Cancer Association of South Africa (CANSA)

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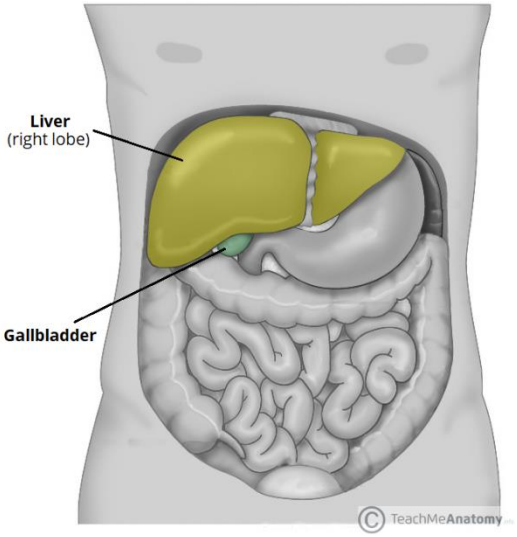
Fact Sheet on Cancer of the Gallbladder

Introduction

The gallbladder is part of the biliary system, which is part of the gastrointestinal tract. It lies in the right upper portion of the abdomen and affixed to the undersurface of the liver. It is approximately the size of a small pear. Its primary function is to concentrate and store vile which is produced by the liver. The stored bile is released via the common bile duct and joins the pancreatic duct where it forms the Ampulla of Vater. The release of bile from the gallbladder is stimulated by the presence of food in the stomach and duodenum.



Cancer of the Gallbladder

Key points of Gallbladder Cancer:

Gallbladder Cancer is rare and nearly all of them are adenocarcinomas. An adenocarcinoma is a cancer that starts in gland-like cells that line many surfaces of the body, including the inside the digestive system.

Gallbladder cancer is a disease in which malignant (cancer) cells form in the tissues of the gallbladder.

- Being female can increase the risk of developing gallbladder cancer.
- Signs and symptoms of gallbladder cancer include jaundice, fever, and pain.
- Gallbladder cancer is difficult to detect (find) and diagnose early.

Recio-Boiles, A., Kashyap, S. & Babiker, H.M. 2020. Gallbladder cancer. ***In***: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. 2020 Nov 19.

"Gallbladder cancer (GC) is a rare malignancy but represents almost 50% of all biliary tract cancer. Biliary cancers are highly fatal malignancies with a 5-year survival rate of 17.6% (2007 to 2013). The prognosis of gallbladder cancer is poor due to the aggressive tumor biology, late presentation, complicated anatomic position, and advanced stage at diagnosis. Locally advanced and metastatic disease treatment is with palliative chemotherapy. Conversely, early-stage is potentially curative with surgical resection followed by adjuvant therapy."

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Sharma. A., Sharma,K.L., Gupta, A., Yadak, A. & Kumar, A. 2019.
"Gallbladder cancer is a malignancy of biliary tract which is infrequent in developed countries but common in some specific geographical regions of developing countries. Late diagnosis and deprived prognosis are major problems for treatment of gallbladder carcinoma. The dramatic associations of this orphan cancer with various genetic and environmental factors are responsible for its poorly defined pathogenesis. An understanding to the relationship between epidemiology, molecular genetics and pathogenesis of gallbladder cancer can add new insights to its undetermined pathophysiology. Present review article provides a recent update regarding epidemiology, pathogenesis, and molecular genetics of gallbladder cancer. We systematically reviewed published literature on gallbladder cancer from online search engine PubMed."

Incidence of Cancer of the Gallbladder
The outdated National Cancer Registry (2017), known for under reporting, does not provide any information about Cancer of the Gallbladder. It combines Cancer of the Gallbladder with that of Cancer of the Liver.

According to **Bruni, *et al*.,** (2019), the burden of Cancer of the Gallbladder for South Africa for 2018 is estimated as (based on Globocan estimates):

- Annual number of Cancer of the Gallbladder cases 574
- Annual number of Cancer of the Gallbladder deaths 287

Risk Factors for Cancer of the Gallbladder
Doctors do not know exactly what causes gallbladder cancer. They do know that, like all cancer, an error, known as a mutation, in a person's DNA causes uncontrolled rapid growth of cells.

Chronic inflammation of the gallbladder is the biggest risk factor for gallbladder cancer.

Some studies have shown that if one has a first degree relative with gallbladder cancer one is five times more likely to develop gallbladder cancer.

People who smoke or work in the metal or rubber industries are more likely to develop gallbladder cancer.

Several other risk factors for gallbladder cancer are being researched, for example, diet, being overweight and taking hormone replacement therapy (HRT).

Lugo, A., Peveri, G. & Gallus, S. 2020.
"The few studies on the association of smoking with gallbladder cancer risk have given conflicting results. Here, we provide the most accurate and up-to-date quantification of the effect of cigarette smoking on gallbladder cancer risk, and investigate for the first time the dose-response relationships. Using an innovative approach for the identification of publications, we conducted a systematic review and meta-analysis of epidemiological studies published until March 2019 on the association of smoking with gallbladder cancer risk. Pooled relative risks (RRs) for smoking were estimated using random-effects models; one-stage random-effects log-linear models were used for dose-response relationships. Out of 22 eligible articles, 20 (11 case-control and 9 cohort studies) were included in the meta-analysis, for a total of 4,676 gallbladder cancer cases. Compared to never smokers, the pooled RR was 1.33 (95% confidence interval [CI]: 1.17-1.51) for current and 1.07 (95% CI: 0.94-1.23) for former smokers. The risk of gallbladder cancer increased linearly with smoking intensity and duration,

the RR being 1.60 (95% CI: 1.21-2.11) for 30 cigarettes/day and 1.25 (95% CI: 1.01-1.56) for 30 years of smoking. There was a nonsignificant linear decrease in gallbladder cancer risk with increasing time since quitting, compared to current smokers. Former smokers reached the risk of those who had never smoked 20 years after quitting. This comprehensive meta-analysis suggests a moderately but significantly higher risk of gallbladder cancer for current but not former smokers. We also provide the first report of a linear increase in gallbladder cancer risk according to smoking intensity and duration."

Schmidt, M.A., Marcano-Bonilla, L. & Roberts, L.R. 2019.
"Gallbladder cancer (GBC) is a form of hepatobiliary malignancy that develops from the mucosal lining of the gallbladder. The early development of gallbladder cancer is usually asymptomatic and gallbladder cancer has a high propensity to metastatic dissemination, thus most patients are diagnosed at intermediate to advanced stages for which there is no curative treatment. Consequently, gallbladder cancer is highly lethal. Though the overall global incidence of gallbladder cancer is low, there is marked geographic variation and ethnic communities in Asia as well as Native American populations in both North and South America are affected disproportionately. This article provides a comprehensive overview of the current epidemiology and risk and protective factors associated with gallbladder cancer development. In addition, the current knowledge on environmental and genetic risk associations for gallbladder cancer and the need for additional large-scale genome wide association studies (GWAS) are discussed."

Signs and Symptoms of Cancer of the Gallbladder
Signs and symptoms of Cancer of the Gallbladder may be caused by gallbladder cancer or by other conditions. Check with a medical doctor if any of the following signs and symptoms are present:

- Jaundice (yellow discolouration of the skin and whites of the eyes)
- Pain and/or discomfort above the stomach
- Loss of appetite
- Fever
- Nausea and vomiting
- Abdominal bloating
- Passing dark yellow urine
- Passing pale-coloured faeces
- Presence of a lump or lumps in the abdomen
- Itchy skin

Diagnosis of Cancer of the Gallbladder
Gallbladder cancer is uncommon. When gallbladder cancer is discovered at its earliest stages, the chance for a cure is very good.

In addition to a physical examination, the following tests may be used to diagnose gallbladder cancer:

Biopsy - the removal of a small amount of tissue for examination under a microscope. The sample of tissue can be taken 1 of several ways:

- During a surgery
- With a minimally invasive surgical technique known as laparoscopy
- With a fine needle or thick needle aspiration (a core biopsy), using a computed tomography (CT or CAT) scan or ultrasound to guide the needle placement

- In some cases, a biopsy is done by passing an endoscope through the mouth, past the stomach, and into the first part of the intestine

Endoscopic retrograde cholangiopancreatography (ERCP) – while the patient is lightly sedated, the doctor inserts an endoscope through the mouth, down the oesophagus, and into the stomach and small bowel. A smaller tube or catheter is passed through the endoscope and into the bile ducts.

Percutaneous cholangiography - a thin needle is inserted through the skin and into the gallbladder area. A dye is injected through the needle so that a clear image will show up on x-rays. By looking at the x-rays, the doctor may be able to see whether there is a tumour in the gallbladder

Laparoscopy – use is made of an endoscope to look at the gallbladder and other internal organs. The tube is inserted through a small incision in the abdomen

Computed tomography (CT or CAT) scan

Magnetic resonance imaging (MRI

Ultrasound

Endoscopic ultrasonography - a special endoscope, which is a long flexible scope, is inserted through the mouth after sedation. It can reach the stomach and some of the intestine. It has an ultrasound probe at the end that can be used to look for tumours and guide biopsy with a small needle

Positron emission tomography (PET) or PET-CT scan

Various blood tests – Liver function test; CA 19-9 tumour marker test; Carcinoembryonic antigen (CEA) test

Ramachandran, A., Srivastava, D.N. & Madhusudhan, K.S. 2021.
"Gallbladder cancer is the most common malignancy of the biliary tract. It is also the most aggressive biliary tumor with the shortest median survival duration. Complete surgical resection, the only potentially curative treatment, can be accomplished only in those patients who are diagnosed at an early stage of the disease. Majority (90%) of the patients present at an advanced stage and the management involves a multidisciplinary approach. The role of imaging in gallbladder cancer cannot be overemphasized. Imaging is crucial not only in detecting, staging, and planning management but also in guiding radiological interventions. This article discusses the role of a radiologist in the diagnosis and management of gallbladder cancer."

John, S., Moyana, T., Shabana, W., Walsh, C. & McInnes, M.D.F. 2020.
"Gallbladder cancer is an uncommon malignancy with an overall poor prognosis. The clinical and imaging presentation of gallbladder cancer often overlaps with benign disease, making diagnosis difficult. Gallbladder cancer is most easily diagnosed on imaging when it presents as a mass replacing the gallbladder. At this stage, the prognosis is usually poor. Recognizing the features of gallbladder cancer early in the disease can enable complete resection and improve prognosis. Recognition of the patterns of wall enhancement on computed tomography can help differentiate gallbladder cancer from benign disease. Gallbladder wall thickening without pericholecystic fluid presenting in an older patient with raised alkaline phosphatase should raise concern regarding gallbladder cancer. Gallbladder polyps in high-risk individuals need close surveillance or surgery as per guidelines. Small gallbladder cancers in the neck can present as biliary dilatation or cholecystitis, and careful examination of this area is needed to assess for lesion. The imaging appearance of gallbladder

cancer is reviewed and supported by local institutional data. Features that differentiate it from its common mimics enabling earlier diagnosis are described."

Tiwari, P.K. 2020.
"Gallbladder cancer (GBC) is associated with various nongenetic and genetic factors. Lack of specific and sensitive diagnostic markers has significantly impacted the mortality of this disease. Here we discuss the recent discovery of epigenetic changes that show great promise as diagnostic biomarkers as well as potential therapeutic targets for GBC."

Moradi, F. & Iagaru, A. 2020.
"F-FDG-PET is complementary to conventional imaging in patients with clinical suspicion for exocrine pancreatic malignancies. It has similar if not superior sensitivity and specificity for detection of cancer, and when combined with contrast enhanced anatomic imaging of the abdomen, can improve diagnostic accuracy and aid in staging, assessment for resectability, radiation therapy planning, and prognostication. Various metabolic pathways affect FDG uptake in pancreatic ductal adenocarcinoma. The degree of uptake reflects histopathology, aggressiveness, metastatic potential, and metabolic profile of malignant cell and their interaction with cancer stroma. After treatment, FDG-PET is useful for detection of residual or recurrent cancer and can be used to assess and monitor response to therapy in unresectable or metastatic disease. The degree and pattern of uptake combined with other imaging features are useful in characterization of incidental pancreatic lesions and benign processes such as inflammation. Several novel PET radiopharmaceuticals have been developed to improve detection and management of pancreatic cancer. Gallbladder carcinoma is typically FDG avid and when anatomic imaging is equivocal PET can be used to assess metastatic involvement with high specificity and inform subsequent management."

Treatment of Cancer of the Gallbladder
Surgery - is a common treatment for gallbladder cancer. It may be performed to completely remove the tumour if the cancer is still localized, or to relieve symptoms or pain if the cancer is more widespread. The procedure to remove the gallbladder is called a cholecystectomy.

D'Souza, M.A., Valdimarsson, V.T., Campagnaro, T., Cauchy, F., Chatzizacharias, N.A., D'Hondt, M., Dasari, B., Ferrero, A., Franken, L.C., Fusai, G., Guglielmi, A., Hagendoorn, J., Hidalgo Salinas, C., Hoogwater, F.J.H., Jorba, R., Karanjia, N., Knoefel, W.T., Kron, P., Lahiri, R., Langella, S., Le Roy, B., Lehwald-Tywuschik, N., Lesurtel, M., Li, J., Lodge, J.P.A., Martinou, E., Molenaar, I.Q., Nikov, A., Poves, I., Rassam, F., Russolillo, N., Soubrane, O., Stättner, S., van Dam, R.M., van Gulik, T.M., Serrablo, A., Gallagher, T.M., Sturesson, C. & E-AHPBA scientific and research committee. 2020.
Background: Hepatopancreatoduodenectomy (HPD) is an aggressive operation for treatment of advanced bile duct and gallbladder cancer associated with high perioperative morbidity and mortality, and uncertain oncological benefit in terms of survival. Few reports on HPD from Western centers exist. The purpose of this study was to evaluate safety and efficacy for HPD in European centers.
Method: Members of the European-African HepatoPancreatoBiliary Association were invited to report all consecutive patients operated with HPD for bile duct or gallbladder cancer between January 2003 and January 2018. The patient and tumor characteristics, perioperative and survival outcomes were analyzed.
Results: In total, 66 patients from 19 European centers were included in the analysis. 90-day mortality rate was 17% and 13% for bile duct and gallbladder cancer respectively. All factors predictive of perioperative mortality were patient and disease-specific. The three-year overall survival excluding 90-day mortality was 80% for bile duct and 30% for gallbladder cancer (P = 0.013). In multivariable analysis R0-resection had a significant impact on overall survival.

Conclusion: HPD, although being associated with substantial perioperative mortality, can offer a survival benefit in patient subgroups with bile duct cancer and gallbladder cancer. To achieve negative resection margins is paramount for an improved survival outcome.

Krell, R.W. & Wei, A.C. 2019.
"Gallbladder cancer is the most common biliary tract malignancy. Margin-clearing surgery is a cornerstone of gallbladder cancer management, but several aspects of surgical management are controversial."

Chemotherapy – is often prescribed in addition to surgery to help prevent recurrence of gallbladder cancer.

Recio-Boiles, A., Kashyap, S. & Babiker, H.M. 2020.
"Gallbladder cancer (GC) is a rare malignancy but represents almost 50% of all biliary tract cancer. Biliary cancers are highly fatal malignancies with a 5-year survival rate of 17.6% (2007-2013). The prognosis of GC is poor due to the aggressive tumor biology, late presentation, complicated anatomic position, and advanced stage at diagnosis. Locally advanced and metastatic disease is treated with palliative chemotherapy. Conversely, early stage is potentially curative with surgical resection followed by adjuvant therapy."

Javle, M., Zhao, H. & Abou-Alfa, C.K. 2019.
"Gallbladder cancer is an aggressive cancer that continues to be an important health care issue in certain regions of the world such as Southeast Asia and Latin America. Most patients are diagnosed at an advanced, unresectable stage and systemic therapy is their only option. Gallbladder cancer patients have traditionally been included in clinical trials for biliary tract cancer. Thus, systemic chemotherapy options for this cancer are similar to those for cholangiocarcinoma, including gemcitabine and cisplatin in the first line and FOLFOX in the second-line setting. Ongoing phase III clinical trials may change the systemic therapy paradigm for this cancer. Molecular profiling has indicated important genetic differences between gallbladder cancer and cholangiocarcinoma, which affects choice of targeted therapy. Her2/neu amplification, PIK3CA mutations and DNA repair genetic aberrations are relatively frequent and represent actionable targets for this cancer."

Radiation therapy - may be prescribed to shrink the size of a tumour or to help kill cancer cells that may be left after surgery.

Verma, V. & Crane, C.H. 2019.
"Locally advanced gallbladder cancer poor prognosis due to a high distant metastatic rate and poor overall disease control. The impact of standard therapeutic options is unfortunately modest. Due to the rarity of the disease, evidence-based management continues to evolve. The goal of this review is to highlight the contemporary landscape of radiation therapy for gallbladder cancer. First, the rationale for radiation therapy is described. This includes the risk of locoregional recurrence following resection based on patterns-of-failure data, along with the high locoregional disease burden being a frequent cause morbidity and mortality in unresected cases. Additionally, improvements in systemic therapy over the next decade could shift contemporary patterns of failure more towards proportionally higher locoregional recurrence rates. Second, clinical data of radiation therapy for gallbladder cancer are discussed. These include consideration of postoperative chemoradiotherapy for margin- and/or node-positive cases. Patients with localized unresectable disease could benefit from ablative radiation therapy, based on promising data in non-gallbladder cancer pancreaticobiliary neoplasms. The use of advanced radiation therapy technologies such as proton beam therapy, as a means to deliver ablative radiation therapy in a potentially safer manner, is also

mentioned. Lastly, the emerging concept of neoadjuvant therapy for gallbladder cancer is also described, in efforts to allow more patients to receive curative resection."

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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Sources and References Consulted and/or Utilised

Bruni, L., Albero, G., Serrano, B., Mena, M., Gómez, D., Muñoz, J., Bosch, F.X.& de Sanjosé, S. 2019. ICO/IARC Information Centre on HPV and Cancer (*HPV Information Centre*). Human Papillomavirus and Related Diseases in South Africa. Summary Report 17 June 2019.

D'Souza, M.A., Valdimarsson, V.T., Campagnaro, T., Cauchy, F., Chatzizacharias, N.A., D'Hondt, M., Dasari, B., Ferrero, A., Franken, L.C., Fusai, G., Guglielmi, A., Hagendoorn, J., Hidalgo Salinas, C., Hoogwater, F.J.H., Jorba, R., Karanjia, N., Knoefel, W.T., Kron, P., Lahiri, R., Langella, S., Le Roy, B., Lehwald-Tywuschik, N., Lesurtel, M., Li, J., Lodge, J.P.A., Martinou, E., Molenaar, I.Q., Nikov, A., Poves, I., Rassam, F., Russolillo, N., Soubrane, O., Stättner, S., van Dam, R.M., van Gulik, T.M., Serrablo, A., Gallagher, T.M., Sturesson, C. & E-AHPBA scientific and research committee. 2020. Hepatopancreatoduodenectomy -a controversial treatment for bile duct and gallbladder cancer from a European perspective. *HPB (Oxford).* 2020 Sep;22(9):1339-1348.

Gallbladder
https://teachmeanatomy.info/abdomen/viscera/gallbladder/
https://www.ncbi.nlm.nih.gov/books/NBK482488/

Gallbladder Cancer
https://www.cancer.gov/types/gallbladder/patient/gallbladder-treatment-pdq#_1
https://www.mayoclinic.org/diseases-conditions/gallbladder-cancer/symptoms-causes/syc-20353370
https://www.cancer.org/cancer/gallbladder-cancer/about/what-is-gallbladder-cancer.html
https://www.cancer.net/cancer-types/gallbladder-cancer/symptoms-and-signs
https://www.nhs.uk/conditions/gallbladder-cancer/
https://www.healthline.com/health/gallbladder-cancer
https://emedicine.medscape.com/article/278641-overview
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3104187/
https://www.msdmanuals.com/home/liver-and-gallbladder-disorders/gallbladder-and-bile-duct-disorders/tumors-of-the-bile-ducts-and-gallbladder
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4649107/
https://www.cancervic.org.au/cancer-information/types-of-cancer/gall_bladder_cancer/gall-bladder-cancer-overview.html
https://medlineplus.gov/gallbladdercancer.html
https://www.health.harvard.edu/a_to_z/gallbladder-and-bile-duct-cancer-a-to-z
https://www.wcrf.org/dietandcancer/gallbladder-cancer
https://www.cancercenter.com/cancer-types/gallbladder-cancer/symptoms

Gallbladder Picture
https://teachmeanatomy.info/abdomen/viscera/gallbladder/

Javle, M., Zhao, H. & Abou-Alfa, C.K. 2019. Systemic therapy for gallbladder cancer. *Chin Clin Oncol* 8(4):44, Aug, 2019.

John, S., Moyana, T., Shabana, W., Walsh, C. & McInnes, M.D.F. 2020. Gallbladder cancer: imaging appearance and pitfalls in diagnosis. *Can Assoc Radiol J.* 2020 Nov;71(4):448-458.

Krell, R.W. & Wei, A.C. 2019. Gallbladder cancer: surgical management. *Chin Clin Oncol*, 8(4):36. Aug 2019.

Lugo, A., Peveri, G. & Gallus, S. 2020. Should we consider gallbladder cancer a new smoking-related cancer? A comprehensive meta-analysis focused on dose-response relationships. *Int J Cancer*. 2020 Jun 15;146(12):3304-3311.

Moradi, F. & Iagaru, A. 2020. The role of positron emission tomography in pancreatic cancer and gallbladder cancer. *Semin Nucl Med*. 2020 Sep;50(5):434-446.

Ramachandran, A., Srivastava, D.N. & Madhusudhan, K.S. 2021. Gallbladder cancer revisited: the evolving role of a datiologist. *Br J Radiol*. 2021 Jan 1;94(1117):20200726.

Recio-Boiles, A., Kashyap, S. & Babiker, H.M. 2020. Cancer, Gallbladder. **In**: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. 2020 Apr 21.

Sharma. A., Sharma,K.L., Gupta, A., Yadak, A. & Kumar, A. 2019. Gallbladder cancer epidemiology, pathogenesis and molecular genetics: recent update. *World J Gastroenterol*. 2017 Jun 14;23(22):3978-3998. doi: 10.3748/wjg.v23.i22.3978.

Schmidt, M.A., Marcano-Bonilla, L. & Roberts, L.R. 2019. Gallbladder cancer: epidemiology and genetic risk associations. *Chin Clin Oncol*. 2019 Aug;8(4):31. doi: 10.21037/cco.2019.08.13.

Shukla, S.K., Singh, G., Shahi, K.S., Bhuvan, & Pant, P. 2018. Staging, treatment, and future approaches of gallbladder carcinoma. *J Gastrointest Cancer*, 49(1):9-15, Mar 2018.

Tiwari, P.K. 2020. Epigenetic biomarkers in gallbladder cancer. *Trends Cancer*. 2020 Jul;6(7):540-543.

Verma, V. & Crane, C.H. 2019. Contemporary Perspectives on the use of radiation therapy for locally advanced gallbladder cancer. *Chin Clin Oncol*, 8(4):41, Aug 2019.