Liver Cancer

What is liver 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

LIVER 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 the most frequent type of liver cancer called hepatocellular carcinoma and appreciate the best treatment choices available according to the subtype of liver 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 liver 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 patients' 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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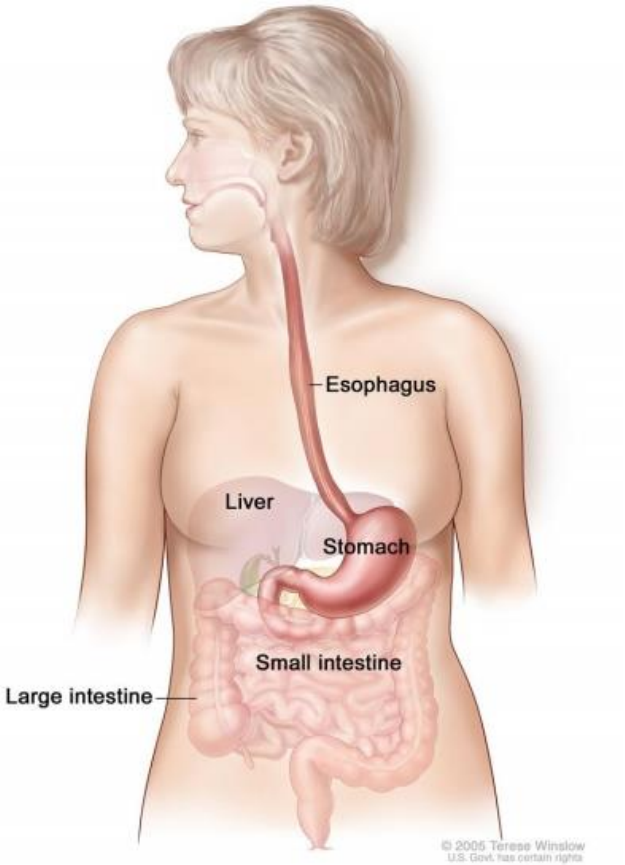
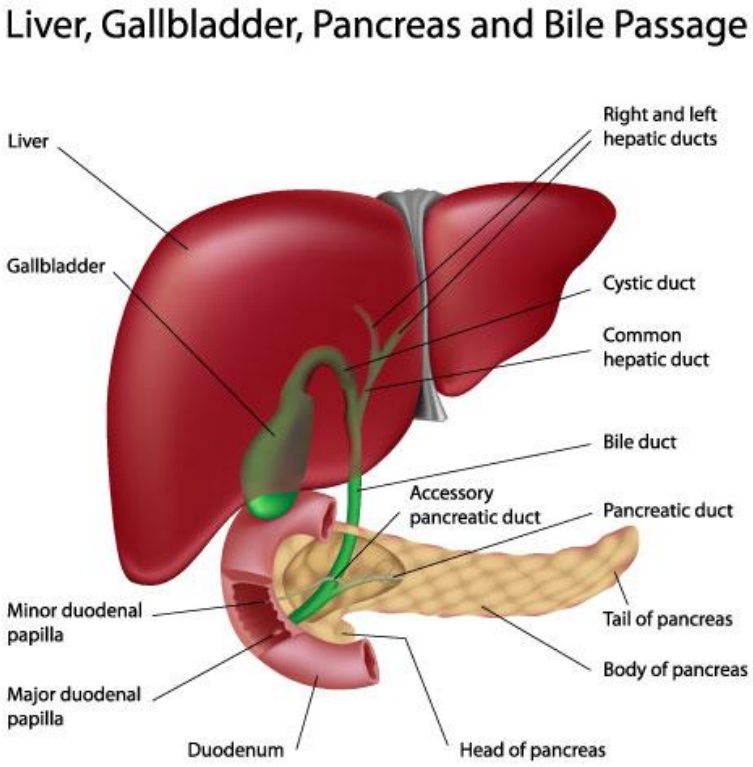
DEFINITION OF LIVER CANCER

Liver cancer is a tumour that initially forms in the tissue of the liver. Different types of liver cancer exist according to the type of cancerous cells.
Hepatocellular carcinoma is the most frequent type of liver cancer. It accounts for 90% of all liver cancers. Hepatocellular carcinoma begins in hepatocytes, the main cells of the liver.



Anatomy of the digestive system.



Anatomy of the liver and surrounding organs

Important note regarding other types of liver cancer

A rare type of liver cancer, mainly occurring in young patients, is called fibrolamellar carcinoma*. This variant is usually well circumscribed, as compared to hepatocellular carcinoma, which grows more invasively. It is also characterized by a central scar when viewed using medical imaging techniques. Fibrolamellar carcinoma* is mostly diagnosed and treated in the same way as hepatocellular carcinoma.

The information provided in this Guide for Patients does not apply to liver cancers that are not hepatocellular carcinoma. The main other types of cancer of the liver are:

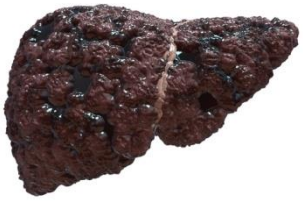
- Tumours developing in the liver but that originated in another organ, for instance colon, stomach or ovary. These tumours are called liver metastases* or secondary liver cancers. Information on the treatment of liver metastasis* is available together with the information dedicated to the cancer where the primary cancer initially occurred.
- Cancers that start in the blood vessels of the liver are called angiosarcomas* and hemangiosarcomas*. For more information about angiosarcomas*, and hemangiosarcomas, click here.
- Cancers that start in the bile ducts are called bile duct cancers or cholangiocarcinomas*. However, if they involve bile ducts in the liver, they are sometimes called liver cancers. For more information on bile duct cancer, click here.
- Tumours called hepatoblastomas* occur in infants and children. For more information about hepatoblastomas*, click here

IS LIVER CANCER FREQUENT?

Liver cancer represents the sixth most common cancer worldwide. In Europe, about 10 in every 1,000 men and 2 in every 1,000 women will develop liver cancer at some point in their life. Worldwide it is much more frequent in South-East Asia and Western Africa. This is mainly due to the fact that infection with the hepatitis B virus increases the risk of developing liver cancer and is more frequent in these areas. In the USA and in Southern Europe, the hepatitis C* virus is seen more frequently as a cause of liver cancer.
In 2008, about 40,000 men and about 20,000 women were diagnosed with liver cancer in Europe.

The median age at diagnosis is between 50 and 60 years, but in Asia and Africa it is usually between 40 and 50 years.

WHAT CAUSES LIVER CANCER?

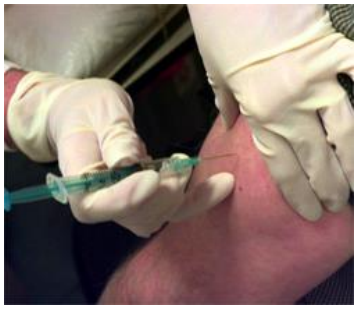


In most patients, cancers of the liver are preceded by cirrhosis of the liver. Liver cirrhosis is a consequence of a chronic liver disease, although only a limited percentage of patients with chronic liver disease will eventually develop cirrhosis. In cirrhosis, tissue of the liver is slowly modified at the expense of normal liver cells and consists more and more of fibrous tissue and scar tissue. The liver cells do not grow or function normally.
The exact mechanisms and reasons why liver cancer occurs are not fully understood. However, cirrhosis and its causes are the main risk factors* of hepatocellular carcinoma, the main type of liver cancer[1].

A risk factor* increases the risk of cancer occurring, but is neither necessary nor sufficient to cause cancer. It is not a cause in itself. **Some people with these risks factors* will never develop liver cancer and some people without any of these risk factors* will nonetheless develop liver cancer.**

The main risk factors* are the ones causing cirrhosis, but others not related to cirrhosis exist as well.

- **Causes of liver cirrhosis:**
  - **Chronic infection with hepatitis-B* virus (HBV) or hepatitis-C* virus (HCV)**. An infection with HBV* or HCV* is considered chronic when the hepatitis virus remains present in the blood for more than 6 months and causes a decline in the functioning of the liver. Worldwide, hepatitis B infection is responsible for 50% and hepatitis C* infection for 25% of all cases of liver cancer. Having chronic hepatitis B* infection increases the risk of developing liver cancer 100-fold and having chronic hepatitis C infection increases the risk 17-fold. Up to 85% of individuals with hepatitis C* infection develop a chronic infection, of these approximately 30% progress to cirrhosis and in these 1 to 2% per year develop liver cancer. Co-infection with HBV*, meaning both viruses occurring at the same time, further increases the risk. Hepatitis B* infection can also cause liver cancer directly, without causing cirrhosis first. The virus can mix its own DNA* (deoxyribonucleic acid) with the DNA of a liver cell, causing mutations* in its genes. These mutations* can lead a cell to lose control over its normal functioning, reproduction and natural cell death. It is generally assumed that if these functions start to get out of control, it can lead to cancer.



It is anticipated that by introducing vaccination everywhere in the world, there would be much fewer cases of hepatitis B*, and also fewer cases of liver cancer related to this virus. It is also anticipated that antiviral treatment against hepatitis B* will reduce liver-related death (including liver cancer) in chronic hepatitis B* infection. Also, recent studies suggest that antiviral treatment of a patient with chronic hepatitis C* infections may reduce significantly his or her risk of liver cancer.

[1] Cirrhosis is not a risk factor* for fibrolamellar carcinoma*.

- **Long-term alcohol abuse** can lead to liver cirrhosis and to liver cancer. In countries where infection by HBV* is low, alcohol is the main cause of liver cancers. Alcohol intake when suffering from hepatitis increases the risk even more.
  Prevention of long-term alcohol consumption can substantially reduce the risk of developing cirrhosis and liver cancer.
- **Some inherited liver conditions** can also cause cirrhosis, such as haemochromatosis or alpha-1-antitrypsin deficiency. Haemochromatosis is a hereditary disease that causes higher absorption of iron from the food. The iron is then deposited in various organs, mainly in the liver. In alpha-1-antitrypsin deficiency an abnormal form of the protein* alpha-1-antitrypsin is deposited in the liver cells. This can cause liver cirrhosis and increase the risk of developing liver cancer.
- **Non-alcoholic fatty liver disease** and **non-alcoholic steatohepatitis** are two conditions affecting the liver that can also lead to cirrhosis and cancer. They are not caused by an infection or by high alcohol intake, but they seem to be linked to severe obesity and diabetes mellitus*. Therefore obesity and diabetes are also seen as risk factors* for liver cancer. Moreover, if a diabetic patient consumes high amounts of alcohol, the risk is a lot more increased.
  Prevention of obesity and type 2 diabetes by adopting a healthy lifestyle can reduce the risk of non-alcoholic fatty liver disease and liver cancer. Lifestyle change interventions in obese or type 2 diabetic people can also reduce this risk.
- There are other, less frequent, medical conditions affecting the liver and increasing the risk of cancer. These conditions include autoimmune hepatitis*, intrahepatic biliary inflammations* (primary biliary cirrhosis* and primary sclerosing cholangitis*) and Wilson's disease*. These conditions are neither caused by an infection, nor by alcohol.

- **Gender**: liver cancer is four to eight times more common in men than in women, although this is probably due to differences in behavior that affects the risk factors* described before.
- Exposure to toxic agents:
  - Anabolic steroids are hormones taken by some athletes to increase their strength and muscle mass. Long-term use of anabolic steroids increases the risk of hepatocellular adenoma, a benign* tumour of the liver which can become malignant* and turn into HCC.
  - Intake of **aflatoxin-contaminated food**: Aflatoxin is a toxic substance produced by a fungus that can grow on food (peanuts, wheat, soybeans, ground nuts, corn, and rice) when stored in warm, damp conditions. When regularly ingested, it can cause mutations* in the DNA* of the liver cells, causing them to become cancer cells.
    Reduction of exposure to aflatoxin-contaminated food may lower the risk of liver cancer, especially in people who are infected with HBV*.

Other factors like smoking have been shown to increase the risk of liver cancer but the evidence is inconsistent. More research is needed to establish these possible risk factors*.

HOW IS LIVER CANCER DIAGNOSED?

Liver cancer can be suspected in different circumstances. Most patients have liver cirrhosis and/or chronic hepatitis before developing liver cancer. People with liver cirrhosis need close surveillance to detect as early as possible a potential liver tumour. The same surveillance is recommended for people infected with HBV* who did not develop cirrhosis and for whom more than 10,000 copies of the virus (viral load) are found per milliliter of blood, and for people infected with HCV whose liver is in advanced stage of fibrosis*. Even though a small subset of patients with non-alcoholic steatohepatitis will develop liver cancer, a similar surveillance is necessary because a cancer can develop in the absence of cirrhosis.

Therefore the circumstances of diagnosis will differ between patients with known liver cirrhosis and patients with no known liver cirrhosis.

Tumour surveillance in patients known to be at risk of developing liver cancer

All patients with liver cirrhosis need close surveillance, as well as some patients with no cirrhosis but with HBV* and HCV* infections, as described above. Every 6 months, an ultrasound* of the liver should be performed, in order to screen for any new nodule*, cyst* or lump* that could turn into cancer.

1. **An ultrasound* test** is used to detect nodules*, which are usually only visible with imaging. When a nodule* is seen on ultrasound*, the following steps depend on the size and the imaging characteristics of the nodule*. These two features give information about the probability that a nodule* might turn into liver cancer.
   - A nodule* smaller than 1 cm should be followed with ultrasound* at intervals of 6 months. The probability that this type of nodule* is, or might turn into, liver cancer within the next months is low.
   - A nodule* between 1 and 2 cm should be investigated with at least two different radiological examinations* (CT-scan* with contrast, ultrasound* or MRI* with contrast).
     - If two different techniques show a typical appearance of liver cancer, the nodule* should be interpreted as such.
     - If that is not the case, the doctor needs to take a biopsy* or remove the nodule* for further examination in a laboratory. A biopsy* is a tissue sample, which in this case is taken using a fine or a thick needle that goes through the skin of the right flank and into the liver, in order to remove a small piece of liver tissue. A sample taken with a fine needle is called fine needle aspiration. Removal of a nodule* can take place during an operation.
   - Sometimes diagnosis is so likely that a biopsy* will not be necessary. The following cases should be considered as proven liver cancer.
     - If an imaging technique shows that the nodule* is bigger than 2 cm and has the typical look of a liver tumour.
     - If there is any nodule* in the liver, and at the same time alpha-fetoprotein* level (see below) in the blood is high (400 ng/ml or more) or continues to increase.

2. **A blood test** for a protein* called alpha-fetoprotein*, or AFP, can give additional information. AFP is normally present at high levels in the blood of foetuses, but its level becomes and stays very low (normal level) shortly after birth. If a higher than normal level is found in the blood of adults, it suggests they may have liver cancer.
   AFP blood tests may be used to look for early tumours in people suffering from cirrhosis*. However, the tests are usually not advised for screening in people without cirrhosis because they are not always accurate. In a minority of liver cancer, there is no increase of the level of AFP in the blood. The level of AFP is also not elevated in fibrolamellar carcinoma*. In many cases, the level of AFP is only elevated at a late stage of liver cancer. In addition, high level of AFP can also be found in other conditions, including non-cancerous liver diseases or tumours developing in other organs like the testis or ovary. In patients with cirrhosis an altered level of AFP is often seen. Therefore this test is only found to be useful in combination with an ultrasound* test.

Possible symptoms of liver cancer

In patients with no specific surveillance as described above, the main symptoms that could be related to liver cancer are the following:

- Unexplainable weight loss
- Fatigue
- Loss of appetite or feeling very full after a small meal
- Nausea or vomiting
- Fever
- An enlarged liver, felt as a mass under the ribs on the right side
- An enlarged spleen, felt as a mass under the ribs on the left side
- Pain in the abdomen or near the right shoulder blade
- Swelling or fluid build-up in the abdomen
- Itching
- Yellowing of the skin and eyes (jaundice)
- Enlarged veins on the abdomen that become visible through the skin

All these symptoms can also be caused by other conditions, or may only be noticed at an advanced stage of liver cancer. However, in case of a combination of several of the symptoms listed above, especially if they persist, further investigations should always be considered.
A deterioration of the liver function can occasionally be detected upon examination of the blood for other reasons. This can be caused by many different conditions and should therefore also lead to further investigations.

Diagnosis

In general, the diagnosis of liver cancer is based on the following examinations:

1. **Clinical examination**
   The doctor will ask about the complaints and symptoms, and examine the abdomen and the rest of the body. The doctor will look for an enlarged liver or spleen, presence of fluid in the abdomen, if there is yellowing of the skin and eyes (indicative for jaundice) or other signs indicating that the liver is not functioning properly.

2. Blood examination

A blood test can reveal elevated levels of alpha-fetoprotein* (AFP), a tumour marker*, but this is seen only in 50-75% of patients with liver cancer. Therefore, if it is not elevated, this does not mean that there is no tumour present. Also, if AFP is elevated, it does not necessarily mean that there is a tumour.

3. Radiological examination*

In the first place an ultrasound* of the liver will be performed to evaluate the consistency of the organ and to look for possible nodules*. In 75% of the cases of liver cancer, the tumours are multifocal at the time of diagnosis. Multifocal means that several nodules* (or tumours) are present in different parts of the liver.

To get a more precise image and to be able to detect smaller nodules*, a CT-scan* or an MRI-scan* might also be performed. An MRI* can be especially useful in patients who already have (benign*) nodules* due to their cirrhosis*. These exams are sometimes performed after intravenous* injection of a contrast liquid, in order to mark any nodule*.

The sequence of tests used for diagnosing liver cancer will depend on the size of the lesions and on the presence of cirrhosis seen after the radiological examinations*.

4. Histopathological* examination

The histopathological* examination is performed on a liver tissue sample called a biopsy*. The decision to perform a biopsy should be discussed with several specialists, including a surgeon specialized in liver surgery. It is the only way to assess whether a lesion seen during a radiological examination* is benign* or malignant*. A biopsy* can be taken using a fine or a thick needle that goes through the skin of the right flank and into the liver to remove a sample of liver tissue. Sometimes an ultrasound* or CT-scan* is used at the same time to make sure the needle goes right into a suspected nodule*. A surgeon can also take a biopsy* during an operation called a laparoscopy*. During laparoscopy*, the surgeon inserts a small camera and fine instruments through one or more small incisions in the skin of the abdomen, in order to see the inside of the abdomen and take a biopsy* without having to make a big incision in the abdomen.

The tissue sample will be examined in a laboratory under a microscope by a specialist called a pathologist*. He may also perform other tests to define the specific type and characteristics of the tumour. However, even if the pathologist concludes the biopsy did not contain any cancer cell, it may not be possible to rule out that the tumour is malignant*.

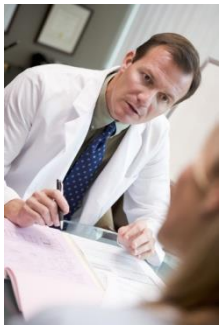
There is a risk of bleeding due to the procedure because the liver is rich in blood vessels and blood coagulation* can be impaired in patients with cirrhosis*. There is also a small risk that a liver biopsy* could spread the cancer along the pathway of the biopsy* needle. If the cancer has not already spread, it is important to avoid this risk. However, this risk is smaller when the biopsy* is taken with a fine needle. There is no risk that a tumour might explode when pierced by a needle.

However, a biopsy* will not be performed in the following situations:

- the patient is considered to be too frail to be able to tolerate any form of therapy
- the patient has an advanced form of cirrhosis* and is on the waiting for liver transplantation
- the patient can be operated with the objective of removing the whole tumour (see paragraph on resectabilty further)

It is also possible in some patients with known cirrhosis* to rely on imaging for the diagnosis. A biopsy can be avoided only when a specific radiological exam* show typical vascular hallmark of liver cancer. This exam can be either a type of CT-scan* (multiple-phase multidetector* CT-scan) or a type of MRI* (dynamic contrast-enhanced* MRI).

WHAT IS IMPORTANT TO KNOW TO GET THE OPTIMAL TREATMENT?



There is not a single best treatment that helps every patient. 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

- Age
- Medical history
- Results of clinical examination. Your doctor will especially:
  - evaluate your nutritional status
  - inspect your skin and eyes looking for any yellowing indicative of jaundice and for any dark skin spots indicative of low platelets level
  - look for indirect signs of increased blood pressure into the vein supplying the liver
  - check if the liver and the spleen are enlarged or if there is a fluid presence in abdomen, called ascites*
  - search for signs of altered mental status within a complex condition called encephalopathy*.
- Presence of other liver diseases and current functioning of the liver, sometimes also called 'residual liver function'. The doctor can examine the liver function through certain parameters in the blood such as prothrombin time*, level of albumin*, level of bilirubin* and number of platelets*.
- Chronic infection with HBV* or HCV*, possible treatment and level of activity of the infection
- Current alcohol consumption
- Drug injection practices
- Performance status, which evaluates cancer patients' general well-being and activities of daily life. The performance status evaluates the patients physical abilities by giving a score from 0, for a fully active patient, to 4 for a patient that is completely disabled due to his/her disease.

Through considering these elements, the doctor will decide whether the patient is in a good condition and is able to undergo resection of part of the liver or liver transplantation.

Relevant information about the disease

- **Staging**

Doctors use staging to assess the extent of the presence of cancer and the prognosis* of the patient. The stage is fundamental in order to make the right decision about the treatment. The more advanced the stage, the worse the prognosis* is. Different investigations are aimed at finding out how far the cancer has grown in- and outside the liver, and whether or not it has already spread to other parts of the body. A CT-scan* or an MRI-scan* of the abdomen will be performed in order to evaluate the local extent of the tumour and whether it has spread to other organs. If there is any

suspicion that the cancer might have spread further away, imaging of other body parts could be performed as well, in particular a chest CT scan* and a bone scan*.
Staging is usually performed twice: after clinical and radiological examination* and after surgery. If surgery is performed, the removed tumour can be examined in the laboratory. The results of this examination may also help staging the disease.

Since most liver cancer occurs on underlying cirrhosis*, the cancer as well as the underlying liver disease (if present) should be staged. Both determine the treatment options and the expected outcome. Several staging system exists and every system has advantages and drawbacks. Here, we will present the 2 fundamental types of staging systems namely, TNM, to stage the cancer, and Child-Pugh, to stage liver disease or cirrhosis. Another more sophisticated system widely used by specialists in liver cancer is also presented. It is called the Barcelona Clinic Liver Cancer (BCLC) staging system and its main advantage is that it identifies those patients with early cancer who may benefit from curative therapies (stage 0 and stage A), those at intermediate (stage B) or advanced stage (stage C) that may benefit from life-prolonging treatments and those with very limited life expectancy (stage D).

- The **TNM staging** classifies the cancer according to the combination of
  - T, size of the tumour and invasion of nearby tissue,
  - N, involvement of lymph nodes*, and
  - M, metastasis* or spread of the cancer to other organs of the body.

  The stages based on the TNM-system are explained in the table below. The definitions are sometimes very technical so it is recommended that you ask your doctor for more detailed explanations.

Stage	Definition
Stage I	*The tumour is unique and has neither invaded blood vessels of the liver nor spread to lymph nodes* or to other parts of the body.*
Stage II	*Either the tumour is unique and has invaded blood vessels of the liver or multiple tumours are found in the liver but none is larger than 5 cm in diameter and none has spread to lymph nodes* or to other parts of the body.*
Stage III	*Stage III is divided into the three following sub-stages. In any case, tumour cells have not spread to the lymph nodes* or to organs that lie further away.*
Stage IIIA	– *Multiple tumours are found in the liver and at least one is larger than 5 cm in diameter.*
Stage IIIB	– *The tumour has invaded a branch of one of the major veins of the liver.*
Stage IIIC	– *The tumour has spread to a nearby organ (other than the gallbladder) or to the outer covering of the liver.*
Stage IV	*The tumour has spread to lymph nodes* or to organs that lie further away.*
Stage IVA	– *Any of the above and invasion of a regional lymph node**
Stage IVB	– *Any of the above and spread of the tumour to other parts of the body*

- The **Child-Pugh score** defines the prognosis* as well as the need for transplantation in chronic liver disease. This score is used for any chronic liver disease and not only for liver cancer. This results in a Child-Pugh score of A, B or C. 'A' indicates less advanced cirrhosis* and 'C' more advanced cirrhosis. It takes into account the accumulation of liquid in the abdomen called ascites*, the level of 2 proteins* (called albumin* and bilirubin*) in the blood, how well blood clotting is still working and the presence of encephalopathy*.

The method used to attribute a Child-Pugh score is complex and is beyond the scope of this guide. It is recommended to ask your doctor for more detailed explanations.

- The **Barcelona Clinic Liver Cancer (BCLC)** staging system

BCLC defines four stages, A to D, of liver cancer. It is based on the size and the number of (the) tumour(s) in the liver, invasion of blood vessels by the tumour, cancer spread outside the liver, blood pressure in the vein going to the liver, level of bilirubin* in the blood, Child-Pugh score and performance status.
The blood pressure in the vein going to the liver (called portal vein*) can be raised when the liver does not let the blood pass through easily, because of a changed consistency. Bilirubin is a protein* that is normally excreted by the liver into the bile. However, when the liver function is impaired, it can be seen in the blood as well. The Child-Pugh score has been described before and takes into account the accumulation of liquid in the abdomen (ascites*), the level albumin* and bilirubin in the blood, how well blood clotting is working and the presence of encephalopathy*. The performance status has been described in the previous section. It evaluates the patients physical abilities by giving a score from 0, for a fully active patient, to 4 for a patient that is completely disabled due to his/her disease.
Because the BCLC includes so many factors, it is found to give the best prediction of the prognosis* for the patient who suffers from cirrhosis* and liver cancer, and to be very useful in planning the treatment.

- **Results of the biopsy***

The biopsy* will be examined in the laboratory. This examination is called histopathology*. The second histopathological* examination is performed on the tumour and the lymph nodes* removed by surgery. This is very important to confirm the results of the biopsy* and to provide more information on the cancer. Results of the examination of the biopsy* should include the following:

First of all, the pathologist* will check if the tumour is actually developed in the liver i.e. a liver tumour, or a distant spread of another tumour (e.g. from the intestines), by examining the tumour cells and determining whether they present the characteristics of liver cells or other cells.
If it is a liver tumour, the pathologist* will define it as a hepatocellular carcinoma or fibrolamellar carcinoma*, or one of the other aforementioned types of liver cancer in the definition of liver cancer.

- **Resectability**

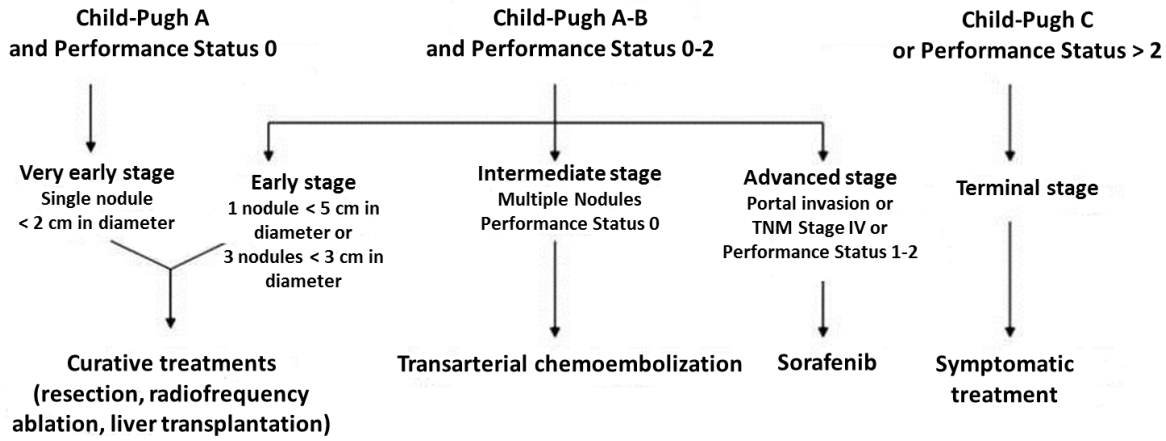
The surgeons will judge a tumour as operable or resectable, meaning that it is possible to remove the complete tumour in an operation, or as not operable or unresectable, meaning that this is not possible to remove it. There is no distinct dividing line between resectable and unresectable in terms of the TNM stage of the cancer, but earlier stage cancers are more likely to be resectable. A tumour can, for example, be unresectable when it is very big or when it is close to an important blood vessel, making it hard to remove it without damaging this vessel.

WHAT ARE THE TREATMENT OPTIONS?

Planning of the treatment involves a multidisciplinary team of medical professionals. This implies a meeting of different specialists, called multidisciplinary opinion* or tumour board review. During this meeting, the planning of treatment will be discussed according to the relevant information mentioned before, such as whether the patient has liver cirrhosis*, what is the extent of the disease, what is the growth pattern of the tumour, how is the liver function, can the cancer be resected and how is the patient's general health status. The risks of each type of treatment are also taken into account.

The extent of the treatment will depend on the stage of the cancer, on the characteristics of the tumour and on the risks involved.
The treatments listed below have their benefits, their risks and their contraindications*. It is recommended to ask doctors about the expected benefits and risks of every treatment in order to be informed of the consequences of the treatment. For some treatments, several possibilities are available and the choice should be discussed in terms of weighing up their respective benefit and risks.

LIVER CANCER



As mentioned in the previous section, the treatment plan mainly depends on the stage according to the Barcelona Clinic Liver Cancer (BCLC) staging system. Treatments by stages are presented in the figure below and details on therapies are given stage per stage further in the text.

Treatment of stage 0 and stage A cancer according to the BCLC classification

For patients with early stage cancers (stage 0 and stage A according to BCLC staging system), it is possible to propose a treatment with the intent of curing the cancer. This treatment can be surgical resection, liver transplantation or local ablation methods and decision will mainly depend on the level of cirrhosis*, and on the size and number of tumours in the liver.*

For these patients, several treatment options are available. The multidisciplinary opinion* will decide which one is most appropriate, according to the relevant information mentioned before. The main 3 options at these stages are:

- Resection of the tumour by surgery
- Liver transplantation
- Local ablation* methods

Resection by surgery

Resection of the tumor by surgery is the preferred option for:

- patients without cirrhosis* and for whom a sufficient part of the liver can be preserved;
- patients with BCLC stage 0 or A whose performance status allows them to undergo surgery and who have a single liver tumor that does not cause any portal hypertension.

In individual cases, more lesions can be safely resected, but since surgery of the liver carries some risks, the risk of the surgery per patient has to be taken into account before making any decision.
Depending on the extent of the tumor and the degree of liver cirrhosis a part of the liver containing the tumor, or the complete liver, can be removed.

The resection of the tumour consists in removing the part of the liver which contains the tumour. This type of surgery is called a partial hepatectomy. This type of surgery can only be performed in patients without cirrhosis* or limited cirrhosis (BCLC stage 0 and stage A), since the liver still functions correctly in these patients. The remaining part of the liver will take over the liver function. After surgery, the resected part will be examined by a pathologist* in the laboratory. The pathologist* will check whether the whole tumour has been removed by analyzing if the tumour is totally surrounded by normal tissue. This is reported either as negative margins of resection, meaning that it is very likely that the whole tumour has been removed or as positive margins of resection, meaning that it is very likely that the whole tumour has not been removed. If margins are negative, it is a sign of a better prognosis*.

Liver transplantation

When a resection of the tumour is not possible, a liver transplantation should be considered either when there is a single tumour of less than 5 cm in diameter, or when there are 2 to 3 tumours, each measuring less than 3 cm in diameter. Those requirements are called the Milan criteria.

- *Criteria to register as a candidate for liver transplantation in patients with liver cancer*

Transplantation is only possible under very strict conditions because of the scarcity of available donor livers. The first condition is that the patient meets the aforementioned Milan criteria

regarding number and size of liver tumours. Regulations on liver donors and transplantations differ from country to country. Country-specific information can be obtained by asking doctor(s) or other professionals involved in liver transplantation. Usually, donor livers come from other patients who recently died, or who are diagnosed 'brain-dead'. Brain-dead means the brain has suffered from oxygen-deficit and therefore will never function again, and breathing and blood circulation can only be maintained by medical equipment. Again, when and how someone can be considered as brain-dead is defined precisely by laws specific to individual countries.
Since these situations are scarce and not every patient can get a donor liver, the patient first has to be judged fit enough for the surgery. Also his or her overall prognosis* should be good enough to be registered on the waiting list.
Patients who suffer from liver cirrhosis* caused by alcohol abuse and are still using alcohol, or patients who have a poor prognosis* due the characteristics of their cancer or due to other concurrent diseases, will not be considered for transplantation. Some centers with a lot of experience are able to perform split-liver transplants (in which several patients get a part of one donor liver), transplants with marginal grafts (livers that are not perfectly healthy) or live donor liver transplantation (meaning a part of the liver of a healthy living donor is transplanted to the patient). Since these are exceptional situations, the possibility for each patient has to be evaluated by the ethics committee as well as by the transplant advisory board of the hospital.

- *Procedure of a liver transplantation*

A liver transplantation is an operation under general anaesthetic* that usually takes 6 to 10 hours. During this time the surgeons will first make an incision shaped like a boomerang on the upper part of the abdomen and remove the patient's old liver, leaving portions of the major recipient blood vessels in place. The new liver will then be inserted and attached to these blood vessels and to the patient's bile ducts.

- *Therapies for patients awaiting liver transplantation*

Owing to organ shortage, liver transplant candidates are confronted with long waiting times, which must not delay the discussion about an alternative effective treatment. In the case of a long anticipated waiting time (>6 months), patients may be offered resection, local ablation* or trans-arterial chemoembolization* in order to minimize the risk of tumour progression and to offer a 'bridge' to transplant. Details on techniques of local ablation and trans-arterial chemoembolization are provided further in this guide.

Local ablation* methods

The goal of local ablation* is to destroy cancer cells by targeting them with chemical or physical means. The two main local ablation methods are radiofrequency ablation and percutaneous* ethanol injection, which will be described further. While these techniques are effective in destroying small tumours, they unfortunately do not prevent the occurrence of new lesions in the surrounding cirrhotic* liver tissue.

They have been put forward as alternatives for surgery. In patients with BCLC stage 0 and who cannot undergo surgical resection or liver transplantation, these techniques are recommended. They are also recommended in the case of a long anticipated waiting time (>6 months) for liver transplantation.

These two techniques show similar results for BCLC stage 0 tumours, i.e. a single nodule* of less than 2 cm in diameter, and they can be considered alternatives to resection. However, radiofrequency ablation gives better results in terms of control of the tumour growth in tumours larger than 2 cm in diameter.

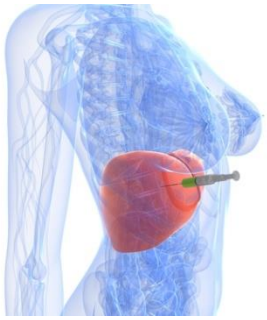
Radiofrequency ablation

Radiofrequency ablation uses high-energy radio waves to destroy cancer cells. A thin, needle-like probe* is inserted through the skin and into the tumour. A high-frequency current is then passed through the tip of the probe. This heats the tumour and in this way destroys the cancer cells. At the same time, heat from radiofrequency energy closes small blood vessels and decreases the risk of bleeding. The dead tumour cells are gradually replaced by scar tissue that shrinks over time. An ultrasound* or a CT-scan* may be used to guide the ablation. The procedure usually takes place under local anaesthetic*, but sometimes it is also performed during open surgery or during laparoscopy*, and thus under general anaesthetic*. During laparoscopy*, the surgeon inserts a small camera and fine instruments through one or more small incisions in the skin of the abdomen. This helps to see the inside of the abdomen and perform interventions without having to make a big incision in the abdomen.

Radiofrequency ablation is most effective in cancers with up to five nodules* and a diameter of no more than 5 cm. In bigger tumours, it is unlikely that they can be completely destroyed by this technique. When a tumour is close to major blood vessels there might be a risk of bleeding and radiofrequency ablation is therefore not advised.

Percutaneous* ethanol injection

Percutaneous* ethanol injection uses ethanol (concentrated alcohol) to scorch the tumour. The ethanol is injected through the skin directly into the tumour. Sometimes an ultrasound* or CT-scan* is used to guide the needle right into the tumour. Percutaneous ethanol injection has been shown to be less effective than RFA in nodules* larger than 2 cm in diameter.



Treatment of stage B cancer according to the BCLC classification

For patients with intermediate stage cancer (stage B according to BCLC staging system), the treatment consists in injecting an anticancer drug and a coil or small degradable particles directly in the artery that supplies the liver with blood. This type of treatment is called transarterial chemoembolization*.*

Transarterial* chemoembolization* (TACE)

In addition to patients with BCLC stage B cancer, patients awaiting liver transplantation can benefit from transarterial chemoembolization* or TACE, to bridge the waiting time if this exceeds 6 months.

TACE is the injection of an anticancer drug directly in the artery that supplies the liver with blood (hepatic* artery). This requires introducing a catheter* into the artery in the groin and leading it into the hepatic* artery. This procedure is done while using an X-ray* to make sure the catheter* is in the

vessel(s) supplying the tumour with blood. The drug used is a chemotherapy*, meaning it aims to kill cancer cells and/or limit their growth. Through the blood vessels the drug reaches the cancer cells and the normal liver cells, but the latter break down the drug before it reaches the rest of the body. Anticancer drugs that can be used are doxorubicin*, cisplatin* and/or mitomycin*. Lipiodol* can also be mixed with the chemotherapeutic* drugs before they are injected. Tumour cells preferentially absorb lipiodol and will at the same time absorb the drugs.
After injection of this drug, either gel foam or small degradable balls are injected to block the small arteries providing blood to the tumour and to cut the tumour's provision of nutrients and oxygen.

TACE can also be used to relieve symptoms experienced by patients with hepatocellular cancer and cirrhosis*. The goal is not to cure the cancer, but to make the patient feel more comfortable. However, as the size and number of tumours in the liver increase, results of TACE are less favorable.
TACE should not be used in patients with

- liver cirrhosis grade C according to Child-Pugh,
- spread of the tumour in 2 lobes of the liver or to other body parts,
- portal-vein thrombosis, or
- an exceptional connection between the artery and the main vein that are going to the liver.

Portal vein* thrombosis is the formation of blood clots in the main vein going to the liver. This is to avoid the toxic drugs being injected ending up somewhere other than the location of the tumour.

Other transarterial* techniques

Transarterial techniques have evolved during the last years. Several alternatives to the typical TACE described before are emerging.

The use of small beads loaded with doxorubicin* (chemotherapy*) instead of the classical TACE aims at embolizing* the vessels supplying the tumour(s) and delivering doxorubicin to the tumour at the same time. These beads have demonstrated less diffusion of chemotherapy outside of the liver, resulting in fewer side effects and at least the same activity than classical TACE.

Internal radiation* with Iodine 131 or Yttrium 90 particles aims to embolize* as well as to bring radiation* therapy* very close to the tumour. This type of treatment is experimental and must be performed in a clinical trial*. 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 Iodine 131 or 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. Due to the precise targeting of this approach, it can deliver a much more potent dose of radiation* than the usual external radiation* therapy*. The radioactivity of the balls is gone after 2 weeks. An advantage is that it can be used regardless of how numerous or how big the nodules* in the liver are, and it can also be used to treat tumours possibly undetected. It can be used in some patients who cannot receive TACE or who already received TACE, but not in patients with cancer which has spread outside the liver.

Sorafenib* in case of progression of the disease despite TACE
In patients whose disease is progressing (development of new tumours or growth of existing tumours), a treatment with drug called sorafenib* is recommended.

Treatment of stage C cancer according to the BCLC classification

The standard treatment at this stage is sorafenib, a drug taken orally. If sorafenib is not well tolerated or if the cancer progresses despite treatment with sorafenib, supportive care and participation to clinical trials* are recommended.*

Because the tumour has spread away from the liver, either to lymph nodes* or to distant organs, the treatment will aim at targeting cancer cells all over the body. This is called systemic therapy*. The main option is sorafenib*. If sorafenib is not well tolerated or is not able to affect the growth of the tumour, the treatment will aim at relieving the symptoms caused by the disease. It is also possible to participate to a clinical trial*. In clinical trial*, new treatments or new combinations of treatments are tested. It is advised to ask the doctor if there are trials going on that are appropriate for the stage of tumour and the specific situation of the patient. In this way the patient can get access to new therapies, and at the same time help scientific progress in relation to developing better cancer treatments.

Systemic therapy*

Sorafenib* is a drug that has shown to prolong overall survival in patients with advanced liver cancer. For example, it extended survival for an average of 2.8 months for patients with Child–Pugh grade A liver disease in a randomized clinical trial*. It is taken orally and reaches the whole body through the blood stream after absorption by the intestines. Sorafenib is called a targeted therapy* since it has been made with the goal of specifically targeting tumour cells.
Other targeted therapies* are under investigation but should not be given outside of clinical trials*.

Chemotherapy* that is given systemically, meaning either orally or in an intravenous* manner and thus not by injection into the artery of the liver, can also be considered. However, none of the chemotherapy* drugs used for liver cancer have shown to prolong the patient's life expectancy, but some chemotherapy regimens like XELOX (consisting of a combination of capecitabine* and oxaliplatin*) and GEMOX (combination of gemcitabine* and oxaliplatin) have shown that they could stop or slow the growth of tumour in some patients. Systemic chemotherapy* should not be included in standards of care, but may be discussed with and offered to selected candidates for systemic treatment* if no other options are available in the hospital where the patient is treated.

Radiotherapy

Radiotherapy uses radiation* to kill cancer cells. It is under investigation for patients with liver cancer whose tumour has invaded the portal vein* or the inferior vena cava. Radiotherapy can be used in case of one large tumour with a few satellites (smaller tumours around it) and a sufficient amount of healthy liver to be spared. Possible techniques are the following:

- Radioembolization* with yttrium-90 microspheres* for patients who suffer from blood clots blocking a branch of one of the main veins of the liver, called portal vein* thrombosis. This treatment has been described before.

External radiotherapy by three-dimensional conformal radiotherapy (3D-CRT). Radiations* are produced by a device outside of the body and are then directed towards the tumour. It is called 3D-conformational because, unlike with classic external radiotherapy technique, a computer calculates the exact direction and shape of the radiation* beams. This helps to direct them very precisely to the tumour and to leave as many normal liver cells as possible unharmed. This promising strategy needs however further validation before it can be recommended.

Treatment of stage D cancer according to the BCLC classification

The standard treatment at this stage is to relieve the symptoms caused by the disease.

For patients with stage D cancer according to the BCLC classification, best supportive care is offered. The goal of best supportive care is not to cure the cancer or to prolong survival. It aims to reduce symptoms and maximize the patient's comfort.

Effective medications exist to control pain, nausea and other symptoms. It is important to tell the doctor or nurse about any discomfort in order to adapt the medication according to their needs.

Jaundice is the yellow discoloration of skin and eyes. It is caused by an excess of bilirubin* that is no longer excreted by the liver because it is blocked by the tumour. It is a very frequent problem for patients with advanced liver cancer. It can be treated by inserting a stent into the biliary duct, either during a surgical intervention or during an endoscopy*. A stent is a small hollow tube that ensures a free passage of the excess of bilirubin into the intestines.

External radiotherapy may be used to control pain caused by bone metastases*.

How is the effect of the treatment measured?

In patients with advanced cancer, it can be difficult to measure the effect of the treatment, especially when the cancer is composed of several tumours. The best way to evaluate if the treatment has a positive effect is to evaluate:

- How the tumour responds to the treatment by using imaging techniques, such as CT-scan* or MRI*. Dynamic techniques of CT-scan or MRI, requiring the injection of a contrast agent, are recommended since they allow observing a decreased activity of the tumour even in the absence of reduction of the size of the tumour. Many of the therapies used to treat liver cancer can actually kill cancer cells or reduce blood supply to the tumour without necessarily causing reduction in tumour size.
- How the patient feels during and after the therapy.
- How the level of alpha-fetoprotein* in the blood evolves over time. This can be particularly useful in patients for whom imaging techniques do not give much information on the tumour response.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF THE TREATMENT?

Risks and side effects of surgical removal of part of the liver

Removal of a part of the liver is a high-risk surgical procedure. There are several risks and it can cause unwanted health problems, called complications. Complications can usually be treated, but are sometimes difficult to treat and can even be fatal.

Some risks are shared by all surgical interventions performed under general anaesthesia*. These complications are infrequent and include deep vein thrombosis*, heart or breathing problems, infection, or reaction to the anaesthesia. Although there are risks, doctors will take the most appropriate steps to minimize them.

Excessive bleeding is the main risk of surgery of the liver in patients with liver cancer. The liver normally controls blood clotting and any damage done to the liver before or during surgery can increase bleeding. Liver failure is another complication of liver surgery, especially in patients whose liver function is not optimal because of a chronic liver disease.

Risks and side effects of liver transplantation

A liver transplantation is major surgery and there is risk of serious complications. The risks of the surgery include excessive bleeding, infections or complications from the anaesthesia*. Bleeding can occur because the liver normally controls blood clotting and may not be able to do so during the first days after it has been transplanted.
After the transplantation, the immune system* might start fighting the new 'unknown' organ. This reaction is called rejection and should be avoided if possible, as it can harm the new liver. Signs of a rejection can be fever, fatigue, breathlessness, itchy feeling and jaundice, which is a yellow discoloration of the skin and the eyes.

The patient will have to take drugs that suppress his or her immune system* for the remainder of his/her life so as to avoid a rejection. The most common anti-rejection drugs are:

- Tacrolimus
- Azathioprine
- Prednisolone or other corticosteroids
- Cyclosporin
- Mycophenolate mofetil or drugs called mTOR inhibitors* (sirolimus, everolimus).

The most important side effect of this suppression is that the patient is very susceptible to infections. It is important to take some precautions to decrease the risk of infection. Hands should be washed regularly and contact with people who might be sick or have a cold should be avoided. The patient should avoid staying in enclosed spaces with a lot of people or consider wearing a mouth mask. Anti-rejection drugs also increase the risk of a new cancer occurring. This is because they also suppress the action of the immune system* against malignant* cells that can develop anywhere in the body. Other side effects include high blood pressure, high cholesterol, diabetes*, and weakening of the bones and kidneys. For this reason, and also to detect a rejection as soon as possible, the blood will be examined regularly. When a rejection occurs, an increase of anti-rejection medications can usually

help the patient recover. Doctors will also propose a close follow-up to monitor liver function and to detect any new tumours as soon as possible.

Side effects of local ablation* methods

Possible side effects after radiofrequency ablation therapy include abdominal pain, infection in the liver, and bleeding into the chest cavity or abdomen.

The most common adverse effects of percutaneous* ethanol injection are pain and fever. Pain most often is localized to the injection site but can occasionally be experienced elsewhere in the abdomen related to leakage of alcohol onto the surface of the liver and into the abdominal cavity.

Side effects of transarterial* chemoembolization* (TACE)

Transarterial* chemoembolization* can cause some nausea, pain or fever after the treatment. Because the drugs do not reach the rest of the body in high concentrations, the other side effects are less severe than in classic chemotherapy*. They can, however, still cause some fatigue, hair loss, diarrhea and decreasing blood cell counts.

Side effects of sorafenib*

The most common side effects (seen in more than 1 patient in 10) of sorafenib include:

- fatigue
- diarrhea
- redness, tenderness, swelling, blistering on the palms of the hands or soles of the feet (called hand-foot syndrome)
- skin rash and skin redness
- nausea and vomiting
- loss of appetite
- high blood pressure
- pain
- swelling
- bleeding
- hair loss
- increased levels of some enzymes produced by the pancreas (amylase and lipase)
- low level of lymphocytes (a type of white blood cell*) in the blood
- low level of phosphate in the blood

Other less common side effects can occur. Any symptom experienced during the treatment with sorafenib* should be reported to your doctors.

Side effects of chemotherapy*

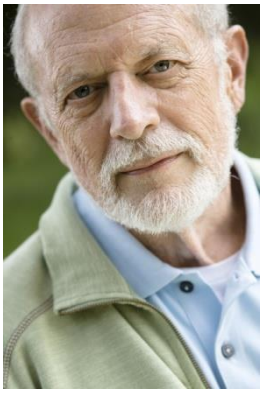
Common side effects of chemotherapy* include fatigue, hair loss, mouth sores, loss of appetite, nausea, vomiting and diarrhea. The drugs can also cause low blood cell counts, leading to an increased chance of infections (due to low white blood cell* counts), easy bruising or bleeding (due

to low blood platelet* counts) and fatigue (due to low red blood cell* counts). Chemotherapy* can be harmful for a baby, so it is important not to be pregnant during the treatment. Beside these, doxorubicin* may cause a temporary red color of the urine, sensitivity to sunlight, watery eyes and in some patients even a permanent loss of fertility. Cisplatin* can damage the kidneys, therefore it is important to drink a lot of water during the treatment. It can also cause some hearing loss.
However, most of these side effects are treatable and temporary.

Side effects of external radiotherapy

Side effects of external radiation* therapy* (like 3D-CRT) include sunburn-like skin problems where the radiation* enters the body, nausea, vomiting, and, most often, fatigue.

WHAT HAPPENS AFTER TREATMENT?



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

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

After transplantation, the patient will have to take drugs that suppress the immune system*, in order to prevent the immune system* from starting to reject the new 'unknown' organ. The most important side effect of this suppression is that the patient is very susceptible to infections. It is advised to take certain precautions so that the risk of infections is always minimal. These precautions include washing hands regularly, avoiding contact with people who are sick or even have a simple cold, and wearing a mouth mask when close contact with other people cannot be avoided.

Follow-up with doctors

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

- evaluate adverse effects of the treatment and treat them
- provide psychological support and information to enhance returning to normal life
- detect possible recurrence* as soon as possible
- after a transplantation
    - detect rejection as soon as possible
    - adjust the dosage of the anti-rejection drugs
    - detect and treat any infection as soon as possible
    - evaluate the functioning of the new liver
    - detect a new tumour (due to the effect of anti-rejection drugs) as soon as possible

Following partial hepatectomy or radiofrequency ablation or percutaneous* ethanol injection, the patient will be proposed to return to the doctor every 3 months for the first two years and every 6 months afterwards.
Following transplantation, follow-up visits will be scheduled in a specialized transplantation centre with the frequency of once monthly for up to 6 months, then once every 3 months for up to 1 year, then twice a year up to 2 years and once a year every year thereafter.
Following transarterial* chemoembolization* or sorafenib* or chemotherapy*, a visit to the doctor is recommended every 2 months to guide further therapy decision.

During the follow-up visits the doctor will

- ask for signs and symptoms

- perform a physical examination and look for signs of gradual loss of function of the liver (liver decompensation)
- draw blood to examine the function of the liver and the level of AFP*
- arrange appointments for a CT-scan*, or MRI* to check the effect of the treatments and to detect any sign of the cancer coming back in the liver or elsewhere in the body.

After a liver transplant, regular blood tests are also important to identify signs of the body rejecting the new liver. Sometimes liver biopsies* are taken to see if rejection is occurring and if changes are needed in the anti-rejection medicines.

In some patients suffering from hepatitis B* or C*, a treatment with antiviral drugs and/or interferon* can be useful to slow down the evolution of cirrhosis* and to maintain the current liver function. If they were already on antiviral treatment before the cancer, this should be resumed if possible.
Close monitoring of the liver function, also in patients without hepatitis, can guide doctors in their efforts to keep the liver working as well as possible.

Return to normal life

It can be hard to live with the idea that the cancer can come back. Today we do not know any specific way of decreasing the risk of recurrence*, which is the medical term for the cancer's coming back. Especially if the cancer was caused by a disease (cirrhosis* due to Hepatitis B* or C* or alcohol abuse), the underlying disease will not be cured by the cancer treatment and will continue to be a risk for recurrence.

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

What if the cancer comes back?

If the cancer comes back, it is called a recurrence* and the treatment depends on the extent of the recurrence.
After treatment by surgery, it is not uncommon that the cancer will come back. It is estimated that half to two thirds of the patients operated will experience a recurrence within 5 years after surgery. New lesions are either metastases* in the liver from the first cancer (often within 2 years following surgery) or a new liver cancer in the remaining liver (occurring beyond 2 years after surgery).
If the cancer comes back locally (meaning only in the liver) the doctors will again decide whether the tumour is resectable or not.

If the tumour is resectable, surgery will be considered.
Sometimes, after a partial liver resection for liver cancer, the tumour might come back on different spots in the remaining part of the liver. In specialized centers, the possibility of liver transplantation might be discussed in these cases. When a cancer comes back inside the new liver after transplantation, the doctors will consider liver resection, re-transplantation or medical treatment, according to the extent of the recurrence* and the other relevant information mentioned above.

If the tumour is not resectable, ablative treatments alone or sorafenib* may be applied.
If there is no cirrhosis* and the surgeons decide the tumour to be unresectable, TACE, or sorafenib* may be applied.

If the tumour comes back after transplantation and spreads outside the liver, sorafenib* is the treatment of choice for selected patients.

DEFINITIONS OF MEDICAL TERMS

(Local) Ablation
Removal or destruction, of tissues using physical or chemical means.

Albumin
A type of protein found in blood, egg white, milk, and other substances.

Alpha-fetoprotein (AFP)
A protein* normally produced by a fetus. AFP levels are usually undetectable in the blood of healthy adult men or women (who are not pregnant). An elevated level of AFP suggests the presence of either a primary liver cancer or germ cell tumor.

Anaesthetic
Substance that causes lack of feeling or awareness. It can be local (causing loss of feeling in a part of the body) and general (putting the person to sleep).

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

Angiosarcoma
A type of cancer that begins in the cells that line blood vessels or lymph vessels. Cancer that begins in blood vessels is called hemangiosarcoma*. Cancer that begins in lymph vessels is called lymphangiosarcoma.

Ascites
Abnormal buildup of fluid in the abdomen that may cause swelling. In late-stage cancer, tumor cells may be found in the fluid in the abdomen. Ascites also occurs in patients with liver disease.

Autoimmune hepatitis
Disease in which the body's immune system* attacks the liver cells, possibly due to genetic predisposition or acute liver infection. In any case this reaction is abnormal. It is characterized by a chronic and progressive inflammation of the liver and it can lead to cirrhosis* and liver failure.

Benign
Not cancerous. Benign tumours may grow larger, but do not spread to other parts of the body. Also called nonmalignant.

Bilirubin
Substance formed when red blood cells* are broken down. Bilirubin is part of the bile, which is made in the liver and is stored in the gallbladder. The abnormal buildup of bilirubin causes jaundice.

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.

Bone scan
A procedure to check for abnormal areas or damage in the bones. A very small amount of radioactive material is injected into a vein and travels through the blood. The radioactive material collects in the bones and is detected by a scanner (a special camera that takes pictures of the inside of the body). A bone scan may be used to diagnose bone tumours or cancer that has spread to the bone. It may also be used to help diagnose fractures, bone infections, or other bone problems.

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

Catheter
A tube that can be inserted into the body. It has many uses, including draining or administering fluids or gases.

Chemoembolization
A method in which a chemotherapeutic* drug is delivered through a catheter* to an artery along with a blood vessel occluding agent right at the site of the tumour. The result is that a very highly concentrated dose of anticancer drug is delivered and the blood vessels are partially blocked with the occluding agent to starve the tumour of its blood supply. This can slow down or stop tumour growth and may also shrink the tumour.

Chemotherapy/Chemotherapeutic
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.

Cholangiocarcinoma
A rare type of cancer that develops in cells that line the bile ducts in the liver. Cancer that forms where the right and left ducts meet is called a Klatskin tumour.

(Liver) Cirrhosis
Liver cirrhosis is a condition in which normal liver tissue is replaced with fibrosis* or scar tissue. It is most commonly caused by alcoholism, hepatitis B and C and some liver diseases. It leads to loss of liver function. In most advanced stages, a liver transplant is the only option.

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

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

Coagulation
The normal process in which blood forms clots with the goal of stopping bleeding. Coagulation disorders (or clotting disorders) can either cause abnormal or excessive bleeding or cause obstructive clotting.

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.

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.

Cyst
A sac or capsule in the body. It may be filled with fluid or other material.

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

Diabetes (mellitus)
Any of several diseases in which the kidneys make a large amount of urine. Diabetes usually refers to diabetes mellitus in which there is also a high level of glucose (a type of sugar) in the blood because the body does not make enough insulin or use it the way it should.

DNA
Abbreviation for deoxyribonucleic acid. DNA serves as the carrier of genetic information.

Doxorubicin
A drug that is used to treat many types of cancer and is being studied in the treatment of other types of cancer. Doxorubicin comes from the bacterium Streptomyces peucetius. It damages DNA* and may kill cancer cells. It is a type of anthracycline antitumour antibiotic.

Dynamic contrast-enhanced (MRI)
Acquisition of MRI images using a contrast substance injected into a vein. This imaging method allows analysis of the blood vessels in a tumour, before, during and after the contrast injection, as opposed to the conventional contrast-enhanced MRI in which a single snapshot is obtained after the contrast injection.

Embolize/Embolization
The blocking of an artery by a clot or foreign material. This can be done as treatment to block the flow of blood to a tumour.

Encephalopathy
Any one of various diseases of the brain.

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

Fibrolamellar carcinoma
Rare subtype of hepatocellular carcinoma, affecting young adults typically. Under the microscope, it is characterized by the presence of fibrous layers of tissue between the cancer cells.

Fibrosis
The growth of fibrous tissue.

Gemcitabine
The active ingredient in a drug that is used to treat pancreatic cancer that is advanced or has spread. It is also used with other drugs to treat breast cancer that has spread, advanced ovarian cancer, and non-small cell lung cancer that is advanced or has spread. It is also being studied in the treatment of other types of cancer. Gemcitabine blocks the cell from making DNA* and may kill cancer cells. It is a type of antimetabolite.

Hemangiosarcomas
A type of cancer that begins in the cells that line blood vessels.

Hepatic
Hepatic refers to the liver. A hepatic vein is a vein that drains blood away from the liver; a hepatic disease is a disease that affects the liver.

Hepatitis-B (HBV)
Infection of the liver caused by the hepatitis B virus (HBV). HBV is carried and passed on to others through the blood or sexual contact. Infants born to infected mothers may also become infected with the virus.

Hepatitis C (HCV)
Infection of the liver caused by the hepatitis C virus (HCV). HCV causes long-lasting inflammation and may lead to cirrhosis* and liver cancer. Hepatitis C is transmitted through contact with infected blood and occasionally by sexual intercourse.

Hepatoblastoma
A very rare type of liver tumour originating from immature liver cells and occurring in infants and children.

Histopathology
The study of diseased cells and tissues using a microscope.

Immune system
The immune system is a biological system of structures and processes that protects the body from diseases by identifying and killing tumour cells and foreign invaders such as viruses and bacteria.

Intrahepatic biliary inflammation
Swelling of the intrahepatic bile ducts, which are bile ducts located within the liver that collect the bile produced by the liver. It is characterized by fever, tiredness, right upper abdominal pain, itching and jaundice. It can lead to cirrhosis* and liver failure.

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.

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

Lipidiol
A form of poppy seed oil that contains iodine. Lipiodol is given by injection and builds up in the blood and lymph vessels in tumours. It is used for imaging (taking pictures) of the salivary glands and the lymph system. It is also being studied in the imaging of other organs such as the liver, lung, stomach, and thyroid. It is a type of diagnostic imaging agent. Also called ethiodized oil and iodized oil.

Lump
A lump is a kind of swelling. It mainly refers to breast tumours.

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.

Malignant
Malignant is used to describe a severe and progressively worsening disease. A malignant tumour is synonym for cancer.

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

Microsphere
A very tiny, hollow, round particle made of glass, ceramic, plastic, or other materials. Microspheres injected into blood vessels that feed a tumour may kill the tumour by blocking its blood supply. They can also be filled with a substance that may help kill more tumour cells.

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.

Mitomycin
A drug used to treat advanced cancer of the stomach and pancreas that has not gotten better with other treatment. It is also being studied in the treatment of other types of cancer. Mitomycin C comes from bacteria. It damages the cell's DNA and may kill cancer cells. It is a type of anticancer antibiotic.

mTOR inhibitors
Group of anticancer drugs that attach to a protein* located inside the cells to form a complex that blocks another protein called mammalian target of rapamycin (mTOR). This protein, among other functions, regulates cell division and may be more active in cancer cells leading to uncontrolled cell proliferation.

Multidisciplinary opinion
A treatment planning approach in which a number of doctors who are experts in different areas (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.

Multiphase multidetector (CT-scan)
Imaging method that uses the principle of CT-scan* but allows multiple slices of the body to be captured at the same time (within the same breath hold). It also uses a contrast substance that allows the evaluation of organs and tissues at different phases depending on the distribution of the contrast. In the liver for example, images are taken both when the contrast substance is seen in the hepatic artery and when it is seen in the portal vein.

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.

Nodule
A small lump* which may have formed due to abnormal formation of cells. Nodules are often benign* and painless, but they can influence the function of the organ on which they develop.

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.

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

Percutaneous
Passing through the skin, as an injection or a topical medicine.

Performance status
The performance status evaluates the patient's physical abilities by giving a score from 0, for a fully active patient, to 4 for a patient that is completely disabled due to his/her disease.

(Blood) platelet
Small cell fragments that play a fundamental role in the formation of blood clots. Patients with a low platelet count are at risk of severe bleeding. Patients with a high count are at risk of thrombosis, the formation of blood clots that can block blood vessels and result in stroke or other severe conditions, and can also be at risk of severe bleeding because of platelet dysfunction.

Portal vein
A blood vessel that carries blood to the liver from the intestines, spleen, pancreas, and gallbladder. Also called hepatic portal vein.

Primary biliary cirrhosis
Liver disease characterized by scarring and fibrosis* due to progressive and slow destruction of liver cells by bile. Primary biliary cirrhosis is characterized by the destruction of the bile duct cells in the liver, possibly caused by an abnormal allergic reaction against the bile duct normal cells (autoimmune reaction). Since the bile ducts are destroyed, the bile, that normally digests food, builds up in the liver and destroys liver cells gradually.

Primary sclerosing cholangitis
Chronic inflammation of the bile ducts possibly caused by an abnormal allergic reaction against the normal bile duct cells (autoimmune reaction). The bile ducts are destroyed progressively and areas of scarring and fibrosis* develop, causing narrowing of some parts of the bile ducts. Consequently the bile builds up within the liver and eventually will destroy liver cells.

Probe
It is a long and thin instrument used to explore wounds, cavities or body passages.

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

Protein
Essential nutrients that are made of amino acids. They are essential for the working of many organisms including the human body. They are responsible for transport and communication between cells, for chemical changes and maintain the structure of , amongst others, cells.

Prothrombin time
A blood test evaluating clotting abilities. It is used for diagnosis and monitoring of some bleeding disorders and for adjusting the dose of drugs used to prevent clots formation.

Radiation
Can be defined as energy travelling through space. Examples of radiation include UV, and x-rays* which are commonly used in medicine.

Radiation therapy
A therapy in which radiation* is used in the treatment of cancer always oriented toward the specific area of the cancer.

Radioembolization
A type of radiation* therapy used to treat liver cancer that is advanced or has come back. Tiny beads that hold the radioisotope yttrium Y 90 are injected into the hepatic* artery (the main blood vessel that carries blood to the liver). The beads collect in the tumour and the yttrium Y 90 gives off radiation. This destroys the blood vessels that the tumour needs to grow and kills the cancer cells. Radioembolization is a type of selective internal radiation therapy (SIRT).

Radiological examination
Test that uses imaging technology (such as radiography, ultrasound*, computed tomography and nuclear medicine) to visualize organs, structures and tissues within the body to both diagnose and treat diseases.

Randomized clinical trial (RCT)
A study in which the participants are assigned by chance to separate groups that compare different treatments; neither the researchers nor the participants can choose which group. Using chance to assign people to groups means that the groups will be similar and that the treatments they receive can be compared objectively. At the time of the trial, it is not known which treatment is best. It is the patient's choice to be in a randomized trial.

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 in another area of the body. Also called recurrent cancer or disease.

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

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

Sorafenib
Sorafenib is a protein kinase inhibitor. This means that it blocks some specific enzymes known as protein kinases. These enzymes can be found in some receptors on the surface of cancer cells, where they are involved in the growth and spread of cancer cells, and in the blood vessels that supply the tumours, where they are involved in the development of new blood vessels. Sorafenib works by slowing down the rate of growth of cancer cells and cutting off the blood supply that keeps cancer cells growing.

Systemic therapy
Treatment using substances that travel through the bloodstream, reaching and affecting cells all over the body. Chemotherapy* and immunotherapy are examples of systemic therapy.

Targeted therapy
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.

Transarterial
Any procedure performed through the arteries.

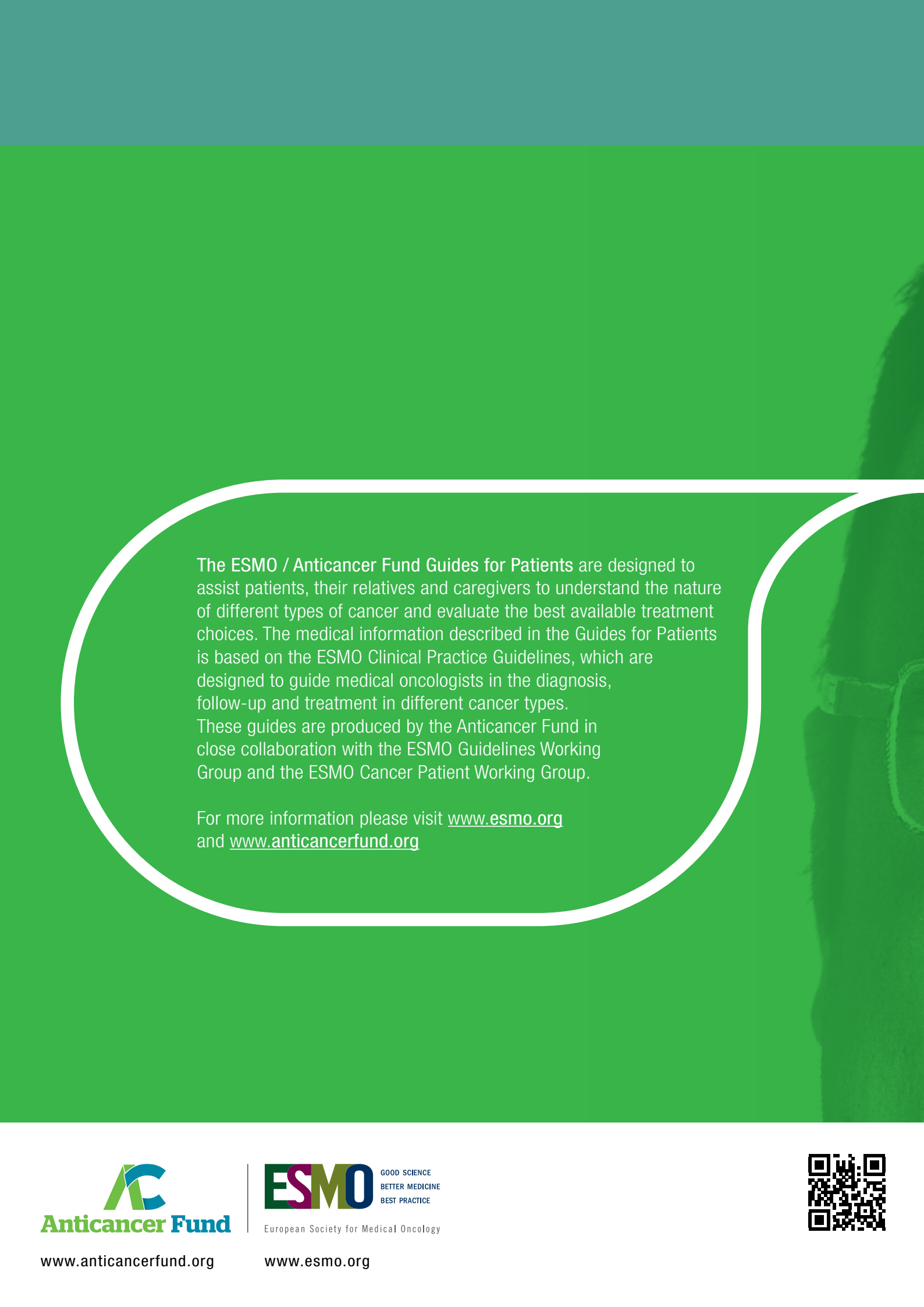
Tumour marker
A diagnostic indication that a disease may develop.

Ultrasound
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.

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

Wilson's disease
A rare genetically inherited disease in which copper accumulates excessively in the tissues of the body, damaging organs such as the liver, brain and eyes. Copper (in small amounts) is necessary for the normal functioning of the body, however in Wilson's disease the normal metabolism of copper is affected and it builds up in the liver. Once liver's storage capability is exceeded copper starts being released through the blood to other organs in the body. Wilson's disease is also called hepatolenticular degeneration.

X-ray
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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