The following content has been generously reviewed and approved by Dr. Monika Krzyzanowska, Medical Oncologist, Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, whose guidance, expertise and outstanding commitment to patient care were the very basis for inspiring the development of a comprehensive, patient-ed document.

A GUIDE TO UNDERSTANDING COLORECTAL CANCER TREATMENT

Cancer begins when normal cells begin to change and grow uncontrollably, forming a mass called a tumour. A tumour can be benign (noncancerous) or malignant (cancerous, meaning it can spread to other parts of the body). Depending upon the size, location and spread of the cancer, different modalities of therapy may be employed to treat the disease. It is important to fully understand the various treatment options available when managing the disease whether the objective involves curative intent or promoting longevity and good quality of life which is why Colorectal Cancer Canada has designed this Guide to Understanding Colorectal Cancer Treatment. The empowerment of colorectal cancer patients and families during their cancer journey is in an important part of our mission.

Treatment for colorectal cancer may involve surgery, systemic therapy, interventional radiology procedures, radiation therapy and/or immunotherapy. Some patients may access one or more of these therapies in the management of their disease. Colorectal cancer treatment is considered to be either local therapy or systemic therapy. Local therapies consist of surgery, radiation therapy and interventional radiology. These therapies can remove or destroy cancer in a particular area of the body such as the colon, rectum, liver, lungs, peritoneum, etc. Systemic therapy consists of chemotherapy and biological therapy, for these drugs enter the bloodstream and destroy or control cancer throughout the body.

The following is a list of colorectal cancer treatment modalities each comprised of the various modality-specific therapies approved or recommended for approval in the treatment and management of colorectal cancer. The sections provide in-depth information on the respective therapies for all stages of colorectal cancer according to anatomical site, treatment modality and stage of disease. Simply click on one of the following links to access current and relevant information on a particular therapy found in this document.
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I. SURGERY

INTRODUCTION

Surgery remains the primary treatment for colorectal cancer. Surgeries can be categorized into curative, palliative, bypass, fecal diversion, or open and close.

Curative: Surgical treatment can be offered with curative intent if the tumour is localized, such as in the following cases:

- Very early cancer that develops within a polyp can often be cured by removing the polyp at the time of colonoscopy.
  In colon cancer, a more advanced tumour typically requires surgical removal of the section of the colon containing the tumour with sufficient margins, and radical en-block (in one piece) resection of mesentery (the peritoneal fold – membranous fold attaching the small intestine to the back of the body wall - see illustration below) and lymph nodes to reduce local recurrence. This is called a colectomy

![Illustration of colectomy](image)

which is discussed in further detail below. If possible, the remaining parts of the colon are anastomosed together (reconnected) to create a functioning colon. In cases when anastomosis is not possible, a stoma (artificial opening) is created.

- Curative surgery in rectal cancer includes total mesorectal excision (lower anterior resection) or abdominoperineal excision (also discussed below).
- If distant metastases are present in a single organ (such as either the liver or lungs) and are limited in size and number, curative surgery may also be employed to effect a cure. Improved chemotherapy has increased the number of patients who are offered surgical removal of isolated liver metastases or isolated lung metastases.

Palliative: In the case of multiple metastases having been identified in distant organs, palliative (non-curative) resection of the primary tumour may be offered for the purpose of reducing further
morbidity caused by tumour bleeding and invasion.

**Bypass**: if the tumour invaded into adjacent vital structures which make excision technically difficult, the surgeons may prefer to bypass the tumour (ileotransverse bypass) or to do a proximal (right sided) **fecal diversion** through a stoma. Fecal diversion refers to the surgical creation of an ileostomy or colostomy. An **ileostomy** is an opening between the surface of the skin and the small intestine; a **colostomy** is an opening between the surface of the skin and the colon. This opening is called a stoma.

**Open and Close Surgery**: When surgeons find the tumour unresectable and the small bowel involved, an open and close surgery usually results. Any more procedures would do more harm than good to the patient. This is uncommon with the advent of laparoscopy and better radiological imaging. Most of these cases formerly subjected to “open and close” procedures are now diagnosed in advance and surgery avoided.

(i) **COLON SURGERY**

Surgeons are continuing to improve their techniques for operating on colorectal cancers. They now have a better understanding of what makes colorectal surgery more likely to be successful, such as making sure enough lymph nodes are removed during the operation. The types of surgery used to treat colon and rectal cancers differ and for this reason are described separately below.

(a) **Polypectomy & Local Excision (Stage 0 and Early Stage I)**

Some early colon cancers (stage 0 and some early stage I tumours) or polyps can be removed by surgery through a colonoscope (the same think, flexible scope used to do a colonoscopy). Early stage cancers that are only on the surface of the colon lining can be removed along with a small amount of nearby tissue. When this is done, the surgeon does not have to cut into the abdomen. For a polypectomy, the cancer is removed as part of the polyp, which is cut at its stalk (the area that resembles the stem of a mushroom). Local excision removes superficial cancers and a small amount of nearby tissue.
Diagram Illustrating technique of endoscopic polypectomy. The polypectomy snare is looped around the stalk of the polyp. Next the snare is closed and polyp is removed by a blend of diatermic cutting and coagulation applied to the stalk.


(b) **Colectomy & Anastomosis (Late Stage I, Stage II, III and possibly IV)**

**Open Colectomy:** An open colectomy (sometimes called a hemicolecctomy or segmental resection) removes part of the colon as well as nearby lymph nodes. It is the most common surgical procedure employed when treating colon cancers. The surgery is performed through a cut (incision) in the abdomen wherein a part of the colon with the cancer and a small segment of normal colon on either side of the cancer are removed. Usually, approximately one fourth to one third of the colon is removed but is subject to the exact size and location of the cancer. The remaining healthy sections of the colon are then anastomosed (sewing the healthy parts of the colon together) – see diagram below. Nearby lymph nodes are removed at this time as well for examination under a microscope by the pathologist during the surgery to determine if they contain any cancer. Removing as many lymph nodes possible for examination is important to determine proper staging and post-operative treatment of the disease.
Diagram illustrating colon cancer surgery with anastomosis. Part of the colon containing the cancer and nearby healthy tissue is removed and then the cut ends of the colon are joined. Source: http://www.cancer.gov/cancertopics/pdq/treatment/colon/Patient/page4

**Laparoscopic-Assisted Colectomy:** This minimally invasive technique is a newer approach to removing part of the colon and nearby lymph nodes and may be an option for some earlier stage cancers. Instead of making one long incision in the abdomen, the surgeon makes several smaller incisions. Special long instruments are inserted through these incisions to remove part of the colon and lymph nodes. One of the instruments has a small video camera on the end, which allows the surgeon to see inside the abdomen. Once the diseased part of the colon has been freed, one of the incisions is made larger to allow for its removal. Because the incisions are smaller than with an open colectomy, patients may recover slightly faster and have less pain than they do after standard colon surgery. Laparoscopic-assisted surgery is as likely to be curative as the standard approach for colon cancers. But the surgery requires special expertise in this field.


(c) **Side Effects**

As with any surgical procedure, colon surgery may result in complications. Please note that these complications are rare and occur in a very small percentage of the population which include:
- Wound infection, dehiscence (bursting of wound) or hernia
- Anastomosis breakdown, leading to abscess or fistula formation, and/or peritonitis (abdominal infection)
- Bleeding with or without hematoma (blood clot) formation
- Adhesions resulting in bowel obstruction
- Adjacent organ injury (most commonly to the small intestine, ureters, spleen or bladder)
- Cardiorespiratory complications such as myocardial infarction, pneumonia, arrhythmia, pulmonary embolism etc.

(ii) Rectal Surgery

Surgery is usually the main treatment for rectal cancer as well, although radiation and chemotherapy will often be given before or after surgery. There are several types of surgery for rectal cancer. Some operations such as polypectomy, local excision and local transanal resection can be done with instruments placed directly into the anus, without having to cut through the skin. One of these methods might be used to remove stage I cancers that are fairly small and not too far from the anus. For some stage I, and most stage II or III rectal cancers, other types of surgery may be performed. All surgeries are described below.

(a) Polypectomy and Local Excision (Early Stage I)

These procedures, described in the colon surgery section appearing above, can be used to remove superficial cancers or polyps. They are done with instruments inserted through the anus, without making a surgical incision in the skin of the abdomen.

(b) Transanal Endoscopic Microsurgery – TEM (Stage I Cancers)

This operation can sometimes be used for early stage cancers that are higher in the rectum than could be reached using the standard transanal resection (see below). A specially designed microscope is placed through the anus, allowing the surgeon to do a transanal resection with great precision and accuracy. This operation is only done at certain centers, as it requires special equipment and surgeons with special training and experience.
(c) **Local Transanal Resection - Full Thickness Resection (Stage I Cancers)**

As with polypectomy and local excision, local transanal resection is done with instruments inserted through the anus, without making an incision in the skin of the abdomen. This operation involves cutting through all layers of the rectum to remove cancer as well as some surrounding normal rectal tissue. This procedure can be used to remove some stage I rectal cancers that are relatively small and not too far from the anus.

(d) **Low Anterior Resection (Some Stage I, Most Stage II or III)**

Some stage I rectal cancers and most stage II or III cancers in the upper third of the rectum (close to where it connects with the colon) can be removed by low anterior resection. In this operation, the tumour is removed without affecting the anus. After low anterior resection, the colon will be attached to the remaining part of the rectum and it will move the waste in the usual way. A low anterior resection is like most abdominal operations. Patients will most likely be instructed to take laxatives and enemas before surgery to completely clean out the intestines. Just before surgery, the patient will be given general anesthesia, which puts them into a deep sleep. The surgeon makes an incision in the abdomen. Then the surgeon removes the cancer and a margin of normal tissue on either side of the cancer, along with nearby lymph nodes and a large amount of fatty and fibrous tissue around the rectum. The colon is then reattached to the rectum that is remaining so that a permanent colostomy is not necessary. If radiation and chemotherapy have been given before surgery, it is common for a temporary
ileostomy to be made (where the last part of the small intestine -- the ileum -- is brought out through a hole in the abdominal wall). Usually the ileostomy is closed after chemotherapy is completed. The usual hospital stay for a low anterior resection is 4 to 7 days, depending on the patient’s overall health. Recovery time at home may be 3 to 6 weeks.

(e) **Proctectomy with Colo-Anal Anastomosis (Some Stage I, Most Stage II and III Cancers)**

Some stage I and most stage II and III rectal cancers in the middle and lower third of the rectum will require removal of the entire rectum (proctectomy) and the colon then attached to the anus. This is called a colo-anal anastomosis (anastomosis meaning connection). Removal of the rectum is necessary to do a total mesorectal excision (TME), (see below) which is required to remove all the lymph nodes near the rectum. This is a harder procedure to do, but modern techniques have made it possible. Sometimes when a colo-anal anastomosis is done, a small pouch is made by doubling back a short segment of colon (colonic J-pouch) or by enlarging a segment (coloplasty). This small reservoir of colon then functions as a storage space for fecal matter like the rectum did before surgery. When special techniques are needed to avoid a permanent colostomy, the patient may need to have a temporary ileostomy. Patients who require chemotherapy may have their ileostomy for approximately 8 weeks after chemotherapy is complete. A second operation is then performed to close the ileostomy opening. The usual hospital stay for a colo-anal anastomosis, like a low anterior resection, is 4 to 7 days, depending on the patient’s overall health. Recovery time at home may be 3 to 6 weeks.

(f) **Abdominoperineal Resection (Some Stage I, Most Stage II or III Cancers)**

This operation is more involved than a low anterior resection. It can be used to treat some stage I cancers and many stage II or III rectal cancers in the lower third of the rectum (the part nearest to the anus), especially if the cancer is growing into the sphincter muscle (the muscle that keeps the anus closed and prevents stool leakage). Here, the surgeon makes one incision in the abdomen, and another in the perineal area around the anus. The perineum is the region between the scrotum and the anus in males, and between the posterior vulva junction (the labial opening to the vagina) and the anus in females. This incision allows the surgeon to remove the anus and the tissues surrounding it, including the sphincter muscle. Because the anus is removed, the patient will require a permanent colostomy to allow stool a path out of the body. As with a low anterior resection or a colo-anal anastomosis, the usual hospital stay for an abdominoperineal resection is 4 to 7 days, depending on the overall health of the patient. Recovery time at home may be 3 to 6 weeks.
Total Mesorectal Excision (Stage II and III)

Total mesorectal excision (TME) was described 20 years ago and is now considered the therapeutic gold standard for middle and lower third rectal cancers in a number of countries worldwide, including Canada. The mesorectum is a fatty tissue directly adjacent to the rectum that contains blood vessels and lymph nodes. When rectal cancers recur, it is often in these lymph nodes. In a TME surgery, surgeons carefully remove the entire mesorectum and lymph nodes, leading to a very low risk that cancer will recur in the local region. TME surgery sometimes impairs rectal function and results in patients requiring a permanent colostomy. Although the risk is never eliminated, having the surgery performed by an experienced physician can make this outcome less likely. Following surgery, patients sometimes also receive radiation and/or chemotherapy and the same can be said before the surgery as well. Combining chemotherapy and radiation either before or after TME is yielding promising long term results and a low risk for local recurrence. Patients who have rectal cancer that is confined to the lower two-thirds of the rectum are generally considered good candidates for TME surgery. However, many factors can determine whether TME is appropriate for the patient and should therefore be discussed with the patient’s surgeon.

In a total mesorectal excision, the surgeon cuts away the piece of rectum with the cancer, some tissue above and below it, and the layer of fatty tissue around the rectum. As previously state, this layer of tissue is called the mesorectum, which is made up of fat, blood vessels, and lymph tubes, and it is closely stuck to the rectum. The surgery aims to catch cancer cells that may have spread outside the wall of the rectum. This reduces the chances that the cancer will return. It also removes lymph nodes in the fatty layer. Older types of surgery do not take away the fatty layer. After the piece of rectum and the mesorectal tissue are removed, the two ends of the bowel that are left are joined back together. The procedure is usually done through one large cut. But some physicians are performing it using several smaller cuts and a camera to guide them (laparoscopic, or keyhole surgery). The research to date indicates that both operations work equally well. Recovery time from a keyhole operation appears to be quicker.
An important point to remember is that after having had a TME, the frequency of bowel movements increases approximately twofold than if other types of surgery had been employed.

(h) Pelvic Exenteration (Stage II, III & IV)

If the rectal cancer is growing into nearby organs, a pelvic exenteration may be recommended. This is an extensive operation. Not only will the surgeon remove the rectum, but also nearby organs such as the bladder, prostate (in men), or uterus (in women) if the cancer has spread to these organs. You will need a colostomy after pelvic exenteration. If the bladder is removed, you will also need a urostomy (opening where urine exits the front of the abdomen and is held in a portable pouch).

(i) Side Effects

Potential side effects of rectal surgery depend on several factors, including the extent of the operation and a person's general health before surgery. Most people will have at least some pain after the operation, although this can usually be controlled with medicines if needed. Eating problems usually resolve within a few days of surgery. Other problems may include bleeding from the surgery, blood clots in the legs, and damage to nearby organs during the operation. Rarely, the connections between the ends of the intestine may not hold together completely and may leak, which can lead to infection. It is also possible that the incision might open up, causing an open wound. After the surgery, you might develop scar tissue that causes tissues in the abdomen to stick together. These are called adhesions. In some cases, adhesions may cause the bowel to become blocked, requiring further surgery. Complications are rare but should be made aware to patients prior to surgery and generally they include:

- Sexual dysfunction
- Irregular bowel movements
- Gas and flatulence
- Diarrhea
- Bladder complications
- Sense of urinary urgency
- Fecal incontinence
- Complications in or around the stoma, if one is created

(iii) Ostomies

An ostomy is a surgically created opening connecting an internal organ to the surface of the
body. Different kinds of ostomies are named for the organ involved. The most common types in intestinal surgery are an “ileostomy” (connecting the ileal part of the small intestine to the abdominal wall) and a “colostomy” (connecting the colon or large intestine to the abdominal wall). An ostomy may be temporary or permanent. A temporary ostomy may be required if the intestinal tract cannot be properly prepared for surgery because of blockage by disease or scar tissue. A temporary ostomy may also be created to allow inflammation or an operative site to heal without contamination by stool. Temporary ostomies can usually be reversed with minimal or no loss of intestinal function. A permanent ostomy may be required when disease or its treatment impairs normal intestinal function or when the muscles that control elimination do not work properly or require removal. The most common causes of these conditions are low rectal cancer and inflammatory bowel disease. Some patients may require a short-term or permanent colostomy or ileostomy after surgery. If so, they will require assistance in learning how to manage it. Specially trained nurses or enterostomal therapists can provide this assistance to patients. They will usually meet with patients before their surgery and again afterwards for more training. Each type of ostomy (colostomy or ileostomy) is discussed below.

(a) Colostomy

When a section of the colon or rectum is removed, the surgeon can usually reconnect the healthy parts. However, sometimes reconnection is not possible. In this case, the surgeon creates a new path for waste to leave the body. The surgeon makes an opening (stoma) in the wall of the abdomen, connects the upper end of the intestine to the stoma, and closes the other end. The operation to create the stoma is called a colostomy. A flat bag fits over the stoma to collect waste, and a special adhesive holds it in place. For most patients, the stoma is temporary. It is needed only until the colon or rectum heals from surgery. After healing takes place, the surgeon reconnects the parts of the intestine and closes the stoma. Some patients especially those with a tumour in the lower rectum, need a permanent stoma, especially if the entire lower colon has been removed. Patients who have a colostomy may have irritation of the skin around the stoma. The doctor, nurse, or enterostomal therapist can teach patients how to clean the area and prevent irritation and infection.
Diagram illustrating Colon cancer surgery with colostomy. Part of the colon containing the cancer and nearby healthy tumour is removed, a stoma is created, and a colostomy bag is attached to the stoma.


The sequential steps occurring throughout the creation of a colostomy are depicted in the following images:
Ileostomies are necessary where disease or injury has rendered the large intestine incapable of safely processing intestinal waste, typically because the colon has been partially or wholly removed. An ileostomy may also be necessary in the treatment of colorectal cancer; one example is a situation where the tumour is causing a blockage. In such a case the ileostomy may be temporary, as the common surgical procedure for colorectal cancer is to reconnect the remaining sections of colon or rectum following removal of the tumour provided that enough of the rectum remains intact to preserve sphincter function. In a temporary ileostomy, a loop of the small intestine is brought through the skin, and the colon and rectum are not removed. Temporary ileostomies are also often made as the first stage in surgical construction of an ileo-anal pouch (see
below), so fecal material doesn't enter the newly-made pouch until it heals and has been tested for leaks – usually a period of eight to ten weeks. The temporary ostomy is then "taken down" or reversed by surgically repairing the loop of intestine which made the temporary stoma and closing the skin incision.

Source: [http://www.clevelandclinic.org/registries/inherited/hnpcc.htm](http://www.clevelandclinic.org/registries/inherited/hnpcc.htm)

(c) J-Pouch (Ileoanal Reservoir)

An ileoanal reservoir surgery is an alternative to a permanent ileostomy. It is completed in two surgeries and used for people who have particular types of colon cancer as well as for familial polyposis. This surgery eliminates the need for an external pouch to collect waste. The ileoanal reservoir (or pouch) is an internal pouch formed of small intestine. This pouch provides a storage place for stool in the absence of the large intestine. Anal sphincter muscles assist in holding in the stool. Several times a day, stool is passed through the anus. This type of surgery gives the patient control of bowel movements and does not require a permanent ileostomy. This procedure is performed in one, two or three stages, but is most often done in two stages, usually 2-3 months apart. The following steps are involved in the creation of an ileoanal reservoir:

**Step 1:** The diseased colon (or part of it) is removed in a procedure that's called a colectomy (removal of colon) as described earlier in this section. The colon is cut from the healthy small intestine and a portion of the tissue in the rectal area is left. The amount of tissue left in the rectal area depends on the extent of the disease. This is a major part of the operation because the colon has many adjacent systems, such as blood vessels, of which it is a part. As with the
other steps of the operation, this step takes great care to perform.

**Step 1 Cont’d:** Once the colon is removed, the procedure moves to the small intestine. A loop is created from the end portion of the intestine. Once the loop is joined, the area of tissue in the middle of the "J" is opened to allow a larger reservoir. Surgical staplers (or less commonly performed suturing) are used during these steps to create the pouch. These precise instruments successfully close off the intestine’s end and form the loop.

**Step 1 Cont’d:** Once the closed loop is formed and in place, an opening is made where the pouch will attach to the rectal tissue (the rectal cuff). The stapling technique (or suturing) must be checked for complete closure and no bleeding. Great care is used by the skilled surgeon to ensure that the patient's risk of post-operative complications is kept to a minimum.
Step 1 Cont’d: Once the J-pouch is successfully in place and connected, another cut is made in the intestine "upstream" from the pouch. This will be an ileostomy that will be on the patient's abdomen (below the belt-line). The ileostomy is temporary and is intended to provide the J-pouch time to heal without being called upon to perform its ultimate function. The patient goes on to lead a normal life with the ileostomy while the body with the new J-pouch recovers.
without being called upon to perform its ultimate function. Here is a view of the patient with the temporary ileostomy and newly-formed J-pouch.

**Step 1 Cont’d:** The ileostomy is temporary and is intended to provide the J-pouch time to heal without being called upon to perform its ultimate function. The patient goes on to lead a normal life with the ileostomy while the body with the new J-pouch recovers. A second operation is performed some time later, usually in a matter of months. This procedure is relatively minor compared to the procedure that made the J-pouch. The patient adapts to successfully live with the ileostomy while awaiting the ileostomy closure.
Step 2: The ileostomy is closed, and the intestine's ends are connected. This is also referred to as a takedown. The pouch now becomes functional so that waste passes into the pouch, where it is stored. When an “urge” is felt, the stool can be passed through the anus, out of the body. This surgical procedure is relatively minor, and the patient usually recovers quickly. The patient gradually adjusts to being continent again, and successfully adapts to the functional J-pouch. In most cases, the second surgery can be done at the ileostomy site without reopening the first incision. The skin at the former ileostomy site is usually left to close on its own. See image below.

Step 2 Cont’d: The patient gradually adjusts to again being continent (having control of bodily discharges), and successfully adapts to the functional J-pouch. Usually the patient goes on to successfully lead a life as active as he or she chooses. The digestive system usually works very
well when it has fully recovered. The patient takes control of his or her life through learning how to manage continence through diet, relaxation, and confidence.


Once a patient starts passing stool through the anus, stools are frequent and liquid. There may be accompanying urgency and leakage of stool. All of these aspects improve over time as the anal sphincter muscles strengthen and the pouch adapts to its new function. Stools become thicker as the small intestine absorbs more water. In addition, medications to decrease bowel activity and bulk-forming agents to thicken the stool may be prescribed. After six months, most people can expect about five to six semi-formed bowel movements during the day and one at night. The pouch takes up to one year to fully adapt. In most patients, functioning of the pouch continues to improve over time.

If an ileoanal reservoir is not possible or feasible, a continent ileostomy may be an alternative to using an outside bag. In continent ileostomy, an internal reservoir pouch is created from part of the small intestine. A valve is constructed, and a stoma is placed through the abdominal wall. A tube is inserted through the stoma and valve to drain the pouch.
(iv) Peritoneum (Stage IV Cancers)

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) – Stage IV:
Some types of cancers are very difficult to treat. Cancer that has spread to the lining surfaces of the peritoneal (abdominal) cavity from primary colorectal cancer--known as peritoneal carcinomatosis—is one such cancer. Despite numerous recent advances in chemotherapy, the overall chance of chemotherapy being curative is still low, and the side effects are difficult for the patient to endure. However, when these cancers are confined to the peritoneal cavity, Hyperthermic Intraperitoneal Chemotherapy (HIPEC) becomes an option for some carefully selected patients whose metastatic disease is generally limited to the peritoneum and not considered to be widespread throughout the peritoneum. The term “Intraperitoneal” means that the treatment is delivered to the abdominal cavity. The term “Hyperthermic Chemotherapy” means that the solution containing chemotherapy is heated to a temperature greater than normal body temperature. Before HIPEC is administered, the surgeon--using standard surgical methods--will remove all visible tumours that can be removed throughout the peritoneal cavity. This is known as cytoreductive surgery and only available at very specialized centres. Following cytoreductive surgery, in the operative setting the surgeon will administer HIPEC treatment. HIPEC is used in conjunction with surgery and chemotherapy to treat patients with colorectal metastases to the peritoneum (lining of the abdomen). Even after surgical removal, cancer often recurs in the abdomen. Hence, when the tumour spreads, it is difficult for doctors to treat with standard chemotherapy. HIPEC involves using a heated sterile solution of chemotherapy (such as mitomycin c, cisplatin, 5FU or oxaliplatin) that is circulated throughout the abdominal cavity. With HIPEC treatment, patients are connected to a series of tubes and a pumping device that bathes the abdominal cavity for two hours with a heated sterile solution containing anticancer (chemotherapeutic) drugs. The high temperature of the chemotherapy increases the effect of the drug. The fluid goes through the abdomen to treat tumour cells that may remain after cytoreductive surgery. Both heat and direct contact with chemotherapy drugs kills the cancer cells. During the HIPEC procedure, the surgeon will continuously circulate a heated sterile solution--containing a chemotherapeutic agent--throughout the peritoneal cavity, for a maximum of two hours. The HIPEC procedure is designed to attempt to kill any remaining cancer cells. The procedure also improves drug absorption and effect with minimal exposure to the rest of the body. In this way, the normal side effects of chemotherapy can be avoided. Please see image below.
Liver (Stage IV)

(a) Introduction to Liver Anatomy

Liver metastases occur in up to 60% of colorectal cancer patients. Hepatic resection provides the best chance for long-term survival. New developments in diagnosis and surgical technique have increased the safety of liver surgery and have the potential to improve clinical outcomes. Because the venous drainage of the colon and upper rectum is through the portal vein which then drains directly into the liver, hepatic metastases will occur in up to 60% of these patients, half of which will have only liver disease.

Surgery provides the best chance for cure in patients with hepatic colorectal metastases. Various factors are important in the selection process for surgical candidates. In order to identify which subset of patients will benefit most from resection, various prognostic factors have been identified. The variables most commonly associated with recurrence are:

- A positive resection margin and extrahepatic disease. Thus, inability to completely remove all tumours or the presence of extrahepatic disease (disease located outside of the liver) is considered contraindications for surgery.
- Synchronous presentation of liver metastases with the primary tumour,
- More than 1 lesion in the liver,
- Extent of liver involvement greater than 50%,
- A margin of resection less than 1 cm,
- CEA level > 200 ng/ml, and
- Intraoperative blood transfusions.

However, none of these prognostic variables are an absolute contraindication to surgery. They were mainly formulated to assist in patient selection.

Increased knowledge of the different segments of the liver has led to the development of segmental-based surgery. The liver can be divided into 8 segments: segment 1 is the caudate lobe, segments 2 through 4 form the anatomic left lobe and segments 5–8 form the anatomic right lobe. See diagram below.
Segmental anatomy of the liver is based on the direction of the hepatic veins in relation to the intrahepatic distribution of blood through the portal vein – see diagram below. It is possible to resect up to 6 segments out of 8 in one stage, but usually one lobe or part of it is removed in a typical surgery.

Lesions confined to the **right lobe** are amenable to en bloc removal (removal in one piece) with a right hepatectomy (liver resection) surgery.

Smaller lesions of the **central or left liver lobe** may sometimes be resected in anatomic “segments”.

Large lesions of the **left hepatic lobe** are resected by a procedure called hepatic trisegmentectomy (see diagram and explanation below).

When lesions are located **peripherally (on the edges of the liver)**, hepatic wedge resection or
anatomic segmentectomy are performed.

If a tumour is adjacent to or involving major intrahepatic vessels, resection of the entire segment or lobe is necessary.

Lobectomy is indicated when multiple lesions are located in different areas of one lobe.

Wedge resection is universally accepted for small superficial lesions.

Diagram Illustrating the usual kinds of partial hepatectomy. Note that there are only four common resections. Source: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2653783/

(b) Types of Hepatic Resections

As the diagram above illustrates, there are only four surgical units that lend themselves to controlled excision and they include lobectomy (right and left), trisegmentectomy (right and left), segmentectomy, and wedge resection as illustrated below:
1. Right lobe which consists of two segments – **Right Lobectomy**

2. Left lobe which consists of two segments – **Left Lobectomy**

3. Removal of the complete left lobe plus the medial segment of the right lobe – **Left Trisegmentectomy** (also known as extended left hepatic lobectomy)
4. Removal of the complete right lobe plus the medial segment of the left lobe – **Right Trisegmentectomy** (also known as extended right hepatic lobectomy)

5. Liver to the left of the falciform ligament (a ligament that attaches part of the liver to the diaphragm and the abdominal wall) in a single segment - **Lateral Segmentectomy**
6. Small triangular-shaped portion of the liver whose tumour is situated on the surface and located \textit{peripherally} (on the edges of the liver), so that it can be safely removed without injury to the blood vessels of the liver. The tumour with a small amount of normal tissue around it are removed – \textbf{Wedge Resection}.

Patients with colorectal cancer and metastatic disease to the liver may be treated in either a single surgery or in staged surgeries (with the colon tumour traditionally removed first) depending upon the fitness of the patient for prolonged surgery, the difficulty expected with the procedure with either the colon or liver resection, and the comfort of the surgery performing potentially complex hepatic surgery.

For a graphical representation of the various hepatic surgeries, please visit the Johns Hopkins website at: http://www.hopkins-gi.org/GDL_Disease.aspx?CurrentUDV=31&GDL_Cat_ID=AF793A59-B736-
(vi) **Lungs (Stage IV)**

(a) **Introduction**

The lungs are part of the respiratory system. They make up most of the space in the chest and are separated from each other by the mediastinum, an area that contains the heart, trachea (windpipe), esophagus, and many lymph nodes which can also be affected by colorectal cancer that metastasizes (see diagram below). The right lung has three sections, called lobes and is a little larger than the left lung, which has two lobes. The lining of the lungs is called the pleura.

![Diagram of lungs](image)

Colorectal cancer can spread to the lungs, pleura, and lymph nodes surrounding the lungs. The cancer cells can grow and spread. Treatment for lung metastases depends on the size, location in the lungs, extent, individual age, general health and feelings about the treatment. Surgery can treat lung metastases consisting of a procedure that may cure lung metastases if it is well confined and if it has not spread to other parts of the body. The treatment includes surgical removal of part or the entire lung called *pulmonary resection*.

(b) **Types of Pulmonary Resections**

Three main types of surgery are used in metastatic lung cancer treatment. The choice depends on the size and location of the tumour, the extent of the cancer, and the general health of the patient. The surgeon will remove only the diseased portion of the lung. All types of lung
operations require a **thoracotomy** which is an incision (cut) into the chest wall. An operation to remove a small part of the lung is called a **segmental or wedge** resection. An operation to remove a lobe of the lung is called a **lobectomy**. A **pneumonectomy** is the removal of an entire lung. See diagrams below.

![Diagrams](http://content.revolutionhealth.com/contentimages(nr551761.jpg)

Source: http://content.revolutionhealth.com/contentimages(nr551761.jpg)

During the procedure, the chest wall is opened, ribs are spread and the lung is entered to remove the diseased portion, thereby causing the lung to collapse. After lung surgery, air and fluid tend to collect in the chest. The air and fluid are drained out through a tube (chest tube) which is connected to a drainage system. An incision (cut) will usually extend from just below your underarm to around the back. The incision is closed with dissolvable sutures (thread) – see diagrams below.

![Diagrams](http://content.revolutionhealth.com/contentimages(nr551761.jpg)

A. The pleural cavity is entered through a limited incision in the 5th intercostal space, through which the lung mass and enlarged lymph node are removed.
(c) Thoracoscopy (Minimally Invasive Thoracic Surgery)

Minimally invasive thoracic surgery, also called **thoracoscopy or thoracoscopic surgery** is surgery of the chest that is performed with a thoracoscope (small video-scope) using small incisions and special instruments to minimize trauma. During thoracoscopic surgery, three small (approximately 1-inch) incisions are used as compared with one long 6- to 8-inch incision that is used during traditional, open thoracic surgery. Other names for this procedure include pleuroscopy or VATS (video-assisted thoracic surgery). It is performed in colorectal cancer patients who have limited disease in their lungs. Thoracic surgery procedures routinely performed using a minimally invasive technique include:

- VATS lobectomy
- Wedge resection

**VATS Lobectomy:** Lobectomy (removal of a large section of the lung) can be performed using a minimally invasive approach. During video-assisted lobectomy, three 1-inch incisions and one 3- to 4-inch incision are made to provide access to the chest cavity without spreading of the ribs. The patient experiences a more rapid recovery with less pain and a shorter hospital stay (usually 3 days) than traditional thoracotomy surgery. The surgical outcomes of video-assisted lobectomy are comparable to traditional lobectomy outcomes. Although minimally invasive approaches are considered for every patient, in some cases, patients who have a large or more central tumour may not be candidates for video-assisted lobectomy.

**VATS Wedge Resection:** As previously stated, a wedge resection is the surgical removal of a wedge-shaped portion of tissue from one, or both, lungs which can also be accomplished using this minimally invasive technique. A wedge resection is typically performed for the diagnosis or treatment of small lung nodules.

II: **SYSTEMIC THERAPIES (DRUGS)**

Systemic therapy refers to treatment that reaches cells throughout the body by traveling through the bloodstream. There are essentially two categories of systemic therapies: **chemotherapy** and **biological therapy**. Each agent is approved or indicated for particular stages of colorectal cancer and discussed in depth below.

(i) **Chemotherapy Treatments**
Chemotherapy uses anticancer drugs to stop the growth of cancer cells, either by killing cells or by stopping them from dividing and may also be used to reduce the likelihood of metastasis developing in a distant organ of the body. The drugs enter the bloodstream and can affect cancer cells all over the body. Chemotherapeutic drugs are usually given through a vein, but some may be given by mouth (orally). Delivery of chemotherapy may be accomplished in an outpatient part of the hospital or at home depending upon the chemotherapy. Rarely is a hospital stay required. Chemotherapeutic drugs can harm normal cells that divide rapidly such as the following:

- **Blood Cells**: These cells fight infection, help blood to clot, and carry oxygen to all parts of the body. When drugs affect the blood cells, patients are more likely to develop infections, bruise or bleed easily, and feel quite weak and fatigued.
- **Cells in Hair Roots**: Chemotherapy can cause hair loss which will eventually grow back, though it may be somewhat different in color and texture when it does grow back.
- **Cells Lining the Digestive Tract**: Chemotherapy can cause poor appetite, nausea and vomiting, diarrhea, or mouth and lip sores because it tends to harm the cells lining the digestive tract, including the colorectum. These cells, much like the cells in hair roots and blood, are rapidly dividing and are therefore subject to damage.

**How Does Chemotherapy Work?**

To understand how chemotherapy works, it is helpful to understand the normal life cycle of a cell, or the cell cycle. All living tissue is made up of cells. Cells grow and reproduce to replace cells lost during injury or normal “wear and tear”. The cell cycle is a series of steps that both normal cells and colorectal cancer cells go through in order to form new cells. Understanding the process can help patients understand how physicians predict which drugs are likely to work well together and how physicians decide how often doses of each drug should be given.

There are 5 phases in the cell cycle, which are labeled in the diagram below. Since cell reproduction happens over and over, the cell cycle is shown below as a circle. All the steps lead back to the resting phase referred to as G0, which is the starting point. After a cell reproduces, the 2 new cells are identical. And each of the 2 cells made from the first cell can go through this cell cycle again when new cells are needed.

- **G0 Phase** (Resting Stage): The cell has not yet started to divide. Cells spend much of their lives in this phase. Depending on the type of cell, G0 can last for a few hours to a few years. When a cell gets a signal to reproduce, it moves into the G1 phase.
- **G1 Phase**: During this phase, the cell starts making more proteins and growing larger, so the new cells will be of normal size. This phase lasts about 18-30 hours.
- **S Phase**: In the S phase, the genetic material is copied so that both of the new cells formed will have matching strands of the genetic material (DNA). It last approximately 18-20 hours.
- **G2 Phase**: In the G2 phase, the cell checks the DNA and gets ready to start splitting into 2 cells.
It lasts from 2-10 hours.

- **M Phase** (Mitosis): In this phase, which lasts only 30-60 minutes, the cell actually splits into 2 new cells.

Source: [http://bioinfo.mbb.yale.edu/expression/cluster/p_control.html](http://bioinfo.mbb.yale.edu/expression/cluster/p_control.html)

Colorectal cancer chemotherapies work only on cells that are actively reproducing (not on cells in the resting phase, G0). And some of the drugs specifically attack cells in a particular phase of the cell cycle (the M or S phase, for example).

When chemotherapy drugs attack reproducing cells (such as those found in hair, bone marrow and the G.I tract), they cannot tell the difference between reproducing cells of normal tissues (those that are
replacing worn-out normal cells) and colorectal cancer cells. The damage to normal cells can cause side effects that may become unpleasant. Hence, the goal of the physician is to find a balance between destroying the cancer cells and sparing the normal cells.

The three possible goals of chemotherapy treatment are as follows:

- **Cure**: if possible, chemotherapy is used to cure the cancer meaning that the tumour or cancer disappears and does not return. However, most physicians do not use the word “cure” except as a possibility or intention. When giving treatment that has a chance of curing a patient’s cancer, the doctor may describe it as treatment with *curative intent*. But it can take many years to know whether a patient’s cancer is actually cured.

- **Control**: If a cure is not possible, the goal may be to control the disease - to shrink any tumours and to stop the cancer from growing and spreading. This can help someone with cancer feel better and hopefully live longer. In many cases, the cancer does not completely go away but is controlled and managed as a chronic disease, much like hypertension or diabetes. In other cases, the cancer may even seem to have gone away for a while, but it is expected to come back.

- **Palliation**: When the cancer is at an advanced stage, chemotherapy drugs may be used to relieve symptoms caused by the cancer. When the only goal of treatment is to improve the quality of life, it is called palliation.

For some people, chemotherapy is the only treatment used for their cancer. In other cases, chemotherapy may be given along with other treatments. It may be used as *neoadjuvant therapy* (before surgery or radiation – to shrink the cancer and render surgery easier), or as *adjuvant therapy* (after surgery or radiation – to decrease the risk of cancer coming back).

- **Adjuvant chemotherapy**: After a colorectal cancer is removed with surgery, there may still be some cancer cells left behind that cannot be seen. When drugs are used to kill those unseen cancer cells, it is called adjuvant chemotherapy. It can increase the survival rate for some patients with stage II and stage III colon cancer and rectal cancer. It is given when there is no evidence of cancer remaining but there is a chance that it might come back. The theory behind adjuvant therapy is that a small number of cancer cells may not have been removed by surgery or may have escaped from the primary tumour located in the rectum or colon and settled in other parts of the body. The hope is that the chemotherapy can kill these cells, wherever they may be.

- **Neoadjuvant chemotherapy** is when chemotherapy is given before the main cancer treatment (such as surgery or radiation). Giving chemotherapy first can shrink a large tumour, making it easier to remove with surgery. Shrinking the tumour may also allow it to be treated more easily with radiation. Neoadjuvant chemotherapy also kills small deposits of cancer cells that cannot
be seen on scans or x-rays. For some rectal cancers, chemotherapy is given (along with radiation) before surgery to try to shrink the cancer and make surgery that much easier.

- **Palliative chemotherapy** is administered to patients whose cancer is advanced and is causing symptoms compromising the quality of life. Palliative chemotherapy may relieve symptoms caused by the cancer as well as shrink tumours in the body. While it is unlikely to cure the cancer in such situations, it may greatly extend survival time in some patients.

**Accessing Multiple Lines of Therapy:** A line of therapy expresses the sequence of therapies a patient undergoes. It does not correspond to a fixed amount of time.

- **First Line Therapy:** Refers to initial treatment used to reduce colorectal cancer. First line therapy may be followed by other treatments. The regimen that is used in first line therapy is usually administered on the basis of empirical evidence for its efficacy.
- **Second Line Therapy:** Refers to treatment after the initial treatment has failed or required cessation due to an accumulation of side effects that had become troublesome.
- **Third Line Therapy:** Refers to treatment that is given when both initial treatment (first line therapy) and subsequent treatment (second line therapy) have stopped working or never showed any efficacy.

Depending upon the stage of the disease, a chemotherapeutic drug will be appropriately prescribed and administered. The chemotherapeutic treatments appearing below have been shown to improve survival and/or reduce mortality rate in colorectal cancer patients.

The following list of chemotherapies has been approved for the treatment of colorectal cancer and can be accessed in accordance with treatment guidelines and disease stage:

(a) **Capecitabine (Xeloda)**

**Potential Indications:** Stage II (Adjuvant), III (Neoadjuvant & Adjuvant), IV (Neoadjuvant, Adjuvant, & Palliative) Colorectal Cancer

**Mechanism of Action:** Capecitabine is a chemotherapy drug that belongs to a group of drugs known as anti-metabolites. Antimetabolites produce their anti-cancer effects by inhibiting the ability of a cell to produce or repair DNA, the genetic material contained within the cell, thereby making the cell unable to replicate or repair itself and ultimately causing cellular death. Cancer cells need to make and repair DNA in order to grow and multiply. This process ultimately reduces the size of the tumour. The body converts capecitabine into a common chemotherapy drug called 5-fluorouracil or 5FU allowing more of the active drug to get to the tumour.

**Method of Administration:** This is an oral chemotherapy, therefore, swallowed with plenty of water. The capsules are taken twice daily every day for two weeks followed by a one week rest
period. The cycle then commences again wherein the patient is on for two weeks and off for one week. Dosage is dependent upon height and body weight.

Common Side Effects: Patients may suffer one or more of the following side effects while on capecitabine therapy:
- fatigue
- diarrhea
- mouth sores (mucositis)
- nausea or vomiting
- decreased white blood cell count with increased risk of infection
- decreased platelet count with increased risk of bleeding
- decreased red blood cell count (anemia) with increased risk of tiredness (fatigue)
- hand and foot syndrome or palmar-plantar syndrome (soreness and redness of hands and feet)
- numbness and tingling in hands and feet
- infertility

(b) Fluorouracil (5FU)

Potential Indications: Stage II (Adjuvant), III (Neoadjuvant, Adjuvant), IV (Neoadjuvant, Adjuvant, Palliative) Colorectal Cancer

Mechanism of Action: 5FU belongs to a class of drugs called anti-metabolites which produce their anti-cancer effects by inhibiting the ability of a cell to produce or repair DNA, thereby making the cell unable to replicate or repair itself and ultimately causing cellular death. Once inside the cell, it is incorporated into DNA, which induces cell cycle arrest and apoptosis (cell death). 5FU is what is commonly referred to as a pyrimidine analog. When using a pyrimidine-based drug, it is important to note that there exists a genetic inability to metabolize this drug in approximately 8% of patients suffering what is termed DPD Enzyme Deficiency. Patients with DPD deficiency may experience very severe, even life-threatening side effects.

Method of Administration: Administered intravenously (into a vein) immediately following folinic acid, which increases the effect of the 5FU on the cancer cells. The dosage is dependent upon body size. There are many different schedules of administration but most frequently it is infused over 22 to 24 hours.

Side Effects: Patients may suffer one or more of the following adverse events:
- Low white blood counts (neutropenia)
- Low red blood counts (anemia)
- Low platelet counts (thrombocytopenia)
• Mouth Sores (mucositis)
• Diarrhea
• Infertility

(c) **Folinic Acid (Leucovorin)**

**Potential Indications:** Stage II (Adjuvant), III (Adjuvant), IV (Neoadjuvant, Adjuvant and Palliative) Colorectal Cancer

**Mechanism of Action:** Folinic acid is commonly used to enhance the effectiveness of the chemo agent 5FU. It is an agent that is similar in structure and function to folic acid (vitamin B9), which is a vitamin that is necessary for cellular life. Folinic acid enhances the anti-cancer effects of 5FU by providing greater binding properties of 5FU within a cell by inhibiting thymidylate synthase (a protein involved in making and repairing the genetic material DNA wherein high levels may be involved in how certain types of cancer form and respond to treatment). Cancer cells that no longer have this enzyme, thymidylate synthase, available are more likely to die when they try to divide in two. Normally, 5FU binds to the enzyme for only a short time, which limits how effective 5FU can be. Folinic acid causes this binding to last for a longer period, which boosts the effect of 5FU. This allows 5FU to stay inside a cell for a greater period, producing longer lasting anti-cancer effects within the cell.

**Method of Administration:** Usually administered intravenously (into a vein) but may also be taken as a pill (orally) whose dosage is dependent upon body size

**Side Effects:** There are no reported common or less common side effects. Rare side effects may consist of
• Nausea
• Skin rash
• Allergic reaction (may include dizziness, shortness of breath, chest pain or tightness, swelling in the mouth or throat, hives, itching, flushing or fever)
• Seizures
• Infertility

(d) **Irinotecan (Camptosar, CPT11)**

**Potential Indications:** Stage IV (Adjuvant, Neoadjuvant, Palliative) Colorectal Cancer

**Mechanism of Action:** Irinotecan is a chemotherapy drug made from a type of plant alkaloid known as a topoisomerase I inhibitor. It works by blocking the action of an enzyme in cells called topoisomerase I. Cells need this enzyme to keep their DNA in the proper shape when
they are dividing into 2 cells. Blocking this enzyme leads to breaks in the DNA, which leads to cell death. Because cancer cells divide faster than normal cells, they are more likely than normal cells to be affected by irinotecan.

**Method of Administration:** Administered intravenously (into a vein) over 90 minutes once every 1-3 weeks, depending upon the regimen. Dosage is dependent upon treatment schedule, body size, age and general health, blood counts, liver function and side effects.

**Side Effects:** Common side effects may consist of
- Diarrhea (“early” type occurs within 24 hours of taking the drug; “late” type occurs after 24 hours of drug administration)
- Nausea/vomiting
- Lowered white blood cell count with increased risk of infection (neutropenia)
- Hair thinning or loss, including face and body hair
- Abdominal pain
- Loss of appetite
- Feeling weak and fatigued
- Infertility

**NB:** Combination Regimen – FOLFIRI/XELIRI

Irinotecan is commonly administered with two other drugs: They are 5FU and Folinic acid (see above). This combination regimen is commonly referred to as FOLFIRI, an acronym whose composition is based on the first letters of the drugs involved (FOL = Folinic acid; F = 5FU and IRI = irinotecan). Irinotecan may also be administered in combination with capecitabine or better known as xeloda and its acronym is commonly referred to as XELIRI, whose composition is based on the first letters of the drugs involved (XEL = Xeloda and IRI = irinotecan).

(e) **Mitomycin C (Mutamycin) – Rarely Used**

**Potential Indications:** Stage IV (Palliative) Colorectal Cancer

**Mechanism of Action:** Mitomycin is part of a general group of chemotherapy drugs known as antibiotics, but it acts as an alkylating agent by stopping cells from making the genetic material contained in cells called DNA, which results in cell death.

**Method of Administration:** Administered by injection into a vein (intravenously) every 6-8 weeks over a period of 20 minutes' time.
Side Effects: Common side effects may consist of the following
- Decreased white blood cell count (neutropenia) with increased risk of infection
- Decreased platelet count with increased risk of bleeding (thrombocytopenia)
- Nausea
- Vomiting
- Loss of appetite
- Fatigue
- Hair loss
- Mouth sores (mucositis)
- Infertility

(f) Oxaliplatin (Eluxatin)

Potential Indications: Stage II (Adjuvant), III (Adjuvant), IV (Neoadjuvant, Adjuvant and Palliative) Colorectal Cancer

Mechanism of Action: Oxaliplatin is a platinum-containing compound that belongs to a class of drugs called alkylating agents which produce their anti-cancer effects by causing a chemical reaction that damages the genetic material contained in cells (DNA). The DNA damage caused by oxaliplatin results in cellular death.

Method of Administration: Administered intravenously (into a vein) every 2-3 weeks depending on the regimen.

Side Effects: Common side effects may include
- Numbness and tingling in hands and/or feet due to nerve irritation better known as neuropathy or neurotoxicity *
- Nausea
- Vomiting
- Numbness of lips
- Diarrhea
- Abdominal pain
- Mouth sores (mucositis)
- Fatigue
- Decreased white blood cell count with increased risk of infection
- Decreased platelet count with increased risk of bleeding
- Infertility

* This drug can cause two types of neuropathy – acute and chronic. Acute neuropathy occurs in most patients and starts immediately following each oxaliplatin infusion. Patients may feel numbness,
tingling or pain in their hands and feet upon exposure to cold temperatures or may feel a sensation of their throat closing with cold drinks. To minimize this type of neuropathy, exposure to cold for 3-5 days should be avoided after oxaliplatin therapy. Ice, cold drinks, and ice packs should also be avoided. Gloves may be worn while handling anything cold or for reaching into the freezer/refrigerator. Dressing warmly is recommended as is covering exposed skin during the winter months. Use caution with air conditioners during the warm months. Acute neuropathy is reversible after a few days. The other form of oxaliplatin neuropathy, chronic neuropathy, usually occurs after the patient has had several treatments and is due to actual damage to the nerves. This type of neuropathy may not be completely reversible and in some patient’s treatment may need to be discontinued early to prevent progression of the neuropathy. In an effort to decrease the risk of severe neuropathy, some cancer centres are administering magnesium and calcium infusions pre and post oxaliplatin infusion as there is data which suggests these type of infusions can help. Discuss the possibility of accessing magnesium and calcium infusions with your physician to decrease the risk of severe, chronic oxaliplatin-induced neuropathy.

**NB: Combination Regimen – FOLFOX/XELOX**

Oxaliplatin is commonly administered with two other drugs: They are 5FU and Folinic acid (see above). This combination regimen is commonly referred to as FOLFOX, an acronym whose composition is based on the first letters of the drugs involved (FOL = Folinic acid; F = 5FU and OX = oxaliplatin). Oxaliplatin may also be administered in combination with capecitabine or better known as xeloda and its acronym is commonly referred to as XELOX, whose composition is based on the first letters of the drugs involved (XEL = Xeloda and OX= oxaliplatin).

**Tegafur-Uracil (UFT or UFUR or Ftorafur, or Uftoral)**

**Potential Indications:** This is an investigational drug which means it has not been approved for use yet by Health Canada. Information available is limited to what has been learned in clinical trials. The drug is being studied for the treatment of colorectal cancer as well as other cancers.

**Mechanism of Action:** Tegafur belongs to the group of chemotherapy drugs known as antimetabolites. UFT is a combination of uracil and tegafur. The body processes tegafur to 5FU, a well-known chemo treatment (see information above). Uracil slows the breakdown of 5FU, allowing it to work in the body longer. UFT prevents cells from making DNA and RNA (the genetic material found in cells). This ultimately stops the growth of cancer cells.

**Method of Administration:** UFT capsules are taken by mouth (orally) whose dosage depends upon patient weight.

**Side Effects:** Common side effects may include the following
• Decreased white blood cell count with increased risk of infection
• Decreased platelet count with increased risk of bleeding
• Nausea
• Vomiting
• Loss of appetite
• Diarrhea
• Mouth sores (mucositis)
• Infertility

(h) Raltitrexed (Tomudex)

Potential Indications: This is an investigational drug and has, therefore, yet to be approved for use throughout the various provincial jurisdictions in Canada. It is in clinical trials and is being studied for the treatment of colorectal cancer as well as other cancers.

Mechanism of Action: Raltitrexed is part of a general group of chemotherapy drugs known as antimetabolites, wherein the cancer cell is tricked into thinking that raltitrexed is a nutrient or building block that is naturally taken in. Consequently, the genetic material in the cell (DNA) is damaged and the cell cannot divide, resulting in cell death.

Method of Administration: The drug is given as an injection in a vein over 15 minutes, usually every 3 weeks. Dosage is dependent upon weight and the nature of the clinical trial in which the patient is enrolled.

Side Effects: The reported side effects to date consist of
• Decreased white blood cell count (neutropenia) with increased risk of infection
• Decreased platelets with increased risk of bleeding (thrombocytopenia)
• Decreased red blood cells with increased risk of fatigue and anemia
• Diarrhea
• Mouth sores (mucositis)
• Nausea
• Vomiting
• Infertility

(ii) Biologics (Targeted Therapy)

(a) Introduction

Targeted therapy is a type of treatment that uses drugs or other substances to identify and attack specific parts of cancer cells, which make them different from normal cells, without
harming the normal cells. Monoclonal antibody therapy is a type of targeted therapy employed in the treatment of colorectal cancer. Monoclonal antibody therapy uses antibodies (proteins) made in the laboratory from a single type of immune system cell originating from man or animal. These antibodies can identify substances on cancer cells or normal substances that may help cancer cells grow. The antibodies attach to the substance and kill the cancer cells, block their growth, or keep them from spreading. Monoclonal antibodies are given by infusion. Some may be used alone while others must be administered in combination with chemotherapy (see explanation below). Because these drugs affect only colorectal cancer cells, they often cause fewer side effects than chemo. Targeted therapies approved for colorectal cancer are designed to treat metastatic colorectal cancer, cancer that has spread to nearby or distant organs. These therapies interfere with cancer cell growth and the spread of cancer. The targeted therapies that are approved for use in colorectal cancer include bevacizumab (avastin), cetuximab (erbitux) and panitumumab (vectibix) all of which are explained below. Other monoclonal antibodies used in the treatment of cancer are used to carry drugs, toxins, or radioactive material directly to cancer cells and newer studies are looking at using them with chemo in earlier stage cancers as part of adjuvant therapy to reduce the risk of recurrence.

(b) **Bevacizumab (Avastin)**

**Potential Indications:** Stage IV Colorectal cancer (Palliative) In Combination with Chemotherapy

**Mechanism of Action:** Bevacizumab is a type of targeted therapy known as a monoclonal antibody. A monoclonal antibody is a man-made version of an immune system protein that fits like a lock and key with a certain protein in the body. Bevacizumab attaches to a protein called vascular endothelial growth factor (VEGF) which is required by the body to grow blood vessels. It is thought that by doing this, the drug stops tumours from being able to create new blood vessels capable of feeding and sustaining the tumour (a process known as angiogenesis). This limits the tumour’s supply of nutrients, which in turn may slow or stop their growth. For this reason, bevacizumab is sometimes referred to as an anti-angiogenic drug. There is another theory regarding bevacizumab’s mechanism of action that speaks to its ability to make tumour blood vessels (which are usually leaky) more stable, allowing chemotherapy to get into cancer cells more effectively. In colorectal cancer, bevacizumab has been approved for use in metastatic disease and in combination with chemotherapeutic drugs such as 5FU, Xeloda, FOLFOX, and FOLFIRI. A recent study showed that the addition of bevacizumab to chemotherapy in earlier stage colorectal cancer did not improve outcomes.
Tumours get what they need to grow and spread from blood vessels.

With avastin, tumours can’t get the nutrients they need to grow.


**Method of Administration:** Administered intravenously (into a vein) once every 2-3 weeks whose dosage is dependent upon body size. The first treatment is usually given over 90 minutes with subsequent treatments given over 60 minutes and perhaps 30 minutes.
Side Effects: The side effects that may be experienced are
- Elevated blood pressure (hypertension) including malignant hypertension*
- Bowel Perforation*
- Leakage of protein in the urine
- Headache
- Mouth sores (mucositis)
- Diarrhea
- Loss of appetite
- Fatigue
- Weakness
- Blood clots*
- Nosebleed
- Low white blood cell count with increased risk of infection (neutropenia)
(* = rare but very serious)

(c) Cetuximab (Erbitux)

Potential Indications: Stage IV Colorectal Cancer (Palliative) – With or without chemotherapy (typically administered with chemotherapy for maximum benefit).

Mechanism of Action: Cetuximab is a type of targeted therapy known as a monoclonal antibody. A monoclonal antibody is a man-made version of an immune system protein that fits like a lock and key with a certain protein appearing on the surface of cancer cells. Cetuximab is designed to seek out and lock onto a protein called epidermal growth factor receptor (EGFR), which is located on certain cells in the body, important for cellular growth, replication and spread. Some cancers, such as colorectal, have higher than normal numbers of these receptors on their surfaces. Once cetuximab attaches to these cells, it brings in other immune cells to help kill them, thereby inhibiting the growth and survival of tumour cells that over-express the EGFR. EGFR is detectable in many human tumours including those of the colon and rectum. This anti-EGFR therapy can be administered as a monotherapy (on its own) or in combination with irinotecan in FOLFIRI.

Method of Administration: Administered by infusion into a vein, usually once a week. The first dose is usually given over two hours, with subsequent treatments given over 1-hour period of time. Total dosage is dependent upon body size.

Side Effects: The common side effects that may be experienced are
- Skin rash on face, neck and trunk (dermal toxicity) that looks like acne
- Fatigue and weakness
- Low blood mineral levels (for example, magnesium)
- Loss of appetite
- Infusion reaction (including fever, headache, chills, itching, hives, nausea, shortness of breath)
- Changes in or loss of fingernails or toenails

NB: Genetic Mutations to Anti-EGFR Therapies - Biomarker Testing – RAS and BRAF Mutations

Personalized medicine has become a reality in the treatment of colorectal cancer. Scientifically, personalized medicine is known as pharmacogenomics (drugs combined with genes), or how genetic differences in individuals affect the way people respond to drugs. Biomarkers are biological molecules found in blood, body fluids, tissues or the tumour itself and they can be a sign of a normal or abnormal process. Biomarkers can be divided into two categories:

- **Prognostic biomarkers**: associated with the likelihood of an outcome such as survival, response and recurrence.
- **Predictive biomarkers**: associated with formerly present biomarkers capable of predicting an outcome. Can be either positive or negative

Although EGFR is expressed in approximately 85% of metastatic colorectal cancers, the clinical efficacy of treatment with anti-EGFR therapies is limited to a subset of patients. Two biomarkers, **KRAS and NRAS**, have been identified to be negative predictive biomarkers for response to anti-EGFR therapies such as cetuximab since they can identify which patients are unlikely to respond to treatment with an anti-EGFR therapy. They are collectively referred to as extended RAS.

**RAS Biomarkers**

KRAS and NRAS genes (RAS biomarkers) are genes present in colorectal cancer tumours and play an important role in cell growth and the development of tumours. These RAS genes can be altered (mutated) or normal (Wild Type) in colorectal cancer cells. Studies have shown that if the RAS genes are mutated, then anti-EGFR therapies, such as cetuximab, are not effective and should not be used. Patients with RAS gene mutations are identified to be **“KRAS mutant”** (occurring in approximately 50% of the colorectal cancer population) and those patients whose RAS genes are identified to be normal are termed **“RAS Wild Type”** (occurring in approximately 50% of the colorectal cancer population). Data shows that colorectal cancer patients with wild-type RAS (non-mutated) have a better response to anti-EGFR therapies, such as cetuximab, as well as longer progression free survival (time before the disease gets worse) and improved overall survival. Patients diagnosed with metastatic colorectal cancer should be tested for RAS mutation status to determine eligibility for anti-EGFR therapies. See diagram below for distribution of mutations in metastatic colorectal cancer.
The RAS mutation test should be performed as soon as a patient is diagnosed with metastatic colorectal cancer. It should be performed on tumour tissue that was likely extracted from either a biopsy or surgical removal of the primary tumour from the colon or rectum. Tumour tissue removed from the body (following biopsy or surgery) is processed into a tissue block and stored at the hospital where the operation took place. Once a decision is made to test for RAS mutations, the patient’s doctor will arrange to have a portion of that saved tissue block sent to a laboratory where RAS testing is conducted. Results are then sent back to the treating physician. The testing process may take up to 10-14 days. See diagram for procedural logistics.
Diagram provided by Mount Sinai Hospital, illustrating an overview of the RAS mutation detection procedures at its centre. Source: http://www.personalizingmedicine.ca/testing.html

If the tumour has no RAS mutations (wild type) then treatment options such as cetuximab can be prescribed. Knowing the RAS mutation status gives clearer direction to the treating physician to help determine the treatment that is most likely to provide positive results. RAS testing can be performed at several pathology labs across Canada. In Ontario, Mount Sinai Hospital Services has been designated by the Ministry of Health and Long Term Care to conduct RAS testing for patients who may be eligible to receive anti-EGFR therapies. Funding is also available for RAS testing to patients in other provinces who may be eligible to receive anti-EGFR therapies and testing can be performed at Mount Sinai Hospital, St. Michael’s Hospital, and University Health Network all of which are located in Toronto, Ontario. The Jewish General Hospital located in Montreal, Quebec is also performing testing as does British Columbia’s BC Cancer Agency.

**BRAF Biomarker**

Unfortunately, having wild-type RAS status does not guarantee a positive response to anti-EGFR therapies. Approximately 50% of the colorectal cancer RAS wild-type population responds to anti-EGFR therapies. The trouble with RAS mutation is that it is “downstream” of EGFR. (Genes have an orientation which is defined by their direction of transcription - the process of copying the genetic material in a cell. Downstream means further in the direction of transcription of a gene and even
possibly beyond its end (opposite is upstream). It doesn’t matter if you plug the socket in, if there is a short downstream of the plug, the power will be disrupted. The RAS mutations turns EGFR into a switch that is always on. But this doesn’t mean that having normal or wild-type RAS is a failsafe. It is not, for a patient can have another mutation down the line present in another gene called BRAF that can create a “short” downstream of the plug.

The BRAF gene makes a protein called B-RAF, which is involved in sending signals in cells and in cell growth. This gene may be mutated (rarely occurring alongside RAS mutations) in colorectal cancer tumor cells which causes a change in the wild-type BRAF protein. The mutated version of the gene can increase the growth and spread of colorectal cancer cells. This mutation in the BRAF gene has been shown to make colorectal cancers resistant to anti-EGFR therapies such as cetuximab (see diagram below). Patients with this mutation in their tumors are, therefore, considered unlikely to benefit from anti-EGFR therapies (see diagram below). It is, therefore, recommended, as per NCCN clinical practice guidelines, that RAS and BRAF mutations be tested simultaneously for determination of anti-EGFR therapy eligibility. See diagram below.

According to the most current data, the BRAF biomarker is deemed to be a negative predictive biomarker as well as a prognostic biomarker. The BRAF and RAS status must be determined to be wild-type to produce a positive response to anti-EGFR therapies.

Testing of BRAF status in Canada is now widely available. For patients harboring the BRAF V600 mutation, clinical trials are offering potential therapies to this patient population. In patients with metastatic colorectal cancer who have mutations in BRAF V600, the addition of the BRAF inhibitor Vemurafenib (Zelboraf) to Cetuximab (Erbitux) and Irinotecan significantly improved progression free
survival as demonstrated in the results of the phase II Southwest Oncology Group (SWOG) 1406 trial. Dr. Scott Kopetz from M.D. Anderson was the principal investigator of the 250 multi-center trial and was quite encouraged by the results.

Personal information about genetic constitution, such as a patient’s RAS status and braf status, provides healthcare professionals with specific information about how the patient may respond to certain treatments. This process is what is commonly referred to as “personalized medicine” – healthcare tailored to each individual’s genetic makeup – and it is becoming more and more of a reality everyday such that more and more patients will be prescribed the most effective therapies possible. More and more biomarkers are being identified and researched so that one day, the patient’s genetic makeup will be the driving force behind treatment selection.

**Panitumumab (Vectibix)**

**Potential Indications:** Stage IV Colorectal Cancer (Palliative) – With or without chemotherapy.

**Mechanism of Action:** Panitumumab is used to treat colorectal cancers that have the epidermal growth factor receptor (EGFR) in patients with metastatic colorectal cancer. It is a type of targeted therapy known as a monoclonal antibody. A monoclonal antibody is a man-made version of an immune system protein that fits like a lock and key with one certain protein. Panitumumab is designed to seek out and lock onto a protein called epidermal growth factor receptor (EGFR), which is found on certain cells in the body. Some cancer cells, such as colorectal, have more than the usual number of these proteins on their surfaces, which help them grow and survive. Panitumumab attaches to these protein receptors and stops their activity which helps stop cancer cells from growing and dividing. It may also help by tagging the cancer cells to be destroyed by the body’s immune system. This anti-EGFR therapy is usually administered as a monotherapy (on its own), with irinotecan or as the literature is reflecting, in combination with folfox or folfox.

**Method of Administration:** Administered by infusion into a vein, usually once every two weeks. The dose is usually given over 60 minutes, although larger doses are given over 90 minutes. And dosage is dependent upon the patient’s weight.

**Side Effects:** Common side effects may involve the following

- Skin rash (redness or rash on face, neck and trunk; acne, dryness, cracking, and itching which may worsen with sun exposure)
- Fatigue
- Diarrhea
- Changes in or loss of fingernails or toenails
- Low blood levels of magnesium, which can cause numbness, weakness, tremors, or irregular heartbeat
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Diagram provided by Mount Sinai Hospital, illustrating an overview of the KRAS mutation detection procedures at its centre. Source: [http://www.personalizingmedicine.ca/testing.html](http://www.personalizingmedicine.ca/testing.html)

If the tumour has no RAS mutation (wild type) then treatment options such as panitumumab can be
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certain treatments. This process is what is commonly referred to as “personalized medicine” – health care tailored to each individual’s genetic makeup – and it is becoming more and more of a reality everyday such that more and more patients will be prescribed the most effective therapies possible. A growing number of biomarkers are being identified and researched so that one day, the patient’s genetic makeup will be the driving force behind treatment selection.

(e) **Regorafenib** (Stivarga)

**Potential Indication:** Stage IV Colorectal Cancer, 3rd or 4th line therapy.

**Mechanism of Action:** an oral drug that targets multiple tyrosine kinases, for patients who progressed on prior therapy. Regorafenib works by blocking particular proteins on cancer cells that encourage the cancer to grow. These proteins are called protein kinases. Regorafenib is called a protein tyrosine kinase inhibitor (TKI) or cancer growth blocker. It works by stopping signals that tell cancer cells to grow. It also stops the cancer cells growing blood vessels that they need. Blocking blood vessel growth is called anti angiogenesis treatment. Regorafenib may shrink the cancer or stop it growing for a time. Please note this treatment is currently not funded in Canada and seldom prescribed.

**Method of Administration:** Regorafenib comes as tablets to be taken with water. You take regorafenib for 3 weeks and then you stop for 1 week. This is one cycle of treatment. Then the cycle starts again. You usually carry on taking regorafenib for as long as it works.

**Side Effects:** The following side effects may occur:

- Fatigue
- Hand/Foot Syndrome
- Headache
- Loss of Appetite
- Diarrhea
- Sore Mouth
- Skin Changes
- Weight Loss

*** Two other drugs are available in the U.S. that are currently not available in Canada.

- **Aflibercept** (Zaltrap), a fusion protein binding the growth factors VEGF-A, VEGF-B and PGF. It behaves very similarly to AVASTIN.
- **Ramucirumab** (Cyramza), an antibody targeting the VEGF receptor 2, which helps the tumour get nutrients, for metastatic colorectal cancer. It too behaves very similarly to AVASTIN.
For those drugs that are currently being developed, access may only take place through a clinical trial setting wherein certain parameters must be adhered to. Oftentimes, a clinical trial may be appropriate for a patient after proper consultation with the caring physician has taken place. Colorectal Cancer Canada has developed a Guide To Understanding Clinical Trials for those patients who wish to explore the possibility of accessing a clinical trial during the management of their disease. The Guide is intended to provide clarification, explanation and extensive information on the Clinical Trials Program in Canada and abroad. Should you wish to access this information, kindly do so by clicking the following link:  http://www.colorectal-cancer.ca/en/treating-cancer/clinical-trials/

PART III: RADIATION THERAPY

Introduction

Radiation therapy, or radiotherapy, is the use of various forms of radiation to safely and effectively treat cancer. It works by damaging the genetic material within cancer cells thereby limiting their ability to successfully reproduce. When these damaged cancer cells die, the body naturally eliminates them. Normal cells are also affected by radiation, but they are able to repair themselves in a way that cancer cells cannot. In an effort to shield as much surrounding healthy tissue as possible, the radiation oncologist develops a plan to deliver the radiation targeting the tumour area only as much as possible. Radiation therapy is a useful tool for treating cancer because cancer cells are growing in the body more rapidly than many normal cells around them, and radiation therapy preferentially treats more rapidly dividing cells.

Radiation therapy may be utilized in several ways. If the goal is to cure the cancer (curative intent), then the radiation therapy may be used to:

- Destroy tumours that have not metastasized to other parts of the body and therefore cure the body of the disease
- Reduce the risk that cancer will return after undergoing surgery or chemotherapy by killing small amounts of cancer that might remain
- Shrink the cancer before undergoing surgery

If the goal is to control or reduce the symptoms caused by growing tumours, thereby improving the quality of life (better known as palliative care or palliation), radiation may be used to:

- Shrink tumours that are interfering with quality of life, such as a lung metastasis causing shortness of breath
- Relieve pain by reducing the size of a tumour

Radiation therapy is considered a local treatment because it is delivered only to the cells in the cancerous area, which is unlike systemic therapy that delivers therapy to the entire body. Radiation
has been known to enhance the effects of chemotherapy (chemo-enhancer). And similarly, chemotherapy agents (such as 5FU or xeloda) are used to increase the effectiveness of radiation by sensitizing tumour cells present (radiation-sensitizer).

There are three types of radiation therapy that are discussed below according to type and anatomical location.

**External Beam Radiation Therapy:** Consists of the most prevalent type of radiation therapy. It uses a machine outside the body (called a linear accelerator or linac) to send radiation toward the cancer in question. During external beam radiation therapy, a beam (or multiple beams) of radiation is directed through the skin to the cancer and the immediate surrounding area in order to destroy the main tumour and any nearby cancer cells. To minimize side effects, the treatments are typically given five days a week, Monday through Friday, for a number of weeks, which allows enough radiation into the body to kill the cancer while giving healthy cells time to recover. The radiation is normally given on an outpatient basis at a hospital or clinic and usually involves a series of daily outpatient treatments to accurately deliver radiation to the area at risk. A considerable amount of planning and preparation is required before this type of therapy is administered to colorectal cancer patients. A team of specialists that always includes a radiation oncologist will determine the exact location at which to aim the radiation beam. Using treatment planning computers and software, the treatment team controls the size and shape of the beam, as well as how it is directed at the body, so as to effectively treat the tumour while sparing the surrounding normal tissue. Patients will be tattooed with small dots onto the body to ensure proper positioning and precision aiming. The entire process may take a number of hours but the treatment itself will last mere minutes. The schedule of treatments may last for several weeks and occur approximately five times a week. Several special types of external beam therapy are discussed in the section below depending upon the stage of disease and body organ affected. They may consist of:

- Three Dimensional Conformal Radiation Therapy (3D-CRT)
- Intensity Modulated Radiation Therapy (IMRT)
- Proton Beam Therapy
- Neutron Beam Therapy
- Image Guided Radiation Therapy (IGRT)
- Stereotactic Radiotherapy (SRT)
- Stereotactic Radiosurgery (SRS)

**Internal Radiation (Implant Radiation or Brachytherapy):** This radiation comes from radioactive material placed in thin tubes or small objects which are directly inserted into or near the tumour. The implant could be a wire, plastic tube, capsule or seed. The radiation travels only a short distance, limiting the effects on nearby healthy tissues. This method is sometimes used in treating people with rectal cancer, particularly ill or older people who would not be able to undergo surgery. The patient is
required to stay in hospital and the implants generally remain in place for several days. Ordinarily, the implants are removed before the patient goes home or may be situated permanently in the tumour area. Internal radiation is usually delivered in one of two ways, and both methods use sealed implants.

- **Interstitial radiation therapy** is inserted into tissue at or near the tumour site.
- **Intracavitary** or intraluminal radiation therapy is inserted into the body with an applicator.

**Intraoperative Radiation Therapy (IORT):** Is a form of external beam radiation involving the administration of radiation during surgery. It delivers a concentrated beam of radiation to cancerous tumours while they are exposed during surgery, thereby allowing the administration of high doses of radiation to tumours without exposing nearby healthy organs to radiation. A single dose of intraoperative radiation may have as much effect on the tumour as 10-20 daily radiation treatments. IORT is effective for tumours that cannot be completely removed surgically because they are either attached or close to healthy tissue that cannot be removed. Recurrent rectal cancer is the most common disease treated this way.

(i) **EXTERNAL BEAM RADIATION**

(a) **Rectum**

External Beam Radiation Therapy is frequently used in patients with rectal cancer because the rectum does not move as much as the colon and is thus easier to target. The indications include:

- Prior to rectal surgery, it is used to shrink the tumour and make it easier to remove. This is what is commonly referred to as **neoadjuvant therapy**. Neoadjuvant therapy is administered to rectal cancer patients whose tumours extend outside the rectum or have spread to regional lymph nodes, in order to decrease the risk of recurrence following surgery or to allow for less invasive surgical approaches (such as low anterior resection instead of an abdomino-perineal resection).

- After surgery, the radiation may kill any remaining cancer cells that couldn’t be removed during surgery. This is what is commonly referred to as **adjuvant therapy** and it is administered to patients whose tumours have perforated the rectum or involves regional lymph nodes.

- Radiation therapy may also be used to relieve the symptoms that are caused by the cancer such as pain or pressure. This is what is commonly referred to as **palliative therapy** because the objective is to decrease the tumour burden in order to relieve or prevent symptoms.
Radiation therapy given in the neoadjuvant setting may also be administered in combination with chemotherapy which may allow the rectal surgeon to spare the anus when removing the tumour. This would ultimately avoid the need for a permanent colostomy and may reduce the chance of the cancer returning. Rectal cancers respond much more positively to radiation based therapies and have been known to improve survival rates.

The following are the different types of external beam radiotherapy that may be employed in the local treatment of rectal cancers:

- **Intensity Modulated Radiation Therapy (IMRT):** Intensity modulated radiation therapy, or IMRT, is a specialized form of 3D-CRT (see below) that allows radiation to be more exactly shaped to fit the tumour. With IMRT, the radiation beam can be broken up into many “beamlets”, and the intensity of each beamlet can be adjusted individually. Using IMRT, it may be possible to further limit the amount of radiation received by healthy tissue near the tumour. In some situations, this may also safely allow a higher dose of radiation to be delivered to the tumour, potentially increasing the chance of a cure.

- **Three-Dimensional Conformal Radiation Therapy (3D-CRT):** Tumours are not regular; they come in different shapes and sizes. Three-dimensional conformal radiation therapy, or 3D-CRT, uses computers and special imaging techniques such as CT, MR or PET scans to show the size, shape and location of the tumour as well as surrounding organs. The radiation oncologist can then precisely tailor the radiation beams to the size and shape of the tumour with multileaf collimators (a device for producing a beam of parallel rays) or custom fabricated field-shaping blocks. Because the radiation beams are very precisely directed, nearby normal tissue receives less radiation and can heal more quickly.

- **Image Guided Radiation Therapy (IGRT):** Radiation oncologists use image guided radiation therapy, or IGRT, to help better deliver the radiation to the cancer since tumours can move between treatments due to differences in organ filling or movements while breathing. IGRT involves conformal radiation treatment guided by imaging, such as CT, ultrasound or x-rays, taken in the treatment room just before the patient is given the radiation treatment on a daily basis. All patients first undergo a CT scan as part of the planning process. The information from the CT scan is then transmitted to a computer in the treatment room to allow doctors to compare the earlier image with the images taken just before treatment. During IGRT, doctors compare these images to see if the treatment needs to be adjusted. This allows doctors to better target the cancer while avoiding nearby healthy tissue. In some cases, doctors will implant a tiny marker in or near the tumour to pinpoint it for IGRT. This helps to account for organ/tumour motion even if the body is immobilized by a casting device.

- **Proton Beam Therapy:** Proton beam therapy is a form of external beam radiation treatment that uses protons rather than electron x-rays to treat certain types of cancer and other diseases. The physical characteristics of the proton therapy beam allow the radiation...
oncologist to more effectively reduce the radiation dose to nearby healthy tissue. Proton therapy is available at only a few centers in North America and is used in unique clinical situations.

- **Neutron Beam Therapy:** Like proton therapy, neutron beam therapy is a specialized form of external beam radiation therapy. It is often used to treat certain tumours that are radiosensitive, difficult to kill using conventional x-ray radiation therapy. Neutrons have a greater biologic impact on cells than other types of radiation. Used carefully, this added impact can be an advantage in certain situations. Neutron therapy is also only available in certain centres in North America.

(b) Colon

External beam radiotherapy is not used routinely in the treatment of colon cancer, as it could lead to radiation enteritis (the syndrome that develops after the intestine is exposed to radiation), and it is difficult to target specific portions of the colon, since the colon has a tendency to move as much as it does. Indications for colon cancer include:

- Pain relief and palliation – targeted at metastatic tumour deposits if they compress vital structures and/or cause pain. External beam radiation therapy can be effective in patients with colon cancer that has attached to an internal organ or the lining of the abdomen. Should this happen, it is difficult to predict whether all the cancer has been removed during surgery, hence, radiation is used to kill the cancer cells left behind after surgery. Therefore, external beam radiation may be employed to improve other controls directed at the cancer and this has been documented to lengthen survival.

The types of external beam radiation which may be employed in the palliative treatment of colon cancer are similar to the ones used in the treatment of rectal cancer as noted above.

(c) Liver

The liver is a common site for colorectal cancer metastases. Depending upon the number and location, liver metastases can be removed surgically. When surgery is not possible, however, radiation therapy may be an option. A specialized external beam radiation treatment called stereotactic body radiation therapy (SBRT) can accurately target some liver tumours (please see below). Another treatment option is the selective internal radiation therapy or SIRT wherein radioactive particles are injected into the blood vessels of the liver. This procedure is discussed in greater detail under the section **Interventional Radiology** appearing below under PART IV.

- **Stereotactic Radiation Therapy (SRT):** SRT is a specialized type of external beam radiation therapy which uses focused radiation beams targeting a well-defined tumour, relying on detailed imaging, computerized three-dimensional treatment planning and precise
treatment set-up to deliver the radiation dose with extreme accuracy (ie stereotactically). There are two types of stereotactic radiation:

- **Stereotactic Body Radiation Therapy (SBRT):** refers to one or several stereotactic radiation treatments with the body, excluding the brain or spine. It is used to treat small tumours in the abdomen, including liver metastases that cannot be removed surgically or treated with conventional radiation therapy. Patients with tumours that are small and few in number are the best candidates for stereotactic techniques.

- **Stereotactic Radiosurgery (SRS):** refers to a single or several stereotactic radiation treatments of the brain or spine. It is delivered by a beam involving a radiation oncologist and a neurosurgeon. It treats cancers that have spread to the brain and spine and patients who have fewer than 5 metastases are the best candidates for it. It is able to target small, well-defined areas with precision. Radiosurgery delivers radiation in single high doses that conform closely to the tumour shape, and fall off sharply at the edge of the tumour. (See brain/spine below for description)

SRT is best for very small tumours. Physicians use specialized scans to pinpoint exactly where within the body the tumour target is located. A customized holder may be used to keep the body perfectly still during treatment, or the treatment machine may have the ability to adjust for patient motion such as during breathing. These techniques allow doctors to give a high dose of radiation to the tumour in short amount of time. It delivers the right amount of radiation to the cancer in a shorter amount of time than traditional treatments. Additionally, the treatment is delivered with extreme accuracy, minimizing the effect on nearby organs. It is able to deliver high doses of radiation safely and accurately over just a few treatments (usually one to five sessions overall).

SRT may be synonymous with the brand name stereotactic treatment machines which deliver SRT. They include: **Cyberknife, Gamma Knife, and TomoTherapy.**

**Lungs**

**Stereotactic Body Radiation Therapy (SBRT)** is a type of external beam radiation and it may be used to treat small tumours in the chest that cannot be removed surgically or treated with conventional radiation therapy including colorectal cancer that has spread to the lungs (lung metastases). The lungs are another common distant site wherein colorectal cancer metastases may appear. Patients with lung metastases that are small and few in number are the best candidates for SBRT. Physicians use specialized scans to pinpoint exactly where within the body the tumour target is located. A customized holder may be used to keep the body perfectly still during treatment, or the treatment machine may have the ability to adjust for patient motion such as during breathing. These techniques allow doctors to give a high dose of radiation to the
tumour in a short amount of time. It delivers the right amount of radiation to the cancer in a shorter amount of time than traditional treatments. Additionally, the treatment is delivered with extreme accuracy, minimizing the effect on nearby organs. It is able to deliver high doses of radiation safely and accurately over just a few treatments (usually one to five sessions overall).

(e) Brain/Spine

Colorectal cancer rarely metastasizes to the brain or spine but there is documented evidence that these distant organs may become affected by the disease. A type of external beam radiation employed in the treatment of brain/spine metastases is Stereotactic Radiosurgery or SRS. It refers to a single or several stereotactic radiation treatments of the brain or spine delivered by a team involving a radiation oncologist, diagnostic radiologist and a neurosurgeon. SRS uses precisely focused radiation to treat metastases in the brain. Computers create 3-D images of the brain, and these images guide radiation oncologists and surgeons in aiming radiation at the target area. This technology allows high doses of radiation to be delivered to the tumour with minimal exposure to surrounding healthy tissue. No incision is made and general anesthesia is not required for adults, therefore no hospital stay. Tumour type, location and size will dictate whether Radiosurgery is the appropriate treatment. SRS delivers radiation in single high doses that conform closely to the tumour shape, and fall off sharply at the edge of the tumour. Treatments can typically be done in a single session.

(f) Bone

Cancer cells that have metastasized to the bone can damage the bone and cause symptoms. Various treatments are available to control the symptoms and the spread of bone metastases. To better understand what happens in metastasis, it helps to know the anatomy of the bones.

Bone Basics

Bone is a type of connective tissue made up of minerals, such as calcium and phosphate, and the protein collagen. The outer layer of bone is called the cortex. The spongy center of bone is
called bone marrow. Bone tissue is porous, with blood vessels running through it. Bone is alive and constantly repairs and renews itself through a process called remodeling. There are two kinds of cells involved in this process.

- Osteoblasts are bone-forming cells
- Osteoclasts are cells that break down, or resorb, bone.

When cells break away from a cancerous tumour, they can travel through the bloodstream or lymph vessels to other parts of the body. Cancer cells can lodge in an organ at a distant location and establish a new tumour. The original tumour that cells break away from is called the primary tumour. The new tumour that the traveling cells create is called the secondary tumour. Secondary tumours in the bone are called bone metastases. Radiation is useful in easing pain and killing tumour cells in the bone metastases. It may be used to prevent a fracture or to treat spinal cord compression. Radiation therapy uses high-energy ionizing radiation to injure or destroy cancer cells. Typically radiation is administered once a day in 10 treatments over a 2-week period. Full effects of this treatment may take 2 to 3 weeks to occur. Side effects of radiation may include skin changes in the area being treated and, rarely, a temporary increase in symptoms of bone metastasis. The goals of palliative treatment of bone metastases are pain relief, preservation of function and maintenance of skeletal integrity. Local field external beam radiation therapy is one well-recognized and effective palliative modality.

**Intensity Modulated Radiation Therapy (IMRT):** Intensity modulated radiation therapy, or IMRT, is a specialized form of 3D-CRT (see above) that allows external beam radiation to be more exactly shaped to fit the tumour. With IMRT, the radiation beam can be broken up into many “beamlets”, and the intensity of each beamlet can be adjusted individually. Using IMRT, it may be possible to further limit the amount of radiation received by healthy tissue near the tumour. In some situations, this may also safely allow a higher dose of radiation to be delivered to the tumour. IMRT may help stop cancer from spreading further, and may decrease pain caused by bone metastasis. This treatment may be done after surgery to decrease pressure on nerves caused by cancer that has spread to the spine. It may also be done after surgery to repair bones or make them more stable. Radiation therapy after surgery can help prevent more surgery, and may help increase daily activity. If many tumours have been identified, radiation therapy may be employed. Consequently, pain may decrease or subside within a few days of the radiation treatment. For some patients, it may require two weeks or longer for the pain to subside.

**ExAblate or Magnetic Resonance-guided Focused Ultrasound (MRgUS):** Patients, who have had external beam radiation therapy and failed to improve, may need to seek other therapies for their painful bone metastases. Some of these (such as radiofrequency ablation or surgery) may be less efficient and have higher treatment related adverse events associated with them. ExAblate or magnetic resonance-guided focused ultrasound is a clinical procedure designed to
non-invasively ablate (destroy) tissue and may meet the needs of these patients.


The therapeutic effects of ExAblate are achieved by heating the bone periosteum (the sheath of connective tissue that surrounds all bones except those at joints), thus ablating the sensory origin of the pain in one treatment. This non-invasive procedure combines focused ultrasound waves designed to generate sufficient heat to destroy the pain caused by nerves in the bone surface surrounding the tumour and magnetic resonance imaging to guide the one-time treatment.

Source:  http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/recently-approveddevices/ucm080704.htm
ExAblate is used in combination with magnetic resonance imaging (MRI) to identify and monitor the precise location of the painful bone lesions. Once the lesion is identified, ExAblate delivers a beam of high intensity focused ultrasound to the target, raising the temperature sufficiently to cause tissue destruction. The precise mechanism of analgesia is unknown, but immediate pain relief may be due to the destruction of nerve tissue, while continued analgesia may result from a decrease in tumour mass and subsequent pressure on the bone. The treatment takes approximately 80 minutes and is performed in an outpatient clinic. Patients are given intravenous sedation and analgesia to prevent movement during the procedure. Potential complications of ExAblate treatment include superficial skin burns and thermal damage to adjacent heat-sensitive organs.

This treatment is currently in phase III clinical trials at a number of centres in the US, Canada (including Toronto) and Israel. The clinical trials identifier is NCT00656305 and can be accessed at [www.clinicaltrials.gov](http://www.clinicaltrials.gov). The procedure has been treating uterine fibroids successfully since 2004. There are restrictions guiding patient eligibility. Patients must present with bone metastases that are 8 cm or less, have tumours clearly visible on MRI and no more than 3 painful metastases to their bones.

(g) Side Effects of External Beam Radiation Therapy

Most of the side effects of external beam radiation therapy are usually in the area being treated. For example, a patient who is having an organ in his chest treated may notice skin irritation on their chest, like a mild to moderate sunburn, while a patient with who is having their midsection treated may report feelings of nausea and vomiting. These side effects are related to injury to rapidly dividing cells. They are usually temporary and can be treated by a physician. Side effects usually begin by the second or third week of treatment, and they may last for several weeks after the final radiation treatment. In rare instances, serious side effects develop after radiation therapy is finished. The side effect most often reported by patients receiving radiation is fatigue. The fatigue patients experience is usually mild or moderate, differs for each patient, and may also relate to the area being treated and the other therapies, such as chemotherapy, the patient is receiving. Patients may be able to continue all or a portion of their normal daily activities.

Radiation therapy will affect normal cells as well as the cancer cells thereby resulting in some unpleasant side effects. Normal cells will not be killed by the radiation, and many of them will recover from the treatment. The patient’s normal cells will be shielded in an effort to prevent any adverse side effects. The following is a list of possible radiation-induced side effects in colorectal cancer patients:

- Radiation therapy to the abdomen may cause more frequent bowel movements,
occasionally with diarrhea, abdominal cramping or rectal discomfort or pressure

- Fatigue and loss of appetite which is temporary
- Possible skin irritation at the treatment site
- More frequent urination
- Burning with urination
- Nausea
- Bloody stools
- Infertility

Side effects often can be controlled with medications or changes in the diet. Patients wishing to access additional information on colorectal cancer treatment-induced side effects may do so by accessing Colorectal Cancer Canada’s website which supplies a comprehensive guide to addressing treatment-induced side effects. Simply click on the section entitled “Side Effects” to access a wealth of information on treatment-induced side effects.

(ii) INTERNAL RADIATION (IMPLANT RADIATION OR BRACHYTHERAPY) – Stage II, III, IV

(a) Rectum

Internal radiation therapy (also called Brachytherapy) uses radiation that is placed very close to or inside the tumour. The radiation source is usually sealed in a small holder called an implant. Implants may be in the form of thin wires, plastic tubes called catheters, ribbons, capsules, or seeds. The radiation travels only a short distance, limiting the effects on nearby healthy tissues. The implant is placed directly into the body and may require a hospital stay. Internal radiation is usually delivered in one of two ways, each of which is described below and both methods use sealed implants:

- **Interstitial Radiation Therapy**: is inserted into tissue at or near the tumour site. It is used to treat tumours of the pelvic region such as rectal cancer. Radioactive sources are positioned into a cancerous tumour and may be removed in some instances or located permanently in others.
- **Intracavitary or Intraluminal Radiation Therapy**: is inserted into the body with an applicator and resembles interstitial radiation therapy except radioactive sources are placed inside body cavities where tumours are located. Typically, the sources are removed after several hours. It is administered in the treatment of rectal cancer.

While the radioactive sources are in place, patients will be required to stay in a private room. During the time when radiation is present in the patient’s system, doctors, nurses and other medical staff will continue to take care of the patient, but will take special precautions to limit their exposure to radiation.
**High Dose Rate Brachytherapy:** involves the remote placement of the powerful radiation source, accurately directed by the radiation oncologist and team, into the tumour for several minutes through a tube called a catheter. It is usually given in multiple doses once or twice daily or once or twice weekly. This treatment will be controlled from outside the treatment room, monitoring the patient as the therapy is being administered. Devices called high dose rate remote afterloading machines allow the treatment to be delivered quickly, in approximately 10-20 minutes.

**Low Dose Rate Brachytherapy:** involves the longer placement of the temporary (several days) or permanent radiation source into the tumour area. Most patients feel little discomfort during Brachytherapy. If the radioactive source is held in place with an applicator, patients may feel discomfort from the applicator. There are medications that can relieve this discomfort.

**(b) Side Effects of Internal Radiotherapy**

Most of the side effects resulting from internal radiation therapy are usually confined to the area being treated. They are usually temporary and can be treated by a physician. The side effect most often reported by patients receiving internal radiation is fatigue. The fatigue patients experience is usually mild or moderate, differs for each patient, and may also relate to the area being treated and the other therapies, such as chemotherapy, the patient is receiving. Patients may be able to continue all or a portion of their normal daily activities. The following is a list of possible internal radiation-induced side effects in colorectal cancer patients:

- More frequent bowel movements, occasionally with diarrhea, abdominal cramping or rectal discomfort or pressure
- Fatigue and loss of appetite which is temporary
- More frequent urination
- Burning with urination
- Nausea
- Bloody stools
- Infertility

Side effects often can be controlled with medications or changes in diet. Patients wishing to access additional information on colorectal cancer treatment-induced side effects may do so by accessing Colorectal Cancer Canada’s website which supplies a comprehensive guide to addressing treatment-induced side effects. Simply click on the section entitled “Side Effects” to access a wealth of information on treatment-induced side effects.
(iii) INTRAOPERATIVE RADIATION THERAPY (IORT) – Stage II, III, IV

(a) Rectum & Colon

Intraoperative Radiation Therapy or IORT is a form of external radiation that is delivered during surgery. IORT is used to treat localized cancers that cannot be completely removed or in cancers that have a high risk of recurring in nearby tissue (such as rectal cancer). After all or most of the cancer is removed, one large, high-energy dose of radiation is aimed directly at the tumour site during surgery (nearby healthy tissue is protected with special shields). See diagram below. A single dose of intraoperative radiation may have as much effect on the tumour as 10-20 daily radiation treatments. The patient stays in the hospital to recover from the surgery. IORT may be indeed used in the treatment of primary colorectal cancers. It is effective for tumours that cannot be completely removed surgically because they are either attached or close to healthy tissue that cannot be removed. Recurrent rectal cancer is the most common disease treated this way and IORT is also administered to patients who have locally advanced rectal and colon cancers who wish to achieve long-term tumour control. IORT is almost always administered in conjunction with external radiation given prior to surgery.

Source: http://www.mayoclinic.org/intraoperative-radiation/

During surgery, after the surgeon has removed as much of the rectal tumour as possible, a machine called a linear accelerator delivers a concentrated beam of electron radiation directly to the exposed cancerous tumours. IORT may be used when the remaining tumour is microscopic and not visible to the naked eye. The surgeon moves healthy organs out of the radiation field to prevent damage, and special tubes are used to focus the beams safely on the tumour or the tumour bed.

(b) Side Effects of Intraoperative Radiotherapy
Most of the side effects resulting from intraoperative radiation therapy are usually confined to the area being treated. They are usually temporary and can be treated by a physician. The side effect most often reported by patients receiving IORT is fatigue. The fatigue patients experience is usually mild or moderate, differs for each patient, and may also relate to the area being treated and the other therapies, such as surgery, the patient is receiving. Since IORT is administered during surgery, patients may not be able to continue all or a portion of their normal daily activities until a proper recovery time has elapsed. The following is a list of possible IORT-induced side effects in colorectal cancer patients:

- More frequent bowel movements, occasionally with diarrhea, abdominal cramping or rectal discomfort or pressure
- Fatigue and loss of appetite which is temporary
- More frequent urination
- Burning with urination
- Nausea
- Bloody stools
- Infertility

Side effects often can be controlled with medications or changes in diet. Patients wishing to access additional information on colorectal cancer treatment-induced side effects may do so by accessing Colorectal Cancer Canada’s website which supplies a comprehensive guide to addressing treatment-induced side effects. Simply click on the section entitled “Side Effects” to access a wealth of information on treatment-induced side effects.

**IV. PROCEDURES IN INTERVENTIONAL RADIOLOGY**

**Introduction**

Oftentimes, if only a small number of metastases are present in the liver or lungs (and nowhere else), they can be removed using surgical methods as described earlier in this document. Surgical candidacy will depend on their size, number, and location. In some cases, however, where surgically removing the tumours is not possible, non-surgical treatments may be used to destroy (ablate) tumours in the liver and lungs. But these methods may be less likely to be curative depending on the extent of the disease. Interventional radiologists are physicians who specialize in minimally invasive, targeted treatments. They offer the most in-depth knowledge of the least invasive treatments available coupled with diagnostic and clinical experience across all specialties. They use x-rays, MRI and other imaging to advance a catheter in the body, usually in an artery, to treat at the source of the disease internally. Interventional oncology is a growing specialty area of interventional radiology. Today many conditions that once required surgery can be treated less invasively by interventional radiologists.
Interventional radiology treatments offer less risk, less pain and less recovery time compared to open surgery. Several different techniques in interventional radiology are described below according to the anatomical site of metastasis.

(a) **Liver – Stage IV**

The liver is divided into the left and right lobe with numbered segments appearing in each. A review of the liver's segments appearing in the illustration below will aid in the understanding of how interventional radiological therapies are administered.

![Liver Diagram](http://www.hopkins-gi.org/GDL_Disease.aspx?CurrentUDV=31&GDL_Cat_ID=AF793A59-B736-42CB-9E1F-E79D2B9FC358&GDL_Disease_ID=A349F0EC-5C87-4A52-9F2E-69AFDB80C3D1)

The following procedures in interventional radiology may be administered and are indicated for the treatment of metastatic colorectal cancer to the liver.

(h) **Percutaneous Ethanol Injection**: Also known as Alcohol Ablation. This procedure involves injecting concentrated alcohol directly into the tumour to kill cancer cells. This is usually done through the skin using a needle, which is guided by ultrasound or CT scan.
Usually, multiple sessions are required producing a one day hospital stay. The procedure is performed in an interventional radiology suite with conscious sedation. The procedure is relatively simple to perform but the metastatic disease has a tendency to respond poorly.

(ii) **Interstitial Thermal Ablation/Interstitial Laser Photocoagulation**: This procedure involves the percutaneous insertion of a single, bare laser fibre into the tumour which scatters light in the optical or near-infrared wavelengths within tissue which is then converted into heat. The heat produces a zone of necrosis (tumour death) – see illustration below.
The liver metastases have a tendency to respond well but a noteworthy concern is the intense inflammatory response that oftentimes takes place after the procedure. The patient is therefore treated with narcotic and non-steroidal anti-inflammatory analgesics. The treatment is usually performed with MRI so that procedure precision may be attained.

(iii) **Cryotherapy**: Also known as cryosurgery. This is a treatment that uses an instrument to freeze and destroy abnormal tissue, such as liver metastases. Probes are used to freeze and destroy metastases under general anesthesia in the operating room. The probe is guided through the skin and into the tumour using ultrasound. Then very cold gasses are passed through the probe to freeze the tumour, killing the cancer cells. Conductive material kills tumour cells by denaturing cellular proteins and rupturing tumour cell membranes – see illustration below.

![Cryotherapy Illustration](http://www.hopkins-gi.org/GDL_Disease.aspx?CurrentUDV=31&GDL_Cat_ID=AF793A59-B736-42CB-9E1F-E79D2B9FC358&GDL_Disease_ID=A349F0EC-5C87-4A52-9F2E-69AFDB80C3D1)

This method can treat larger tumours that cannot be treated by other ablation techniques but does require general anesthesia. The liver metastases tend to respond fairly well.

(iv) **Microwave Coagulation**: Ultra high-speed microwaves are emitted from a percutaneously placed probe. A 14-gauge needle is inserted, followed by the microwave probe. Liver metastases have responded very well especially in Japan.

(v) **Chemoembolization**: Chemoembolization of the hepatic artery may be used to treat cancer that has spread to the liver. This involves embolizing (blocking) the hepatic artery (the main artery that feeds most cancer cells in the liver) and injecting anticancer drugs between the blockage and the liver. The liver’s arteries then deliver the drugs throughout the liver. Only a small amount of
the drug reaches other parts of the body. The blockage may be temporary or permanent, depending on what is used to block the artery. Most of the healthy liver cells will not be affected because they get their blood supply from the hepatic portal vein, which carries blood from the stomach and intestine. Therefore, no systemic effects will be felt. For this procedure, the interventional radiologist puts a catheter into an artery in the inner thigh (femoral artery) and threads it up into the liver. A dye is usually injected into the bloodstream to allow the doctor to monitor the path of the catheter via angiography, a special type of x-ray. Once the catheter is in place, small particles are injected into the artery to plug it up. This procedure will induce necrosis (cell death) of the liver tumours while sparing normal hepatic tissue. The hepatic artery is blocked with an infusion of emulsification of iodinated oil (lipiodol) and then chemotherapeutic agents (such as 5FU or mitomycin C) are infused between the blockage and the liver. See diagram below.

Source: [http://www.cpmc.org/advanced/liver/patients/topics/LT-livercancer.html](http://www.cpmc.org/advanced/liver/patients/topics/LT-livercancer.html)

This technique has shown promising results especially in patients who have multiple lesions that may be difficult to treat. Many patients who have failed IV chemo may still show response to chemoembolization and sometimes in combination with other techniques such as ethanol or RFA (see below). If responsive, patients may undergo 3 or 4 embolizations over a period of months or years. Complications are usually minor and response rate is very good.

(vi) Radiofrequency Ablation: Radiofrequency ablation (RFA) uses high-energy radio waves for treatment. A thin, needle-like probe with tiny electrodes is placed through the skin and into the tumour of the liver. Placement of the probe is guided by ultrasound or CT scans. The tip of the
probe releases high-frequency radio waves that heat the tumour and destroy the cancer cells. Tumour necrosis is produced by thermal coagulation and protein denaturation. High frequency alternating current flows from noninsulated electrode tips into the surrounding tissue, which differs from direct heating from a probe. As a result of the change in direction of the alternating current, agitation of the tissue occurs and results in frictional heating. The tissues surrounding the electrode (rather than the electrode itself) are the primary source of heat. The result is tumour necrosis (death).

Liver metastases respond well with complete ablation rates in the range of approximately 90% depending upon tumour size and location. Ordinarily, the hospital stay is limited to one day.

(vii) **Selective Internal Radiation Therapy**: Also known as **Microspheres or Theraspheres**. In this procedure, millions of radioactive particles (called yttrium 90) contained within tiny resin spheres are injected into the blood vessels of the liver. A catheter is threaded through the femoral artery and positioned in the hepatic artery (the main artery that feeds most cancer cells in the liver). Once the catheter is guided into the branch of the hepatic artery that feeds the tumour, microspheres are infused through the catheter into the tumour’s blood supply. Once in the liver, the microspheres become trapped in the small blood vessels (capillaries) that feed the tumour and radiation gets delivered directly to the tumour, sparing surrounding healthy tissue, as a direct result of sphere breakdown.
It is performed on an outpatient basis with little to no toxicity experienced systemically and the response rate has been documented to be as high as 30%. The procedure is able to deliver high doses of radiation directly to the site of tumours. This minimally-invasive treatment allows millions of radioactive microspheres to be infused into the liver where they selectively target liver tumours with a dose of internal radiation up to 40 times higher than conventional radiotherapy, while sparing healthy tissue.

(viii) Portal Vein Embolization: The liver is a unique organ because it can hypertrophy (re-grow) after part of it has been removed. However, the body does require that a minimum amount of liver be left behind following surgery in order to give the body enough time for this re-growth to occur. In some circumstances, the metastases in the liver are so large, that a large amount of liver would be required to be removed so that all the disease can be taken out. In these circumstances, Portal Vein Embolization can be utilized to help the liver re-grow before the surgery. Patients who previously were not candidates for surgery, due to the small amount of liver that would be left behind, can now undergo surgery and have successful and safe removal of their metastases. Portal vein embolization is currently being used in colorectal cancer patients to cause the atrophy or shrinking of a part of the liver and the hypertrophy or extra growth of the remaining liver prior to liver resection surgery. During the procedure, a needle is placed percutaneously (through the skin) into the liver. The interventional radiologist will identify the blood vessel (portal vein) going to the side of the liver that has the largest portion of the disease (see diagram). This blood vessel (portal vein) is then embolized (cut-off), thereby “tricking” the liver into making the other side of the liver grow. After several weeks, the side of the liver which has not been embolized should have grown.
to the point where there is now enough liver to perform surgery.

![Liver Diagram](http://hoptechno.com/livercancer.jpg)

**Source:** [http://hoptechno.com/livercancer.jpg](http://hoptechno.com/livercancer.jpg)

The setting in which this can be of benefit is in the preoperative patient in which you need to shrink the bad liver that you are going to remove and grow the good liver that you are going to leave behind. This is a useful technique in some patients in which a large resection needs to be done and the remaining liver will be a fairly small volume. When the portal vein on one side of the liver is occluded (blocked), that lobe of the liver atrophies, but the opposite lobe grows (hypertrophies). As the portal vein is occluded, diversion of blood flow to the opposite side of the liver triggers hypertrophy. Liver regeneration begins within hours throughout the nonembolized part of the liver, while tumour death leads to atrophy of the embolized lobe. Portal vein embolization increases the volume and function of the liver remnant and it allows the future liver remnant to adjust to portal pressure changes several weeks before becoming a candidate for surgery.

For a graphical representation of the procedure, please visit the Johns Hopkins website at: [http://www.hopkinsmedicine.org/liver_tumour_center/treatments/portal_vein_embolization.html](http://www.hopkinsmedicine.org/liver_tumour_center/treatments/portal_vein_embolization.html)

**(viii) Hepatic Arterial Infusion Pump:** Hepatic arterial infusion pump (HAIP) chemotherapy is a therapy that delivers chemotherapy drugs directly to the liver through a catheter placed in the hepatic artery, the main blood vessel pathway through which liver tumours receive their blood supply. The rationale for HAIP is to expose the metastases to high chemotherapy concentrations while minimizing systemic toxicity. This can be
achieved by infusing a drug into the hepatic artery that mostly supplies blood to liver metastases, whereas the portal vein mostly supplies normal liver cells. Multiple chemotherapeutic agents such as 5-fluorouracil (5-FU), mitomycin, cisplatin, and doxorubicin have been infused, but 5-fluoro-2′-deoxyuridine (flouxuridine, FUDR) has been the chemotherapeutic agent most frequently studied. FUDR has a 95% hepatic extraction when continuously infused in the hepatic artery, resulting in a 16-fold higher concentration in liver metastasis compared with venous administration. Infusing FUDR in the hepatic artery is achieved through an implantable subcutaneous infusion pump connected to a surgically placed hepatic artery catheter, which delivers the chemotherapeutic agent at a slow fixed rate, usually for 2 weeks (see diagram below).


HAIP has generally been used in patients with colon or rectal metastases to the liver. The pump is implanted through an operation in which a tube (catheter) is threaded into the hepatic artery and subsequently, chemotherapy drugs are injected periodically through the skin into the
chamber of the pump, which then, through a gas driven bellows, places the right amount of chemotherapy drug into the liver itself. The therapy is currently available at the Odette Cancer Centre, Sunnybrook Health Sciences Centre in Toronto, Ontario as a clinical trial for patients who have unresectable liver metastases from colorectal cancer and a maximum of 1-5 lung nodules that can be treated pre-therapy.

(b) Lungs

(i) Radiofrequency Ablation (RFA): Treatment for lung metastases typically consists of the surgical removal of the cancer, radiation therapy, targeted therapy, or chemotherapy. The type of therapy used depends largely upon the individual patient and characteristics of the disease. Because treatment is often not well tolerated, researchers continue to evaluate ways to improve outcomes for patients with metastatic lung tumours. Radiofrequency ablation (RFA) is commonly used for the treatment of tumours in the liver that are not amenable to surgery. The procedure involves the use of a small probe inserted into the site of cancer. The physician guides the probe through scans so that the treatment can be contained within the site of cancer, limiting the impact on surrounding tissue. Radio waves flow through the probe to the site of cancer, thereby destroying the cells. RFA typically requires local anesthesia, no surgery, and affects only the site of cancer without causing side effects to the rest of the body. RFA is currently being evaluated in lung tumours as well as other tumours affecting different parts of the body. During the procedure, an interventional radiologist guides a small needle through the skin into the tumour, generally by computed tomography (CT). Radiofrequency (electrical) energy is transmitted to the tip of the needle where it produces heat in the tissues. Rapidly alternating current is applied with a frequency in the range of 460-500 kHz through the RFA electrode. The alternating current causes movement of ions in the tissue resulting in tissue heating. Applying a temperature greater than 50 degrees C for 5 minutes results in tumour cell death. The dead tumour tissue shrinks and slowly forms a scar. At the same time, heat from radiofrequency energy closes small blood vessels and lessens the risks of bleeding. See diagram below.
RFA usually causes little discomfort. Radiofrequency energy can be given without affecting a patient’s overall health, and most people can resume their usual activities in a few days. It is a safe, minimally invasive tool for local pulmonary tumour control with negligible mortality, little morbidity, short hospital stay and positive gain in quality of life. Lung function is generally better preserved after RFA than after surgical removal of a tumour. This is especially important for those whose ability to breathe is impaired, such as current or former cigarette smokers. It can also be repeated if necessary or combined with other treatment options. Patients with tumours that are 5cm or smaller are best suited for RFA treatment. The number of metastases should not exceed 5 as well.

(ii) **Cryoblation:** Cryoblation, or cryosurgery, is a minimally invasive technique that has shown promise in patients with a limited number of small pulmonary metastases. It is limited to situations in which surgical resection is not an option due to advanced age and/or coexistent medical morbidities. It is done with a machine which uses pressurized argon and helium gases to regulate freezing and thawing processes. There is scanning during placement of the probe. Once the probe is activated, freezing and thawing cycles are monitored with MRI. Multiple
cycles may be performed to obliterate as much of the tumour as possible. Freezing tumour cells interrupts critical cell functions and results in cell death. Cells that remain within the body are absorbed along with scar tissue. The effectiveness of Cryotherapy has been well documented as it is utilized in the treatment of numerous lesions throughout the body. The procedure is performed under general anesthesia. After freezing, the probe is removed and the incision is closed with two or three sutures. Recovery time ranges from two to eight days, depending on the location of the lesion and depth of treatment. The technological advances which have caused renewed interest in cryosurgery are the development of intraoperative ultrasound to monitor the therapeutic process and the development of new cryosurgical equipment designed to use super-cooled liquid nitrogen. The thin, highly efficient probes, available in several sizes, can be placed in diseased sites via endoscopy or percutaneously in minimally invasive procedures. The manner of use is to place the probe in the desired location in the diseased tissue with ultrasound guidance. If required by the size or location of the tumour, as many as five probes can be inserted and cooled to -195 degrees C simultaneously. The process of freezing is monitored by ultrasound which displays a hypoechoic (dark) image when the tissue is frozen. Rapid freezing, slow thawing, and repetition of the freeze/thaw cycle are standard features of technique. Risks of the procedure include freezing of non-target tissues, internal bleeding, infection and damage to normal structures near the target tumour.

PART V: IMMUNOTHERAPY FOR COLORECTAL CANCER

Current Immunotherapies for colorectal cancer fall into 7 broad categories. Most of these therapies are still in early-phase clinical testing (phase I and phase II) for colorectal cancer, but their successful use in other types of cancers suggests that they may ultimately prove useful for colorectal cancer as well.

i. **Checkpoint inhibitors and immune modulators:** a promising avenue of clinical research in colorectal cancer is the use of immune checkpoint inhibitors. These treatments work by targeting molecules that serve as check and balances on immune responses. By blocking these inhibitory molecules or, alternatively, activating stimulatory molecules, these treatments are designed to unleash or enhance pre-existing anticancer immune responses. Examples are: Pembrolizumab (Keytruda), Nivolumab (Opdivo), Ipilimumab (Yervoy), Durvalumab (MEDI4736), Tremelimumab, Atezolizumab (MPDL3280A), Varlilumab (CDX-1127).

**PD-1 (Programmed Cell Death – 1) and PDL-1 (Programmed Death Ligand -1):** PD-1 is a checkpoint protein on immune cells called T cells (T cells are a type of white
blood cell). It normally acts as a type of “off switch” that helps keep the T cells from attacking other cells in the body. It does this when it attaches to PD-L1, a protein on some normal (and cancer) cells. When PD-1 binds to PD-L1, it basically tells the T cell to leave the other cell alone. Some cancer cells have large amounts of PD-L1, which helps them evade immune attack.

ii. **Monoclonal antibodies**: Monoclonal antibodies are molecules, generated in the lab, that target specific antigens on tumours. Several monoclonal antibodies are currently being tested in clinical trials.

iii. **Therapeutic vaccines**: Cancer vaccines are designed to elicit an immune response against tumour-specific or tumour-associated antigens, encouraging the immune system to attack cancer cells bearing these antigens. Tumour antigens that have been targeted in colorectal cancer include carcinoembryonic antigen (CEA), MUC1, and NY-ESO-1.

iv. **Adoptive cell therapy**: In this approach, immune cells are removed from a patient, genetically modified or treated with chemicals to enhance their activity, and then reintroduced into the patient with the goal of improving the immune system’s anticancer response.

v. **Oncolytic virus therapy**: Oncolytic virus therapy uses a modified virus that can cause tumour cells to self-destruct and generate a greater immune response against the cancer.

vi. **Adjuvant immunotherapies**: Adjuvants are substances that are either used alone or combined with other immunotherapies to boost the immune response. Some adjuvant immunotherapies use ligands—molecules that bind to proteins such as receptors—to help control the immune response. These ligands can be either stimulating (agonists) or blocking (antagonists).

vii. **Cytokines**: Cytokines are messenger molecules that help control the growth and activity of immune system cells.

**PART VI: SOURCES**

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