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INCIDENTAL FINDINGS OF GALL BLADDER CANCER IN 7th OCTOBER HOSPITAL

SUBMITTED FOR PARTIAL FULFILLMENT OF MASTER DEGREE OF GENERAL SURGERY

BY

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In partial fulfillment for the Master Degree in
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DEDICATION

TO THE SOUL OF MY FATHER

TO MY MOTHER
MAY SHE BE ALWAYS THE LIGHT OF MY LIFE

TO MY BROTHER MOHAMMED

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SUMMARY

This is a retrospective study that assesses the chance of occurrence of gall bladder cancer in patients subjected to cholecystectomy for reasons other than the suspicion of cancer .
This study included all patients subjected of cholecystectomy in 7th October Hospital Benghazi – Libya.
Histopathology records were reviewed for evidence of gall bladder cancer among cholecystectomised patients.
The study covered a 6 years period from Jan 2000 year to Jan 2006 year .
13 cases of gall bladder cancer were found in a total of 1208 patients being more common in females with mean age of 61.2 years.
More patients were found at stage 1 & 2 , patients died within one year .
In conclusion early cholecystectomy for asymptomatic gall bladder stones is advised in elderly patients .

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Abbreviations

AJCC	American Joint Committee of Cancer
BUN	Blood urea nitrogen
CBC	Complete blood culture
CBD	Common bile duct
CCK	Cholecystokinin
CEA	Carceno embryonic antigen
CT	Computed tomography
ERCP	Endoscopicretrograde cholangiopancreatography
EUS	Endoscopic ultrasonographic
FU	5-fluorouracil
GBS	Gall bladder stone
INH	Isoniazide
LFT	Liver function test
MMC	Migrating Motor Complex
MRA	Magnetic resonance angiogram
MRCP	Magnetic resonance cholangiogram
MRI	Magnetic resonance imaging
PTC	Percutaneoustranshepatic cholangiography
SEER	Surveillance, Epidemiology & End Results
UK	United kingdom
US	United states
USS	Ultrasonograghy scan

Introduction

Cancers of the biliary tract include cholangiocarcinoma (cancers arising from the bile duct epithelium), ampulla of Vater cancer, and gallbladder cancer. All subtypes of biliary tract cancers are rare and have an overall poor prognosis. They are also difficult to diagnose. These diseases are often discussed together and are mingled in therapeutic trials. However, this leads to significant confusion. Gallbladder cancer is the fifth most common GI cancer in the United States and the most common hepatobiliary cancer. According to 1992-2000 data from the Surveillance, Epidemiology, and End Results (SEER) program, gallbladder cancer accounts for 46% of the biliary tract cancers in the United States.[1] About 20% arise from the extrahepatic biliary tract and 20% arise from the ampulla of Vater.[2]

Gallbladder cancer incidence increases with age and is more common in women. According to the American Cancer Society 2008 statistic projections, the number of new cases of gallbladder and other biliary cancers in the United States in men was predicted to be 4500 and in women is predicted to be 5020.[3]

The number of deaths projected for 2008 in the United States according to the American Cancer Society is 1250 and 2090 for men and women, respectively. The total number of gallbladder and other biliary tract cancers for 2008 is 3340[3]

In the United States, incidence varies substantially with racial and ethnic group and sex. Gallbladder cancer rates are the highest among American Indians/Alaska Natives and among white Hispanic peoples. Within both groups, incidence of gallbladder cancer is significantly higher in women.[2] The white Hispanic female incidence rate is 4.2 per 100,000 person-year. The American Indian/Alaskan Native female incidence rate is 4.1 per 100,000 person/year. The corresponding male rates are 1.4 and 3,3 per 100,000 person/year, respectively. The lowest incidence rate for gallbladder cancer is among non-Hispanic white males and is 0.7 per 100,000 person/year.

The incidence of gallbladder cancer rises with age. Seventy-five percent of patients with gallbladder cancer are older than 64 years.[3] In non-Hispanic whites and blacks, the rate of gallbladder cancer rises more slowly than among Hispanic whites and American Indian/Alaskan Natives. The rates for gallbladder cancer are higher among women than men in all age groups.[2]

Overall, the incidence (cases per year) has dropped by more than 50% in the general population since 1973. In Native American women, the incidence has decreased by 70%

1- Embryology of Gall Bladder and Biliary Tree

The liver and biliary tree develop from the foregut. In the middle of the third week, a liver bud (or a hepatic diverticulum) appears as an outgrowth of the endoderm of the lower end of the foregut.
As the liver bud enlarges, the connection between it and the foregut (in the area of the future duodenum) becomes narrow and forms the common bile duct. The liver bud divides into two parts:
a- Pars Hepatica: a large part which will form the liver itself.
b- Pars Cystica: a smaller part which will form the gall bladder and cystic duct.

The pars hepatica divides into two branches (right and left); each branch will give rise to columns of hepatic cells to form the two lobes of the liver. As the pars hepatica with its rapidly dividing and branching cell columns enlarges, it penetrates the septum transversum; the rapidly growing cells erode the vitelline veins in the septum transversum converting them into sinusoids of the liver.
As the liver enlarges, it begins to leave the septum transversum and gradually protrudes into the abdominal cavity.

The mesoderm of the septum transversum between the liver and the anterior abdominal wall becomes stretched and forms the falciform ligament. The umbilical veins which lie originally in the mesoderm of the septum transversum lies now in the free lower margin of the new falciform ligament.
The mesoderm of the septum transversum between the liver and the foregut (stomach and duodenum) becomes stretched and forms the lesser omentum (gastrohepatic ligament), with the portal vein, hepatic artery and common bile duct (CBD) lying in its free border.

The mesoderm on the surface of the liver differentiates into peritoneum except on its cranial surface (in the region in which the liver remains in contact with the part of the septum transversum which will form an important part of the diaphragm). This area of the liver will never be covered by peritoneum and will form the bare area of the liver.
The right and left hepatic ducts develop as the stems of the right and left braches of the pars hepatica become canalized. The original stalk of the liver bud elongates to form the common bile duct.
At first the CBD opens into the anterior wall of duodenum; later as a result of rotation of the duodenum, the opening of the CBD moves posteriorly and the CBD then lies posterior to the duodenum.[4]

2- The anatomy of the gall bladder:

The gall bladder is a sac like hollow organ that lies in a fossa on the under surface of the liver. Through its fossa passes the imaginary boundary between the functional right and left lobes of the liver. The gall bladder is attached to the liver by loose areolar tissue rich in small blood vessels and lymphatics. The extrahepatic portion of the gall bladder is covered by peritoneum; fewer than 10% of gall bladders are completely covered by peritoneum and are attached to the liver by a mesentery.
The average measures of the gall bladder is 7 to 10 cm long, 2 - 4 cm broad, and 30 - 50 ml in capacity in normal condition, It is described as having a fundus, body and neck [5].

a- **The Fundus**:

It is the rounded blind end of the gall bladder, which usually projects a little beyond the sharp lower border of the liver and touches the parietal peritoneum of the anterior abdominal wall at the tip of the right ninth costal cartilage where the transpyloric plane crosses the right costal margin, at the lateral border of the right rectus sheath. The fundus lies on the commencement of the transverse colon, just to the left of the hepatic flexure [4].

b- **The body**:

It is the largest segment of the organ, is directed up and back to the right end of porta hepatis, and is continuous with the neck. It is related above to the liver, below to the transverse colon, and further back to the first and upper end of the second part of the duodenum [5].

c- **The neck**:

It is the narrow portion following the body, curves up and forwards and then abruptly back and downwards, to become the cystic duct, at which transition, there is a constriction. The neck is attached to the liver by areolar tissue containing the cystic artery. Also the neck may show a small recess termed as Hartmann's pouch [5].

Hartmann's pouch:

It is a small bulbous diverticulum, which arises from right side of the neck and typically bulges from the inferior surface of the gall bladder. This anatomic site is clinically significant because of its proximity to the duodenum [5].
However, the Hartman's pouch is not a constant feature of the normal gall bladder, and is always associated with a pathological condition [4].
Also, the Hartmann's pouch may obscure the common hepatic duct and constitute a real danger point during cholecystectomy [6].

Blood Supply of the Gall Bladder:

The Arterial blood supply of the gall bladder is mainly by the cystic artery and many small vessels from its hepatic bed. The cystic artery usually arises from the right hepatic artery crossing anterior or posterior to the common bile or common

hepatic duct (in the Calot's triangle) to reach the gall bladder. It may arise from the hepatic trunk, left hepatic, gastroduodenal, celiac trunk or superior mesenteric artery. An accessory cystic artery may be present and arise from the common hepatic artery or one of its branches [4].
The cystic artery divides into superficial and deep branches, coursing over the neck and one or two pairs of its branches encircle it and anastomose posteriorly. Division into the two principal longitudinal branches occur at any point along the neck; each then gives off many branches to form vascular circles of arterial anastomosis around the gall bladder which are described as a bipinnate pattern [5].
Errors in biliary surgery are frequently the result of failure to appreciate the variations in the anatomy of the biliary system; so, it is imperative that before dividing any structure and removing the gall bladder to have all the three biliary ducts clearly identified, together with the cystic and hepatic arteries. So study of the anatomical variations of the cystic artery may help the surgeon to avoid complications like ligating the common bile duct or right hepatic artery assuming that they take the anatomical expected position of the cystic artery [5].
Thrombosis of the cystic artery does not usually lead to ischemia of the gall bladder because the blood supply from the gall bladder bed is adequate [4].

The venous drainage:

The venous drainage of the gall bladder is by multiple small veins in the gall bladder bed into the substance of the liver and so into the hepatic veins. One or more cystic veins may be present and run from the neck of the gall bladder into the right portal vein [4].

The lymphatic drainage:

The lymphatic drainage from the gall bladder may take one of the following routes:

1. The cholecysto-retropancreatic pathway, which can be regarded as the main pathway. At the retroportal segment, these routes converged at a large principal retroportal node lymph node.

2. The cholecysto-celiac pathway is the route by which some of the lymphatics from the gallbladder run to the left through the hepatoduodenal ligament to reach the celiac nodes.
3. The cholecysto-mesenteric pathway is the route by which some of the lymphatics run to the left in front of the portal vein and connect with the nodes at the superior mesenteric root. These three pathways converge with the abdomino-aortic lymph nodes near the left renal vein [7].

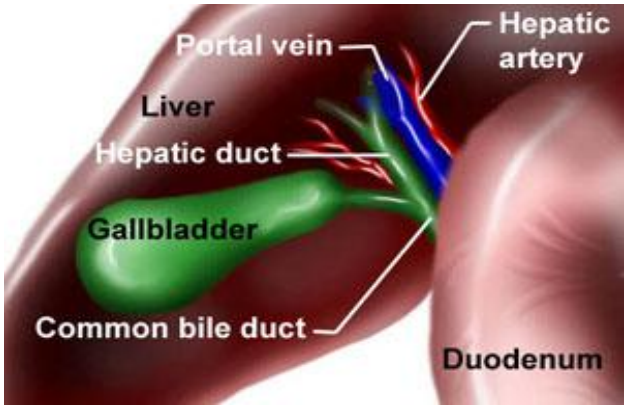

Fig. (1) anatomy of biliary system
(http://www.yoursurgery.com)

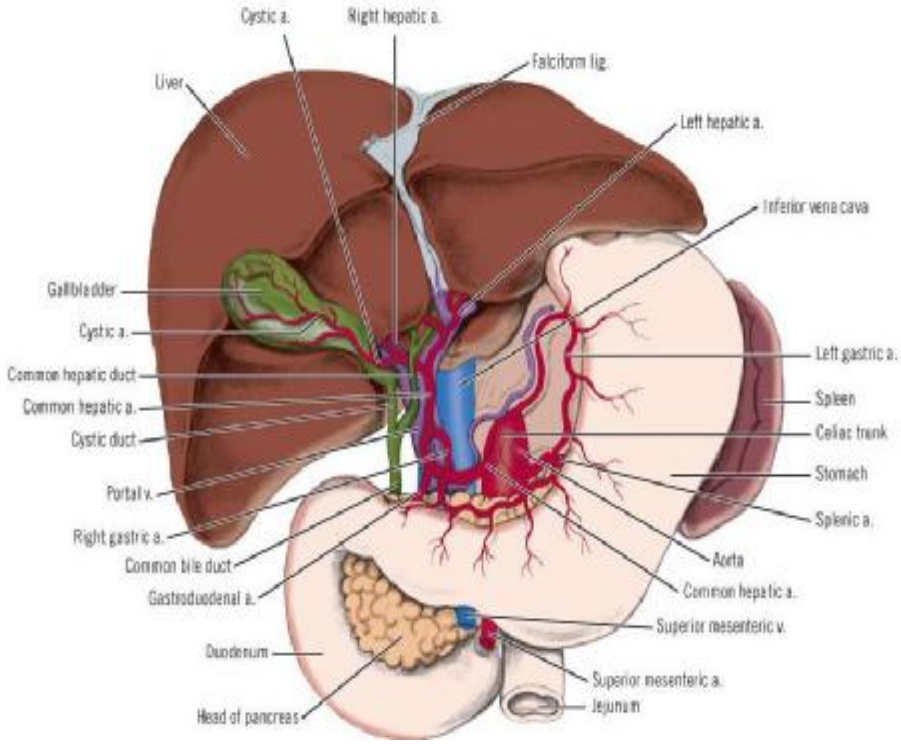

Fig. (2) Blood supply of gall bladder
(http://www.yoursurgery.com)

3- Anomalies of the biliary tract

a- **Anomalies of the gall bladder:**

1- Congenital absence of the gall bladder is due to failure of the distal end of the cystic duct to expand which is the original biliary sacculation. This result in either hypoplasia or agenesis of the gall bladder only discovered on laparotomy and the possibility of a completely intrahepatic gall bladder must be ruled out [8].

2- Anomalous forms of the gall bladder include:

a) Phrygian cap where the fundus is constricted and turned back on itself.

b) Bilobar gall bladder with a single duct.

c) Double gall bladder with two cystic ducts.

d) Septum of the gall bladder which may be partial or complete within the lumen.

e) Congenital diverticulum of the gall bladder with a muscular wall [6]

3- Anomalies of the mesentery may cause the so called floating gall bladder which has a complete serosal covering and this floating gall bladder predisposes to torsion [9].

4- Abnormal positions of the gall bladder are probably due to improper migration of the original gall bladder sacculation (pars cystica). The gall bladder may lie in an intrahepatic position completely, to the left of the falciform ligament and may be in an ectopic location [10].

Other miscellaneous anomalies such as the presence of ectopic hepatic, gastric, or pancreatic tissues within the wall of the gall bladder may occur[11].

b- **Anomalies of the extrahepatic biliary ducts :**

1) Anatomical variations in the mode of union of the cystic duct with the common hepatic duct may be:

A. An angular union which is found in 75% of cases, or

B. A parallel course to the common hepatic duct in 20% of cases for a long distance before union.

C. Finally the union may be a spiral fashion curving around it from the anterior or posterior aspects [6]

2) Accessory bile ducts represent a common anomaly and are found in more than 90% in the Calot's triangle [12].

3) Biliary atresia and stenosis include any segment of the extrahepatic ductal system or variable lengths of biliary tree. It may be the result of an inflammatory process (viral in origin), rather than a failure of embryogenesis.

4) Choledochal cyst: Congenital choledochal cyst is usually a fusiform dilatation of the common bile duct due to a specific weakness in a part of the whole thickness of the wall of the common bile duct. The cyst may contain as much as 1-2 liters.

5) Congenital dilatation of the intra-hepatic ducts (Caroli's disease) is a rare congenital, non familial condition that may occur leading to biliary stasis, stone formation and repeated attacks of cholangitis[13].

4- Physiology of the gall bladder & Biliary tract

a- Gallbladder functions

1- Filling

The liver secretes bile continuously. Because the hepatic end of the system is blind, secretion results in the generation of hydostatic pressure within the ducts. The secretory pressure normally ranges between 10 and 20 mmHg.
The maximal secretory pressure, above which bile cannot be produced, has been measured at 23 mm Hg. During the interdigestive period, the gall bladder is flaccid and the sphincter of Oddi at the opening of the duct into the duodenum is closed. This causes bile to flow into the gall bladder. The capacity of the human gall bladder ranges between 20 and 60 ml. The volume of bile produced by the liver before the gallbladder empties, however, may be several times this amount [14]

2- Fluid transport and its regulation

The gallbladder concentrates hepatic bile by selective reabsorption of bile constituents and under both physiological and pathological conditions, reversal of fluid transport across the gallbladder mucosa occurs and net secretion into the gallbladder lumen results. Sodium and chloride ions are absorbed from the gallbladder lumen by both active and passive transport mechanisms.
Water absorption is thought to be passive and secondary to active solute movement resulting from osmotic equilibration of transported solutes within the epithelium. The secretion of water and electrolytes by the gallbladder mucosa is an active process which can take place against hydrostatic and osmotic gradients[15].
Accumulating evidence suggests that normally during fasting the gallbladder absorbs fluid at a rate corresponding to one third of the fasting gallbladder volume. After feeding there is reversal of the direction of gallbladder transport from a net absorption to a net secretion into the gallbladder lumen [6].
Bile remains isosmotic to plasma even though the organic constituents are concentrated greatly. The bile salts, cholesterol, and phospholipids are present in osmotically inactive micelles [14]
The ability of the gallbladder to secrete hydrogen ions is an active process which can take place against hydrostatic and osmotic gradients [15].
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The ability of the gallbladder to secrete hydrogen ions is an important function of the normal mucosa [16].
A low pH prevents the formation of CaCO3 crystals but favours the formation of bihrubin polymers and the precipitation of calcium bilirubinate [17].
Factors which mitigate against gallstone formation include the capacity of the human gallbladder to absorb cholesterol and to secrete water during digestion thereby reducing the risk of cholesterol precipitation and sludge formation[18].

3- Expulsion of Bile

It is thought that the gallbladder volume gradually increased during fasting until the mean maximal volume is reached and only empties after a food stimulus. However, studies have shown that the gallbladder contracts up to 40% of maximal contractile capacity during the interdigestive period. Ultrasound estimation of gallbladder volume confirm that a cyclical pattern of gallbladder volume changes occurs in association with phase III of the Migrating motor complex (MMC) [19].

The controlling mechanism which produces gallbladder volume changes during fasting is unknown. A potential candidate is motilin, a hormone produced by the mucosa of proximal small intestine. Serum motilin levels show cyclic changes during MMC cycles with the peak values preceding phase III MMC activity.

The periodic gallbladder contractions during fasting empty concentrated viscous bile and enable gallbladder refilling dilute hepatic bile[6].

The gallbladder empties at an average rate of 1 ml/min. The average flow rate in the duct is about 0.5 – 1.0 ml/min for fasting gallbladder and 2 – 3 ml/ min after meal[20].

The average time to empty a gallbladder with a mean volume of 35 ml of bile is about 30 min[21].

The gallbladder begins to contract rhythmically and expel bile into the duodenum within 30 min of a meal.

The principal stimulus is hormonal although concentration is also stimulated somewhat by vagal activity during all phases of digestion. The major stimulus for gallbladder contraction is cholecystokinin (CCK) released by fat and protein digestion products within the lumen of the duodenum. CCK has two actions that result in bile expulsion: It contracts the smooth muscle of the gall bladder and relaxes the sphincter of Oddi [14]

Endogenous cholecystokinin is released from the mucosa of proximal small intestine and studies which measure serum CCK levels by radio-immunoassay have shown that gallbladder contraction induced by intraduodenal infusion of fat correlates directly with the level of circulating CCK [22].

The role of autonomic nerves in regulating gallbladder volume is not clear. Increased fasting volume of the gallbladder was demonstrated after vagotomy [23].

A number of studies have investigated the effect of vagal stimulation and vagotomy on gallbladder contractility, but the results generally have been inconclusive[24].

Similarly, studies of sympathetic innervation have produced inconstant and variable findings, and the role of the sympathetic autonomic nervous system in gallbladder motility requires further study[25].

Organic constituents of bile

Bile is a complex mixture of inorganic and organic components, the physical properties of which account for the ability of bile to solubilize normally insoluble fat digestion products. In fact, bile itself contains molecules that are insoluble in water but that are sulobilized in bile because of the interactions of its various organic constituents.

I- Bile Acids

Bile acids account for about 50% of the organic components of bile. They are synthesized in the liver from cholesterol. The liver synthesizes two bile acids, cholic and chendeoxycholic acid. These are the primary bile acids.
Within the lumen of the gut, a fraction of each is dehydroxylated by bacteria to form deoxycholic and lithocholic acids. These are called secondary bile acids.
All four are returned to the liver in the portal blood and secreted into bile.
The liver conjugates the bile acids to the amino acids glycine or taurine to be largely ionized and water soluble. These conjugated bile acids exist as salts of various cations, primarily sodium, and are referred to as bile salts. Bile salts are amphipathic molecules that is they have both hydrophilic and hydrophobic portions. Above a certain concentration, called the critical micellar concentration, bile salts form molecular aggregates called micelles. Micelles are cylindrical having the bile salts on the outside with their hydophilic portions oriented outward.

The inside of the micelle is made up of various molecules that are insoluble in water. Within bile itself, the bile salts are always present in amounts above the critical micellar concentration, and the micelles also contain phospholipids and cholesterol [14]

II- Phospholipids

Phospholipids, primarily lecithins, are the second most abundant organic component of bile and account for approximately 30-40% of the solids present. Phospholipids are also amphipathic. The phospholipids themselves are insoluble and are solubilized in micelles. Phospholipids, however, are extremely important because they increase the ability of bile salts to form micelles and solubilize cholesterol. Approximately 2 mol of lecithin are solubilized per mole of bile salt [14]

III- Cholesterol

Bile is the primary excretory pathway for cholesterol. The insoluble cholesterol makes up roughly 4% of the organic material in bile and is solubilized in the core of the micelle. If more cholesterol is present than that can be solubilized, crystals of cholesterol form in the bile. These crystals may serve as the nidus for gallstone formation [14]

IV-Bile Pigments

The fourth significant group of organic compounds found in bile is the bile pigments and it accounts for approximately 2% of the solids. The principal bile pigment is bilirubin produced from hemoglobin by cells of the reticuloendothelial system. Bilirubin is insoluble in water, but within the liver it is made soluble by conjugation to glucuronic acid. It is secreted as the soluble salt bilirubin glucoronide, and, therefore, is not found within the micelles [14]

b- Cystic duct

Accumulating evidence suggests that the cystic duct is not merely a passive conduit between the gallbladder and the common bile duct, but may play an active role in the flow of bile into and out of the gallbladder.

Histologically and anatomically prominent sphincter, as described by Lutken, does not appear to be present; however, a thin layer of smooth muscle is evident in the wall of the duct and along with the prominent mucosal folds which make up the valves of Heister, the cystic duct may act as a variable resistor to flow[6].

c- Common bile duct

The role of the common bile duct in the control of bile flow remains unclear. As in the cystic duct, histological studies have demonstrated only thin longitudinally orientated layers of smooth muscle within the wall of the common bile duct [19].
The major tissue component appears to be elastic fibres. The weight of experimental evidence suggests that the common bile duct does not have a primary propulsile function. However, the elastic fibres and the longitudinally orientated smooth muscle probably provide a tonic pressure that may help overcome the tonic resistance of the sphincter of Oddi. The diameter of the common bile duct is estimated to be less than 6mm by ultrasonography, 10mm by endoscopic retrograde cholangiography and less than 12mm by intraoperative extraluminal measurements [6].

d- Sphincter of Oddi

The sphincter of Oddi has both a variable basal pressure and phasic contractile activity. The former seems to be the predominant mechanism, regulating outflow of pancreaticobiliary secretion into the intestine. Although phasic sphincter of Oddi contraction may aid in regulating the flow of bile and pancreatic juice, the primary role seems to be maintaining a sterile intraductal milieu. Phasic wave activity of the sphincter is closely tied to the migrating motor complex of the duodenum. Sphincter regulation is under both neural and hormonal control. Studies in humans and experimental animals have demonstrated neuronal connections between the proximal bile ducts, gallbladder, and sphincter of Oddi
These connections take part in reflex stimulation of the sphincter of Oddi to produce relaxation following distension of the gallbladder and proximal ducts and may contribute to postprandial relaxation of the sphincter of Oddi [26].
Cineradiographic studies of the sphincter of Oddi exhibit rhythmic contractions which propel contrast into the duodenum.
Sphincter of Oddi pressure studies demonstrated variations in pressure thought to be the manometric equivalent of the cineradiogiaphic contractions [27].
Resistance to outflow of fluid from the common bile duct into the duodenum also was demonstrated by the intraoperative studies. This resistance was reduced after administration of cholecystokinin, octapeptide or smooth muscle relaxants

Manometric recordings from within the sphincter of Oddi segment have demonstrated that the human sphincter of Oddi is characterised by prominent phasic contractions superimposed on a basal pressure of 3 mmHg above the pressure in the common bile duct and pancreatic duct.
The amplitude of the phasic contractions is approximately 130 mmHg and the mean frequency is four per minute. Analysis of the direction of propagation of the phasic contractions during a continuous 3-min period demonstrated that the majority of contractions (60%) are orientated in an antegrade direction from the common bile duct towards the duodenum. A smaller number of contractions occurred either simultaneously (25%) or had a retrograde orientation

(15%). Intravenous bolus injection of cholecystokimn octapeptide (20 ng/kg) normally produces inhibition of the phasic contractions and a fall in the basal sphincter of Oddi pressure[28].

Studies from patients with T-tubes inserted in the common bile duct following bile duct exploration have shown that the frequency of sphincter of Oddi phasic contractions during fasting exhibits a periodicity in relation to duodenal migrating motor complexes[29].

Although regulatory processes vary among species, cholecystokinin and secretin seem to be most important in causing sphincter relaxation, whereas nonadrenergic, noncholinergic neurons, which at least in part transmit vasoactive intestinal peptide and nitric oxide, also relax the sphincter[30].

Glucagon is thought to relax the sphincter of Oddi directly by increasing intracellular cyclic-AMP levels[31].

The activity of the choledochal sphincteric complex is independent of the duodenal musculature but may be influenced by it. Thus, the effect of certain drugs on the choledochal sphincter differs from their action on the duodenal wall, and duodenal muscular peristaltic activity has no significant effect on the common bile duct pressure. The choledochal sphincter is an active structure and measures up to 2.5 cm in length. It consists of welldeveloped longitudinal and circular smooth muscle. Contraction of the longitudinal muscle tends to open the duct lumen, whereas the circular muscle has the opposite effect. These contracted (systolic) and relaxed (diastolic) states of the choledochal sphincter lead to quite distinct appearances of the lower end of the common bile duct at cholangiography. During contraction, contrast often forms a meniscus with the concavity facing downwards simulating a stone (the pseudocalculus phenomenon)[27].

5- Histology of gall bladder & biliary tract

a- Gallbladder

The empty or partially filled gallbladder has numerous deep mucosal folds. The mucosal surface consists of simple columnar epithelium. The lamina propria of the mucosa is particularly rich in fenestrated capillaries and small venules , but there are no lymphatic vessels in this layer. The lamina propria is also very cellular containing large numbers of lymphocytes and plasma cells. The characteristics of the lamina propria resemble those of the colon, another organ specialized for the absorption of electrolytes and water. Mucin-secreting glands are sometimes present in the lamina propria in the normal gallbladder, especially near the neck of the organ, but they are more commonly found in inflamed gallbladders. Cells that appear identical to enteroendocrine cells of the intestine are also found in these glands [32].

External to the lamina propria is a muscularis externa that has numerous collagen and elastic fibers among the bundles of smooth muscle cells. Despite its origin from a foregut-derived tube, the gallbladder does not have a muscularis mucosa or submucosa. The smooth muscle bundles are somewhat randomly oriented, unlike the layered organization of the intestine. Contraction of the smooth muscle reduces the volume of the bladder, forcing its contents out through the cyst duct[32]

External to the muscularis externa is a thick layer of a dense connective tissue. This layer contains large blood vessels, extensive lymphatic network, and the autonomic nerves that innervate the muscularis externa and the blood vessels (cell bodies of parasympathetic neurons are found in the wall of the cystic duct). The connective tissue is also rich in elastic fibers and adipose tissue. Where the gallbladder attaches to the liver surface, this layer is referred as the adventitia. The unattached surface is covered by a serosa or visceral peritoneum consisting of a layer of mesothelium and a thin layer of loose connective tissue[32]

b- Bile ducts

The large biliary ducts have external fibrous and internal mucosal layers. The former is fibrous connective tissue which contains a variable amount of longitudinal, oblique and circular smooth muscle cells. The mucosa is continuous with that of the hepatic ducts, gallbladder and duodenum. The epithelium is columnar. Many tubuloalveular mucous glands occur in the walls of these ducts[33].

6- Pathophysiology

Gallbladder cancer arises in the setting of chronic inflammation. In the vast majority of patients (>75%), the source of this chronic inflammation is cholesterol gallstones. The presence of gallstones increases the risk of gallbladder cancer 4- to 5-fold.[34] Other more unusual causes of chronic inflammation are also associated with gallbladder cancer. These causes include primary sclerosing cholangitis, ulcerative colitis,[35] liver flukes, chronic *Salmonella typhi* and paratyphi infections,[36] and *Helicobacter* infection.[37]

However, chronic gallbladder inflammation is likely only part of the cause of the malignant transformation seen in gallbladder cancer. Many other factors have been identified. Ingestion of certain medications (eg, oral contraceptives, INH, methyldopa) can increase the risk of gallbladder cancer. Likewise, certain chemical exposures (eg, pesticides, rubber, vinyl chloride) and occupational exposures associated with working in the textile, petroleum, paper mill, and shoemaking industries increase the risk of gallbladder cancer. In addition, exposures through water pollution (organopesticides, eg, dichlorodiphenyltrichloroethane and benzene hexachloride); heavy metals (eg, cadmium, chromium, lead); and radiation exposure (eg, radon in miners) are associated with gallbladder cancer. Obesity[38] may contribute to gallbladder cancer through its association with gallstones, its association with increased endogenous estrogens, or through the ability of fat cells to secrete a large number of inflammatorymediators.[2]

An increased incidence of gallbladder cancer also occurs in hereditary syndromes including Gardner syndrome, neurofibromatosis type I, and hereditary nonpolyposis colon cancer.[2] The role of various oncogenic mutations in gallbladder cancer is an area of active research. For example, a small study of gallbladder cancer from Japan reported an excess risk associated with polymorphism of the cytochrome P450 1A1 gene (*CYP1A1*), which encodes a protein involved in catalyzing the synthesis of cholesterol and other lipids.[39] Another study looked at polymorphisms within the apolipoprotein B gene.[40]

Abnormal anatomy such as congenital defects with anomalous pancreaticobiliary duct junctions and choledochal cysts increase the risk of gallbladder cancer.[41,42]The tumor is usually located in the fundus of the gallbladder. Local spread through the gallbladder wall can lead to direct liver invasion, or, if in the opposite direction, leads to transperitoneal spread (20% of patients at presentation), with implants on the liver, on the bowel, and in the pelvis. Tumor may also directly invade other adjacent organs such as the stomach, duodenum, colon, pancreas, and extrahepatic bile duct. At diagnosis, the gallbladder is often replaced or destroyed by the cancer, and approximately 50% of patients have regional lymph node metastases.

7- Mortality/Morbidity

Survival is correlated with staging based on the American Joint Committee on Cancer (AJCC) tumor, node, metastases (TNM) staging system.[43] Most patients have regional disease or distant metastases at presentation. Therefore, the prognosis in gallbladder disease is poor, with 5-year survival rates of 15-20%.[2]

Patients with stage IA disease (T1N0M0) should be cured with a simple cholecystectomy. In selected surgical series, patients with stage IB (T2N0M0) disease treated with extended cholecystectomy have a 5-year survival rate of 70-90%, and patients with stage IIB (T1-3N1M0) treated with extended cholecystectomy have a 5-year survival of 45-60%. Stage III (T4, any N, M0) gallbladder cancer is generally not surgically curable. The 1-year survival rate for advanced gallbladder cancer is less than 5%. The median survival is 2-4 months.

The SEER registry from 1995-2001 shows 5-year survival rates for localized gallbladder cancer of approximately 40%. The 5-year survival rate for regional disease is listed at approximately 15%, and the 5-year survival rate for distant metastatic disease is reported at less than 10%.[1] However, survival data are variable from institution to institution for each stage.

Unfortunately, only about 10-20% of patients present with tumor confined to the gallbladder wall. At diagnosis, 40-60% of patients have lesions that perforate the gallbladder wall and invade adjacent organs (T3) and 45% of patients have regional lymph node involvement (N1). Approximately 30% of patients present with metastatic disease.

Race

The highest rates of gallbladder cancer in the US are found in the US Native American and Hispanic, especially Mexican, populations.

Sex

A substantial female predominance exists worldwide, with female-to-male ratios of approximately 2.5:1 to 3:1.

Age

Gallbladder cancer is most typically diagnosed in the seventh decade of life, with a median age of 62-66 y

Considerable variation exists in the incidence of gallbladder cancer throughout the world. Areas with the highest incidence rates include India, Korea, Japan, Czech Republic, Slovakia, Spain, Columbia, Chile, Peru, Bolivia, and Ecuador. The high incidence rates reported in Peru and Chile are thought to reflect the Hispanic populations with Indian heritage. Females from India have the highest international rate of gallbladder cancer at between 8.8 per 100,000 person-years and 21.2 per 100,000 person-years.[2, 36] The United Kingdom, Denmark, and Norway have the lowest international incidence rates. Gallbladder cancer is the most common cancer affecting women in Chile.

8- Clinical presentation

a- History

The symptoms of gallbladder cancer overlap with the symptoms of gallstones and biliary colic. Abdominal pain may be of a more diffuse and persistent nature than the classic right upper quadrant pain of gallstone disease. Jaundice, anorexia, and weight loss often indicate more advanced disease.

b- Physical findings

- Palpable mass in the right upper quadrant
- Jaundice
- Left supraclavicular adenopathy (Virchow node)
- Pelvic seeding: Mass is palpated on digital rectal examination (Blumer shelf).

c- Causes

See Pathophysiology. Associated conditions include the following:

- Chronic gallstones
- Calcification of the gallbladder (porcelain gallbladder) - 10-25% incidence of gallbladder cancer
- Crohn ileocolitis
- Ulcerative colitis
- Occupational chemical exposure
- Estrogens
- Typhoid carriers
- Anomalous pancreatobiliary duct junction
- Gallbladder polyps

d- Differential Diagnoses

Acalculous Cholecystitis
Acalculous Cholecystopathy
Ampullary Carcinoma
Bile Duct Strictures
Bile Duct Tumors
Biliary Colic
Biliary Disease
Biliary Obstruction
Carcinoma of the Ampulla of Vater
Cholangiocarcinoma
Cholangitis
Cholecystitis
Choledochal Cysts
Choledocholithiasis
Cholelithiasis
Clostridial Cholecystitis
Gallbladder Mucocele
Gallbladder Volvulus
Hepatic Carcinoma, Primary
Liver Abscess
Neoplasms of the Endocrine Pancreas
Pancreatic Cancer
Pericholangitis
Primary Biliary Cirrhosis
Primary Sclerosing Cholangitis

9- Workup

a- Laboratory Studies

- Tumor marker CA 19-9
    - CA 19-9 may be significantly elevated in both cholangiocarcinoma and gallbladder cancer.
    - CA 19-9 tests may be helpful in the appropriate situation if the clinical suspicion for gallbladder cancer is high.
    - CA 19-9 can be useful in conjunction with CEA.
- Liver function tests: Elevated alkaline phosphatase and bilirubin levels are often found with more advanced disease.
- BUN, creatinine, urinalysis: Assess renal function prior to performing an enhanced CT scan.
- CBC: Anemia may be an indicator of more advanced disease.

b- Imaging Studies

- Ultrasonography (US) is a standard initial study in patients with right upper quadrant pain. A mass can be identified in 50-75% of patients with gallbladder cancer. It also can delineate metastatic lesions in the liver.
- Computed tomography (CT) scans also may be useful in patients with upper abdominal pain and can demonstrate tumor invasion outside of the gallbladder and identify metastatic disease elsewhere in the abdomen or pelvis. Liver invasion occurs in 60% of cases, and the combination of CT scan and US provides accurate details of disease extension.
- Magnetic resonance imaging (MRI) has been useful in examining this region for disease extension into other tissues or metastatic disease in the liver. It can provide details of the vasculature for preoperative planning via magnetic resonance angiogram (MRA) and bile duct passages via magnetic resonance cholangiogram (MRCP).
- Cholangiography, via a percutaneous route, or endoscopic retrograde cholangiography (ERCP) may establish the diagnosis of gallbladder cancer by bile cytology.
- Endoscopic ultrasonography can be useful to assess regional lymphadenopathy and depth of tumor invasion into the wall of the gallbladder. In conjunction with other studies, it also can provide a means of obtaining bile for cytologic analysis, which has a sensitivity of 73% for the diagnosis of gallbladder cancer.[44]
- Angiography may be used to confirm encasement of the portal vein or hepatic artery and may assist in preoperative planning for definitive resection.
- A routine chest radiograph should also be obtained.

c- Procedures

- ERCP can demonstrate the site of the obstruction by direct retrograde dye injection, as well as exclude ampullary pathology by endoscopic evaluation. Brush cytology, biopsy, needle aspiration, and shave biopsies via ERCP can provide material for histology. Palliative stenting to relieve biliary obstruction can be performed at the time of the evaluation.
- MRCP shows the anatomy of biliary system , cause & site of obstruction
- Percutaneous transhepatic cholangiography (PTC) may allow access to the proximal biliary tree that has become obstructed by extensive tumor growth from the gallbladder. Material for cytology can be obtained and drainage performed as well.
- Other methods to obtain tissue include CT or ultrasound needle aspiration if a mass lesion is present and endoscopic ultrasonographic (EUS) fine-needle aspiration.

d- Histologic Findings

Adenocarcinoma is the primary histologic finding in 80-85% of gallbladder carcinomas, with several histologic subtypes, including papillary, nodular, and infiltrative. The papillary type appears to be less aggressive and more often localized and has a better prognosis than the other forms. Additional rare histologic types of gallbladder cancer exist. These include squamous cell cancer, sarcomas, carcinoid, lymphoma, and melanoma.

Grade is also important, with poorly differentiated tumors associated with a poorer prognosis than the typically less infiltrative, better differentiated tumors with metaplasia.

Staging

Staging of tumor extent is essential in selection of the appropriate treatment approach.

The AJCC 6th edition guidelines follow the TNM system, with depth of tumor penetration and regional spread defined pathologically.[43] Survival is correlated directly with stage of disease.

Primary tumor

- Category T
    - TX - Primary tumor cannot be assessed
    - T0 - No evidence of primary tumor
    - Tis - Carcinoma in situ
    - T1 - Tumor invades lamina propria or muscle layer
        - T1a - Tumor invades lamina propria
        - T1b - Tumor invades muscle layer

    - T2 - Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver
    - T3 - Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
    - T4 - Tumor invades main portal vein or hepatic artery or invades multiple extrahepatic organs or structures
    - Regional lymph node
- Category N
    - NX - Regional lymph nodes cannot be assessed
    - N0 - No metastases in regional lymph nodes
    - N1 - Metastases in regional lymph nodes
    - Distant metastases
- Category M
    - MX - Presence of metastases cannot be assessed
    - M0 - No distant metastases
    - M1 - Distant metastases
- TNM groupings by stage
    - Stage 0- Tis N0 M0
    - Stage IA - T1 N0 M0
    - Stage IB - T2 N0 M0
    - Stage IIA - T3 N0 M0
    - Stage IIB - T1-3 N1 M0
    - Stage III - T4 any N M0
    - Stage IV - Any T any N M1

10-Treatment

a-Medical Care

Although complete surgical resection is the only therapy to afford a chance of cure, en bloc resections of the gallbladder and portal lymph nodes carry a high morbidity and mortality (similar to bile duct carcinoma). Adequate surgical margins may be difficult to achieve. The role of adjuvant radiation therapy is to control microscopic residual deposits of carcinoma in the tumor bed and regional lymph nodes. The rationale for radiation therapy with or without concurrent chemotherapy in patients with unresectable disease is to provide palliation of symptoms. Rarely, it may increase survival.

The role of radiotherapy for carcinoma of the gallbladder is unclear because the available literature is derived from small, single institutional experiences over many years, with a variety of treatment methods used. Complicating this is the fact that only approximately 25% of patients with carcinoma of the gallbladder can undergo curative surgery.

Even large institutions do not accrue more than single-digit numbers of patients per year, and many are not on protocol. Available reports contain small numbers of patients with incomplete reporting of technical treatment data, histological grading, and tumor extent. The literature is strongly biased by patient selection, and interpretation of the reports is difficult. Given these difficulties, the data support the following statements:

Radiotherapy has been delivered in a variety of situations, including after curative resections with close or positive microscopic margins, gross macroscopic residual disease, and palliative debulking with bypass.

- Significant increases in survival rates have been reported after curative surgery is attempted and only microscopic residual disease remains. Survival in these patients after surgery alone ranges from 6-7 months and can be prolonged to longer than 12 months with external beam radiotherapy administered as adjuvant therapy. This excludes patients with T1 or stage I disease confined to the mucosa of the gallbladder. Their survival rates are extremely high and they are at very low risk for lymph node metastases.
- All patients with tumors beyond the mucosa are candidates for external beam radiotherapy. Patients with curative resection and AJCC stages T2-T4 who have had complete resection who receive radiation have a mean survival of over 16 months. This is compared to less than 6 months mean survival with surgery alone.

5-FU–based chemotherapy is usually given in conjunction with concurrent radiation therapy in the adjuvant setting. Adjuvant chemotherapy can be given with single

agent gemcitabine or a fluorpyrimidine-based agent. No evidence-based clinical study exists to demonstrate the benefit of any form of adjuvant therapy in gallbladder cancer. Wherever possible, patients eligible for adjuvant therapy should be entered in a clinical trial. Gemcitabine by itself is an effective agent in the treatment of patients with unresectable recurrent or metastatic disease. The combination of gemcitabine and cisplatin[45] or the combination of gemcitabine and capecitabine may be more effective than gemcitabine alone.

In the UK ABC-02 trial,[46] gemcitabine plus cisplatin demonstrated a survival advantage over gemcitabine alone. This was a multicenter phase III randomized trial. In the BINGO trial,[47] a phase II clinical trial, gemcitabine in combination with oxaliplatin, alone or in combination with cetuximab, demonstrated a benefit for the gemcitabine and oxaliplatin plus cetuximab arm. More definitive phase III clinical trials are needed to direct therapy for patients with this malignancy. Selected patients with unresectable disease may be considered for surgical resection after response to chemotherapy. This is based on a retrospective study showing markedly improved survival in a small number of patients who received gemcitabine and cisplatin followed by surgery.[48] More trials are needed to evaluate this benefit. Patients with a good performance status should be considered for a clinical trial or for treatment with the regimens described in this section. Patients with a poor performance status may be best treated with supportive care.

b-Surgical Care

Complete surgical resection is the only therapy to offer a chance of cure in this disease. Unfortunately, only a minority of patients present with early-stage disease and are, therefore, considered for curative resection.

- Because of the high incidence of gallbladder cancer in a calcified (porcelain) gallbladder, patients with this finding should be strongly considered for an open cholecystectomy even if they are asymptomatic. It is best to avoid a laparoscopic cholecystectomy in this setting to avoid the risk of peritoneal seeding if, indeed, gallbladder cancer is present.
- Gallbladder cancer is sometimes an incidental pathology finding after a cholecystectomy is performed for reasons other than cancer. If the tumor is carcinoma in situ (Tis) or only invades the lamina propria (T1a) and the margins of resection are negative, then postoperative observation alone is acceptable. If the tumor is T1b or greater or the margins of resection are positive, then further surgical resection is necessary if no metastatic disease is present on evaluation (CT, MRI, chest radiograph). This additional surgery should include partial hepatic resection and regional lymphadenectomy (porta hepatis, gastrohepatic ligament, and retroduodenal lymph nodes). A bile duct resection may also be necessary depending on tumor size and location. If the original surgery was performed via a laparoscopic approach, then the port sites should also be resected to avoid tumor seeding.
- Patients who present with a gallbladder mass or jaundice are evaluated preoperatively for resectability as previously described. If the tumor is

resectable, the patient undergoes a cholecystectomy with en bloc liver resection and regional lymphadenectomy. Bile duct excision may also be necessary (especially if jaundice is present). The operative morbidity and mortality rate increases with the complexity of the operative procedure.

- The surgical role in treatment of unresectable disease is usually limited to biopsy of the tumor for diagnosis and possible biliary decompression procedures.
- Lymph node evaluation is a critical component of radical resections for gallbladder cancer and has been shown to improve survival in a recent retrospective trial.[49]

c- Medication

Historically, chemotherapy has not shown significant activity in gallbladder carcinoma. Typically, 5-fluorouracil (5-FU) has been used with response rates of 10-24% in advanced disease. Often 5-FU is administered either as a bolus or as a prolonged infusion regimen with radiation. Capecitabine is a currently available oral alternative to a prolonged 5-FU infusion.

More recently, gemcitabine has shown activity in gallbladder cancer. Early phase studies show an increased response rate with gemcitabine combination therapy over historical treatment response rates with 5-FU alone. Gemcitabine has been studied in combination with cis-platinum and capecitabine.

Currently, no clearly defined standard exists for chemotherapy in gallbladder cancer. Patients should be encouraged to participate in clinical trials.

Antineoplastic agents :

These agents inhibit cell growth and proliferation.

1- Gemcitabine (Gemzar)

Cytidine analog, after intracellular metabolism to active nucleotide, inhibits ribonucleotide reductase and competes with deoxycytidine triphosphate for incorporation into DNA. Cell cycle-specific for S phase.
This drug has been shown to have activity in a phase-2 trial against relapsed germ cell tumors 1000 mg/m^2 once weekly for as long as 7 wk or until toxic effects not tolerated; follow with 1 wk rest and subsequent cycles of once weekly infusion for 3 consecutive wk q4wk

Documented hypersensitivity

Pregnancy D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus
Precautions May cause myelosuppression (particularly thrombocytopenia); toxicities

include flulike syndrome, LFT abnormality, maculopapular rash, pruritus, nausea, vomiting, dyspnea, hematuria, proteinuria, and hemolytic uremic syndrome; clearance reduced in women and elderly individuals

2- Cisplatin (Platinol)

Platinum-containing compound that exerts antineoplastic effect by covalently binding to DNA with preferential binding to N-7 position of guanine and adenosine. Can react with 2 different sites on DNA to cause cross-links. Platinum complex also can bind to nucleus and cytoplasmic protein. A bifunctional alkylating agent, once activated to aquated form in cell, binds to DNA, resulting in interstrand and intrastrand cross-linking and denaturation of double helix.
Modify dose on basis of CrCl. Avoid use if CrCl <60 mL/min.

Adult 20 mg/m^2/d IV over 20-60 min for 5 d; repeat q21d for 4 cycles

Increases toxicity of bleomycin and ethacrynic acid

Documented hypersensitivity, pre-existing renal insufficiency, myelosuppression, and hearing impairment

Pregnancy D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus

Precautions Administer adequate hydration before and 24 h after cisplatin dosing to reduce risk of nephrotoxicity; myelosuppression, ototoxicity, nausea and vomiting, may occur

3- Capecitabine (Xeloda)

Prodrug of fluorouracil that undergoes hydrolysis in liver and tissues to form the active moiety (fluorouracil), inhibiting thymidylate synthetase, which in turn blocks methylation of deoxyuridylic acid to thymidylic acid. This step interferes with DNA, and to a lesser degree with RNA synthesiAdult 1250 mg/m^2 PO q12h pc for 2 wk followed by 1 wk of rest period; administer as 3 wk cycle

11-Follow-up

Further Outpatient Care

- Because survival is usually very short in patients with advanced disease, close follow-up is essential to preserve the best quality of life. For patients with earlier stage disease who are treated with surgery and postoperative radiation therapy and chemotherapy, intermittent posttreatment imaging studies can be considered (particularly in the first few years).
- Hospice referral is important early in the disease course for patients with metastatic disease because their survival is typically 6 months or less.

Prevention

- Because a calcified (porcelain) gallbladder has up to a 25% incidence of associated gallbladder cancer, this is an indication for a cholecystectomy even in an asymptomatic patient.
- A small percentage (<10%) of patients with gallbladder polyps are found to have underlying gallbladder cancer. The risk increases with age and the size of the polyp. A cholecystectomy should be considered if a gallbladder polyp greater than 1 cm in size is found in a patient older than 50 years.

Prognosis

Survival at 5 years is correlated with stage of disease at presentation. Only 10-20% of patients present with localized disease. The remainder present with regional or distant spread. According to the SEER registry on gallbladder cancer, the 5-year survival rates for localized, regional, and distant disease are approximately 40%, 15%, and less than 10%, respectively. The median survival for advanced disease is short (2-4 mo).

12-porcelain gall bladder

Porcelain gallbladder is a calcification of the gallbladder believed to be brought on by excessive gallstones but more studies are necessary to determine the exact cause.

It is predominantly found in overweight female patients of middle age.

Association with cancer

Porcelain gallbladder often results in a diagnosis of gallbladder cancer. The association with the two is uncertain; some studies have suggested an increased risk of gallbladder cancer with porcelain gallbladder.

Two review articles found the incidence of calcified gallbladder associated with cancer of the gallbladder was only about 1%. They also found that of 69 calcified gallbladders only 3 of them contained cancer.[1][2]

Symptoms

Symptoms can include abdominal pain (especially after eating), jaundice, and vomiting.

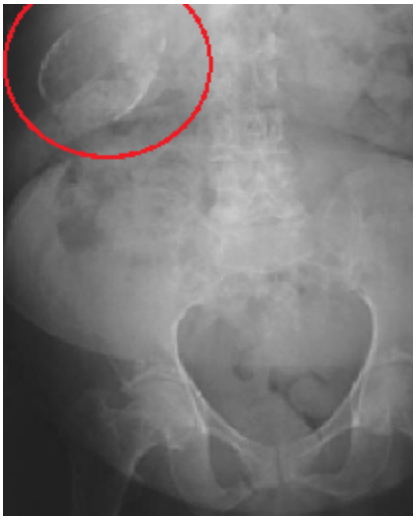

Fig (3) plain abdominal x ray shows porcelain gall bladder (http://www.yoursurgery.com)

Treatment

If porcelain gallbladder is found very early before symptoms present themselves (such as during a surgery of some sort), the gallbladder can be removed and the chances for recovery are very good. Treatments are still being developed and doctors are studying new ways to treat this condition at more developed stages.

Aim of the study

To assess:

- The prevalence & age incidence of GB cancer discovered incidentally after cholecystectomy for GBS in 7th October hospital / Benghazi .

- Types of malignancy of Gall bladder cancer in Libyan patients .

Patients and Methods

I reviewed and analyzed the data available in the department of surgery 7th October Hospital in collaboration with the histopathology department – Benghazi University ,which was the only source of histopathology reports in a period of 6 years (Jan 2000 – Jan 2006).

I found about 13 cases of carcinoma of gall bladder (incidentally discovered after cholecystectomy).
10 cases from 7th October hospital & the other 3 cases was from other hospitals.
The study included 1208 cases in the 6 years period .
there was 13 cases of carcinoma gall bladder after open & laparoscopic cholecystectomy . which was not suspected preoperatively (incidentally discovered at the histopathological examination)

Results

- 13 cases of cancer of gallbladder were discovered during a 6 year period among 1208 choleccystectomy performed .
- This gives a prevalence figure of 1.08% among cholecystomised patients
- The age ranged from 35-80 years (Mean=61.2 years) .
- The study shows that cholecystectomy was done more in females than males with a ratio of 4:1 . table (1) Fig (3)
- In case of Gall bladder cancer , the ratio was 8:5 (F:M)
- Adenocarcinoma was the commonest histopathological type 76.9% of the cases table (2) fig (4)

  other types including :

  - Papillary carcinoma
  - Sequmous carcinoma
  - Mucinous carcinoma

- 93% of cases of Gall bladder cancer were associated with gallbladder stone and only 7% were associated with obstructive jaundice . table (3)

Tables

Table (1):
Distribution of No. of choleccystectomies, sex &gallbladder cancer per year of study

Date	No	M	F	Ca. Gall bladder
2000	136	26	110	5
2001	100	10	90	1
2002	125	31	94	1
2003	336	55	281	3
2004	227	56	171	1
2005	284	81	203	2

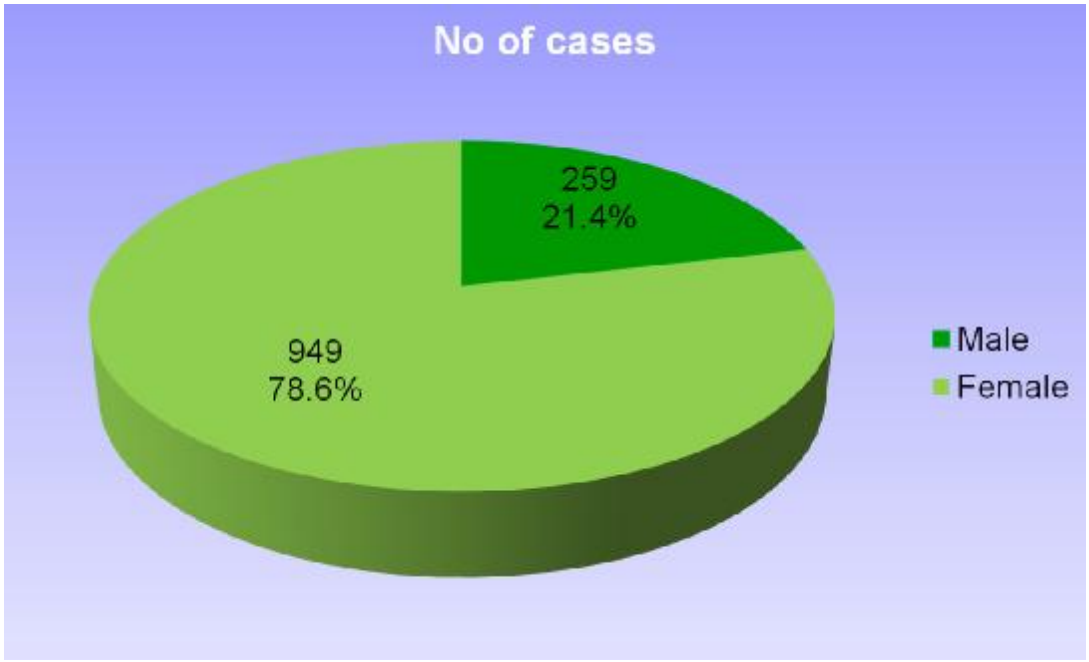

Fig (4) Number of cases

Table (2) :

Histological finding in patients with gallbladder carcinoma

Histopathology finding	No. of cases	M	F
Adenocarcinoma	10	5	5
Papillary carcinoma	1	0	1
Sequamous carcinoma	1	0	1
Mucoid carcinoma	1	0	1

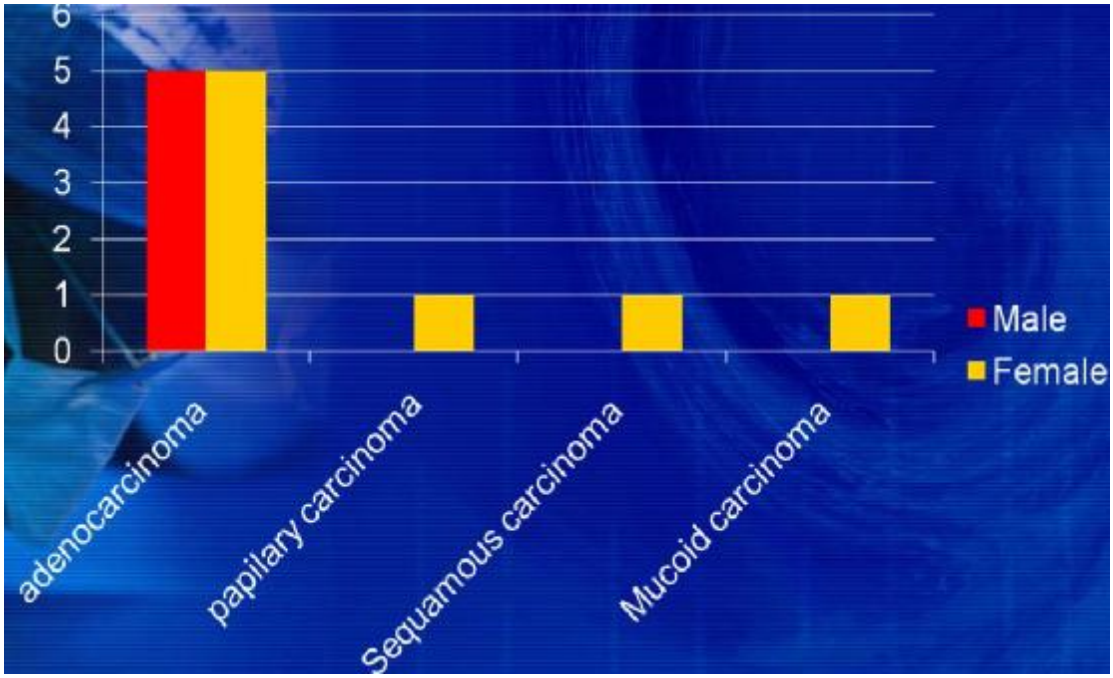

Fig (5) Types of cancer

Table (3) :

Clinical finding in cases of gallbladder cancer :-

Clinical finding	No. of cases
Jaundice	1
Palpable mass	4
No sign	8

Discussion:

Gallbladder malignancy is a quite rare entity, however, is common in the gastrointestinal tract, The Roswell Park Experience Carcinoma of the gallbladder is the most common malignancy of the biliary tract, comprising two thirds of biliary-tract cancers. it is the fifth most common gastrointestinal malignancy (and the most common of the biliary tract) and is usually discovered accidentally [50,] De Stoll in 1771 was the first to report on gallbladder carcinoma [51,] The western literature review revealed that 0.3% to 2.85% of the patients who underwent cholecystectomy for presumed benign disease were found to have carcinomas of gall bladder[52-55,] The cancer of gallbladder is known to be high in some countries like Chili & Mexico(≈ 5%). In the present study the prevalence of carcinoma gall bladder was 1.08%.

While the incidence of gallbladder cancer in the United States has been calculated by Burdette to be 2.5 per 100,000 inhabitants. Among patients undergoing surgery for biliary-tract disease, cancer has been found in 1% to 2%, with the frequency of gallbladder cancer peaking in the seventh decade of life.[56,] However carcinoma of the gallbladder has been recorded in an 11-year-old child. Demographically, gallbladder carcinoma is more common in women and its frequency increases with age with a preponderance of female patients (75%).[57,] In this study 62% of cases are female patients.

The overall increased frequency of gallbladder cancer in women and bile duct cancer in men suggests that hormonal factors play a role. Among African Bantus, cholelithiasis and gallbladder cancer are both very rare, whilein Southwestern American Indians the incidence of both is high. Population differences such as these [58,] suggest a possible genetic susceptibility. Chemical carcinogens, especially nitrosamines and methylcholanthrene, have been implicated in the etiology of gallbladder cancer.[59,] Laboratory studies have suggested a multifactorial etiology, where gallstones, inflammatory processes, and chemical carcinogens all play roles of inducers and facilitators.[60,] Benign gallbladder tumors do not seem to be precursor lesions for gallbladder carcinoma. Strauch found only one case of carcinoma in situ arising in an adenomatous gallbladder polyp.[61,] A similar case was reported by Glenn.[62,]

Risk factors include cholelithiasis found in 70±90% of cases where there was established association between carcinoma of gallbladder and gall bladder stone formation but the causative role of gallbladder stone in the formation of carcinoma is not yet clear [63,] The estimated risk of developing cancer in patients with lithiasis of gallbladder is 1-3%[64] .
In the present study we found that gall bladder carcinoma was associated with gall stones in 93% of the cases .

Also, the report by working group of Royal college of Pathologists stated that gallbladder should be examined, as significant pathology may be present with normal gross morphology.

Early detection is not possible due to delayed onset of symptoms or is masked off by chronic cholecystitis, and is usually detected during simple cholecystectomy as incidental finding.
Gallbladder cancer can be found as a polypoid projection into the lumen of the gallbladder (the type most often reported as an incidental finding) or as a diffuse thickening of the wall of the organ, with or without extension into the liver and other adjacent organs.

The most common symptoms gallbladder carcinoma are pain , weight loss and jaundice with a frequency of 76% , 39% and 39% respectively [64,65], other symptoms include fever in 30.8% and ascites in 14%. Relevant laboratory data showed obstructive jaundice in 51.7%, abnormal liver function tests in 37%, leukocytosis in 34.4% and anemia in 22.4% [66,].
A proportion of patients presents a clinical picture of acute cholecystitis manifested by fever , leukocytosis , localized pain and tenderness . Some patients present with a clinical picture of empyema yet others show more advanced signs of the disease , with a variety of symptoms such as anorexia weight loss , vomiting and jaundice [67,68,69].

Most of our cases were not suspected preoperatively and were operated as cases of GBS or its complications.

Conclusion

1. The prevalence of carcinoma gallbladder among cholecystectomized patients in Benghazi area was 1.08%.

2. Carcinoma gall bladder was more common in female patients (F:M =8:5).

3. Carcinoma gall bladder was more common among older age group.

4. The most common histological type of Gall bladder carcinoma was Adenocarcinoma (76.9%).

5. Carcinoma of the gall bladder was associated with gall stones in 93% of cases .

So early cholecystectomy of a symptomatic gall bladder stones is advised in elderly patients .

Reference:

1. National Cancer Institute. Cancer Statistics. SEER Surveillance, Epidemiology, and End Results. Available at http://seer.cancer.gov/. Accessed 2008.

2.Schottenfeld D and Fraumeni J. Cancer. Epidemiology and Prevention. 3rd. Oxford University Press; 2006:787-800.

3.American Cancer Society. Key Statistics for Gallbladder Cancer. Available at http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_are_the_key_statistics_for_gall_bladder_cancer_68.asp?sitearea=.. Accessed March 29, 2008.

4. Gadzijev EM (2002): Surgical anatomy of hepatoduodenal ligament and hepatic hilus. J Hepatobiliary Pancreat Surg. 9(5):531-3.

5. Danzinger RG, Nauta R, and Park J (2005): Biliary Tract. In Essentials of General Surgery, Lawrence PF (ed.); Fourth Edition; Lippincott Williams & Wilkins.

6. Smadja C and Blumgart LH (1994): The biliary tract and the anatomy of biliary exposure. In: Blumgart LH, editor. Surgery of the liver and biliary tract. 2nd ed. Edinburgh [UK]: Churchill Livingstone;.

7. Ito M, Mishima Y, Sato T (1991): An anatomical study of the lymphatic drainage of the gallbladder. Surg Radiol Anat.; 13 (2):89-104.

8. Singh B, Satyapal KS, Moodley J, Haffejee AA (1999): Congenital absence of the gall bladder. Surg Radiol Anat.; 21(3):221-4.

9. Lyons KP, Challa S, Abrahm D, Kennelly BM (2000): Floating gallbladder: a questionable prelude to torsion: a case report. Clin Nucl Med. Mar; 25 (3):182-3.

10. Chowbey PK, Wadhwa A, Sharma A, Khullar R, Soni V, Baijal M(2004): Ectopic gallbladder: laparoscopic cholecystectomy. Surg Laparosc Endosc Percutan Tech. Feb; 14(1):26-8.

11. Isik I, Sezer C, Dursun A (2002): Gastric heterotopia in the gallbladder: a case report. Turk J Gastroenterol. Sep; 13 (3):172-4.

12. Bhattacharjee PK (2005): Bile duct injuries: Mechanism and prevention. Indian J Surg. 67:73-77.

13. Nagral S (2005): Anatomy relevant to cholecystectomy. J Min Access Surg 2005; 1:53-58.

14. Johnson LR, Byrne JH, Downey JM, Goodman HM, Granger DN, Johnson DA, Powell FL, Schafer JA, Schultz SG and Weisbrodt NW (2003): Essential medical physiology (3rd edition). Elservier Academic Press.

15. Wood JR and Svanvik J (1983): Gallbladder water and electrolyte transport and its regulation. Gut 24: 579-593.

16. Plevris JN, Hayes PC, Harrison DJ and Bouchier IAD (1992): Evidence of hydrogen ion secretion from the gallbladder In vitro. Gut.

17. Rege RV and Moore EW (1987): Evidence for H+ secretion by the in vivo canine gallbladder. Gastroenterology; 92: 281-289.

18. Jacyna MR, Ross PE, Hopwood DH and Bouchier IAD (1989): Effects of secretion on sodium ion transport in the human gallbladder. Alimentary Pharmacology and Therapeutics; 3: 293- 297.

19. Toouli J, Bushell M, Stevenson G, Dent J, Wycherley A and Iannos J (1986): Gallbladder emptying in man related to fasting duodenal migrating motor contractions. Australian and New Zealand Journal of Surgery 56: 147-151.

20. Howard PJ, Murphy GM and Dowling RH (1991): Gallbladder emptying patterns in response to a normal meal in healthy subjects and patients with gallstones: ultrasound study. Gut 32, 1406–1411.

21. Dodds WJ, Hogan WJ and Geenen JE (1989): Motility of the biliary system. In: Schultz, S.G. (Ed.), Handbook of Physiology: the Gastrointestinal system, Vol 1, Section 6, Part 2 (28). American Physiological Society, Bethesda, MD, pp. 1055–1101.

22. Weiner I, Kazutomo I, Fagan CJ, Lilja P, Watson LC and Thompson JC (1981): Release of cholecystokinin in man, correlation of blood levels with gallbladder contraction. Annals of Surgery; 194: 321-327.

23. Johnson FE and Boyden EA (1952): The effect of douole vagotomy on the motor activity of the human gallbladder. Surgery 32: 591-601.

24. Benevantano TC and Rosen RG (1969): The physiological effect of acute vagal section on canine biliary dynamics. Journal of Surgical Research 9: 331-334.

25. Persson CGA (1972): Adreno-receptors in the gallbladder. Acta Pharmacologia 32: 177-185.

26. Muller EL, Lewinski MA and Pitt HA (1984): The cholecysto-sphincter of Oddi reflex. J Surg Res; 36: 377-83.

27. Cuschieri A, Steele RJC and Moossa AR.(2002): essential surgical practice 4th ed: disorders of the biliary tract: 375-380.

28. Geenen JE, Hogan WJ, Dodds WJ, Steward ET and Arndorver RC (1980): Intraluminal pressure recording from the human sphincter .

29. Worthley CS, Baker RA, Iannos J, Saccone GTP and Toouli J (1989): Human fasting and post-prandial sphincter of Oddi motility. British Journal of Surgery 76: 709-714.

30. Becker JM and Parodi JM (1993): Basic control mechanisms of sphincter of Oddi motor function. Gastrointest Endosc Clin N Am; 3: 42–66.

31. Bordley J and Olson JE (1979): The use of glucagon in operative cholangiography. Surg Gynecol Obstet; 149: 583– 4.

32. Ross MH and Pawlina W (2006): Histology, Atext and atlas with correlated cell and molecular biology (5th edition). Lippincott Williams & Wilkins.

33. Standring S, Ellis H, Healy JC, Johnson D, Williams A, Collins P and Wigley C (2005): Gray 's anatomy: The anatomical basis of clinical practice (39 edition). Elservier Churchill Livingstone.

34. Lowenfels AB, Maisonneuve P, Boyle P, Zatonski WA. Epidemiology of gallbladder cancer. Hepatogastroenterology. May-Jun 1999;46(27):1529-32.

35. Bernstein CN, Blanchard JF, Kliewer E, Wajda A. Cancer risk in patients with inflammatory bowel disease: a population-based study. Cancer. Feb 15 2001;91(4):854-62. [Medline]

36. Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. Int J Cancer. Apr 1 2006;118(7):1591-602. [Medline].

37. Matsukura N, Yokomuro S, Yamada S, Tajiri T, Sundo T, Hadama T, et al. Association between Helicobacter bilis in bile and biliary tract malignancies: H. bilis in bile from Japanese and Thai patients with benign and malignant diseases in the biliary tract. Jpn J Cancer Res. Jul 2002;93(7):842-7. [Medline].

38.Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. Apr 24 2003;348(17):1625-38. [Medline].

39.Tsuchiya Y, Sato T, Kiyohara C, Yoshida K, Ogoshi K, Nakamura K. Genetic polymorphisms of cytochrome P450 1A1 and risk of gallbladder cancer. J Exp Clin Cancer Res. Mar 2002;21(1):119-24. [Medline].

40.Singh MK, Pandey UB, Ghoshal UC, Srivenu I, Kapoor VK, Choudhuri G. Apolipoprotein B-100 XbaI gene polymorphism in gallbladder cancer. Hum Genet. Feb 2004;114(3):280-3. [Medline].

41.Benjamin IS. Biliary cystic disease: the risk of cancer. J Hepatobiliary Pancreat Surg. 2003;10(5):335-9. [Medline]

42.Hu B, Gong B, Zhou DY. Association of anomalous pancreaticobiliary ductal junction with gallbladder carcinoma in Chinese patients: an ERCP study. Gastrointest Endosc. Apr 2003;57(4):541-5. [Medline]

43.American Joint Committee on Cancer. Staging Resources. AJCC Staging Resources. Available at http://www.cancerstaging.org/staging/index.html. Accessed 2008.

44.Mohandas KM, Swaroop VS, Gullar SU, Dave UR, Jagannath P, DeSouza LJ. Diagnosis of malignant obstructive jaundice by bile cytology: results improved by dilating the bile duct strictures. Gastrointest Endosc. Mar-Apr 1994;40(2 Pt 1):150-4. [Medline].

45.Gupta P, Chitalkar P, Sen A, et al. Combination of gemcite and cisplatin chemotherapy in unresectable gallbladder cancer. J Clin Oncol. ASCO Annual Meeting Proceedings (Post-Meeting Edition). 2007;25, No18s (June 20 Supplement):15166.

46.Valle JS, Wasan HS, Palmer DD, et al. Gemcitabine with or without cisplatin in patients (pts) with advanced or metastatic biliary tract cancer (ABC): Results of a multicenter, randomized phase III trial (the UK ABC-02 trial). J Clin Oncol. (suppl; abstr 4503) 2009;27:15s. [Full Text].

47.Valle JW, Wasan HS, Palmer DD, et al. A multicenter, randomized phase II trial of gemcitabine and oxaliplatin (GEMOX) alone or in combination with biweekly cetuximab in the first-line treatment of advanced biliary cancer: Interim analysis of the BINGO trial. J Clin Oncol. (suppl; abstr 4503) 2009;27:15s. [Full Text].

48.Gallardo J, Rubio B, Ahumada M, et al. Therapy for advanced gallbladder cancer: Improving survival. J Clin Oncol. (May 20 suppl; abstr 15566) 2008;26:[Full Text].

49.Jensen EH, Abraham A, Jarosek S, Habermann EB, Al-Refaie WB, Vickers SA, et al. Lymph node evaluation is associated with improved survival after surgery for early stage gallbladder cancer. Surgery. Oct 2009;146(4):706-11; discussion 711-3. [Medline].

50.Targarona EM, Pons MJ, Viella P, Trias M. Unexpected carcinoma of the gallbladder, a laparoscopic dilemma. Surg Endosc 1994;8:211±13.

51.De Stoll M. Rationis medendi in practice Unindobonensi. Part 1. Vienna:Bernard, 1777.

52. Yamaguchi K, Chijiiwa K, Ichimiya H, Sada M, Kawa Kami K, Nishi Kata F, et al. Gall bladder carcinoma in the era of laparoscopic cholecystectomy. Arch Surg 1996;131:981-4.

53. Silecchia G, Raparelli L, Navalon JM, Gomez AS, Azcoita MM, Materia A, et al. Laparoscopic cholecystectomy and incidental carcinoma of the extrahepatic biliary tree. JSLS 2002;6:339-44.

54. Mori T, Souda S, Hashimoto J, Yoshikawa Y, Oshima M. Unsuspected gallbladder cancer diagnosed by laparoscopic cholecystectomy: A clinicopathological study. Surg Today 1997;27:710-3.

55. Bergdahl L. Gall bladder carcinoma first diagnosed at microscopic examination of gall bladders removed for presumed benign disease. Ann Surg1980;191:19-22.

56. Shieh CJ, Dunn E, Standard JE. Primary cancer of the gallbladder: a review ofa 16 year experience at the Waterbury Hospital Health Center. Cancer 1981; 47:996-1004.

57. Donohue JH, Andrew KS, Herman RM. The national cancer database report on carcinoma of the gallbladder, 1989-1995. Cancer 1998;83:2618±28.

58. Moertel CG. The gallbladder. In Holland JF, Frei E III, eds. Cancer Medicine. 2nd Ed. Philadelphia: Lea & Ferbiger, 1982. pp. 1782-1785.

59. Fortner JG. The experimental induction of primary cancer of the gallbladder. Cancer 1955; 8:689-700.

60. Kowalewski K, Todd EF. Carcinoma of the gallbladder induced in hamsters by insertion of cholesterol pellets and feeding dimethylnitrosamine (35293). Proc Soc Exp Biol Med 1971; 136:482-486.

61.Shieh CJ, Dunn E, Standard JE. Primary cancer of the gallbladder: a review ofa 16 year experience at the Waterbury Hospital Health Center. Cancer 1981; 47:996-1004.

62. Glenn F, Hays DM. The scope of radical surgery in the treatment of malignant tumors of the extrahepatic biliary tract. Surg Gynecol Obstet 1954; 99:529-541.

63. Diehl AK (1980) ; Epidemiology of gallbladder cancer : National cancer Inst ; 60 : 1209-1214 .

64.Piecher JM .(1978) . primary carcinoma of gallbladder . Surg gynaecol obeset ; 147:929-942 .

65.Henson DE , Albres Saavedra J, Corl D. (1992) Carcinoma of gallbladder Histological types , stage of disease , grade &survival rates Cancer 70: 1493-1494

66. Arnaud JP, Casa C, Georgeac C, et al. Primary carcinoma of the gallbladder ± review of 143 cases. Hepatogastroenterology 1995;42:811±15.

67.Hart J , Baruch M , Mordechai S . (1971) Choleithiasis in etology of gallbladder neoplasms . Lancet ; 1151-1153 .

68.Hughes-OD ; Haray-PN ;Williams-IM , Roberts ; Lewis-MH . (1997) . J R Col Surg Edind ; 42(4):280-2 .

69.Muris IM , Morris DL . (1986) . Carcinoma gallbladder . Brit J Hos Med ; 36: 287-280 .