Gallbladder and Bile Duct Cancers

Hepatobiliary Cancers

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Cholangiocarcinoma Foundation
The Cholangiocarcinoma Foundation is honored to partner with NCCN to provide this vital resource for bile duct (cholangiocarcinoma), liver, and gallbladder cancer patients. Patients First is a core value of our organization. We believe that the most powerful and positive force in medicine is that of a knowledgeable and self-advocating patient. - Stacie Lindsey, Founder and CEO, Cholangiocarcinoma Foundation. cholangiocarcinoma.org

Global Liver Institute
The Global Liver Institute is honored to partner with the NCCN Foundation in our ongoing efforts to empower patients who are at risk for or are facing liver cancer. We hope that liver cancer patients will utilize this resource and that the high-quality information within these guidelines will help you make decisions about your care and ease your journey. globalliver.org

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Gallbladder and bile duct cancers

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The liver, gallbladder, and bile ducts work together to make, store, and secrete bile. Bile is a fluid that helps digest fat in the food you eat. Together, the gallbladder and bile ducts are known as the biliary tract.

The hepatobiliary system

The digestive system takes in food, breaks it down (digestion), absorbs nutrients, and removes waste from the body. The prefix “hepato” means liver, while “biliary” refers to the gallbladder and bile ducts. Together, they form the hepatobiliary system, which makes bile to aid in the digestion of fat.

Bile
Liver cells make bile. Bile is a yellow or green fluid made up of cholesterol, bilirubin, salts such as potassium and sodium, water, and other elements found in the body.

The gallbladder
The gallbladder is a small, pear-shaped organ found under the liver. It is sometimes described as sac-like because it holds bile made by the liver. Bile is saved in the gallbladder, and when you eat, it then passes through the bile ducts into the small intestine to help digest food.
Bile ducts
Liver cells make bile. Bile flows into small channels that drain into thin tubes called ducts. These ducts form larger and larger channels that flow into the left and right hepatic (liver) ducts. The left and right hepatic ducts join to form the common hepatic bile duct. The common hepatic duct joins with the cystic duct to form the common bile duct. The common bile duct carries bile to the first part of the small intestine called the duodenum. In the small intestine, the bile and other fluids break down food to allow your small intestine to absorb nutrients and send waste to your large intestine, also known as the colon.

A more in-depth explanation of how bile travels through the bile ducts is described next.

Bile duct anatomy
The left and right hepatic ducts join to form the common hepatic duct. The common hepatic duct joins with the cystic duct to form the common bile duct. The common bile duct is joined by the pancreatic duct just before it enters the small intestine (duodenum).

Intrahepatic bile ducts of varying sizes are found inside your liver. Hilar bile ducts are the main bile ducts just outside the liver. Intrahepatic and hilar bile ducts carry bile between the liver and gallbladder. Bile leaves the liver through the left and right hepatic ducts. These together join to form the common hepatic duct. Bile then travels up the cystic duct and into the gallbladder for temporary storage between meals.

The cystic and common bile ducts carry bile from the gallbladder to the small intestine. Bile leaves the gallbladder through the cystic duct where it connects to the common bile duct. The common bile duct is joined by the pancreatic duct inside the pancreas just before it enters the small intestine.
Gallbladder cancer

Gallbladder cancer is a rare cancer that can grow and spread quickly. Not all gallbladder cancers are the same. Adenocarcinoma is the most common type of gallbladder cancer. An adenocarcinoma is cancer in the cells that secrete fluids or other substances. Other rare types of cancer can grow in the wall of the gallbladder. Gallbladder adenocarcinoma is the type of cancer described in this book.

How gallbladder cancer is found
Gallbladder cancer is often found by chance. This is called an incidental finding. For example, a tumor in the gallbladder may be found on an ultrasound being done for other reasons. Since gallbladder cancer doesn't always have symptoms and it spreads quickly, it is usually found in an advanced stage.

Gallbladder cancer can be found in 3 ways:

- During surgery
- During pathology review after removal of the gallbladder for what was thought to be gallstone-related conditions
- On imaging tests

During surgery
Some gallbladder cancers are found during abdominal (belly) surgery for something other than gallbladder cancer. This could be for treatment for suspected gallstones (cholelithiasis) or inflammation of the gallbladder (cholecystitis). Gallstones are hardened deposits of bile.

During pathology review
It is common for a pathologist to review all tissue that has been removed during surgery. A pathologist is an expert in examining cells under a microscope to find disease. Often, gallbladder cancers are found during pathology review of a condition that was originally felt to be non-cancerous.

On imaging tests
A mass or tumor might be found on imaging tests done for other reasons. Cancer is confirmed by biopsy or at surgery.
Bile duct cancers

The bile ducts carry bile from the liver to the gallbladder and from the gallbladder to the small intestine. Cholangiocarcinoma, also known as bile duct cancer, is a type of adenocarcinoma. An adenocarcinoma is cancer in the cells that secrete fluids or other substances.

There are 2 types of cholangiocarcinomas:

- Intrahepatic bile duct cancers start in the bile ducts found inside the liver.
- Extrahepatic bile duct cancers grow in the bile ducts outside the liver.

There are 2 subtypes of extrahepatic bile duct cancer:

- Hilar bile duct cancer (Klatskin tumors) is found in the common hepatic duct.
- Distal bile duct cancer is found in the common bile duct.

Cancer that forms in the ampulla of Vater (ducts from the liver and pancreas that enter at the small intestine) is not covered in this book.

Gallbladder and bile ducts

The bile ducts carry bile from the liver to the gallbladder and from the gallbladder to the small intestine.
How cancer spreads

Unlike normal cells, cancer cells can spread and form tumors in other parts of the body. Cancer that has spread is called a metastasis.

- Cancer that has grown into a nearby area or has spread to nearby lymph nodes is called a local metastasis or locally advanced.

- Cancer that has spread to a site far from the primary tumor is called a distant metastasis. A distant metastasis could be in the lung, bone, or abdominal lining. This is metastatic cancer.

Cancer can spread through the blood and lymphatic system. The lymphatic system is made up of a network of vessels that carry a clear fluid called lymph. Lymph gives cells water and food, and has white blood cells that fight germs. Lymph nodes filter lymph and remove the germs.

Gallbladder cancer most commonly spreads into nearby lymph nodes or organs, such as the pancreas, bile ducts, or liver.

Bile duct cancers can grow into nearby blood vessels, organs, and other structures. It might also grow into nearby lymphatic or blood vessels, and from there spread to nearby lymph nodes or to other parts of the body.

Lymph nodes

There are hundreds of small bean-shaped structures throughout the human body called lymph nodes. Lymph nodes catch and filter out foreign particles and harmful cells, including cancer cells.
Key points

- The liver, gallbladder, and bile ducts are part of the hepatobiliary system.
- The biliary tract includes the gallbladder and bile ducts inside and outside the liver.
- Cancers in the bile ducts or gallbladder are known as biliary tract cancers.
- Gallbladder cancer is the most common type of biliary tract cancer worldwide.
- Adenocarcinoma is the most common type of gallbladder cancer. An adenocarcinoma is cancer in the cells that secrete fluids or other substances.
- The bile ducts carry bile from the liver to the gallbladder and from the gallbladder to the small intestine. Cholangiocarcinoma, also known as bile duct cancer, starts in the bile ducts.
- Cancer can spread to distant parts of the body through the blood or lymphatic system.
## Testing for gallbladder and bile duct cancers

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Treatment planning starts with testing. This chapter presents an overview of the tests you might receive and what to expect.

Test results

Results from blood tests, imaging studies, and biopsy will be used to determine your treatment plan. It is important you understand what these tests mean. Ask questions and keep copies of your test results. Online patient portals are a great way to access your test results.

Keep these things in mind:

- Bring someone with you to doctor visits, if possible.
- Write down questions and take notes during appointments. Don’t be afraid to ask your care team questions. Get to know your care team and let them get to know you.
- Get copies of blood tests, imaging results, and reports about the specific type of cancer you have.
- Organize your papers. Create files for insurance forms, medical records, and test results. You can do the same on your computer.
- Keep a list of contact information for everyone on your care team. Add it to your phone. Hang the list on your fridge or keep it in a place where someone can access it in an emergency. Keep your primary care physician informed of changes to this list.

Create a medical binder

A medical binder or notebook is a great way to organize all of your records in one place.

- Make copies of blood tests, imaging results, and reports about your specific type of cancer. It will be helpful when getting a second opinion.
- Choose a binder that meets your needs. Consider a zipper pocket to include a pen, small calendar, and insurance cards.
- Create folders for insurance forms, medical records, and tests results. You can do the same on your computer.
- Use online patient portals to view your test results and other records. Download or print the records to add to your binder.
- Organize your binder in a way that works for you. Add a section for questions and to take notes.
- Bring your medical binder to appointments. You never know when you might need it!
General health tests

**Medical history**
A medical history is a record of all health issues and treatments you have had in your life. Be prepared to list any illness or injury and when it happened. Bring a list of old and new medicines and any over-the-counter medicines, herbals, or supplements you take. Tell your doctor about any symptoms you have. A medical history will help determine which treatment is best for you.

**Liver disease history**
Your doctor will also ask about your history of any previous liver problems, such as cirrhosis; viral hepatitis B or C infection; episodes of jaundice, gallstones, alcohol use, and fatty liver disease; or risk factors (such as obesity and diabetes).

**Family history**
Some cancers and other diseases can run in families. Your doctor will ask about the health history of family members who are blood relatives. This information is called a family history. You can ask family members about their health issues like heart disease, cancer, and diabetes, and at what age they were diagnosed.

**Physical exam**
During a physical exam, your health care provider may:

- Check your temperature, blood pressure, pulse, and breathing rate
- Check your weight
- Listen to your lungs and heart
- Look in your eyes, ears, nose, and throat
- Feel and apply pressure to parts of your body to see if organs are of normal size, are soft or hard, or cause pain when touched. Tell your doctor if you feel pain.
- Feel for enlarged lymph nodes in your neck, underarm, and groin. Tell your doctor if you have felt any lumps or have any pain.

Doctors should perform a thorough physical exam along with a complete health history.
Blood tests

Blood tests check for signs of disease and how well organs are working. They require a sample of your blood, which is removed through a needle placed into your vein.

**Complete blood count**
A complete blood count (CBC) measures the levels of red blood cells, white blood cells, and platelets in your blood. Your doctor will want to know if you have enough red blood cells to carry oxygen throughout your body, white blood cells to fight infection, and platelets to control bleeding.

**Comprehensive metabolic panel**
A comprehensive metabolic panel (CMP) is a test that measures 14 different substances in your blood. A CMP provides important information about how well your kidneys and liver are working, among other things.

**Liver function panel**
Liver function tests (LFTs) look at the health of your liver by measuring chemicals that are made or processed by the liver. Levels that are too high or low signal that the liver is not working well or the bile ducts might be blocked.

One of the LFTs measured is bilirubin, a chemical that gives bile its color. There may be too much bilirubin in the blood if a tumor is blocking a bile duct and preventing the free flow of bile from the liver into the intestines or the liver is not working as well as it should. Too much bilirubin causes a yellowing of the eyes and skin called jaundice. It might cause itchy skin and dark-colored urine.

**Hepatitis panel**
Hepatitis is a type of liver disease. Viruses called hepatitis A, hepatitis B (HBV), and hepatitis C (HCV) are the most common types of hepatitis. A hepatitis panel is a blood test that checks to see if you have a hepatitis infection caused by one of these viruses. Chronic (long-term) hepatitis B and a current or past infection with hepatitis C increase the risk for liver cancer and biliary tract cancers. Hepatitis causes the liver to become inflamed and not work as it should. HCV can cause scarring of the liver, liver failure, and cancer.

A hepatitis panel will tell your treatment team if you had hepatitis in the past or if you have it today. You may be referred to a hepatologist if you test positive. A hepatologist is a doctor who specializes in the care of the liver, biliary tract, gallbladder, and pancreas.

**Tumor markers in the blood**
Your doctor may order additional blood tests to look for alpha-fetoprotein (AFP), cancer antigen 19-9 (CA 19-9), and/or carcinoembryonic antigen (CEA). These are protein or glycoprotein tumor markers found in blood. These tests are only one piece of information your treatment team might consider.
Imaging tests

Imaging tests take pictures of the inside of your body. Images can be made with scanning machines or scoping tools. Imaging tests may show if the tumor involves any veins, arteries, and other organs or if there is a blocked bile duct.

A radiologist, an expert in interpreting imaging tests, will write a report and send this report to your doctor. Your doctor will discuss the results with you.

CT scan
A computed tomography (CT or CAT) scan uses x-rays and computer technology to take pictures of the inside of the body. It takes many x-rays of the same body part from different angles. All the images are combined to make one detailed three-dimensional (3D) picture.

A CT scan of your chest, abdomen, and/ or pelvis may be one of the tests to look for cancer. In most cases, contrast will be used. Contrast material is used to improve the pictures of the inside of the body. Contrast materials are not dyes, but substances that help enhance and improve the images of several organs and structures in the body. It is used to make the pictures clearer. The contrast is not permanent and will leave the body in your urine immediately after the test.

Tell your doctors if you have had allergic reactions to contrast in the past. This is important. You might be given medicines, such as Benadryl® and prednisone, to avoid the effects of those allergies. Contrast might not be used if you have a serious allergy or if your kidneys aren’t working well.

Dynamic CT scan
In a dynamic CT scan, there are two scans: one without contrast and one with contrast. First, a scan is done without contrast. Then, contrast is injected into a vein and another scan is done.

Multiphasic CT scan
A multiphasic CT scan is similar to a dynamic CT scan. It starts without contrast. Then contrast is added and multiple sets of pictures are taken as the contrast moves through the arteries and veins of the liver. This allows doctors to see where the tumor is in the liver and if the tumor involves any arteries, veins, or other organs.

MRI scan
A magnetic resonance imaging (MRI) scan uses radio waves and powerful magnets to take pictures of the inside of the body. It does not use x-rays. Most often, contrast is used. If you are afraid of confined spaces (claustrophobic) or cannot hold your breath, an MRI might not be used.

Dynamic MRI scan
In a dynamic MRI scan, there are two scans. First, a scan is done without contrast. Then, contrast is injected into a vein and another scan is done.

MRCP
A magnetic resonance cholangiopancreatography (MRCP) is a type of MRI scan that makes very clear pictures of the bile ducts (cholangio) and pancreas (pancreatography). No contrast is used because bile and other fluids act as their own contrast. An MRCP is usually done with an MRI scan. Contrast is often used with an MRI.
PET scan
A positron emission tomography (PET) scan uses a radioactive drug called a tracer. A tracer is a substance injected into a vein to see where cancer cells are in the body and if they are using sugar to grow. Cancer cells show up as bright spots on PET scans. However, not all tumors will appear on a PET scan. Also, not all bright spots are cancer. It is normal for the brain, heart, kidneys, and bladder to be bright on PET. When a PET scan is combined with CT, it is called a PET/CT scan. It may be done with one or two machines depending on the cancer center.

Ultrasound
An ultrasound (US) uses high-energy sound waves to form pictures of the inside of the body. A probe will be pressed onto your abdomen. This is similar to the sonogram used for pregnancy. Ultrasound is painless and does not use x-rays, so it can be repeated as needed. It can show small areas of cancer that are near the surface of the body. Sometimes, an ultrasound or CT is used to guide a biopsy.

A contrast-enhanced ultrasound (CEUS) might be used in addition to other tests. Contrast is injected into a vein and another US is performed.

PTC
A percutaneous transhepatic cholangiography (PTC) uses contrast and an x-ray to take pictures of the biliary tract. An x-ray uses small amounts of radiation to make pictures of organs and tissues inside the body. The contrast is injected using a needle or a catheter (thin, flexible tube) passed through the skin (percutaneous) into a bile duct in the liver (transhepatic). For this test, you will be given medicine to make you feel relaxed.

If necessary, a catheter can be inserted during the PTC to drain fluid from the biliary tract. This can drain into a bag outside of the body or the bile bag can be removed and the bile can drain into the small intestine. A metal stent may also be placed for an obstruction or blockage of the bile duct.

Scoping tests
Some imaging tests use a thin, tube-shaped tool called a scope that is inserted into the body to take pictures. One end of the scope has a small light and camera lens to see inside your body. The image is sent to a television monitor. This will help guide your doctor in a biopsy, stent placement, or other tasks.

The scope is guided into the body through a natural opening, such as the mouth, nose, or anus. It may also be inserted through a small surgical cut.

More than one type of scope may be used for imaging tests. The type of scope often used for gallbladder and bile duct cancer is called an endoscope. An endoscope is often guided into the body through the mouth.

Imaging tests with scopes might include:

- Endoscopic ultrasound (EUS)
- Endoscopic retrograde cholangiopancreatography (ERCP)
- Esophagogastroduodenoscopy (EGD)
- Colonoscopy
EUS
An EUS uses an endoscope that has a small ultrasound (US) probe at the end. The endoscope is inserted through your mouth and guided down your throat into your stomach and then the first part of the small intestine (duodenum). The ultrasound probe bounces sound waves off your liver and other organs to make pictures of the inside of your body.

Sometimes, an EUS can detect small lesions in the liver or pancreas that are difficult to see on a CT or MRI scan. It might be used to get a closer look at your bile ducts.

An EUS is done under sedation to keep you comfortable during the procedure. It might be done with an ERCP.

ERCP
An ERCP uses an endoscope and x-rays to take moving pictures of the inside of the body. For this test, the endoscope will be inserted through your mouth and guided down your throat and stomach to the duodenum. Next, a thinner tube called a catheter will be passed through the middle of the endoscope. The catheter will be used to inject a contrast material into the liver and bile ducts. The contrast material allows the ducts to be clearly seen on the x-ray pictures.

An ERCP is used to open a blocked bile duct caused by a tumor in the liver, bile duct, or pancreas. During an ERCP, biopsy samples may be taken from the common bile duct. Samples are removed with a small brush at
Biopsy

A biopsy is a procedure that removes samples of fluid or tissue to be tested for cancer. A biopsy can be negative when cancer is present.

Types of possible biopsies include:

- **Fine-needle aspiration (FNA) or fine-needle biopsy (FNB)** uses a thin needle to remove a sample of tissue or fluid. An ultrasound (US) may guide the FNA biopsy.
- **Brushings** are tumor or cell samples removed with a small brush at the end of the endoscope, usually during an ERCP procedure.
- **Fluid samples from ascites** (fluid in abdominal cavity) can be used to look for cancer cells.
- **Core needle biopsy** removes tissue samples with a hollow needle about the same size as a needle used for an IV (intravenous) line.

The biopsy samples will be sent to a pathologist. A pathologist is an expert in examining cells under a microscope to find disease. A sample from a biopsy of your tumor will be tested to look for biomarkers or proteins. This information is used to choose the best treatment for you. It is sometimes called biomarker or molecular testing.
Biomarker tests

A sample from a biopsy of your tumor may be tested to look for specific DNA (deoxyribonucleic acid) mutations, protein levels, or other molecular features. It is sometimes called molecular testing or tumor profile testing.

CA 19-9, CEA, and AFP
Cancer antigen 19-9 (CA 19-9), carcinoembryonic antigen (CEA), and alpha-fetoprotein (AFP) are examples of tumor markers that are occasionally made by tumors and can be detected in the blood.

Tumor mutation testing
A sample of your tumor or blood may be used to see if the cancer cells have any specific DNA mutations. This is a different type of DNA testing than the genetic testing for mutations you may have inherited from your parents. In tumor mutation testing, only the tumor is tested and not the rest of your body. Some mutations such as NTRK gene fusions, FGFR2 fusions, IDH1, and BRAF V600E can be targeted with specific therapies. When a tumor has a high number of mutations, it is referred to as tumor mutational burden-high (TMB-H).

Genetic tests

Genetic testing is done using blood or saliva (spitting into a cup). The goal is to look for gene mutations inherited from your parents called germline mutations. Some mutations can put you at risk for more than one type of cancer. You can pass these genes on to your children. Also, family members might carry these mutations. Tell your doctor if there is a family history of cancer.

Genetics can increase the risk of different cancers. Depending on your family history or other features of your cancer, your health care provider might refer you for hereditary genetic testing to learn more about your cancer. A genetic counselor will speak to you about the results.

BRCA tests
Everyone has genes called BRCA1 and BRCA2. Normal BRCA genes help to prevent tumor growth. They help fix damaged cells and help cells grow normally. Mutations in BRCA1 or BRCA2 increase the risk of breast, ovarian, prostate, colorectal, or melanoma skin cancer, as well as some biliary tract cancers. These mutations can also affect how well some treatments work.

MSI-H/dMMR
Microsatellites are short, repeated strings of DNA. When errors or defects occur, they are fixed by mismatch repair (MMR) genes. Some cancers prevent these errors from being fixed. This is called microsatellite instability (MSI) or deficient mismatch repair (dMMR). When cancer cells have more than a normal number of microsatellites, it is called MSI-H (microsatellite instability-high). This is often due to deficient MMR genes.
Cancer stages

A cancer stage is a way to describe the extent of the cancer at the time you are first diagnosed. The American Joint Committee on Cancer (AJCC) created a staging system to determine how much cancer is in your body, where it is located, and what subtype you have. AJCC is just one type of staging system.

AJCC staging is used for the following cancers:

- Gallbladder carcinoma
- Intrahepatic bile duct tumors (intrahepatic cholangiocarcinoma)
- Perihilar bile duct tumors (extrahepatic cholangiocarcinoma), also known as Klatskin tumor
- Distal bile duct tumors (extrahepatic cholangiocarcinoma)

Staging is based on a combination of information to reach a final numbered stage. Often, not all the information is available at the initial evaluation. More information can be gathered as treatment begins. Doctors may explain your cancer stage in different ways than described next.

TNM scores

The tumor, node, metastasis (TNM) system is used to stage gallbladder and bile duct cancers. In this system, the letters T, N, and M describe different areas of cancer growth. Based on imaging and pathology results, your doctor will assign a score or number to each letter. The higher the number, the larger the tumor or the more the cancer has spread to lymph nodes or other organs. These scores will be combined to assign the cancer a stage. A TNM example might look like this: T1N0M0 or T1, N0, M0.

The TNM letters represent the following:

- **T (tumor)** - Size of the main (primary) tumor
- **N (node)** - If cancer has spread to nearby (regional) lymph nodes
- **M (metastasis)** - If cancer has spread to distant parts of the body or metastasized

Grade

Grade describes how abnormal the tumor cells look under a microscope (called histology). Higher-grade cancers tend to grow and spread faster than lower-grade cancers. GX means the grade can’t be determined, followed by G1, G2, and G3. Well differentiated (G1) means the cancer cells look similar to normal cells. Poorly differentiated (G3) means the cancer cells look very different compared to normal cells. G3 is the highest grade for gallbladder and bile duct cancers.

- **GX** Grade cannot be determined
- **G1** Well differentiated
- **G2** Moderately differentiated
- **G3** Poorly differentiated

Numbered stages

Numbered stages are based on TNM scores. Stages range from stage 1 to stage 4, with 4 being the most advanced. Doctors write these stages as stage I, stage II, stage III, and stage IV. For example, stage 1 might be T1, N0, M0.
Key points

- Tests are used to find cancer, plan treatment, and check how well treatment is working.
- Your health history and physical exam inform your doctor about your overall health.
- Blood tests check for signs of disease and how well organs are working.
- Imaging tests take pictures of the inside of your body.
- A biopsy removes tissue or fluid from your body to diagnose cancer or perform additional tests.
- In tumor tests, samples of your tumor are tested for specific DNA mutations, protein levels, or other molecular features.
- Some mutations can run in families and increase the risk of cancer. In hereditary genetic tests, your normal cells (such as blood or cells from a saliva sample) are tested for mutations.
- Staging is a rating by your doctors of the extent of the cancer at the time you are first diagnosed.
- Doctors may explain your cancer stage in different ways to make it less confusing.
- Results from blood tests, imaging studies, and biopsy will determine your treatment plan. Often, information is collected over time, even as treatment begins.
- Online portals are a great way to access your test results.

Imaging and other tests are not always accurate. A multidisciplinary team should review the results.
3  Gallbladder and bile duct cancer treatments

25  Surgery
29  Systemic therapy
30  Radiation therapy
31  Arterially directed therapy
32  Clinical trials
34  Supportive care
36  Treatment team
38  Key points
There is more than one treatment for gallbladder and bile duct cancers. This chapter describes treatment options and what to expect. Discuss with your doctor which treatment might be best for you.

Gallbladder and bile duct cancers are treatable. Treatment can be local, systemic, or a combination of both. It is important to have regular talks with your doctor about your goals for treatment and your treatment plan. If possible, seek treatment at a hospital or cancer center that specializes in your type of cancer.

There are 2 types of treatment:

- **Local therapy** focuses treatment on a certain area. It includes surgery, embolization, ablation, and radiation therapy.

- **Systemic therapy** works throughout the body. It includes chemotherapy, targeted therapy, and immunotherapy.

There are many treatment options. However, not everyone responds to treatment in the same way. Some people will do better than expected. Others will do worse than expected. Many factors play in a role in how you respond to treatment.

**Surgery**

Surgery is a primary treatment for gallbladder and bile duct cancers. Primary treatment is the main treatment used to rid the body of cancer. The goal of surgery is to remove all of the cancer, or to remove as much as possible so other treatments may be given. Surgery may also be used to reduce symptoms caused by the cancer or extend life. This is called palliative surgery.

When preparing for surgery, you should seek the opinion of an experienced surgeon. You can ask for a referral to a hospital or cancer center that has experience in treating your type of cancer. Surgery for the gallbladder and bile duct cancers can be complex. The surgeon should be an expert in performing these types of surgery.

The removal of the cancer through surgery can be accomplished in different ways depending on the specific circumstances, such as the size and location of the tumor, and if there is cancer in any surrounding organs and tissues. Surgery is based on the safest and best way to remove the cancer.

**Open surgery**

Open surgery or laparotomy removes tissue through one large surgical cut below your ribs. The large cut lets your doctor directly view and access the tumor to remove it. Open surgery may take several hours or longer. After the surgery, you will need to stay in the hospital to recover.
Minimally invasive surgery
Minimally invasive surgery (or key-hole surgery) uses several small incisions or cuts. Small tools are inserted through each incision to perform the surgery. One of the tools, called a laparoscope, is a long tube with a video camera at the end. The camera lets your doctor see your gallbladder and other tissues inside your abdomen. Other tools are used to remove the tumor. Laparoscopic surgery can also be done using robotic arms to control the surgical tools. This is called robot-assisted laparoscopic surgery.

Cholecystectomy
A cholecystectomy removes the gallbladder and some tissue around it. The goal is to have negative surgical margins, which means there is no cancer in the remaining area.

During a cholecystectomy, some people will also have a hepatic resection (parts of liver removed), lymphadenectomy (nearby lymph nodes removed), and bile duct removal. The tumor size and location will help your surgeon decide on the extent of surgery. Ask what might be removed during surgery, how this might affect recovery, and what further treatment might be needed.

**Cholecystectomy**
In a cholecystectomy, the gallbladder and part of the cystic duct are removed.
Tumor resection
Imaging tests will be used to see if your cancer is resectable (can be removed completely with surgery) or unresectable (cannot be removed with surgery). The goal of surgery or tumor resection is to remove all of the cancer. To do so, the tumor is removed along with some normal tissue around its edge called the surgical margin. The surgical margin may look normal, but cancerous cells may be found when viewed under a microscope.

Surgical margin
The goal of surgery is a cancer-free surgical margin. After surgery, you may receive treatment such as radiation or systemic therapy to kill any remaining cancer cells.

- In a clear or negative margin (R0), no cancerous cells are found in the tissue around the edge of the tumor.
- In an R1 positive margin, the surgeon removes all of the visible tumor, but the microscopic margins are still positive for tumor cells. Despite best efforts this can happen.
- In an R2 positive margin, the surgeon is unable to remove all of the visible tumor. Therefore, the tumor is left at the time of surgery.

A negative margin (R0) is the best result. Your surgeon will look carefully for cancer not only along the surgical margin, but also in nearby areas. Despite best efforts, it is not always possible to find all of the cancer. Sometimes, surgeons can’t safely remove the tumor with a cancer-free margin.

You might have more than one surgery. You might also have a wound drain to prevent fluid from collecting in the body after surgery. These drains are usually removed a few days after surgery.

Liver resection
Surgery to remove part of the liver is called a partial hepatectomy or hepatic resection. Surgery depends on the size and location of the tumor and how healthy your liver is. You might have surgery to remove a small piece or an entire liver lobe. The part of the liver that remains will keep working, and if the liver is healthy enough, the missing section will regrow. A partial hepatectomy is different than a liver transplant.

Liver transplant
A liver transplant is rarely an option, but might be considered for certain types of bile duct cancer. In a liver transplant, the entire liver is removed and replaced with a healthy, donor liver. The new liver may be donated from a person who recently died, or a section of liver may be donated from a living person. A liver transplant should be performed by an experienced surgeon who is prepared to completely remove the tumor.
Surgery

Liver transplant

The liver is divided into 8 sections or segments based on the location of the portal vein, hepatic vein, and bile ducts.

transplant is based on certain size limits and tumor locations.

The liver is divided into 8 sections or segments based on hepatic artery, portal vein, and bile duct locations. Structures such as the inferior vena cava, portal vein, hepatic artery, and bile ducts are reconnected to the new liver.

There can be long wait times to receive a liver transplant. Treatments may be given while you wait for a transplant. These treatments are called bridge or bridging therapy and include embolization or radiation therapy.

There is still a chance that cancer will return after a liver transplant. It is also possible your body will reject the donor liver. You will be given medicine to prevent rejection.

Lymphadenectomy

During a lymphadenectomy, the lymph nodes are removed and a sample of tissue is checked under a microscope for signs of cancer. For a regional lymphadenectomy, some of the lymph nodes in the tumor area are removed. For a radical lymphadenectomy, most or all of the lymph nodes in the tumor area are removed. A lymphadenectomy is sometimes called lymph node dissection.
Systemic therapy

Systemic therapy works throughout the body. Types include chemotherapy, targeted therapy, and immunotherapy. Systemic therapy might be used alone or with other therapies. Goals of systemic therapy should be discussed before starting treatment. Your wishes about treatment are important.

- When systemic therapy is given before surgery, it is called neoadjuvant therapy.
- When systemic therapy is given after surgery, it is called adjuvant therapy.
- When systemic therapy is given for advanced disease, it may be called palliative therapy.

Chemotherapy

Chemotherapy is the main type of systemic therapy for bile duct cancers. It kills fast-growing cells throughout the body, including cancer cells and some normal cells. All chemotherapies affect the instructions (genes) that tell cancer cells how and when to grow and divide. Often, chemotherapies are combined. This is called multiagent chemotherapy. One example is FOLFOX (fluorouracil, leucovorin, and oxaliplatin).

Some examples of chemotherapies include:

- 5-fluorouracil
- Albumin-bound paclitaxel (Abraxane®)
- Capecitabine (Xeloda®)
- Cisplatin
- Gemcitabine (Gemzar®, Infugem™)
- Oxaliplatin (Eloxatin®)

Chemoradiation

Treatment that combines chemotherapy with radiation therapy is called chemoradiation. Chemotherapy may improve how well radiation works, and that is why they are sometimes used together. Chemotherapies used with radiation to treat gallbladder and bile duct cancers include 5-fluorouracil or capecitabine (Xeloda®). Chemoradiation may be used to control symptoms caused by a tumor.

Targeted therapy

Targeted therapy focuses on specific or unique features of cancer cells. Targeted therapies seek out how cancer cells grow, divide, and move in the body. These drugs stop the action of molecules that help cancer cells grow and/or survive. A tyrosine kinase inhibitor (TKI) is a type of targeted therapy that blocks the signals that cause some cancers to grow and spread. Regorafenib (Stivarga®) and lenvatinib (Lenvima®) are examples of targeted therapies.

Targeted therapies may be used to treat tumors that have certain gene mutations, which may include:

- Entrectinib (Rozlytrek®) or larotrectinib (Vitrakvi®) for NTRK gene fusion
- Pemigatinib (Pemazyre™) or infgratinib (Truseltiq™) for FGFR2 fusions or rearrangements
- Dabrafenib (Tafinlar®) with trametinib (Mekinist®) for BRAF-V600E mutated tumors
- Ivosidenib (Tibsovo®) for IDH1 mutations
**Immunotherapy**
Immunotherapy is a targeted therapy that increases the activity of your immune system. By doing so, it improves your body’s ability to find and destroy cancer cells. Immunotherapy can be given alone or with other types of treatment. Pembrolizumab (Keytruda®) and nivolumab (Opdivo®) are types of targeted immunotherapies.

**Radiation therapy**
Radiation therapy (RT) uses high-energy radiation from x-rays, gamma rays, protons, and other sources to kill cancer cells and shrink tumors. It is given over a certain period of time. Radiation therapy can be given alone or before or after surgery to treat or slow the growth of cancer. Sometimes, radiation is given with certain supportive systemic therapies. It may be used as supportive care to help ease pain or discomfort caused by cancer.

Radiation may be given:

- As the primary (first) treatment
- Before surgery, called neoadjuvant radiation therapy, to shrink the tumor before surgery
- During surgery, called intraoperative radiation therapy (IORT)
- After surgery, called adjuvant radiation treatment, to kill any cancerous cells that remain
- As palliative treatment to reduce pain caused by cancer

**External beam radiation therapy**
External beam radiation therapy (EBRT) uses a machine outside of the body to aim radiation at the tumor(s). There is more than one type of EBRT used in the treatment of gallbladder and bile duct cancers. These allow for safer, higher doses of radiation.

Types of EBRT that may be used to treat your cancer include:

- **Stereotactic body radiation therapy (SBRT)** uses high-energy radiation beams to treat cancers.
- **Proton beam radiation therapy** uses streams of particles called protons to kill tumor cells.
- **Three-dimensional conformal radiation therapy (3D-CRT)** uses computer software and CT images to aim beams that match the shape of the tumor.
- **Intensity-modulated radiation therapy (IMRT)** uses small beams of different strengths to match the shape of the tumor. This limits the amount of radiation to normal tissues.
- **Image-guided radiation therapy (IGRT)** uses a computer to create a picture of the tumor. This helps guide the radiation beam during treatment. It is used with IMRT and 3D-CRT. Tumors can shift slightly within the body and can change shape and size between and during treatment visits. Because of this, IGRT can improve how well 3D-CRT and IMRT target the tumor.
- **Intraoperative radiation therapy (IORT)** uses radiation treatment aimed directly at the tumor during surgery.
- **Palliative EBRT** is used to treat pain caused by cancer.
Arterially directed therapy

Arterially directed therapies include embolization, chemoembolization, drug-eluting bead embolization, and radioembolization. They treat tumors by injecting particles, chemotherapy, or radioactive beads directly into the blood vessels that supply the tumor(s). For the procedure, you will be injected at the groin with a needle. A small catheter will be inserted into an artery and be guided to the area of the tumor in the liver. Once in place, the particles, chemotherapy, or beads will be injected.

There are risks with any treatment. Arterially directed therapy might not be used if your bilirubin level is above 3 mg/mL.

Types of arterially directed therapy include:

- **Transarterial embolization (TAE)** blocks the blood supply to the tumor by injecting tiny particles into the blood vessels feeding the tumor(s). Stopping the blood flow cuts off the oxygen supply to the tumor and causes cancer cells to die.

- **Chemoembolization (also known as TACE or transarterial chemoembolization)** blocks the blood supply to the tumor(s) plus injects a chemotherapy mixture into the tumor.

- **DEB-TACE (drug-eluting bead transarterial chemoembolization)** uses tiny particles loaded with chemotherapy that are injected into the blood vessels feeding the tumor(s). The particles give off small amounts of chemotherapy to the tumor over several days.

- **Transarterial radioembolization (TARE)** uses tiny glass or resin beads filled with the radioactive isotope yttrium-90 (Y-90) that are injected directly into the tumor(s).

- **Hepatic artery infusion (HAI)** is a medical procedure that delivers chemotherapy directly to the liver.

Depending on the circumstances, arterially directed therapy may be used as definitive treatment or for palliation. Definitive treatment is defined as the best treatment after all choices have been considered. The type of arterially directed therapy recommended will depend on the size, number, and location of tumors as well as your previous medical history and the expertise of your treating physicians.
Clinical trials

A clinical trial is a type of medical research study. After being developed and tested in a laboratory, potential new ways of fighting cancer need to be studied in people. If found to be safe and effective in a clinical trial, a drug, device, or treatment approach may be approved by the U.S. Food and Drug Administration (FDA).

Everyone with cancer should carefully consider all of the treatment options available for their cancer type, including standard treatments and clinical trials. Talk to your doctor about whether a clinical trial may make sense for you.

Phases
Most cancer clinical trials focus on treatment. Treatment trials are done in phases.

> **Phase I trials** study the dose, safety, and side effects of an investigational drug or treatment approach.

> **Phase II trials** study how well the drug or approach works against a specific type of cancer.

> **Phase III trials** test the drug or approach against a standard treatment. If the results are good, it may be approved by the FDA.

> **Phase IV trials** study the long-term safety and benefit of an FDA-approved treatment.

Finding a clinical trial

**In the United States**

NCCN Cancer Centers
NCCN.org/cancercenters

The National Cancer Institute (NCI)
cancer.gov/about-cancer/treatment/clinical-trials/search

**Worldwide**

The U.S. National Library of Medicine (NLM)
clinicaltrials.gov/

Need help finding a clinical trial?
NCI’s Cancer Information Service (CIS) 1.800.4.CANCER (1.800.422.6237) cancer.gov/contact
Who can enroll?
Every clinical trial has rules for joining, called eligibility criteria. The rules may be about age, cancer type and stage, treatment history, or general health. These requirements ensure that participants are alike in specific ways and that the trial is as safe as possible for the participants.

Informed consent
Clinical trials are managed by a group of experts called a research team. The research team will review the study with you in detail, including its purpose and the risks and benefits of joining. All of this information is also provided in an informed consent form. Read the form carefully and ask questions before signing it. Take time to discuss with family, friends, or others you trust. Keep in mind that you can leave and seek treatment outside of the clinical trial at any time.

Start the conversation
Don’t wait for your doctor to bring up clinical trials. Start the conversation and learn about all of your treatment options. If you find a study that you may be eligible for, ask your treatment team if you meet the requirements. If you have already started standard treatment you may not be eligible for certain clinical trials. Try not to be discouraged if you cannot join. New clinical trials are always becoming available.

Frequently asked questions
There are many myths and misconceptions surrounding clinical trials. The possible benefits and risks are not well understood by many with cancer.

What if I get the placebo?
A placebo is an inactive version of a real medicine. Placebos are almost never used alone in cancer clinical trials. All participants receive cancer treatment. You may receive a commonly used treatment, the investigational drug(s), or both.

Do I have to pay to be in a clinical trial?
Rarely. It depends on the study, your health insurance, and the state in which you live. Your treatment team and the research team can help determine if you are responsible for any costs.
Supportive care

Supportive care is health care that relieves symptoms caused by cancer or its treatment and improves quality of life. It might include pain relief (palliative care), emotional or spiritual support, financial aid, or family counseling. Supportive care is given during all cancer stages. Tell your care team how you are feeling and about any side effects. Best supportive care is used with other treatments to improve quality of life. Best supportive care, supportive care, and palliative care are often used interchangeably.

Distress
Distress is an unpleasant experience of a mental, physical, social, or spiritual nature. It can affect how you feel, think, and act. Distress might include feelings of sadness, fear, helplessness, worry, anger, and guilt.

Depression, anxiety, and sleeping problems are common in those with cancer. Talk to your doctor and with those whom you feel most comfortable about how you are feeling. There are services and people who can help you. Support and counseling are available. It is recommended that all patients be screened for depression.

For more information, read NCCN Guidelines for Patients: Distress During Cancer Care, available at NCCN.org/patientguidelines.

Blocked bile duct
A tumor may grow large enough to block your bile duct. A bile duct is a small tube that drains digestive fluid (bile) from the liver. The common bile duct carries bile from the liver through the pancreas and into the first part of the small intestine (duodenum). A blocked duct causes bile to build up in the liver. As a result, you may have pain, itching, discomfort, and/or yellowing of the skin and eyes. This is called jaundice. This blockage can cause an infection of the bile duct called cholangitis.

A blocked bile duct may be treated by placing a biliary stent or doing a biliary bypass. A biliary stent is a tiny plastic or metal tube that is placed in the bile duct to unblock it or keep it open. You may need a new or second stent during or after cancer treatment if the tumor grows. A biliary bypass is a surgery to re-route the flow of bile from the common bile duct into the small intestine. The result is that the bile flow avoids (bypasses) the blocked part of the duct.
When biliary drainage is an option
Biliary drainage before surgery may help improve your health and recovery after surgery. Biliary drainage may be an option even if you cannot have surgery. It may also be recommended if you have metastatic disease, in order to improve your liver function and nutrition, and to reduce the risk of infection.

Biliary drainage requires careful planning. Your treatment team should discuss and decide if this is a safe procedure for you.

If it is an option, you may have biliary drainage using one of the following methods.

- **Surgical bypass** involves attaching the gallbladder or bile duct directly to the small intestine to drain the fluid. However, this way of draining fluid is rarely used. It carries the same risks as major surgery.

- **Endoscopic retrograde cholangiopancreatography (ERCP)** uses an endoscope to reach the bile ducts and drain the fluid. Your doctor may insert a stent so the fluid drains directly into the small intestine. This is usually an outpatient procedure performed by a gastroenterologist that does not require you to stay in the hospital.

- **Percutaneous transhepatic cholangiography (PTC)** places a stent through the skin to drain the fluid. This approach may be used when the endoscope cannot reach the blocked bile duct. This is usually an outpatient procedure performed by an interventional radiologist that does not require you to stay in the hospital.

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**Keep a pain diary**

A pain diary is a written record that helps you keep track of when you have pain, how bad it is, what causes it, and what makes it better or worse. Use a pain diary to discuss your pain with your care team. You might be referred to a specialist for pain management.

Include in your pain diary:

- The time and dose of all medicines
- When pain starts and ends or lessens
- Where you feel pain
- Describe your pain. Is it throbbing, sharp, tingling, shooting, or burning? Is it constant, or does it come and go?
- Does the pain change at different times of day? When?
- Does the pain get worse before or after meals? Does certain food or drink make it better?
- Does the pain get better or worse with activity? What kind of activity?
- Does the pain keep you from falling asleep at night? Does pain wake you up in the night?
- Rate your pain from 0 (no pain) to 10 (worst pain you have ever felt)
- Does pain get in the way of doing the things you enjoy?
Treatment side effects
All cancer treatments can cause unwanted health issues. Such health issues are called side effects. Side effects depend on many factors. These factors include the drug type and dose, length of treatment, and the person. Some side effects may be harmful to your health. Others may just be unpleasant.

Ask for a complete list of side effects of your treatments. Also, tell your treatment team about any new or worsening symptoms. There may be ways to help you feel better. There are also ways to prevent some side effects.

Trouble eating
Sometimes side effects from surgery, cancer, or other treatments might cause you to feel not hungry or sick to your stomach (nauseated). You might have a sore mouth. Healthy eating is important during treatment. It includes eating a balanced diet, eating the right amount of food, and drinking enough fluids. A registered dietitian who is an expert in nutrition and food can help. Speak to your care team if you have trouble eating or maintaining your weight.

For more information, read the NCCN Guidelines for Patients: Nausea and Vomiting, available at NCCN.org/patientguidelines.

Treatment team
Treating cancer takes a team approach. Treatment decisions should involve a multidisciplinary team (MDT). An MDT is a team of doctors, health care workers, and social care professionals from different professional backgrounds who have knowledge (expertise) and experience with your type of cancer. This team is united in the planning and implementing of your treatment. Ask who will coordinate your care.

Some members of your care team will be with you throughout cancer treatment, while others will only be there for parts of it. Get to know your care team and let them get to know you.

Depending on your diagnosis, your team might include the following specialists:

- A hepatologist is an expert in diseases of the liver, gallbladder, bile ducts, and pancreas.
- A pathologist interprets tests the cells, tissues, and organs removed during a biopsy or surgery.
- A diagnostic radiologist reads the results of x-rays and other imaging tests.
- A hepatobiliary gastroenterologist performs ERCP procedures to place and exchange stents within the biliary tract if the cancer is causing blockage. This specialist may also perform an EUS, ERCP biopsy, or brushing procedure.
- An interventional radiologist performs needle biopsies, ablations, and arterially directed therapies, and places ports for treatment. This person may also place percutaneous biliary drains if the bile ducts are blocked.
A surgical oncologist performs operations to remove cancer.

A medical oncologist treats cancer in adults using systemic therapy.

A radiation oncologist prescribes and plans radiation therapy to treat cancer.

An anesthesiologist gives anesthesia, a medicine so you do not feel pain during surgery or procedures.

A gastroenterologist is an expert in digestive diseases. A specific type of gastroenterologist that focuses on liver disease is called a hepatologist.

Palliative care nurses and advanced practice providers help provide an extra layer of support with your cancer-related symptoms.

Residents and fellows are doctors who are continuing their training, some to become specialists in a certain field of medicine.

Oncology nurses provide your hands-on care, like giving systemic therapy, managing your care, answering questions, and helping you cope with side effects. Sometimes, these experts are called nurse navigators.

Nutritionists and dietitians can provide guidance on what foods are most suitable for your condition.

Psychologists and psychiatrists are mental health experts who can help manage issues such as depression, anxiety, or other mental health conditions that can affect how you feel.

Social workers help people solve and cope with problems in their everyday lives.

You know your body better than anyone. Help other team members understand:

> How you feel
> What you need
> What is working and what is not

Keep a list of names and contact information for each member of your team. This will make it easier for you and anyone involved in your care to know whom to contact with questions or concerns.
Key points

- Local therapy focuses treatment on a certain area. It includes surgery, radiation therapy, and arterially directed therapy.

- Surgery is a main treatment option for gallbladder and bile duct cancers.

- Systemic therapy works throughout the body. It includes chemotherapy, targeted therapy, and immunotherapy.

- Targeted therapies can block the ways cancer cells grow, divide, and move in the body.

- Immunotherapy uses your body’s natural defenses to find and destroy cancer cells.

- Radiation therapy (RT) uses high-energy radiation from x-rays, gamma rays, protons, and other sources to kill cancer cells and shrink tumors.

- Arterially directed therapy treats tumors by injecting particles, chemotherapy, or radioactive beads directly into the blood vessels that supply the tumor(s).

- A clinical trial is a type of research that studies a treatment to see how safe it is and how well it works. It is often one of the preferred treatments for gallbladder cancer.

- Supportive care is health care that relieves symptoms caused by cancer or cancer treatment and improves quality of life.

Did you know?

The terms “chemotherapy” and “systemic therapy” are often used interchangeably, but they are not the same. Chemotherapy, targeted therapy, and immunotherapy are all types of systemic therapy.
# 4

Gallbladder cancer

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Gallbladder cancer starts in the innermost layer and grows outward through the layers of the gallbladder wall. Cancer can spread to nearby veins, arteries, bile ducts, and organs such as the liver. Together, you and your doctor will choose the treatment plan that is best for you.

Overview

The gallbladder is a pear-shaped organ found under the liver. It is made up of several layers of tissue. The inner and outer layers are membranes. A membrane is a very thin layer that covers a surface. In between these membranes are layers of muscle and connective tissue.

Gallbladder cancer starts in the innermost layer and grows outward through the layers of the gallbladder wall. Cancer can spread to nearby veins, arteries, bile ducts, and organs such as the liver.

The layers of the gallbladder wall include:

- Epithelium – A thin, moist (mucous) layer of tissue that covers the inside of the gallbladder.
- Lamina propria – A type of connective tissue found under the epithelium membrane
- Muscle – A type of soft tissue
- Perimuscular fibrous tissue – A type of connective tissue that surrounds muscle
- Serosa – An outer membrane that covers the gallbladder

Gallbladder cancer stages

Gallbladder cancer is staged by how much the tumor has grown into the layers of the gallbladder wall and if the tumor is on the side nearest to the liver (hepatic) or the small intestine (peritoneal). It can be difficult to determine the exact location of the tumor. Cancer can spread beyond the visible tumor making it difficult to find. Staging for cancer in lymph nodes is based on the number of lymph nodes rather than their location.

For gallbladder cancer stages, see Guide 1.

Guide 1

Gallbladder cancer stages

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<td>Stage 1</td>
<td>T1, N0, M0</td>
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<td>T2b, N0, M0</td>
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<td>Any T, Any N, M1</td>
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</table>
**4 Gallbladder cancer**

Gallbladder cancer stages

**T = Tumor**

Carcinoma *in situ* (Tis) is the earliest stage of gallbladder cancer. Cancer cells are found inside the lining of the gallbladder wall (epithelium). Cancer has not grown into any other layers of the gallbladder. Gallbladder cancers are rarely found this early.

- **Tis** Carcinoma *in situ* (cancer has not grown beyond the innermost epithelial layer)
- **T1a** Tumor invades lamina propria
- **T1b** Tumor invades muscle layer
- **T2a** Tumor invades the perimuscular connective tissue on the peritoneal side, but has not grown into the serosa (visceral peritoneum)
- **T2b** Tumor invades the perimuscular connective tissue on the hepatic side, but has not grown into the liver
- **T3** Tumor perforates the serosa and/or invades the liver and/or nearby organs or structures such as the stomach, duodenum, colon, pancreas, and bile ducts outside the liver (extrahepatic)
- **T4** Tumor invades main portal vein or hepatic artery or invades 2 or more organs or structures outside the liver (extrahepatic)

---

Layers of the gallbladder wall

- **Epithelium**
- **Lamina propria**
- **Muscularis**
- **Perimuscular fibrous tissue**
- **Serosa**

---

Gallbladder
N = Node
There are hundreds of lymph nodes throughout your body. They work as filters to help fight infection and remove harmful things from your body. Regional lymph nodes are those located near the tumor. The cystic duct lymph node is one example of a regional lymph node.

- **N0** No cancer in regional lymph node
- **N1** Cancer is found in 1 to 3 regional lymph nodes
- **N2** Cancer is found in 4 or more regional lymph nodes

M = Metastatic
Cancer that has spread to distant parts of the body is shown as M1. The most common site for metastasis is the lining that surrounds the abdominal organs (visceral peritoneum) and the liver.

### Treatment options

Gallbladder cancer is often found by chance. This is called an incidental finding.

Gallbladder cancer can be found in 3 ways:

- During surgery
- During pathology review
- On imaging tests

Treatment is based on how the cancer was found, if the cancer has spread, and if there is cancer in any nearby organs and blood vessels. Tests will determine if the tumor can be removed with surgery.

### Found during surgery

Gallbladder cancer might be found by chance during surgery for something other than gallbladder cancer. This could be for treatment for suspected gallstones or inflammation of the gallbladder known as cholecystitis. A sample of the tumor might be taken and tested for cancer. Also, if any lymph nodes look like they might have cancer, they will be biopsied and tested.

### Tests

Imaging tests will determine if your tumor can be removed with surgery (resectable) or cannot be removed with surgery (unresectable).

You will have the following imaging tests:

- Multiphasic CT and MRI of the abdomen and pelvis with contrast
- Chest CT with or without contrast
A CT and MRI are used to learn more about the cancer and if it involves any nearby veins, arteries, or ducts. A chest CT is used to see if the cancer has spread (metastasized) to the lungs.

**Treatment**

Treatment will be based on if the cancer is resectable or unresectable. You might have treatment before surgery called neoadjuvant therapy. This is to reduce the amount of cancer. Sometimes, neoadjuvant therapy can shrink a tumor enough that it can be removed with surgery. This means that a previously unresectable tumor might become resectable.

Treatment after surgery is called adjuvant therapy. It is given to kill any cancer cells that might have been left behind from surgery. It is not always possible to remove all of the cancer during surgery. Adjuvant therapy also helps prevent the return of cancer called recurrence.

It is important to know that not everyone responds the same way to treatment. Some people respond better than expected. Others do worse. Talk with your doctor about your goals for treatment. Your wishes are important.

**Order of treatments**

Most people with gallbladder cancer will receive more than one type of treatment. Next is an overview of the order of treatments and what they do.

- **Neoadjuvant (before) treatment** is given to shrink the tumor before primary treatment (surgery). This might change an unresectable tumor into a resectable tumor.
- **Primary treatment** is the main treatment given to rid the body of cancer. Surgery is usually the main treatment for resectable gallbladder cancer.
- **Adjuvant (after) treatment** is given after primary treatment to rid the body of any cancer cells left behind from surgery. It is also used when the risk of cancer returning (recurrence) is felt to be high.
- **First-line treatment** is the first set of systemic (drug) treatment given.
- **Second-line treatment** is the next set of treatment given if cancer progresses during or after systemic therapy.

Talk to your doctor about your treatment plan and what it means for your stage of gallbladder cancer.
Found at pathology

Gallbladder cancer can be found during pathology review following a cholecystectomy for cholelithiasis (gallstones) or of a condition that was originally felt to be non-cancerous. An expert hepatobiliary pathologist should review your pathology results. Your doctor will check the pathology report for details on the tumor size and location, and if there were signs of disease in the cystic duct, other ducts, or nearby areas.

Treatment is based on test results and staging. For treatment options, see Guide 2.

Guide 2
Treatment options: Cancer found by chance at pathology

<table>
<thead>
<tr>
<th>T1a (with negative margins)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Observation</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cystic duct lymph node is positive for cancer</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Possible neoadjuvant chemotherapy</td>
<td></td>
<td>• Liver surgery with lymphadenectomy and possible bile duct removal</td>
</tr>
<tr>
<td>• Clinical trial</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>T1b or greater</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Resectable</td>
<td></td>
<td>• Liver surgery with lymphadenectomy and possible bile duct removal</td>
</tr>
<tr>
<td>• Unresectable</td>
<td></td>
<td>• Systemic therapy (preferred)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Clinical trial (preferred)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Palliative radiation therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Best supportive care</td>
</tr>
</tbody>
</table>
**T1a tumor**
A T1a tumor has grown through the innermost layer (epithelium) into the lamina propria. If the tumor is small with negative margins, then observation will be considered. You might hear this called watch-and-wait. During observation, you might have imaging and blood tests to monitor tumor growth.

**Cystic duct node-positive**
The cystic duct lymph node is found near the cystic duct. Cancer found outside the gallbladder and in the nearby cystic duct lymph node is called cystic duct node-positive.

Before starting treatment, you might have the following:

- Multiphasic CT and MRI of the abdomen and pelvis with contrast
- Chest CT with or without contrast
- Staging laparoscopy
- MSI/MMR testing

Treatment is often surgery. This would remove part of the liver (hepatic resection), nearby lymph nodes (lymphadenectomy), and possibly the bile duct. If there is cancer in the cystic duct lymph node, then you might have treatment before surgery called neoadjuvant therapy. Neoadjuvant therapy aims to reduce the amount of cancer or to shrink the tumor in order to make surgery easier. However, if there is a large tumor invading the liver and/or cancer is near the lymph nodes, then neoadjuvant chemotherapy might be given to see if your cancer is fast-growing. If this is the case, then surgery would not be used.

A clinical trial is also an option for cancer found in the cystic duct lymph node.

**T1b or larger**
A T1b tumor has invaded the muscle layer of the gallbladder wall.

Before starting treatment, you might have the following:

- Multiphasic abdominal and pelvic CT and MRI with contrast
- Chest CT with or without contrast
- Staging laparoscopy
- MSI/MMR and other biomarker testing

For a tumor that is T1b or greater, surgery might be possible. This would remove part of the liver (hepatic resection), nearby lymph nodes (lymphadenectomy), and possibly the bile duct.

Unresectable treatment options include:

- Systemic therapy (preferred)
- Clinical trial (preferred)
- Palliative radiation therapy
- Best supportive care
Found on imaging

Sometimes, a tumor or mass may be found on an imaging test being done for other medical reasons. If there is concern for gallbladder cancer, more tests will be ordered. Treatment will be based on if the tumor is resectable or unresectable.

Tests

Before starting treatment, you might have imaging and blood tests. Tumor markers known as CA 19-9 and CEA might be measured as a baseline before treatment to see if there are any changes after treatment.

It can be difficult to see exactly how much cancer there is and where it might have spread using imaging tests alone. As a result, a laparoscopy can be helpful to stage your cancer. If you have jaundice, biliary drainage might be done to see if it can relieve any bile duct blockage.

Ask questions about the tests and procedures you might have. You will meet with a surgeon during this time.

For possible tests and procedures you might have, see Guide 3.

Treatment

Treatment will be based on if the cancer is resectable or unresectable.

Guide 3
Possible tests: Tumor found on imaging

<table>
<thead>
<tr>
<th>Medical history and physical exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiphasic CT and MRI with contrast of the abdomen and pelvis</td>
</tr>
<tr>
<td>Chest CT with or without contrast</td>
</tr>
<tr>
<td>Liver function tests (LFTs)</td>
</tr>
<tr>
<td>Assess liver function and health (liver reserve)</td>
</tr>
<tr>
<td>CEA and CA 19-9</td>
</tr>
<tr>
<td>Staging laparoscopy</td>
</tr>
<tr>
<td>Biliary drainage</td>
</tr>
</tbody>
</table>
Jaundice with cancer

Bile is made by the liver. It contains bilirubin, the yellow-brown substance that gives bile its color. Jaundice is a yellowing of the skin and whites of the eyes due to a buildup of bilirubin in the body. Sometimes, a tumor can block the flow of bile, leading to increased bilirubin levels in the blood, as well as jaundice. You may have itching and dark-colored urine. If the common bile duct or the common hepatic duct is blocked, your stool may turn white.

Testing
If you have jaundice with gallbladder cancer, you will have tests found in Guide 4.

Tests include an x-ray of the bile ducts called a cholangiography. Magnetic resonance cholangiopancreatography (MRCP) is the preferred type of cholangiography.

Guide 4
Possible tests: Jaundice with gallbladder cancer

- Medical history and physical exam
- Liver function tests (LFTs)
- Chest CT with or without contrast
- Multiphasic CT and MRI with contrast of the abdomen and pelvis
- Cholangiography (magnetic resonance cholangiopancreatography [MRCP] is preferred)
- CEA and CA 19-9
- Staging laparoscopy
- Biliary drainage

Treatment
You might meet with a surgeon to learn about treating your jaundice and cancer. You might have a staging laparoscopy to find out the extent of disease and why there is a blockage causing the jaundice.

If you have a blocked bile duct or jaundice, then biliary drainage will be done before surgery or treatment with systemic therapy. Endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) are used to treat jaundice.
Resectable

A resectable tumor can be removed with surgery. You will have surgery to remove the gallbladder (cholecystectomy), part of the liver (en bloc hepatic resection), some lymph nodes (lymphadenectomy), and possibly the bile duct.

A gallbladder cancer operation requires a skilled surgeon. Sometimes, a resectable tumor cannot be removed during surgery. This might be due to the tumor being wrapped around major veins or arteries. If cancer has spread to lymph nodes, bile ducts, or organs, it may not be possible to remove all of the cancer.

Treatment before surgery
You might have systemic therapy before surgery called neoadjuvant therapy.

Neoadjuvant therapy is used to reduce the size of the tumor or amount of cancer. This might make it easier to remove the tumor.

Neoadjuvant systemic therapy options include:
- 5-fluorouracil with oxaliplatin
- Capecitabine with oxaliplatin
- Gemcitabine with capecitabine
- Gemcitabine with cisplatin
- Gemcitabine with cisplatin and albumin-bound paclitaxel
- Gemcitabine with oxaliplatin
- 5-fluorouracil or capecitabine or gemcitabine

Cholecystectomy

A cholecystectomy is the removal of the gallbladder. Surgery can be open or minimally invasive (laparoscopic).
Treatment after surgery
Treatment after surgery is called adjuvant therapy. It is determined by the risk of the tumor coming back and/or if not all tumor could be resected. See Guide 5.

- In a clear or negative margin (R0), no cancerous cells are found.
- In an R1 positive margin, there is a higher risk that very small (microscopic) cancer cells remain.
- In an R2 positive margin, cancer that can be seen without a microscope remains.

Those with R1 or R2 resections should be evaluated by a multidisciplinary team.

For R0 and R1 surgical margins, systemic therapy or a clinical trial are the preferred adjuvant treatment options. A preferred treatment is one proven to have a better result. Other options include fluoropyrimidine-based chemoradiation used alone or with chemotherapy. Adjuvant chemotherapy or chemoradiation has been associated with survival benefit, especially in those with lymph node-positive disease. Observation might also be an option in those with an R0 result.

Guide 5
Adjuvant treatment based on surgery results: Gallbladder cancer

<table>
<thead>
<tr>
<th>Is there cancer after surgery?</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No cancer remains (R0) and no cancer found in regional nodes or Carcinoma in situ at surgical margin</strong></td>
<td>• Observation&lt;br&gt;• Systemic therapy (preferred)&lt;br&gt;• Clinical trial (preferred)&lt;br&gt;• Fluoropyrimidine-based chemoradiation</td>
</tr>
<tr>
<td><strong>Risk that microscopic cancer cells remain (R1) or Cancer found in regional nodes</strong></td>
<td>• Systemic therapy (preferred)&lt;br&gt;• Clinical trial (preferred)&lt;br&gt;• Fluoropyrimidine-based chemoradiation&lt;br&gt;• Fluoropyrimidine-based or gemcitabine-based chemotherapy followed by fluoropyrimidine-based chemoradiation&lt;br&gt;• Fluoropyrimidine-based chemoradiation followed by fluoropyrimidine-based or gemcitabine-based chemotherapy</td>
</tr>
<tr>
<td><strong>Visible cancer remains (R2)</strong></td>
<td>• See treatment for unresectable disease</td>
</tr>
</tbody>
</table>
If you will have systemic therapy after surgery, then capecitabine is the preferred option.

Other options include:

- 5-fluorouracil with oxaliplatin
- Capecitabine with oxaliplatin
- Gemcitabine with capecitabine
- Gemcitabine with cisplatin
- 5-fluorouracil or gemcitabine

**Surveillance**

After completing treatment for resectable disease, you will enter surveillance. Surveillance is a period of testing to watch for signs that cancer has returned. It includes tests for CA 19-9, CEA, as well as imaging every 3 to 6 months for 2 years, then every 6 to 12 months for up to 5 years, or as needed.

**Unresectable**

An unresectable tumor cannot be removed with surgery. Before treatment begins, biomarker and genetic tests might be done to learn more about your cancer. If you have MSI/dMMR or a family history of *BRCA1* or *BRCA2* mutations, then you might be referred to a genetic counselor.

**Treatment options**

Treatment options depend on extent and location of cancer and what is available at your hospital or treatment center. Seek treatment at an experienced center.

Unresectable treatment options include:

- Systemic therapy (preferred)
- Clinical trial (preferred)
- Palliative radiation therapy
- Best supportive care

Systemic therapy or a clinical trial are the preferred treatment options for unresectable tumors. A preferred treatment is one proven to have the best result. Other options include palliative radiation therapy and best supportive care. When radiation is used to reduce symptoms caused by the cancer or to extend life, it is called palliative radiation. Best supportive care is treatment to relieve the side effects of cancer and its treatment.
Systemic therapy
Systemic therapy is one of the preferred treatments for unresectable gallbladder cancer. Gemcitabine with cisplatin is the preferred option. There are other recommended options. If you have a tumor that has NTRK gene fusion, then entrectinib or larotrectinib will be used. For a MSI-H/dMMR tumor, pembrolizumab will be given. Ask your medical oncologist why one systemic therapy might be chosen over another to treat your type of cancer.

Systemic therapy options for unresectable and resectable gallbladder cancer can be found in Guide 6.

Metastatic disease
Metastatic cancer is cancer that has spread to distant sites in the body. Your doctor will do a biopsy and MSI testing. Treatment options are based on the size and location of the cancer.

Treatment options for metastatic gallbladder cancer include:

- Systemic therapy (preferred)
- Clinical trial (preferred)
- Best supportive care

Systemic therapy or a clinical trial are the preferred choices. Best supportive care is used with other treatments to improve quality of life.

Guide 6
Systemic therapy options: Unresectable and metastatic gallbladder cancer

<table>
<thead>
<tr>
<th>Preferred option</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Gemcitabine with cisplatin</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Other recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 5-fluorouracil with oxaliplatin</td>
</tr>
<tr>
<td>• 5-fluorouracil with cisplatin</td>
</tr>
<tr>
<td>• Capecitabine with cisplatin</td>
</tr>
<tr>
<td>• Capecitabine with oxaliplatin</td>
</tr>
<tr>
<td>• Gemcitabine with albumin-bound paclitaxel</td>
</tr>
<tr>
<td>• Gemcitabine with capecitabine</td>
</tr>
<tr>
<td>• Gemcitabine with oxaliplatin</td>
</tr>
<tr>
<td>• Gemcitabine with cisplatin and albumin-bound paclitaxel</td>
</tr>
<tr>
<td>• 5-fluorouracil or capecitabine or gemcitabine</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Used in some cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>For NTRK gene fusion-positive tumors:</td>
</tr>
<tr>
<td>• Entrectinib</td>
</tr>
<tr>
<td>• Larotrectinib</td>
</tr>
<tr>
<td>For MSI-H/dMMR tumors:</td>
</tr>
<tr>
<td>• Pembrolizumab</td>
</tr>
</tbody>
</table>
Disease progression

When unresectable cancer progresses during or after systemic therapy, then your medical oncologists might try a different systemic therapy.

For disease progression, the preferred option is FOLFOX. FOLFOX is a combination of chemotherapy drugs that includes 5-fluorouracil (5-FU), leucovorin, and oxaliplatin. FOLFIRI is a combination of 5-FU with leucovorin and irinotecan. If your tumor has a specific gene mutation, then you might receive drug therapy that targets the mutation. See Guide 7.

Guide 7
Systemic therapy options: Disease progression

<table>
<thead>
<tr>
<th>Preferred option</th>
<th>• FOLFOX</th>
</tr>
</thead>
</table>
| Other recommended | • FOLFIRI  
• Regorafenib  
• Preferred and other recommended options listed in Guide 6 |

| Used in some cases | For NTRK gene fusion-positive tumors:  
• Entrectinib  
• Larotrectinib  
For MSI-H/dMMR or TMB-H tumors:  
• Pembrolizumab  
For FGFR2 fusions or rearrangements:  
• Pemigatinib  
• Infiratinib  
For IDH1 mutations:  
• Ivosidenib  
For BRAF V600E mutated tumors:  
• Dabrafenib with trametinib  
Other options:  
• Nivolumab  
• Lenvatinib with pembrolizumab |
Key points

- Cancer starts inside the gallbladder and grows through the layers of the gallbladder wall.
- Gallbladder cancer is found by chance during surgery, during pathology review, or on an imaging test.
- When a tumor blocks fluid from draining from the bile ducts, it can cause jaundice.
- Treatment for gallbladder cancer is based on if the cancer can be removed with surgery (resectable), cannot be removed with surgery (unresectable), has spread to other parts of the body (metastatic), and the risk of recurrence.
- Treatment options for gallbladder cancer may include surgery, systemic therapy, chemoradiation, palliative radiation therapy, clinical trial, and best supportive care.
- Systemic therapy or a clinical trial are the preferred treatment options for unresectable or metastatic gallbladder cancer.
- If your tumor has a specific gene mutation, then you might receive drug therapy that targets the mutation.
- Best supportive care may offer symptom relief.

Let us know what you think!

Please take a moment to complete an online survey about the NCCN Guidelines for Patients.

NCCN.org/patients/response
5

Intrahepatic bile duct cancer

55 Overview
56 Cancer stages
58 Testing
59 Treatment
60 Resectable
62 Unresectable
63 Metastatic
64 Disease progression
64 Key points
A cholangiocarcinoma (CCA) is a cancer of the bile duct. Intrahepatic cholangiocarcinoma (ICC) or intrahepatic bile duct cancer is found in the bile ducts of the liver. It is also known as Together, you and your doctor will choose the treatment plan that is best for you.

Intrahepatic bile duct anatomy

Inside the liver is a network of ducts, blood vessels, and lymph vessels. Intrahepatic cholangiocarcinoma is cancer that is found in the bile ducts of the liver.
that starts inside these ducts is intrahepatic bile duct cancer. It is not liver cancer, which arises from liver cells called hepatocytes.

There can be more than one tumor and it can be found in the small ductules or in the larger hepatic ducts. Treatment aims to prevent or slow the spread of cancer.

Cancer stages

A bile duct is made up of several layers. The inner and outer layers are membranes. A membrane is a very thin layer that covers a surface. In between these membranes are muscle and connective tissue.

The layers of the bile duct wall are:

- Epithelium – A thin, moist (mucous) layer of tissue that covers the inside of the duct
- Lamina propria – A type of connective tissue found under the epithelium membrane
- Muscle – A type of soft tissue
- Perimuscular fibrous tissue – A type of connective tissue that surrounds muscle
- Serosa – An outer membrane

Cancer stages for intrahepatic bile duct cancer can be found in Guide 8.

Guide 8
Intrahepatic bile duct cancer stages

<table>
<thead>
<tr>
<th>Stage 0</th>
<th>• Tis, N0, M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td></td>
</tr>
<tr>
<td>Stage 1A</td>
<td>• T1a, N0, M0</td>
</tr>
<tr>
<td>Stage 1B</td>
<td>• T1b, N0, M0</td>
</tr>
<tr>
<td>Stage 2</td>
<td>• T2, N0, M0</td>
</tr>
<tr>
<td>Stage 3</td>
<td></td>
</tr>
<tr>
<td>Stage 3A</td>
<td>• T3, N0, M0</td>
</tr>
<tr>
<td>Stage 3B</td>
<td>• T4, N1, M0</td>
</tr>
<tr>
<td>Stage 4</td>
<td>• Any T, Any N, M1</td>
</tr>
</tbody>
</table>

Guide 8
Intrahepatic bile duct cancer stages

Stage 0
• Tis, N0, M0

Stage 1
Stage 1A
• T1a, N0, M0
Stage 1B
• T1b, N0, M0

Stage 2
• T2, N0, M0

Stage 3
Stage 3A
• T3, N0, M0
Stage 3B
• T4, N1, M0

Stage 4
• Any T, Any N, M1
Intrahepatic bile duct cancer

**T = Tumor**
The primary tumor size can be measured in centimeters (cm) or millimeters (mm). Cancer can grow or spread into nearby blood vessels, the liver, or structures outside the liver.

- **Tis** Carcinoma *in situ* (this is an intraductal tumor)
- **T1a** One tumor that is 5 cm or smaller and has not grown into blood vessels
- **T1b** One tumor that is larger than 5 cm and has not grown into blood vessels
- **T2a** One tumor that has grown into blood vessels inside the liver (intrahepatic) or multiple tumors that may or may not be in intrahepatic (liver) blood vessels
- **T3** Tumor perforating the visceral peritoneum
- **T4** Tumor has grown into nearby structures outside the liver (extrahepatic)

**N = Node**
There are hundreds of lymph nodes throughout your body. They work as filters to help fight infection and remove harmful products from your body. Regional lymph nodes are those located near the tumor. These include hilar, cystic duct, common bile duct, hepatic artery, posterior pancreatoduodenal, and portal vein lymph nodes.

- **N0** No cancer in regional lymph nodes
- **N1** Cancer is found in a regional lymph node

**M = Metastatic**
Cancer that has spread to distant parts of the body is shown as M1. The most common site for metastasis is the lung.

- **M0** means no distant metastasis
- **M1** means distant metastasis is found. This is metastatic cancer.
Testing

Once it is confirmed that the isolated tumor found on imaging is not liver cancer (hepatocellular carcinoma), then you will have tests found in Guide 9.

Blood tests will measure CEA, CA 19-9, AFP, and liver function, and will check for a past or current viral hepatitis infection. Hepatitis is a risk factor for bile duct cancer. Some cancer treatment can wake up (or reactivate) the virus. If this happens, it can cause harm to the liver.

You will meet with a surgeon to discuss if:

› You will have a biopsy
› You are healthy enough for surgery or a liver transplant
› The cancer can be removed with surgery

Imaging tests may include a CT of the chest, a multiphasic CT of the abdomen and pelvis, and a multiphasic MRI of the abdomen and pelvis. Imaging of this area allows your doctor to see the size of the cancer, if it spread to the liver, or if it invaded the lymph nodes or blood vessels.

Sometimes intrahepatic bile duct cancers can be confused with stomach, small intestine, or colon tumors that spread to the liver. An esophagogastroduodenoscopy (EGD) and colonoscopy may be done to check if cancer has spread to the liver rather than occurring in the bile ducts. You might be referred to a hepatologist. A hepatologist specializes in the care of the liver, biliary tract, gallbladder, and pancreas.

Guide 9
Possible tests: Intrahepatic bile duct cancer

Medical history and physical exam

Multiphasic CT and/or MRI with contrast of the abdomen and pelvis

Chest CT with or without contrast

CEA, CA 19-9, alpha-fetoprotein (AFP)

Liver function tests (LFTs)

Esophagogastroduodenoscopy (EGD) and colonoscopy

Viral hepatitis tests

Biopsy
Treatment

Treatment is based on if the tumor is:

- **Resectable** – can be removed with surgery
- **Unresectable** – cannot be removed with surgery
- **Metastatic** – cancer has spread to other parts of the body

If the cancer is unresectable or metastatic, then MSI/MMR testing and other biomarker testing will be done. For those with dMMR/MSI-H tumors or a family history that suggests BRCA1 or BRCA2 mutations, then you might have genetic testing and be referred to a genetic counselor.

Treatment options can be found in Guide 10.

---

Guide 10

Treatment options: Intrahepatic bile duct cancer

| **Resectable** | • Possible staging laparoscopy  
• Resection with regional lymphadenectomy | • For adjuvant treatment based on surgery results, see Guide 11 |
| --- | --- | --- |
| **Unresectable** | • MSI/MMR and other biomarker testing | • Systemic therapy, see Guide 13  
• Clinical trial  
• Chemoradiation  
• Possible radiation therapy or arterially directed therapy  
• Best supportive care |
| **Metastatic** | • MSI/MMR and other biomarker testing | • Systemic therapy, see Guide 13  
• Clinical trial  
• Possible radiation therapy or arterially directed therapy  
• Best supportive care |
Resectable

A resectable tumor is one that can be removed with surgery. Surgery to remove the tumor is called liver resection (or partial hepatectomy). During resection, some lymph nodes might be removed in a lymphadenectomy. A lymphadenectomy is done to check for cancer. Also, your surgeon will look for cancer in nearby veins, arteries, and tissues.

For intrahepatic bile duct cancers, resection with cancer-free or negative margins (R0) is the goal. Because this type of cancer occurs in the bile ducts inside the liver, surgery may include the removal of a section or piece of the liver. The extent of surgery will depend on the tumor size and location. If cancer has spread beyond the nearby lymph nodes or to distant sites, treatment other than surgery may be offered.

Treatment after surgery

Treatment after surgery is called adjuvant therapy. It is determined by the risk of the tumor returning and/or if not all tumor could be removed during surgery. For all treatment options, see Guide 11.

- In a clear or negative margin (R0), no cancerous cells are found.
- In an R1 positive margin, there is higher risk that very small (microscopic) cancer cells remain.
- In an R2 positive margin, cancer that can be seen without a microscope remains.

Guide 11

Adjuvant treatment based on surgery results: Intrahepatic bile duct cancer

<table>
<thead>
<tr>
<th>Does cancer remain after surgery?</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cancer remains (R0)</td>
<td>• Observation</td>
</tr>
<tr>
<td></td>
<td>• Systemic therapy (see Guide 12)</td>
</tr>
<tr>
<td></td>
<td>• Clinical trial</td>
</tr>
<tr>
<td>Risk that microscopic cancer cells remain (R1) or Cancer found in regional nodes</td>
<td>• Systemic therapy (see Guide 12)</td>
</tr>
<tr>
<td></td>
<td>• Fluoropyrimidine-based chemoradiation</td>
</tr>
<tr>
<td></td>
<td>• Fluoropyrimidine-based or gemcitabine-based chemotherapy followed by fluoropyrimidine-based chemoradiation</td>
</tr>
<tr>
<td></td>
<td>• Fluoropyrimidine-based chemoradiation followed by fluoropyrimidine-based or gemcitabine-based chemotherapy</td>
</tr>
<tr>
<td></td>
<td>• Clinical trial</td>
</tr>
<tr>
<td>Visible cancer remains (R2)</td>
<td>• See treatment for unresectable disease</td>
</tr>
</tbody>
</table>
Adjuvant systemic therapies can be found in Guide 12.

**No cancer remains**
If no cancer remains (R0), the preferred adjuvant treatment options are systemic therapy or a clinical trial. A preferred treatment is one proven to have a better result. Observation might be considered. This is sometimes called watch-and-wait. After treatment, you will enter surveillance.

**Microscopic cancer remains**
If there is a higher risk that microscopic cancer cells remain (R1) or cancer is found in nearby lymph nodes, then treatment options include systemic therapy, fluoropyrimidine-based chemoradiation used alone or with chemotherapy, or a clinical trial. Adjuvant chemotherapy or chemoradiation has been associated with survival benefit, especially in those with lymph node-positive disease. After treatment, you will enter surveillance.

**Visible cancer remains**
If visible cancer remains, then treatment will be for unresectable disease.

**Surveillance**
After treatment is finished, you will enter surveillance. This is a period of testing to watch for cancer recurrence. During this time you might have multiphasic CT and MRI scans and a chest CT every 3 to 6 months for 2 years, then every 6 to 12 months for up to 5 years, or as needed. Your doctor will discuss a surveillance plan with you. It is important to keep any follow-up doctor visits and imaging test appointments.

### Guide 12
#### Adjuvant systemic therapy options: Intrahepatic bile duct cancer

<table>
<thead>
<tr>
<th>Preferred option</th>
<th>• Capecitabine</th>
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</thead>
</table>
| **Other recommended** | • 5-fluorouracil with oxaliplatin  
• Capecitabine with oxaliplatin  
• Gemcitabine with capecitabine  
• Gemcitabine with cisplatin  
• 5-fluorouracil or gemcitabine |
Unresectable

An unresectable tumor cannot be removed with surgery. However, there are a number of treatment options.

These include the following:

- Systemic therapy, see Guide 13
- Clinical trial
- Chemoradiation (EBRT with fluoropyrimidine)
- Locoregional radiation therapy or arterially directed therapy
- Best supportive care

Guide 13
Systemic therapy options: Unresectable and metastatic

Preferred option

- Gemcitabine with cisplatin

Other recommended

- 5-fluorouracil with oxaliplatin
- 5-fluorouracil with cisplatin
- Capecitabine with cisplatin
- Capecitabine with oxaliplatin
- Gemcitabine with albumin-bound paclitaxel
- Gemcitabine with capecitabine
- Gemcitabine with oxaliplatin
- Gemcitabine with cisplatin and albumin-bound paclitaxel
- 5-fluorouracil or capecitabine or gemcitabine

Used in some cases

For NTRK gene fusion-positive tumors:
- Entrectinib
- Larotrectinib

For MSI-H/dMMR tumors:
- Pembrolizumab
Metastatic cancer is cancer that has spread to other parts of the body. Treatment options will be based on your wishes and your doctor’s recommendations. Best supportive care is always given.

Treatment options include the following:

- Systemic therapy, see Guide 13
- Clinical trial
- Locoregional radiation therapy or arterially directed therapy
- Best supportive care

### Guide 14
**Systemic therapy options: Disease progression**

<table>
<thead>
<tr>
<th>Preferred option</th>
<th>• FOLFOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other recommended</td>
<td>• FOLFIRI</td>
</tr>
<tr>
<td></td>
<td>• Regorafenib</td>
</tr>
<tr>
<td></td>
<td>• Preferred and other recommended options listed in Guide 13</td>
</tr>
</tbody>
</table>

**Used in some cases**

- For *NTRK* gene fusion-positive tumors:
  - Entrectinib or larotrectinib
- For MSI-H/dMMR or TMB-H tumors:
  - Pembrolizumab
- For *FGFR2* fusions or rearrangements:
  - Pemigatinib or infigratinib
- For *IDH1* mutations:
  - Ivosidenib
- For *BRAF* V600E mutated tumors:
  - Dabrafenib with trametinib
- Other options:
  - Nivolumab
  - Lenvatinib with pembrolizumab
Disease progression

If unresectable or metastatic intrahepatic bile duct cancer progresses during or after systemic therapy, then FOLFOX is the preferred option. FOLFOX is a combination of chemotherapy drugs that includes 5-fluorouracil (5-FU), leucovorin, and oxaliplatin. FOLFIRI is a combination of 5-FU with leucovorin and irinotecan. If your tumor has a high number of mutations (TMB-H) or a specific gene mutation such as \textit{NTRK}, \textit{MSI-H/dMMR}, \textit{FGFR2}, \textit{IDH1}, or \textit{BRAF V600E}, then you might receive drug therapy that targets the mutation. A clinical trial is always an option. See Guide 14.

Key points

- Not all bile duct cancers are the same.
- A cholangiocarcinoma (CCA) is a rare cancer that forms in the bile ducts. Intrahepatic cholangiocarcinoma (ICC) is found in bile ducts inside the liver. It is also called intrahepatic bile duct cancer.
- Treatment is based on if the cancer can be removed with surgery (resectable), cannot be removed with surgery (unresectable), has spread to other parts of the body (metastatic), and the risk of recurrence.
- Treatment before surgery is called neoadjuvant. Treatment after surgery is called adjuvant.
- ICC can spread to blood vessels inside the liver. From here it can spread throughout the liver and structures outside the liver such as the lining that surrounds the abdominal organs (visceral peritoneum).
- If your tumor has a high number of mutations (TMB-H) or specific gene mutation such as \textit{NTRK}, \textit{MSI-H/dMMR}, \textit{FGFR2}, \textit{IDH1}, or \textit{BRAF V600E}, then you might receive drug therapy that targets the mutation.
6

Extrahepatic bile duct cancer

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68 Testing
69 Perihilar (Klatskin tumor) cancer stages
70 Distal cancer stages
71 Treatment options
71 Resectable
73 Treatment after surgery
74 Unresectable
75 Metastatic

76 Disease progression
77 Key points
Extrahepatic bile ducts are small tubes that carry bile outside of the liver. In perihilar extrahepatic bile duct cancer, cancer is found in the common hepatic duct. In distal extrahepatic bile duct cancer, cancer is found in the common bile duct. Together, you and your doctor will choose the treatment plan that is best for you.
The perihilar bile duct starts where the right and left hepatic ducts join outside the liver and form the common hepatic duct. It ends where the cystic duct from the gallbladder joins to form the common bile duct. The distal bile duct starts where the cystic duct connects and forms the common bile duct.

A cholangiocarcinoma (CCA) is a rare cancer that forms in the bile ducts. Intrahepatic cholangiocarcinoma (ICC) is found inside the liver. Extrahepatic cholangiocarcinoma (ECC) is found outside the liver. Extrahepatic bile duct cancers are also known as ECC.

**Klatskin tumor**

A Klatskin tumor is found in the common hepatic duct/right or left hepatic ducts. It is a proximal (perihilar) extrahepatic bile duct cancer.
Testing

Extrahepatic cholangiocarcinoma might be suspected if you have pain, jaundice, abnormal liver function test results, or a blockage or tumor found on images tests. If your doctor suspects extrahepatic bile duct cancer, then you might have the tests found in Guide 15.

Imaging tests
Imaging tests may include a CT of the chest, along with a CT or MRI of the abdomen and pelvis. Imaging of this area allows your doctor to see the size of the cancer, if it spread to the liver, or if it invaded the lymph nodes or blood vessels.

You may have a test called a cholangiography to see if the bile ducts are blocked. Endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography (MRCP) are types of cholangiography. MRCP is preferred.

Blood tests
You might have blood tests to measure CEA, CA 19-9, AFP, liver function, and serum IgG4. Serum IgG4 is used to rule out autoimmune cholangitis or other IgG4-related disease. Cholangitis is an inflammation of the bile duct. This disease of the immune system may be chronic and affect the liver and biliary tract.

Other procedures
Sometimes, an endoscopic ultrasound (EUS) is done to get a closer look at the bile ducts.

Guide 15
Possible tests: Extrahepatic bile duct cancer

Medical history and physical exam

Multiphasic abdominal and pelvic CT and/or MRI with IV contrast (to look for blood vessel involvement)

Chest CT with or without contrast

Cholangiography such as ERCP or MRCP. MRCP is preferred

CEA and CA 19-9

Liver function tests (LFTs)

Endoscopic ultrasound (EUS)

Serum IgG4 to rule out autoimmune cholangitis. Those with with IgG-4–related cholangiopathy should be referred to an expert treatment center.
Perihilar (Klatskin tumor) cancer stages

Perihilar bile duct (Klatskin) tumors start where the right and left hepatic ducts meet. Staging might be done during laparoscopic surgery to remove the cancer called resection. For perihilar bile duct cancer stages, see Guide 16.

T = Tumor
The primary tumor size might be measured in centimeters (cm) or millimeters (mm). A large pea is about 1 cm (10 mm).

- **Tis** Carcinoma in situ (cancer is found only in the duct)
- **T1** Tumor is confined to the duct, but has grown through the muscle layer or the fibrous tissue
- **T2** Tumor has grown beyond the wall of the bile duct to surrounding adipose (fat) tissue, or tumor invades the working part of the liver (parenchyma)
- **T3** Tumor has invaded branches of the portal vein or hepatic artery
- **T4** Tumor has invaded the main portal vein or its branches, or the common hepatic artery, or other ducts that join or empty the portal vein or hepatic artery

N = Node
Lymph nodes are found throughout your body. Regional lymph nodes are those located near the tumor. These include hilar, cystic duct, common bile duct, hepatic artery, posterior pancreatoduodenal, and portal vein lymph nodes.

- **N0** No cancer in regional lymph node
- **N1** Cancer is found in 1 to 3 regional lymph nodes
- **N2** Cancer is found in 4 or more regional lymph nodes

M = Metastatic
Cancer that has spread to distant parts of the body is written as M1. Stage 4B is metastatic cancer. The most common site for metastasis is the lining that surrounds the abdominal organs (visceral peritoneum) and the liver.

Guide 16
Perihilar bile duct cancer stages

<table>
<thead>
<tr>
<th>Stage 0</th>
<th>Tis, N0, M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>T1, N0, M0</td>
</tr>
<tr>
<td>Stage 2</td>
<td>T2, N0, M0</td>
</tr>
<tr>
<td>Stage 3</td>
<td></td>
</tr>
<tr>
<td>Stage 3A</td>
<td>T3, N0, M0</td>
</tr>
<tr>
<td>Stage 3B</td>
<td>T4, N0, M0</td>
</tr>
<tr>
<td>Stage 3C</td>
<td>Any T, N1, M0</td>
</tr>
<tr>
<td>Stage 4</td>
<td></td>
</tr>
<tr>
<td>Stage 4A</td>
<td>Any T, N2, M0</td>
</tr>
<tr>
<td>Stage 4B</td>
<td>Any T, Any N, M1</td>
</tr>
</tbody>
</table>
Distal cancer stages

Distal bile duct cancer starts in the common bile duct. This is found below where the cystic duct joins the bile duct. Staging might be done during laparoscopic surgery. This would be before surgery to remove the cancer called resection. For distal bile duct cancer stages, see Guide 17.

T = Tumor
The primary tumor size is measured in millimeters (mm). Cancer can grow or spread into nearby ducts, arteries, veins, or organs.

- **Tis** Carcinoma in situ (cancer has not grown beyond the innermost epithelial layer)
- **T1** Tumor has grown into the bile duct wall with a depth of less than 5 mm
- **T2** Tumor has grown into the bile duct wall with a depth of 5 to 12 mm
- **T3** Tumor has grown into the bile duct wall with a depth of more than 12 mm
- **T4** Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery

N = Node
There are hundreds of lymph nodes throughout your body. They work as filters to help fight infection and remove harmful things from your body. Lymph nodes are found throughout your body. Regional lymph nodes are those located near the tumor. These include hilar, cystic duct, common bile duct, hepatic artery, posterior pancreatoduodenal, and portal vein lymph nodes.

- **N0** No cancer in regional lymph node
- **N1** Cancer is found in 1 to 3 regional lymph nodes
- **N2** Cancer is found in 4 or more regional lymph nodes

M = Metastatic
Cancer that has spread to distant parts of the body is written as M1. Stage 4 is metastatic cancer. The most common sites for metastasis are the liver, lungs, and the lining that surrounds the abdominal organs (visceral peritoneum).

<table>
<thead>
<tr>
<th>Guide 17</th>
<th>Distal bile duct cancer stages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 0</strong></td>
<td>• Tis, N0, M0</td>
</tr>
<tr>
<td><strong>Stage 1</strong></td>
<td>• T1, N0, M0</td>
</tr>
</tbody>
</table>
| **Stage 2** | • T1, N1, M0  
| | • T2, N0, M0  
| **Stage 2A** | • T2, N1, M0  
| | • T3, N0, M0  
| | • T3, N1, M0  
| **Stage 2B** | • T4, N0, M0  
| | • T4, N1, M0  
| | • T4, N2, M0  
| **Stage 3** | • T1, N2, M0  
| | • T2, N2, M0  
| | • T3, N2, M0  
| **Stage 3A** | • T4, N0, M0  
| | • T4, N1, M0  
| | • T4, N2, M0  
| **Stage 3B** | • Any T, Any N, M1  
| |
Treatable

Treatment is based on if the tumor is:

- **Resectable** – can be removed with surgery
- **Unresectable** – cannot be removed with surgery
- **Metastatic** – cancer has spread to other parts of the body

For an overview of treatment options, see Guide 18.

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### Guide 18

**Treatment options: Extrahepatic bile duct cancer**

| **Resectable** | • Exploratory surgery  
|                | • Possible staging laparoscopy  
|                | • Possible biliary drainage before surgery  
|                | • Multidisciplinary review  
|                | ➔ • Surgery followed by adjuvant therapy (see Guide 18) |

| **Unresectable** | • Biliary drainage, if needed  
|                  | • Evaluate if candidate for liver transplant. If candidate referral to transplant center before biopsy  
|                  | • Biopsy with biomarker testing  
|                  | ➔ • Systemic therapy, see Guide 19  
|                  | • Clinical trial  
|                  | • Chemoradiation  
|                  | • Palliative EBRT  
|                  | • Best supportive care |

| **Metastatic** | • Biliary drainage, if needed  
|               | • Biopsy with biomarker testing  
|               | ➔ • Systemic therapy, see Guide 19  
|               | • Clinical trial  
|               | • Best supportive care |

Before surgery you might have biliary drainage. Exploratory surgery may be performed when suspicion of cancer is high. A staging laparoscopy might be used to gain a better understanding of the size and location of the tumor. Extrahepatic cancers can spread to the liver, gallbladder, pancreas, and various arteries and veins. Therefore, you might have a staging laparoscopy or exploratory surgery to gain knowledge about the amount and location of your cancer.

Your treatment team of experts will discuss if surgery is safe for you and whether the cancer can be removed. This is called multidisciplinary review.
Surgery
Surgery is based on where the cancer is located in your body. You may have biliary drainage to drain fluid from the biliary tract before surgery. During surgery, the bile duct and nearby lymph nodes are removed.

Distal tumors
Distal tumors are in the common bile duct that passes through the pancreas. If the tumor has invaded the pancreas, then a Whipple procedure (pancreaticoduodenectomy) might be needed. A Whipple procedure is surgery that removes the head of the pancreas, the gallbladder, duodenum (first part of the small intestine), part of the bile duct, and often part of the stomach.

Hilar or perihilar tumors (Klatskin tumors)
Hilar tumors are in the upper part of the common bile duct that is closest to the liver. Surgery to remove part of the liver (hepatic resection) is likely for tumors in the hilar area.

Guide 19
Adjuvant treatment options based on surgery results: Extrahepatic bile duct cancer

<table>
<thead>
<tr>
<th>Does cancer remain after surgery?</th>
<th>Treatment options</th>
</tr>
</thead>
</table>
| No cancer remains (R0) and no cancer found in regional nodes or Carcinoma in situ at surgical margin | • Observation  
• Systemic therapy  
• Fluoropyrimidine chemoradiation  
• Clinical trial |
| Risk that microscopic cancer cells remain (R1) or Cancer found in regional nodes | • Systemic therapy  
• Fluoropyrimidine-based chemoradiation  
• Fluoropyrimidine-based or gemcitabine-based chemotherapy followed by fluoropyrimidine-based chemoradiation  
• Fluoropyrimidine-based chemoradiation followed by fluoropyrimidine-based or gemcitabine-based chemotherapy  
• Clinical trial |
| Visible cancer remains (R2) | • See treatment for unresectable disease |
Treatment after surgery

Treatment after surgery is called adjuvant therapy. It is determined by the risk of the tumor returning and/or if not all tumor could be resected. The goal is to kill any remaining microscopic cancer cells.

For adjuvant treatment options, see Guide 19.

Adjuvant systemic therapy options include:

- Capecitabine (preferred)
- 5-fluorouracil with oxaliplatin
- Capecitabine with oxaliplatin
- Gemcitabine with capecitabine
- Gemcitabine with cisplatin
- 5-fluorouracil or gemcitabine

Microscopic cancer remains

If there is a higher risk that very small (microscopic) cancer cells remain (R1) or cancer is found in nearby lymph nodes, then treatment options include systemic therapy, fluoropyrimidine-based chemoradiation used alone or with chemotherapy, or a clinical trial. Adjuvant chemotherapy or chemoradiation has been associated with survival benefit, especially in those with lymph node-positive disease. After treatment, you will enter surveillance.

Visible cancer remains

In an R2 positive surgical margin, cancer that can be seen without a microscope remains. If visible cancer remains, then treatment will be for unresectable disease.

Surveillance

Surveillance is a period of testing to monitor for the return of cancer. During this time you will have imaging tests every 3 to 6 months for 2 years, then every 6 to 12 months for up to 5 years, or as needed. Your doctor will discuss with you a surveillance plan. It is important to keep any follow-up doctor visits and imaging test appointments.

No cancer remains

In a clear or negative surgical margin (R0), no cancerous cells are found. If no cancer remains (R0) and no cancer is found in the regional lymph nodes or cancer is found in situ, then options include observation, systemic therapy, fluoropyrimidine chemoradiation, or a clinical trial. Observation is sometimes called watch-and-wait. After treatment, you will enter surveillance.
Unresectable

Before treatment, you will be evaluated to see if resection might be an option or if you are a candidate for a liver transplant. If a liver transplant is an option, then you will be referred to a specialized transplant center before a biopsy is done.

Liver transplant
Liver transplant is only for hilar tumors. It requires an early visit to a specialized center. Percutaneous biopsies should be avoided if this is a possibility. You will have treatment and operative staging before the actual transplant.

In a liver transplant, the entire liver is removed and replaced with a healthy, donor liver. The new liver may be donated from a person who recently died, or a section of liver may be donated from a living person. A liver transplant is based on certain size limits and tumor locations.

It is possible for someone to donate a portion of the liver. Structures such as the inferior vena cava, portal vein, hepatic artery, and bile duct are reconnected to the new liver. Other treatments may be given if you are waiting for a transplant. These treatments are called bridge or bridging therapy.

Treatment
Treatment options include the following:

- Systemic therapy
- Clinical trial
- Chemoradiation (EBRT with fluoropyrimidine)
- Palliative radiation therapy (EBRT)
- Best supportive care

There are a variety of treatment options for unresectable extrahepatic bile duct cancers. Best supportive care is always given. You may consider joining a clinical trial. Systemic therapy, chemoradiation, and palliative radiation are all options. Ask your doctor why one treatment might work better in your situation. Not everyone responds the same way to treatment. Some people do better than expected. Others do worse. Talk to your doctor about what to expect from treatment.

Systemic therapy
If you have jaundice, then your doctor will consider biliary drainage before starting systemic therapy. The preferred systemic therapy is gemcitabine with cisplatin. However, there are many recommended options. See Guide 20.
Metastatic

Metastatic cancer is cancer that has spread to other parts of the body. Fluid may block the bile ducts, causing jaundice. If you have jaundice, your doctor will attempt to treat the blocked bile duct. A biopsy may be done of the metastasis to confirm that the cancer is bile duct cancer.

**Treatment**

Treatment options will be based on your wishes and your doctor’s recommendations. Options include systemic therapy, clinical trial, and best supportive care. Best supportive care is always given. You may consider joining a clinical trial.

### Guide 20

**Systemic therapy options: Unresectable and metastatic cancer**

<table>
<thead>
<tr>
<th>Preferred option</th>
<th>Gemcitabine with cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other recommended</strong></td>
<td>5-fluorouracil with oxaliplatin</td>
</tr>
<tr>
<td></td>
<td>5-fluorouracil with cisplatin</td>
</tr>
<tr>
<td></td>
<td>Capecitabine with cisplatin</td>
</tr>
<tr>
<td></td>
<td>Capecitabine with oxaliplatin</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine with albumin-bound paclitaxel</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine with capecitabine</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine with oxaliplatin</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine with cisplatin and albumin-bound paclitaxel</td>
</tr>
<tr>
<td></td>
<td>5-fluorouracil or capecitabine or gemcitabine</td>
</tr>
</tbody>
</table>

**Used in some cases**

For *NTRK* gene fusion-positive tumors:
- Entrectinib
- Larotrectinib

For MSI-H/dMMR tumors:
- Pembrolizumab
Disease progression

If unresectable or metastatic extrahepatic bile duct cancer progresses during or after systemic therapy, then FOLFOX is the preferred option. FOLFOX is a combination of chemotherapy drugs that includes 5-fluorouracil (5-FU), leucovorin, and oxaliplatin. FOLFIRI is a combination of 5-FU with leucovorin and irinotecan. If your tumor has a specific gene mutation, then you might receive drug therapy that targets the mutation. A clinical trial is always an option. See Guide 21.

Guide 21

Systemic therapy options: Disease progression

<table>
<thead>
<tr>
<th>Preferred option</th>
<th>• FOLFOX</th>
</tr>
</thead>
</table>
| Other recommended| • FOLFIRI  
|                  | • Regorafenib  
|                  | • Preferred and other recommended options listed in Guide 19 |
| Used in some cases| For *NTRK* gene fusion-positive tumors:  
|                  | • Entrectinib or larotrectinib  
|                  | For MSI-H/dMMR or TMB-H tumors:  
|                  | • Pembrolizumab  
|                  | For *FGFR2* fusions or rearrangements:  
|                  | • Pemigatinib or infigratinib  
|                  | For *IDH1* mutations:  
|                  | • Ivosidenib  
|                  | For *BRAF* V600E mutated tumors:  
|                  | • Dabrafenib with trametinib  
|                  | Other options:  
|                  | • Nivolumab  
|                  | • Lenvatinib with pembrolizumab |

NCCN Guidelines for Patients®
Gallbladder and Bile Duct Cancers, 2021
Key points

» Not all bile duct cancers are the same.
» Extrahepatic bile ducts are small tubes that carry bile outside of the liver. They include the common hepatic duct and the common bile duct.
» A cholangiocarcinoma (CCA) is a rare cancer that forms in the bile ducts. Extrahepatic cholangiocarcinoma (ECC) is found in bile ducts outside the liver. It is also called extrahepatic bile duct cancer.
» There are 2 types of extrahepatic bile duct cancers: perihilar and distal types.
» Treatment is based on if the cancer can be removed with surgery (resectable), cannot be removed with surgery (unresectable), has spread to other parts of the body (metastatic), and the risk of recurrence.
» Treatment before surgery is called neoadjuvant. Treatment after surgery is called adjuvant.
» If your tumor has a high number of mutations (TMB-H) or a specific gene mutation such as NTRK, MSI-H/dMMR, FGFR2, IDH1, or BRAF V600E, then you might receive drug therapy that targets the mutation.

We want your feedback!

Our goal is to provide helpful and easy-to-understand information on cancer.

Take our survey to let us know what we got right and what we could do better:

NCCN.org/patients/feedback
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Making treatment decisions

79 It’s your choice
79 Questions to ask your doctors
88 Resources
Making treatment decisions

It’s your choice

It’s important to be comfortable with the cancer treatment you choose. This choice starts with having an open and honest conversation with your doctor.

In shared decision-making, you and your doctors share information, discuss the options, and agree on a treatment plan. It starts with an open and honest conversation between you and your doctor.

Treatment decisions are very personal. What is important to you may not be important to someone else.

Some things that may play a role in your decision-making:

- What you want and how that might differ from what others want
- Your religious and spiritual beliefs
- Your feelings about certain treatments like surgery or chemotherapy
- Your feelings about pain or side effects such as nausea and vomiting
- Cost of treatment, travel to treatment centers, and time away from work
- Quality of life and length of life
- How active you are and the activities that are important to you

Think about what you want from treatment. Discuss openly the risks and benefits of specific treatments and procedures. Weigh options and share concerns with your doctor. If you take the time to build a relationship with your doctor, it will help you feel supported when considering options and making treatment decisions.

Second opinion

It is normal to want to start treatment as soon as possible. While cancer can’t be ignored, there is time to have another doctor review your test results and suggest a treatment plan. This is called getting a second opinion, and it’s a normal part of cancer care. Even doctors get second opinions!

Things you can do to prepare:

- Check with your insurance company about its rules on second opinions. There may be out-of-pocket costs to see doctors who are not part of your insurance plan.
- Make plans to have copies of all your records sent to the doctor you will see for your second opinion.

Support groups

Many people diagnosed with cancer find support groups to be helpful. Support groups often include people at different stages of treatment. Some people may be newly diagnosed, while others may be finished with treatment. If your hospital or community doesn’t have support groups for people with cancer, check out the websites listed in this book.

Questions to ask your doctors

Possible questions to ask your doctors are listed on the following pages. Feel free to use these questions or come up with your own. Be clear about your goals for treatment and find out what to expect from treatment.
Questions to ask about testing and staging

1. What tests will I have? How often will they be repeated? Will my insurance pay for these tests?

2. Do I need a biopsy? Will I have more than one? What are the risks?

3. Will a stent be placed during my biopsy? What else might be done?

4. How soon will I know the results and who will explain them to me?

5. Who will talk with me about the next steps? When? Should I see any other specialists?

6. What will you do to make me comfortable during testing?

7. What stage is my cancer? Is it resectable, unresectable, inoperable, or metastatic? What does this mean?

8. Is the cancer in any other areas like my lymph nodes, lungs, or bone?

9. Where can I learn more information about my cancer?
Questions to ask doctors about their experience

1. What is your experience treating biliary cancers?
2. What is the experience of those on your team?
3. Do you only treat biliary cancers? What else do you treat?
4. How many patients like me (of the same age, gender, race) have you treated?
5. Will you be consulting with experts to discuss my care? Whom will you consult?
6. How many procedures like the one you’re suggesting have you done?
7. Is this treatment a major part of your practice?
8. How many of your patients have had complications? What were the complications?
9. How many biliary cancer surgeries have you done?
10. Who will manage my day-to-day care?
Making treatment decisions

Questions to ask about options

1. What will happen if I do nothing?

2. How do my age, cancer stage, overall health, and other factors affect my options?

3. Am I a candidate for a clinical trial?

4. Which option is proven to work best for my situation?

5. Does any option offer a cure or long-term cancer control? Are my chances any better for one option than another? Less time-consuming? Less expensive?

6. Is surgery an option? Why or why not?

7. How do you know if treatment is working? How will I know if treatment is working?

8. What are my options if my treatment stops working?

9. Can I stop treatment at any time? What will happen if I stop treatment?

10. Is there a social worker or someone who can help me decide?
Questions to ask about treatment

1. Does the order of treatment matter?

2. How long do I have to decide about treatment?

3. Is there a combination of treatments you recommend and why? In which order will they be given?

4. Will I have to go to the hospital or elsewhere for treatment? How often? How long is each visit? Will I have to stay overnight in the hospital or make travel plans?

5. Do I have a choice of when to begin treatment? Can I choose the days and times of treatment? Should I bring someone with me?

6. How much will the treatment hurt? What will you do to make me comfortable?

7. How much will this treatment cost me? What does my insurance cover? Are there any programs to help me pay for treatment?

8. Will I miss work or school? Will I be able to drive?

9. What type of home care will I need? What kind of treatment will I need to do at home?

10. When will I be able to return to my normal activities?

11. Which treatment will give me the best quality of life? Which treatment might extend my life? By how long?

12. I would like to get a second opinion. Is there someone you can recommend? Who can help me gather my records for a second opinion?
Questions to ask about surgery

1. What type of surgery do you recommend? Why?
2. Does my cancer involve any veins or arteries? How might this affect surgery?
3. Is there cancer in any nearby organs such as my gallbladder, liver, or pancreas?
4. Is there cancer in the lymph nodes? Will I have surgery to remove the lymph nodes? Will this be a separate surgery or done at the same time to remove the tumor?
5. Will I have more than one surgery? Why?
6. Will surgery be open or laparoscopic? What will the recovery from surgery be like?
7. What is the difference between my surgery options? What are the risks of each option?
8. Will I have surgery to remove the tumor or part of my liver (partial hepatectomy)? Am I a candidate for a liver transplant?
9. What do I need to know about a liver transplant?
10. Is there a hospital or treatment center you can recommend for my surgery?
11. How often will I need check-ups after surgery? What are the chances that the cancer will return?
Questions to ask your doctors about radiation therapy

1. What type of radiation therapy will I have?
2. What will you target?
3. What is the goal of this radiation treatment?
4. How many treatment sessions will I require? Can you do a shorter course of radiation?
5. Do you offer this type of radiation here? If not, can you refer me to someone who does?
6. What side effects can I expect from radiation?
7. What should I wear?
Questions to ask about clinical trials

1. What clinical trials are available for my type and stage of cancer?
2. What are the treatments used in the clinical trial?
3. What does the treatment do?
4. Has the treatment been used before? Has it been used for other types of cancer?
5. What are the risks and benefits of this treatment?
6. What side effects should I expect? How will the side effects be controlled?
7. How long will I be on the clinical trial?
8. Will I be able to get other treatment if this doesn’t work?
9. How will you know the treatment is working?
10. Will the clinical trial cost me anything? If so, how much?
11. How do I find out about clinical trials that I can participate in? Are there online sources that I can search?
Questions to ask about side effects

1. What are the side effects of the treatment you are recommending?

2. What are the side effects of this cancer?

3. How long will these side effects last? Do any side effects lessen or worsen in severity over time?

4. What side effects should I watch for? What side effects are expected and which are life threatening?

5. When should I call the doctor? Can I text? What should I do on weekends and other non-office hours?

6. What emergency department or ER should I go to? Will my treatment team be able to communicate with the ER team?

7. What medicines can I take to prevent or relieve side effects?

8. What can I do to help with pain and other side effects?

9. Will you stop treatment or change treatment if there are side effects? What do you look for?

10. What can I do to lessen or prevent side effects? What will you do?

11. What medicines may worsen side effects of treatment?
## Resources

- **American Association for Clinical Chemistry**
  [labtestsonline.org](http://labtestsonline.org)

- **American Cancer Society**
  [cancer.org/cancer/gallbladder-cancer/about.html](http://cancer.org/cancer/gallbladder-cancer/about.html)

- **CancerCare**
  [cancercare.org](http://cancercare.org)

- **Cancer Support Community**
  [cancersupportcommunity.org/quality-life-cancer-patients](http://cancersupportcommunity.org/quality-life-cancer-patients)

- **Chemocare**
  [chemocare.com](http://chemocare.com)

- **Cholangiocarcinoma Foundation**
  [cholangiocarcinoma.org](http://cholangiocarcinoma.org)

- **Global Liver Institute**
  [globalliver.org](http://globalliver.org)

- **MedlinePlus**
  [medlineplus.gov/gallbladdercancer.html](http://medlineplus.gov/gallbladdercancer.html)
  [medlineplus.gov/bileductcancer.html](http://medlineplus.gov/bileductcancer.html)

- **My Survival Story**
  [mysurvivalstory.org](http://mysurvivalstory.org)

- **National Cancer Institute (NCI)**
  [cancer.gov/types/gallbladder](http://cancer.gov/types/gallbladder)
  [cancer.gov/about-cancer/treatment/clinical-trials/search](http://cancer.gov/about-cancer/treatment/clinical-trials/search)

- **National Hospice and Palliative Care Organization**
  [nhpco.org/patients-and-caregivers](http://nhpco.org/patients-and-caregivers)

- **OncoLink**
  [oncolink.org](http://oncolink.org)

- **Radiological Society of North America**
  [radiologyinfo.org](http://radiologyinfo.org)

- **National Coalition for Cancer Survivorship**
  [canceradvocacy.org/toolbox/](http://canceradvocacy.org/toolbox/)

- **Sharsheret**
  [sharsheret.org](http://sharsheret.org)

- **The Bili Project Foundation**
  [thebiliproject.org](http://thebiliproject.org)

- **Young Survival Coalition (YSC)**
  [youngsurvival.org](http://youngsurvival.org)
Words to know

**abdomen**
The belly area between the chest and pelvis.

**adjuvant therapy**
Treatment that is given to lower the chances of the cancer returning.

**advanced cancer**
Cancer that has spread beyond the area near the main tumor.

**allergic reaction**
An abnormal response by the body to a foreign substance that is harmless.

**alpha-fetoprotein (AFP)**
A protein made by some cancers that is usually present in babies growing in the womb.

**ascites**
Abnormal buildup of fluid in the abdomen.

**best supportive care**
Treatment that improves quality of life.

**bile**
A yellowish-brown fluid that is made by the liver and helps to digest food.

**bile duct**
A small tube-shaped structure that drains digestive fluid (bile) from the liver.

**bilirubin**
A yellow-brown substance that is part of a digestive fluid called bile.

**biopsy**
A procedure that removes fluid or tissue samples to be tested for disease.

**blood clot**
A thickened mass of blood. Also called a thrombosis.

**blood vessel**
A tube-shaped structure that carries blood throughout the body.

**bypass**
An operation to re-route the flow of fluid in the body.

**cancer antigen 19-9 (CA 19-9)**
A protein made by certain cancer cells and found in blood.

**cancer grade**
A rating of how much cancer cells look like normal cells.

**cancer stage**
A rating of the outlook of a cancer based on its growth and spread.

**carcinoembryonic antigen (CEA)**
A protein that is present when some types of cancer form.

**carcinoma in situ**
A cancer that has not grown into tissue that would allow it to spread.

**catheter**
A tube-shaped device that is used to give treatment or drain fluid from the body.

**chemoembolization**
Treatment that blocks the blood supply to the tumor(s) and injects a chemotherapy mixture into the tumor.

**chemoradiation**
Treatment with a combination of chemotherapy and radiation therapy.

**chemotherapy**
Drugs that kill cancer cells by damaging or disrupting the making of the genetic code.

**cholangiography**
An x-ray of the exam of the bile ducts.
Words to know

cholangitis
An infection of the vessels that drain digestive fluid from the liver (bile ducts).

cholecystectomy
An operation to remove the gallbladder.

cholecystitis
Inflammation of the gallbladder.

cholelithiasis
The presence of gallstones.

clinical trial
A type of research that assesses health tests or treatments.

colon
The hollow organ in which eaten food turns from a liquid into a solid form.

colonoscopy
A procedure to work inside the colon with a device that is guided through the anus.

common bile duct
A tube-shaped structure through which digestive fluid (bile) drains into the small intestine.

computed tomography (CT)
A test that uses x-rays from many angles to make a picture of the insides of the body.

contrast
A substance put into your body to make clearer pictures during imaging tests.

core needle biopsy
A procedure that removes tissue samples with a hollow needle. Also called core biopsy.

donor
A person who gives their organs, tissues, or cells to another person.

embolization
A treatment that blocks blood supply to tumors with beads inserted into an artery.

endoscope
A device that is passed through a natural opening to do work inside the body.

diagnostic radiology
A test that uses x-rays from many angles to make a picture of the insides of the body.

computed tomography (CT)
A test that uses x-rays from many angles to make a picture of the insides of the body.

endoscopic retrograde cholangiopancreatography (ERCP)
A procedure to work on pancreatic and bile ducts with an imaging device that is guided down the throat.

endoscopic ultrasound (EUS)
A procedure that takes detailed pictures of the digestive tract and nearby tissue with a device passed through a natural opening.

epithelium
A thin layer of tissue that covers organs, glands, and other structures within the body.

esophagogastroduodenoscopy (EGD)
A procedure to do work in the first parts of the digestive tract with a device guided down the throat. Also called an upper GI endoscopy.

external beam radiation therapy (EBRT)
A cancer treatment with radiation received from a machine outside the body.

fine-needle aspiration (FNA)
A procedure that removes tissue samples with a very thin needle.

fluoropyrimidine-based therapy
A combination chemotherapy regimen in which the main drug used is 5-FU (5-fluorouracil).

FOLFIGI
A combination chemotherapy regimen that includes 5-FU, leucovorin, and irinotecan.

FOLFOX
A combination chemotherapy regimen that includes 5-FU, leucovorin, and oxaliplatin.

gallbladder
A small organ that holds digestive fluid (bile) from the liver.
**gastroenterologist**
A doctor who is an expert in digestive diseases.

**gastrointestinal (GI) tract**
The group of organs through which food passes after being eaten. Also called digestive tract.

**gene**
Coded DNA instructions in cells for making new cells and controlling how cells behave.

**general anesthesia**
A drug-induced, sleep-like state for pain relief.

**hepatologist**
A doctor who is an expert in treating diseases of the liver, gallbladder, bile ducts, and pancreas.

**hereditary**
Passed down from parent to child through coded information in cells.

**imaging**
A test that makes pictures (images) of the insides of the body.

**immune system**
The body’s natural defense against infection and disease.

**immunotherapy**
A treatment with drugs that help the body find and destroy cancer cells.

**infection**
An illness caused by germs.

**intensity-modulated radiation therapy (IMRT)**
Treatment with radiation that uses small beams of different strengths based on the thickness of the tissue.

**intestine**
The organ that food passes through after leaving the stomach.

**interventional radiologist**
A doctor who is an expert in imaging tests and using image-guided tools to perform minimally invasive techniques to diagnose or treat disease.

**intravenous (IV)**
A method of giving drugs by a needle or tube inserted into a vein.

**jaundice**
Yellow-colored skin or whites of the eyes due to a buildup of bilirubin in the body.

**lamina propria**
A type of connective tissue found under the thin layer of tissues covering a mucous membrane.

**laparoscopic surgery**
A procedure that uses small incisions or a tool placed into the opening of the body to reduce damage to body tissue.

**liver**
The largest organ and gland in the body with many vital functions.

**liver function test (LFT)**
A lab test that measures chemicals made or processed by the liver.

**lymph node**
A small, bean-shaped, disease-fighting structure.

**magnetic resonance cholangiopancreatography (MRCP)**
A test that uses radio waves and powerful magnets to make pictures of the pancreas and bile ducts.

**magnetic resonance imaging (MRI)**
A test that uses radio waves and powerful magnets to make pictures of the insides of the body.

**medical history**
A report of all your health events and medications.
Words to know

**medical oncologist**
A doctor who is an expert in cancer drugs.

**metastasis**
The spread of cancer cells from the first (primary) tumor to a new site.

**microsatellite instability (MSI)**
Errors made in small, repeated DNA parts during the copy process because of an abnormal repair system.

**microsatellite instability-high (MSI-H)**
Mutations in 30% or more microsatellites.

**minimally invasive procedure**
A procedure that uses small incisions or a tool placed into the opening of the body to reduce damage to body tissue.

**mutation**
An abnormal change.

**neoadjuvant treatment**
A treatment that is given before the main treatment to reduce the cancer. Also called preoperative treatment if given before an operation.

**observation**
A period of testing for changes in cancer status while not receiving treatment.

**oncologist**
A doctor who is an expert in the treatment of cancer.

**palliative care**
Health care that includes symptom relief but not cancer treatment. Also sometimes called supportive care.

**pancreas**
An organ that makes fluids that help digest food and chemicals that control blood sugar.

**pathologist**
A doctor who is an expert in testing cells and tissue to find disease.

**pelvis**
The body area between the hipbones.

**percutaneous transhepatic cholangiography (PTC)**
A procedure to view the biliary tract with an x-ray and possibly place a catheter to drain fluid from the biliary tract.

**peritoneum**
The tissue that lines the abdominal wall and covers most of the organs in the abdomen (viscera). Also called visceral peritoneum.

**positron emission tomography (PET)**
A test that uses radioactive material to see the shape and function of body parts.

**primary treatment**
The main treatment used to rid the body of cancer.

**primary tumor**
The first mass of cancer cells.

**prognosis**
The likely course and outcome of a disease based on tests.

**progression**
The growth or spread of cancer after being tested or treated.

**radiation therapy**
A treatment that uses high-energy rays.

**radiologist**
A doctor who is an expert in imaging tests.

**recurrence**
The return of cancer after a cancer-free period.

**resectable**
Cancer that can be removed with surgery.

**serosa**
The outer lining of organs and body cavities of the abdomen and chest, including the stomach. Also called serous membrane.
Words to know

**side effect**
An unhealthy or unpleasant physical or emotional response to treatment.

**small intestine**
A digestive organ that absorbs nutrients from eaten food.

**stereotactic body radiation therapy (SBRT)**
Treatment with high-dose radiation within one or a few sessions.

**subtype**
A smaller group within a type of cancer that is based on certain cell features.

**supportive care**
Health care that includes symptom relief but not cancer treatment. Also called palliative care.

**surgery**
An operation to remove or repair a part of the body.

**surgical margin**
The normal-looking tissue around the edge of a tumor that is removed during surgery.

**surveillance**
Testing that is done after treatment ends to check for the return of cancer.

**targeted therapy**
A drug treatment that impedes the growth process specific to cancer cells.

**three-dimensional conformal radiation therapy (3D-CRT)**
A treatment with radiation that uses beams matched to the shape of the tumor.

**tumor marker**
A substance found in body tissue or fluid that may be a sign of cancer.

**ultrasound (US)**
A test that uses sound waves to take pictures of the insides of the body.

**unresectable**
Cancer that can’t be removed by surgery.

**visceral peritoneum**
The lining (serous membrane) that surrounds the internal organs in the abdomen.

**widespread metastatic disease**
The spread of cancer from the first tumor to many new sites in the body.
This patient guide is based on the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hepatobiliary Cancers, Version 2021. It was adapted, reviewed, and published with help from the following people:

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## NCCN Cancer Centers

### Abramson Cancer Center
at the University of Pennsylvania  
Philadelphia, Pennsylvania  
800.789.7366 • pennmedicine.org/cancer

### Fred & Pamela Buffett Cancer Center
Omaha, Nebraska  
402.559.5600 • ummc.edu/cancercenter

### Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute  
Cleveland, Ohio  
800.641.2422 • UH Seidman Cancer Center  
uhhospitals.org/services/cancer-services  
866.223.8100 • CC Taussig Cancer Institute  
my.clevelandclinic.org/departments/cancer  
216.844.8797 • Case CCC  
case.edu/cancer

### City of Hope National Medical Center
Los Angeles, California  
800.826.4673 • cityofhope.org

### Dana-Farber/Brigham and Women’s Cancer Center | Massachusetts General Hospital Cancer Center
Boston, Massachusetts  
617.732.5500  
youhaveus.org  
617.726.5130  
massgeneral.org/cancer-center

### Duke Cancer Institute
Durham, North Carolina  
888.275.3853 • dukecancerinstitute.org

### Fox Chase Cancer Center
Philadelphia, Pennsylvania  
888.369.2427 • foxchase.org

### Huntsman Cancer Institute at the University of Utah
Salt Lake City, Utah  
800.824.2073  
huntsmancancer.org

### Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance
Seattle, Washington  
206.606.7222 • seattlecca.org  
206.667.5000 • fredhutch.org

### The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Baltimore, Maryland  
410.955.8964  
www.hopkinskimmelcancercenter.org

### Robert H. Lurie Comprehensive Cancer Center of Northwestern University
Chicago, Illinois  
866.587.4322 • cancer.northwestern.edu

### Mayo Clinic Cancer Center
Phoenix/Scottsdale, Arizona  
480.301.8000 • Arizona  
904.953.0853 • Florida  
507.538.3270 • Minnesota  
mayoclinic.org/cancercenter

### Memorial Sloan Kettering Cancer Center
New York, New York  
800.525.2225 • mskcc.org

### Moffitt Cancer Center
Tampa, Florida  
888.663.3488 • moffitt.org

### The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute
Columbus, Ohio  
800.293.5066 • cancer.osu.edu

### O’Neal Comprehensive Cancer Center at UAB
Birmingham, Alabama  
800.822.0933 • uab.edu/onealcancercenter

### Roswell Park Comprehensive Cancer Center
Buffalo, New York  
877.275.7724 • roswellpark.org

### Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine
St. Louis, Missouri  
800.600.3606 • siteman.wustl.edu

### St. Jude Children’s Research Hospital/ The University of Tennessee Health Science Center
Memphis, Tennessee  
866.278.5833 • sjude.org  
901.448.5500 • uthsc.edu

### Stanford Cancer Institute
Stanford, California  
877.668.7535 • cancer.stanford.edu

### UC Davis Comprehensive Cancer Center
Sacramento, California  
916.734.5959 | 800.770.9261  
health.ucdavis.edu/cancer

### UC San Diego Moores Cancer Center
La Jolla, California  
858.822.6100 • cancer.ucsd.edu

### UCLA Jonsson Comprehensive Cancer Center
Los Angeles, California  
310.265.2686 • cancer.ucla.edu

### UCSF Helen Diller Family Comprehensive Cancer Center
San Francisco, California  
800.689.8273 • cancer.ucsf.edu

### University of Colorado Cancer Center
Aurora, Colorado  
720.848.0300 • coloradocancercenter.org

### University of Michigan Rogel Cancer Center
Ann Arbor, Michigan  
800.865.1125 • rogelcancercenter.org

### The University of Texas MD Anderson Cancer Center
Houston, Texas  
844.269.5922 • mdanderson.org

### University of Wisconsin Carbone Cancer Center
Madison, Wisconsin  
608.265.1700 • uwhealth.org/cancer

### UT Southwestern Simmons Comprehensive Cancer Center
Dallas, Texas  
214.648.3111 • utsouthwestern.edu/simmons

### Vanderbilt-Ingram Cancer Center
Nashville, Tennessee  
877.936.8422 • vicc.org

### Yale Cancer Center/ Smilow Cancer Hospital
New Haven, Connecticut  
855.4.SMILOW • yalecancercenter.org
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