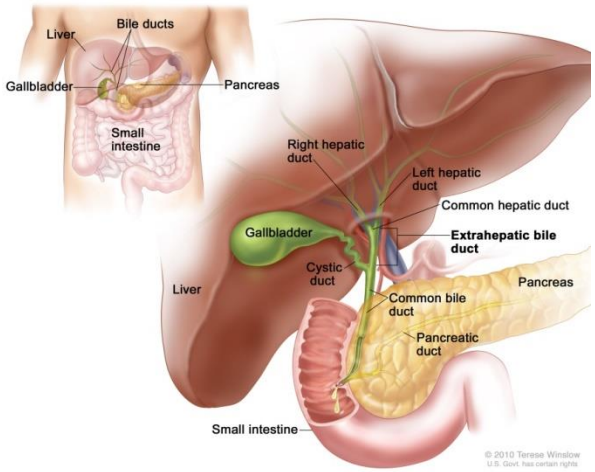
Cancer Association of South Africa (CANSA)

Fact Sheet
on
Bile Duct Cancer

Introduction

The biliary system consists of the organs and ducts (bile ducts, gallbladder, and associated structures) that are involved in the production and transportation of bile.



[Picture Credit: Biliary System]

Bile Duct Cancer

Bile duct cancer (cholangio-carcinoma) is rare. It is almost always a type of cancer called adenocarcinoma, which starts in the lining of the bile duct. If cancer starts in the part of the bile ducts within the liver, it is known as intra-hepatic carcinoma and if it starts in bile ducts outside the liver, it is known as extra-hepatic carcinoma.

There are three general locations where this type of cancer may arise within the bile drainage system:

- Within the liver (intrahepatic) affecting the bile ducts located within the liver
- Just outside of the liver (extrahepatic or perihilar) located at the notch of the liver where the bile ducts exit
- Far outside of the liver (distal extrahepatic) near where the bile ducts enter the intestine (called the ampulla of Vater)

Bile duct cancers are most commonly found just outside of the liver in the perihilar area and least commonly found within the liver.

Khan, A.S. & Dageforde, L.A. 2019.
"Cholangiocarcinoma is a rare malignancy and accounts for 2% of all malignancies. Incidence is on the increase in the Western world. Cholangiocarcinoma arises from the malignant growth of the epithelial lining of the bile ducts and can be found all along the biliary tree. It can be classified into subtypes based on location: intrahepatic (arising from the intrahepatic biliary tract in the hepatic parenchyma), perihilar (at the hilum of the liver involving the biliary confluence) and distal (extrahepatic, often in the head of the pancreas). Margin status and locoregional lymph node metastases are the most important determinants of postsurgical outcomes."

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Incidence of Bile Duct Cancer

The outdated National Cancer Registry (2016), known for under reporting, does not furnish information regarding the incidence of bile duct cancer. According to the National Cancer Registry (2013) the following number of liver and bile duct cancer cases combined was histologically diagnosed in South Africa during 2016:

Group - Males 2016	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	306	1:607	0,78%
Asian males	6	1:1 167	0,61%
Black males	178	1:756	1,34%
Coloured males	26	1:640	0,57%
White males	96	1:375	0,44%

Group - Females 2016	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	206	1:1 208	0,49%
Asian females	8	1:1 127	0,64%
Black females	112	1:1 546	0,56%
Coloured females	20	1:1 623	0,43%
White females	67	1:594	0,39%

The frequency of histologically diagnosed cases of liver and bile duct cancer in South Africa for 2016 was as follows (National Cancer Registry, 2016):

Group - Males 2016	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	10	8	28	40	77	58	66	19
Asian males	1	0	0	1	1	1	2	1
Black males	6	7	22	33	46	28	25	7
Coloured males	2	0	0	2	10	7	6	0
White males	1	1	2	5	20	22	33	12

Group - Females 2016	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	4	4	16	34	49	46	38	21
Asian females	0	0	0	2	1	2	2	1
Black females	4	4	13	20	27	22	16	5
Coloured females	0	0	0	4	4	6	4	2
White females	0	0	3	8	17	16	16	7

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Causes and Possible Risk Factors of Bile Duct Cancer

The cause of most bile duct cancers is unknown. There are a number of risk factors that may increase the risk of developing bile duct cancer.

These include:

Increasing age – As with most cancers, increasing age plays a role in the incidence of bile duct cancer. Research shows that more than two out of three cases of bile duct cancer occurs in people over 65.

Abnormal bile ducts – there appears to be an increased risk of bile duct cancer in individuals who have congenital (born with) abnormalities of the bile ducts

Inflammatory conditions – as an example, chronic inflammatory conditions of the bowel are known factors to increase the risk of bile duct cancer. Another example is primary sclerosing cholangitis.

Infection - in Africa and Asia, many of the bile duct cancers are thought to be caused by infection with a parasite known as the liver fluke.

[Picture Credit: Liver Fluke]

Bile duct cancer, like other cancers, is not infectious and cannot be passed on to other people.

Signs and Symptoms of Bile Duct Cancer

People with bile duct cancer may experience the following symptoms or signs:

Jaundice, which is a yellowing of the skin and the whites of the eyes. When the bile duct is blocked, the liver cannot excrete bile, and the bile backs up into the bloodstream.

[Picture Credit: Jaundice]

Other symptoms of bile duct cancer include:

- Itching, caused by a buildup of bile salts and bilirubin in the body that is then deposited in the skin
- Fever
- Loss of appetite
- Weight loss
- Abdominal discomfort.

Diagnosis of Bile Duct Cancer

The following tests are commonly used to diagnose bile duct cancer:

Ultrasound Scan - This uses sound waves to make up a picture of the bile ducts and surrounding organs.

CT (Computerised Tomography) Scan - A CT scan takes a series of x-rays that build up a three-dimensional picture of the inside of the body.

Spiral CT scan - In this test, the X-ray machine rotates continuously around the body to make cross-sectional pictures.

Endoscopic retrograde cholangiopancreatography (ERCP) - is a specialised test used to examine the bile duct as it enters the duodenum. ERCP is performed by a gastroenterologist using a fibreoptic camera at the end of a flexible viewing tube. The tube is passed through the mouth and threaded through the stomach into the first part of the small intestine where the common bile duct enters. This test is commonly performed to examine the lining of the oesophagus and stomach, but is also very effective in detecting conditions that affect the bile ducts, including bile duct cancer, gallstones stuck in the bile duct, and abnormal narrowing of the bile duct. Dye can be injected through the tube into the bile duct opening to outline the bile ducts and detect obstruction. Biopsies or cell washings can be obtained to look for cancer cells. If a blockage is found, during the same procedure the gastroenterologist may be able to place a stent to keep the duct open and allow bile to drain.

Endoscopic Ultrasound Scan (EUS) - This scan is similar to an ERCP, but involves an ultrasound probe being passed down the endoscope to take an ultrasound scan of the bile ducts and surrounding structures.

Angiogram - This is a test to look at the blood vessels.

MRI (Magnetic Resonance Imaging) Scan - This test is similar to a CT scan but uses magnetism, instead of X-rays, to build up a detailed picture of areas of the body.

Angiogram - This is a test to look at the blood vessels.

PTC (Percutaneous Transhepatic Cholangiography) - This procedure is done following injection of a dye into the bile duct within the liver. X-rays are then taken to see if there is any abnormality or blockage of the duct(s).

Biopsy - There is no blood test that can specifically diagnose bile duct cancer. The diagnosis is confirmed by tissue sample obtained by biopsy by a surgeon, gastroenterologist, or interventional radiologist and a pathologist using a microscope to exam the cells obtained by that biopsy sample.

Laparotomy - An operation called a laparotomy is sometimes used to help diagnose bile duct cancer. The operation is carried out under a general anaesthetic.

Huguet, J.M., Lobo, M., Labrador, J.M., Boix, C., Albert, C., Ferrer-Barceló, L., Durá, A.B., Suárez, P., Iranzo, I., Gil-Raga, M., de Burgos, C.B. & Sempere. J. 2019.
"Biliary tract cancer, or cholangiocarcinoma, comprises a heterogeneous group of malignant tumors that can emerge at any part of the biliary tree. This group is the second most common type of primary liver cancer. Diagnosis is usually based on symptoms, which may be heterogeneous, and nonspecific biomarkers in serum and biopsy specimens, as well as on imaging techniques. Endoscopy-based diagnosis is essential, since it enables biopsy specimens to be taken. In addition, it can help with locoregional staging of distal tumors. Endoscopic retrograde cholangiopancreatography is a key technique for the evaluation and treatment of malignant biliary tumors. Correct staging of cholangiocarcinoma is essential in order to be able to determine the degree of resectability and assess the results of treatment. The tumor is staged based on the TNM classification of the American Joint Committee on Cancer. The approach will depend on the classification of the tumor. Thus, some patients with early-stage disease could benefit from surgery; complete surgical resection is the cornerstone of cure. However, only a minority of patients are diagnosed in the early stages and are suitable candidates for resection. In the subset of patients diagnosed with locally advanced or metastatic disease, chemotherapy has been used to improve

outcome and to delay tumor progression. The approach to biliary tract tumors should be multidisciplinary, involving experienced endoscopists, oncologists, radiologists, and surgeons."

Staging of Bile Duct Cancer

Staging is the process of finding out how far a cancer has spread. The stage (extent) of bile duct cancer is one of the most important factors in selecting treatment options and estimating a patient's outlook for recovery and outlook (prognosis).

Intrahepatic bile duct cancers (those starting within the liver) are staged separately from extrahepatic bile duct cancers.

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"The tumor is staged based on the TNM classification of the American Joint Committee on Cancer. The approach will depend on the classification of the tumor. Thus, some patients with early-stage disease could benefit from surgery; complete surgical resection is the cornerstone of cure. However, only a minority of patients are diagnosed in the early stages and are suitable candidates for resection. In the subset of patients diagnosed with locally advanced or metastatic disease, chemotherapy has been used to improve outcome and to delay tumor progression. The approach to biliary tract tumors should be multidisciplinary, involving experienced endoscopists, oncologists, radiologists, and surgeons."

The TNM system, used in staging, for all bile duct cancers contains three (3) key pieces of information:

- **T** describes whether the main tumour is still within the organ or whether it has invaded nearby organs or tissues.
- **N** describes whether the cancer spread to nearby (regional) lymph nodes
- **M** indicates whether the cancer has metastasised (spread) to other organs

Numbers or letters appear after T, N, and M to provide more details about each of these factors:

- The numbers 0 to 4 indicate increasing severity
- The letter X means that the cancer cannot be assessed

Treatment of Bile Duct Cancer

The main treatment for bile duct cancer is surgery, however, surgery is not always possible. The type of surgery depends on where the cancer is in the bile duct. It also depends on whether it has spread to other nearby organs.

Surgery can also involve surgical removal of the bile duct or removal of the bile duct and part of the liver.

In cases of unresectable cancers (those that cannot be operated, chemotherapy and/or radiation therapy may be used first to try to shrink the cancer and make it resectable. Radiation therapy and/or chemotherapy may help to shrink or slow the growth of the cancer for a time.

Treatment for bile duct cancer depends upon where the cancer is located and whether it is possible for it to be completely removed by surgery. Unfortunately, those afflicted with this cancer tend to be older and may be unable to tolerate and recover from a significant operation. The decision regarding surgery needs to be individualized for the specific patient and their situation.

Photodynamic therapy is another alternative to help shrink the tumour and control symptoms.

Radioembolization is an option if the tumour cannot be removed by surgery. With radioembolization, small amounts of radioactive material are injected into the arteries that supply the tumour in hopes of shrinking the tumour size by impeding its blood supply.

ERCP may be used to stent the bile duct, keeping it open to allow bile drainage from the liver and gallbladder into the intestine. This is often very helpful in controlling symptoms but does not treat the tumour itself.

Messina, C., Merz, V., Frisinghelli, M., Trentin, C., Grego, E., Veccia, A., Salati, M., Messina, M., Carnaghi, C. & Caffo, O. 2019.
Background: The role of adjuvant chemotherapy (ACT) for resected biliary tract cancer (BTC) is still unclear and there is no specific recommendation by international guidelines.
Aim: To perform a meta-analysis of randomized clinical trials (RCTs) to better define the clinical benefit and risks of ACT or observation in resected BTC.
Method: A systematic literature search of Pubmed, Embase, and the Cochrane Library was performed up to April 2019. A meta-analysis was carried out using the random effects model.
Results: ACT provided a mild improvement in recurrence free survival (RFS) (HR:0.83, 95%CI 0.69-0.99) and no effect on overall survival (OS) (HR:0.91, 95%CI 0.75-1.09). Similarly, ACT showed no effect on OS in lymph-node positive subgroup (HR:0.84, 95% CI 0.65-1.08) and surgical margin positive subgroup (HR:0.95, 95%CI 0.69-1.31). Moreover, ACT led to a substantial increase of chemotherapy-associated adverse events (RR:3.03, 95%CI 2.22-4.15).

Navarro, J.G. & Kang, C.M. 2019.
"The oncologic safety and feasibility of laparoscopic radical cholecystectomy for a preoperatively suspected gallbladder cancer is continually being challenged even in an era of minimally invasive surgery. A seventy-four-year-old woman was presented in the outpatient department with a history of fever, abdominal pain, and vomiting. CT scan showed an irregular wall thickening of the body to the cystic duct of the gallbladder and portocaval lymph node. In addition, EUS revealed no subserosal invasion of the tumor. PET scan showed an intense FDG uptake of in the gallbladder and in the portocaval lymph node. The laparoscopic radical cholecystectomy was performed with 6 trocars. The procedure included simple cholecystectomy, hepatoduodenal and aortocaval lymphadenectomy, and common bile duct resection. The hepaticojejunal anastomosis was constructed laparoscopically, while the jejunal continuity was established via an extracorporeal anastomosis. The patient was discharged on the 7th postoperative day with no complications and adjuvant chemotherapy was started on the 14th day after surgery. Based on our experienced,

laparoscopic radical cholecystectomy with combined common bile duct resection is technically safe and feasible."

Bolm, L., Kaesmann, L., Bartscht, T., Schild, S.E. & Rades, D. 2017.
BACKGROUND/AIM: The role of radio(chemo) therapy for non-metastatic bile duct cancer is not well defined. This study provides additional data for this rare situation.
PATIENTS AND METHODS: Data of eight patients receiving radio(chemo)therapy for non-metastatic bile duct cancer were retrospectively analyzed regarding local control, metastases-free survival and overall survival. In addition to the entire cohort, five tumor- or treatment-related factors were investigated: tumor stage, histologic grading, point in time of radio(chemo)therapy, upfront surgery and concurrent chemotherapy.
RESULTS: Median overall survival was 37 months. Overall survival rates at 3 and 5 years were 56% and 38%, respectively. Lower histologic grading was significantly associated with better overall survival (p=0.042). Metastases-free survival rates at 3 and 5 years were 38% and 19%, while local control rates were 43% and 21%, respectively. Concurrent radiochemotherapy (vs. radiotherapy alone) resulted in significantly improved local control (p=0.014).
CONCLUSION: Radiochemotherapy can achieve promising results in selected patients with non-metastatic bile duct cancer.

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The *South African National Clinical Trials Register* provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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