Colorectal Cancer

What is colorectal cancer?

Let us explain it to you.

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European Society for Medical Oncology

ESMO/ACF Patient Guide Series

based on the ESMO Clinical Practice Guidelines

COLORECTAL CANCER: A GUIDE FOR PATIENTS

PATIENT INFORMATION BASED ON ESMO CLINICAL PRACTICE GUIDELINES

This guide for patients has been prepared by the Anticancer Fund as a service to patients, to help patients and their relatives better understand the nature of colorectal cancer and appreciate the best treatment choices available according to the subtype of colorectal cancer. We recommend that patients ask their doctors about what tests or types of treatments are needed for their type and stage of disease. The medical information described in this document is based on the clinical practice guidelines of the European Society for Medical Oncology (ESMO) for the management of colorectal cancer. This guide for patients has been produced in collaboration with ESMO and is disseminated with the permission of ESMO. It has been written by a medical doctor and reviewed by two oncologists from ESMO including the leading author of the clinical practice guidelines for professionals. It has also been reviewed by patient representatives from ESMO's Cancer Patient Working Group.

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

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

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This is the first update of this guide. Updates reflect changes in the successive version of the ESMO Clinical Practice Guidelines. This first update was done by Dr. Gauthier Bouche (Anticancer Fund), Dr. Ana Ugarte (Anticancer Fund) and was reviewed by Dr. Svetlana Jezdic (ESMO).

FACT SHEET ABOUT COLORECTAL CANCER

Definition of colorectal cancer

- Cancer that develops in the large intestine.

Diagnosis

- Colorectal cancer causes complaints more often when it is advanced. Common symptoms are change in bowel habits, abdominal discomfort, fatigue, weight loss. Blood in stools could be a sign of alert. It could be visible to the naked eye or through a laboratory analysis of stools.
- Endoscopy is an examination in which a lighted tube is inserted through the anus into the intestine. It allows seeing the inside of the intestine. When a tumour is found within 15 cm from the anus it is considered rectal tumour, further away it is considered colon tumour.
- Special radiological tests also help to visualize the localisation and size of the tumour.
- Blood analysis looking for carcinoembryogenic antigen (CEA), a tumour marker, might be useful in selected situations, but diagnosis should not be relied solely on it.
- The confirmation of diagnosis is only given by laboratory analysis of the tumour and tissues affected (histopathology).

Treatment according to the extension of the disease

Treatment of malignant polyps

- Polyps found to be cancerous should be removed from the colon. Depending on the degree of the invasion of malignant cells in the polyp a wider surgical procedure could be recommended.

Treatment according to disease stage

Note: Sometimes after initial treatment and analysis of the tumour removed it could be determined that the cancer is more advanced so that the treatment protocol has to be adapted.

- In stage 0 the cancer is confined to the most superficial layer of the bowel wall of the mucosa. The tumour should be removed surgically.
- Stage I involves one layer deeper, the submucosa, and it even reaches the muscle of the colon or rectum. The tumour should be surgically removed as well as local lymph nodes.
- Stage II involves the muscle of the intestine and invades surrounding organs. The treatment consists of surgical removal of all affected tissues and for some patients additional chemotherapy in case of colon cancer and radiotherapy or radiotherapy combined with chemotherapy for rectal cancer is necessary.
- Stage III involves structures adjacent to the colon but also regional lymph nodes. The treatment consists of surgical removal of the tumours and other affected tissues and adjuvant therapy i.e. chemotherapy for colon cancer and radiotherapy or chemotherapy plus radiotherapy for rectal cancer.
- Stage IV involves distant organs, such as liver and lungs. Chemotherapy and biological targeted therapy are treatment options. Chemotherapy helps reducing the size of the metastatic tumours to make them, if possible, operable.

Follow-up

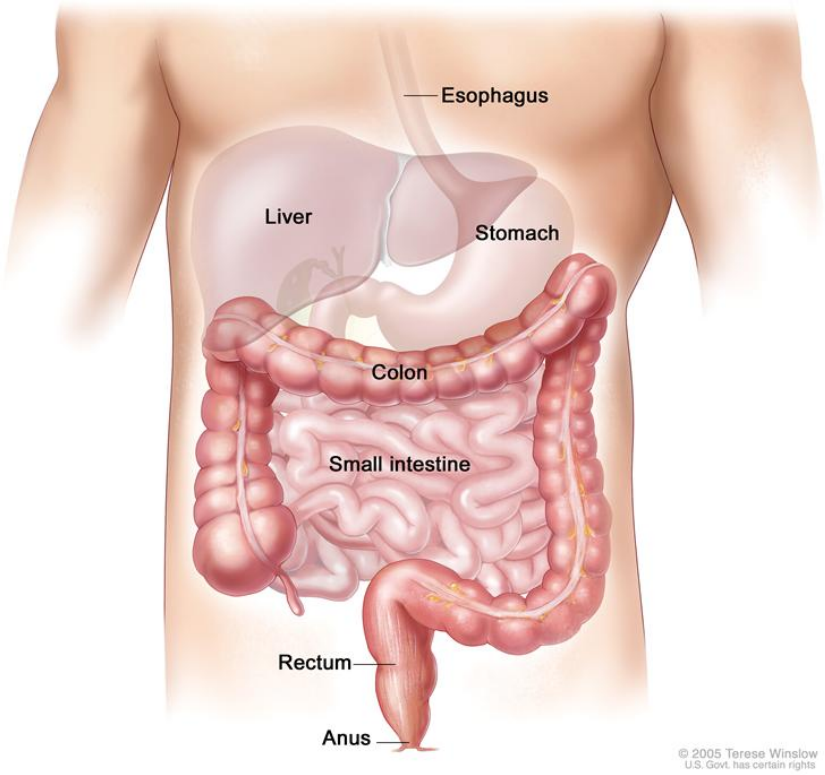
- There is no follow-up protocol generally accepted. Your doctor will schedule visits after the treatment completed with purpose of monitoring side effects of the treatment, possible recurrence of the disease and to provide you with support to be back to your normal life. The follow-up may last up to 5 years.

DEFINITION OF COLORECTAL CANCER

Colorectal cancer is a cancer that develops in the large intestine.

Colon cancer refers to cancer that develops in the colon, the longest part of the large intestine. Rectal cancer develops in the rectum, the final straight part of the large intestine that ends in the anus.

The anus is the opening of the rectum to the exterior. Stool is evacuated through the anus. Cancer may also develop in the anus, but anal cancer is a distinct disease. Anal cancer is not included in this guide.



Anatomy of the digestive system. The consecutive parts of the gastro-intestinal system are the esophagus, stomach, small intestine, large intestine (consisting of the colon and rectum) and the anus. Also shown is the liver.

IS COLORECTAL CANCER FREQUENT?

Colorectal cancer is the most common cancer in Europe and the third most common cancer worldwide. In 2012, approximately 447,000 patients were diagnosed with colorectal cancer in Europe. This accounts for approximately 13% of all cancers in this region.

The majority of colorectal cancers are located in the colon; these are called colon cancer and account for 9% of all cancers in Europe. Approximately one third of colorectal cancers are located only in the rectum, these are called rectal cancer.

Colorectal cancer is more frequent in men than in women. In Europe, around one in every 20 men and around one in every 35 women will develop colorectal cancer at some point in their lifetime. In other words, every year, in Europe, around 35 out of 100,000 men and around 25 out of 100,000 women are diagnosed with colorectal cancer. Overall, the frequency of colorectal cancer is higher in more industrialized and urbanized regions.

Most patients with colorectal cancer are more than 60 years old at the time of the diagnosis, and colorectal cancer below the age of 40 years is rare.

WHAT CAUSES COLORECTAL CANCER?

Today, it is not entirely clear why colorectal cancer occurs. A number of risk factors* have been identified. A risk factor* increases the risk of cancer occurring, but is neither necessary nor sufficient to cause cancer. A risk factor* is not a cause in itself.

Some people with these risk factors* will never develop colorectal cancer and some people without any of these risk factors* may nonetheless develop colorectal cancer.

Colorectal cancer most commonly occurs as a sporadic disease*, meaning that it is not related to inherited genes* that convey a risk for this type of cancer.
Approximately 20% of colorectal cancers occur in a familial context. Less than half of these arise as a result of a known hereditary condition*. In the remainder of the familial cases the cause is unknown. The familial occurrence may not only be due to shared inherited genes but also to shared factors in the environment that increase the risk.

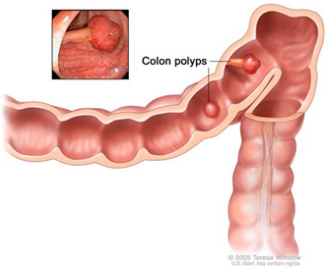
The main risk factors* of colorectal cancer are:

- Aging: the risk of colorectal cancer increases as a person gets older.

- Lifestyle-related risk factors*:
  - Diet: diet is the most important environmental risk factor* for colorectal cancer. A diet that is high in red meat (beef, lamb, or pork) and processed meat (hot dogs and some luncheon meats), high in fat and/or low in fiber can increase the risk of developing colorectal cancer. High consumption of alcohol is also a risk factor* for colorectal cancer.

  - Obesity: overweight increases the risk of developing colorectal cancer.
  - Sedentary lifestyle: individuals who are not very physically active are at a higher risk of developing colorectal cancer. This is independent of the person's weight.
  - Diabetes mellitus type 2* increases the risk of developing a tumour in the large intestine. This is independent of whether the person is overweight or not.
  - Smoking: smoking increases the risk of developing large colorectal polyps*, which are well-known precancerous lesions*.

- Previous history of colorectal polyps: growths in the bowel, called polyps* or adenomas*, are not cancerous. However, these growths can develop into cancer over a long period of time. Polyps* are therefore recognized as well-determined pre-cancerous lesions*. When polyps* are found in the large intestine, for example during a screening investigation, they should be removed to prevent them from turning into cancer.



- Previous history of colorectal cancer: even if the tumour has been completely removed during previous treatment, there is an increased risk of developing a new tumour in another part of the large intestine or in the rectum.
- Previous history of other types of cancer: a previous history of other tumours, like lymphoma*, testicular cancer* or endometrial cancer* enhances the risk of developing colorectal cancer.
- Inflammatory bowel disease such as Crohn's disease* or ulcerative colitis*. These are conditions in which the large intestine is inflamed over a long period of time. After many years, this may cause dysplasia*, a disordered organization of the cells of the inner lining of the intestine. Dysplasia* can evolve into cancer over time. The risk increases with the duration of the inflammatory bowel disease and with the severity and extent of the inflammation. Colorectal cancer in patients with Crohn's disease* or ulcerative colitis accounts for approximately two thirds of all sporadic* colorectal cancers.
- Family history: approximately 20 % of colorectal cancers occur in a familial context. If a first-degree relative has colorectal cancer, the risk for developing colorectal cancer doubles. This can be due to inherited genes or to shared environmental factors*.
  Investigation into a possible family history of colorectal cancer is important. In selected cases, screening at a young age and/or genetic counselling* should be considered.

  Known hereditary syndromes* that predisposes one to colorectal cancer are:

  - Familial Adenomatous Polyposis* (FAP). Individuals with this condition have a mutation* or a loss of the FAP* gene, which causes hundreds or thousands of polyps* to grow in the large intestine at a young age. Cancer may develop in one or more of these polyps* before the age of 40, and sometimes as early as age 20. To prevent this from occurring, the large intestine should be surgically removed. A variant is the AFAP syndrome: Attenuated FAP* syndrome in which polyps* are less frequent and occur at a later age, compared to FAP* syndrome.
  - Lynch syndrome*, also called Hereditary Non-polyposis Colorectal Cancer (HNPCC). Individuals with this condition have certain gene mutations* that cause failure of the DNA repair mechanisms*. A consequence hereof is that a benign colorectal tumour may develop into cancer at a faster pace (on average 2 to 3 years) than in individuals who do not have Lynch syndrome*. When colorectal cancer occurs in Lynch syndrome, the average age at diagnosis is 45 years. Lynch syndrome* also carries an increased risk for certain other types of cancer such as endometrial cancer* or ovarian cancer*.

  Other, less frequent, hereditary syndromes include Turcot syndrome*, Peutz-Jeghers syndrome* and MYH-associated polyposis*. Individuals who have an Ashkenazi Jewish background are at a higher risk of developing colorectal cancer because of certain inherited genetic mutations* in this population group.

Some factors may have a protective effect against the development of colorectal cancer:

- A diet high in vegetables, fruit, and whole grains decrease the risk of colorectal cancer.
- An increase in physical activity may help to reduce this risk of colorectal cancer.

- Long-term intake of anti-inflammatory drugs such as aspirin has been suggested as a way of reducing the recurrence* of non-hereditary colorectal polyps. Aspirin has been shown to reduce the risk of colorectal cancer in people with Lynch syndrome*. It has also been suggested to support regression of colorectal polyps* in FAP* patients but, more research is necessary to obtain definitive evidence.
- Intake of female hormones by postmenopausal women has been suggested as a way of reducing the risk of colorectal cancer. However, more research is necessary to obtain definitive evidence.

HOW IS COLORECTAL CANCER DIAGNOSED?

The suspicion of colorectal cancer may arise in various circumstances, but most commonly when a patient presents certain complaints or symptoms. Colorectal cancer may also be detected as a result of a screening examination. Many countries offer a systematic screening program to individuals over 50 years old to detect colorectal polyps* and to detect colorectal cancer at an early stage. The screening procedure is explained in the next chapter.

Symptoms and signs of colorectal cancer

Symptoms

The principal symptoms of an early colorectal tumour are often vague. Moreover, these symptoms commonly occur in the context of other, non-malignant medical conditions and are therefore not specific for colorectal cancer. In a very early phase, most colorectal cancers do not cause any complaints or symptoms at all.

Signs

The presence of blood in stools can be a sign of colorectal cancer or of a polyp. Blood in the stool can be red, or black when the blood is digested. Dark blood in this context is called melena and often results from lesions bleeding at a larger distance from the anus. The blood loss can sometimes not be visible with the naked eye (microscopic). Blood loss may lead to iron-deficiency and/or anaemia* (low red blood cell count* and low hemoglobin*) and lead to symptoms of fatigue, shortness of breath and pale skin.

Diagnosis

A combination of the following complaints, particularly if persistent over a longer period of time, should raise the suspicion of colorectal cancer and should warrant further investigation:

- a change in bowel habits
- general abdominal discomfort
- unexplained weight loss
- prolonged fatigue

The diagnosis of colorectal cancer is based on the examinations detailed below. Of note, in women, it is important to rule out presence of synchronous breast, ovarian and endometrial cancers*.

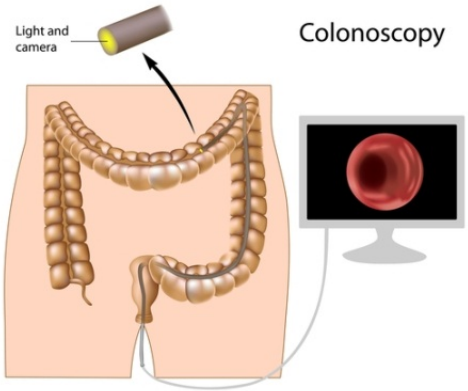
1. **Clinical examination**

   This includes a physical examination of the abdomen and a rectal examination. By palpating the abdomen the doctor determines whether the tumour has caused the liver to enlarge, and whether it has caused excess fluid in the abdomen, called ascites. During a rectal examination, the doctor will use the finger of a gloved hand to examine the interior of the anus and the rectum in order to detect abnormal swellings or traces of blood.

2. **Endoscopy***

During endoscopy* of the large intestine, a fine lighted tube with a camera is inserted through the anus into the large intestine. This allows the doctor to inspect the interior of the bowel for abnormal areas or growths in the inner lining of the intestine. Insertion of fine instruments through the endoscope also allows the doctor to perform a biopsy* of an abnormal area, or - if a polyp is found - to remove the entire polyp. This tissue is sent to the laboratory for histopathological examination* (see below).

Endoscopy* can be performed in different areas, by inserting the relevant instrument at varying distances into the colorectal area. A rectoscope* is a short, rigid instrument that is inserted into the rectum only (the procedure is called rectoscopy). A sigmoidoscope* is a somewhat longer flexible instrument that is inserted in the lowest part of the large intestine, above the rectum (the procedure is called sigmoidoscopy*). A colonoscope* is a long and flexible instrument that can be passed through the entire large intestine (the procedure is called colonoscopy*).



Tumours found within 15 cm of the anus are classified as rectal tumours, whereas any tumour further away from the anus is called a colonic tumour.

When a rectal tumour is found during rectoscopy, a complete colonoscopy is also required, either preoperatively or postoperatively.

3. **Radiological investigation.**

- **CT colonography***. This examination involves a CT scan* of the abdomen, after which a computer produces 3-dimensional images from the interior wall of the large intestine. This procedure is also called a **virtual colonoscopy**. It is not a routine procedure but may be helpful when colonoscopy is difficult, for example in obstructive tumours. It may also be helpful for surgeons to accurately locate the tumour before an operation.

- **Double contrast barium enema.** During this examination, barium sulphate (a chalky liquid commonly used in radiological examinations) and air are introduced into the colon via the anus. Both barium and air will be visible on X-ray* film and this will visualize an outline of the interior wall of the colon and rectum. This examination is used only occasionally, typically when the right-sided part of the colon is difficult to reach with the colonoscope*, but today it is usually replaced by a CT colonography*.
- **For the colonoscopy and virtual colonoscopy adequate preparation of the bowel is needed.**

4. Laboratory investigations

- **Routine blood tests** are performed and include complete blood count, liver function and kidney function tests.

- **Tumour markers** are factors that are produced by tumours and that can be measured using a blood test. Together with results from the routine investigations, tumour markers may help to diagnose a recurrence* of cancer after initial treatment at an early stage or to follow the evolution of cancer during or after therapy. A great deal of research effort is being spent in search of tumour markers for colorectal cancer. Except for carcinoembryonic antigen (CEA, see below), which may be useful in selected situations, so far no such test is available.

- **Carcinoembryonic antigen* (CEA)**. Colorectal cancer cells may produce the factor CEA* and this can be measured using a blood test. However, not all colorectal cancers produce CEA*, and CEA* may also be elevated in other cancers and in non-malignant conditions. Therefore, in colorectal cancer, CEA* is not useful as a screening test. In patients with colorectal cancer who have elevated CEA* at diagnosis, however, it may be useful for evaluation of prognosis* and for follow-up after treatment.

5. Histopathological examination*.

This is the laboratory investigation of the tumour tissue. It is performed using a microscope on the biopsy* or the polyp obtained via endoscopy*. The histopathological* information will confirm the diagnosis of colorectal cancer and reveals specific characteristics of the tumour.

If surgery is done, a histopathological examination* is performed not only on the tumour tissue itself, but also on lymph nodes* that are routinely removed, and on organs that have been invaded by tumour and resected during surgery. It may also be necessary to perform a histopathological examination* on metastases*. Histopathology* is part of a diagnostic process called staging*. Staging* means that the doctor defines the extent to which the colorectal tumour has invaded other organs or has caused metastases*. Staging* allows the doctors to direct the optimal treatment.

The chapter 'What is important to know to define the optimal treatment' explains how histopathological* information is used to direct treatment.

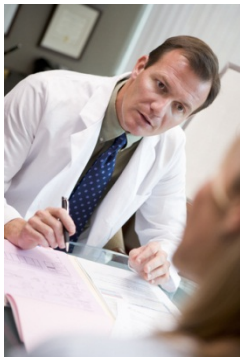
SCREENING FOR COLORECTAL CANCER

Many countries offer a systematic screening program to individuals over 50 years of age to detect colorectal polyps* and to detect colorectal cancer at an early stage. The reasons for this are firstly, that early colorectal cancer often produces vague or no symptoms, secondly, that polyps* are well determined precancerous lesions*, and third, that aging is an important risk factor*.

The screening program usually includes a Faecal Occult Blood Test (FOBT)*, and a colonoscopy* for confirmation. The FOBT* is used by doctors to examine the patient's stool for traces of blood: a colorectal tumour may shed small amounts of blood that may not be visible to the naked eye.
During a colonoscopy, a fine lighted tube with a camera is inserted through the anus into the large intestine: this allows the doctor to inspect the interior of the colon and rectum, and to detect polyps* or other colorectal tumours.

In Europe, screening is recommended to men and women aged 50 or older, with an interval of 1 to 2 years, until the approximate age of 74 years. The screening programme considers a FOBT* and a colonoscopy* for individuals who have a positive FOBT*.

WHAT IS IMPORTANT TO KNOW TO GET THE OPTIMAL TREATMENT?



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

Relevant information about the patient

- Gender
- Age
- Personal medical history, previous illnesses and treatments
- Family history of colorectal cancer, colorectal polyps* and other forms of cancer
- General wellbeing and general performance status
- Specific physical complaints
- Results of the clinical examination
- Results of laboratory tests on blood counts, kidney and liver function, CEA*
- Results of endoscopic and radiological investigations

Relevant information about the cancer

- **Staging***

When doctors determine the stage of the cancer, they use different methods to assess the extent to which the cancer has spread locally and at a distance in the body. This process is called staging*.
The stage is fundamental in order to make the right decision about the treatment. The stage also determines the prognosis* of the patient: the lower the stage, the better the prognosis*.
Staging* is usually performed twice. After clinical and radiological examination the doctors estimate the stage of the cancer. If surgery is performed, staging* is influenced by the histopathological examination* of the removed tumour, lymph nodes* and/or other organs that may have to be surgically removed. This process is called surgical staging*. The histopathological examination* should include examination of all the resection margins of the surgical specimen, to determine if the tumour has spread beyond the resected tissue. At least 12 lymph nodes* should be removed to allow accurate staging*. Also, the histopathological examination* should verify whether the tumour has invaded blood vessels or nerves.

The TNM staging* system is commonly used. The combination size of the tumour and invasion of nearby tissue (T), involvement of lymph nodes* (N), and metastasis* or spread of the cancer to other organ of the body (M), will classify the cancer as being at one of the stages explained in the table below. The definitions are somewhat technical and refer to the anatomy of the intestine and the abdominal cavity. It is recommended to ask doctors for more detailed explanations.

Stage	Definition	Category
Stage 0	Carcinoma in situ: a malignant tumour that is confined to the mucosa*, and that does not invade the submucosa*	Localized colorectal cancer
Stage I	The tumour invades the submucosa* or the muscularis propria*	
Stage IIA	The tumour invades through the muscularis propria* into the subserosa* or into neighboring tissues in the intraperitoneal space*	
Stage IIB	The tumour penetrates the visceral peritoneum* and/or directly invades organs or structures in the intraperitoneal space*	
Stage III	The tumour has produced metastasis* in regional lymph nodes*. Stage III is divided into 3 different stages depending on the invasion of the local tumour and the number of lymph nodes* with metastases*[a] • Stage IIIA: The tumour invades the submucosa* or muscularis propria* and has spread to 1-3 regional lymph nodes* • Stage IIIB: The tumour invades the subserosa*, visceral peritoneum* or neighboring organs, and has spread to 1-3 regional lymph nodes* • Stage IIIC: The tumour, irrespective of the degree of local invasion, has spread to 4 or more regional lymph nodes*	
Stage IV	The tumour has spread to distant organs, irrespective of the degree of local invasion and/or spread to regional lymph nodes*	Advanced colorectal cancer

[a] during surgical staging*, at least 12 lymph nodes* should be removed to accurately determine the number of lymph nodes* involved.

- **Radiological investigations**

Radiological investigations may help to determine the local spread of the tumour and the presence of metastases*. These may include:

- **Computed tomography (CT)*** of chest and abdomen are routinely performed preoperatively to detect metastatic spread of the tumour.
- **Intra-operative ultrasound* of the liver** may help in determining the presence of liver metastases* and in determining whether they are suitable for resection.
- **Nuclear magnetic resonance imaging* (MRI)** is useful to accurately visualize the extent of tumour spread, and to detect or confirm the presence of metastases*. MRI* of the rectum is a routine staging* procedure in rectal cancer.
- **Endoscopic ultrasound*** can be used as an alternative for MRI* in early stage rectal cancer to determine the extension of the tumour.

– **Positron emission tomography* (PET)** is not performed as a routine investigation, but may be useful to visualize metastases*. PET* can help to determine whether a distant lesion is malignant in nature, particularly if it is used in combination with computed tomography (CT). PET* also helps to accurately visualize liver metastases* that may be suitable for surgical resection. PET* may also be useful to help visualize residual or recurring* tumours after radiotherapy* and/or surgery.

- **Histopathological examination***

During colonoscopy, a biopsy* is taken from suspicious areas, and– if possible – polyps* are entirely removed. These tissues are examined in the laboratory. This examination is called histopathology*. When surgery is indicated, a second histopathological examination* involves the examination of the tumour tissue and the lymph nodes* after surgical removal. This is very important to confirm the first histopathology* results and to provide more information on the cancer.

Results of the histopathological examination* should include:

- **Histological type of the lesion**
  The histological type refers to the type of cells that compose the lesion. Most of the colorectal cancers are adenocarcinomas* or subtypes of adenocarcinomas* (mucinous or signet-ring). Other rare types of colorectal cancers include squamous cell carcinomas*, adenosquamous carcinomas*, undifferentiated carcinomas, and medullary carcinomas.
  Neuroendocrine carcinomas* are cancers that develop from neuroendocrine cells of the colon or rectum. These cancers exhibit different behavior, making their treatment different. The information in this guide does not apply to this form of colorectal cancer.

- **Grade**
  The grade is determined on the basis of how different the tumour cells look from the cells normally found in the healthy colorectal lining. The abnormal features indicate the rate at which the cells multiply and the degree to which they are invasive.
  In colorectal cancer, four grades are distinguished. In **grade 1**, the tumour tissue closely resembles normal colorectal tissue, whereas in **grade 4**, the tumour cells look very abnormal. **Grades 2 and 3** are intermediate grades. The grade of colorectal cancer is often referred to more generally, as **low grade** (grade 1-2) and **high grade** (grade 3-4). Signet-ring cell carcinomas, small cell carcinomas, and undifferentiated carcinomas are always classified as high grade.

- **Level of invasion in malignant colorectal polyps***
  Colorectal cancer usually develops from a benign colorectal polyp. When a colorectal polyp is removed and examined for the presence of invasive carcinoma, the pathologist* will specifically look for features that may predict the aggressiveness of the cancer.

Several systems have been proposed to stage these so-called 'malignant polyps*' to direct treatment. One of these is the 'level of invasion', referring to how far the carcinoma has invaded the structure of the polyp. In **pedunculated polyps*** (polyps* attached to the bowel lining by a narrow elongated stalk) four levels of invasion have been defined. In **sessile polyps*** (polyps* that do not have a stalk) three levels of invasion have been defined.

Other histological findings that predict an aggressive outcome are the presence of cancer cells in the excision margins of the resected polyp, invasion of the blood or lymphatic vessels* by cancer cells, and a high grade lesion.

- **Molecular profiling**

Cancer develops when genes responsible for regulating cell growth and differentiation are altered. Such gene alterations include for example a change in the DNA sequence of a gene (called a mutation*), a change in the number, or breakage, of chromosomes* (called chromosomal instability*) and a change in the length of specific repeat sequences in the DNA (called microsatellite instability*).
Molecular profiling is a technique that reveals the entire set of genes expressed in a cell or a tissue. This technique is increasingly being used to determine the profile of genes and gene alterations expressed in cancers. By comparing these so-called molecular profiles amongst cancers, and by relating them to clinical information, it helps doctors to understand the origin of the cancer, its potential to metastasize, its responsiveness to treatment, and the likelihood of recurrence.
For colon cancer, a number of gene alternations have been described, such as RAS mutations*, BRAF mutation*, MLH1 mutation*, chromosomal instability* and microsatellite instability*. The presence or absence of these molecular profiles helps to classify colorectal tumours and helps to determine the optimal treatment. This is particularly true for RAS mutations* (either KRAS or NRAS) which will determine whether two specific drugs might be effective or not.

WHAT ARE THE TREATMENT OPTIONS?

Planning of the treatment involves an interdisciplinary team* of medical professionals. This usually implies a meeting of different specialists, called multidisciplinary opinion* or tumour board review*. In this meeting, the planning of treatment will be discussed according to the relevant information mentioned before.

The treatment will usually combine therapies that:

- Act on the cancer locally, such as surgery or radiotherapy*
- Act on the cancer cells systemically (all over the body) such as chemotherapy* and biological targeted therapy*

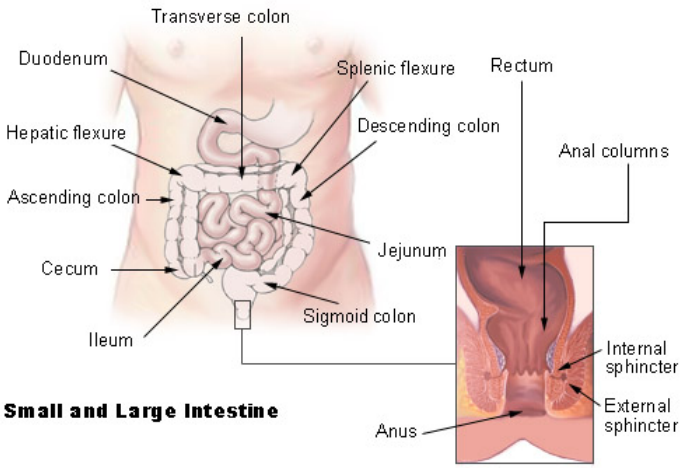
The extent of the treatment will depend on the stage of the cancer, on the characteristics of the tumour and on the risks for the patient.

Below, the general principles of treatment in colorectal cancer are listed first. Colorectal cancer is usually found within a polyp; the treatment of so-called malignant polyps* is described separately. This is followed by a description of the treatment plans per stage. Colon cancer and rectal cancer are described separately.
All treatments have their benefits, their risks and their contraindications*. It is recommended that patients ask their doctors about the expected benefits and risks of every treatment in order to be informed about the consequences of the treatment. For some patients, several possibilities are available and the choice should be discussed according to the balance between benefits and risks.

PRINCIPLES OF TREATMENT

Surgery

Surgery aims to remove the primary tumour. In patients with advanced disease, surgery may also be performed to remove metastatic lesions.



The extent of surgery on the primary tumour will depend on the local spread of the tumour. In a **simple excision**, the tumour is removed locally from superficial inner layer of the bowel wall. When the cancer develops from a polyp, the entire polyp is removed, a procedure called **polypectomy***. In a **segmental resection**, the bowel segment where the tumour is located is surgically removed and the bowel ends are reconnected.

Standardized resections are now considered more appropriate than segmental resections in the treatment of colon cancer. Depending on the location of the tumour, such standardized resection consists of removing either the ascending colon (right hemicolectomy*) or the descending colon (left hemicolectomy) or the sigmoid colon (sigmoid resection). Right and left hemicolectomy* are sometimes extended to the transverse colon and are then called extended (right or left) hemicolectomy*. The corresponding segment of the bowel is removed as well as the regional lymph nodes* and any part of the adjacent organs that are invaded by the tumour. It is necessary to remove at least 12 regional lymph nodes* to perform accurate staging*. The surgeon will also need to take the structure of the blood supply into account and the margins may therefore be wider. When in the case of rectal cancer the entire rectum, along with the mesorectum* containing the regional lymph node* is removed, the procedure is called **total mesorectal excision (TME)**.

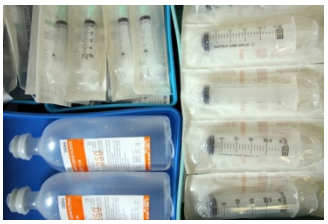
Usually, the healthy ends of the bowel are surgically reconnected during the initial operation (called **anastomosis***). When a total mesorectal excision is performed for rectal cancer, a colo-anal anastomosis* is performed. However, in selected patients, the surgeon needs to create a temporary connection between the small or large bowel and the wall of the abdomen, called an ileo**stoma or colostoma**, respectively (the procedure is called **ileostomy** and **colostomy**, respectively, see below). The stoma is usually temporary, but in some patients it may be permanent, especially in patients operated on because of a cancer in the lower part of the rectum.

For rectal cancer, local excision can be performed using a magnifying scope that is inserted via the anus into the rectum. This procedure is called **transanal endoscopic microsurgery*** and requires specific expertise. For colon tumours, simple excision and polypectomy* can be performed using a **colonoscope***.

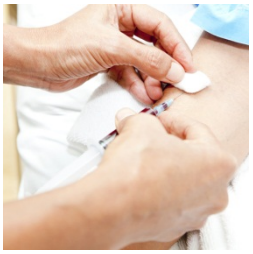
Surgical resections can be performed by **laparotomy**, but also by **laparoscopy**. Laparotomy refers to open surgery, meaning that the surgeon makes a large incision in the abdomen to perform the operation. During **laparoscopy**, fine lighted tubes and instruments are inserted through 3 or 4 small incisions in the abdomen. After laparoscopy, patients experience a quicker and easier recovery then after laparotomy.

When the cancer has caused obstruction of the bowel, it may be necessary for the surgeon to relieve the obstruction and let the bowel heal by inserting a **stent**, or by performing a **colostomy**. A stent is a tube that is placed in the bowel at the level of the tumour to open the natural passage. When a colostomy is performed, the healthy bowel above the level of the tumour is connected directly to the skin of the abdomen and the lower end of the bowel is closed; stool can now leave the body through this new path and is collected in a plastic bag attached to the skin. This new opening is called a **stoma**. Usually, the stoma is temporary, meaning that - when the tumour is resected and the bowel has had time to heal - a second operation is performed to join the two ends of the bowel together (**anastomosis***), and to close the stoma. The stoma may be permanent in some patients (e.g. those with very low position of tumour in the rectum).

Chemotherapy*



Chemotherapy* aims to kill or harm the tumour cells. Chemotherapy* is given orally or through a vein, and therefore acts systemically. The mainstay of chemotherapy* for colorectal cancer is treatment with drugs called fluoropyrimidines*, given either as single therapy (called monotherapy), or in combination with other drugs (called combination therapy).



The fluoropyrimidines* that are used are **5-fluorouracil* (5-FU)**, given intravenously*, and **capecitabine*** or **tegafur-uracil* (UFT)**, given orally. Fluoropyrimidines* are usually given in combination with **leucovorin* (LV)**, also known as folinic acid*, a drug that enhances the efficiency of the fluoropyrimidine*. Commonly, 5-FU* is given with LV*, abbreviated **5-FU/LV**.

In combination chemotherapy*, fluoropyrimidines* are combined with other chemotherapeutic drugs such as **oxaliplatin*** or **irinotecan***.

Biological targeted therapy*

Biological targeted therapy* refers to the therapeutic use of substances that are specifically designed to interfere with the growth of cells.

Bevacizumab* is a monoclonal antibody* that binds to vascular* endothelial growth factor* (VEGF), a growth factor for blood vessels. Colorectal cancer cells produce high amounts of VEGF*, which stimulates the formation of new blood vessels in and around the tumour (that feed the tumour). Blocking VEGF* using bevacizumab* therefore may prevent this from occurring.

Cetuximab* and **panitumumab*** are monoclonal antibodies* which act against epidermal growth factor receptor (EGFR*), a structure on the surface of all normal cells that helps them grow. Colorectal cells carry high amounts of EGFR* on their surface, and binding of cetuximab* or panitumumab* to EGFR* interferes with the growth of tumour cells and causes them to die.

Aflibercept* is a recombinant fusion protein that binds to circulating VEGF* and inhibits activity of different molecules belonging to VEGF* family. It inhibits the growth of blood vessels in the tumour.

Regorafenib* is an oral targeted therapy*, a multi-kinase inhibitor. It targets receptor tyrosine kinases, high affinity cell surface receptors that are key regulators of normal processes in the cell, but also have a critical role in development and progression of tumours.

Radiotherapy*

Radiotherapy* aims to kill tumour cells through ionizing irradiation. Radiotherapy* is used either alone or in combination with chemotherapy* (chemoradiotherapy*), prior to surgery in selected stages of rectal cancer. Surgery is usually performed 6-8 weeks after termination of chemoradiotherapy*.

In rectal cancer, radiotherapy* or chemoradiotherapy* is recommended to be given preoperatively whenever possible. Postoperative radiotherapy* or chemoradiotherapy* is reserved for selected patients with rectal cancer who have a high risk of recurrence* and who had not received radiotherapy* preoperatively.
In experienced centers, brachytherapy* or special contact techniques* can be used as an alternative to local surgery (with or without adjuvant chemoradiotherapy*) for selected forms of rectal cancer.

TREATMENT OF MALIGNANT POLYPS*

When a carcinoma is found in a colon or rectal polyp, it is known as a malignant polyp. The treatment of this lesion depends on the extent to which the carcinoma has invaded the polyp itself or beyond the polyp into the bowel wall, and whether unfavourable histological features are present (see: Histopathological examination*).*

Malignant polyps* in the colon

If the carcinoma in the polyp shows no invasion or a low/intermediate level of invasion (level 1-3 in pedunculated polyps, level 1-2 in sessile polyps), a **polypectomy*** is sufficient. If a high level of invasion (level 4 in pedunculated polyps, level 2-3 in sessile polyps) or unfavorable histological features are present, a **segmental or standardized surgical resection**, as described in the previous section (and therefore including lymph nodes*), is indicated.

Malignant polyps* in the rectum

If the carcinoma in the polyp* shows no invasion or a low/intermediate level of invasion (level 1-3 in pedunculated polyps*, level 1-2 in sessile polyps*), a local excision procedure using the **transanal endoscopic microsurgery*** technique is sufficient.
If the carcinoma in the resected polyp* shows a high level of invasion (level 4 in pedunculated polyps*, level 2-3 in sessile polyps*) or unfavorable histological features, it is recommended to perform a more extensive surgical resection, called **total mesorectal excision (TME)**, in which the entire rectum is removed as well as the regional lymph nodes* that are located in the mesorectum*. In patients who are not fit for a more extensive surgical intervention, postoperative chemoradiotherapy* is recommended.

If the invasive carcinoma is diagnosed on a biopsy* of the polyp* and if a local treatment is envisaged using the **transanal endoscopic microsurgery*** approach, **chemoradiotherapy*** should be given preoperatively.

In selected patients, doctors may consider to give **local radiotherapy*** (also called **brachytherapy***) or **local contact therapies*** as an alternative to local surgery either with or without chemoradiotherapy*.

TREATMENT PLANS ACCORDING TO DISEASE STAGE

Treatment plan for Stage 0

At this stage, the cancer is confined to the mucosa and does not invade the submucosa*. Since the tumour is confined to the most superficial layer of the bowel wall, the main goal of the treatment is to remove the local tumour by surgery, and additional treatment is not needed.*
A clinical stage is attributed to the cancer before surgery based on the clinical and radiological examinations. Actually, the definitive stage is only known after examination of the tumour tissue resected during surgery. Therefore, the treatment plan may be modified after surgery.

The colon or rectal tumour is removed by simple **surgical excision**. Larger lesions in the colon are more difficult to excise, and in these cases, the bowel segment containing the tumour is removed (called **segmental resection**), followed by anastomosis*. For rectal cancer the doctor will use the **transanal endoscopic microsurgery** technique*.

Treatment plan for Stage I

At this stage, the cancer has grown into the submucosa and may have grown into the muscle layer of the bowel. Since the tumour has grown deeper into the bowel wall, the treatment requires a wider surgical resection of bowel tissue, as well as resection of the regional lymph nodes*. However, since the tumour is still considered to be local, no further treatment is necessary.*
A clinical stage is attributed to the cancer before surgery based on the clinical and radiological examinations. The definitive stage is only known after examination of the tumour tissue resected during surgery. Therefore, the treatment plan may be modified after surgery.

For colon cancer the doctor performs a **surgical resection** of the bowel, thereby removing the segment of the colon where the cancer is localized, as well as the regional lymph nodes*. For rectal cancer the procedure is a **total mesorectal excision**, during which the entire rectum is removed, as well as well as the regional lymph nodes* located in the mesorectum*.

Treatment plan for Stage II

At this stage the cancer has grown beyond the muscle layer of the bowel and may have invaded the organs surrounding the colon or rectum. The primary treatment consists of surgery, which aims to remove the tumour and the adjacent organs invaded by the tumour. However, for selected patients, additional treatment could be recommended since it decreases the risk that the tumour may come back. For colon cancer this consists of chemotherapy, for rectal cancer this consists of radiotherapy* or chemoradiotherapy*.*
A clinical stage is attributed to the cancer before surgery based on the clinical and radiological examinations. The definitive stage is only known after examination of the tumour tissue resected during surgery. Therefore, the treatment plan may be modified after surgery.

Colon Cancer

The doctor performs a **surgical resection** of the bowel, thereby removing the segment of the bowel where the cancer is localized, the regional lymph nodes*, as well as the adjacent organs that are invaded by the tumour.

For patients presenting high-risk disease, **adjuvant chemotherapy*** is recommended. It is given in addition to primary, initial surgical treatment to prevent that tumour occurs again. In general, patients with stage IIB are considered to be at high risk, as well as patients presenting at least one of the following features: the tumour causes obstruction, the tumour penetrates the visceral peritoneum* and/or invades adjacent organs, the surgeon could not remove sufficient (minimum 12) regional lymph nodes* to determine lymph node* involvement, the tumour is poorly differentiated, or the tumour invades vascular*, lymphatic* or perineural* tissues*.

Chemotherapy* consists of **oxaliplatin*** and **5FU/LV**, given intravenously*. This combination is known as **FOLFOX**. This can also be replaced by the combination of oral capecitabine* with intravenous* oxaliplatin*. Alternatively, a regimen with **5FU/LV** by the intravenous* route or with **capecitabine*** by mouth can be considered. Chemotherapy* is given for 6 months.
In patients older than 70, one should be cautious in advising combination chemotherapy* drugs such as with oxaliplatin*.

Participation in clinical trials is encouraged so as to help develop the optimal treatment for patients in this category.

Rectal Cancer

In rectal cancer, an MRI* of the pelvis is fundamental to determine the local spread of the tumour before initiating treatment. In some selected cases, no pre-operative treatment is required since surgery alone is sufficient. For all other cases, it is recommended to give radiotherapy* or chemoradiotherapy* before surgery. The recommended regimen depends on the local spread of the tumour. If the tumour can be entirely removed by **total mesorectal excision** and the tumour has spread only to organs that can be readily resected, pre-operative **radiotherapy*** or **chemoradiotherapy*** is indicated**.**
If a **total mesorectal excision** does not allow removing the tumour completely, and/or if the tumour has spread to organs that cannot be resected, **chemoradiotherapy*** should be given.
The **radiotherapy*** regimen consists of 25 Gray*, given in 5 fractions of 5 Gray*, over 1 week, followed immediately by surgery. The **chemoradiotherapy*** regimen consists of radiotherapy* with 46 - 50.4 Gray* given in fractions of 1.8 to 2 Gray*, together with chemotherapy* with 5FU* (intravenously* or by mouth), or capecitabine* or UFT* (by mouth), followed by surgery 6-8 weeks later. In patients older than 80 or patients unfit for chemoradiotherapy*, the radiotherapy* regimen with 5 fractions of 5 Gray* may be considered and surgery should be delayed for 6-8 weeks after the end of the radiotherapy*.

During surgery, the doctor performs a **total mesorectal excision**, thereby removing the entire rectum, the regional lymph nodes* located in the mesorectum*. The surgeon also removes the adjacent organs that are invaded by the tumour, if that is possible.

Treatment plan for Stage III

At this stage, the cancer has metastasized to regional lymph nodes*. The primary tumour may be limited to the bowel or may have invaded the adjacent organs. Since the cancer has spread beyond the bowel, the treatment not only consists of surgery to remove all tumour tissue but also of adjuvant therapy since it decreases the risk that the tumour may come back. For colon cancer this consists of chemotherapy*, for rectal cancer it consists of radiotherapy* or chemoradiotherapy*.*

A clinical stage is attributed to the cancer before surgery based on the clinical and radiological examinations. Actually, the definitive stage is only known after examination of the tumour tissue resected during surgery. Therefore, the treatment plan may be modified after surgery.

Colon Cancer

The doctor performs a **surgical resection**, thereby removing the segment of the bowel where the cancer is localized, the regional lymph nodes*, as well as the adjacent organs that are invaded by the tumour.
The standard **adjuvant chemotherapy*** consists of **oxaliplatin*** and **5FU/LV**, given intravenously*. This combination is known as **FOLFOX. A combination of capectabine and oxaliplatin* (**a combination known as **CAPOX) can also be proposed**. **Oxaliplatin*** in some patients is contraindicated*: in these cases, the standard regimen is therapy with **5FU/LV** by the intravenous* infusion or **capecitabine*** by mouth. Chemotherapy* is given for 6 months.

Rectal Cancer

In rectal cancer, an MRI* of the pelvis is fundamental to determine the local spread of the tumour before initiating treatment. Unfortunately, neither MRI* nor any other radiological exam can accurately tell if the cancer has spread to regional lymph nodes*. In most cases, it is recommended to give radiotherapy* or chemoradiotherapy* before surgery. The recommended regimen depends on the local spread of the tumour.
If the tumour can be entirely removed by **total mesorectal excision** and the tumour has spread only to organs that can be readily resected, pre-operative **radiotherapy*** or **chemoradiotherapy*** is indicated**.**

If a **total mesorectal excision** does not allow for complete removal of the tumour, and/or if the tumour has spread to organs that cannot be resected, **chemoradiotherapy*** should be given.
The **radiotherapy*** regimen consists of 25 Gray*, given in 5 fractions of 5 Gray*, over 1 week, followed immediately by surgery. The **chemoradiotherapy*** regimen consists of radiotherapy* with 46 - 50.4 Gray* given in fractions of 1.8 to 2 Gray*, together with chemotherapy* with 5FU* (intravenously* or orally), or capecitabine* or UFT* (orally), followed by surgery 6-8 weeks later. In patients older than 80 or patients unfit for chemoradiotherapy*, the radiotherapy* regimen with 5 fractions of 5 Gray* may be considered and surgery should be delayed for 6-8 weeks after the end of the radiotherapy*.

During surgery, the doctor performs a **total mesorectal excision**, thereby removing the entire rectum and the regional lymph nodes* located in the mesorectum*. The surgeon also removes the adjacent organs that are invaded by the tumour, if possible.

Treatment plan for metastatic colorectal cancer: Stage IV

At this stage, the tumour has spread significantly and caused metastasis in distant organs such as the liver and lungs. The treatment therefore not only aims to remove the tumour by surgery, but also to target the tumour cells systemically with chemotherapy*, or with a combination of chemotherapy* and biological targeted therapy*.*

Metastatic disease should be confirmed by adequate radiological investigations. Usually it is necessary to obtain histopathological confirmation of metastases* before chemotherapy* is started. The treatment plan should be individually optimized for each patient. It is determined by a multidisciplinary team* and should take several factors into account. Most patients present unresectable metastases*. However, careful staging* allows doctors to identify metastases* that may become suitable for surgical removal when their volume is reduced by chemotherapy*. It is therefore critical to determine whether the patient has resectable disease, unresectable disease, or disease that is unresectable but may become amenable to resection after chemotherapy*. Furthermore, the patient's general condition, the patient's organ function, the presence of possible other illnesses and the patient's preference also direct the decision-making in designing the optimal individual treatment.*

The principles of treatment are discussed below. Chemotherapy and biological targeted therapy* are discussed according to whether or not the metastases* are resectable. Surgery includes resection of the primary tumour, but may also include operative removal of metastases*.*

During treatment, follow-up is recommended in order to evaluate the response to chemotherapy. A possible regimen recommends a 2- to 3-month evaluation of history, general condition, side effects of chemotherapy*, impact of chemotherapy* on quality of life, physical examination, laboratory investigation of the CEA* level (if it was initially elevated), and CT* of the involved regions.*

Treatment options

The main therapies used at this stage of the disease are briefly introduced in this section. Reading this section will help understanding the next section which describes the best treatment strategy depending on the characteristics of the disease and the general health status of the patient.

Surgery

Surgery on primary tumour

The doctor performs a **surgical resection**, thereby removing the segment of the bowel where the cancer is localised, the regional lymph nodes*, as well as the adjacent organs that are invaded by the tumour.

Resection of metastases*

The most frequent location of metastases* of colorectal cancer is in the liver. Surgical resection should be considered for solitary or confined liver metastases*, since it offers these patients the best chance of long-term survival even if, in about 3 out of 4 patients, liver metastases* can come back after resection. Radiofrequency ablation*, in combination with systemic treatment, is under investigation as an alternative, or a complement, to surgical resection of liver metastases* in cases where this is not possible or complete.

Selected metastases* in the lungs can also be surgically removed. This may be useful only if there are no other poor prognostic signs.

In general, resection of metastases* may be successful on the condition that the location of the metastasis* does not create an operative risk, and on the condition that resection would leave sufficient functional tissue (for example at least 30% of the liver tissue). Hence multiple resections may be performed. Some metastases* may become resectable if they are downsized during chemotherapy*; such patients should receive specific chemotherapeutic regimens (see above).

Chemotherapy* and biological targeted therapy*

The list of drugs approved in the treatment of stage IV colorectal cancer has grown gradually during the past 10 years. In addition, clinical trials have brought useful information regarding several combination of drugs and their respective efficacy. The main drugs and combinations available are presented below.

Individual chemotherapy* drugs

- 5-fluorouracil (abbreviated 5-FU)*
  - 5-FU* is always used in combination with leucovorin (abbreviated LV)*. Leucovorin* is reduced folinic acid* and increases the efficacy of 5-FU*. The combination of the two is abbreviated 5-FU/LV or FOLF.
  - 5-FU* is given in the veins and is either administered as a shot in a short period of time (<60 min) or infused slowly over 24 hours. Slow infusions should be preferred as they are better tolerated.
- Capecitabine (abbreviated CAP)*
  - Capecitabine* is transformed into 5-FU* in the body.
  - Capecitabine* is given orally.
- Oxaliplatin (abbreviated OX)*
  - Oxaliplatin* is usually given in combination with other drugs in the treatment of colorectal cancer.
  - Oxaliplatin* is infused into a vein usually over 2 hours.
- Irinotecan (abbreviated IRI)*
  - Irinotecan* is rarely given alone in the treatment of colorectal cancer.
  - Irinotecan* is infused into a vein usually over 90 minutes.

Chemotherapy* combinations for the treatment of colorectal cancer

- FOLFOX is the combination of 5-FU*, LV* and oxaliplatin*.
- FOLFIRI is the combination of 5FU*, LV* and irinotecan*.
- FOLFOXIRI is the combination of 5-FU*, LV*, oxaliplatin* and irinotecan*.
- CAPOX is the combination of capecitabine* and oxaliplatin*.

Biological targeted therapies*

- Aflibercept*
  - Aflibercept* is only given in combination with FOLFIRI in patients who already received oxaliplatin*-based therapy.
  - Aflibercept* is infused into a vein usually over 60 minutes.
- Bevacizumab (abbreviated BEV)*
  - Bevacizumab* can be given together with any of the chemotherapy* combinations.
  - Bevacizumab* is infused into a vein usually over 30 to 90 minutes.

- Cetuximab*
  - Cetuximab* can be given either alone or in combination with chemotherapy*.
  - Its use is limited to patients whose tumour does not present a RAS mutation*. A RAS mutation* is detected after analysis of a tumour sample in the lab.
  - Cetuximab* is infused into a vein over 1 to 2 hours.
- Panitumumab*
  - Panitumumab* can be given either alone or in combination with chemotherapy*.
  - Its use is limited to patients whose tumour does not present a RAS mutation*. A RAS mutation* is detected after analysis of a tumour sample in the lab.
  - Panitumumab* is infused into a vein over 1 hour.
- Regorafenib*
  - Regorafenib* is given as a single drug. It can be proposed to patients who already received all other treatment options.
  - Regorafenib* is given orally.

Radiotherapy*

Radiotherapy* should be considered (possibly combined with chemotherapy*) for patients with metastatic rectal cancer to alleviate symptoms from the primary tumour. Radiotherapy* can also be used to relieve symptoms caused by metastases* in the bones. Types of radiation therapy that use radiation from an external source (radiotherapy* machine) are called external radiotherapy*.

Selective internal radiation therapy involves injecting tiny microspheres or radioactive material into arteries that supply the tumour. This radioembolisation could be proposed when patients have metastases* in the liver only and received all available chemotherapeutic options. Radioembolisation using Yttrium 90 particles aims to embolize as well as to bring radiation therapy* very close to the tumour. A small tube is placed in the main artery going to the liver (hepatic artery), through which microscopic balls are released. These balls reach the tumour through the blood vessels of the liver and contain a radioactive substance called Yttrium 90. They block the supply of blood to the tumour, and at the same time emit radiation* that destroys the tumour cells surrounding them. Since the radiation* is delivered directly into the blood vessels supplying the tumour, the radiation* is more potent than the usual external radiation therapy*. The radioactivity of the balls is gone after 2 weeks.

Treatment strategy or how to decide what the best treatment is

Decision about the best treatment has become complex as the list of drugs approved in the treatment of metastatic colorectal cancer has become longer. In some cases direct comparison between treatments have been performed and it can guide decisions.
Whenever possible, resection of the tumour(s) by surgery is recommended. Answering the question about the “possibility” of removing the tumour(s) will actually guide the treatment strategy by grouping patients in several groups.

1- **Patients for whom removing metastases* is deemed feasible by the multidisciplinary team*. These patients have what is called resectable metastastic* disease.**

For patients who present liver and/or lung metastases* that can be operatively removed, the treatment consists of surgical resection of the metastases* and combination chemotherapy*. Chemotherapy* consists of a 6-month regimen of **5-FU/LV with oxaliplatin* (FOLFOX).** FOLFOX can be given either perioperatively, meaning that it is given for 3 months before and for 3 months after surgery or, after the operation, for 6 months.

2- **Patients for whom removing metastases* is deemed not immediately feasible by the multidisciplinary team*, but may become feasible if shrinkage of the metastases* is obtained. These patients have what is called unresectable disease that may become resectable after chemotherapy*.**

Selected patients may present liver metastases* that initially are unresectable, but that can become resectable when they are downsized by chemotherapy*. Such patients are treated with standard combination chemotherapy* consisting of **5-FU/LV and irinotecan* (FOLFIRI)** or **5-FU/LV and oxaliplatin*** (**FOLFOX**). The addition of a third chemotherapeutic drug **(FOLFOXIRI)**, or the biologic agents **bevacizumab***, **cetuximab*** or **panitimumab*** increases the toxicity of the treatment but may be considered in selected patients. Cetuximab* and panitumumab* seems to provide better results than bevacizumab* in this specific situation, but cannot be given to patients whose tumour presents a RAS mutation*.
The patient is closely monitored during chemotherapy*. Surgery is indicated as soon as the metastases* are considered to have become resectable. However, this needs to be delayed allowing at least 4 weeks after the last cycle of cetuximab*, and at least 6 week after the last cycle of bevacizumab*, before surgery is undertaken. This delay reduces the risk of complications of the surgery.

3- **Patients for whom removing metastases* is deemed never feasible by the multidisciplinary team*. These patients have what is called disseminated disease technically never or unlikely resectable.**

Depending on the general health condition of the patients, a more or less intensive treatment will be proposed. Treatment will rely on chemotherapy* and biological targeted therapy*.

Doctors are trying to continually improve the treatment for unresectable metastatic disease and the optimal treatment is therefore rapidly evolving. The goal of the treatment and the different options to reach this goal are tailored to the individual patient and may thus vary between patients. In case of symptomatic disease, combination therapy is the preferred choice, and a sequential approach remains a valid option in selected and frail patients.

Several **first-line chemotherapeutic regimens** can be proposed. If a patient fails to respond to first-line chemotherapy*, and the general condition allows, further treatment in the form of **second-line chemotherapy*** should be considered.

Biological targeted therapy* should be considered for selected patients. The optimal treatment regimen is tailored to the individual patient and the type of first-line therapy received.

The duration of the treatment can vary between individual patients. Options are either a fixed treatment period of 3 to 6 months, or treatment until doctors document that the disease progresses. After an initial period of combination chemotherapy*, maintenance treatment can improve outcome in comparison to treatment break, and restart of combination chemotherapy* is recommended if progression occurs. The principle behind a maintenance treatment is to continue using a drug that has been well tolerated. This usually consists of 5-FU or capecitabine*, in combination with bevacizumab* can be considered. Combination chemotherapy* may be discontinued or changed to a less intensive regimen if increasing toxicity occurs, when the disease is controlled, or when metastases* have become surgically resectable.

First-line chemotherapy*:

Possible regimens are:

- Therapy with **5-FU/LV** given intravenously*, or monotherapy with **capecitabine*** given orally.
- Combination therapy of **5-FU/LV plus oxaliplatin* (FOLFOX)** or **5-FU/LV plus irinotecan* (FOLFIRI)**, given intravenously. This is the preferred treatment. These regimens are given as 48-hour treatment infusions every two weeks. Both are equally effective but have different side effects.
  An alternative regimen, based on a fluoropyrimidine* given orally (namely capecitabine*), is the combination of **capecitabine* plus oxaliplatin* (CAPOX)** which is given in three weeks regimen**.** The combination of **capecitabine* plus irinotecan*** is less frequently used because of higher toxicity but it seems to be better supported than was previously thought.
- Combination of 3 drugs (5-FU*, oxaliplatin* and irinotecan* called **FOLFOXIRI**) has not been extensively studied but suggest that, even though patients experience more side effects, this combination could prolong survival of the patients. In frail patients these agents may be given sequentially rather than as a combination, in order to reduce toxicity.

Second-line chemotherapy*

The choice of second-line chemotherapy* depends on the regimen given as first-line therapy:

- If a therapy with 5-FU/LV or capecitabine* was administered in first-line, it can be followed by **5-FU/LV plus oxaliplatin* (FOLFOX)** or **5-FU/LV plus irinotecan* (FOLFIRI)**
- If a combination therapy with 5-FU/LV plus oxaliplatin* (FOLFOX) or capecitabine* plus oxaliplatin* (CAPOX) was administered in first-line, it can be followed by combination therapy with **5-FU/LV plus irinotecan* (FOLFIRI)**
- If a combination therapy with 5-FU/LV plus irinotecan* (FOLFIRI) was administered in first-line, it can be followed by **capecitabine* plus oxaliplatin* (CAPOX), or 5-FU/LV plus oxaliplatin* (FOLFOX)**

Biological targeted therapy*

Biological targeted therapy* should be considered in combination with selected chemotherapy* regimens:

- **Bevacizumab*** should be considered in combination with first-line therapy with 5-FU*, capecitabine*, 5-FU/LV plus oxaliplatin* (FOLFOX) and 5-FU/LV plus irinotecan* (FOLFIRI). It can also be considered in combination with second-line 5-FU/LV plus oxaliplatin* (FOLFOX) or FOLFIRI therapy. Treatment with bevacizumab* can be continued in combination with chemotherapy* until disease progression, toxicity or metastases* become resectable.
- **Cetuximab*** can be considered in combination with 5-FU/LV plus irinotecan* (FOLFIRI), 5-FU/LV plus oxaliplatin* (FOLFOX) and in combination with irinotecan. **Panitumumab*** can be considered in combination with 5-FU/LV plus oxaliplatin* (FOLFOX) and with 5-FU/LV plus irinotecan* (FOLFIRI).
  Molecular profiling of the tumour helps determining the appropriate choice of combination therapy. Approximately 50% of metastatic colorectal cancers have a genetic mutation* in RAS* and 5-10% have the BRAF mutation*. The combination of cetuximab* and FOLFIRI is the recommended treatment in medically fit patients who have a tumour without a RAS mutation*. Cetuximab* and panitumumab* are not active against colorectal tumours with the RAS mutation*, and it is unclear whether they are active against tumours with the BRAF mutation*. Cetuximab* and panitumumab* should therefore only be used for tumours that do not have RAS mutations*.
  If first- and second-line therapy has failed, cetuximab* with irinotecan* is the preferred treatment, although cetuximab* or panitumumab* monotherapy may also be considered.
- **Aflibercept*** is given in combination with FOLFIRI in patients who already received oxaliplatin-based therapy.
- **Regorafenib*** can be considered after all the above options have been used. It is an oral drug given alone.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF THE TREATMENT?

Surgery

General risks and side effects

Some risks are common for every surgical intervention performed under general anesthesia*. These complications are unusual and include deep vein thrombosis*, heart or breathing problems, bleeding, infection or reaction to the anesthesia*. These are maximally prevented by thorough medical evaluation before surgery.

After a surgical intervention on the colon, it is frequent to experience problems of the intestinal motility. This includes colicky pain, diarrhoea, constipation and nausea. Intestinal obstruction is not an uncommon complication that requires immediate medical care. Vomiting or loss of any bowel movement (no stool, no gas) may be signs of intestinal obstruction and should be immediately reported.

Rapid oral intake of food after surgery is recommended and can be done by using a nasogastric tube* in some patients. Nutritional advice should be given by health professionals to minimize intestinal discomfort.

The colon is located in the abdomen and extends throughout the entire abdomen. It is located partly in the intraperitoneal space*, and partly in the retro- and infraperitoneal space*. The lower two thirds of the rectum are located in the infraperitoneal space*. The colorectal bowel therefore lies in close proximity to several organs, lymph nodes* and major blood vessels. During the surgical intervention, depending on the extent of tumour spread and the extent of surgical resections needed to obtain the best results, some of these structures may become damaged. Accurate preoperative staging* and imaging will help to minimize such risk.

Colostomy

If the cancer has caused obstruction of the bowel, it may be necessary for the surgeon to relieve the obstruction and let the bowel heal by performing a colostomy. In this procedure, the healthy bowel above the level of the tumour is connected directly to the skin of the abdomen, and the lower end of the bowel is closed. Stool can now leave the body through this new path and is collected in a plastic bag attached to the skin. This new opening is called a stoma. The stoma is usually temporary, meaning that - when the tumour is resected and the bowel has had time to heal - a second operation is performed to surgically join the two ends of the bowel together (anastomosis*), and to close the stoma. In some patients the stoma may be permanent.

Chemotherapy*

Side effects of chemotherapy* are frequent, even if progress has been made in controlling them using adequate supportive measures. They will depend on the drug(s) administered, on the doses and on individual factors. If a patient has suffered from other medical problems in the past, some precautions should be taken and/or adaptation of the treatment should be made.

Listed below are the side effects that are known to occur with one or several of the chemotherapy* drugs currently used for colorectal cancer. The nature, frequency and severity of the side effects vary for every chemotherapeutic drug combination used.

The most frequent general side effects of chemotherapy* are:

- Decreased blood cell counts, which may lead to anaemia*, bleeding, bruising, and infections
- Fatigue, which may be prolonged
- Nausea or vomiting
- Diarrhea
- Sore mouth or mouth ulcers*

Listed below are other more specific side effects that may occur with chemotherapeutics used for colorectal cancer. For some of the side effects it may be necessary to adjust treatment.

- Treatment with **5-Fluorouracil* (5-FU**)
  - Severe side effects may occur in individuals who have the inborn condition dihydropyrimidine dehydrogenase (DPD) deficiency*: these individuals have low levels of the enzyme dihydropyrimidine dehydrogenase needed by the body to break down this drug
  - Skin sensitivity to sunlight: sun exposure should be avoided for at least one year following completion of treatment
  - Hand and foot syndrome (see below)

- Treatment with **capecitabine***:
  - Hand and foot syndrome (also called palmo-plantar erythema*): the skin of palms and soles shows reddening and feels sore; the skin may peel. The syndrome is usually mild.
  - Dihydropyrimidine dehydrogenase (DPD) deficiency* (see above) may cause severe side effects
  - Capecitabine* may interact with other treatments, increasing the risk of side effects of medications. All additional medications, especially folic acid*, warfarin* and St John's wort* should be disclosed and discussed upfront with the doctor.
- Treatment with **tegafur-uracil* (UFT)**
  - Skin rashes
  - Skin sensitivity to sunlight

- Treatment with **irinotecan***
  - Sweating
  - Watery eyes
  - Increased production of saliva
  - Cramping pain in the abdomen
  - Diarrhoea starting the day after treatment
  - Hair loss or hair thinning

- Treatment with **oxaliplatin***
  - Numbness of the lips, hands or feet
  - Tingling of hands or feet
  - Sensitivity to cold
  - These specific side effects may be persistent after treatment with oxaliplatin*.

Biological targeted therapy*

Listed below are the most frequent side effects of the biologics used in colorectal cancer. The combination of biologic therapies with chemotherapy* increases the risk of chemotherapy* side effects, particularly with cetuximab* and panitumumab*.

- Treatment with **cetuximab*** and **panitumumab**
  - Acneiform rash occurs in most patients
  - Hypomagnesaemia
  - Allergic reactions, slightly more frequent after cetuximab* than after panitumumab*.

- Treatment with **bevacizumab***
  - Hypertension* and proteinuria* are rather frequent
  - Other rare but severe side effects include arterial thrombosis*, mucosal* bleeding (mouth, nose, vagina, rectum), gastrointestinal perforation* and problems with wound healing.

- Treatment with **aflibercept***
  - Headaches
  - Fatigue
  - Liver problems which will be monitored by looking at the level of liver enzymes
  - Hypertension* and proteinuria*
  - Diarrhoea
  - Decreased blood cell counts, which may lead to anaemia*, bleeding, bruising, and infections
  - Bleeding

- Treatment with **regorafenib***
  - Hand and foot skin reaction: the skin of palms and soles shows reddening and feels sore, very characteristically localised to areas of pressure or friction on the skin
  - Skin rash
  - Fatigue
  - Liver problems which will be monitored by looking at the level of liver enzymes
  - Hypertension* and proteinuria*
  - Diarrhoea
  - Bleeding

Radiotherapy*

During radiotherapy*, side effects may occur in organs that are directly targeted, but also in healthy organs that lie close to the region that needs to be irradiated and that cannot be avoided by the X-rays*. Side effects are more intense when radiotherapy* is administered together with chemotherapy*. Use of radiotherapy* in addition to surgery also increases the risk of surgical complications.

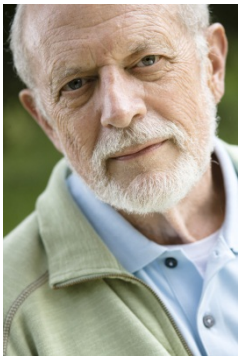
Effects of radiation on the lower digestive tract include rectal discomfort, diarrhea, and mucus and blood rectal discharge.

Effects of radiation on the urinary tract are rarer. They include painful urination, an urgent need to urinate, presence of blood in the urine, urinary tract obstruction*, and ulceration* or necrosis* of the bladder lining.

In women, vaginal narrowing is a possible late effect of pelvic radiotherapy*.

Strategies to maximally prevent and relieve post-radiation reactions are provided by the radiation oncologist*.

WHAT HAPPENS AFTER THE TREATMENT?



It is not unusual for cancer patients to experience treatment-related symptoms after the treatment has been completed.

- Patients may experience anxiety, sleeping difficulty or depression, and may need psychological support.
- During and after treatment, nutrition may become problematic due to reduced appetite, nausea and general malaise
- Difficulties in concentrating and memory loss are not uncommon side effects of systemic chemotherapy*.

Follow-up with doctors

After completion of treatment the doctor will propose a follow-up aiming to:

- Detect and prevent adverse effects of the treatment
- Detect possible recurrence* as soon as possible and direct appropriate treatment
- Provide medical information, psychological support and referral to specialized support providers to optimize returning to normal daily life.

The follow-up protocol will include regularly timed office visits and investigations. The protocol depends on the staging* of the cancer that was treated, and on the type of treatment given. In general, follow-up visits may include a combination of the following investigations:

- Questions on general physical health and colorectal cancer-related symptoms
- Physical examination
- Laboratory test for carcinoembryonic antigen* (CEA) level may help in detecting recurrence*
- Colonoscopy to detect recurrence*
- Radiological investigations to detect progression or recurrence* of the primary tumour, or the appearance of metastasis*

For patients who have had a **colorectal polyp** removed, it is necessary to follow-up with history and colonoscopy.

Patients treated for **colorectal cancer** should be followed up intensively. However, there is not one generally accepted follow-up protocol.

The following is a possible follow-up protocol after treatment for **localised colon cancer**.

- History and physical examination every 3 to 6 months for 3 years, and every 6 to 12 months in year 4 and 5.
- During these follow-up visits, CEA* could be determined
- Colonoscopy at 1 year, and thereafter every 3 to 5 years to detect new cancerous or non-malignant tumours. It is important to note that when colon cancer is diagnosed, the entire colon should be visualised prior to surgery, so as to detect other simultaneous colon tumours.
- In patients who are considered to be at high risk of recurrence*, a CT scan* of the chest and abdomen every 6 to 12 months for the first 3 years can be considered
- Abdominal CT scan* can be replaced by contrast enhanced ultrasound*

- In patients presenting specific symptoms that raise concern for recurring disease, appropriate additional laboratory or radiological investigations should be performed

In patients with **rectal cancer**, the follow-up protocol is similar to the one for colon cancer described above.

Returning to normal life

Returning to a normal daily life may be difficult knowing that the cancer may come back. If any of the known risk factors* for colorectal cancer are present, it is advised to eliminate these to a maximal extent.

Follow-up visits with the doctor provide an opportunity for the patient to obtain medical information, psychological support and referral to specialized support providers. Additional expert psychological advice may be valuable, and some patients may find support from patient groups or patient-targeted information media. Dieticians may provide advice on adequate nutrition. Social workers may help in finding resources to ensure successful rehabilitation.

What if the cancer comes back?

If the cancer returns, it is called 'recurrence*'. The extent of the recurrence* will direct the treatment decision, and this should be carefully determined for each individual patient.

If after being treated for primary **colon cancer**, a patient presents local or distant recurring disease, he/she will be treated according to the treatment plan for advanced disease (see 'what are the treatment options'). Patients with advanced disease failing to respond to first-line treatment with either chemotherapy* or chemotherapy* with biological targeted therapy* will be treated with second-line treatment; if second-line therapy fails, treatment with biological targeted therapy* (like regorafenib*) is recommended (see 'what are the treatment options').

The treatment for patients who present local recurrence* of **rectal cancer** depends on whether the prior treatment included radiotherapy* and whether salvage surgery is possible.

If radiotherapy* was not given in the primary situation, radiotherapy* should be given along with chemotherapy*. If the previous treatment included radiotherapy*, additional radiotherapy* can be considered in the form of either external, intraoperative, or local radiotherapy*. However, if radiotherapy* was already administered, additional radiotherapy* can rarely achieve appropriate control of the cancer growth.

Surgery is indicated 6-10 weeks after radiotherapy*. If salvage surgery is not an option, chemotherapy* should be considered.

In colon cancer, the lung is the first site of recurrence* in approximately 20% of patients and pulmonary resection could be considered if feasible. Lung metastases* are more frequent in rectal cancer.

If the cancer returns in the form of metastasis* in the liver, surgical resection of the metastases* can be considered in selected patients, as described in the paragraph "Treatment plan for advanced colorectal cancer: stage IV".

DEFINITIONS OF DIFFICULT WORDS

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

Adenocarcinomas (mucinous or signet-ring)
Cancer that begins in cells that line certain internal organs and that have gland-like (secretory) properties.

Adenoma
Benign tumour of glandular origin. Over time this benign growth may become malignant, and even while benign it can have health consequences by compressing other structures.

Adenosquamous carcinomas
A type of cancer that contains two types of cells: squamous cells* (thin, flat cells that line certain organs) and gland-like cells.

Aflibercept
A drug used to treat colorectal cancer. It is also used for the treatment of macular degeneration, a medical condition that results in a loss of vision. Aflibercept is an inhibitor of VEGF*. Structurally it is a recombinant fusion protein that binds to circulating VEGF* and inhibits activity of different molecules belonging to VEGF* family. In the tumour, it inhibits the growth of blood vessels.

Anastomosis
A procedure to connect healthy sections of tubular structures in the body after the diseased portion has been surgically removed.

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

Anesthesia
Reversible state of loss of awareness in which the patient feels no pain, has no normal reflexes, and responds less to stress, induced artificially by the employment of certain substances known as anesthetics. It can be complete or partial and allows patients to undergo surgery.

Arterial thrombosis
The presence of a blood clot in an artery.

Bevacizumab
A drug used to treat certain types of colorectal cancer, lung cancer, kidney cancer and glioblastoma (a type of brain cancer). It is also being studied in the treatment of other types of cancer. Bevacizumab binds to a protein called vascular endothelial growth factor* (VEGF). This may prevent the growth of new blood vessels that tumours need to grow. It is a type of antiangiogenesis agent and a type of monoclonal antibody*.

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

Brachytherapy
A type of radiation therapy in which radioactive material sealed in needles, seeds, wires, or catheters is placed directly into or near a tumour. Also called implant radiation therapy, internal radiation therapy, and radiation brachytherapy.

BRAF mutation
A specific mutation* (change) in the BRAF gene, which makes a protein that is involved in sending signals in cells and in cell growth. This BRAF gene mutation* may be found in some types of cancer, including melanoma and colorectal cancer. It may increase the growth and spread of cancer cells. Checking for this BRAF mutation* in tumour tissue may help to plan cancer treatment.

Capecitabine
A drug used to treat stage III colon cancer in patients who had surgery to remove the cancer. It is also used to treat metastatic breast cancer that has not improved after treatment with certain other anticancer drugs. Capecitabine is being studied in the treatment of other types of cancer. It is taken up by cancer cells and breaks down into 5-fluorouracil*, a substance that kills tumour cells. Capecitabine is a type of antimetabolite.

Carcinoembryonic antigen (CEA)
A substance that may be found in the blood of people who have colon cancer, other types of cancer or diseases, or who smoke tobacco. Carcinoembryonic antigen levels may help keep track of how well cancer treatments are working or if cancer has come back. It is a type of tumour marker. Also called CEA.

Cetuximab
A drug used to treat certain types of head and neck cancer, and a certain type of colorectal cancer that has spread to other parts of the body. It is also being studied in the treatment of other types of cancer. Cetuximab binds to a protein called epidermal growth factor receptor (EGFR*), which is on the surface of some types of cancer cells. This may stop cancer cells from growing. Cetuximab is a type of monoclonal antibody*.

Chemoradiotherapy
Treatment that combines chemotherapy* with radiation therapy. Also called chemoradiation.

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

Chromosomal instability
An increased tendency to lose or gain whole chromosomes* or large parts of chromosomes* during cell division, resulting in chromosomal aberrations.

Chromosomes
An organized structure which encodes genes which are the body's code for characteristics such as hair color or gender. Human cells have 23 pairs of chromosomes (total of 46 chromosomes). Cancer or leukemia cells often have a chromosomal abnormality which is a change to their chromosomes, such as a chromosomal duplication or an extra chromosome (47 chromosomes) or have a chromosomal deletion or a loss of a chromosome (45 chromosomes). A chromosomal or genetic inversion is when no extra chromosomes are added or deleted, but instead a portion is backwards.

Colonoscope
A thin, tube-like instrument used to examine the inside of the colon. A colonoscope has a light and a lens for viewing and may have a tool to remove tissue.

Contraindication
Condition or symptom that prevents the administration of a given treatment or procedure to the patient. Contraindications are either absolute, meaning the treatment should never be given to patients with this condition or symptom, or relative, meaning that the risk can be outweighed by the benefits in some patients with this condition or symptom.

Crohn's disease
Chronic inflammation of the gastrointestinal tract, most commonly the small intestine and colon. Crohn disease increases the risk for colorectal cancer and small intestine cancer. Also called regional enteritis.

CT colonography
A method to examine the inside of the colon by taking a series of X-rays*. A computer is used to make 2-dimensional (2-D) and 3-D pictures of the colon from these X-rays*. The pictures can be saved, changed to give better viewing angles, and reviewed after the procedure, even years later. Also called computed tomographic colonography, computed tomography colonography, CTC, and virtual colonoscopy.

CT scan
A form of radiography in which body organs are scanned with X-rays* and the results are synthesized by a computer to generate images of parts of the body.

Deep vein thrombosis
The formation of a blood clot in a deep vein of the leg or lower pelvis. Symptoms may include pain, swelling, warmth, and redness in the affected area. Also called DVT.

Diabetes mellitus type 2
Metabolic disease in which glucose builds up in the blood as consequence of insulin deficiency or resistance of the body cells to the action of insulin. Insulin is a hormone that takes glucose from the blood into the body cells so that they can use it for energy. Diabetes mellitus type 2 as opposed to diabetes mellitus type 1 is non-insulin dependent, since the insulin deficiency is not absolute.

Dihydropyrimidine dehydrogenase (DPD) deficiency
Inherited metabolic disorder in which there is a decreased or absent activity of the enzyme dihydropyrimidine dehydrogenase. This enzyme normally breaks down the molecules thymine and uracil in cells. This disorder may or may not cause symptoms and signs. However, regardless of any disease manifestation, all individuals with this condition are at risk of toxic reactions to drugs called fluoropyrimidines* which are used in cancer treatment.

DNA repair mechanisms
Processes that help genes maintain their stability and integrity.

Dysplasia
Cells that look abnormal under the microscope but are not cancerous.

Endometrial cancer
Cancer that forms in tissues of the uterus (the small, hollow, pear-shaped organ in a woman's pelvis in which a fetus develops). Two types of uterine cancer are endometrial cancer and uterine sarcoma. Endometrial cancer is cancer that begins in cells lining the uterus. Uterine sarcoma is a rare cancer that begins in muscle or other tissues in the uterus.

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

Epidermal growth factor receptor (EGFR)
The protein found on the surface of some cells and to which epidermal growth factor binds, causing the cells to divide. It is found at abnormally high levels on the surface of many types of cancer cells, so these cells may divide excessively in the presence of epidermal growth factor. Also called EGFR, ErbB1, and HER1.

Faecal Occult Blood Test (FOBT)
A test to check for blood in the stool. Small samples of stool are placed on special cards and sent to a doctor or laboratory for testing. Blood in the stool may be a sign of colorectal cancer. Also called FOBT.

Familial Adenomatous Polyposis (FAP)
An inherited condition in which numerous polyps* (growths that protrude from mucous membranes) form on the inside walls of the colon and rectum. It increases the risk of colorectal cancer. Also called familial polyposis and FAP.

Fluoropyrimidine
One of a group of substances used to treat cancer. A fluoropyrimidine is a type of antimetabolite. Examples are capecitabine*, floxuridine, and fluorouracil (5-FU*).

Folic acid
Folic acid is a water soluble vitamin known as vitamin B9. It is required to produce healthy red blood cells*.

Gastrointestinal perforation
Medical emergency in which a hole develops through the wall of any part of the digestive tract from the esophagus to the rectum, including the gallbladder.

Genetic counselling
A communication process between a specially trained health professional and a person concerned about the genetic risk of disease. The person's family and personal medical history may be discussed, and counseling may lead to genetic testing.

Gray (Gy)
Unit to measure energy, generally per kilogram of tissue.

Hemicolectomy
Surgery in which approximately half of the colon is removed. It could be right or left, depending whether the ascending (right) or descending (left) colon is removed.

Hemoglobin
A protein inside red blood cells* that carries oxygen from the lungs to tissues and organs in the body and carries carbon dioxide back to the lungs. Testing for the amount of hemoglobin in the blood is usually part of a complete blood cell (CBC) test. It is used to check for conditions such as anaemia*, dehydration, and malnutrition.

Histopathological examination/histopathology
The study of diseased cells and tissues using a microscope.

Hypertension
A blood pressure of 140/90 or higher. Hypertension usually has no symptoms. It can harm the arteries and cause an increase in the risk of stroke, heart attack, kidney failure, and blindness. Also called high blood pressure.

Infraperitoneal space
Area within the abdominal cavity located below the intraperitoneal space*.

Intraperitoneal space
Area within the abdominal cavity surrounded by a membrane called peritoneum*.

Intravenous
Into or within a vein. Intravenous usually refers to a way of giving a drug or other substance through a needle or tube inserted into a vein. Also called IV.

Irinotecan
Irinotecan is a drug used for the treatment of cancer. Irinotecan prevents DNA from unwinding by inhibition of topoisomerase I. In chemical terms, it is a semisynthetic analogue of the natural alkaloid campthotecin. Its main use is in colon cancer, in particular, in combination with other chemotherapy agents. This includes the regimen FOLFIRI, which consists of infusional 5-fluorouracil, leucovorin, and irinotecan.

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

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

Lymphatic vessel / tissue
The lymphatic tissue is a kind of tissue of which the tissues and organs of the lymphatic system are made. The lymphatic system produces, stores, and carries white blood cells that fight infections and other diseases. This system includes the bone marrow, spleen, thymus, lymph nodes*, and lymphatic vessels (a network of thin tubes that carry lymph and white blood cells). Lymphatic vessels branch, like blood vessels, into all the tissues of the body. They are thin tubes that carry lymph (lymphatic fluid) and white blood cells through the lymphatic system. Also called lymph vessels.

Lymphoma
Cancer that begins in cells of the immune system. There are two basic categories of lymphomas. One kind is Hodgkin lymphoma, which is marked by the presence of a type of cell called Reed-Sternberg cell. The other category in non-Hodgkin lymphomas, which includes a large, diverse group of cancers of immune system cells. Non-Hodgkin lymphomas can be further divided into cancers that have an indolent (slow-growing) course and those that have an aggressive (fast-growing) course. These subtypes behave and respond to treatment differently. Both Hodgkin and non-Hodgkin lymphomas can occur in children and adults, and prognosis* and treatment depend on the stage and the type of cancer.

Lynch syndrome
An inherited disorder in which affected individuals have a higher-than-normal chance of developing colorectal cancer and certain other types of cancer, e.g. endometrial cancer*, often before the age of 50. Also called hereditary nonpolyposis colon cancer and HNPCC.

Magnetic Resonance Imaging (MRI)
An imaging technique that is used in medicine. It uses magnetic resonance. Sometimes, a fluid is injected that enhances the contrast between different tissues to make structures more clearly visible.

Mesorectum
The fold of peritoneum* or mesentery that supports the rectum.

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

Microsatellite instability
A change that occurs in the DNA of certain cells (such as tumour cells) in which the number of repeats of microsatellites (short, repeated sequences of DNA) is different to the number of repeats that was in the DNA when it was inherited. The cause of microsatellite instability may be a defect in the ability to repair mistakes made when DNA is copied in the cell. Also called MSI.

MLH1 mutation
Change in a gene called MLH1, associated with hereditary nonpolyposis colon cancer.

Monoclonal antibody
Monoclonal antibodies are antibodies that are exactly the same because they are produced by clones of the same parent cell.

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

Multidisciplinary opinion
A treatment planning approach in which a number of doctors who are experts in different specialties (disciplines) review and discuss the medical condition and treatment options of a patient. In cancer treatment, a multidisciplinary opinion may include that of a medical oncologist* (who provides cancer treatment with drugs), a surgical oncologist* (who provides cancer treatment with surgery), and a radiation oncologist* (who provides cancer treatment with radiation). Also called tumour board review.

Muscularis propria
Layer of muscle of many organs. It is located next to the submucosa* and is involved in movements such peristalsis.

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

MYH-associated polyposis
Hereditary condition in which there is a tendency to develop multiple polyps* in the colon and higher risk of colon cancer.

Nasogastric tube
Flexible plastic tube used to reach the stomach. It is inserted through the nose.

Necrosis
Refers to the death of living tissues.

Neuroendocrine (carcinomas/cells)
Neuroendocrine cells are type of cells that bring integration between nervous and endocrine systems. In particular, they produce and release hormones into the blood in response to stimulation of the nervous system. Neuroendocrine cells are found throughout the body. Therefore, neuroendocrine carcinomas can start in a number of organs, including the lungs and gastrointestinal tract. They are sometimes slow growing but because they arise from cells that produce hormones, neuroendocrine cancers produce hormones as well or hormone-like substances which excessive level may cause some symptoms.

Oncologist
A doctor who specializes in treating cancer. Some oncologists specialize in a particular type of cancer treatment. For example, a radiation oncologist specializes in treating cancer with radiation.

Ovarian cancer
Cancer that forms in tissues of the ovary. An ovary is one of a pair of female reproductive glands in which the ova, or eggs, are formed. Most ovarian cancers are either ovarian epithelial carcinomas or malignant germ cell tumours. Ovarian epithelial carcinomas is cancer that begins in the cells on the surface of the ovary. Malignant germ cell tumours is cancer that begins in egg cells.

Oxaliplatin
A drug used with other drugs to treat colorectal cancer that is advanced or has come back. It is also being studied in the treatment of other types of cancer. Oxaliplatin attaches to DNA in cells and may kill cancer cells. It is a type of platinum compound.

Palmo-plantar erythema (hand and 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 anticancer drugs. Also called palmar-plantar erythrodysesthesia.

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

Pathologist
A doctor who identifies diseases by studying cells and tissues under a microscope.

Perineural tissue
Tissue around a nerve or group of nerves.

Peritoneum
The tissue that lines the abdominal wall and covers most of the organs in the abdomen.

Peutz-Jeghers syndrome
A genetic disorder in which polyps* form in the intestine and dark spots appear on the mouth and fingers. Having PJS increases the risk of developing gastrointestinal and many other types of cancer. Also called PJS.

Polypectomy
Surgery to remove a polyp.

Polyps (pedunculated or sessile)
Growths that protrude from a mucous membrane. When they are attached to the mucous membrane by a thin stalk they are called pendunculated polyps; if no stalk is present they are sessile polyps.

Positron emission tomography (PET)
A procedure in which a small amount of radioactive glucose (sugar) is injected into a vein, and a scanner is used to make detailed, computerized pictures of areas inside the body where the glucose is taken up. Because cancer cells often take up more glucose than normal cells, the pictures can be used to find cancer cells in the body.

Precancerous lesions
Abnormality in a tissue that does not indicate yet malignancy, however it has signs that cancer is likely to develop in the future.

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

Proteinuria
Higher-than-normal amount of protein in the urine.

Radiofrequency ablation
A procedure that uses radio waves to heat and destroy abnormal cells. The radio waves travel through electrodes (small devices that carry electricity). Radiofrequency ablation may be used to treat cancer and other conditions.

Radiotherapy
A therapy in which radiation is used in the treatment of cancer always oriented to the specific area of the cancer.

RAS gene (mutation*)
A family of genes that may cause cancer when they are mutated (changed). They make proteins that are involved in cell signaling pathways, cell growth, and apoptosis (cell death). Agents that block the actions of a mutated ras gene or its protein may stop the growth of cancer. Members of the RAS gene family include KRAS, HRAS, and NRAS.

Rectoscope
A thin, tube-like instrument used to look inside the anus and rectum. A rectoscope has a light and a lens for viewing. It may also have a tool to remove tissue to be checked under a microscope for signs of disease. A shorter instrument consisting of a thin tube with a light source, used to examine the inside of the rectum is called proctoscope.

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

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

Regorafenib
A drug used for the treatment of colorectal cancer and gastrointestinal stromal tumours. It is oral targeted therapy; a multi-kinase inhibitor that targets receptor tyrosine kinases with mechanisms involved in tumour growth and progression – angiogenesis, oncogenesis and the tumour microenvironment. It inhibits several VEGF* receptor tyrosine kinases that play a role in the growth of new blood vessels in tumour. In addition to VEGFR 1-3, it also inhibits other kinases such as TIE-2, RAF-1, BRAF, KIT, RET, PDGFR and FGFR.

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

Sigmoidoscope/sigmoidoscopy
A thin, tube-like instrument used to examine the inside of the colon. A sigmoidoscope has a light and a lens for viewing and may have a tool to remove tissue.

Special contact techniques/Local contact therapies
Local treatment options, whether radiotherapy* or surgery to treat small tumours.

Sporadic disease/sporadic cancer
Cancer that occurs in people who do not have a family history of that cancer or an inherited change in their DNA that would increase their risk of developing that type of cancer.

Squamous cell carcinoma
Cancer that begins in squamous cells. Squamous cells are thin, flat cells that look like fish scales, and are found in the tissue that forms the surface of the skin, the lining of the hollow organs of the body, and the lining of the respiratory and digestive tracts. Most cancers of the anus, cervix, head and neck, and vagina are squamous cell carcinomas. Also called epidermoid carcinoma.

St John's wort
Hypericum perforatum (St. John's wort) is a popular anti-depressant agent which is also being promoted as an alternative cancer therapy. Even though some preliminary pre-clinical investigations have generated encouraging findings, there are no clinical studies to show that St. John' wort would change the natural history of any type of cancer. St. John's wort may reduce the blood levels of many conventional drugs, including some cancer drugs.

Staging
Performing exams and tests to learn the extent of the cancer within the body, especially whether the disease has spread from the original site to other parts of the body. It is important to know the stage of the disease in order to plan the best treatment.

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

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

Surgical staging/pathological staging
A method used to find out the stage of cancer (amount or spread of cancer in the body) by removing tissue samples during surgery. The pathological stage is based on how different from normal the cells in the samples look under a microscope.

(Biological) targeted therapy/treatment
A type of treatment that uses drugs or other substances, such as monoclonal antibodies, to identify and attack specific cancer cells. Targeted therapy may have fewer side effects than other types of cancer treatments.

Tegafur-uracil (UFT)
A substance being studied in the treatment of some types of cancer. It is a combination of tegafur and uracil. The tegafur is taken up by the cancer cells and breaks down into 5-FU*, a substance that kills tumour cells. The uracil causes higher amounts of 5-FU to stay inside the cells and kill them. Tegafur-uracil is a type of antimetabolite.

Testicular cancer
Cancer that forms in the tissues of the testicle. A testicle (or testis) is one of the two egg-shaped glands, contained in the scrotum, that produce sperm and male sex hormones.

Thrombosis
The formation or presence of a thrombus (blood clot) inside a blood vessel.

Transanal endoscopic microsurgery
Local excision of rectal cancer. It is performed using a special microscope that is inserted via the anus into the rectum.

Turcot syndrome
Condition in which cells in the colon become abnormal and form masses called polyps*. It is also characterized by nervous system tumours.

Ulceration
The development of an ulcer which is a break on the skin, in the lining of an organ, or on the surface of a tissue.

Ulcerative colitis
Chronic inflammation of the colon that produces ulcers* in its lining. This condition is marked by abdominal pain, cramps, and loose discharges of pus, blood, and mucus from the bowel.

Ultrasound (intra-operative and endoscopic)
A procedure in which high-energy sound waves are bounced off internal tissues or organs and make echoes. The echo patterns are shown on the screen of an ultrasound machine, forming a picture of body tissues called a sonogram. Also called ultrasonography.

Vascular (tissue)
Relating to the blood vessels, e.g. the tissue from which blood vessels are made of is called vascular tissue.

Vascular endothelial growth factor (VEGF)
A substance made by cells that stimulates new blood vessel formation. Also called VEGF.

Visceral peritoneum
The layers of tissue that cover the outer surface of most organs in the abdomen, including the intestines.

Warfarin
A drug that prevents blood from clotting. It belongs to the family of drugs called anticoagulants.

X-rays
X-rays are a form of radiation used to take images of the inside of objects. In medicine, X-rays are commonly used to take images of the inside of the body.

The ESMO / Anticancer Fund 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.
These guides are produced by the Anticancer Fund in close collaboration with the ESMO Guidelines Working Group and the ESMO Cancer Patient Working Group.

For more information please visit www.esmo.org and www.anticancerfund.org

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