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The European Oesophageal and Gastric Cancer Roadmap

Improving
the patient
pathway



DIGESTIVE CANCERS
EUROPE

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Executive Summary and Recommendations

Oesophageal and gastric cancers are estimated to **189.031 new cases** and **142.508 deaths per year in Europe**.¹ Combined, their total costs amount to 8,6 billion Euros in 2018 in Europe.² As a result of the ageing and growing population, the burden of these two cancers is growing heavier, causing increased disability-adjusted life years (DALYs). The premature death of the population due to these diseases and the resources required to support those who survive create productivity loss and result in heavy costs on health-care systems.

Despite the rising human and financial stakes in both gastric and oesophageal cancers, best practices fail to be applied, disease management guidelines are not harmonised, and the management of the disease is still not optimal in many countries and regions.

Current policy efforts do not fully address the 360-degree holistic approach to oesophageal and gastric cancer, and research tends to focus on cancer treatments.

Today's efforts should also focus on prevention and early diagnosis but also on the morbidities, which treating these cancers cause. Indeed, most of the patients who survive are faced with long-term medical challenges, which hinder their ability to return to normal life, go back to work and achieve a good quality of life. Today only a limited number of medical options to support and relieve patients are available, and care management is unfortunately not optimised across Europe to adequately support patients during and after treatment.

These two cancers require a 360-degree, precise and adequate disease management approach, which encompasses every aspect of the patient journey and includes the patient in every part of the decision-making process. They also require an approach which integrates critical aspects of patients' long-term recovery and quality of life, such as mental health, nutrition and physical assessment. Moreover, any approach to managing oesophageal and gastric cancers should target a behavioural change across populations and healthcare professionals; this would help prevent

and diagnose these cancers as early as possible, and therefore, reduce mortality rates, which are high due to late detection.

For this to happen, an overarching effort at EU level needs to be implemented to promote the development and harmonisation of such national plans.

We will give this reflection a start with this roadmap.

Oesophageal cancer and gastric cancer have important similarities when it comes to late diagnosis and the heavy impact of their treatments on quality of life, mental health and nutrition. For this reason, they will be tackled together into a single document. They have, however, important differences, in particular, in terms of risk factors and prevention strategies (both primary and secondary prevention). This roadmap will highlight the important distinctions between these two cancers where appropriate.

Top-line recommendations ●

Prevention and early diagnosis

- Invest in innovative education campaign models regarding the risks of developing oesophageal and gastric cancer at national level to empower the population to be in control of its own health and reduce risk factors related to these two cancers
- Empower and inform family doctors/primary care professionals about the risk factors and the symptoms of oesophageal and gastric cancer and the importance of timely referral to experts
- Promote the application of harmonised guidelines that define risk groups, the optimal referral and early diagnosis process and follow-up specific to oesophageal and gastric cancer, using European best practices
- Ensure the harmonisation and application of primary preventive measures to help reduce the main risk factors of oesophageal and gastric cancers, in line with the European Society for Gastrointestinal Endoscopy (ESGE)'s MAPS II guidelines and the European Society of Medical Oncology (ESMO)'s clinical practice guidelines:
 - for **oesophageal cancer**: the early identification and treatment of gastro-oesophageal reflux disease (GORD) and the promotion of a healthy lifestyle
 - for **gastric cancer**: the early identification and treatment of *Helicobacter pylori* bacteria and the promotion of a healthy lifestyle
- Ensure the harmonisation and application of secondary preventive measures in line with ESGE's MAPS II guidelines that would allow the systematic surveillance and screening of pre-cancer medical lesions and conditions specific to each cancer
- Use population-based cancer registries as a key policy tool to evaluate the effectiveness and impact of cancer prevention strategies

Diagnostics

- Promote the development of information campaigns about patients' rights to request timely diagnosis and referral for oesophageal and gastric cancer
- Promote the application of harmonised guidelines for timely diagnosis of gastric and oesophageal cancer
- Promote the systematic referral to multidisciplinary expert centres where medical expertise and high-quality materials are optimal for timely and accurate diagnosis of oesophageal and gastric cancer
- Promote the surveillance of patients with precancerous lesions as indicated by European guidelines



Treatment

- Encourage the development of the Comprehensive Cancer Care Network (CCCN) model
- Recommend the inclusion of nutritional and health fitness assessment and support in every aspect of oesophageal and gastric cancer patient care, before the start of the treatment and in support of the short- and long-term side effects from treatment
- Empower patient organisations in informing and supporting patients about their right to choose their centre/team
- Optimise patient access to medicines or biomarkers intended for use as companion diagnostics after EMA authorisation
- Focus care management guidelines on the side effects of treatment for oesophageal and gastric cancer



Surgery

- Ensure that surgery is performed in centres with sufficient expertise and according to the current guidelines
- Ensure that the post-operative success rates of each hospital of surgeries performed to treat oesophageal and gastric cancer are systematically reported and made public
- Encourage the development of the Comprehensive Cancer Care Network (CCCN) model, where multidisciplinary care management, shared decision-making and 360-degree patient support are ensured
- Develop and harmonise across Member States a cancer infrastructure accreditation system which evaluates the expertise of each cancer centre for oesophageal and gastric cancer and requires a minimum number of cancer cases to ensure that surgeries are performed in high-volume, expert hospitals
- Harmonise guidelines for the reporting of patient survival and surgery success rates by all European hospitals
- Focus care management guidelines on the side effects and long-term effects of surgeries which treat oesophageal and gastric cancer

Research



- Invest in further research which could allow to recommend primary prevention of gastric cancer by eradicating the *Helicobacter pylori* bacteria on a population level
- Invest in further research which could allow non-invasive mass screening for and surveillance of pre-cancerous lesions and conditions for oesophageal and gastric cancer
- Invest in more research at EU and national level on patient nutrition and health fitness before, during and after treatment to help better address and fight nutritional problems which are common in oesophageal and gastric cancer patients
- Invest in basic research for both cancers that drives understanding into the hereditary forms of oesophageal and gastric cancer and in biomarkers that can be used for developing new drugs

Nutrition

- Promote the implementation of specific nutritional protocols for oesophageal and gastric cancer, which include early assessment of patient nutritional status at cancer diagnosis and the ensured provision of nutritional support prior, during and after each treatment stage, in line with ESPEN guidelines and **ERAS protocols**
- Ensure a specialist dietitian is included in the shared decision-making process for patient care and is available to support the patient before, during and after treatment
- Harmonise guidelines on the use of nutrition support to improve patient recovery time and overall nutritional outcomes for patients treated for oesophageal or gastric cancer
- Invest in more research at EU and national level on patient nutrition before, during and after treatment to help better address and fight malnutrition in cancer patients
- Recommend nutritional assessment as a prerequisite before the start of treatment for oesophageal and gastric cancer
- Empower patient organisations in guiding and supporting patients about nutrition before, during and after treatment
- Focus medical research on nutrition-related side-effects of gastro-oesophageal cancer

Mental Health

- Promote the assessment of distress and psychological morbidity specific to oesophageal and gastric cancer patients as part of the patient's routine prehabilitation to treatment and surgery, and also at each step of the patient pathway
- Include psycho-oncology services in the standard care services in all national cancer care facilities
- Include psychological support solutions to help patients face the challenges which arise with survivorship in patient care guidelines

Quality of life

- Patient and family support during and after treatment should be offered systematically as part of the patient care plan
- Pain management should be included in all cancer management guidelines
- Patient organisations should be involved in shaping new healthcare policies that ensure optimal quality of life for patients

End-of-life

- Ensure that care management guidelines include palliative care and end-of-life support for patients, families and caregivers
- Empower patient organisations in guiding patients and families through the medical, legal and ethical matters related to their possible end-of-life scenarios



Introduction

Gastric and oesophageal cancers, combined, account for 142.508 deaths and 189.031 new cases every year.¹ They incur a huge burden on healthcare systems, costing 8,6 billion Euros in Europe.²

In the majority of cases these cancers are diagnosed at late stages. This means that most often when patients present symptoms, their cancer is already advanced, which hinders their prognosis. This is all the more problematic because the options/methods for treating and managing these cancers are complex; in the best scenarios, treating oesophageal and gastric cancers requires heavy surgeries, which leave the patients with a poor quality of life and lifelong medical issues. Delayed diagnosis and inadequate disease management are noticeable across Europe and need to be improved.

The mortality rate of gastric and oesophageal cancers is very high and their cost on society is substantial. While the European Commission's recent Europe's *Beating Cancer*

*Plan*³ shows the EU's commitment and vision to eradicate cancer, it does not provide an efficient and tailored strategy to address oesophageal and gastric cancer specifically.

This Roadmap is the first step towards creating a European vision to address the current gaps in the management of gastric and oesophageal cancer. It will present the ideal scenario from a patient perspective at each stage of the patient journey (Prevention and early diagnosis; Diagnostics; Surgery; Treatment; Nutrition; Quality of life/Survivorship; End-of-life), shed light on the current situation and existing challenges, and provide key recommendations to improve overall patient outcomes.

In an ideal environment where rational disease management is the priority, policy decisions are made based on the previous year's statistics on patient population and segmentation, treatment outcomes, patient satisfaction, best practices and total costs. However, up-to-date statistics about the state of health of citizens and patients are hard to

find, and often outdated. It is even rarer to have long term objectives by disease area that provide a sense of direction and purpose.

Digestive Cancer Europe's goal and commitment are clear: to save 280.000 patients with digestive cancer annually in Europe by the end of the decade.

This Roadmap has the ambition to bring these elements together to move in this direction.

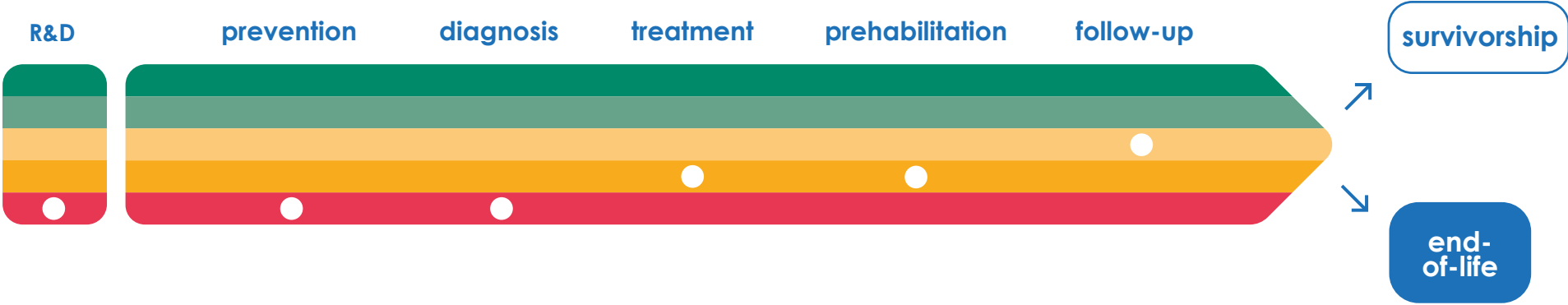


The framework

The patient journey from prevention to overall survival or end of life

We will provide recommendations on how to best manage and optimise each step of the patient pathway so that healthcare systems can be as rational as possible and patient outcomes improved. The patient pathway is represented in the graph below:

Figure 1: The patient pathway of patients with oesophageal and gastric cancer



Overview and current status

Incidence & survival rates of oesophageal cancer

Globally, oesophageal cancer is responsible for 572.034 new cases and causes 508.585 deaths per year,⁴ making it the sixth in overall cancer mortality.⁵ Approximately 70% of oesophageal cancer cases occur in men and incidence and mortality rates are particularly high in Eastern Asia and Eastern and Southern Africa.⁶ In Europe, there are 52.993 new cases and 45.511 deaths of oesophageal cancer per year.¹

As indicated by the incidence and mortality rates, 5-year survival rates are very low: 20% in the United States⁷ and 10% in Europe.⁸

Survival rate depends on several factors, notably the stage of the cancer at diagnosis. Indeed, the 5-year survival rate of people with a cancer located only in the oesophagus is 47%; when the disease has spread to other organs or the regional lymph nodes, survival rate is 25%. If it has spread to distant parts of the body, the survival rate is 5%.⁹

Oesophageal cancer caused 9,7 million disability-adjusted life years (DALYs) worldwide in 2017.¹⁰

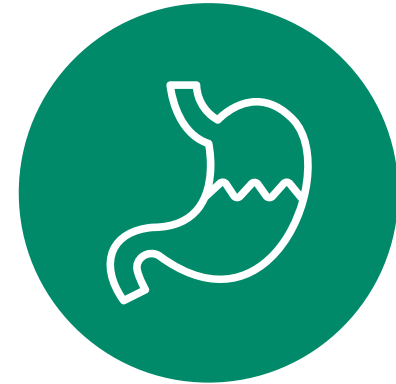


Table 1: Incidence and mortality of oesophageal and gastric cancers in Europe¹⁹

	annual number of cases	annual number of deaths
Oesophageal cancer	52.993	45.511
Gastric cancer	136.038	96.997
TOTAL	189.031	142.508

Overview and current status

Incidence & survival rate of gastric cancer

Gastric cancer, also referred to as stomach cancer, is responsible for 1.033.701 new cases and causes 782.685 deaths per year globally,⁴ placing it at the fifth place in terms of incidence and the third place in terms of mortality worldwide. Occurrence in men is twice as high as in women and incidence rates are particularly high in Western and Eastern Asia. It often affects older people; about 60% of people who are diagnosed are older than 64 years of age.¹¹ In Europe, there is an estimate of 136.038 new cases and 96.997 deaths of gastric cancer per year.¹

The overall 5-year survival rate for gastric cancer is 32% in the US.¹¹ If the cancer is localised, the 5-year survival rate is 69%. If the cancer has spread to surrounding tissues or organs and/or the regional lymph nodes, the 5-year survival rate is 31%. If the cancer has spread to a distant part of the body, the 5-year survival rate is 5%.⁹ Overall survival rates in Europe are 25% but there are no available data on survival per cancer stage.¹²

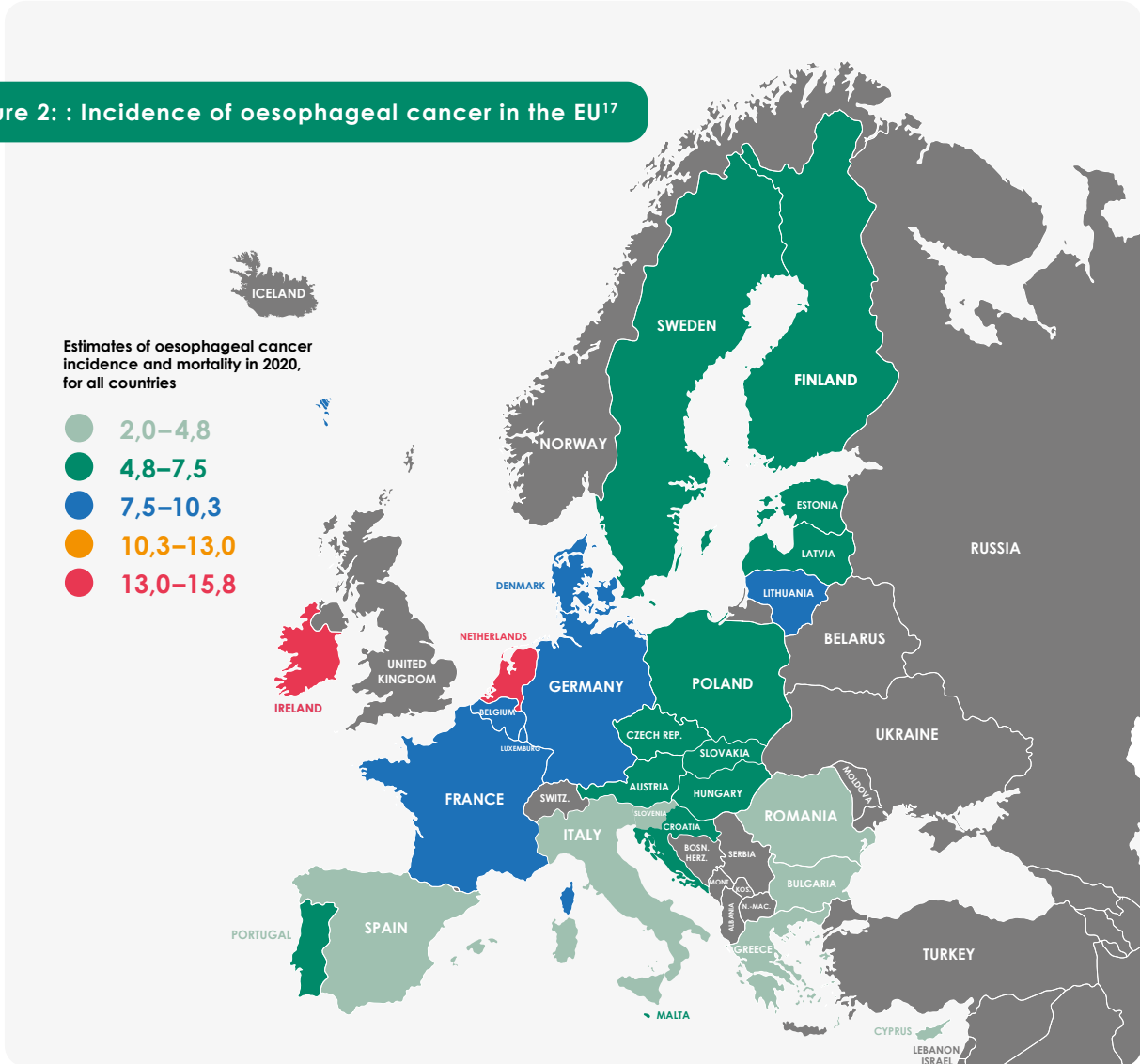
Gastric cancer contributed to 19,1 million DALYs worldwide in 2017.¹³

According to a 20.528-people survey done in England and Wales on oesophago-gastric cancer, it was shown that among patients diagnosed at stage 0-III, only 60% had a curative treatment plan (72% at stage 0/I, 62,5% at stage II, and 55% at stage III).¹⁴ These constitute the best cases. Patients diagnosed at stage 4 are only given treatment options which can improve their quality of life and might extend their life expectancy. The 5-year survival rate for patients with metastatic gastric cancer is in fact 3%.¹⁵

On the positive side, cancer control and survival rates have improved for both cancers in most European countries over time. All countries have recorded a concurrent decrease in both incidence and mortality rates since 1995. For gastric cancer, the incidence rate was halved between 1995 and 2018 and the 5-year survival rate has increased from 20% to 33% over the last 20 years, particularly in Ireland.¹⁶ During the same period, the 5-year survival rate from oesophageal cancer increased by 11% in Norway and Ireland.¹⁶



Figure 2: : Incidence of oesophageal cancer in the EU¹⁷

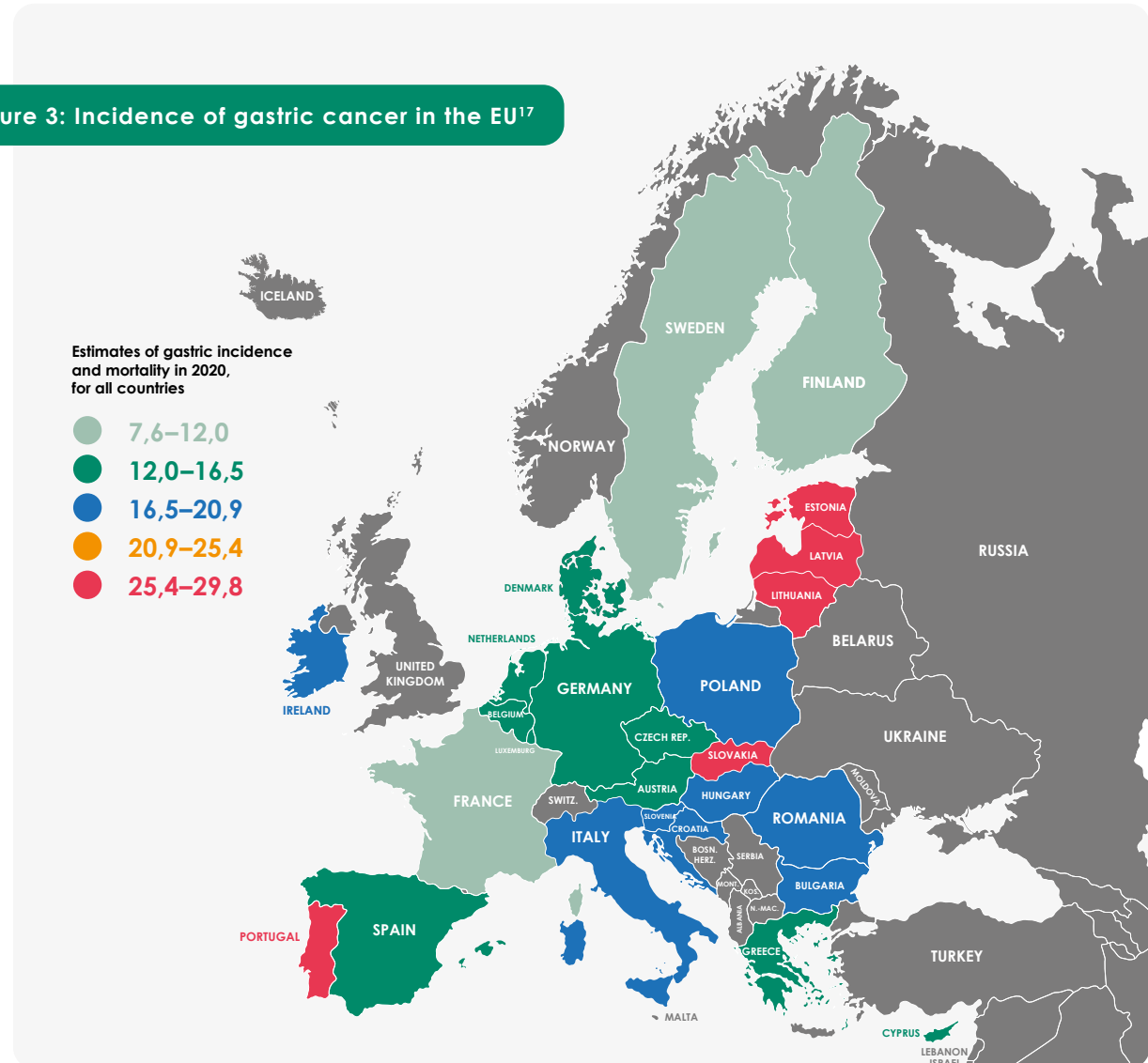




Observation: The high levels of gastric cancer in the Baltic countries are the result of high prevalence of *Helicobacter pylori* bacteria (*H. pylori*) and lower preventive measures compared to the rest of Europe.¹⁸ The high levels of oesophageal and gastric cancer in Ireland and Netherlands are attributed to an increase of the adenocarcinoma type, which is associated with a high BMI and an increase in reflux.¹³

With the exception of some specific and very common risk factors (e.g. gastroesophageal reflux disease for oesophageal cancer and *H. pylori* infection for gastric cancer), both cancers have similar risk factors and, consequently, similar geographical incidence.

Figure 3: Incidence of gastric cancer in the EU¹⁷



Prevention & early diagnosis

Risk factors

Oesophageal cancer

There are two types of oesophageal cancers: squamous cell carcinoma (SCC), which occurs in the upper part of the oesophagus, and adenocarcinoma (AC) which occurs at the junction of the oesophagus and the stomach. Squamous cell carcinoma is the most common type, accounting for 88% of cases.²⁰ It is slowly declining, probably due to dietary improvements and declines in cigarette consumption. The prevalence of adenocarcinoma is however increasing in developed countries, possibly because of increased obesity, gastro-oesophageal reflux disease (GORD) and chronic infections.

Risk factors for squamous cell carcinoma (SCC) are:

- Smoking
- Human papilloma virus (causing between 12% and 39% of squamous cell carcinoma²²)
- Oesophageal achalasia: a condition whereby the lower oesophageal sphincter fails to relax, and food is retained in the oesophagus. This condition is responsible for a 16–28% increased risk of squamous cell carcinoma²¹

Risk factors for oesophageal adenocarcinoma are:

- Gastro-oesophageal reflux disease (GORD): stomach acid damaging the lining of the oesophagus increases the risk of adenocarcinoma. In Europe, 15,2% of the population has weekly symptoms of GORD.²³
- Barrett oesophagus: it is the advanced condition for acid reflux disease, an intermediate stage between GORD and oesophageal adenocarcinoma

Common risk factors for both types of oesophageal cancer:

- Obesity
- Alcohol consumption
- Previous surgery or health conditions can hinder the patient's capacity to digest food properly or absorb certain vitamins such as pernicious anaemia, or achlorhydria

Gastric Cancer

There are two types of gastric cancer: the **non-cardia gastric cancer**, or distal gastric cancer (arising in the two lower parts of the stomach) and cancer of the **gastric cardia**, which arises at the top part of the stomach, in the area where the oesophagus joins the stomach (gastro-oesophageal junction – GOJ); 90% of gastric cancers are adenocarcinomas.^{11,24} The remaining 10% represent different uncommon types of gastric cancer.

The non-cardia cancer is more common than the cardia cancer globally, with a higher prevalence in Asia,²⁰ but its rates have been steadily declining in the last 50 years.²⁵ This can be attributed to improvements in the preservation and storage of food and decreased prevalence of *H. pylori*.

Risk factors for gastric cancer are (in order of importance):

- *H. pylori* bacterial infections - approximately 90% of new cases of non-cardia gastric cancer are caused by bacterial infections,²⁵ which prevail overall in 50% of the global population, in particular in developing countries. The bacteria are contagious and often transmitted to close family members. The remaining factors (below) account for less than 10%.
- Salted, smoked, pickled food
- Alcohol consumption
- Age/gender/race
- Industrial chemical exposure (people exposed to dusty and high-temperature environments in their daily life)
- Genetics: family inherited diseases or disorders are known to increase the risk of gastric cancer. These include Tylosis A and Plummer Vinson syndrome, hereditary diffuse gastric cancer (caused by *CDH1* genetic mutation), Lynch syndrome, hereditary breast and ovarian cancer (HBOC), and familial adenomatous polyposis (FAP)

Gastric cardia cancer has, however, similar characteristics to oesophageal cancer (in particular, adenocarcinoma),²⁵ and its risk factors also include:

- Obesity
- Gastroesophageal reflux
- Barrett's oesophagus

For both gastric and oesophageal cancers, the combination of these risk factors increases the chance of developing the cancers.

Moreover, increasing evidence points to healthy lifestyle habits reducing the prevalence of both gastric and oesophageal cancers. Notably, limiting the consumption of food preserved by salting and grilled, barbecued or processed meat increases the risks.^{20,21}

Symptoms

The progression of both oesophageal and gastric cancers usually takes several years, and symptoms remain rather mild, sometimes even unnoticeable, until the disease is advanced. For oesophageal cancer, symptoms are even less noticeable, and can be easily confused with general digestive problems, viruses or ulcers.

For **oesophageal cancer**, these symptoms include:

- Pressure or burning in the chest
- Indigestion
- Acid reflux, indigestion or heartburn (gastro-oesophageal reflux disease – GORD)
- Vomiting
- Frequent choking on food
- Unexplained weight loss
- Coughing or hoarseness
- Difficulty/pain with swallowing
- Pain behind the breastbone or in the throat?
- Dysphagia (sensation of food getting stuck in the throat while eating, problems swallowing certain foods or liquids)

For **gastric cancer**, symptoms include:

- Dyspepsia, a condition which includes various types of digestive problems
 - Indigestion or heartburn
 - Pain or discomfort in the abdomen
 - Nausea and vomiting, particularly vomiting up solid food shortly after eating
- Bloating of the stomach after meals
- Loss of appetite
- Weakness and fatigue
- Vomiting with or without blood or having blood in the stool

According to the results of a recent European patient survey led by Digestive Cancers Europe, the five most common symptoms patients with oesophageal and gastric cancer experienced prior to diagnosis were indigestion and gastric discomfort, gastric pains, trouble swallowing, weight loss for no known reason and acid reflux.²⁶

Prevention & early diagnosis

Systematic screening of the population is not realistic nor feasible; it would not be sustainable for healthcare systems as risk factors are too numerous and currently there is no reliable diagnostic test available.

There are, however, two ways of efficiently preventing the appearance of these cancers or diagnosing them early:

- **Primary prevention:** this consists of identifying, treating or removing the common **risk factors** of the disease.
- **Secondary prevention:** this consists of the regular surveillance of the **early symptoms** of the disease.

Primary prevention of oesophageal and gastric cancer:

Oesophageal cancer

Primary prevention of oesophageal cancer essentially consists of treating patients with gastro-oesophageal reflux disease (GORD). GORD is often felt like a mild and common symptom and many don't see it as a reason to consult a doctor. For example, several weeks of continuous indigestion or heartburn is an appropriate time for people to visit their doctor.

Gastric cancer

Since the most common risk factor of gastric cancer is *H. pylori* bacterial infection, the best way of reducing the incidence and burden of gastric cancer is decreasing the transmission and eradicating this bacterium. This can be done by ensur-

ing that the infection is treated as early possible, leading to a reduction in its prevalence. As was rightly mentioned in the EU Beating Cancer Plan,³ treating *H. pylori* as a means to prevent gastric cancer should be a priority. Eradicating *H. pylori* bacterial infection as a strategy for preventing gastric cancer is also recommended by the International Agency for Research on Cancer (IARC)'s *H. pylori* Working Group,²⁷ the Maastricht V Guidelines on the Management of *H. pylori* infection²⁸ and the Taipei Consensus on screening and eradication of *H. pylori* for gastric cancer prevention.²⁹

Educating about the other risk factors of oesophageal and gastric cancer and promoting a healthy lifestyle should also be part of the optimal prevention strategy.



Secondary prevention of oesophageal and gastric cancer:



Secondary prevention strategies for oesophageal and gastric cancer consist of screening for and surveillance of precancerous lesions as well as screening for early gastric cancer.

There are important distinctions between precancerous lesions in oesophageal and gastric cancer.

For oesophageal cancer, precancerous lesions take the form of a conditions called Barrett's oesophagus in which the lining of the swallowing tube (oesophagus) that connects the mouth to the stomach becomes damaged by acid reflux, which causes the lining to thicken and become red. It can be caused by untreated gastro-oesophageal reflux disease (GORD).

For gastric cancer, defined precancerous lesions are clearly defined in current guidelines and include: atrophic gastritis, intestinal metaplasia, dysplasia (low, high-grade or indefinite).

Such precancerous medical conditions need to be checked regularly, notably with endoscopic surveillance. The optimal approach to the surveillance and treatment of these lesions and the strategy for the people at risk (1st degree relatives, people with genetic predispositions) should follow the European Society for Gastrointestinal Endoscopy (ESGE)'s MAPS II guidelines³⁰ and ESMO's clinical practice guidelines on diagnosis, treatment and follow-up for Hereditary Gastrointestinal Cancers.³¹

The importance of timing

Primary prevention of oesophageal and gastric cancer consists of educating citizens and primary care professionals about the most common risk factors and early symptoms of gastric cancer and ensuring they are addressed quickly. This requires timely intervention both by the patient (asking to see a doctor) and of the primary care professional (identifying and treating the risk factors in a timely manner).

Primary care professionals (general practitioners/family doctors) are indeed the first to intervene. Their intervention can be two- fold:

- **Treating the symptoms**
 - Oesophageal cancer: for instance, prescribing, proton-pump inhibitors-PPI- for GORD
 - Gastric cancer: prescribing antibiotics to treat *H. pylori* infections
- **Referring to a gastroenterologist/specialist** for a proper diagnosis
 - For oesophageal cancer: if GORD persists, or if the presence of other symptoms of oesophageal cancer are identified
 - For gastric cancer: if the presence of other symptoms of gastric cancer are identified or if any **of the genetic/family history or preconditions** are identified, which can predispose the patient to develop gastric cancer (for instance, if the patient has tested positive to the *CDH1* mutation)

Secondary prevention requires consistent and regular surveillance and follow-up of patients with existing precancerous lesions. This surveillance is in the hands of medical experts, mainly gastroenterologists.

Once the patient has been referred to a gastroenterologist, he will undergo a series of initial diagnostic tests (explained in further details in the next section), which will determine if the patient is at risk of developing a cancer or if a tu-



mour has already developed. Timely intervention by the primary care professional or family doctor is critical. Late **diagnosis means a delay in the patient's access to treatment, which can worsen his prognosis.** A misdiagnosis or failure to refer to a specialist can also defer the time of diagnosis. The timing for the patient's decision to consult his family doctor is also key.

Unfortunately, such issues are **very common across Europe.** In a recent survey undertaken by the Royal College of Surgeons among gastric and oesophageal cancer patients, it was found that 60% of patients received the start of their curative treatment after more than 62 days from referral, the target time for referral to treatment in the UK.¹⁴ The same survey showed that out of all the patients who were diagnosed with gastric or oesophageal cancer, 11% of patients with oesophageal cancer and 19% of patients with gastric cancer were diagnosed after emergency admissions.¹⁴ It has also been demonstrated that patients who are diagnosed after an emergency admission to a hospital often have advanced disease, and therefore, are less likely to be candidates for curative treatments.³²

According to the results of a recent European patient survey led by Digestive Cancers Europe, although a 59% of patients with oesophageal or gastric cancer were very satisfied or quite satisfied with the time it took to receive a cancer diagnosis, 36% of the patients were not very satisfied with this time. Importantly, 14% of the patients were very dissatisfied with the time to diagnosis, highlighting patients' unmet need for prompt diagnosis. In addition, 41% of respondents were initially misdiagnosed with another condition such as irritable bowel syndrome, bloating, jaundice, excessive fatigue, etc.²⁶



The patient

Patients have the most acute sense of what is happening in their body and may have the feeling that something is not right. They are entitled to request a consultation or a follow-up should they feel any discomfort or have any doubts about their well-being and can demand a referral or a **second opinion** should they feel more needs to be done.

Therefore, a reliable, transparent and trustworthy relationship between the patient and his/her general practitioner (family doctor) is important.

If the patient has a family history or genetic predisposition to cancer, s/he should ask for a referral to a **geneticist**, in addition to the gastroenterologist, to ask about the risks.

Behavioural change is necessary. Citizens should be empowered and informed about optimising their health and understanding risk factors. This information should be made available to the population systematically via targeted information campaigns and empowered primary care professionals.

Recommendations

- With the support of patient organisations, invest in and develop **innovative education campaign models at national level to empower the population to be in control of its own health** and reduce cancer risk factors related to these two cancers by prompting behavioural change towards healthy and active living
- Empower and **inform family doctors and primary care professionals about the risk factors and the symptoms** of oesophageal and gastric cancer and the importance of timely referral to experts, with the objective of improving the progression of patients from referral through to diagnosis and treatment
- Ensure the **harmonisation and application of primary preventive measures** to help reduce the main risk factors of oesophageal and gastric cancers, in line with ESGE's MAPS II guidelines³⁰ and ESMO's clinical practice guidelines³¹:
 - For oesophageal cancer: the early identification and treatment of Gastro-oesophageal reflux disease (GORD) and the promotion of a healthy lifestyle
 - For gastric cancer: the early identification and treatment of *H. pylori* bacterial infection and the promotion of a healthy lifestyle
- Ensure the **harmonisation and application of secondary preventive measures** in line with ESGE's MAPS II guidelines, which would allow the systematic surveillance and screening of pre-cancer medical lesions and conditions specific to each cancer
- Use **population-based cancer registries** as a key policy tool to evaluate the effectiveness and impact of cancer prevention strategies

Diagnostics ●

Diagnostic tools

There are testing tools to identify certain early symptoms and precancerous lesions of gastric and oesophageal cancers, which include:

- **Endoscopy with biopsy** (or upper endoscopy): a thin, flexible tube with a light and a video camera on the end entered through the mouth, which allows to see the lining of the oesophagus. This is the most common test undertaken at early stages in patients suffering from any recurring symptoms. During the endoscopy, biopsies (samples of abnormal looking areas) are undertaken to analyse if they are cancerous.
- **Breath tests, stool tests, and in exceptional cases, blood tests** that can identify *H. pylori* bacterial infections for gastric cancer
- **Symptom-based evaluation** of gastro-oesophageal reflux disease (GORD)
- **24-hour pH monitoring, optimally – in combination with impedance measurement**, to confirm gastro-oesophageal reflux disease (GORD) if symptoms are not convincing. This is usually undertaken when the patient does not respond to the initial treatment of proton-pump inhibitors-PPI and when nothing is found during an endoscopy. A thin tube which contains a sensor is passed up through the nose down the oesophagus and measures acidity level (pH).
- **Non-invasive pepsinogen testing** for gastric precancerous lesions

The other common, yet more invasive diagnostic tools, which allow for imaging tests include:

- **Bronchoscopy**: a thin, flexible tube with a light and a video camera on the end entered through the nose or mouth, which allows to see the lining of the oesophagus. This is an alternative to endoscopy if the tumour is located higher up in the oesophagus and may have grown towards the airways.
- **Computed Tomography (CT) scan, Barium swallow, Magnetic Resonance Imaging (MRI) or Positron Emission Tomography and Computed Tomography (PET-CT) Scan**: these are various imaging techniques which allow to get a clear picture of what is happening inside the organs and tissues.
- **Laparoscopy**: the surgeon inserts a thin, flexible tube called a laparoscope into the abdominal cavity. It is undertaken specifically if there is a suspicion of gastric cancer which may have spread to the lining of the abdominal cavity or the liver.
- **Molecular testing**: If cancerous cells have been found in the biopsies, molecular testing of the tumour is recommended. These are laboratory tests, which help to determine the specificity of the cancer, and are key in determining the types of cancer and treatment options. They can even predict the potential development of an aggressive cancer in basic lesions such as gastric dysplasia.





Staging

A multidisciplinary team will interpret the results of all the diagnostic tests undertaken and will determine the type of cancer, where it is located and how fast it is spreading, as precisely as possible. This is called staging. The highest possible degree of accuracy of the staging should always be ensured³³; this allows to determine the prognosis and treatment options.

There are different stage descriptions for each type of cancer, but the staging system always combines information about the tumour (T), the nodes (N), and the level of metastasis (M). It is called the TNM staging system.⁹ There are usually

four stages (stages I-IV), with substages (such as IIB or IIIA); stage I is the first (earliest) stage, when the cancer is localised and only found in the lining tissues; and stage IV is the most advanced stage, when the cancer has spread to outer parts of the body and/or the lymph nodes. The grade (G) is an additional parameter used by doctors to determine how healthy the cancer cells look. Under the microscope, normal cells look uniform, with similar sizes and orderly organisation. Cancer cells look less orderly and with varying sizes.

For oesophageal cancer, the TNM system and G grades are used for staging adenocarcinomas; for squamous cell carcinoma, G grade is

combined with a staging system which specifies where the tumour is located in the oesophagus. For stomach cancer, the TNM system is used. A CT scan of the neck, chest and abdomen is usually the first test that is undertaken to define the stage, size and location of the tumour once cancerous cells have been found in the biopsies.

Staging is usually done at each stage of the treatment process: first at diagnosis, then after each step of the treatment, which can be once perioperative chemotherapy or radiotherapy has been done. This is called restaging. It allows to establish the effectiveness of the treatment on the cancer and adapt future interventions.

Expertise

High-quality, up-to-date materials and medical expertise are the two important prerequisites for an accurate and precise diagnosis and for establishing the treatment pathway.

The above diagnostic tools should be handled by clinical experts (gastroenterologists), and laboratory tests (biopsies, molecular tests and clinical results) should be analysed by a multidisciplinary expert team, which should include a pathologist, a radio-oncologist and a gastroenterologist. The team should be involved in the diagnosis and at every restaging exercise.

Expert centres specialised in digestive cancers provide expertise and a multidisciplinary approach, allowing for timely and accurate diagnosis and intervention.

The patient

Undergoing testing can be emotionally difficult for patients, and medical expertise is a critical element for them to feel secure as they embark on their medical journey, and for optimising health outcomes.

The patient can, therefore, request to be diagnosed in an **expert centre** and choose his medical team for the diagnosis and follow-up. He is entitled to question his diagnosis and treatment options and ask for a second opinion. It is in fact recommended by the Royal College of Surgeons of England for patients to gather a second opinion when receiving a diagnosis, such as a dysplasia, which can be interpreted subjectively.³²

Patient organisations are an especially useful platform for patients to ask questions and recommendations.

Recommendations

- With the support of patient organisations, promote the development of **information campaigns** about patients' rights to request a timely diagnosis and referral for oesophageal and gastric cancer, a second opinion and his preferred treatment centre
- Promote the **application of harmonised guidelines** for timely diagnosis of gastric and oesophageal cancer using European best practices
- Promote the systematic referral to **multidisciplinary expert centres where medical expertise and high-quality materials are optimal** for timely and accurate diagnosis of oesophageal and gastric cancer
- Promote the **surveillance of patients with precancerous lesions** as indicated by European guidelines

Treatment ●

Standard procedures

Oesophageal and gastric cancers are treated with medication aimed to destroy cancer cells and strengthen the body's immune system.

The treatment options are decided upon via shared decision-making between the multidisciplinary medical team and the patient, and depend on the stage and type of cancer.

The types of systemic therapies used for oesophageal and gastric cancer include:

- **Chemotherapy:** Drugs which destroy cancer cells, usually by keeping the cancer cells from growing, dividing, and making more cells.
- **Radiotherapy:** High-energy X-rays or other particles to destroy cancer cells usually provided by a radiation oncologist. Radiation therapy can be either external (external-beam radiation therapy-EBRT) or internal (brachytherapy).
- **Targeted therapies:** Treatment that targets the cancer's specific genes, proteins, or the tissue environment and contributes to cancer growth and survival. This type of treatment blocks the growth and spread of cancer cells, while limiting damage to healthy cells. It can be determined by the genes, proteins, and other factors in the tumour, some of which are identified by molecular testing performed on tissue from biopsies.

Targeted therapies include:

- HER2-targeted therapies
- Anti-angiogenesis therapies
- TRK-targeted therapies

It is essential that the molecular profile of patients with gastric cancer is examined at the appropriate cancer stage to determine whether HER2- or TRK-targeted treatments can be used as treatment options.

- **Immunotherapy:** Drugs designed to boost the body's natural defences to fight the cancer. Immunotherapy aims to improve, target, or restore immune system function. It is usually used for advanced types of cancer.

Radiation, chemotherapy and surgery are often combined, and the order varies. Very early-stage cancers can sometimes be treated with only chemoradiotherapy (term used for the treatment that combines chemotherapy and radiotherapy). These medications can be given before and after surgery (peri-operative chemotherapy), after surgery (adjuvant chemotherapy), or without surgery if the cancer is not operable or if surgery is not considered an option by the medical team or the patient. Preoperative treatment with chemotherapy or chemoradiotherapy increases the possibility of removing the tumour successfully, and therefore, improves overall survival rates.³³



Chemotherapy and radiotherapy may also be used as a **palliative care** option for patients whose cancer has spread to other organs, as a means to extend their prognosis and improve their quality of life.

Treatment availability

Currently, there are 21 drugs available for gastric and oesophageal cancer combined in Europe. Since the first biosimilar for trastuzumab - used in HER2-targeted therapy - gained market access in 2017, new opportunities for a wider access to biologic treatments across Europe have become available. Trastuzumab (Herceptin®) is the only HER2-targeted therapy, which has been approved by both the Food and Drug Administration (FDA) in the US and the European Medicines Agency (EMA) in Europe, while five trastuzumab biosimilars have already been approved by EMA (Ontruzant™; Kanjinty™; Trazimera™; Ogivry™; Zerceptac™). Recently, trastuzumab deruxtecan (Enhertu®) has been approved by the FDA for gastric cancer (as of January 2021).

Ramucirumab (Cyramza®) is an anti-angiogenesis therapy approved by both the FDA and EMA. There are two types of targeted therapy treat-

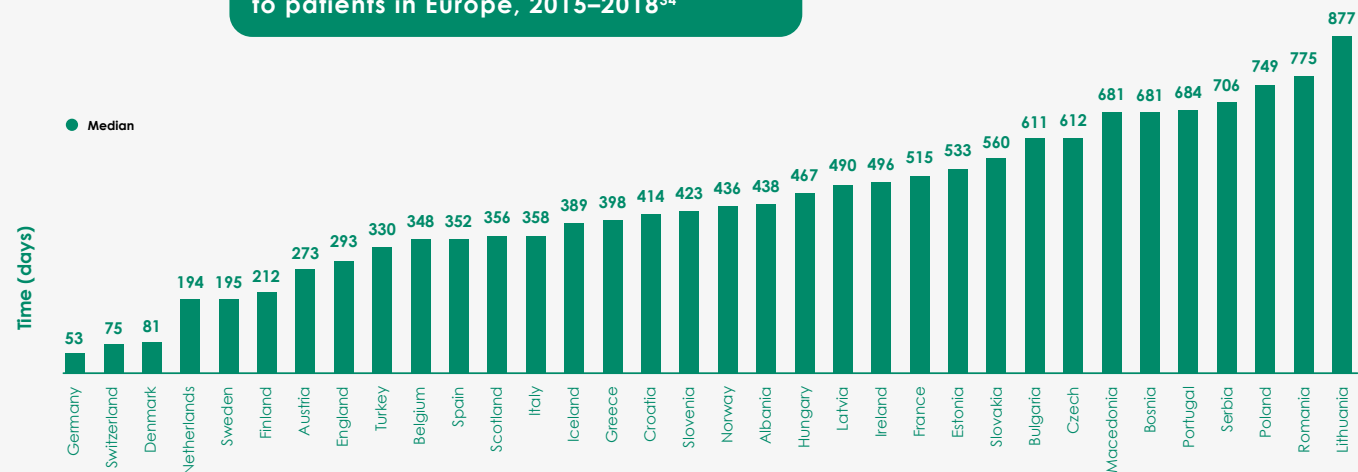
ments approved in the US and in Europe designed only for patients whose tumours have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion: entrectinib (Rozlytrek®) and larotrectinib (Vitrakvi®).

As mentioned above, these treatments may benefit patients with specific molecular profiles; thus, in addition to these treatments being reimbursed, it is essential that the required molecular testing is also available and reimbursed at national level.

There are two immunotherapy treatments available in the US: pembrolizumab (Keytruda®), available since 2017, and nivolumab (Opdivo®), available since 2020. In Europe, nivolumab is the only availa-

ble immunotherapy drug since December 2020. Most importantly, **patient access to the latest medicines is essential** and should not be conditional to a country's lengthier administrative process. Yet, time to availability of some oncological medicines varies tremendously from one country to another. Indeed, once the EMA and the European Commission have approved a drug, it can take up to several years for it to become available for patients in some European countries. The best practice is observed in Germany, where drugs become available immediately after approval, and pricing and reimbursement take place after market entry.³⁴

Figure 4: Time to availability of medicines to patients in Europe, 2015–2018³⁴





Treatment side effects

In addition to the strong side effects of surgery, cancer treatments alone can have important side effects.

Side effects from radiation therapy may include fatigue, mild skin reactions, soreness in the throat and oesophagus, difficulty or pain when swallowing, upset stomach, nausea, and diarrhoea.

The side effects of chemotherapy depend on the individual and the dose used, but they can include fatigue, risk of infection, loss of appetite, joint pain, shortness of breath, nausea and vomiting, hair loss, loss of appetite, and diarrhoea.

The side effects of targeted therapies are different depending on the drug and not everyone experiences all side effects. Some of the common side effects of targeted therapies for oesophageal and gastric cancer include allergic reactions, diarrhoea, fatigue, flu-like symptoms including fever, muscle aches and sickness and low blood counts. Trastuzumab can cause some damage to the heart and regular checks are needed for monitoring heart function.³⁵

Different types of immunotherapies can cause different side effects. Some of the common side effects of pembrolizumab include skin problems, diarrhoea or constipation, fatigue, feeling or being sick, breathlessness, low levels of thyroid hormones, headaches and pain, while those of nivolumab include increased risk of infection, skin problems, diarrhoea, fatigue, changes in blood sugar levels, feeling sick, and changes to blood counts.³⁵

Expertise



Similar to surgery, administering cancer treatments and radiotherapy requires a high level of expertise and should be the result of a multidisciplinary decision which includes the patient. Such expertise is guaranteed in a specialised **Comprehensive Cancer Care Network (CCCN) model**.

The patient

The patient should be allowed and encouraged to discuss and question the recommended course of treatment proposed by his medical team. Any side effects or reactions should be reported by the patient and a continuous follow-up plan should be in place so that these symptoms and side effects are part of the patient's cancer care plan.

The patient should be informed about all available treatments and any clinical trials that he can take part in.

Recommendations

- Encourage the **development of the Comprehensive Cancer Care Network (CCCN) model** where multidisciplinary care management, shared decision-making and 360-degree patient support are ensured
- Recommend the **inclusion of** nutritional and health fitness assessment and support in every aspect of oesophageal and gastric cancer patient care, before the start of the treatment and in support of the short- and long-term side effects from treatment
- **Empower patient organisations in informing and supporting patients about their right** to choose their medical centre, medical team and treatment pathway and take part in the shared decision-making process
- Optimise **patient access to medicines after EMA authorisation** using European best practices. The use of EMA-approved biosimilars should be encouraged to allow more patients to have access to medicines that are critical for achieving the best possible outcomes, and to free healthcare budgets for the reimbursement of additional innovative medicines for oesophageal and gastric cancer as well as for providing additional services for patients
- Ensure **molecular testing is offered and reimbursed** to all eligible patients and is performed according to high standards
- **Focus care management guidelines** protocols on the **side effects of treatment of oesophageal and gastric cancer** for improved patient quality of life and overall patient outcomes

Surgery ●

Standard procedures

Dissecting the tumour with surgery is the standard and main approach for treating oesophageal and gastric cancer. It is only possible in patients whose tumour is considered operable. As mentioned before, for advanced cancers, chemoradiotherapy or chemotherapy, or a combination of both, will be undertaken before surgery to reduce the size of the tumour (covered in the previous section on “treatment”).

The surgery consists of removing the tumour and some healthy tissue surrounding it. It is performed by a surgical oncologist who is specialised in operating on patients with these types of cancer. Depending on the size and location of the tumour, the medical team will either opt for an open surgery or for a keyhole surgery (laparoscopy). For a very early-stage cancer, an endoscopic resection, which allows to dissect neoplastic lesions “en blok” using an endoscope, can be undertaken. This is less invasive.

For oesophageal cancer, the surgery is called an **oesophagectomy**. The surgeon removes the affected parts of the oesophagus and connects it back to the stomach.

For gastric cancer, the surgery is called **gastrectomy** and consists of removing the part of the stomach affected by the cancer. If the cancer is only in the distal part of the stomach, the surgeon performs a subtotal or partial gastrectomy, where the remaining part of the stomach is re-attached to the oesophagus or small intestine. If the cancer is located in the upper part of the stomach, the surgeon will perform a total gastrectomy, removing all of the stomach and attaching the oesophagus directly to the small intestine.

Regional lymph nodes are always removed during these surgeries. This is called a lymphadenectomy. The extent and type of lymphadenectomy depends on the location of tumour and the qualification of the surgery unit.

A full functional assessment of the patient should be undertaken before surgery. This should include an assessment of the patient's symptoms, any comorbidities, his nutritional status, psychological evaluation and the patient's preferences (to be discussed further in the paper).³³

Healthy people who have a family history of oesophageal cancer or gastric cancer and have tested positively for the *CDH1* gene mutation may decide to have their oesophagus or stomach removed preventively.

Surgery side effects

Oesophagectomy and gastrectomy are **lengthy, complex surgeries** which are high-risk and potentially have serious side effects on the patient. Whilst aiming to remove the cancer, they can create lifelong medical problems and hinder the patient's quality of life.

After these surgeries, the patient's digestive system has been modified and the patient has to dramatically adjust to this new reality. The removal of his oesophagus or stomach, or parts of them, means that the patient will only be able to eat small amounts of food. Often, he will no longer feel hunger and will have to schedule to eat small meals every two hours.

Important side effects include all sorts of digestive discomforts such as Dumping syndrome, nausea, diarrhoea, cramps, dizziness. Other common issues include weight loss and vitamin/mineral deficiencies. Some of these issues are covered in more detail in the section below dedicated to nutrition.



Post-operative mortality

Unfortunately, in 30% to 50% of locally advanced cancers, a complete tumour resection cannot be achieved. Moreover, long-term survival after surgery rarely exceeds 20%.³³

In the last decade, attention has been given to the improvement of patient outcomes and recovery after surgery with the development of **ERAS protocols**. These aim to reduce the length of hospital stay, accelerate postoperative recovery and reduce the surgical stress and complications. A recent patient survey in the UK has shown that patients who were placed on an **ERAS protocol** had indeed shorter hospital stays.³² Multidisciplinary expert cancer centres are usually in line with ERAS protocol recommendations, and therefore, present more optimal perioperative results.

Palliative surgery & care

In the UK, it is reported that only 25% of patients diagnosed with oesophageal and gastric cancer undergo curative surgery. The remaining 75% undergo palliative care.³⁶

When the oesophageal or gastric cancer is too advanced and cannot be operated, some surgical options can be envisaged to simply relieve the symptoms caused by the cancer and improve the patient's quality of life. Such interventions include:

- Inserting a feeding tube, called a **gastrostomy or jejunostomy**, to give the patient appropriate nutrition directly into the stomach or intestine. This is to ensure the nutritional stability of the patient and maintaining his strength and weight.
- Removing certain blockages in the oesophagus caused by the tumour using a bypass or an **oesophageal stent**. These procedures are performed when the tumour cannot be removed surgically.
- **Oesophageal dilation**: using an endoscope, the doctor can dilate parts of the oesophagus that may be constricted and cause issues when swallowing.

There are other less common non-surgical techniques, which are used for palliative care or to relieve symptoms, such as:

- **Cryotherapy**: This is a type of palliative treatment that uses an endoscope with a probe attached, which freezes and removes tumour tissue. It can be used to reduce the size of a tumour to help a patient swallow better.
- **Photodynamic therapy**: In photodynamic therapy, a light-sensitive substance called a photosensitizer is given through the vein. Then, a laser is directed at the oesophageal lesions using an endoscope. In laser surgery, a laser is used to burn the oesophageal lesions through an endoscope.
- **Laser therapy**: laser is used to burn the oesophageal lesions through an endoscope.
- **Brachytherapy**: a type of internal radiation therapy used to kill the cancer cells.^{9,11}

Expertise

In light of the complexity of these types of surgeries, skilled medical expertise is essential. All the medical experts who will take part in the treatment pathway should be highly experienced to deal with the specific cancer in question.

According to the results of a recent European patient survey led by Digestive Cancers Europe, 40% of patients with oesophageal or gastric cancer indicated that either they were not aware or that their treatment was not discussed by a multidisciplinary team.²⁶

Oesophago-gastric surgery should be concentrated in expert centres, which are able to apply European and international guidelines regarding the treatment and management of the diseases and which have sufficient expertise; the latter is usually closely related to the number of surgeries performed. Early cancer can be even managed endoscopically in expert centres. Surgery should be performed with proper extend (including the groups of lymph nodes that have to be removed) and proper histopathology reporting.

Because the aftermath of surgeries is difficult, every aspect of the patient's recovery should be included in the equation when determining his treatment pathway. To design the best treatment plan and optimise the patient recovery, survival and long-term quality of life, the **multidisciplinary team** should be composed of a:

- **Gastroenterologist – endoscopy expert**, a doctor who specialises in the gastrointestinal tract including the stomach and intestines
- **Surgeon or surgical oncologist**, a doctor who specialises in treating cancer using surgery
- **Medical oncologist**, a doctor who specialises in treating cancer with medication
- **Radiation oncologist**, a doctor who specialises in giving radiation therapy to treat cancer
- **Pathologist**, a doctor who specialises in interpreting laboratory tests and evaluating cells, tissues, and organs to diagnose disease
- **Radiologist**, a medical doctor who specialises in using imaging tests to diagnose a disease
- **Dietitian**, an expert in nutrition who will help to assess and optimise the patient's physical and nutritional status

- **Specialist nurse**
- **Endocrinologist**, a doctor who specialises in hormonal imbalances

In best practice countries or regions, there are dedicated, cancer-specific expert centres which follow the Comprehensive Cancer Care Network (CCCN) **model**, where such medical expertise is ensured, and multidisciplinary teams are set-up for each patient. CCCNs see a **higher volume** of patients, which gives them expertise and perspective.

It has also been demonstrated that lower hospital volume is associated with higher post-operative mortality after cancer resection. For gastric and oesophageal cancer, surgeries are complex and high-risk; therefore, the experience and performance gained through experience and practice in higher volume hospitals allows for better patient outcomes.^{37,38} The results of a large European multicentre study demonstrated that high-volume centres had a lower rate of morbidity and better infrastructure to deal with complications following major surgery preventing further mortality.³⁹

In Belgium, the Netherlands and Sweden, hospital outcomes data show that patients have a significant higher risk to die in the low volume hospitals compared with high volume ones, with a factor of 10, 13 and 20, respectively.⁴⁰⁻⁴² Moreover, as stated in the European Cancer Organisation's Essential Requirements for Quality Cancer Care: Oesophageal and Gastric Cancer, complex surgeries, such as those performed on oesophageal and gastric cancer patients, should only be performed in high-volume hospitals.³⁶

Post-operative mortality and success rates for every hospital or expert centre should be made accessible to patients. Hospitals have an obligation to report them to the national ministry. However, unsurprisingly, numerous low-volume hospitals do not provide patient statistics, and there are numerous low-volume hospitals still treating patients with gastric and oesophageal cancer and performing complex surgeries.³⁷

In Belgium, as of January 2020, only 10 hospitals are allowed to perform and treat oesophageal and gastric cancer patients, where quality care, success rate and expertise are guaranteed. In Germany, part of the National Cancer Plan is the establishment of a certification committee, which evaluates each medical centre on their ability to diagnose and treat each type of cancer. The centres which meet the requirements (including patient volume minimums) receive the accreditation of "Certified Oncology Centre" and are listed as expert centres by specific type of cancer.⁴³ These types of quality control mechanisms are best practice examples on how to ensure patients access the best possible care and should be replicated at Member State level.



The patient



The patient's voice should be central in deciding his treatment options. He should be informed about the treatment options, the recovery, the side effects, the prognosis and be given the option to question and doubt at any point. Involving the patient in the multidisciplinary discussions about his health and treatment pathway is called "shared decision-making".

The patient should also be informed about the expert medical centres which are best suited to treat him. He should be informed about the success rates of each of these centres so that he can make an informed decision on where he would like to be treated. Sometimes he may decide to travel to another part of the country.

Local patient organisations can also act as a reference point to guide the patient in his choice of hospital, medical team, treatment options and to help him prepare for the aftermath of surgery.

The patient is entitled to have a reference person to act as direct medical point of contact to accompany him and his family in his journey. This could be his family doctor, an expert nurse or the oncologist.

The full rights of cancer patients are covered in The European Cancer Organisation's Essential Requirements for Quality Cancer Care: Oesophageal and Gastric Cancer.⁴⁴

Recommendations

- Ensure that **surgery is performed in centres with sufficient expertise** and according to the current guidelines
- Ensure that the **post-operative success rates of surgeries of each hospital are systematically reported and made public** by health ministries so that patients and primary care professionals can make informed choices
- Encourage the **development of the Comprehensive Cancer Care Network (CCCN) model where multidisciplinary care management, shared decision-making and a 360-degree patient support** are ensured
- Develop and harmonise across Member States a **cancer centre accreditation system** which evaluates the expertise of each cancer centre for each type of cancer and requires a **minimum number of cancer cases** to ensure that surgeries are performed in high-volume, expert hospitals
- Harmonise **guidelines for the reporting** of survival and surgery success rates by all European hospitals to allow for a benchmarking of hospitals
- **Focus care management guidelines** (such as the use of ERAS protocols) on the **side effects and long-term effects** of surgeries, which treat oesophageal and gastric cancer for improved patient quality of life and overall patient outcomes

Research

During Horizon 2020, €72.74 million of the overall €80 billion budget were allocated to all digestive cancers. Although the exact amount of budget research allocation for oesophageal and gastric cancers specifically is not clear, research on oesophageal and gastric cancers needs to be prioritised similar to other types of digestive cancers; the overall survival and quality of life of patients with these cancers in Europe could improve if all aspects of the patient journey were investigated in a more systematic and better prioritised manner. With this in mind, more studies on oesophageal and gastric cancers need to be undertaken across Europe and within different regions of the same country on a variety of topics that expand from the general biology to the, so far limited, health services research. Research into overlooked topics, such as the importance and benefits of nutrition and physical activity, should be supported as they can bring new insights into actions to improve patient outcomes and quality of life.





Clinical trials form the cornerstone of translational research. Although the total number of oncology clinical trials performed in European countries increased by 33% between 2010 and 2018, with a much greater increase in early phase trials (61% increase in phase I & II trials) than late-phase trials (7% increase in phase II–III trials), Europe is still behind than the US in terms of cancer trials. This can be linked to the lower survival of gastric & oesophageal cancer patients in late stages in Europe (10%) compared to the ones in the US (20%). In addition, the number of trials performed in different European countries varies considerably, with numbers ranging from a low of 0,14 clinical trials per 100.000 population in Albania to a high of 11,06 per 100.000 population in Belgium.⁴⁵ When it comes to oesophageal and gastric cancers, the US has the lead in the number of clinical trials compared to the number performed in Europe (Tables 2 and 3).

Table 2: Currently developed drugs (phase II & III) for gastric and oesophageal cancers

Type of digestive cancer	No of drugs in development	US	Europe	Rest of the world
Gastric	23	11 (48%)	9 (39%)	3 (13%)
Oesophageal	11	5 (42%)	6 (50%)	1 (8%)

Countries in Europe with drug development are Switzerland, France, the UK/Sweden, Spain and Germany; countries in the rest of the world include China, Japan, S. Korea and Taiwan.

Data are extracted from <https://digestivecancers.eu/pharmaceutical-treatments/>

Table 3: Number of active digestive cancer-related trials recorded in clinicaltrials.gov

Cancer type (key word used)	Total*	US	Europe	East Asia
Digestive cancers	3324	1082	835	835
Gastric cancer	897	230	154	307
Oesophageal	682	197	131	218

Numbers are captured from clinicaltrials.gov (accessed 16 December 2020; active includes recruiting and non-recruiting).



Diagnostics

As mentioned above, some advances are being made to help diagnose oesophageal and gastric cancers at earlier stages in a non-invasive way.

There are, for instance, two recent tools in development to diagnose Barrett oesophagus, oesophagitis or gastrointestinal reflux disease: the Cytosponge Cell Collection Device and the breath test. Less invasive than an endoscopy, the Cytosponge consists of a small pill swallowed by the patient, which then opens up into a small sponge and collects the cells from the oesophagus. The test can be done by a nurse or primary care professional who then sends the sample to the lab for analysis.⁴⁶ The breath test detects volatile organic compounds in the breath, a sign of Barrett oesophagus.⁴⁷

As mentioned under the section on “diagnostics”, non-invasive pepsinogen tests allow to screen for precancerous lesions related to gastric cancer, which are markers for precancerous conditions.

Although not yet widely adopted as screening methods, such tools could potentially allow mass and systematic screening of cancer and precancerous lesions that may cause cancer. They would allow to scan and promote higher surveillance of patients with a higher risk of developing these cancers. Certain molecular panels and breath testing for volatile organic compounds have shown promise in this direction.⁴⁸

Treatment

Clinical trials are underway to find better ways to reduce symptoms and side effects of current gastric cancer treatments, and hence, improve comfort and quality of life for patients.

- **Chemotherapy:** Doctors are studying combinations of different drugs, such as capecitabine (Xeloda®), cisplatin, docetaxel (Docetaxel®, Taxotere®), fluorouracil (5-FU, Efudex®), irinotecan (Camptosar®), oxaliplatin (Eloxatin®), paclitaxel, and trifluridine-tipiracil combination (Lonsurf®).
- **Targeted therapy:** Several types of targeted therapies are currently being studied, notably newer drugs that target HER2 for advanced oesophageal adenocarcinoma. Researchers are also looking at new drugs that block vascular endothelial growth factor (VEGF).
- **Immunotherapy:** New drugs and combinations that include checkpoint inhibitors continue to be studied.

Research is ongoing to find new drugs that are effective for oesophageal and gastric cancer. It is important to note that pharmaceutical treatments are still limited, especially for oesophageal cancer. This is in line with the results of a recent study on the costs of digestive cancers, which showed that the costs of drugs for oesophageal cancer constitute only 4% of all direct costs. This is much less than the drug expenditure for other types of digestive cancers, which amounts to 10% for gastric, 24% for colon and 23% for rectal cancer.²

Recommendations

- Invest in **further research** which could allow to recommend primary prevention of gastric cancer by **eradicating the *H. pylori* bacteria** on a population level
- Invest in further research which could allow **non-invasive mass screening for and surveillance of pre-cancer medical lesions** and conditions for oesophageal and gastric cancer
- Invest in more research at EU and national levels on **patient nutrition and health fitness** before, during and after treatment to help better address and fight nutritional problems, which are very common among oesophageal and gastric cancer patients
- Invest in basic research for both cancers that drives understanding into the **hereditary forms of oesophageal and gastric cancer and in biomarkers** that can be used for developing new drugs

Nutrition ●

Prevalence of nutritional problems in oesophageal and gastric cancer

Nutritional problems are prevalent in oesophageal and gastric cancer patients and include issues related to malnutrition and overnutrition. Cancer patients are the most malnourished of all patient groups.⁴⁹ Statistics from the 1990's revealed that severe malnourishment was the principal cause of death for up to 20% of cancer deaths.⁵⁰ Today, it affects 60% of patients with oesophageal or gastric cancer⁵¹ and despite its negative consequences on survival, quality of life and patient outcomes, it is often underdiagnosed. It is more frequent in older patients and those with more advanced cancers.

Nutritional issues are often already present before the patient's diagnosis, and this is due to the symptoms caused by the disease. Dysphagia, for example, is a very common mechanical cause of malnutrition. A survey undertaken on cancer patients at their first oncology visit showed that 64% of patients had already lost weight and over 40% were experiencing anorexia (loss of appetite)

before being diagnosed with cancer.⁴⁹ Patients with oesophageal cancer are in fact known to undergo weight loss for at least 3 years after their surgical intervention.⁵² The diagnosis can also result in low mood and depression in patients, further reducing their appetite.

There are three types, or three levels, of malnutrition:

- **Malnutrition:** this is a first step which includes weight loss, reduction in mass or muscle function and decreased food intake.
- **Sarcopenia:** condition where more important loss of strength and muscle mass is identified via various tests including abdominal CT scans, X-ray absorptiometry and other physical tests. The term is often used in the context of age-related inflammation. This stage results in the loss of physical function.
- **Cachexia:** extreme weight loss and loss of skeletal muscle with an inflammatory setting. The term is often used in the context of cancer-related inflammation.

Particularly in the past 10 years, an increasing number of patients also present with overnutrition (overweight and obesity) and with complex poorly controlled co-morbidities such as diabetes and heart disease.

Criteria for identifying nutritional problems in patients include for instance measuring body mass index (BMI), body proportions, food intake, biological parameters, including inflammation, C-reactive protein (CRP), mineral and vitamin deficiencies, body composition, and abdominal CT scan.^{50,51} However, malnutrition is very personal and individual and will manifest itself differently in each patient. Malnutrition assessments do not necessarily follow a standard protocol; they require a **personalised approach throughout the patient's care pathway by an expert oncology dietitian.**

Importance of nutritional assessment before, during and after treatment

Unfortunately, today, only one in three patients at risk of malnutrition receive nutritional support.⁴⁹

The high-prevalence of cancer-induced nutritional problems and its negative consequences are still taken too lightly in numerous oncology centres across Europe. This is unfortunate because malnutrition has several direct consequences on patient outcomes: it can increase the risk of complications (such as surgical site infections, reoperation, pulmonary infection), prevent the patient from receiving or recovering from his treatment or surgery, and lengthen his hospital stay. It, **therefore, reduces his chance of survival.**

A 2015 study has indeed shown that malnutrition is prevalent in gastric cancer patients, and that it increases the risk of post-operative site infections.⁵³ In fact, patients who are malnourished have a 2-to-5-fold higher risk of dying compared to those with no evidence of malnutrition.⁴⁹ Malnutrition causes death when weight loss exceeds 30–40%.⁵⁰

According to the results of a recent European patient survey led by Digestive Cancers Europe, 58% of patients with gastric or oesophageal cancer requested the support of a dietitian when asked what would help them that is not currently available in their country, which was the most common response of all.²⁶

Nutritional assessment should in fact routinely take place as part of the patient's prehabilitation for surgery and treatment and further be undertaken before each step of the treatment. Substantive research now demonstrates that a **thorough and regular nutrition and physical assessment check-up before, during and after treatment and surgery** significantly improve treatment outcomes, quality of life and overall survival.^{49–52,54} As highlighted in the European Society for Enteral and Parenteral Nutrition (ESPEN) guidelines on nutrition in cancer patients and covered in the enhanced recovery after surgery (**ERAS protocols**), supporting the patient in **strengthening his nutritional and physical state** is widely known to:

- mitigate the toxic effects of chemotherapy and support the body in coping with the inflammation which results from the surgery and treatments
- reduce the risk of infectious complications and surgical site infections
- reduce the risk of balance disorders and falls in patients
- improve postoperative mobilisation and physical functioning
- avoid any interruptions in the recommended course of treatment which can hinder patient outcomes (a great percentage of patients are not able to complete their postoperative chemotherapy regimens because of poor physical and nutritional status⁵²)

From a healthcare system perspective, ensuring malnutrition is accurately managed in all cancer patients will ultimately reduce hospital stays, in-patient costs, comorbidities and mortality rates⁴⁹ – in other words, reduce the burden on healthcare systems.

The priority for cancer patients is about optimising nutrition, not just correcting undernutrition or malnutrition.

Nutrition problems caused by cancer treatments

As covered in a previous section, surgery and treatment for oesophageal and gastric cancer cause a number of physical discomforts for the patient, which can last for months, or years, sometimes causing lifelong issues for patients. Common problems which can impede on the patient's nutrition include:

- **changes in bowel habits**
- **early satiety and lack of hunger**
- **pain and obstructions**
- **acid reflux**
- **dysphagia**
- **malabsorption of nutrients and minerals leading to deficiencies**
- **obligation to eat small portions of food at regular times**
- **hypoglycaemia and Dumping syndrome**
- **bacterial overgrowth in the small intestine**
- **bloating and diarrhoea**

Chemotherapy and radiotherapy can also induce more immediate nutrition-related discomforts, as mentioned in the previous section on treatment side effects.



The role of the dietitian

Access to specialist dietetic support varies and is quite limited across Europe despite its critical role.

Nutritional assessments and nutritional support play a central role when designing the patient care pathway. Oncologists should defer to the nutritional specialist to design an optimised treatment course, which includes nutritional support.

In best practice scenarios, the **dietitian should intervene at every stage** of the patient journey, supporting them through the **complete change in lifestyle, which treatment for oesophageal and gastric cancer often requires**. Patients need to be informed about new feeding requirements and ways to optimise their recovery and quality of life.

The dietitian may also help **identify discomforts, which may require surgical or medical interventions**, and refer the patient to the right medical expert if required (surgeon, gastroenterologist, endocrinologist, etc.).

For example, s/he may suggest the use of a feeding tube (enteral feeding), which is often seen as beneficial to help secure nutrients for the patients right after surgery, ensure a quick recovery and remove some of the pressure the patient may feel to eat.⁵⁵

The dietitian, with the support of a physical therapist, who helps injured or ill people improve movement and manage physical pain, also plays a critical role in encouraging the patient to commit to an active and healthy lifestyle after cancer to sustain and improve his quality of life.

Dietitians often act as a reference point of contact in the patient's daily life. As opposed to surgeons who tend to focus on shorter term outcomes (success of surgery), the dietitian focuses on the patient's longer-term objectives and quality of life. He should be an **integral part of the multidisciplinary team in charge of the patient**, a model which is proposed in a number of expert centres in Europe, notably the **Comprehensive Cancer Care Network (CCCN)** model.

Recommendations

- Promote the **implementation of specific nutritional protocols** for oesophageal and gastric cancer, which include early assessment of patient nutritional status at cancer diagnosis and the ensured provision of nutritional support prior, during and after each treatment stage, in line with ESPEN guidelines and **ERAS protocols**
- Ensure a **specialist dietitian is included in the shared decision-making process** for patient care and is available to support the patient before, during and after treatment
- **Harmonise guidelines on the use of nutrition support** to improve patient recovery time and overall nutritional outcomes for patients treated for oesophageal or gastric cancer
- Invest in more **research at EU and national level on patient nutrition** before, during and after treatment to help better address and fight malnutrition in cancer patients
- Recommend **nutritional assessment** as a prerequisite before the start of treatment for oesophageal and gastric cancer
- **Empower patient organisations** in guiding and supporting patients about nutrition before, during and after treatment
- Focus medical research on **nutrition-related side effects** of gastro-oesophageal cancer

Mental health

Once the diagnosis has been given, the emotional impact on a patient and his or her family is strong. The diagnosis is disruptive to a patient's life. Everything changes, all perspectives, all plans. It weighs on self-image and relational aspects. It has often financial consequences that make the situation even worse.

Cancer diagnosis means patients, families and caregivers deal with their new roles and issues which may come with it:

- Understand the disease and its symptoms and side effects
- Talking with the healthcare team
- Giving medications and providing practical care on a daily basis
- Coordinating medical appointments
- Providing a ride to and from appointments
- Assisting with meals

A substantial number of cancer patients and survivors experience high levels of cancer-related distress. A survey conducted on 4000 cancer patients by All.Can indicated that 69% of respondents needed psychosocial support during or after their cancer care. However, 34% of those said this support was not available. The survey also indicated that cancer not only had an impact on the patients but also on their families, and that psychological support should be available to them as well.⁵⁶

Cancer patients may develop more serious mental health problems such as adjustment disorders, anxiety and depression and these conditions negatively impact on clinical outcomes such as treatment compliance, survival and quality of life and require specialised psychosocial care. Psychosocial problems



also affect the patient's family with a resultant increase in the emotional distress among the patient's caregivers that may continue into the bereavement period with greater risk of complicated or traumatic grief among relatives. Patients' and their families' supportive care needs must be a central component of quality comprehensive cancer care.⁵⁷ Psychosocial oncology care contributes to better clinical outcomes and patients' well-being, and even improves overall patient survival.⁵⁷

According to the results of a recent European patient survey led by Digestive Cancers Europe, 45% of patients with gastric or oesophageal cancer requested the support of a psychologist when asked what would help them that is not currently available in their country.²⁶

Evidence-based psychosocial interventions

Despite the major implications of psychosocial morbidity for clinical care, psychosocial issues in cancer are still all too often dismissed or underestimated, and not yet regularly offered to cancer patients. Methods for assessing distress and psychological morbidity in cancer patients are often not routinely employed in cancer settings.⁵⁷

In 2014, the International Psycho-Oncology Society (IPOS) proposed a new international standard of quality cancer care,⁵⁸ which states:

- **Psychosocial cancer care should be recognised as a universal human right**
- **Distress should be routinely measured as the 6th vital sign (alongside temperature, blood pressure, pulse, respiratory rate, and pain)**
- **Quality cancer care must integrate the psychosocial domain into routine care⁵⁷**

A wide range of psycho-oncology approaches and treatments, such as educational and psychological support interventions, counselling, coping skills and psychotherapy (individual, group or family), can be employed.

Psychological distress in cancer patients should be routinely assessed as part of their prehabilitation to the surgery and treatment. 'Prehabilitation' is the process of ensuring the patient is in optimal shape to undergo surgery or receive treatment, both physically and mentally. The allocation of specialised healthcare professionals in psycho-oncology for these services and a budget for its sustainability will be the best way to ensure service provision and quality of services.

Survivorship

Survivorship is a very complicated part of having cancer. Every patient who survives from cancer experiences it differently. Survivors may undergo a mixture of feelings, which includes joy, anxiety, relief, guilt, and fear. Some feel grateful to have survived, others become anxious about their health.

Daily life may become even more difficult as the support they receive fades down and they must face the worries **and challenges of life after cancer** (fear of recurrence, sexual health and fertility concerns, and financial and workplace issues).

It is, therefore, even more important that patients receive support as survivors, once they are no longer cancer patients per se. It is a time when counselling and psychosocial support will also be of great help.

Recommendations

- Promote the **assessment of distress and psychological morbidity** specific to oesophageal and gastric cancer patients and provide psychological interventions when needed, as part of the patient's routine prehabilitation to treatment and surgery and at each step of the patient pathway
- **Include psycho-oncology services in the standard care services** in all national cancer care facilities
- **Include psychological support solutions** to help patients face the challenges which arise with survivorship in patient care guidelines

Quality of life ●

Patient and family support



Life with and after oesophageal or gastric cancer requires changes and adaptations in all areas of the patient's life, such as: nutrition, pain and comorbidities, hormonal imbalance, admin & work and family-related issues. These changes can negatively impact the patient's quality of life, and psychosocial support for the patient and his family is essential.

Another important aspect for which patients and families require support is the **administrative and financial one**. Cancer treatments are expensive, and the number of medical appointments and hospitalisations may require the patient and his family members to be absent from work for a certain period of time. Child care, insurance and bills also become an issue for families dealing with cancer.

Talking about these issues is just as important as talking about the medical treatment. Families and patients can address these issues to their main point of contact within their medical team, to the **specialist nurse, or social worker**.

Patient support groups are also a vital source of support and information for patients and families. They offer support, perspective, preparation

and advice in all aspects of the patient journey, which can help patients and carers tremendously, and prevent them from feeling lost and isolated.

Patient to patient and patient organisation support are important and can work in collaboration with healthcare professionals to help give the support needed emotionally as well as answering questions the healthcare professionals cannot or have time for.

Recommendations

- **Patient and family support during and after treatment should be offered systematically** as part of the patient care plan, with a recommended access to a dietitian, psycho-oncologist, social worker and local patient group
- **Pain management** should be included in all cancer management guidelines to ensure optimal quality of life for the patient and his family
- **Patient organisations should be involved in the shaping of new healthcare policies** to provide the patient perspective and help determine healthcare priorities with national governments, aiming at improving patients' quality of life



End-of-life ●

From palliative care to end-of-life, these important decisions belong to the patient and his family. When cancer is not curable, the patient is faced with choices about his palliative care options, which he should discuss with his medical team, family and caregivers.

As mentioned in this document, there are a number of options (surgical and non-surgical) which can relieve the patient of his symptoms, especially the ones related to pain, and improve his quality of life.

Patient organisations can be of great support in guiding and advising the patient about his options and in providing the patient and his family some perspective on what other families have experienced.

Such decisions include the setting; some patients prefer to spend the last moments of their lives being taken care for in their homes, if their families or carers can help, and others are more comfortable in dedicated hospices.

Recommendations

- **Ensure that care management guidelines include palliative care and end-of-life support** for patients, families and caregivers
- **Empower patient organisations in guiding patients and families** through the medical, legal and ethical matters related to their possible end-of-life scenarios



Conclusions

While the survival rates of gastric and oesophageal cancer have improved over the last decades, and diagnostics and treatment options have become more precise and efficient, the mortality rates are still extremely high and late diagnosis remains a critical challenge for these two cancer types.

Issues related to the management and quality of care of these two cancers are threefold: first, diagnosis happens too late, limiting the chances for patients to access curative treatments; second, the best treatment options consist of invasive surgical interventions, which induce important side effects, comorbidities and mortality; finally, the management of these cancers requires high-quality multidisciplinary expertise, which is not always guaranteed for patients.

Gastric and oesophageal cancers induce today a heavy financial burden on society. Healthcare budget allocations and policymaking should shift towards a more visionary approach to the disease, with the view to:

- **Improve primary prevention**
- **Improve early detection and diagnosis**
- **Ensure 360-degree care management, which looks beyond surgery and treatment and incorporates nutrition and long-term medical and psychosocial patient support**
- **Harmonise clinical and care guidelines across European countries**
- **Ensure the full patient pathway is at the centre of all future healthcare decisions**

Policies which offer rational disease management recommendations are the only possible route towards better controlling of these cancers and reducing their mortality.

With these efforts in mind, we hope to meet Digestive Cancers Europe's objective to save 280,000 patients with digestive cancers annually in Europe by the end of the decade.

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DIGESTIVE CANCERS EUROPE



The European Oesophageal and Gastric Cancer Roadmap



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