



Treatment of Gall Bladder Cancer: A Review

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ABSTRACT: Cancer of the gallbladder is rare and more common in women and Native Americans. Gallbladder cancer is a comparatively rare cancer and has poor outcome due to their anatomy and location. It is hard to diagnose gallbladder cancer in its early stages. Sometimes doctors find it when they remove the gallbladder for another reason. But people with gallstones rarely have gallbladder cancer. Because it is often found late, it can be hard to treat gallbladder cancer. Treatment options include surgery, chemotherapy, radiation or a combination. It is fifteen uncommon cancers in the world with high mortality rate. The diagnosis is made very late due to its silent course. The majority of patients have advanced disease at the time of presentation which carries a poor prognosis. The modes of spread of gall bladder carcinoma are direct, lymphatic, vascular, neural, intraperitoneal and intraductal. Ultra Sound, CT and MRI are helpful in diagnosis and staging of the disease. Surgery remains the mainstay of treatment and chemotherapy has a very limited role. © 2011 IGJPS. All rights reserved.

KEYWORDS: Gall Bladder Cancer; Women; Chemotherapy.

†This article is dedicated to Late Smt. Rani Verma M/O Dr. Nitin Verma, who was died due to Gall Bladder cancer.

INTRODUCTION

Gall bladder is a pear-shaped organ under your liver. It stores bile, a fluid made by your liver to digest fat. As your stomach and intestines digest food, your gallbladder releases bile through a tube called the common bile duct. The duct connects your gallbladder and liver to your small intestine. Symptoms include jaundice (yellowing of the skin and whites of the eyes), pain above the stomach, fever, nausea, vomiting, bloating and lumps in the abdomen [1]. The gallbladder is a pear-shaped organ that lies just under the liver in the upper abdomen. The gallbladder stores bile, a fluid made by the liver to digest fat. When food is being broken down in the stomach and intestines, bile is released from the gallbladder through a tube called the common bile duct, which connects the gallbladder and liver to the first part of the small intestine. The wall of the gallbladder has 3 main layers of tissue. Mucosal

(innermost) layer, Muscularis (middle, muscle) layer and Serosal (outer) layer. Between these layers is supporting connective tissue. Primary gallbladder cancer starts in the innermost layer and spreads through the outer layers as it grows. The poor prognosis associated with GBC is thought to be related to advanced stage at diagnosis, which is due both to the anatomic position of the gallbladder, and the vagueness and nonspecificity of symptoms.

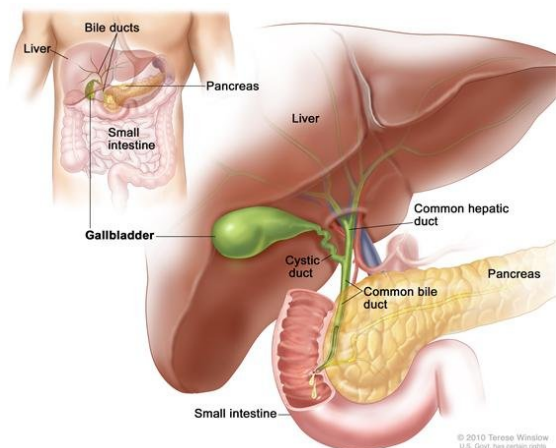


Fig. 1. Anatomy of the gallbladder.

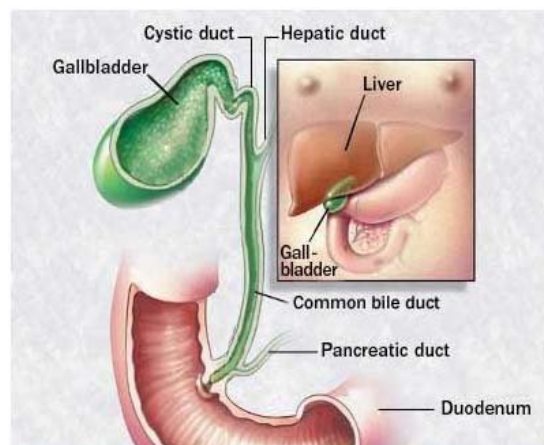


Fig. 2. Development of tumor blocks in the Gall bladder.

Epidemiology

Globally, there is a prominent geographic variability in GBC incidence that correlates with the prevalence of cholelithiasis. High rates of GBC are seen in South American countries, particularly Chile, Bolivia, and Ecuador, as well as some areas of India, Pakistan, Japan and Korea [2]. In Chile, mortality rates from GBC are the highest in the world. These populations all share a high prevalence of gallstones and/or salmonella infection, both recognized risk factors for GBC [3]. Both genetic factors and socioeconomic issues that delay or prevent access to cholecystectomy for gallstones are thought to be contributory [4]. North America is considered a low incidence area. In the United States, GBC is the most common cancer arising in the biliary tract [5]. Estimates from the Surveillance, Epidemiology and End Results database reveal an incidence of 1 to 2 cases per 100,000 population in the US [5]. In contrast to the general population, GBC is the most common malignancy in both Southwestern Native Americans and in Mexican Americans [6]. The incidence of gall bladder disease is high among people living near the Ganga and its tributaries, says the largest-ever study of the local population over six years in this region the prevalence. Recent study shows the high rate of gall bladder in the Bihar, located near the river Gandak. About 20,000 and 30,000 people develop gall bladder disease each year because of the environmental factors in Uttar Pradesh and Bihar. In addition to geography, there are also age, race, and gender-related differences in the incidence of GBC. Incidence steadily increases with age, women are affected two to six times more often than men [7], and GBC is more common in Caucasians than in blacks [8]. At least some data suggest that the incidence is increasing in younger individuals [9].

Risk factor and etiology

In spite of high frequency and grave mortality risk factors for this disease have not been clearly understood [10]. Because of their elevated humanity rate researches found some risk factor such as gallstones, duration of disease, dietary factors including vitamin intake and smoking. Numerous individuals suggested that the reality may be a corollary of the older age of the population [11]. Even though, it occurs most often in people with porcelain gall bladders. Due to recurring [inflammation](#) and from passing gallstones leads to calcification of the gall bladder. Gallstones are the most common risk factor for gallbladder cancer because of these are so hard, rock-like formations of cholesterol and other substances that form in the gallbladder and can cause chronic inflammation ultimately developed the growth of undefined cells. Approximately, 3 out of 4 people with gallbladder cancer have gallstones but this is quite

rare. Another second condition is Porcelain gallbladder in which the wall of the gallbladder becomes covered with calcium deposits. It sometimes occurs after long-term inflammation of the gallbladder and this has high possibility to [developing](#) gallbladder cancer [12]. According to the report, gallbladder cancer occurs more than twice as often in women. Gallstones and gallbladder inflammation are the 2 important risk factors for gallbladder cancer and are also much more common in women than men. Gallbladder cancer can occur in younger people, but it's seen mainly in older people. The average age of people when they are diagnosed is 73. Almost 3 out of 4 people with gallbladder cancer are older than age 65 when it is found. Studies also suggested the Obesity or overweight or obese than people without this disease a risk factor for gallstones, and link to cancer. Most important risk factor are, Choledochal cysts are bile-filled sacs that are connected to the tube that carries bile from the liver and gallbladder to the small intestine. The cysts can grow over time and may contain as much as 1 to 2 quarts of bile. The cells lining the sac often have areas of pre-cancerous changes, which increase a person's risk for developing gallbladder cancer [13].

The pancreas is another organ that releases fluids through a duct into the small intestine to help digestion. This duct normally meets up with the common bile duct just as it enters the small intestine. Due to abnormalities in the bile duct that allow juice from the pancreas to reflux (flow backward) into the bile ducts. This backward flow also prevents the bile from being emptied through the bile ducts as quickly as normal. Abnormalities passing of bile involved in the DNA damage and initiate the uncontrolled growth of cell.

A gallbladder polyp is a growth that bulges out from the surface of the inner gallbladder wall. Some polyps are formed by cholesterol deposits in the gallbladder wall. Others may be small tumors (either cancerous or benign) or may be caused by inflammation. Polyps larger than 1 centimeter (almost a half inch) are more likely to be cancerous, so doctors often advise removing the gallbladder in patients with gallbladder polyps that size or larger. Typhoid, chronically infected with salmonella and those who are carriers of the disease having more chance to develop gallbladder cancer than those not infected. But typhoid is rare in the United States. Some chemical have been identified as risk factor for gallbladder cancer nitrosamines, rubber and textile industries but still is not common and clear [14].

Certain factors affect the prognosis (chance of recovery) and treatment options: The prognosis (chance of recovery) and treatment options depend on the following:

- (a) The stage of the cancer (whether the cancer has spread from the gallbladder to other places in the body).
- (b) Whether the cancer can be completely removed by surgery.
- (c) The type of gallbladder cancer (how the cancer cell looks under a microscope).
- (d) Whether the cancer has just been diagnosed or has recurred (come back).

Stages of gall bladder cancer

There are five stages: stage 0 (zero) and stages I through IV (one through four), depending on how far they have grown. These are defining common pathway of cancer and also described, how many possibility to cure the cancer. TNM is an abbreviation for tumor (T), node (N), and metastasis (M) and three factors to determine the stage of cancer like Location, their place and largamente of the primary tumor? (**Tumor, T**); Tumor spread to the lymph nodes? (**Node, N**); the cancer metastasized to other parts of the body? (**Metastasis, M**)

Tumor	Stage information
TX	The primary tumor cannot be evaluated.
T0	No evidence of cancer was found in the gallbladder.
Tis	This refers to carcinoma (cancer) in situ, which means that the tumor remains in a pre-invasive state and its spread, if any, is very confined.
T1	The tumor is only in the gallbladder and has only invaded the lamina propria (a type of connective tissue found under the

thin layer of tissue covering a mucous membrane) or muscle layer.

T1a The tumor has invaded the lamina propria.

T1b The tumor has invaded the muscle layer.

T2 The tumor has invaded the perimuscular connective tissue (the layer between the muscle layer and the serosa) but has not extended beyond the serosa (the outer layer) or into the liver.

T3 The tumor extends beyond the gallbladder and/or has invaded the liver and/or one other adjacent organ or structure, such as the stomach, duodenum (part of the small bowel), colon, or pancreas.

T4 The tumor has invaded the main portal vein or hepatic artery or has invaded more than one organ or structure beyond the liver.

Node The “N” in the TNM staging system stands for lymph nodes, the tiny, bean-shaped organs that help fight infection. Lymph nodes near the gallbladder are called regional lymph nodes.

NX The regional lymph nodes cannot be evaluated.

N+0 There is no regional lymph node metastasis.

N1 There is regional lymph node metastasis.

N2 There is more distant lymph node metastasis.

M+0 There is no distant metastasis.

M1 There is metastasis to one or more other parts of the body.

Stages of gall bladder cancer

The following stages are used for gallbladder cancer:

Stage 0 (Carcinoma in Situ): In stage 0, abnormal cells are found in the inner (mucosal) layer of the gallbladder. These abnormal cells may become cancer and spread into nearby normal tissue. Stage 0 is also called carcinoma in situ.

Stage I: In stage I, cancer has formed and has spread beyond the inner (mucosal) layer to a layer of tissue with blood vessels or to the muscle layer.

Stage II: In stage II, cancer has spread beyond the muscle layer to the connective tissue around the muscle.

Stage IIIA: In stage IIIA, cancer has spread through the thin layers of tissue that cover the gallbladder and/or to the liver and/or to one nearby organ (such as the stomach, small intestine, colon, pancreas, or bile ducts outside the liver).

Stage IIIB: In this stage, cancer has spread to nearby lymph nodes and beyond the inner layer of the gallbladder to a layer of tissue with blood vessels or to the muscle layer; or beyond the muscle layer to the connective tissue around the muscle; or through the thin layers of tissue that cover the gallbladder and/or to the liver and/or to one nearby organ (such as the stomach, small intestine, colon, pancreas, or bile ducts outside the liver).

Stage IVA: In stage IVA, cancer has spread to a main blood vessel of the liver or to 2 or more nearby organs or areas other than the liver. Cancer may have spread to nearby lymph nodes.

Stage IVB: Lymph nodes along large arteries in the abdomen and/or near the lower part of the backbone; or to organs or areas far away from the gallbladder [15].

For gallbladder cancer, stages are also grouped according to how the cancer may be treated. There are two treatment groups:

1. Localized (Stage I): Cancer is found in the wall of the gallbladder and can be completely removed by surgery.
2. Unresectable, recurrent, or metastatic (Stage II, Stage III, and Stage IV): Unresectable cancer cannot be removed completely by surgery. Most patients with gallbladder cancer have unresectable cancer. Recurrent cancer is cancer that has recurred

(come back) after it has been treated. Gallbladder cancer may come back in the gallbladder or in other parts of the body. [Metastasis](#) is the spread of cancer from the [primary](#) site (place where it started) to other places in the body. [Metastatic](#) gallbladder cancer may spread to surrounding [tissues, organs](#), throughout the [abdominal cavity](#), or to distant parts of the body.

Diagnosis

Tests and procedures to detect, diagnose, and stage gallbladder cancer are usually done at the same time but there are so many facing difficult to detect and diagnose for the following reasons:

- (1) There aren't any noticeable signs or symptoms in the early stages of gallbladder cancer.
- (2) The symptoms of gallbladder cancer, when present, are like the symptoms of many other illnesses.
- (3) The gallbladder is hidden behind the liver.

Sometimes found cancer after the removal of gall bladder due to other reasons so there are following examination which may be used to detect:

Physical exam and history: An exam of the body to check general signs of health, including checking for signs of disease, such as lumps or anything else that seems unusual. A history of the patient's health habits and past illnesses and treatments will also be taken.

Ultrasound exam: A procedure in which high-energy sound waves (ultrasound) are bounced off internal tissues or organs and make echoes. The echoes form a picture of body tissues called a sonogram. An abdominal ultrasound is done to diagnose gallbladder cancer.

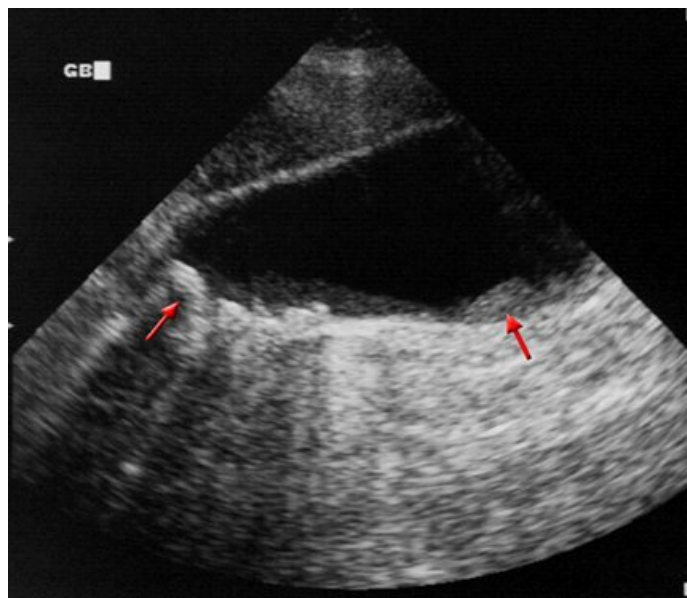


Fig.3. Ultrasound examination of gall bladder

Liver function tests: A procedure in which a blood sample is checked to measure the amounts of certain substances released into the blood by the liver. A higher than normal amount of a substance can be a sign of liver disease that may be caused by gallbladder cancer.

Carcinoembryonic antigen (CEA) assay: A test that measures the level of CEA in the blood. CEA is released into the bloodstream from both cancer cells and normal cells. When found in higher than normal amounts, it can be a sign of gallbladder cancer or other conditions.

CA₁₉₋₉ assay: A test that measures the level of CA 19-9 in the blood. CA 19-9 is released into the bloodstream from both cancer cells and normal cells. When found in higher than normal amounts, it can be a sign of gallbladder cancer or other conditions.

CT scan (CAT scan): A procedure that makes a series of detailed pictures of areas inside the body, taken from different angles. The pictures are made by a computer linked to an x-ray machine. A dye may be injected into a vein or swallowed to help the organs or tissues show up more clearly. This procedure is also called computed tomography, computerized tomography, or computerized axial tomography.

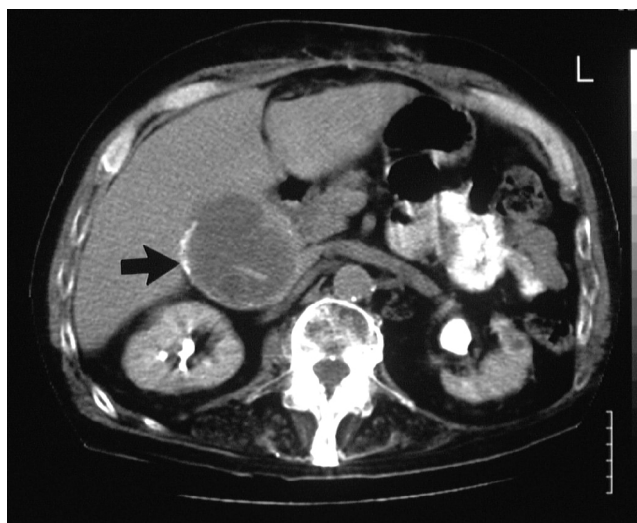


Fig. 4. CT scan of gall bladder.

Blood chemistry studies: A procedure in which a blood sample is checked to measure the amounts of certain substances released into the blood by organs and tissues in the body. An unusual (higher or lower than normal) amount of a substance can be a sign of disease in the organ or tissue that produces it.

Chest X-ray: An x-ray of the organs and bones inside the chest. An x-ray is a type of energy beam that can go through the body and onto film, making a picture of areas inside the body.

MRI (magnetic resonance imaging): A procedure that uses a magnet, radio waves, and a computer to make a series of detailed pictures of areas inside the body. This procedure is also called nuclear magnetic resonance imaging (NMRI). A dye may be injected into the gallbladder area so the ducts (tubes) that carry bile from the liver to the gallbladder and from the gallbladder to the small intestine will show up better in the image. This procedure is called MRCP (magnetic resonance cholangiopancreatography). To create detailed pictures of blood vessels near the gallbladder, the dye is injected into a vein. This procedure is called MRA (magnetic resonance angiography).

ERCP (endoscopic retrograde cholangiopancreatography): A procedure used to x-ray the ducts (tubes) that carry bile from the liver to the gallbladder and from the gallbladder to the small intestine. Sometimes gallbladder cancer causes these ducts to narrow and block or slow the flow of bile, causing jaundice. An endoscope (a thin, lighted tube) is passed through the mouth, esophagus, and stomach into the first part of the small intestine. A catheter (a smaller tube) is then inserted through the endoscope into the bile ducts. A dye is injected through the catheter into the ducts and an x-ray is taken. If the ducts are blocked by a tumor, a fine tube may be inserted into the duct to unblock it. This tube (or stent) may be left in place to keep the duct open. Tissue samples may also be taken.

Biopsy: The removal of cells or tissues so they can be viewed under a microscope by a pathologist to check for signs of cancer. The biopsy may be done after surgery to remove the tumor. If the tumor clearly cannot be removed by surgery, the biopsy may be done using a fine needle to remove cells from the tumor.

Laparoscopy: A surgical procedure to look at the organs inside the abdomen to check for signs of disease. Small incisions (cuts) are made in the wall of the abdomen and a laparoscope (a thin, lighted tube) is inserted into one of the incisions. Other instruments may be inserted through the same or other incisions to perform procedures such as removing organs or taking tissue samples for biopsy. The

laparoscopy helps to determine if the cancer is within the gallbladder only or has spread to nearby tissues and if it can be removed by surgery.

PTC (percutaneous transhepatic cholangiography): A procedure used to x-ray the liver and bile ducts. A thin needle is inserted through the skin below the ribs and into the liver. Dye is injected into the liver or bile ducts and an x-ray is taken. If a blockage is found, a thin, flexible tube called a stent is sometimes left in the liver to drain bile into the small intestine or a collection bag outside the body.

Treatment and management of gall bladder cancer

Different types of treatments are available for patients with gallbladder cancer. Some treatments are standard (the currently used treatment), and some are being tested in clinical trials. A treatment clinical trial is a research study meant to help improve current treatments or obtain information on new treatments for patients with cancer. When clinical trials show that a new treatment is better than the standard treatment, the new treatment may become the standard treatment. Patients may want to think about taking part in a clinical trial. Some clinical trials are open only to patients who have not started treatment

Three types of standard treatment are used:

1. *Surgery*: Gallbladder cancer may be treated with a cholecystectomy, surgery to remove the gallbladder and some of the tissues around it. Nearby lymph nodes may be removed. A laparoscope is sometimes used to guide gallbladder surgery. The laparoscope is attached to a video camera and inserted through an incision (port) in the abdomen. Surgical instruments are inserted through other ports to perform the surgery. Because there is a risk that gallbladder cancer cells may spread to these ports, tissue surrounding the port sites may also be removed.

If the cancer has spread and cannot be removed, the following types of palliative surgery may relieve symptoms:

(a) Surgical biliary bypass: If the tumor is blocking the small intestine and bile is building up in the gallbladder, a biliary bypass may be done. During this operation, the gallbladder or bile duct will be cut and sewn to the small intestine to create a new pathway around the blocked area.

(b) Endoscopic stent placement: If the tumor is blocking the bile duct, surgery may be done to put in a stent (a thin, flexible tube) to drain bile that has built up in the area. The stent may be placed through a catheter that drains to the outside of the body or the stent may go around the blocked area and drain the bile into the small intestine.

(c) Percutaneous transhepatic biliary drainage: A procedure done to drain bile when there is a blockage and endoscopic stent placement is not possible. An x-ray of the liver and bile ducts is done to locate the blockage. Images made by ultrasound are used to guide placement of a stent, which is left in the liver to drain bile into the small intestine or a collection bag outside the body. This procedure may be done to relieve jaundice before surgery.

2. *Radiation therapy*: Radiation therapy is a cancer treatment that uses high-energy x-rays or other types of radiation to kill cancer cells. There are two types of radiation therapy. External radiation therapy uses a machine outside the body to send radiation toward the cancer. Internal radiation therapy uses a radioactive substance sealed in needles, seeds, wires, or catheters that are placed directly into or near the cancer. The way the radiation therapy is given depends on the type and stage of the cancer being treated.

3. *Chemotherapy*: Chemotherapy is a cancer treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping the cells from dividing. When chemotherapy is taken by mouth or injected into a vein or muscle, the drugs enter the bloodstream and can reach cancer cells throughout the body (systemic chemotherapy). When chemotherapy is placed directly into the cerebrospinal fluid, an organ, or a body cavity such as the abdomen, the drugs mainly affect cancer cells in those areas (regional chemotherapy). The way the chemotherapy is given depends on the type and stage of the cancer being treated.

4. *Radiation sensitizers*: Clinical trials are studying ways to improve the effect of radiation therapy on tumor cells, including the following:

(a) Hyperthermia therapy: A treatment in which body tissue is exposed to high temperatures to damage and kill cancer cells or to make cancer cells more sensitive to the effects of radiation therapy and certain anticancer drugs.

(b) Radiosensitizers: Drugs that make tumor cells more sensitive to radiation therapy. Giving radiation therapy together with radiosensitizers may kill more tumor cells.

5. *Clinical trial*: For some patients, taking part in a clinical trial may be the best treatment choice. Clinical trials are part of the cancer research process. Clinical trials are done to find out if new cancer treatments are safe and effective or better than the standard treatment. Many of today's standard treatments for cancer are based on earlier clinical trials. Patients who take part in a clinical trial may receive the standard treatment or be among the first to receive a new treatment. Patients who take part in clinical trials also help improve the way cancer will be treated in the future. Even when clinical trials do not lead to effective new treatments, they often answer important questions and help move research forward. Patients can enter clinical trials before, during, or after starting their cancer treatment. Some clinical trials only include patients who have not yet received treatment. Other trials test treatments for patients whose cancer has not gotten better. There are also clinical trials that test new ways to stop cancer from recurring (coming back) or reduce the side effects of cancer treatment. Clinical trials are taking place in many parts of the country. See the Treatment Options section that follows for links to current treatment clinical trials. These have been retrieved from NCI's listing of clinical trials.

6. *Follow-up tests*: Some of the tests that were done to diagnose the cancer or to find out the stage of the cancer may be repeated. Some tests will be repeated in order to see how well the treatment is working. Decisions about whether to continue change, or stop treatment may be based on the results of these tests. This is sometimes called re-staging. Some of the tests will continue to be done from time to time after treatment has ended. The results of these tests can show if your condition has changed or if the cancer has recurred (come back). These tests are sometimes called follow-up tests or check-ups. All treatment are depend on the age and wide-ranging of the patient health and whether the cancer is causing symptoms [16-18].

S. No	Plant name	Nature and affinity
1	Bulbus Iphigeniae	Sweet and lightly pungent in flavour, cold in property, slightly poisonous
2	Artemisia scoparia and Artemisia capillaries Thunb. (Fam. Compositae)	It is bitter and pungent in taste and slightly cold in nature, and in distributed to the Spleen, Stomach, Liver and Gall Bladder Channels.
3	Gentiana macrophylla Pall., Gentiana straminea Maxim., Gentiana crassicaulis Duthie Gentiana dahurica Fisch. (Fam. Gentianaceae).	it is pungent and bitter in taste, neutral in nature, and distributed to the Stomach, Large Intestine, Liver, and Gall Bladder Channels.
4	Rheum palmatum L., Rheum tanguticum Maxim. Rheum officinale Baill (Fam. Poly-gonaceae).	It is bitter in taste and cold in nature. Its therapeutical action is related to the channels of the Spleen, Stomach, Large Intestine, Liver and Pericardium.
5	Coix lacrymajobi L. var. ma-yuen (Fam. Gramineae).	It is sweet and tasteless in taste and cool nature, and is distributed to the Spleen, Stomach and Lung Channels.

6	Lysimachia christinae (Fam. Primulaceae)	This herb is sweet and tastelessness in taste and neutral in nature, and is distributed to the Liver, Gall Bladder, Kidney and Urinary Bladder Channels.
7	Curcuma wenyujin Curcuma longa L., Curcuma kwangsiensis Curcum phaeoaulis Val. (Fam. Zingiberaceae).	It is pungent and bitter in taste and cold in nature, and is distributed to the Liver, Heart and Lung Channels.

Chart 1. Various herbal plants used in the treatment of gall bladder cancer.

CONCLUSION

Gallbladder cancer can be cured only if it is found before it has spread, when it can be removed by surgery. If the cancer has spread, palliative treatment can improve the patient's quality of life by controlling the symptoms and complications of this disease. Nowadays, various clinical techniques are developed but the rate of mortality day by day increasing due to gall bladder cancer.

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