For patients who have, or have been previously treated for, colorectal cancer (CRC), it can be distressing to learn that the cancer has spread to another organ. However, this spread (called metastasis*) is quite common, and there are many treatment options available.

The liver is the most frequent site for metastatic* tumors to appear in patients with CRC. In fact, over 50% of people who have CRC receive treatment for tumors in the liver.1,2

This booklet will answer some of your questions about how CRC can lead to metastatic tumor(s) at a new site in the body, what happens when CRC spreads to the liver and the different types of treatments available.

*The words used to describe metastasis can be confusing:

Metastasis – as a tumor grows, cells break away and travel through the blood or lymph vessels. These breakaway cells may form a new (secondary) tumor in another part of the body. This process is known as metastasis.

Metastases is the plural form of metastasis, i.e. it is used when referring to more than one secondary tumor

Metastatic is the adjective used to describe, for example, tumor(s) occurring as a result of metastasis
As a tumor grows, cells may break away and travel through the blood or lymph vessels. These breakaway cells may form a new (secondary) tumor in another part of the body. This process is known as metastasis.

The secondary (metastatic) tumor is the same type of cancer as the primary (original) tumor, so if you have CRC with a metastatic tumor in your liver, it does not mean you have liver cancer, but that the primary CRC cells have spread to your liver.

There is a direct blood supply between the colon and the liver (the hepatic portal vein), which explains why the liver is the part of the body that most commonly develops metastases from CRC. *Lymph is a clear, watery liquid that helps to fight infection and to keep fluids in balance. Lymph travels through vessels that connect nodes (lymph glands), where it is filtered and processed to remove harmful substances. The colon is also referred to as the bowel, or large bowel. CRC may also be referred to as bowel cancer.*
The presence or absence of metastasis is one factor doctors consider when “staging” a patient’s cancer. Staging is used to describe how developed the cancer is – whether it is at an early or advanced “stage”. Staging is important as it helps doctors decide on the most appropriate treatment for each patient.4

One staging system is the TNM system, T refers to how far the tumor has grown in the bowel. There are four T-stages in CRC:

- **T1** means the tumor is only in the inner layer of the bowel
- **T2** means the tumor has grown into the muscle layer of the bowel wall
- **T3** means the tumor has grown into the outer lining of the bowel wall
- **T4** means the tumor has grown through the outer lining of the bowel wall

**Metastatic CRC can be T1, T2, T3 or T4**

The N in TNM refers to whether the cancer has spread via the lymph vessels to the lymph nodes:

- **N0** means that none of the lymph nodes contain cancer cells
- **N1** means that one, two or three of the lymph nodes close to the bowel contain cancer cells
- **N2** means there are cancer cells in four or more lymph nodes

**Metastatic CRC can be N0, N1 or N2**

M stands for metastasis:4

- **M0** means that metastasis has not occurred – there are no metastatic/secondary tumors
- **M1** means that one or more metastatic/secondary tumor has developed

**Metastatic CRC is M1**

There is also a number-based system (1–4 or I–IV) for staging tumors. **CRC with liver metastases is stage 4 (or IV).**
What does the liver do?

The liver makes many substances that are important to the body. These include:

- Cholesterol – an essential part of cells
- Bile – helps with the digestion of food
- Proteins – e.g. to help with blood clotting, and maintaining the body’s fluid balance

The liver also stores many substances, for example:

- Fats – which your body uses for energy
- Carbohydrates – the liver helps control the levels of sugar in the blood

And cleans:

- Blood, by removing alcohol, drugs and normal body waste products, such as ammonia from the breakdown of proteins

---

Your doctor, and published information about the liver, will sometimes use the terms ‘hepatic’ or ‘hepato-’ – from hepar, the Greek word for the liver.
If CRC has led to tumors developing in your liver, you may notice new symptoms, for example feeling more tired than usual. Other symptoms you may experience include:

- Loss of appetite
- Yellow coloration in the skin or eyes (jaundice)
- Itchy skin
- Dark-colored urine
- Pain in the abdomen
- Swelling/bloating of the abdomen
- High temperature (fever), sweating

But everyone is different – and you may have none of these symptoms.

Always let your cancer care team know immediately if you experience new symptoms or any other change in your condition. They may suggest tests to find out the reasons for how you are feeling and they will usually be able to offer you medication or practical advice to help you manage your symptoms.
Liver metastases are often detected as part of the routine tests and scans given during or following treatment for primary CRC. In some cases, the presence of metastatic cancer may be diagnosed at the same time as primary CRC.

To find out more about the tumor(s) in your liver – and to help choose the best treatment for you – your doctor may suggest some additional tests, for example:

- Further scans, such as computerized tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET), may be used to gain accurate information on the size and location of the metastatic tumor(s)
- Blood tests to assess how your liver is functioning

It is probable that you will also need to have a colonoscopy to check for any new tumor(s) in the colon.

Your doctor may also need to examine a sample of tissue (biopsy) from the liver tumor – this may be obtained via keyhole surgery or using a needle inserted into your liver following administration of local anesthesia.

Laboratory examination of the tumor sample can help doctors select the most appropriate treatment for you. The sample may be tested to determine whether certain genes are normal or if their structure has changed (mutated). Some genes, e.g. KRAS and BRAF, affect the way tumors respond to specific targeted therapies (see pages 16-17), so the test results can help doctors decide on your treatment course.

You may have already had tests for KRAS and BRAF to help determine treatment for your primary CRC, but sometimes these are repeated as the metastatic tumor may have different genetic characteristics.
There have been great advances in recent years in the treatment of metastatic CRC. Your doctor will discuss with you which of the many options are most suitable in your case, for example:

- Drug therapies (see pages 16 and 17) – it is probable that the drug treatment(s) you are receiving for CRC will also help to treat the liver tumor(s), but you may receive some additional or different drugs, or drug combinations

- Surgery (see page 19) or minimally invasive methods for destroying the tumor(s) (see pages 20–23)

- Treatments, including radiation therapies or drugs, which are delivered directly to the area where the liver tumor is located. These are referred to as “liver-targeted” or “locoregional” therapies (see pages 20–23)

You may receive more than one type of treatment, either in combination or one after the other.

You will be looked after by a team of doctors and other healthcare professionals from more than one specialty, for example, experts in surgery, drug treatment, imaging, and radiation treatment. As a group, these specialists are often referred to as a multidisciplinary team or MDT.

There may be some team members that you have not met before; for example, you may now have a surgeon who is a specific expert in operating on the liver. Together, the team will apply their specialist knowledge and experience of CRC with liver metastases, and will discuss and agree the best possible treatment strategy for you as an individual.
Several different types of drugs are used to treat both primary CRC and liver metastases from CRC. In fact, the many drugs now available for CRC with liver metastases can be combined in lots of different ways. Your doctor will advise on which combination is likely to be best for you.

If a particular combination does not work or does not suit you – for example, if you develop side effects which are not manageable – there are likely to be other combinations to consider.

Drug treatment may also be suggested to reduce the size of the tumor(s) before surgery (see page 19).

<table>
<thead>
<tr>
<th>Treatment type</th>
<th>Why it’s used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>To kill or block the growth/multiplication of tumor cells</td>
</tr>
<tr>
<td>Targeted therapy</td>
<td>To prevent tumor growth by blocking specific functions (‘targets’) present in some tumors</td>
</tr>
<tr>
<td>Supportive therapy</td>
<td>To prevent or reduce the symptoms you may have as a result of either the cancer or treatment side effects</td>
</tr>
</tbody>
</table>

Chemotherapy combinations, e.g.:

- **FOLFOX**: 5-Fluorouracil, Oxaliplatin
- **CAPOX/XELOX**: Capecitabine, Oxaliplatin
- **FOLFIRI**: 5-Fluorouracil, Irinotecan

* May be referred to as FOLFOX4, mFOLFOX4, FOLFOX6, and FOLFOX7, depending on dose given.

Targeted drugs may be used on their own or in combination with chemotherapy, e.g.:

- **FOLFOX + Bevacizumab**
- **FOLFIRI + Panitumumab**
- **CAPOX + Bevacizumab**

If you are particularly worried about a side effect, or develop serious symptoms that your doctor has warned you to look out for, phone your cancer care team.
Your doctors, and some of the information you read, may use the term ‘resection’ when referring to surgery for liver cancer and may refer to liver segments by number, as shown above.

Remember to ask your doctor or care team to explain possible complications of surgery and what to expect in terms of how you will feel afterwards, length of hospital stay, etc.

The multidisciplinary team will be choosing and reviewing your treatment with the aim of maximizing the benefits while keeping side effects to a minimum. All drugs and treatments bring a risk of side effects or complications – even the tablets used for a mild headache can cause problems for a small number of people. However, side effects are not an inevitable part of cancer treatment. Some people have few side effects or very mild ones, and not all cancer drugs have the same impact. While some drugs can cause nausea or hair loss, others do not. Importantly, lack of side effects IS NOT a sign that your cancer treatment is not working.

Whatever drug therapy or treatment is suggested to you, make sure you ask your doctor to explain possible side effects and complications. You should report all side effects to your doctor or nurse, who can suggest ways of preventing, reducing or managing these problems.

If you are particularly worried about a side effect, or develop serious symptoms that your doctor has warned you to look out for, phone your cancer care team.

Reduced tumor size

Better quality of life

Reduced symptoms

Clinic attendance

Possible side effects

If feasible, surgery is the best treatment for liver metastases from CRC – your surgeon may be able to completely remove the tumor(s) in your liver. Even if it is not possible to remove all of your tumor(s), the operation should significantly improve your condition.

In some cases, doctors may treat a large or advanced tumor in the liver, which is not suitable for surgery with drug treatment or a therapy directed specifically at your liver (liver-targeted therapy; see pages 20–23). This is done to see if it is possible to reduce the size of the tumor enough to make surgery an option. After this process of tumor shrinkage – referred to as downstaging or downsizing – the tumor(s) may be operable. It is important to recognize that this downstaging approach is not suitable for all patients and does not work in all cases.

The liver has an amazing ability to regenerate itself – it is able to return to its original size even if more than two-thirds of its bulk are removed during surgery.
Liver-targeted therapy: ablation

Ablation means destruction of tissue. Ablation of liver tumors is carried out by an interventional radiologist (a specialist doctor who uses imaging equipment to see inside the body and gain access to the tumor(s) via the blood vessels). The procedure is ‘minimally invasive’ – which means that open surgery is not required. If you have an ablation procedure, you will be given light/moderate sedation to ensure that it is not painful. You may be offered ablation if surgical resection is not considered suitable for you or you may have one or more tumor(s) surgically removed and another treated by ablation. You may have some drug treatment before ablation to stabilize the disease.

For example, drug treatment may kill cancer cells in the liver which may not yet have developed into tumor(s) or make the tumor smaller, which help to make the ablation procedure easier and increase the chances of it destroying the tumor(s).

The following types of ablation therapy are commonly used to treat CRC liver metastases:

- Radiofrequency and microwave ablation use high temperatures to destroy the tumor
- Cryoablation uses freezing temperatures to destroy the tumor
- Irreversible electroporation (IRE) uses high-energy pulses of electricity (without heat) to destroy the tumor

Remember to ask your doctor or care team to explain possible complications of ablation and what to expect in terms of how you will feel afterwards, length of hospital stay, etc.
Liver-targeted therapy: embolization

Embolization is a liver-targeted or locoregional treatment that has been used for many years to treat primary liver cancers. It uses small particles to block the blood vessels feeding the tumor in order to starve it of the nutrients it needs to grow. These particles are often combined with chemotherapy drug, so the drug is delivered directly into the liver. Today, specialist types of embolization therapies are increasingly being used for the treatment of metastatic tumors in the liver, where their effectiveness relies less on the embolic (blocking) effect and more on targeted delivery of a powerful treatment dose to the liver.26-29

Embolization therapies may be used to treat metastatic tumors if surgery or ablation are not appropriate,27,29 and can be effective in downstaging liver tumors (making them smaller, so they become suitable for surgery).27 They may be used on their own or in combination with drug therapies.

As with ablation, embolization is carried out by the interventional radiologist, who uses special imaging equipment to guide a catheter (a long, thin, flexible tube) from a tiny entrance site in the groin, through the blood vessels and up into the liver.29 Tiny particles are then injected through the catheter.

The particles can be used to carry chemotherapy or radiotherapy doses:

- Transarterial chemoembolization (TACE) delivers embolic material combined with a chemotherapy drug (usually irinotecan when treating CRC liver metastases) directly to the liver.26-29

- Transarterial radioembolization (TARE): uses tiny particles containing radioactive Yttrium-90, which is delivered directly to the liver tumors, offering radiotherapy ‘from the inside’.29 TARE is also sometimes referred to as selective internal radiotherapy treatment (SIRT)

Remember to ask your doctor or care team to explain possible complications of embolization therapies and what to expect in terms of how you will feel afterwards, length of hospital stay, etc.
Looking after yourself

When you were diagnosed with CRC, your cancer care team will have discussed with you the importance of a healthy lifestyle, to give the treatments you receive the best possible chance of success and help you tolerate any side effects. Now that you may be receiving new treatments for the tumor(s) in your liver, this advice is more important than ever.

Healthy habits
If you smoke, ask your doctor for advice and help on how to stop. If you regularly drink alcohol, talk to your doctor about whether this may have an impact on your treatment, and ask for guidance on whether you need to cut down or give up.

Healthy food
Good nutrition is important. Make sure you eat a balanced diet that meets your calorie needs, and drink plenty of fluid. Discuss your individual needs with members of your care team.

Keeping active
Many patients who have had cancer find that they benefit from keeping active. However, people vary in their exercise needs, particularly after receiving treatment for cancer, so talk to your care team about what activities might be good for you.

Keeping in touch
People with cancer, and their family and friends, find local support groups a great source of information, practical tips – and friendship. Your hospital will have information on the groups in your area and a list of national groups can be found below.

Colorectal Cancer Support Groups in the US

Fight Colorectal Cancer
www.fightcolorectalcancer.org
Helpline: 877.427.2111

Colorectal Cancer Awareness
www.crcawareness.com

Colon Cancer Alliance
www.ccalliance.org
Helpline: 877.422.2030

Don’t smoke
Healthy food
Exercise
Ablation  
Destruction of tissue (e.g. cancer cells).

Bile  
A substance produced by the liver and stored in the gall bladder. Helps to digest fats in the intestine. Contains bilirubin.

Bilirubin  
A yellow pigment that is a waste product from dead red blood cells. Gives bruises their yellow color and discolors skin and whites of the eyes when someone has jaundice.

Biopsy  
A sample of tissue taken for examination in the laboratory to help doctors understand more about an individual patient’s disease and how to treat it.

Bowel  
Processes food from the stomach, taking out nutrients and fluids and expelling waste. The bowel is made up of the small intestine (small bowel) and colon (large bowel).

BRAF  
A gene that may determine how an individual patient will respond to specific types of anti-cancer drug.

Catheter  
A long, thin, flexible tube that can be inserted into a blood vessel; used to deliver treatment directly to specific parts of the body.

Chemoembolization  
Embolization (blocking) of the blood supply (e.g. to a tumor) combined with chemotherapy. See also TACE.

Chemotherapy  
Drugs that kill cancer cells or block their growth and/or multiplication; may also affect normal cells.

Colon  
See bowel.

Colonoscopy  
Examination of the inside of the colon using a tiny camera fixed to a long, narrow tube inserted into the rectum; can be used to obtain biopsies.

Colorectal cancer  
Cancer in the colon (also called the large bowel or large intestine) or rectum (final segment of the large bowel/intestine).

Combination therapy  
Use of one or more treatment in one course of therapy.

CRC  
See colorectal cancer.

Cryoablation  
Use of cold temperatures to freeze and kill cancer cells.

CT-scan  
Computerized tomography, in which a computer builds up many X-rays to make a detailed 3-dimensional picture of internal organs and tissues.

Downsize  
Make a tumor smaller.

Downstage  
Use of a treatment, e.g. drug therapy, to make a tumor suitable for a potentially curative therapy, such as surgery or ablation.

Embolization  
Blockage of the blood supply (e.g. to a tumor).

Hepatectomy  
Surgical removal of all or part of the liver.

Hepatic/hepato-  
Relating to the liver (from hepar, the Greek word for liver).

Hepatic portal vein  
The vein that carries blood containing nutrients to the liver from food digested in the intestine.

Imaging  
A tool such as X-ray, CT scan or PET scan that is used to provide pictures of the inside of the body.

Irreversible electroporation (IRE)  
Use of high-energy pulses of electricity (without heat) to kill cancer cells.

Jaundice  
A yellow coloration of the skin or whites of the eyes caused by build-up of bilirubin when liver is not functioning properly.

KRAS  
A gene that may determine how an individual patient will respond to specific types of anti-cancer drug.

Liver  
Large, four-lobed organ situated under the right side of the diaphragm with a number of functions important to maintaining good health.

Liver-directed  
See liver-targeted.

Liver-targeted  
Describes a locoregional therapy or treatment which is delivered to the liver.

Locoregional therapy  
Treatment delivered at or close to the site of a disease (e.g. cancer).

Lymph  
A clear, watery liquid that helps to fight infection and keep fluids in balance.

Lymph node (or gland)  
One of several hundred small structures throughout the body that filter and process lymph to remove harmful substances and help fight infection.

MDT  
See multidisciplinary team.

Metastasis  
(i) The process whereby cells from a tumor in one part of the body travel via the blood or lymph vessels to another location and form a new secondary/metastatic tumor.  
(ii) A secondary or metastatic tumor (plural: metastases).

Metastasize  
To form one or more metastases (verb).

Metastatic  
Adjective used to describe the process of metastasis and the tumors that form as a result.

Microwave  
Energy source used for ablation therapy.

MRI scan  
Magnetic resonance imaging, which uses a magnetic field rather than X-rays to look more closely at internal organs and tissues.

Multidisciplinary team  
Group of healthcare professionals from a variety of specialties who work together to look after a particular patient.

PET scan  
Positron emission tomography which produces detailed 3-dimensional images of the inside of the body.

Primary tumor  
The initial tumor that develops in the body.

Radiation treatment  
Use of radioactive substances or waves to treat certain diseases, particularly cancer (also known as radiotherapy).
<table>
<thead>
<tr>
<th>Glossary</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radioembolization</strong></td>
<td>See TARE.</td>
</tr>
<tr>
<td><strong>Radiofrequency ablation</strong></td>
<td>Treatment that uses high-frequency radio waves to heat and destroy tumor cells.</td>
</tr>
<tr>
<td><strong>Resection</strong></td>
<td>Surgical removal of tissue, e.g. a tumor.</td>
</tr>
<tr>
<td><strong>Secondary tumor</strong></td>
<td>A tumor formed as a result of cells breaking away from the primary tumor (see metastasis).</td>
</tr>
<tr>
<td><strong>Side effect</strong></td>
<td>An unwanted condition which occurs as a result of treatment.</td>
</tr>
<tr>
<td><strong>Stage (of cancer)</strong></td>
<td>Measure of how advanced the cancer is.</td>
</tr>
<tr>
<td><strong>Staging</strong></td>
<td>A process used by doctors to determine how advanced the cancer is.</td>
</tr>
<tr>
<td><strong>Supportive therapy</strong></td>
<td>Treatment given to reduce the symptoms that patients may experience as a result of either cancer or the side effects of other treatments (does not treat the cancer itself). Examples include pain relief, or anti-nausea drugs.</td>
</tr>
<tr>
<td><strong>Symptom</strong></td>
<td>An effect that patients experience as a result of a disease.</td>
</tr>
<tr>
<td><strong>TACE</strong></td>
<td>Transarterial chemoembolization; blocking of the blood supply (e.g. to a tumor) combined with chemotherapy.</td>
</tr>
<tr>
<td><strong>TARE</strong></td>
<td>Transarterial radioembolization. Liver-targeted therapy using radiation-loaded beads.</td>
</tr>
<tr>
<td><strong>Targeted therapy</strong></td>
<td>A drug that blocks a specific function ('target') that is present in some but not all cancers; patients may be tested to see if their tumors contain the specific target.</td>
</tr>
<tr>
<td><strong>TNM</strong></td>
<td>A system for describing how far a cancer has developed (T= tumor, N=nodes, M=metastasis).</td>
</tr>
<tr>
<td><strong>Transarterial</strong></td>
<td>Performed through the arteries.</td>
</tr>
<tr>
<td><strong>Tumor</strong></td>
<td>A lump or growth; may or may not be cancer.</td>
</tr>
<tr>
<td><strong>X-rays</strong></td>
<td>A type of radiation used to examine the inside of the body.</td>
</tr>
<tr>
<td><strong>Y-90</strong></td>
<td>Radioactive material used in TARE.</td>
</tr>
</tbody>
</table>

You may wish to use this space to record additional information, or to note questions for your doctor.
References


5. Cancer Research UK. The liver. Available at: www.cancerresearchuk.org/cancer-help/type/liver-cancer/about/the-liver#whatwhat


