You will be able to discuss any concerns you have at your follow-up appointments

After treatment for stomach cancer, your doctor will arrange follow-up appointments to ensure that you are receiving dietary and psychological support, any **recurrences** are diagnosed and treated quickly, and any side effects are managed effectively.

Your doctor will let you know how often you need to return for further follow-up appointments; the schedule will vary between regions. During these appointments, you may have a physical examination, blood tests and/or a CT scan.



# What if I need more treatment?

Despite the best possible treatment at diagnosis, there is a chance that your cancer may return. Cancer that comes back is called a **recurrence**. The treatment that you will be offered depends on the extent of the **recurrence**, your previous treatment and your overall health. Usually, **recurrences** of stomach cancer are treated in the same way as **metastatic** stomach cancer, but your doctor will discuss all of the treatment options with you.

# Looking after your health

After you have had treatment for stomach cancer, you may feel very tired and emotional. Give your body time to recover and make sure you get enough rest, but there is no reason to limit activities if you are feeling well. It is important to take good care of yourself and get the support that you need.

The following eight recommendations can form a good foundation for a healthy lifestyle after cancer (Wolin et al., 2013):

- Don't smoke.
- Avoid second-hand smoke.
- Exercise regularly.
- Avoid weight gain.
- Eat a healthy diet as far as possible.
- Don't drink alcohol
- Stay connected with friends, family and other cancer survivors
- Attend regular check-ups.



A healthy, active lifestyle will help you to recover physically and mentally

A healthy diet and regular exercise are essential parts of a healthy lifestyle, helping you to keep physically fit and maintain a healthy weight. You should receive advice from a **dietician** and any weight loss should be investigated. It is very important that you listen carefully to the recommendations of your doctor or nurse and talk to them about any difficulties you have with exercise. It is also important that you do not change your diet or start a new exercise programme without talking to your doctor or nurse first.

For further information and advice regarding how to regain your life as far as possible after treatment for cancer, see ESMO's patient guide on survivorship (https://www.esmo.org/for-patients/patient-quides/survivorship).



# **Support groups**

In Europe, there are patient advocacy groups, which help patients, caregivers and their families to navigate the stomach cancer landscape. They can be local, national or international, and they work to ensure patients and caregivers receive appropriate and timely care and education. These groups can provide you with the tools you may need to help you better understand your disease, and to learn how to cope with it, living the best quality of life that you can.



Digestive Cancers Europe (DiCE) is a community of patient organisations dedicated to empowering and providing a voice for people affected by digestive cancers, including stomach cancer. For further information about DiCE and to find support groups in your country, visit: https://digestivecancers.eu/members/

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**5-FLUOROURACIL (5-FU)**A type of **chemotherapy** that is administered through a drip into a vein in your arm or chest

# ADENOCARCINOMA

Additional treatment given after the primary treatment to reduce the chance of the cancer coming back; usually refers to radiotherapy and/or chemotherapy after

# **ALOPECIA**

### ANAEMIA

A condition in which there is a shortage of haemoglobin (a protein in red blood cells that carries oxygen throughout the body)

A type of drug used to treat and prevent bacterial infections

# **ARTHRALGIA**

# **ASTHENIA**

A condition in which the body's immune system mistakes its own healthy tissues as foreign and attacks them. Most autoimmune diseases cause inflammation that can affect many parts of the body

### BIOMARKER

### **BONE MARROW**

A spongy tissue found inside some bones (e.g. hip and thigh bones). It contains stem cells, which are cells that can develop into red blood cells, white blood cells or

# **CAPECITABINE**

### **CHEMOTHERAPY**

### **CISPLATIN**

A type of **chemotherapy** that is administered through a drip into a vein in your arm or chest

# CLAUDIN-18.2

tumours

# **CLINICAL TRIAL**

A study that compares the effects of one treatment with another

# COLD CAP

follicles

# COMPUTED TOMOGRAPHY (CT)

A scan using **x-rays** and a computer to create detailed images of the inside of the body

A qualified health professional who is an expert on diet and nutrition

### **DOCETAXEL**

A type of **chemotherapy** that is administered through a drip into a vein in your arm or chest

### DUODENUM

### **DYSPLASIA**

within a tissue or organ. **Dysplasia** is not cancer, but it may sometimes develop into cancer

# **DYSPNOEA**

A substance that breaks up into particles with electrical charges when it is dissolved in water or body fluids. Son examples of ions are sodium, potassium and calcium

### **ENDOSCOPE**

A thin, tube-like instrument used to look at tissues inside

# **ENDOSCOPIC RESECTION**

# **ENDOSCOPIC SURVEILLANCE**

Regular examination of the digestive system with an endoscope to look for dysplasia and early signs of cancer

# **ENDOSCOPIC ULTRASOUND**

Use of a thin, tube-like instrument used to look at tissues inside the body

### ENZYME

Leakage of fluid, such as an anti-cancer drug, from a blood vessel or tube into the tissue around it

# FIBROBLAST GROWTH FACTOR RECEPTOR (FGFR)

A protein that is involved in cell division, cell maturation, formation of new blood vessels, wound healing and bone growth and development. A mutation in an FGFR gene may cause an FGFR protein to become overactive in certain cancers

# FIRST-LINE (TREATMENT)

### **FLOT**

A type of chemotherapy that is a combination of 5-FU, folinic acid, oxaliplatin and docetaxel

# **GASTROINTESTINAL STROMA TUMOUR**

A type of **tumour** that usually begins in cells in the wall of the gastrointestinal system

GASTROINTESTINAL SYSTEM
The system of organs responsible for getting food into and out of the body and for making use of food to keep the body healthy – includes the oesophagus, stomach and intestine

# **GASTRO-OESOPHAGEAL REFLUX**

oesophagus

A piece of **DNA** responsible for making a substance that the body needs to function

# **GENERAL ANAESTHETIC**

### **GENETIC COUNSELLING**

Communication between a specially trained health professional and a person with a possible genetic risk of disease

# HAND-FOOT SYNDROME

A condition marked by pain, swelling, numbness, tingling or redness of the hands or feet. It sometimes occurs as a side effect of certain anti-cancer drugs

# HELICOBACTER PYLORI (H. PYLORI)

Inflammation of the liver with increased liver **enzyme** levels. As an immune-related side effect, this is noninfectious

A substance made by glands in the body. **Hormones** circulate in the bloodstream and control the actions of certain cells or organs

# **HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2**

## **HYPERTENSION**

# **IMMUNOTHERAPY**

# **INTERSTITIAL LUNG DISEASE**

A group of diseases that cause scarring of the lungs. This is an immune-related side effect of some cancer therapies

### INTRAEPITHELIAL

### INTRAVENOUS

# **IONISING RADIATION**

A type of **chemotherapy** that is administered through a drip into a vein in your arm or chest

### **JEJUNOSTOMY**

Surgery to create an opening into the jejunum (part of the small intestine) from the outside of the body. A

# **LAMINA PROPRIA**

A thin layer of connective tissue under the thin layer of tissues covering the **oesophagus** 

# LAPAROSCOPY

A decrease in the number of leukocytes (a type of white blood cell) in the blood, which places individuals at increased risk of infection

**LOCAL ANAESTHETIC**A medication that causes reversible absence of pain sensation around the site of administration

### LYMPH

The fluid that circulates throughout the lymphatic

# LYMPH NODES

Small structures throughout the **lymphatic system** that work as filters for harmful substances, such as cancer cells or bacteria

# LYMPHATIC SYSTEM

lymph, a fluid containing infection-fighting white blood

# LYMPHOPENIA

An abnormally low level of lymphocytes (a type of white blood cell) in the blood, which places individuals at increased risk of infection

## (RESECTION) MARGIN

margin is described as positive or involved when cancer

Cancerous **tumours** that have originated from a primary **tumour**/growth in another part of the body

A cancer that has spread from its site of origin to different parts of the body

Cancer cells that have a high number of **mutations** within microsatellites (short, repeated sequences of **DNA**). **MSI-high** cancer cells may not be able to correct mistakes that occur when **DNA** is copied in the cell

### MISMATCH REPAIR-DEFICIENT (MMR-DEFICIENT)

Cancer cells that have **mutations** in certain **genes** that are involved in correcting mistakes made when **DNA** is copied in a cell. MMR-deficient cells usually have many

# **MOLECULAR TESTING**

A laboratory method that uses a sample of tissue, blood, or other body fluid to check for certain **genes**, proteins or other molecules

# **MONOCLONAL ANTIBODY**

A type of targeted therapy. Monoclonal antibodies recognise and attach to specific proteins produced by cells. Each monoclonal antibody recognises one particular protein. They work in different ways depending on the protein they are targeting

Inflammation and ulceration of the membranes lining the gastrointestinal system

# MULTIDISCIPLINARY TEAM

A group of healthcare workers who are members of different disciplines (e.g. oncologist, nurse specialist,

# MUSCULARIS MUCOSAE

A thin layer of muscle in the innermost layer of the stomach

# **MUSCULARIS PROPRIA**

# MUSCULOSKELETAL

Relating to muscles, bones, tendons, ligaments, joints and cartilage

# MYALGIA

Treatment given as a first step to shrink a **tumour** before the main treatment (usually surgery) is given. Examples of neoadjuvant therapy include chemotherapy and radiotherapy

### **NEPHROTOXICITY**

# **NEUTROPENIA**

# **NEUTROPHIL**

A type of white blood cell that plays an important role in fighting off infection

# NIVOLUMAB

A type of immunotherapy that blocks a protein called PD-1 on the surface of certain immune cells called T cells; this activates the T cells to find and kill cancer

Abnormal or excessive fat accumulation that may impair health

# **OESOPHAGUS**

The food pipe; the tube that connects your throat with your stomach

### OXALIPLATIN

A type of **chemotherapy** that is administered through a drip into a vein in your arm or chest

A type of **chemotherapy** that is administered through a drip into a vein in your arm or chest

The care of patients with advanced, progressive illness. It focuses on providing relief from pain, symptoms and physical and emotional stress, without dealing with the cause of the condition

# PEMBROLIZUMAB

A type of immunotherapy that blocks a protein called PD-1 on the surface of certain immune cells called T cells; this activates the T cells to find and kill cancer

# PERIPHERAL NEUROPATHY

Damage to the nerves in the extremities of the body. Symptoms may include pain, sensitivity, numbness or weakness in the hands, feet or lower legs

# **PNEUMONITIS**

# **PROGNOSIS**

# PROGRAMMED CELL DEATH PROTEIN-1 (PD-1)

# **PROGRAMMED DEATH-LIGAND 1 (PD-L1)**

A cellular protein thought to be involved in helping the **tumour** to evade detection by the body's immune system

# **RADIOTHERAPY**

Treatment involving the use of high-energy radiation, which is commonly used to treat cancer

# **RAMUCIRUMAB**

A type of targeted therapy that blocks the action of tumour growth. It is administered through a drip into a

# RISK FACTOR

### SARCOMA

A type of cancer that begins in bone or in the soft tissues of the body, including cartilage, fat, muscle, blood vessels, fibrous tissue or other connective or supportive

Cancer that begins in squamous cells, which are thin, flat cells forming the surface of the skin, the lining of hollow organs of the body, and the lining of the respiratory and digestive tracts

A surgically-created opening from an area inside the body to the outside

the oesophagus

# **TARGETED THERAPY**

substances to precisely identify and attack cancer cells, usually while doing little damage to normal cells

# THIRD-LINE (TREATMENT)

A third treatment regimen given to a patient once the previous two lines (first-line and second-line) of therapy have not worked or have been stopped because of the occurrence of side effects or other concerns

# THROMBOCYTOPENIA

A decrease in platelets in the blood. This causes bleeding into the tissues, bruising, and slow blood

A gland located in the neck, which helps to regulate growth and metabolism

# TRASTUZUMAB

A type of **targeted therapy** used to treat **HER2**-positive stomach cancer

TRASTUZUMAB DERUXTECAN
A type of targeted therapy combined with
chemotherapy used to treat HER2-positive stomach

# TRIFLURIDINE + TIPIRACIL (TAS-102)

A lump or growth of abnormal cells. **Tumours** may be benign (not cancerous) or malignant (cancerous). In this guide, the term '**tumour**' refers to a cancerous growth, unless otherwise stated

# **VASCULAR ENDOTHELIAL GROWTH FACTOR**

**RECEPTOR 2 (VEGFR2)**A receptor for vascular endothelial growth factor, which is a protein produced by cells that stimulates the growth

An imaging test, using a type of radiation that can pass through the body, which allows your doctor to see images of inside your body

### Stomach cancer

This guide has been prepared to help you, your friends and your family better understand the nature of stomach cancer and the treatments that are available. 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. We recommend that you ask your doctor about the tests and types of treatments available in your country for your type and stage of stomach cancer.

This guide has been written by Kstorfin Medical Communications Ltd on behalf of ESMO.

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European Society for Medical Oncology (ESMO) Via Ginevra 4 6900 Lugano Switzerland

Tel: +41 (0)91 973 19 99 Fax: +41 (0)91 973 19 02

E-mail: patient\_guides@esmo.org



We can help you understand stomach cancer and the available treatment options.

The ESMO Guides for Patients are designed to assist patients, their relatives and caregivers to understand the nature of different types of cancer and evaluate the best available treatment choices. The medical information described in the Guides for Patients is based on the ESMO Clinical Practice Guidelines, which are designed to guide medical oncologists in the diagnosis, follow-up and treatment in different cancer types.

For more information, please visit www.esmo.org

