INCIDENCE, CLINICAL PRESENTATION, MANAGEMENT AND OUTCOME OF GALLBLADDER CANCER AS SEEN AT KENYATTA NATIONAL HOSPITAL (1988-2000).

A THIRTEEN YEAR RETROSPECTIVE STUDY FROM 1ST JANUARY, 1988 TO 31ST DECEMBER, 2000.

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A THESIS SUBMITTED IN PART FULFILMENT FOR THE DEGREE OF MASTER OF MEDICINE (SURGERY), AT THE UNIVERSITY OF NAIROBI.

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DECLARATION

I certify that this thesis is my original work and it has not been presented for a degree in any other University.

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DEDICATION

This work is dedicated to my dear parents for their understanding, sacrifice and endurance during the difficult times when my foundation in the speciality of surgery was being laid.

ABBREVIATIONS

APBDJ	-	Anomalous Pancreatobiliary Ductal Junction
CT	-	Computerised Tomography
ERCP	-	Endoscopic Retrograde Cholangiopancreatography
EUS	-	Endoscopic Ultrasonography
FNAC	-	Fine Needle Aspiration Cytology
GIT	-	Gastrointestinal Tract
IORT	-	Intraoperative Radiation Therapy
KNH	-	Kenyatta National Hospital
MRI	-	Magnetic Resonance Imaging
PTC	-	Percutaneous Transhepatic Cholangiography

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SUMMARY

This was a retrospective study of patients with histologically confirmed diagnosis of gallbladder cancer seen and managed at Kenyatta National Hospital during the period 1st January 1988 to 31st December 2000.

A total of 24 patients were seen at Kenyatta National Hospital over the thirteen year period, with an average of 1.9 cases per year. Gallbladder cancer accounted for 0.09% of all malignancies and 0.003% of all admissions during the study period.

The incidence of gallbladder cancer in cholecystectomy specimens at KNH was 1.97%. A total of 203 cholecystectomies were performed for benign gallbladder diseases during the study period, with an average of 15.6 operations per annum. 30.5% of the patients undergoing cholecystectomy for benign gallbladder disease were above 51.0 years of age, with a female to male ratio of 3:1.

The peak age incidence for patients with cancer was 51 - 55 years, with a mean age of 52.0 years of age (range 27 - 82 years). 62.5% of the patients were above 51.0 years of age. There was a female predominance, with a female to male ratio of 2:1.

Most of the patients presented with advanced disease. The commonest presenting symptom was abdominal pain, followed by jaundice, pruritus, nausea, vomiting, anorexia, weight loss, and abdominal distension or mass. 87.5% of the patients had symptoms for less than one year.

The most common physical findings were abdominal tenderness, jaundice, hepatomegaly, pallor, palpable gallbladder, fever and ascites.

Abdominal ultrasound was performed in 83.3% of the patients. Other radiological investigations done include abdominal CT scans, plain abdominal x-rays, barium meal studies, oesophagogastro-duodenoscopy, and percutaneous transhepatic cholangiography.

The laboratory findings were non-specific and not diagnostic of gallbladder cancer. The frequent abnormalities detected include anaemia, leucocytosis, hypoalbuminaemia and elevated serum alkaline phosphatase.

The commonest histological type of gallbladder cancer seen was adenocarcinoma of varying degrees of differentiation (87.5%). Gallstones were present in 41.7% of the patients with gallbladder carcinoma.

The correct pre-operative diagnosis of gallbladder cancer was made in only 8.3% of the patients. In the majority of patients (75%), the diagnosis was established at operation with no preoperative suspicion of the diagnosis. Cholelithiasis, chronic cholecystitis, pancreatic carcinoma, bile duct cancer and liver cancer were considered the most likely preoperative diagnoses. In 16.7% of the patients the diagnosis was first made by the pathologist after cholecystectomy for presumed benign disease.

One third of the patients with gallbladder cancer had exploratory laparotomy and biopsy only. Cholecystectomy was carried out in 7 patients. One patient had partial cholecystectomy performed. No radical surgery was undertaken. 33.3% of the patients underwent palliative biliary-enteric or gastrointestinal bypass procedures.

Only 8.3% of the patients received adjuvant post-operative radiation therapy, while one patient was given postoperative chemotheraphy.

The duration of follow-up was short; with 41.7% of the patients on follow-up for less than two months. One quarter of the patients with gallbladder cancer died within the first month postoperatively, whereas only 4.2% of the patients were still alive and on follow-up one year after the diagnosis of cancer.

INTRODUCTION

Carcinoma of the gallbladder is the most frequent malignant tumour of the biliary tract and the fifth most frequent tumour of the digestive tract [1]. It accounts for 2 to 4% of all gastrointestinal malignancies, with an annual incidence of 2.5 – 2.7 per 100,000 [2,3]. The tumour has a worldwide distribution but there are large geographical and ethnic variations in the incidence of the carcinoma. The reported incidence of the gallbladder cancer in patients who have had operations on the biliary tract is approximately 1% in most series [1,4]. Carcinoma of the gallbladder is commonly seen in females and elderly people, especially those above 65 years of age [1,2,4,5,6,7].

Gallstones and chronic inflammation of the gallbladder are the factors most frequently implicated in the aetiology of gallbladder cancer. The incidence of gallstones in patients with carcinoma of the gallbladder ranges from 70 to 90% in most series[1,3,4,6,8,9], but only 1 to 2% of patients with gallstone disease are at risk of developing cancer [1].

Gallbladder cancer is characterised by late diagnosis, ineffectual treatment and poor prognosis. The signs and symptoms of carcinoma of the gallbladder frequently are those of advanced malignant disease, and unfortunately represent unresectable lesions. The presentation of an early, potentially curable gallbladder carcinoma are generally non-specific and mimic benign diseases of the gallbladder, such as cholelithiasis and cholecystitis. The carcinoma is either discovered incidentally at laparotomy or cholecystectomy for presumed benign disease. Laboratory and radiological studies are seldom helpful in the diagnosis of gallbladder carcinoma [10,11,12,13]. Piehler and Crichlow reported a mean correct pre-operative diagnosis of 8.6% [1].

Surgery is the only treatment modality with a curative potential for carcinoma of the gallbladder but only between 10 and 30 percent of the patients have resectable disease on presentation

[14]. Based on the facts that the major route of spread of the carcinoma appears to be local-regional rather than distant metastasis, and that most of the treatment failures are due to local recurrences, some researchers advocate for aggressive surgical management in selected patients with localised disease in order to improve long-term survival and produce a number of cures. The response of gallbladder cancers to chemotherapy and radiotherapy is generally poor [10,11,12,13,14].

Since Mühe performed the first laparoscopic cholecystectomy in 1985 [11], the technique has rapidly become the surgical procedure of choice over conventional open cholecystectomy, for the surgical removal of the gallbladder in the treatment of symptomatic cholelithiasis and cholecystitis. An unusual complication of this relatively new minimal access procedure is the dissemination of incidental gallbladder cancer to the peritoneum and incisions at the time of laparoscopic cholecystectomy. When carcinoma of the gallbladder is suspected pre-operatively or at the time of laparoscopy, conversion to an open procedure is indicated, as laparoscopic cholecystectomy could be associated with bad prognosis [15,16].

The overall five-year survival rate for gallbladder cancer is less than 5 percent and most long-term survivors are patients whose carcinomas are incidental findings after cholecystectomy for symptomatic gallstone disease [1,11,13].

This retrospective study examines the incidence, the patients' profiles, the various modes of clinical presentation, the management and outcome of gallbladder cancer at Kenyatta National Hospital, the national referral and teaching hospital over a thirteen-year period from 1st January 1988 to 31st December 2000. The study also examines the number of incidental carcinomas of the gallbladder after cholecystectomy for presumed benign gallbladder disease at Kenyatta National Hospital.

LITERATURE REVIEW

HISTORICAL PERSPECTIVE

Carcinoma of the gallbladder is a highly aggressive tumour and its historical background is closely intertwined with that of gallstone disease. Gallstones are the commonest benign disorder of the biliary system. Gallstones have been most frequently implicated in the aetiology of gallbladder cancer [11,12,13,14,17].

Numerous gallstones have been found in the gallbladder of a mummy priestess of Ameren in 21st Egyptian Dynasty (1500 BC). The Greek physician Alexander Tralliarus described calculi within hepatic radicles of the human liver in the 5th century AD. In 1420, Antonio Benivieni gave the first case report of gallstones in man, followed two centuries later by the first good description of jaundice by Riolaus [18]. The first cases of carcinoma of the gallbladder were recorded by Stoll in1777 and Halle in 1786. Frerichs in 1861 mentioned the possible relation of carcinoma to gallstones [18].

The earliest discussions of the surgical treatment of tumours are found in the Edwin Smith papyrus from Egyptian Middle Kingdom about 1600 BC. John Collins Warren, in 1846, introduced the use of ether anaesthetic, and Joseph Lister, in 1867, introduced the principles of antisepsis, leading to subsequent development in the surgical treatment of tumours [10]. The Berlin Surgeon, Carl Johann Langenbuch performed the earliest successful removal of the gallbladder in Lazerus Hospital in 1882 [18]. The safety of biliary surgery in patients with long-standing bile duct obstruction increased greatly in 1935 when Dam suggested the use of vitamin K to decrease the bleeding tendency [18].

Resection of the liver for tumour was first reported in 1890 by Tiffany [10], but haemorrhage was the main cause of the high mortality and morbidity rates encountered by early liver surgeons. Couinaud's description of the segmental anatomy of the liver in 1957, and advances in surgical

techniques, anaesthesia and blood replacement lead to major liver resections been undertaken with low morbidity and mortality [11, 12]. In 1985, Mühe performed the first laparoscopic cholecystectomy [11].

SURGICAL ANATOMY

Embryology

The liver, gallbladder and the biliary tract are derived from the most caudal part of the foregut. During the third week of intrauterine life, proliferation of the endodermal lining of the foregut gives rise to the hepatic diverticulum or bud. The large cranial portion of the diverticulum forms the liver. The small caudal portion expands into the ventral mesentery and gives rise to the gallbladder and the cystic duct. The stalk connecting the hepatic and cystic ducts to the duodenum becomes the bile duct. With the rotation of the duodenum, the common bile duct moves to a posterior position and comes to lie behind the duodenum and pancreas [19].

Gallbladder

The gallbladder is a pear shaped reservoir, 5-12 cm in length with a capacity of about 30-50 mls. It is located on the under-surface of the liver along the junction between the right and left lobes of the liver. It is covered by peritoneum and is separated from the liver parenchyma by the connective tissue of the cystic plate.

It is anatomically divided into the fundus, the body, the infundibulum and the neck. The fundus is the rounded, blind end that normally extends beyond the free anterior edge of the liver. The body is the main storage area and lies in the cystic fossa of the liver. The neck is the funnel-shaped, narrow upper end of the gallbladder and is situated near the right end of the porta hepatis. The neck usually follows a gentle curve and leads to the cystic duct. The convexity of the neck may be distended into a dilatation known as the infundibulum or Hartmann's pouch, in which gallstones may be lodged [11,13,20].

Microscopic structure of the gallbladder

The wall of the gallbladder consists of the following layers: -

i- A mucous membrane composed of simple, high columnar epithelia. The epithelial cells have microvilli on their apical border. The mucous membrane lining the gallbladder is thrown into many folds when the organ is empty giving the interior of the gallbladder a honeycombed appearance. There are no glands in the mucosa of the gallbladder except a few mucous-secreting globular cells in the mucosa lining the neck.

ii- A lamina propria of delicate, reticular connective tissue. There is no muscularis mucosa in the gallbladder.

iii- The muscularis consisting of a layer of smooth muscle equivalent to muscularis externa of the intestine.

iv- A well developed perimuscular (subserosal) coat containing blood vessels and nerves.

v- A serous membrane which blends in some regions with the connective tissue of the liver capsule [21].

Anomalies of the gallbladder [11,13,20]

1. Congenital absence or agenesis of the gallbladder is extremely rare.
2. Bi-lobed gallbladder with a single cystic duct but two fundi.
3. Duplication of the gallbladder with two separate cavities and two separate cystic ducts.
4. Diverticulum of the gallbladder.
5. Septum of the gallbladder.
6. "Phrygian cap" or unusual kinking of the fundus is the most common anomaly of the gallbladder.
7. The gallbladder may be completely invested by peritoneum and may be suspended from the liver by a mesentery. The so-called "floating gallbladder" occurs in about 5% of patients.
8. Left sided gallbladder with the cystic duct entering directly into the left hepatic duct or common duct is extremely rare.
9. Intra-hepatic gallbladder.

10. Several anomalies of ectopic drainage of the intra-hepatic ducts into the gallbladder and cystic duct exist.

Cystic Duct

The cystic duct arises from the neck of the gallbladder and ends by joining the common hepatic duct to form the common bile duct. Its lumen usually measures some 1-3mm. It is variable in length, with an average of 3-4cm. The mucosa of the cystic duct is arranged in a series of spiral folds known as valves of Heister, but do not have any valvular function. The wall of the cystic duct contains muscle fibers which form the sphincter of Lutkens [11,13,20].

The triangle bounded by the common hepatic duct medially, the cystic duct inferiorly and the inferior surface of the liver superiorly is known as Calot's triangle. It is an important area of dissection during cholecystectomy because the cystic artery runs within the triangle [11,13,20].

Variations in the modes of union of the cystic duct and common hepatic duct [11,20]

The mode of union of the cystic duct and common hepatic duct may be angular, parallel or spiral. The cystic duct more commonly enters the bile duct anteriorly or posteriorly, but laterally in only 15 to 20% of the cases.

i) Angular union is the most frequent and is found in 75% of the patients. The cystic duct joins the common hepatic duct at an acute angle.

ii) Parallel union is seen in 20% of cases. Cystic duct joins the common hepatic duct after running parallel to it for a short distance with a common fibrous connective tissue sheath.

iii) Spiral union is seen in 5% of cases. The cystic duct may curve about the common hepatic duct, usually from the posterior aspect.

Points of Union of Cystic Duct with Common Hepatic Duct

i) The cystic duct joins the common hepatic duct in its supraduodenal segment in 80% of cases.

ii) The cystic duct may extend downwards and join the common hepatic duct in retroduodenal or even retropancreatic area.

iii) Occasionally, the cystic duct may join the right hepatic duct or right hepatic sectoral duct.

Blood supply of the gallbladder

The principal blood supply to the gallbladder is derived from the cystic artery. It normally originates from the right hepatic artery behind the common hepatic duct, and courses above and behind the cystic duct for a variable distance, until it passes down the peritoneal surface of the gallbladder and branches. A smaller component of the supply arises from vessels passing directly from the liver [11,13,20].

Variations of the arteries to the gallbladder [11, 13, 20].

1 Cystic artery arises from the right hepatic artery, emerging from behind the common hepatic duct.

2. Cystic artery arises from the right hepatic artery, but courses anterior to the common hepatic duct.

3. Cystic artery originating from the left hepatic artery.

4. Low origin of the cystic artery from the common hepatic or gastroduodenal artery.

5. Double cystic arteries occur in 25% of cases. They may both arise from the right hepatic artery, or the accessory cystic artery may arise from the left hepatic, common hepatic or gastroduodenal artery.

6. Looped right hepatic artery with a short cystic artery arising from the summit of the right hepatic arterial arch.

Venous Drainage of the gallbladder

Venous return is carried through the 2 to 20 small cholecystic veins on the hepatic side of the gallbladder, which drain directly into segment IV of the liver. Venous drainage of the peritoneal side of the gallbladder consists of 1 or 2 cystic veins that also drain into segments IV of the liver and only rarely empty into right portal vein [13,20].

Lymphatic Drainage of the gallbladder

Lymphatic drainage begins in intramural plexus, moves to the cystic node situated at the junction between cystic and common hepatic ducts in the triangle of Calot. Lymph then flows into hiatal nodes, to superior and posterior pancreatico-duodenal nodes and finally to the peri-aortic nodes. Some lymph flows directly from gallbladder to the liver [11,13,20].

Nerve Supply of the Gallbladder

The nerves of the gallbladder arise from the coeliac plexus and reach the gallbladder along the hepatic artery. Motor nerves are made up of vagus parasympathetic fibers mixed with postganglionic sympathetic fibers from the coeliac ganglion. The preganglionic sympathetic level is at T8 and T9. Sensory supply is provided by fibers in the sympathetic nerves coursing to the coeliac plexus through the posterior root ganglion at T8 and T9 on the right side [11,13,20].

EPIDEMIOLOGY

INCIDENCE

Cancer of the gallbladder has a worldwide distribution but its incidence shows enormous variation in populations of different origins. It is the most common malignancy of the biliary tract and the fifth most common malignancy of the gastrointestinal tract; pancreatic cancer occurring about five times as frequently [1,2].

Burdette estimated the annual incidence of carcinoma of the gallbladder to be approximately 2.5 per 100,000 in the United States [2]. Some 6500 deaths due to carcinoma of the gallbladder were recorded in the United States in 1936. Piehler and Crichlow RW in a collective review of 55,543 cases of autopsies found an incidence of 0.55 per cent, varying between 0.18 and 0.81 per cent [1].

In contrast cancer of the gallbladder and biliary ducts accounted for 5.25 per cent of all cancer deaths in Chile in 1975, making it that nation's fourth leading source of cancer mortality and giving Chile the highest gallbladder cancer mortality rate in the world [17].

The incidence of carcinoma of the gallbladder found in patients undergoing biliary tract operations has been reported as 1 to 2 per cent in different series [1, 5]. Diehl and Beral (1981) showed that the incidence and mortality from gallbladder cancer in some countries is decreasing in parallel with the rising rate of cholecystectomy. Mortality from gallbladder cancer seems to have declined in the decade 1971 - 1981 in Britain, USA and Canada. Mortality rates in Sweden and Poland have risen however during the corresponding years. It is suggested that the changes in mortality are inversely related to the cholecystectomy rates [22].

GEOGRAPHIC VARIATIONS

Large geographical, racial and ethnic variations are seen in the incidence of cancer of the gallbladder. Populations identified as having an increased incidence of gallbladder cancer include Southwest American Indians, Northeast Europeans, Mexican Americans, Israelis, Chileans, Bolivians and Japanese immigrants to USA [3, 8, 23].

The incidence of carcinoma of the gallbladder is six to ten-fold higher in American Indians, Mexicans and Alaskan natives than in Caucasians [8]. It is the second most common malignant disease of the gastrointestinal tract in South West American Indians [1]. The high incidence of cancer observed in certain populations correlates with a high incidence of cholelithiasis in these populations [11, 24].

Black Americans and Africans have the lowest incidence [13, 14]. Low rates have been observed among South African Bantus, Nigerians, New Zealand Maoris and Chinese natives and immigrants. Increased incidence of gallbladder cancer has been identified in African Rhodesian women, Japanese women and European immigrant women in Israel [17]. Carcinoma of the gallbladder may occasionally occur in family clusters [4, 11].

AGE / SEX DISTRIBUTION

Cancer of the gallbladder predominates in the elderly females, with a male: female ratio of 3.2 to 1 [1]. Over 90% of the patients are over 50 years and the peak age of incidence is in the 65 to 75 year group [1, 6]. There were no consistent differences in the ages of affected males and females [1]. The incidence of gallbladder cancer increases with age, especially in women with cholelithiasis. The incidence in patients who underwent operations upon the biliary tract is 0.3 per cent in women under 50 years of age, 3.8 per cent when greater than 50 years and 8.8 per cent in those over the age of 65 years [25].

AETIOLOGY

Whereas the aetiology of gallbladder cancer is unknown, several causative factors can be related to the development of this tumour, although the exact pathogenesis remains controversial. Numerous risk factors have been postulated including advanced age, female sex, ethnicity, pre-existing biliary tract disease, chronic inflammation of the gallbladder, benign gallbladder neoplasms, occupational exposures, chemical carcinogens, diet, bile stasis, radiation, and chronic mechanical irritation [17].

A - CHOLELITHIASIS

The presence of gallstones is the most common associated factor in the aetiology of carcinoma of the gallbladder [1, 8, 10, 11, 12, 23]. The fact that cholelithiasis has been observed in between 70 to 90 per cent of patients with gallbladder cancer [1, 2, 4, 6, 8, 9, 23, 26, 27, 28, 29] has led some investigators to speculate that gallstones may be important in the pathogenesis of gallbladder cancer or that risk factors for gallstones may likewise predispose to carcinoma. Advanced age, female sex, increasing parity, ethnic predisposition, obesity, consumption of diets high in fats and calories, which are also risk factors for gallstones, increase the risk of gallbladder cancer [17, 23].

Other researchers have concluded that there is no aetiological relationship between the two. Derman et al suggested that the low incidence of carcinoma of the gallbladder in patients with gallstones decreases the likelihood of gallstones being the aetiology [24].

In 1971, Hart J and associates documented a greater incidence of stones in patients with carcinoma than in the general population at all age levels, a similar frequency of gallstones in both males and females with carcinoma despite the higher frequency of stones in females in the general population and the long history of abdominal complaints ascribed to cholelithiasis seen in a significant number of patients with carcinoma of the gallbladder [30].

Warren and Balch found that only 16% of secondary carcinoma of the gallbladder, even with mucosal involvement, are associated with cholelithiasis, making formation of stones secondary to tumour influences unlikely [9]. There has been no predominance of any single type of calculus in association with carcinoma of the gallbladder [1].

The epidemiology of cholelithiasis parallels that of gallbladder carcinoma. The high incidence of cancer in certain ethnic groups correlates with the high incidence of cholelithiasis in these populations [11, 29]. Symptomatic cholelithiasis has been found to occur two or three times more frequently and at an earlier age in Southwest American Indians, who have a high incidence of carcinoma of the gallbladder, than in the Caucasian populations [31]. The risk of gallbladder cancer is approximately 4 to 5 times higher in patients with gallstones, than in patients without gallstones. In those populations where onset of gallstone disease occurs in the first few decades, the risk is much higher [23].

Biochemical factors have also been suggested as playing a role in carcinogenesis. The biliary tract is continually exposed to bile, a complex combination of chemicals that have the potential to be quite toxic. The composition of both the bile and gallstones in countries with a high incidence of carcinoma of the gallbladder was different from that of bile and gallstones in countries with low incidence [14, 32]. Abnormal hepatic bile with low ratios of bile acid and lecithin to cholesterol has been identified in Southwest American Indians both with and without gallstones [32].

Levels of glycolithocholic acids were increased in Bolivian patients with cholelithiasis and increased even further in patients with cholelithiasis and cancer. There were virtually no lithocholic acid conjugates in the bile of US patients with and without gallstones. Thus the large proportion of lithocholic acid in the patients' bile may predispose to gallstone formation, and such patients may have an increased susceptibility to cancer because their bile contains a large

proportion of glycolithocholic acid, a known co-carcinogen [33]. Lithocholic acid is formed during the enteric portion of the enterohepatic circulation of chenodeoxycholic acid by removal of the 7α-hydroxyl group by bacterial 7α-dehydroxylase.

Gall bladder cancer is more common among females, as is gallstone disease [4, 29]. Gallstones and the female sex are risk factors which operate independently. In 1984 Sellner analysed 19167 autopsy records and showed a predominance of cancer in females in both groups with and without cholelithiasis with a ratio of 2.2:1 and 3.2:1 respectively. Cholelithiasis was present in 6289 cases and gallbladder cancer in 342 of these (5.44%). In 48 cases, a gallbladder cancer occurred in absence of cholelithiasis. The study confirmed the well-established relationship between gallbladder cancer and cholelithiasis and reveals a significant correlation between female sex and carcinoma of the gallbladder [34].

The role of gallstones in the development of carcinoma has also been suggested in studies that have reviewed the relationship between the frequency of cholecystectomy and the incidence of carcinoma. In 1981, Diehl and Beral observed a decrease in the incidence of carcinoma of the gallbladder, as the frequency of cholecystectomy increases per 100,000 inhabitants [22].

In the majority of patients with gallstones, the risk for developing gallbladder cancer while increased is still quite low. In autopsy studies, the incidence of carcinoma of the gallbladder in all patients with cholelithiasis is only 1 to 3% irrespective of age [1]. Maringhini et al (1987) estimated the risk of developing carcinoma to be 1% of calculus gallbladders 20 years after initial diagnosis of gallstones, with the risk increased mainly in men [35].

The risk of malignant degeneration correlates with the length of time gallstones have been present. Gallbladder cancer developed in only 5 of 2583 patients with gallstones followed for a median of 13 years [35]. Patients with gallstones larger than 3cm have a 10-fold risk of developing a gallbladder cancer compared to those with stones less than 1cm [36].

One-quarter of carcinomas of the gallbladder develop without documented cholelithiasis [1]. Hutts (1973) reported acalculous carcinoma developing in Uganda, a population where cholelithiasis is a rarity, yet still maintaining a female predominance, pointing out the possibility of other factors [37].

The mechanism of how gallstones relate to the development of carcinoma remains controversial. Chronic trauma and inflammation of the gallbladder mucosa produced by stones leading to hyperplasia and dysplastic changes and carcinoma, has been suggested as a possible hypothesis. Stone-containing gallbladders have been shown to have an increased cell turnover and cellular mucosal dysplasia has been frequently reported in gallbladders harbouring carcinoma [11, 13, 14].

Some experimental studies in laboratory animals have been successful in inducing cancer of the gallbladder by implantation of foreign materials e.g. human gallstones, glass beads, etc., in the gallbladders of guinea pigs. The results have been inconclusive particularly regarding chemical and / or mechanical irritation as possible aetiologies, and the reproducibility and relevance of these studies to humans is uncertain. Petrov NH and Krotkina NA (1947) were able to induce carcinoma of the gallbladder in animals after the implantation of radium-containing rods [38]. Induction of cancer of the gallbladder has been most successful in the cat. Fortner and Randall (1961) placed gallstones into the gallbladders of 126 cats and after 4 to 5 years they found carcinoma of the gallbladder in three cats [39].

B – CHRONIC CHOLECYSTITIS

Chronic cholecystitis is also associated with gallbladder carcinoma and this has led to the theory that cholecystitis per se is a causative factor in the disease. In 1980, Broden and Bengtsson found that the relative risks of cancer is increased when the signs and symptoms of

cholecystitis have previously occurred [40]. In a series, between 40% and 50% of patients with carcinoma of the gallbladder had histories of antecedent chronic cholecystitis [1].

Histologically, cholecystitis is usually present in gallbladders with carcinoma, and when chronic cholecystitis has led to gallbladder calcification, the risk of malignancy is higher, varying between 12.5% to 61% [41, 42]. Calcification of the wall of the gallbladder, the porcelain gallbladder is an end-stage of chronic cholecystitis secondary to gallstones.

The isolated role of calcified gallbladders in neoplastic degeneration has not been subjected to epidemiological scrutiny as the majority of calcified gallbladders contain gallstones. Prophylactic cholecystectomy for the prevention of carcinoma in patients with porcelain gallbladders is justified because of the very high risk of cancer in these patients [41].

C - ANOMALOUS PANCREATICOBILIARY DUCTAL JUNCTION

Anomalous pancreaticobiliary ductal junction (APBDJ), an anatomical mal-junction between the pancreas and the bile duct, with or without choledochal cyst, is frequently associated with biliary tract carcinoma. An APBDJ is associated with 15 to 25% incidence of gallbladder cancer [43, 44].

It has been postulated that the junction allows the reflux of pancreatic juice into the biliary tree, and the mixture of refluxed pancreatic juice and stagnant bile juice acts as an irritant factor to the biliary tract epithelium leading to chronic inflammation, epithelial hyperplasia and metaplasia. These mucosal changes could be precursors of the development of invasive carcinoma [13, 14, 43, 44]. p53 mutations may contribute to the transition from premalignancy to malignancy in the early stage of carcinogenesis of gallbladder mucosa.

In 1985, Kimura, using endoscopic retrograde cholangiopancreatography revealed an anomalous pancreaticobiliary ductal union in 16.7% of 95 patients with gallbladder cancer. An

anomalous union was noted in only 2.8% of 681 patients with hepatobiliary or pancreatic diseases excluding gallbladder carcinoma [44].

D – CHEMICAL CARCINOGENS

A variety of chemical carcinogens including methylcholanthrene, dimethylnitrosamine, α-aminoazotoluene, various nitrosamines induce carcinoma of the gallbladder in laboratory animals [45, 46]. No gallbladder carcinogens have yet been identified in humans.

Fortner (1955) was able to induce cancer by implanting pellets of methyl cholanthrene, which has chemical similarity to the naturally occurring bile acids, into the gallbladders of cats and dogs [46].

Kowalewski and Todd (1971) reviewed the multifactorial aetiology of the disease in animal experiments and suggested the possible dual role of gallstones and carcinogens in cancer production. Carcinoma of the gallbladder was induced in 68% of hamsters who had cholesterol pellets inserted into the gallbladder and were subsequently fed dimethylnitrosamine, while only 6% of controls fed the carcinogen alone had cancer develop [47].

In 1978 Lowenfels suggested that stasis and infection may favour conversion of bile acids to more active substances [48]. Irving (1981) reported gallbladder cancer in patients following 5 years of therapy with chenodeoxycholic acid which could theoretically be due to conversion of bile acid to an active carcinogenic intermediate [49].

A high incidence of gallbladder cancer is seen in people who worked in rubber, automobile, wood finishing and metal fabricating industries [1, 17].

E - BENIGN LESIONS OF THE GALLBLADDER

Gallbladder adenomas [50, 51], epithelial dysplasia [52] and adenomyomatosis [53] have been associated with gallbladder carcinoma. Selzer and co-workers (1962) reviewed 70 benign tumours of the gallbladder without associated cholelithiasis and concluded that the risk of malignant degeneration in benign tumours of the gallbladder without associated cholelithiasis is very small [54].

Epithelial dysplasia has been observed in the mucosa surrounding gallbladder carcinoma and co-exists with metaplasia in a high percentage of cases. Aidridge and Bismuth found one case of dysplasia within an area of metaplasia in 277 cholecystectomy specimens, while dysplasia of metaplastic epithelium surrounded neoplasm in 67% of the 15 carcinomatous specimens [50]. Albores-Saavedra (1980) found 83% of the cholecystectomy specimens excised for cholelithiasis or cholecystitis exhibited epithelial hyperplasia, 13.5% atypical hyperplasia and 3.5% carcinoma in situ. Carcinoma in situ was also observed in the mucosa adjacent to invasive carcinomas in 79% of surgical cases and in 52.9% of autopsy cases. Thus suggesting that metaplasia and hyperplasia of the gallbladder may progress to dysplasia and finally invasive carcinoma [52].

The presence of gallbladder polyps has been associated with an increased incidence of neoplasia in upto 8% of patients. Large polyp size, gallstones that have been present for a long time and single polyps appear to be more frequently associated with carcinoma of the gallbladder [17]. Most polypoid lesions of the gallbladder are pseudotumours, such as cholesterol polyps or hyperplastic polyps. Both inflammatory and cholesterol polyps are associated with no appreciable risk of malignant degeneration [1].

Gallbladder adenomas have been noted together with carcinoma and carcinoma in situ has been discovered within adenomata, suggesting progression from adenoma to carcinoma. Kozuka et al (1982) demonstrated the direct relationship between benign adenoma, adenoma containing carcinoma in situ and invasive carcinomas. In 1605 cholecystectomy specimens, 11

harboured benign adenomas, 7 harboured adenomas with malignant change and 79 harboured invasive carcinomas [51].

The incidence of carcinoma developing in a polypoid lesion increases appreciably when the polyp is larger than 10 mm [51, 55]. Cholecystectomy for polypoid lesions of the gallbladder is best justified when stones are present, although cholecystectomy has been recommended if polyps greater than 10 mm in diameter has been diagnosed in asymptomatic patients even in the absence of stones [49, 52].

Adenomyomatosis of the gallbladder is generally considered a benign condition but recently cases of carcinoma arising in areas of adenomyomatosis have been reported [53].

F - CHRONIC INFLAMMATORY BOWEL DISEASE

Patients with chronic inflammatory bowel disease have a fivefold to tenfold increased risk of developing carcinoma of the bile ducts. Occasionally the gallbladder is the site of origin of the tumour. In a review by Ritchie and co-workers, only 13% of malignant tumours of the biliary tract in association with ulcerative colitis were found to have originated in the gallbladder [56]. These malignant lesions frequently occur without pre-existing hepatobiliary disease, including cholelithiasis and have been noted to occur upto 13 years after total colectomy and proctectomy [57].

G - OTHERS

Typhoid infection of the gallbladder has been associated with cancer occurring many years later. It has been suggested that the typhoid bacillus could alter the bile, making it more carcinogenic [58].

Polyposis coli has also been associated with carcinoma of the gallbladder. By 1984, four cases of polyposis coli coexisting with a carcinoma of the biliary tract have been reported in the literature [59].

Previous gallbladder surgery has also been associated with a higher incidence of carcinoma of the gallbladder. The presence of retained gallbladder after cholecystostomy is associated with an increased risk of developing carcinoma from 1.3 to 50 years after the original procedure, with a mean of 16 years [6, 60].

PATHOLOGY

The gallbladder has a simple histologic structure but it gives rise to a variety of malignant tumours. Over 98% of such tumours are carcinomas, which result from the neoplastic transformation of the lining epithelium [17].

A) MACROSCOPIC FEATURES

The common gross appearance of the carcinoma of the gallbladder is usually a diffuse thickening and induration of the gallbladder wall, that may cover a variable proportion of the organ, often with infiltration of the surrounding structures. These infiltrating tumours are usually scirrhous and firm in consistency [11, 17, 61].

The gallbladder may be distended, contracted or collapsed, or have an hourglass deformity if the tumour constricts the lateral walls [17]. As the tumour progresses, the gallbladder may fill with tumour or may contain mucinous exudate with or without gallstones. Occassionally, the proteinaceous material within the lumen becomes infected and leads to cholangitis. Calcification of the tumour is occasionally seen [11].

Less frequently, the tumour is found to be polypoid or papillary with projections into the lumen or cystic duct. Papillary carcinomas grows into the lumen as an irregular, fungating, cauli-flower like mass but at the same time invade the underlying wall. The luminal portion may be necrotic, haemorhagic and ulcerated [11, 17].

Most commonly, the cancer originates in the gallbladder fundus followed by the neck [61]. Marcial Rojas and Medina found that 60% of the carcinomas in their series were located in the fundus of the gallbladder, 30% in the mid portion and 10% in the neck [62].

B) MICROSCOPIC FEATURES

A variety of histological types are seen, none of which discernibly exhibits different patterns of growth or clinical effects. Histologically, well-differentiated adeno-carcinomas are the most common type accounting for 80% to 95% of the malignant primary tumours of the gallbladder [11, 61, 63]. In spite of the aggressiveness of gallbladder adenocarcinomas, most are well-differentiated, mucus secreting tumours.

Results of a review of 2091 patients by Piehler and Crichlow in 1978 revealed the histologic appearance of adenocarcinoma in 82.3%, undifferentiated carcinoma in 6.9%, squamous cell carcinoma in 7.3%, adenocanthoma in 1.4%, carcinoma in situ in 0.7%, other mixed malignant lesions of epithelial origin including carcinoid and melanoma in 1% and unspecified malignant tumours in 4.4% [1].

Papillary carcinomas are well-differentiated adenocarcinomas that show a papillary or a papillotubular structure at macroscopy and have a polypoid growth from the epithelial surface. Papillary adenocarcinomas are more localized than other types of adenocarcinomas and may have a better prognosis. Invasion of the liver and lymph node metastasis are less frequent in papillary adenocarcinoma [13, 17, 63, 64]. Hart and Modan, reviewing 334 patients with carcinoma of the gallbladder observed 5-year survival rate of 24% in patients with papillary adenocarcinomas while only 10% of patients with other types of adenocarcinomas were alive after 1 year [11].

Recently unusual histologic types of gallbladder carcinoma have been identified. In a review of 159 cases of gallbladder carcinoma, Albores-Saavedra identified four unusual histologic types: oat-cell carcinoma, giant-cell adenocarcinoma, intestinal-type adenocarcinoma and adenocarcinoma with choriocarcinoma-like areas, which are negative on immunohistochemical staining for human chorionicgonadotrophin. Except for oat-cell carcinomas, the other three histological types may probably represent variants of adenocarcinomas. These four histologic

types were more common in women than in men, usually coexisted with lithiasis, and had a highly aggressive clinical behaviour [65].

Less than 5% of the tumours of the gallbladder are squamous cell carcinomas and mixed adenosquamous or adenocanthoma. Squamous cell carcinomas are rare and nearly always associated with squamous metaplasia of the lining epithelium [17]. Adenosquamous carcinomas have a mixture of glandular and squamous elements. These tumours may show a different behaviour from squamous cell carcinoma, with lymph-node metastases occurring late in the evolution of the disease in spite of the extensive growth. The better prognosis for this particular form of carcinoma may justify radical operative procedures [13, 17].

Another 5% of tumours are undifferentiated or anaplastic carcinomas and among these are found a small number of small cell and oat cell carcinomas. In 1988 Guo K J et al classified 21 among 284 cases of carcinoma of the gallbladder as undifferentiated and found that they were associated with poorer prognosis than that of patients with differentiated adenocarcinoma [66]. A few adenocarcinomas are poorly differentiated and composed of small cells. Oat cell carcinomas are similar to oat cell tumours of other sites, particularly the lung [65]. They can give rise to Cushing's syndrome and other endocrine syndromes as well. Clinically patients with oat cell carcinomas cannot be differentiated from those with the more common adenocarcinomas. The oat cell carcinomas may be related to APUD tumours [17].

Other rare primary tumours of the gallbladder include carcinosarcoma, sarcomas-including leiomyosarcoma, haemangiosarcoma, malignant melanoma, and very rarely primary malignant lymphoma. Carcinoid tumours may also occur [13, 17]. Secondary tumours are found in the gallbladders of 6% of patients dying with cancer [61].

Carcinoma of the Cystic Duct

Carcinoma of the cystic duct is an extremely rare lesion, making upto 2.6 to 12.6% of all extrahepatic bile duct cancers. Its prognosis is much better than carcinoma of the gallbladder, as it will cause symptoms at an early stage. It may present with features of obstruction of gallbladder producing mucocele, or when advanced, will mimic carcinoma of the hepatic duct. In occasional instances, it may compress the common bile duct and mimic the Mirrizzi syndrome [11, 12].

MODES OF SPREAD

Gallbladder tumour spread by direct extension, lymphatic, vascular, neural, intraductal and intraperitoneal means [67].

1) LYMPHATIC SPREAD

The lymphatic drainage of the gallbladder begins in the intramural plexus, moves to the cystic nodes, and choledochal nodes, into hiatal nodes, to superior and posterior pancreaticoduodenal nodes and finally to periaortic chain. Lymph drainage of the gallbladder is primarily to the nodes along the common bile duct and not to the hilus of the liver, and so nodal metastasis can occur in the absence of liver involvement.

The incidence of nodal metastasis varies from 20 to 70% of the cases [4, 63, 67]. Chao (1991) reported 53% incidence of lymphadenopathy in 74 cases with nodes involved being pancreatic (22%), porta hepatis (18%), choledochal (8%), cystic (6%), periaortic (16%), mesenteric (6%) [68].

In 1997 Tsukada K et al noted that the peri-choledochal lymph node was the most common metastatic lymph node followed by the cystic node. There was no neurovascular invasion or lymph node involvement in 15 patients with pT_1 tumour. The frequency of lymph node involvement is strongly influenced by the depth of invasion of the primary tumour [69].

2) VASCULAR SPREAD

The venous drainage on the hepatic side of the gallbladder takes place through the cholecystic veins, ranges from 2 to 20 in number, which drain directly into segment IV of the liver. On the peritoneal side of the gallbladder, one or sometimes two cholecystic veins, which lie subperitoneally, also drain into segment IV of the liver and rarely empty into the portal vein.

Vascular invasion, a relatively minor form of carcinomatous spread in the gallbladder is seen in only 10 to 20% of cases. Vascular metastasis of the carcinoma leads initially to localised involvement of the liver adjacent to the gallbladder [67].

3) INTRADUCTAL SPREAD

Spread of the tumour intraluminally through the bile duct system occurs in 19% of patients and is characteristic of papillary subtype. The intraluminal and intraductal extension of carcinomas, with less aggressive invasion of the gallbladder could create symptomatic obstruction in the early stage of tumour development, leading to earlier diagnosis and more favourable prognosis [67].

4) INTRANEURAL SPREAD

Fahim et al reported neural invasion in 23.8% of their surgical cases, although involvement was demonstrated only in the wall of the gallbladder [67].

5) DIRECT INVASION / INTRAPERITONEAL SPREAD

Intraperitoneal spread leads initially to local invasion of the liver and other surrounding abdominal organs – duodenum, stomach, hepatic flexure of the colon, anterior abdominal wall or omentum. Fistula formation to adjacent organs may occur [61].

Liver invasion is reported in 50% of patients in different series [63, 67, 68]. Sumiyoshi found that liver invasion and lymph node metastasis were present regardless of the histologic types and were more related to the extent of subserosal involvement present [63]. Fahim and associates observed that 85% of patients with involvement of the liver had metastases localised to the area of the primary carcinoma [67].

The gallbladder fossa is involved at an early stage by direct invasion and by haematogenous permeation along cholecystic veins draining from the gallbladder into the liver. Haematogenous spread through veins draining from gallbladder neck along cystic duct and into quadrate lobe also occurs at an early stage [11].

The common hepatic duct is frequently involved by direct extension, particularly with tumour originating in neck of the gallbladder or Hartman's pouch. The gallbladder cancer can closely mimic the clinical presentation and radiographic features of hilar bile duct tumours [11].

Haematogenous spread to distant sites and transcoelomic spread do not occur until the tumour is locally advanced. Sites of distant metastases include small bowel, bone, adrenals, ovary, bladder, umbilicus and thyroid [70]. Distant metastasis may be found in trancheobronchial and supraclavicular lymph node [17].

STAGING OF GALLBLADDER CARCINOMA

A – TNM STAGING OF UICC / AJCC

The American Joint Commission on Cancer (AJCC) and the Union Internationale Centre de Cancer (UICC) established a staging system using TNM classification with 4 stages.

TNM Staging

T – PRIMARY TUMOUR

T_0: No evidence of primary tumor

T_{1S}: Carcinoma in situ

T_1: Tumor confined to mucosal or muscular layer

T_{1A}: Tumor limited to mucosa

T_{1B}: Tumor invades the muscle layer

T_2: Tumor invades the perimuscular connective tissue

T_3: Tumor invades the serosa and / or invades one adjacent organ (extension 2 cm or less into the liver)

T_4: Tumor extends more than 2 cm into the liver, and/or into two or more adjacent organs

N – REGIONAL LYMPH NODES

N_0: No regional lymph node metastasis

N_1: Regional lymph node metastasis

N_{1A}: Metastasis in cystic duct, pericholedochal or hilar nodes (i.e. in the hepatoduodenal ligament)

N_{1B}: Metastasis in peripancreatic (head only), periportal, coeliac, or superior mesenteric lymph nodes

M – DISTANT METASTASIS

M_0: No distant metastasis

M_1: Distant metastasis

Stage Grouping

Stage 0	T_{IS}, N_0, M_0
Stage I	T_1, N_0, M_0
Stage II	T_2, N_0, M_0
Stage III	T_1, N_1, M_0
	T_2, N_1, M_0
	T_3, Any N, M_0
Stage IVA	T_4, Any N, M_0
Stage IVB	Any T, Any N, M_1

B – NEVIN STAGING SYSTEM

Nevin JE et al in 1976 devised a staging system, from review of 66 cases and a literature review of 399 cases, that divided the disease into 5 stages based on the depth of invasion [25].

Stage I- Intramucosal only

Stage II – Involvement of mucosa and muscle layer

Stage III – Transmural involvement

Stage IV– Transmural invasion and cystic duct, lymph node metastasis

Stage V – Metastasis to liver and distant sites

The Mayo clinic proposed a modification of Nevin System by placing contiguous extension of tumour into the liver into Stage III rather than Stage IV [13].

CLINICAL FEATURES

The lack of specific signs or symptoms prevents detection of carcinoma of the gallbladder at an early and resectable stage. Clinical diagnosis of a gallbladder carcinoma is usually only possible in the advanced and invasive stages, when the tumour becomes symptomatic [1, 5, 12, 13]. At this stage, there is no hope of cure. The signs and symptoms of gallbladder cancer are generally non -specific, often resembling those of cholecystitis and cholelithiasis. The diagnosis is seldom made with conviction preoperatively. In only 10 to 25% of patients is the correct diagnosis made before surgery [10, 11, 12, 13].

Most carcinomas of the gallbladder are unexpected findings at laparotomy or are initially detected by the pathologist on cholecystectomy specimens removed with presumed diagnosis of symptomatic cholelithiasis. Piehler and Crichlow observed that 12% cases of cancer of the gallbladder were discovered by the pathologist on cholecystectomy specimens which were removed for a presumed benign disease [1]. Incidental carcinomas have no characteristic symptomatology and symptoms attributable to gallstones, ranging from vague dyspepsia or biliary colic to acute or chronic cholecystitis, are present [11].

Nearly all patients with gallbladder cancer exhibit one of the following clinical syndromes : (1) acute cholecystitis, (2) chronic cholecystitis, (3) obstructive jaundice, (4) non-specific abdominal complaints. 16% of patients with carcinoma of the gallbladder present with the clinical syndrome of acute cholecystitis preoperatively [1]. In Thorbjarnasons experience, approximately 1% of all patients operated upon for acute cholecystitis were found to have carcinoma of the gallbladder at the time of operation in association with cholecystitis. These patients have less advanced carcinoma with both a higher incidence of resectability (70%) and longer survival [71].

Obstruction of the cystic duct by tumour or stone sometimes initiates an attack of acute cholecystitis. Occassionally papillary tumour will produce cystic duct obstruction without invasion by impaction of the tumour in Hartman's pouch [13].

About 43% of patients with gallbladder cancer present with histories consistent with the diagnosis of chronic cholecystitis [1]. Between 20 and 60% of symptomatic patients in various series had a definite and recent change in symptomatology, usually relating to change in quality or frequency of pain and occasionally to development of new symptoms such as jaundice, anorexia or weight loss [1].

Jaundice is found in 30 to 60% of patients and is usually the result of common bile duct obstruction. Widespread liver metastases are responsible for jaundice less often [17]. Jaundice is a poor prognostic sign, since 85% of patients with jaundice have non-resectable lesions at operation [7]. Other features e.g. palpable abdominal masses, ascites, duodenal obstruction are associated with irresectability.

Tumour may present with non-specific constitutional symptoms of malignant nature or with features of an intra-abdominal malignancy of uncertain origin. Symptomatic invasion by the carcinoma of, or fistulization to, adjacent liver, stomach, duodenum, colon, or kidney, often in the presence of non-specific constitutional symptoms of malignant disease frequently led to the diagnosis of carcinoma originating in the symptomatic organ [1].

A small percentage of patients may present as non-specific benign gastrointestinal disorder. About 10% of patients present with duodenal obstruction [17]. Invasion of the upper GIT can lead to obstruction or bleeding mimicking peptic ulcer disease. Gastrointestinal bleeding may result from haematobilia, from direct invasion of stomach, duodenum or colon, from altered coagulation from hepatic failure as a terminal manifestation of the disease and may also be a result of benign peptic ulceration in association with malignant disease [1].

Advanced disease commonly presents itself with multiple symptoms, including abdominal pain, nausea and vomiting, weight loss, jaundice, anorexia and pruritus [5, 70]. In their collective review, Piehler and Crichlow found 76% of symptomatic patients had pain, 38% had jaundice, 32% had nausea and vomiting and 39% had weight loss [1]. 80% of patients have symptoms for less than six months prior to their presentation [6, 70]. The most common presenting complaint is right upper quadrant pain similar to previous episodes of biliary colic but more persisitent [68]. Wanebo in 1982 found that the major clinical signs included tenderness in the right upper quadrant and epigastrium (57%), mass in the same area (54%), hepatomegaly (37%), jaundice (37%), cachexia and fever (10-16%) and ascites (7%) [6].

Carcinomas of the gallbladder have occasionally been associated with paraneoplastic syndromes such as Cushing's syndrome, acanthosis nigricans, pemphigoid skin lesions, Leser-Trelat sign, and Zollinger-Ellison syndrome. Carcinomas of the gallbladder can also cause Krukenberg tumours of the ovary [17]. Patients with carcinoma of the gallbladder may have atypical presentations and unusual associations such as, gastric outlet obstruction, liver abcess, gallbladder empyema, Mirrizzi's syndrome, inguinal or left supraclavicular lymph node metastasis and umbilical metastasis.

INVESTIGATIONS

The preoperative diagnosis of gallbladder cancer at an early and resectable stage is exceptional and difficult because of the non-specific clinical, biochemical and radiological features of the tumour. Once the tumour has become symptomatic the diagnosis is easier [1, 5, 11, 68, 72]. In 1991 Chijiiwa found that accurate preoperative diagnosis had important therapeutic implications. The use of new imaging techniques combined with a high index of clinical suspicion should lead to a preoperative diagnosis in the majority of advanced cases [73].

LABORATORY INVESTIGATIONS

Laboratory findings, although abnormal, are non-specific and are not diagnostic of neoplasms of the gallbladder.

Anaemia of a mild degree is common. Vaittinen's study of 390 patients with cancer of the gallbladder revealed mild anaemia, hemoglobin less than 12 grams percent in 55%, severe anaemia, hemoglobin less than 10 grams percent in 22%; leukocytosis greater than 10,000 in 41% and leukamoid reaction in 1% [4].

Majority of non-jaundiced patients have elevated alkaline phosphatase, in the presence of normal serum bilirubin levels [1,4]. This may be due to the early invasion of the gallbladder bed, unilateral obstruction of a hepatic duct, cholangitis or liver metastasis [11]. Vaittinen found 63% of patients with carcinoma of the gallbladder to have elevated alkaline phosphatase levels without hyperbilirubinaemia, and noted that 42% of such patients had resectable lesions [4].

RADIOLOGICAL INVESTIGATIONS

A. PLAIN ABDOMINAL X-RAYS

Plain abdominal x-rays are of limited value in the assessment of patients with gallbladder cancer, although the radiographs may occasionally show evidence of gallstones, a tumour mass or gallbladder calcification. Only 15 to 20% of gallstones are radio-opaque. Rogers LF et al (1973) noted that gallbladder calcification not producing characteristic porcelain gallbladder may also be associated with malignant change [74].

B. ORAL CHOLECYSTOGRAPHY

Oral cholecystography is performed by oral administration of an iodinated lipid-soluble contrast medium that is absorbed from the gastrointestinal tract and concentrated in the gallbladder where it becomes visible on a radiograph.

Over 90% of patients with carcinoma of the gallbladder will not have visualization of the gallbladder with oral cholecystography because of cystic duct obstruction or because the gallbladder mucosa is unable to absorb fluid and concentrate the contrast material [4]. Grieco RV et al (1963) found that in the overwhelming majority of the 50 patients with fixed filling defects in well opacified gallbladders, the lesions were due to cholesterolosis and in the absence of gallstones, malignancy is most unlikely [75].

Non-visualization of the gallbladder is a non-specific finding and can be considered to be reliable evidence of gallbladder disease if extrabiliary causes of non-visualization can be excluded. These include failure to ingest the oral contrast medium, vomiting, malabsorption, liver disease or diarrhea. In recent years oral cholecystography has been superceded by ultrasonography.

C. PERCUTANEOUS TRANSHEPATIC CHOLANGIOGRAPHY (PTC)

With fluoroscopic guidance, a 22-gauge Chiba needle is introduced under local anaesthesia through the skin and into the substance of the liver. After positioning in a bile duct, contrast medium is then injected to fill the whole biliary tree and a cholangiogram is obtained.

PTC in jaundiced patients may demonstrate several features within the intrahepatic bile ducts highly suggestive of gallbladder cancer. These features include stricturing, distortion or nonfilling of bile ducts draining segments IV and V of the liver and are due to the direct intrahepatic invasion of the bile ducts by the cancer.

Collier NA (1984) observed changes within intrahepatic ducts in 5 of the 14 jaundiced patients with gallbladder cancer leading to the correct pre-operative diagnosis in all 5 [76]. PTC is an invasive procedure with major complications, such as bile leakage into the peritoneum, haemorrhage and cholangitis occurring in about 4% of the patients.

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D. ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATICOGRAPHY (ERCP)

Using a duodenoscope, the papilla of the Vater can be cannulated and the biliary tract and the pancreatic duct can be visualized after injecting a water soluble contrast.

Ogoshi K and Niwa M (1977) reviewed 1600 cases who had ERCP over a 5 year period and in 60 the diagnosis was gallbladder cancer. Nonfilling of the gallbladder in 3 cases and infiltration of the common bile duct in 8 cases [76]. ERCP requires expensive equipment and technical skill and is not widely available. Sepsis and acute pancreatitis are the major complications of ERCP.

E. ULTRASONOGRAPHY

Ultrasonographic findings in carcinoma of the gallbladder may be classified into :-

i) Primary - these are specific features indicative of carcinoma and include thickening of the gallbladder wall and the presence of a fungating or polypoid mass in the bladder.

ii) Associated – these are features associated with gallbladder cancer e.g. gallstones, dilated bile ducts, metastatic lesions in the liver or retroperitoneal lymph node enlargement.

Olken SM et al (1978) first reported the pre-operative diagnosis of a case of gallbladder cancer with nodal metastases based on ultrasound findings in a non-jaundiced patient [78].

The use of grey-scale ultrasonography may have a high rate of diagnostic accuracy in detecting gallbladder cancer especially in advanced cases. Yeh HC (1979) diagnosed carcinoma of the gallbladder by ultrasonography in 84.6% of patients [79] Dalla Palma L et al(1980) and Chijiiwa K et al (1991) reported correct pre-operative diagnosis of gallbladder cancer in approximately 80% of patients by ultrasonography [73, 80].

Ultrasonography should be routinely performed in investigation of gallbladder disease when cancer is suspected. It in non-invasive, non-ionising, less expensive, readily available in most centres and can be used in jaundiced patients and may detect the carcinoma at an early and potentially curable stage. Polypoid lesions and mass lesions are commonly diagnosed whereas flat and infiltrating lesions are less likely to be identified.

Bach A M et al (1998) concluded that sonographic findings do not accurately reflect the full extent of disease, and sonography is particularly limited in the diagnosis of metastases to the peritoneum and lymph nodes. Sonography correctly identified 15 (94%) of 16 patients with potentially resectable disease and 7 (37%) of 19 patients with advanced disease. 12 patients

with advanced disease were understaged, 9 had peritoneal metastases, 2 had liver metastases and one had celiac adenopathy [81].

F. ABDOMINAL COMPUTERIZED TOMOGRAPHY (CT SCAN)

Chijiwa K et al (1991) reported the correct pre-operative diagnosis by computed tomography in 60% of gallbladder cancers [73]. CT scanning more readily diagnosis advanced lesions and is used to stage the disease.

Itai Y et al (1980) undertook the CT assessment of 27 patients with gallbladder carcinomas and correctly diagnosed twenty cases as cancer, and made false positive diagnosis in 5 patients. 70% had mass shadows in the region of the gallbladder, 22% demonstrated thickening of the gallbladder wall, 15% intraluminal masses and 78% low density area of liver adjacent to tumour. Itai Y also reported difficulty in differentiating some cases of chronic cholecystitis and liver tumour from gallbladder cancer [82].

G. MAGNETIC RESONANCE IMAGING (MRI)

MRI can be used to diagnose gallbladder cancer and by demonstrating vascular anatomy can assist with the assessment of resectability of invasive cancer.

Wilbur AC et al (1988) described the MRI features in a case of carcinoma of the gallbladder presenting as a fungating mass associated with gallstones and biliary obstruction due to pancreaticoduodenal lymph node metastases [83].

H - ENDOSCOPIC ULTRASONOGRAPHY (EUS)

Endosonography is a useful modality for the diagnosis and staging of gallbladder carcinoma. EUS is useful in the diagnosis of the depth of invasion of gallbladder carcinoma. Inui K et al

(1998) found the detection rate of tumours with EUS was 91.3% (63 of 69). All 6 (100%) patients with pedunculated lesions (1p type) were correctly diagnosed with EUS [84].

I - ANGIOGRAPHY

Selective angiography has a high degree of diagnostic accuracy and may differentiate tumour from inflammation and determine the presence or extent of spread of lesion. Pre-operative angiography has the advantage of assessing a gallbladder carcinoma for resectability.

The common angiographic findings are enlargement of the cystic artery, abnormal vessels in the wall of the gallbladder with luminal irregularities, neovascularization, uneven thickness of the wall of the gallbladder and displacement of adjacent hepatic and portal vessels [85].

J - UPPER GASTRO-INTESTINAL CONTRAST STUDIES

The most common abnormality noted in contrast examinations of the upper gastro-intestinal tract is extrinsic pressure and invasion of the bulb and first portion of the duodenum by tumour from the gallbladder. Less frequently, invasion of the gastric antrum and pylorus is seen. All patients with abnormal results of upper gastro-intestinal series from carcinoma of the gallbladder have been found to have extensive disease and successful resection is a rarity [1].

In 1982, Hamlick found that the upper gastro-intestinal contrast-barium x-ray studies were abnormal in 16 of the 46 patients studied. Gastric outlet obstruction was seen in eight patients, and external duodenal compression was seen in six patients. Three patients had gastric ulcers identified [70].

K – FINE NEEDLE ASPIRATION CYTOLOGY

Percutaneous fine needle aspiration cytology (FNAC) guided by ultrasound or CT will often provide proof of malignancy when investigating mass lesions in the abdomen. Percutaneous FNAC of the gallbladder is a safe, rapid, reliable, cost-effective and accurate procedure in

diagnosing gallbladder carcinoma [86]. Evander and Ihse (1981) used this technique in 13 of the patients in their series, and a pre-operative diagnosis of carcinoma was made in 11 (85%) of these patients [87].

FNAC is particularly relevant for gallbladder cancer when non-operative methods of palliation are being considered to relieve obstructive jaundice. Cytological examination of aspirated bile is a fairly insensitive technique for diagnosing carcinoma, partially due to the degradative effect of biliary salts on cellular morphology [86].

MANAGEMENT

A) SURGICAL TREATMENT

The primary treatment modality for carcinoma of the gallbladder with a curative potential is surgical resection of the primary tumour and the most common areas of metastasis. The most common area of spread is the gallbladder bed in the liver, with frequent spread to the cystic, common duct, retropancreatic, coeliac nodes and to the periaortic lymph nodes [67]. Based on the fact that the major route of spread of carcinoma of the gallbladder appears to be local-regional rather than distant metastasis, the surgical treatment more likely to achieve tumour clearance includes removal of the gallbladder and resection of the liver substance adjacent to the gallbladder bed combined with regional lymphadenectomy [1, 57].

The approach to the management and eventual outcome of gallbladder cancer depends largely on the mode of presentation [11]. Only between 10 and 30 per cent of the patients have resectable disease on presentation [14]. Successful resection with cure has generally been limited to those cases in which the carcinoma was not recognised at operation for benign biliary disease and was only later diagnosed by pathologic examination of the resected specimen. The majority of patients present with advanced disease and are not treated or undergo palliative procedures for biliary or gastrointestinal obstruction. The review of Piehler and Crichlow (1978) revealed that 12.0 % of patients underwent cholecystectomy, 16.1% underwent presumed complete resection of identified tumour and 71.9% underwent palliative procedures or biopsy alone [1].

The lymph node dissection should remove the cystic node in the Calots triangle, the nodes along the common bile duct and in the porta hepatis, the nodes behind the first and second parts of the duodenum and head of pancreas, across to the coeliac axis [11]. The extrahepatic

ary tree may be resected to achieve a more complete lymph node dissection and to ensure plonged patency of the biliary tree [14].

e recommended extent of resection of liver substance has ranged from non-anatomical edge resection of the gallbladder bed to formal removal of segments IV and V, including the allbladder fossa and even to right hepatic lobectomy. Hepatic wedge resection of the allbladder bed is the least radical procedure, but it is often difficult and complicated by gnificant blood loss because of the non-anatomical dissection. Segmental liver resection ased on the precise knowledge of the anatomical organisation of the liver is the best option if ver resection is indicated. Right hepatectomy is not warranted when tumour is confined to the allbladder bed and is unlikely to prolong survival when more extensive invasion is present [11]. vasion of the liver has such a poor prognosis that extended resections should be carried out nly in highly selected patients.

The optimal surgical management of gallbladder carcinoma is controversial. Different surgical eatment options fluctuate between simple cholecystectomy and radical procedures that nclude resections of the liver and pancreaticoduodenectomy with local and para-aortic ymphadenectomy. The question of whether radical procedures offer a survival benefit and better chance of cure than less radical procedures is the center of debate.

Most of the reports of surgical therapy of carcinoma of the gallbladder are retrospective, single-institution series involving small number of patients without clear criteria for selecting aggressive v/s conservative approaches making comparisons impossible and analysis of results difficult. In addition, most patients had advanced stages of disease, and any surgical therapy would produce limited results.

Radical resection has been reported to improve survival in some series [1, 4, 5, 6, 28, 67, 70, 95] but other reports show no improvement in survival with these procedures [25, 87, 88, 89]. The majority

of patients with carcinoma of the gallbladder die from obstructive failure of the liver from local recurrence and not from distant metastases, pointing out the inadequacy of simple cholecystectomy to control local disease. Only 16.5% of patients with resected tumours survive five years, and only 5.0% of all procedures for this disease involve surgical procedures more aggressive than simple cholecystectomy [1]. This poor prognosis after surgery, despite the tumour's propensity to remain locally invasive, has been attributed to late diagnosis, ineffectual treatment and intervention at an advanced stage of the disease [1]. Aggressive surgical therapy is associated with morbidity rates of upto 54% and significant operative mortality rates around 5%, although some cases of long-term survival has been reported in patients with extensive disease [10].

Evander and Ihse (1981) felt that radical surgery does not confer any survival advantage in a group of 44 patients, 10 of whom had undergone radical resection of gallbladder tumour. Only one percent in their series was alive and symptom-free at 36 months [87]. In 1975, Bivins concluded that aggressive surgical therapy will probably not change the prognosis for invasive carcinoma [88]. Cubertafond reviewed the results of the French surgical association survey of the surgical treatment of 724 patients with carcinoma of the gallbladder and observed no difference in survival among the different surgical procedures adopted [89]. Glenn and Hays (1954) had failed to demonstrate any significant improvement in survival in 15 of the patients subjected to radical surgical procedures [25].

Radical surgery has the best chance of achieving complete tumour clearance and prolonging survival in patients with early, localised disease [1, [illegible], 90, 91]; although in the vast majority of patients, advanced disease is found which precludes such an approach. Koo (1981) reported very high hospital mortality for radical surgery performed when gross tumour extension beyond the gallbladder has occurred, and felt that cure by cholecystectomy was impossible unless either a carcinoma in-situ or a small mucosal lesion was present [90].

Wanebo (1981) found that out of 100 patients with carcinoma of the gallbladder the disease was localised to the gallbladder in approximately one fourth of the patients and there were only 3 long-term survivors, two after cholecystectomy alone and one after partial liver resection. Although long-term survival may accompany cholecystectomy alone for a favourable early-staged cancer, this is still uncommon and recommended a more aggressive approach including resection of the hepatic bed with the gallbladder, regional node dissection in selected patients with early gallbladder cancer [6]. Vaittinen (1970) reported that 16.7 percent of patients undergoing radical excision survived five years as opposed to 10.6 percent after curative cholecystectomy [4].

Nakamura (1989) believed that long-term survival may be achieved by aggressive surgery if it is suitably indicated. Two of the thirteen patients with stage V carcinoma who underwent an extended operation are alive without recurrence 7 years 8 months and 8 years 5 months after surgery [92]. In 1981, Adson and Farnell reported the Mayo clinic experience with 12 patients out of 112 with gallbladder cancer who had resectable tumours. 7 of the 8 patients treated by simple cholecystectomy died within 15 months. 4 patients underwent radical lymphadenectomy or liver resection and all 4 had prolonged tumour-free survival. The authors felt that inadequate surgical therapy was a factor in the poor prognosis associated with cancer of the gallbladder [93].

In 1990, Donohue J.H., found that there was no overall survival advantage for radical cholecystectomy compared with cholecystectomy alone. However, there were some long-term survivors in patients with positive lymph nodes undergoing radical cholecystectomy, which included adjacent liver and regional lymph node dissection, leading to the recommendation for an aggressive surgical approach in selected patients [28].

In 1992, Matsumoto and colleagues produced convincing evidence that an aggressive surgical approach is associated with improved results. 28 patients having received potentially curative

resections had survival of 32 +/- 20 months. 4 patients with stage I disease had a mean of 50 +/- 21 months of follow-up and were all alive. 8 of the 9 patients with stage IV disease were alive and well at 32 +/- 17 months [94].

Because prognosis is primarily related to depth of invasion of the gallbladder wall, therapy is best tailored to the degree of wall involvement. In patients with tumours limited to the mucosa, simple cholecystectomy appears to suffice [26, 96]. The presence of local dissemination or metastatic disease in these patients is rare, and a different approach is unjustified. It remains unclear whether more radical resection, including gallbladder bed resection offers any advantage for disease limited to the mucosa.

In 1976, Nevin correlated the depth of invasion with survival in a large group of patients. The study confirmed that patients with disease localized to the mucosa had the greatest probability of cure with cholecystectomy alone, and strongly recommended extended resection for carcinoma involving all layers of the wall of the gallbladder, since the chance of cure by cholecystectomy alone is small. In stage V there were no 2 years survivors and felt that surgery did not influence outcome [26].

When the tumour infiltrates the muscular or subserosal layer, a more aggressive surgical approach is beneficial. Piehler and Crichlow [1], Fahim and associates [65] and others [7,26] have advocated radical treatment consisting of enbloc excision of the gallbladder with wedge resection of adjacent liver and regional lymphadenectomy of the hepatoduodenal ligament. Some add resection of the extrahepatic biliary tree.

Some authors believe that radical surgery is of no benefit in patients with tumours involving the muscularis compared with simple cholecystectomy [14]. Ouchi in 1987 found that patients with tumours superficial to the subserosa survived longer after undergoing extended cholecystectomy than those who underwent simple cholecystectomy [64].

Ogura Y et al (1991) concluded that cholecystectomy alone may be adequate in patients with tumour limited to the mucosa. Patients with gallbladder carcinoma invasion beyond the mucosa benefit from more radical procedures such as extended cholecystectomy with lymph node resection and resection of the gallbladder bed [96]. In 1992, Matsumoto concluded that extended cholecystectomy with resection of the bile duct in the hepato-duodenal ligament is the optimum procedure for patients with stage I and II carcinomas. For patients with stage III and IV tumours more radical procedures might result in curative resection [94].

For patients with serosal invasion and extension of tumour to adjacent organs, surgical therapy with curative intent is controversial because survival is unlikely to be affected significantly. Morrow CE et al (1983) did not find any benefit to radical surgery when all layers of the gallbladder wall were involved with or without involvement of the cystic duct node. Of the 13 patients with cystic node involvement (stage IV), the cumulative survival rate was only 37% at 6 months, and all patients were dead within 18 months. Of 14 patients with advanced disease (stage V) treated with aggressive surgical therapy the mean survival rate was only 3 months [27].

In 1987, Ouchi confirmed the poor prognosis in patients with these tumours. In 17 patients treated with simple cholecystectomy, no patient survived 2 years, whereas the 3-year survival rate for patients treated with radical surgery was 17%. The difference was not statistically significant, and no patient survived 5 years [64].

Reports of more aggressive surgery, including pancreaticoduodenectomy and extensive liver resection are associated with a higher morbidity and mortality, and they usually represent few cases. Benefits, if any, are limited. Pancreaticoduodenectomy has been recommended by some authors in those patients with lymph node metastasis posterior to the head of the pancreas and with invasion to the duodenum[96]. Nakamura (1994) was of the opinion that hepatopancreatoduodenectomy had the potential to improve both survival and the quality of life

for carefully selected patients with advanced gallbladder carcinoma. The 2-year survival rates were 28.6% compared to 5.8% for patients with non-resectable tumours. Post-operative complications occurred in 5 of the 7 patients with Nevin stage V resectable tumours after hepatopancreatoduodenectomy, but there were no operative deaths [97].

SURGICAL TREATMENT OF INCIDENTAL CARCINOMA

The diagnosis of cancer of the gallbladder is made in about one-third of cases incidentally at the time of cholecystectomy for presumed benign disease or by the pathologist examining the removed gallbladder. Piehler and Crichlow (1978) found 36% of patients of the gallbladder cancer presented with either acute or chronic cholecystitis without suspicion of malignancy [1].

Proper management begins with the opening and inspection of all resected gallbladders immediately after operation and any suspicions lesions should be sent for immediate histologic examination by frozen-section, and an attempt should be made to establish the extent of invasion of the wall by tumour [11, 70]. If unsuspected gallbladder tumour is found at operation for benign disease, the surgeon should fully assess the extent of spread of the lesion and decide whether curative excision procedure or biopsy only should be carried out [11].

The surgical treatment of incidentally discovered carcinomas after cholecystectomy for gallstone disease, is controversial as to whether patients will benefit from reoperation and a more radical procedure. When cholecystectomy has been performed for presumed benign disease and the pathologic report indicates carcinoma of the gallbladder, the therapy chosen should also be based on the degree of infiltration of the gallbladder wall.

Patients with mucosal lesions do not require additional surgery. Simple cholecystectomy may be curative for the few cases in which the cancer has not penetrated the muscularis layer, since reports of local recurrence after cholecystectomy for carcinoma superficial to the muscularis layer is unusual. With deeper involvement of the wall of the gallbladder, the chances of

localized recurrence increases demonstrating the inadequacy of reliance upon cholecystectomy alone. Thus, reoperation for delayed hepatic resection and lymph node dissection should be considered in selected patients, to increase resection margins, leading to removal of residual tumour and subsequent survival of the patient [14].

Patients with tumour infiltration limited to the subserosa benefit most from operative re-intervention and resection of the gallbladder bed and regional lymphadenectomy. With extension of tumour to the serosa or periserosal structures or perilymphatic structures, the decision of reoperation should be individualized since extensive surgery has poor results in this group of patients [14].

Bergdahl (1980) reported on 32 patients who underwent cholecystectomy for presumed benign disease and found to have microscopic gallbladder carcinomas. The prognosis was far better in the 11 patients in whom the cancer was confined to the mucosa or submucosa. 64% of the patients were alive after 5 years and 44% after 10 years. Five of the 11 patients died because of recurrence. When the cancer involved all the layers of the gallbladder wall, the one-year survival rate was 30%. Radical cholecystectomy including a wedge resection of liver and dissection of the regional lymph nodes was recommended in all patients with in-apparent gallbladder carcinomas [98].

In 1992, Shirai concluded that a radical second operation should be carried out for pT2 or more advanced in-apparent carcinoma, whereas follow-up without a second operation is recommended for pT1 cancer without positive margin. All patients with disease limited to mucosa (pT1) survived 5 years following cholecystectomy alone. 35 of the 45 patients with tumour extending to the gallbladder serosa, but not through it (pT2) underwent cholecystectomy alone with 40% 5-year survival. 10 patients with pT2 cancer who underwent cholecystectomy followed at second operation by hepatic wedge resection, common bile duct resection and en bloc dissection of regional lymph nodes, had a 5-year survival of 90% [99].

LAPARASCOPIC CHOLECYSTECTOMY AND CARCINOMA OF GALLBLADDER

Incidental carcinoma of the gallbladder occurs in 1-2% of patients who undergo conventional cholecystectomy for benign diseases of the biliary tracts [1]. Laparascopic cholecystectomy is a proven, well accepted surgical technique for removing the diseased gallbladder, and has rapidly become the surgical procedure of choice over conventional open cholecystectomy.

When carcinoma of the gallbladder is encountered in a patient undergoing laparascopic cholecystectomy it can pose a number of dilemmas. In recent years, there have been an increasing number of case reports of port-site metastasis and early appearance of peritoneal carcinomatosis following laparoscopic cholecystectomy for unsuspected carcinoma of the gallbladder [14,15,16].

Paolucci and associates (1999) reported 409 incidental gallbladder carcinomas following 117,840 laparoscopic cholecystectomies. Port-site recurrence was identified in 70 of 409 patients (17.1%) with a median of 180 days following laparoscopic cholecystectomy for non-apparent gallbladder carcinoma. Six patients without port-site metastases were found to have a diffuse peritoneal carcinomatosis a median of 120 days after cholecystectomy [16].

When planning a laparoscopic cholecystectomy extensive preoperative evaluation is warranted in patients with the risk factors for malignant gallbladder disease. When carcinoma is identified preoperatively, cholecystectomy should be performed as an open procedure. If malignancy is encountered unexpectedly during laparoscopic cholecystectomy, the procedure should be converted to an open resection to allow for appropriate evaluation of the stage of disease and appropriate surgical management [15].

Most commonly, malignancy is identified postoperatively, only after pathological examination of the resected gallbladder. Gallbladder carcinoma at the pT_{is} or pT_1 stage removed

laparoscopically needs no other treatment. Open re-operation is necessary to achieve an adequate curative resection for the other stages [15]. The use of gasless laparoscopy, slow desufflation, trocar site wash out and specimen bags have been recommended preventive measures of tumour recurrences.

B) PALLIATION

Over one-third of the patients with gallbladder cancer will present with obstructive jaundice, many of whom will be correctly diagnosed as having malignant obstruction of the biliary tract [1]. Patients with irresectable lesions or those not fit for tumour resection, some form of palliative procedure will usually be necessary. Palliative therapy may include surgical methods of palliation using biliary enteric bypass or surgical intubation, and non-operative endoprosthetic insertion.

A non-operative approach to palliation may be undertaken because the tumour is considered unresectable by preoperative staging studies, including ultrasound, percutaneous cholangiography, CT scan and angiography; or because the patient is elderly and unfit for surgery. Criteria that excludes patients from surgery include poor general medical condition, refusal of surgery, distant metastasis, extensive tumour extension into both the right and left lobes of the liver, and portal vein or main hepatic artery occlusion [14].

Patients undergoing non-operative palliation may have biliary decompression performed using either percutaneously or endoscopically placed stents or external drainage tubes. Endoprosthesis insertion carries a significant morbidity and mortality, whether performed by endoscopic or radiological methods. Complications associated with endoprosthesis include tube displacement, blockage, migration and recurrent cholangitis [11].

There is no universally suitable palliative surgical procedure and the choice of operation must take into account the general risk to the patient, the likely effect of surgery and the patient's principal symptoms of pain, jaundice and itch, nausea and / or vomiting. Surgical biliary bypass is not straight forward as the level of tumour obstruction is usually at the common hepatic duct or above.

There is increasing evidence that segment III cholangiojejunostomy provides effective long-term decompression of the left biliary tree [100]. Complete decompression of both hepatic lobes is not necessary to achieve palliation of jaundice and itching. This technique, first described by Soupault and Couinard in 1957, uses the round ligament approach to segment III branch of the left hepatic duct followed by a biliary enteric anastomosis to a Roux-en-Y jejunal limb. Excellent palliation for gallbladder cancer is produced because of the distance between the anastomosis and the primary site of tumour. Malignant obstruction of the anastomosis will not occur until at a late stage and prolonged relief of jaundice may be obtained [100].

Removal or drainage of the gallbladder, if possible, may be necessary to prevent the subsequent development of acute cholecystitis from cystic duct obstruction related to tumour growth. Gastric outlet obstruction may frequently complicate gallbladder cancer and satisfactory palliation can be achieved in most patients by gastrojejunostomy [100].

C) OTHER THERAPIES

Chemotherapy and radiotherapy have been employed separately or in combination both as adjuvant therapy after operation and for palliation of locally advanced and metastatic disease in the hope of improving survival and providing palliation. The effectiveness of chemotherapy and radiotherapy in gallbladder carcinoma is unpredictable and the response is generally poor, probably because most patients undergoing these forms of therapy have very advanced disease [72].

Most of the studies reported have involved small series of patients that combines patients with biliary carcinoma and gallbladder carcinoma, making results difficult to evaluate.

CHEMOTHERAPY

The chemotherapy response rates for carcinoma of the gallbladder do not differ significantly from intrahepatic cholangiocarcinoma or extrahepatic bile duct cancer [10]. Available chemotherapeutic agents seem to have little influence on gallbladder cancer, either in the patient with advanced disease or as an adjuvant to surgery.

Von Eyben F et al (1980) showed no objective remission in 10 patients with advanced gallbladder carcinoma treated by mitomycin C [101]. Hejna M et al (1998) reviewed the role of chemotherapy in the management of biliary cancer and suggested that it may be of benefit in advanced disease [102].

Systemic chemotherapy.

Systemic chemotherapy in patients with gallbladder cancer has been employed for symptomatic palliation only. Prolongation of survival has not been demonstrated with any single agent or with any combination therapy [14]. The average response rates for single agent and multi-agent systemic chemotherapy regimes are 16% and 18% respectively [10].

Falkson G et al (1984) reported on the Eastern Co-operative Oncology Group experience on the chemotherapy of 87 patients with in-operable gallbladder and bile duct cancers with 5-fluorouracil alone, 5-fluorouracil with streptozotocin and 5-fluorouracil with methyl-CCNU in a randomized trial. There was no significant difference in survival rates or response between the different regimes or compared with historical controls who received no chemotherapy [103].

Harvey JH et al (1984) reported a 31% partial response in 14 patients with advanced or recurrent biliary tract cancer treated with 5-fluorouracil, doxorubicin and mitomycin C (FAM regimen) [104]. Takada T et al (1998) reported that combination chemotherapy consisting of 5-fluorouracil, doxorubicin and mitomycin C inhibited the tumour progression for significantly longer duration and to a lesser extent, reduced tumour size in non-resectable gallbladder carcinoma compared to a non-administered chemotherapy group [105].

Adjuvant chemotherapy

The benefit of adjuvant therapy after surgical resection has not been fully evaluated. Treadwell TA and Hardin WJ (1976) reported some slight improvement in 2 year survival in 15 patients who received adjunctive radiotherapy, chemotherapy or combination of both post-operatively. No patient with tumour outside the gallbladder survived more than 2 year [106].

Regional Chemotherapy

The basis for regional chemotherapy is due to the fact that carcinoma of the gallbladder is often confined to a regional site; the gallbladder bed, adjacent liver and regional nodes. The response rates with hepatic artery infusion with chemotherapy are generally higher and average 45% [10].

In 1983, Morrow et al employed intra-arterial therapy for adjuvant treatment and reported a slightly improved survival time [27]. Smith et al (1984) reported a non-significantly increased

survival rate in comparison of hepatic arterial infusion of 5-fluorouracil and mitomycin-C, and controls [107].

Cao L et al in 1998 found a significantly higher over-expression of MDRI mRNA and Pgp in gallbladder carcinoma than in normal gallbladder and postulated that it could be an important reason why gallbladder cancer is generally not responsive to chemotherapy [108].

RADIATION THERAPY

The high incidence of treatment failure after surgical resection due to local recurrence has been a strong point in favour of adjuvant radiotherapy. Kopelson G and Gunderson LL in 1983 found that local recurrence was present or was the cause of death of 95 of 110 patients (86%) who died within 5 years after simple cholecystectomy. Of the 25 patients who survived beyond 5 years, 11 (44%) experienced local recurrence. Among 16 patients selected for radical cholecystectomy, 12 (75%) died with or as consequence of local recurrence [109].

Isolated reports demonstrate that radiotherapy may be efficient in the enhancement of the curative potential of surgery or in symptomatic palliation. Houry S (1999) commented that gallbladder carcinoma may not be as radio-resistent as was formerly thought. Slight improvement of survival after adjuvant or palliative radiotherapy especially in advanced stage of gallbladder carcinoma has been reported. Local control of tumour and reduction of tumour size has been reported in several publications [110].

The ability of irradiation to control microscopic residual carcinoma forms the basis for adjuvant radiotherapy. Todoroki T et al in 1999 exhibited a significant improvement of long-term survival when adjuvant radiation was used appropriately in patients with microscopic residues only [111].

Vaittinen (1970) reported a median survival of 63 months for patients receiving post-operative radiation therapy compared with 29 months for patients undergoing surgery alone [4]. Hanna SS and Rider WD (1978) used external beam radiation and in a non randomized study of 18 patients with irresectable carcinoma of the gallbladder or extrahepatic bile ducts showed a median survival of 11 months as compared to those not given radiotherapy who had a significantly shorter survival time 5 months [112].

Bosset JF et al (1989) advocated post-operative adjuvant external beam irradiation after apparently curative surgery with encouraging outcomes. They described the management of 7

patients treated to 54 Gy (45 Gy the tumour bed and regional nodes plus a 9 Gy boost dose) after complete resection of carcinoma. Five patients are alive with no evidence of disease after 5 to 58 months. Two patients died of abdominal recurrence [113].

Houry S et al (1989) found the median survival time of 16 patients who underwent radiotherapy with partial or no resection was 8.1 months compared with the median survivals of 1.8 to 2.0 months in historical control series without radiation therapy. Of the 4 other patients with Nevin stage III or IV tumours that received 4500 to 5500 cGy post-operative radiation therapy after complete resection, one patient with stage III disease was alive at 84 months [114].

Todoroki T et al (1999) reported a significantly higher 5-year survival rate (8.9%) in 47 patients with stage IV gallbladder cancer who received adjuvant radiotherapy after aggressive resection than resection alone (2.9%) [111].

Intra-operative radiation therapy (IORT) has been used in the management of patients with residual or unresectable carcinoma of the gallbladder but its use as a surgical adjuvant therapy has not been documented. IORT alone does not appear significantly to improve survival. IORT has been used both with and without external beam radiation, in order to deliver higher doses to gallbladder bed.

Todoroki T et al (1980) used intra-operative radiotherapy in a single dose of 2500-3000 rad in 11 patients with malignant bile duct obstruction, 6 of whom had unresectable carcinoma of the gallbladder and produced mean survival time of 11 months, and in some patients recanalization of the obstructed bile duct was demonstrated by post-operative cholangiography. They were unable, however, to show prolongation of long-term survival [115].

Busse PM et al (1991) treated 10 patients with IORT for gross residual or unresected carcinoma of the gallbladder, and reported median survival of 1 year with no long survival, and suggested

that IORT may be of value in treatment of minimal residual disease after total resection rather than in the palliative treatment of unresectable tumours [116].

In 1991, Todoroki T et al, reported on 17 patients with TNM stage IV gallbladder cancer who received a single dose of 20 to 30 Gy intra-operatively and a mean total dose of 36.4 Gy of external beam radiotherapy added to IORT in 10 patients. The 3 year survival was 10% for resection plus IORT with the longest survivor free of disease at 3 years compared with no 3 year survival among 9 stage IV patients with resection alone [117].

Houry S 1999 found it preferable to give boost (15Gy) to gross lesion or residual lesion at operation (intra-operative irradiation or brachytherapy) and deliver an additional 45-50 Gy post-operatively [118].

PREVENTION

The incidence and mortality of gallbladder cancer has decreased in recent years as the frequency of cholecystectomy has increased. Diehl and Beral estimated that one case of gallbladder cancer is prevented for every 100 cholecystectomies performed for gallstone disease [22].

Prophylactic cholecystectomy for the prevention of carcinoma in patients with asymptomatic cholelithiasis is not justified, since carcinoma of the gallbladder occurs only in about 1 to 2 percent of patients with gallstones and the operative risks exceeds the risk of developing cancer [1, 5, 22, 23]. The risk of cancer in porcelain gallbladder is very high and justifies prophylactic cholecystectomy [41].

PROGNOSIS

In the review of Piehler and Crichlow (1978), the overall five year survival of 5836 patients of carcinoma of the gallbladder was 4.1 percent and the one year survival was 11.8 per cent [1]. No improvement in survival has occurred in the last 30 years despite increasingly aggressive surgical resection [72].

Survival from gallbladder carcinoma depends more on the method of presentation than the type of treatment undertaken. Most long-term survivors are patients who underwent cholecystectomy for cholelithiasis and in whom malignancy was an incidental finding. The five-year survival of patients whose tumours were unexpected findings after cholecystectomy was 14.9 percent and the survival was 2.9 percent in patients whose tumours were identified by the surgeon and resected [1].

The majority of long term survivors are patients whose tumours are confined to the mucosa or had minimal involvement of muscularis. Nevin and colleagues correlated depth of invasion and histologic grade of tumour with survival. 79 percent of patients with carcinoma of the gallbladder invading mucosa or muscularis alone were cured by cholecystectomy. Patients with involvement of the liver or distant metastases, all died of the disease within 2 years, regardless of therapy. Histologic grading of the malignant lesion was also found to correlate well with survival, with 63% of patients with well differentiated tumours surviving five years, while only 4 per cent of those with poorly differentiated tumours did so [26].

Ouchi in 1987 found that the 5-year survival rate of the patients with tumour exposed to the serosa was significantly lower than that of the patients with tumour only limited to the mucosa., muscularis or subserosa. The papillary or well-differentiated carcinoma had a higher survival than the moderately or poorly differentiated carcinoma present in 7 of 17 tumours with spread to the serosa [64].

RATIONALE AND JUSTIFICATION OF THE STUDY

Carcinoma of the gallbladder is an unusual but not rare neoplasm, it is the commonest malignant tumour of the biliary tract with a reported incidence of 2.5 per 100,000 per annum [2]. Gallstones are the most commonly associated causative factor in the pathogenesis of gallbladder cancer [29]. High prevalence of gallbladder cancer is reported in areas where gallstones is also prevalent [11, 13, 17]. The prevalence of gallstones in America and Europe is reported to be increasing in the last 50 years. With the changing lifestyle of our people, the incidence of gallstones and probably carcinoma of the gallbladder might also increase [88].

"*The diseased gallbladder is one of the most frequent specimens submitted to the surgical pathology laboratory* [17]." Nearly 10% of gallbladders removed from patients above 65 years will harbour a carcinoma [25]. Piehler and Crichlow observed that 12% cases of cancer of the gallbladder were discovered by the pathologist on cholecystectomy specimens which are removed for a presumed benign disease. It has been noted that changes in the cholecystectomy rates produces changes in the prevalence of cholelithiasis and consequently in carcinoma of the gallbladder incidence and mortality [22, 23]. Since laparascopic cholecystectomy has quickly emerged as a popular alternative to open cholecystectomy , an increasing number of cases of port–site metastasis and dissemination of incidental carcinoma of the gallbladder during laparascopic cholecystectomy have been reported [16].

There are no adequate studies done in our local setup on this tumour. Awason [118], on his dissertation on gallstones noted 7 cases of gallbladder cancer with only one case associated with gallstones over a five-year period (1982-1986). In view of the foregoing reasons, the author was motivated to carry out this study in the hope that it may act as a baseline data bank for future studies and also be able to provide guidelines for the management of this condition in our setup.

OBJECTIVES OF THE STUDY

Main Objective:

1) To review the epidemiology, presentation, management and outcome of gallbladder cancer at Kenyatta National Hospital over a thirteen year period.

2) To determine the number of patients with incidental gallbladder carcinomas first diagnosed at microscopic examination of gallbladders removed for gallstones.

Specific Objectives:

1) To determine the annual incidence of gallbladder carcinoma.

2) To establish the age / sex distribution and the ethnic distribution of gallbladder cancer.

3) To determine the modes of clinical presentation and critically review the management and outcome of gallbladder cancer.

4) To determine the total number of cholecystectomies done annually and the age / sex distribution.

5) To determine the number of patients presenting with incidental carcinoma of the gallbladder at Kenyatta National Hospital.

6) To establish the frequency of gallstones among gallbladder cancer patients.

MATERIALS AND METHODS

Study Design

The study was a descriptive retrospective study of all cases of gallbladder cancer seen at Kenyatta National Hospital over a thirteen year period.

Study Area

The study was undertaken at KNH, the national referral and teaching hospital for the University of Nairobi medical school.

Study Period

The study covered the period from January 1988 to December 2000.

Data Collection

All the files of patients with the diagnosis of gallbladder cancer during the study period were retrieved from the Medical Records Department. Data was collected initially by perusing the theatre record book to identify patients who had undergone cholecystectomy for symptomatic gallstones, then the files and the histopathological reports were retrieved from the Medical Records Department and the pathology department respectively.

The clinical notes were studied and the relevant data obtained was recorded on the pre-designed data collection form (see appendix). Data collection was done by the researcher.

Data Analysis

All the data obtained was transferred from the data collection form onto a coded sheet for computer analysis. The SPSS statistical package was used for data entry and analysis and the results presented in graphical, tabular and chart forms. Statistical significance was determined by the Chi-square test.

Inclusion Criteria.

1) All patients with histologically confirmed diagnosis of gallbladder cancer were included in the study.
2) All patients who have undergone cholecystectomy for gallstones in the surgical units and later found at histopathological examination of the resected specimen to have gallbladder cancer were also considered.

Exclusion Criteria

1) Any patient without a histopathological report confirming the diagnosis of cancer.
2) Case files that have incomplete or insufficient data for the purposes of analysis.

Sample Size

All the cases of cholecystectomies for gallstones done at KNH during the study period were included in the study in order to determine the number of incidental carcinomas of the gallbladder. The minimum sample size was estimated to be 15 cases of gallbladder cancer, using the formula below.

$$n = \frac{Z^2_{1-\alpha/2}\, p(1-p)}{d^2} = \frac{(1\text{-}96)^2 \times 0.01 \times 0.99}{(0.05)^2} = 15$$

where

α = significance level of 5%

$Z^2_{1-\alpha/2}$ = standard normal deviation of 1.96

d = degree of precision set at +-5%

p = assumed incidence of 1%

Ethical considerations and confidentiality.

The study commenced following the approval by the Ethical and Research Committee of Kenyatta National Hospital. Strict confidentiality with regard to information arising from the study was observed.

Constraints.

Missing histopathologic reports and the inability to trace some case files were the main constraints encountered in this study causing the exclusion of some of the patients from the study.

RESULTS

A total of 32 cases of carcinoma of the gallbladder were recorded at Kenyatta National Hospital between 1988 and 2000. However, only 24 patients were included in the study because the other 8 lacked histological diagnosis.

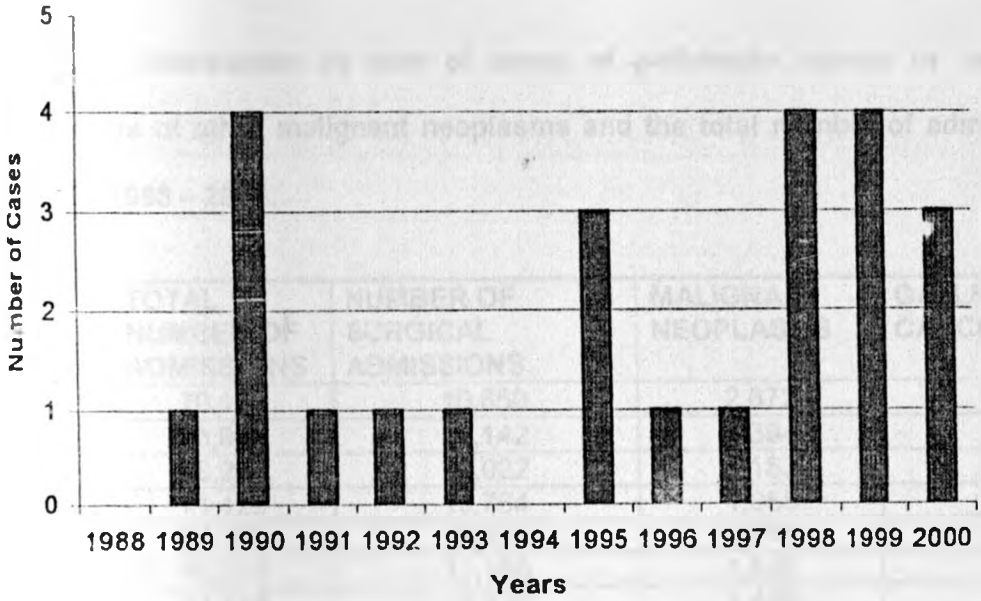
Incidence

The number of cases recorded during the thirteen year period varied from one (1) to four (4), with an average of 1.9 cases per annum. No cases were recorded in 1988 and 1994. There was a problem with records and file retrieval of patients seen in 1994, and this seems to be a consistent finding in other retrospective studies conducted in KNH.

Table 1 : **Annual Distribution of Gallbladder Cancer as Recorded at KNH 1988 - 2000.**

YEAR	NUMBER OF CASES
1988	0
1989	1
1990	4
1991	1
1992	1
1993	1
1994	0
1995	3
1996	1
1997	1
1998	4
1999	4
2000	3
TOTAL	**24**

Figure 1: A histogram showing the yearly distribution of cases of gallbladder cancer as recorded at KNH 1988-2000.



There were a total of 869,167 admissions to KNH during the study period. The cases of gallbladder carcinoma therefore represents only 0.003% (percent) of all the admissions at KNH, and 0.09% (percent) of all malignant neoplasms seen over the same period. The incidence of gallbladder cancer at KNH was 2.76 per 100,000.

Table 2 shows the relationship between the total number of admissions at KNH, the admissions of other malignant neoplasms and gallbladder cancer during the study period.

Table 2 : Distribution by year of cases of gallbladder cancer in comparison with admissions of other malignant neoplasms and the total number of admissions at KNH between 1988 – 2000.

YEAR	TOTAL NUMBER OF ADMISSIONS	NUMBER OF SURGICAL ADMISSIONS	MALIGNANT NEOPLASMS	GALLBLADDER CANCER
1988	70,111	10,650	2,672	0
1989	76,936	11,142	2,394	1
1990	68,240	12,022	2,153	4
1991	71,125	10,764	1,058	1
1992	63,271	9,972	1,781	1
1993	67,216	11,180	1,936	1
1994	47,454	9,222	1,456	0
1995	49,378	7,667	2,182	3
1996	52,759	8,621	2,661	1
1997	59,108	12,419	2,234	1
1998	67,261	10,612	2,486	4
1999	92,540	20,606	2,480	4
2000	83,768	12,246	2,378	3
TOTAL	**869,167**	**147,273**	**27,871**	**24**

Age Distribution

The mean age was 52.0 years, with a range of 27 to 82 years. The average age in the female patients was 51.6 years, and in the male patients 57.6 years.

The peak age incidence in this study was 51 - 55 years, accounting for 29.2% of the cases. 62.5% of the patients (i.e. 15) were above 51 years of age.

Table 3 : **Age and sex distribution of gallbladder cancer at KNH 1988 – 2000.**

AGE GROUP (Years)	MALE (M)	FEMALE (F)	TOTAL	PERCENTAGE
< 35	0	2	2	8.3
36 – 40	2	1	3	12.5
41 – 45	1	1	2	8.3
46 – 50	0	2	2	8.3
51 – 55	3	4	7	29.2
56 – 60	0	5	5	20.8
> 61	2	1	3	12.5
TOTAL	**8**	**16**	**24**	**100.0**

Sex Distribution

In the study, there were 16 females (66.7%) and 8 males (33.3%), giving a female to male ratio of 2:1. See illustrations under figure 2 and figure 3.

Figure 2: Histogram showing age and sex distribution of gallbladder cancer at Kenyatta National Hospital (1988 - 2000).

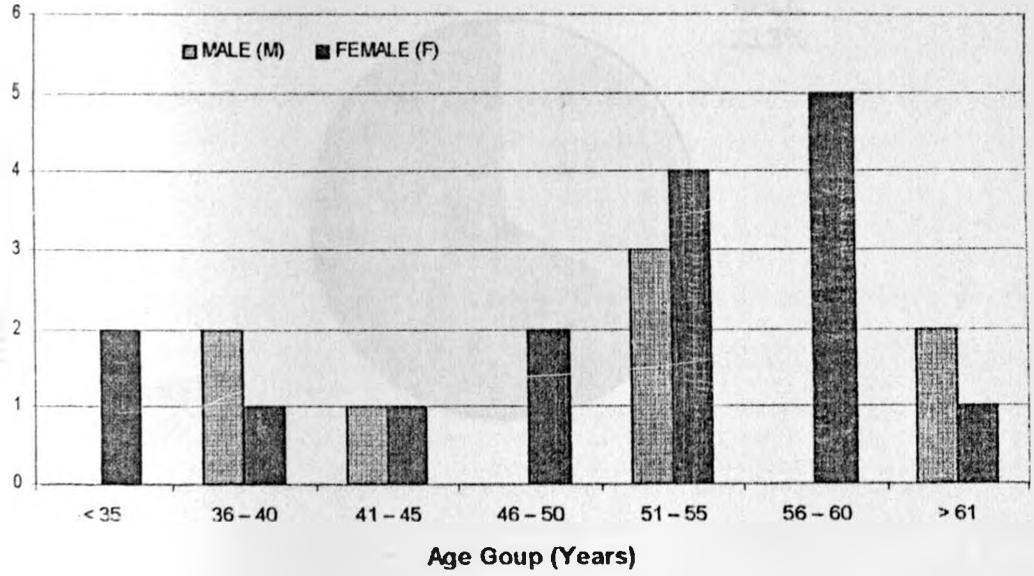
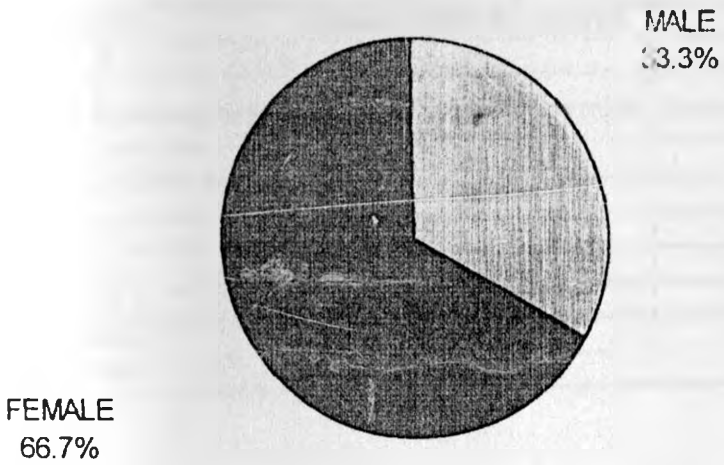


Figure 3 : Pie Chart showing the sex ratio of gallbladder cancer at Kenyatta National Hospital (1988 - 2000).



Parity

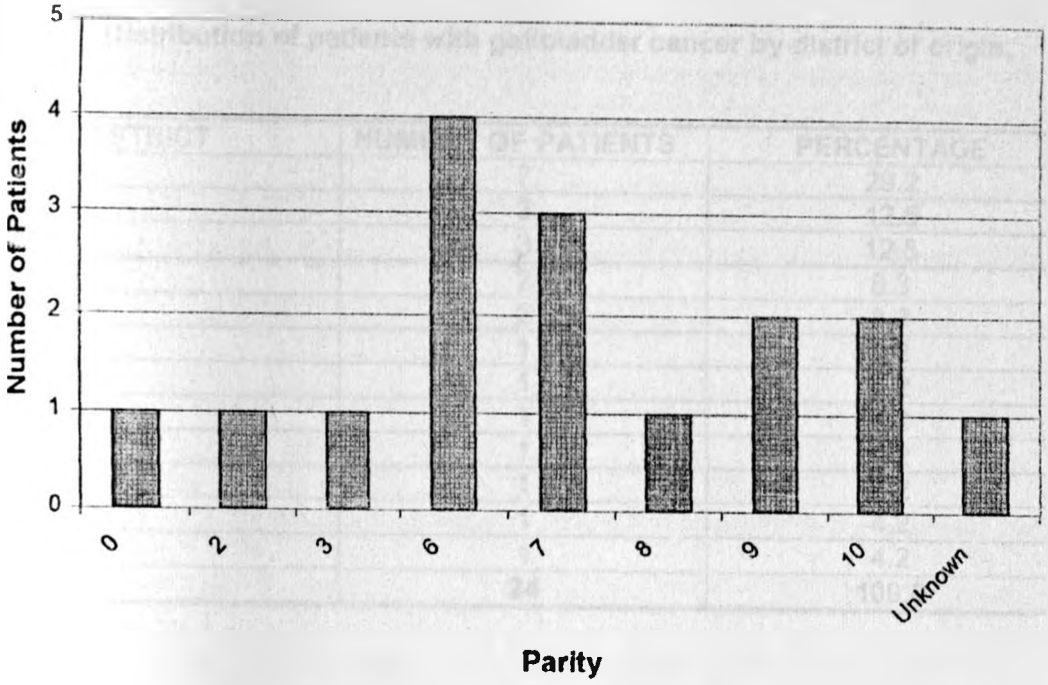
Table 4 and Figure 4 show the parity of the female patients with gallbladder cancer.

75% (i.e. 12) of the female patients with gallbladder cancer had a parity of 6 or greater. The average parity of the female patients with gallbladder cancer in this study was 6.

Table 4: Parity of female patients with gallbladder cancer as seen at KNH 1988 - 2000.

PARITY	NUMBER OF PATIENTS	PERCENTAGE
0	1	6.25
2	1	6.25
3	1	6.25
6	4	25.00
7	3	18.75
8	1	6.25
9	2	12.50
10	2	12.50
Unknown	1	6.25
Total	**16**	**100.00**

Figure 4: **Histogram showing the parity of female patients with gallbladder cancer as seen at KNH 1988 - 2000.**



Geographical Distribution

Table 5 and table 6 show the frequency of distribution of patients seen at Kenyatta National Hospital with diagnosis of gallbladder cancer during the study period of January 1998 to December 2000 according to the district and province of origin respectively.

Table 5: Distribution of patients with gallbladder cancer by district of origin.

HOME DISTRICT	NUMBER OF PATIENTS	PERCENTAGE
Muranga	7	29.2
Nyeri	3	12.5
Kiambu	3	12.5
Nakuru	2	8.3
Siaya	2	8.3
Nairobi	1	4.2
Kirinyaga	1	4.2
Machakos	1	4.2
Migori	1	4.2
Nyandarua	1	4.2
Nyambeni	1	4.2
Lamu	1	4.2
TOTAL	**24**	**100.0**

Table 6: **Distribution of study patients by province of origin.**

PROVINCE OF ORIGIN	NUMBER OF PATIENTS	PERCENTAGE (%)
Central	15	62.5
Nyanza	3	12.5
Rift Valley	2	8.3
Eastern	2	8.3
Nairobi	1	4.2
Coast	1	4.2
Western	0	0.0
North Eastern	0	0.0
TOTAL	**24**	**100.0**

Most of the patients seen with gallbladder cancer at Kenyatta National Hospital were from Muranga district 29.2%, followed by Nyeri district 12.5% and Kiambu district 12.5%. Thus the majority of patients in this study originated from Central Province (62.5%) and none of the patients originated from the Western or North Eastern Provinces.

Only 4.2% of the patients were from Nairobi despite its proximity to the hospital. The low figures under Nairobi could be explained by the fact that most of the residents of Nairobi do not consider it as its province of origin.

Occupation

Table 7 shows the distribution of the patients with gallbladder cancer by occupation. 33.3% were housewives, 20.8% were unemployed, 16.7% were traders, 12.5% were farmers, 8.3% were teachers and 1 patient was a waiter while another was a cook by profession.

Table 7: Distribution of patients with gallbladder cancer by occupation.

OCCUPATION	TOTAL NUMBER OF PATIENTS	PERCENTAGE
House-wife	8	33.3
Trader / Business	4	16.7
Farmer	3	12.5
Teacher	2	8.3
Cook	1	4.2
Waiter	1	4.2
Unemployed	5	20.8
TOTAL	**24**	**100.0**

CLINICAL PRESENTATION

Presenting Symptoms

The commonest presenting symptom was abdominal pain, and was present in 19 patients (79.2%). Jaundice (62.5%), pruritus (58.3%), nausea and vomiting (41.7%), anorexia (33.3%), weight loss (25.0%) and abdominal distension or mass (25%) were the next common presenting symptoms. Other less common symptoms present included backache, headache, night sweats, constipation and haematemesis.

The frequency of the presenting symptoms are illustrated in Table 8.

Table 8: **Presenting symptoms of patients with gallbladder cancer.**

SYMPTOMS	NUMBER OF PATIENTS	PERCENTAGE
Abdominal pain	19	79.2
Jaundice	15	62.5
Pruritus	14	58.3
Nausea / Vomiting	10	41.7
Anorexia	8	33.3
Abdominal Distension / Mass	6	25.0
Weight Loss	6	25.0
Headache	1	4.2
Backache	1	4.2
Night Sweats	1	4.2
Constipation	1	4.2
Haematemesis	1	4.2

Duration of Symptoms

The duration of symptoms ranged from 2 weeks to over 1 year, with a mean of 4.0 months. 87.5% of the patients had symptoms for less than one year. Half of the patients had symptoms for two months or less. There are three patients with symptoms lasting over a year.

Table 9 shows the duration in months of the presenting symptoms.

Table 9: **Duration in months of the presenting symptoms.**

DURATION (MONTHS)	NUMBER OF PATIENTS	PERCENTAGE
<1	5	20.8
2	7	29.2
3	3	12.5
4	1	4.2
5	1	4.2
6	1	4.2
8	1	4.2
9	2	8.3
>12	3	12.5
Total	**24**	**100.0**

Findings on Physical Examination

Table 10 shows the frequency of various clinical signs at first presentation seen in patients with gallbladder cancer.

Abdominal tenderness was noted in 19 patients (79.2%) and represents the most common physical finding. The other major clinical signs included jaundice (70.8%), hepatomegaly (66.7%), pallor (33.3%), palpable gallbladder (29.2%), abdominal masses other than the liver and gallbladder (20.8%), ascites (8.3%) and fever (4.2%).

Table 10 : Clinical signs seen in patients with gallbladder cancer at KNH 1988 – 2000.

CLINICAL SIGNS	TOTAL NUMBER OF PATIENTS	PERCENTAGE
Abdominal Tenderness	19	79.2
Jaundice	17	70.8
Hepatomegaly	16	66.7
Pallor	8	33.3
Palpable Gallbladder	7	29.2
Abdominal Masses (other than liver & gallbladder)	5	20.8
Ascites	2	8.3
Lower Limb Oedema	2	8.3
Obesity	2	8.3
Fever	1	4.2
Hyper pigmented patchy Skin lesion	1	4.2

Associated Conditions

Table 11 shows the conditions associated or coexisting with gallbladder cancer. 3 (12.5%) of the patients had peptic ulcer disease, whereas one patient was previously being managed for diabetes mellitus. One patient developed an incisional hernia postoperatively. Other associated conditions include liver abscess and umbilical hernia.

Table 11 : Associated conditions.

ASSOCIATED CONDITION	NUMBER OF PATIENTS	PERCENTAGE (%)
None	17	70.8
Duodenal ulcer	3	12.5
Liver abscess	1	4.2
Diabetes mellitus	1	4.2
Umbilical hernia	1	4.2
Incisional hernia	1	4.2

INVESTIGATIONS

Radiological

Abdominal ultrasound was performed in 83.3% of the patients. Plain abdominal x-ray, abdominal CT scan, Barium meal studies, oesophagogastroduodenoscopy were each performed in 8.3% of the patients. Percutaneous transhepatic cholangiogram (PTC) was done in one patient.

Table 12: **shows the radiological investigations performed.**

TYPE OF INVESTIGATION	NUMBER OF PATIENTS	PERCENTAGE
Abdominal Ultrasound	20	83.3
Abdominal CT Scan	2	8.3
Plain Abdominal X-Ray	2	8.3
Barium Meal	2	8.3
Oesophagogastroduodenoscopy	2	8.3
PTC	1	4.2

Table 13 shows the ultrasound features seen in patients with gallbladder cancer at KNH. The abnormal findings were dilated gallbladder (29.2%), gallbladder mass (20.8%), collapsed gallbladder (8.3%), and gallbladder wall thickening (8.3%). Other ultrasonographic features associated with gallbladder cancer detected include dilated bile ducts (58.3%), gallstones (37.5%), liver masses (8.3%), pancreatic masses (8.3%) and ascites (4.2%).

Table 13: Ultrasound abnormalities seen in patients with gallbladder cancer at KNH 1988 - 2000.

ULTRASOUND FEATURE	NUMBER OF PATIENTS	PERCENTAGE
Dilated Gallbladder	7	29.2
Gallbladder Mass	5	20.8
Gallbladder wall thickening	2	8.3
Collapsed Gallbladder	2	3.3
Dilated Bile Ducts	14	58.3
Gallstones	9	37.5
Liver Masses	2	8.3
Pancreatic Mass	2	8.3
Ascites	1	4.2

Laboratory

Table 14 shows the laboratory investigations performed.

Table 14: Laboratory investigations done.

LABORATORY TEST	NUMBER OF PATIENTS	PERCENTAGE
Haemogram	21	87.5
Liver function test	18	75.0
Prothrombin time	19	79.2
Urea / electrolytes	22	91.7
Serum Creatinine	15	62.5
HbsAg	5	20.8
Alpha - fetoprotein	3	12.5
Serum amylase	3	12.5
Elisa for HIV	3	12.5
Random blood sugar	3	12.5
Widal test	2	8.3
Urinalysis	2	8.3
Stool microscopy	2	8.3

1. Haemoglobin Levels

21 patients in the study had their haemoglobin levels done. 23.8% (5) had anaemia with values less than 10g/dl Hb, while 76.2% (16) had normal values (Hb greater than 10.1g/dl).

Table 15: Haemoglobin levels

HAEMOGLOBIN LEVEL (G/DL)	FREQUENCY	PERCENTAGE (%)
6 – 10	5	23.8
10.1 – 12.0	8	38.1
12.1 – 16.0	5	23.8
> 16.1	3	14.3
Total	**21**	**100**

2. White cells counts

Leueocytosis (white cell counts > $11x10^9$ /l) was present in 23.5% (4) of the 17 patients who had their white blood cells count determined.

3. Liver function tests

18 patients had their serum alkaline phosphatase checked. 22.2% (4) of the patients had their values within their normal range of 30-110 IU / litre. 77.8% (14) of the patients had elevated levels of serum alkaline phosphatase with values greater than 110 IU / litre.

15 patients had their serum albumin levels checked. 12 patients (80%) had hypoalbuminaemia with serum albumin levels less than 35 g/litre.

Total serum bilirubin was elevated in 66.7% of the 15 patients who had their levels checked in this study. Serum alanine and aspartate aminotransferase levels were elevated in 57.1% and 75.0% of the patients respectively.

4. Urea, electrolytes and serum creatinine

Urea, electrolytes and serum creatinine levels were checked preoperatively in most of the patients. Two patients had high serum creatinine levels (values > 130 μmol / litre).

5. Other laboratory investigations

Urinalysis done in 2 patients showed bilirubinuria. The other laboratory investigations done had negative results or values within the normal limits.

HISTOPATHOLOGICAL FINDINGS

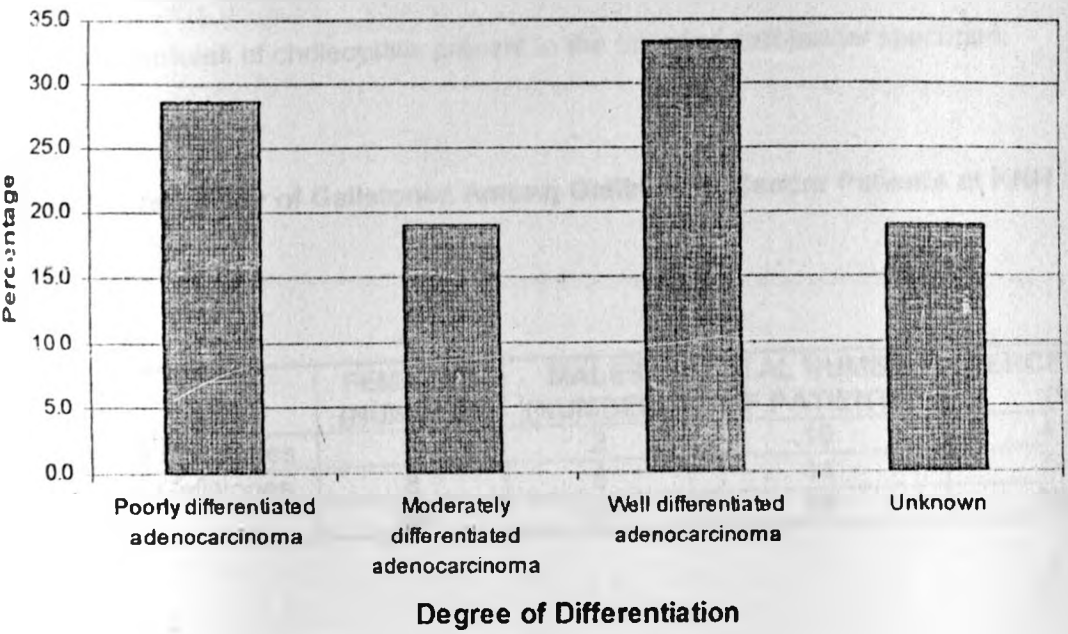
All the patients seen in this study had a histological diagnosis of malignant tumour. The most common histological type of gallbladder tumour was adenocarcinoma, which was seen in 21 of the patients (87.5%). 3 of the patients had unclassified histology as per report, but with features of cancer of the gallbladder.

Table 16 and figure 5 show the distribution of the patients with adenocarcinoma according to the histological grades of differentiation. 28.6% (6) of the patients had poorly differentiated adenocarcinoma, 19.0% (4) had moderately differentiated adenocarcinoma and 33.3% (7) had well differentiated adenocarcinoma.

Table 16 – Degree Of Differentiation

DEGREE OF DIFFERENTIATION	NUMBER OF PATIENTS	PERCENTAGE
Poorly differentiated adenocarcinoma	6	28.6%
Moderately differentiated adenocarcinoma	4	19.0%
Well differentiated adenocarcinoma	7	33.3%
Unknown	4	19.0%
TOTAL	**21**	**100.0%**

Figure 5: Histogram showing the degree of differentiation



Frequency of Gallstones

Cholelithiasis was demonstrated in 10 of the 24 patients with gallbladder cancer (41.7%). This is illustrated in table 17.

One patient with adenocarcinoma of the gallbladder was found to have cholelithiasis with histological features of cholecystitis present in the resected gallbladder specimen.

Table 17– Frequency of Gallstones Among Gallbladder Cancer Patients at KNH 1988 – 2000.

	FEMALES (NUMBER)	MALES (NUMBER)	TOTAL NUMBER OF PATIENTS	PERCENTAGE (%)
Presence of Gallstones	8	2	10	41.7
Absence of Gallstones	8	6	14	58.3
TOTAL	16	8	24	100.0

MODES OF PRESENTATION AND DIAGNOSIS.

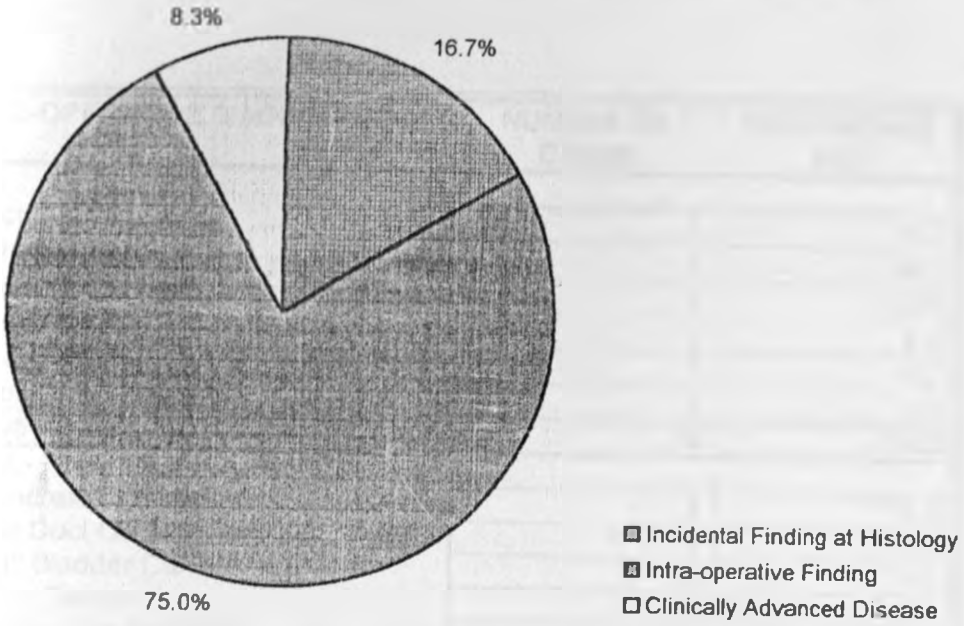
Table 18 and Figure 6 show the various modes of presentation and diagnosis in patients with gallbladder cancer seen at Kenyatta National Hospital.

The diagnosis of carcinoma of the gallbladder was established at operation in 18 (75.0%) of the patients, in whom there was no preoperative suspicion of the diagnosis. A preoperative diagnosis of cancer of the gallbladder was made in only 2 (8.3%) of the patients who presented clinically with advanced disease. In 16.7% (4) of the patients the diagnosis was made by the pathologist after the microscopic examination of the resected gallbladder for presumed benign disease.

Table 18 -- Modes of Presentation and Diagnosis of Patients With Gallbladder Cancer At KNH 1988 - 2000

MODES OF PRESENTATION	FEMALES (NUMBER)	MALES (NUMBER)	TOTAL NO. OF PATIENTS	PERCENTAGE (%)
Incidental Finding at Histology	2	2	4	16.7
Intra-operative Finding	12	6	18	75.0
Clinically Advanced Disease	2	0	2	8.3
TOTAL	**16**	**8**	**24**	**100.0**

Figure 6 : **Pie chart showing modes of diagnosis in patients with gallbladder cancer at KNH 1988 – 2000.**



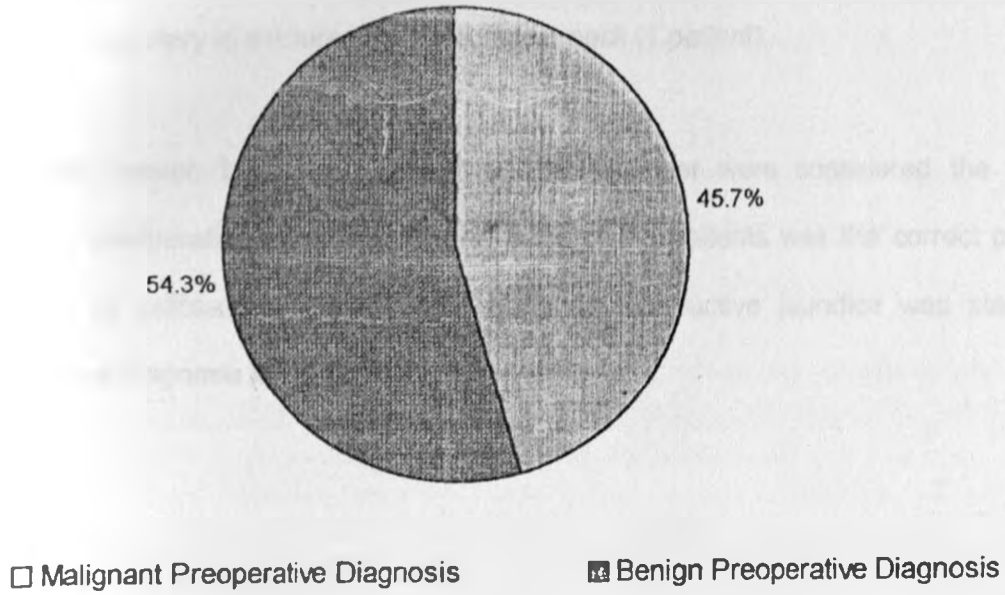
Preoperative Diagnosis

The preoperative diagnosis in patients with gallbladder cancer in this study are elaborated in Table 19 and Figure 7.

Table 19 – Pre-Operative Diagnosis of Patients with Gallbladder Cancer as seen at KNH 1988 – 2000.

PRE-OPERATIVE DIAGNOSIS	NUMBER OF CASES	PERCENTAGE (%)
Benign -		
Acute Cholecystitis	1	4.2
Cholelithiasis Only	4	14.7
Chronic Cholecystitis & Cholelithiais	5	20.8
Liver Cyst	1	4.2
Liver Abscess	1	4.2
Obstructive Jaundice	1	4.2
Sub - Total	**13**	**54.3**
Malignant -		
Pancreatic Carcinoma	3	12.5
Bile Duct Cancer	2	8.3
Gall Bladder Cancer	2	8.3
Liver Cancer	2	8.3
Obstructive Jaundice	2	8.3
Sub – total	11	45.7
TOTAL	**24**	**100.0**

Figure 7 : Pie chart showing the ratios of benign and malignant preoperative diagnosis in patients with gallbladder cancer.



The preoperative diagnosis in patients with gallbladder cancer suggested a benign process in 54.3% of the patients and a malignant process in 46.7%.

Chronic cholecystitis and / or cholelithiasis formed the bulk of the preoperative benign diagnoses (69.2%) i.e. 9 out of 13 patients. Other benign preoperative diagnoses included acute cholecystitis (1 patient), liver cyst (1 patient), liver abcess (1 patient) and obstructive jaundice secondary to stricture of the gallbladder neck (1 patient).

Pancreatic cancer, biliary tract cancer and liver cancer were considered the most likely malignant preoperative diagnoses. In only 8.3% of the patients was the correct preoperative diagnosis of gallbladder cancer made. Malignant obstructive jaundice was stated as the preoperative diagnosis in two patients.

CHOLECYSTECTOMY AND GALLBLADDER CANCER

A total of 203 patients had cholecystectomy at Kenyatta National Hospital for benign gallbladder diseases during the study period. The number of cholecystectomies done varied from 5 to 37, with an average of 15.6 operations per annum.

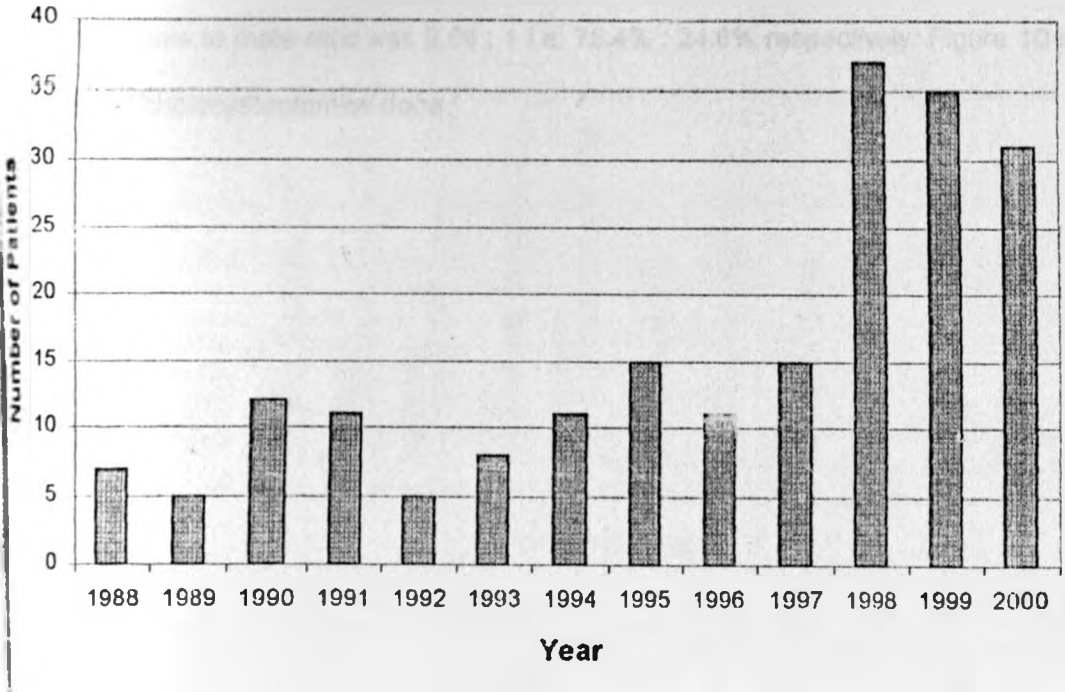
Table 20 shows the yearly distribution of cholecystectomy for benign disease and the total number of patients seen with gallbladder cancer at Kenyatta National Hospital.

Table 20 : Comparison between yearly distribution of gallbladder cancer and total number of cholecystectomy for benign disease at KNH 1988 – 2000.

YEAR	NUMBER OF CHOLECYSTECTOMIES	TOTAL NUMBER OF PATIENTS WITH GALLBLADDER CARCINOMA
1988	7	0
1989	5	1
1990	12	4
1991	11	1
1992	5	1
1993	8	1
1994	11	0
1995	15	3
1996	11	1
1997	15	1
1998	37	4
1999	35	4
2000	31	3
TOTAL	**203**	**24**

Figure 8 shows the yearly distribution of cholecystectomies done at KNH for benign gallstone diseases 1988 – 2000.

Figure 8 : Histogram showing yearly distribution of cholecystectomies done at KNH for benign gallstone diseases 1988 – 2000.



Age and Sex Distribution of Cholecystectomies

Figure 9 shows the age and sex distribution of patients undergoing cholecystectomy for benign gallbladder disease at Kenyatta National Hospital.

The mean age was 44.5 years with a peak incidence at 31 – 40 years age group. The youngest patient was 19 years, and the oldest was 96 years. 30.5% of the patients undergoing cholecystectomy for benign gallbladder disease were above 51 years of age.

The female to male ratio was 3.06 : 1 i.e. 75.4% : 24.6% respectively. Figure 10 shows the sex ratio of cholecystectomies done.

Figure 9 : Histogram showing the age and sex distribution of cholecystectomies done at KNH 1988 – 2000.

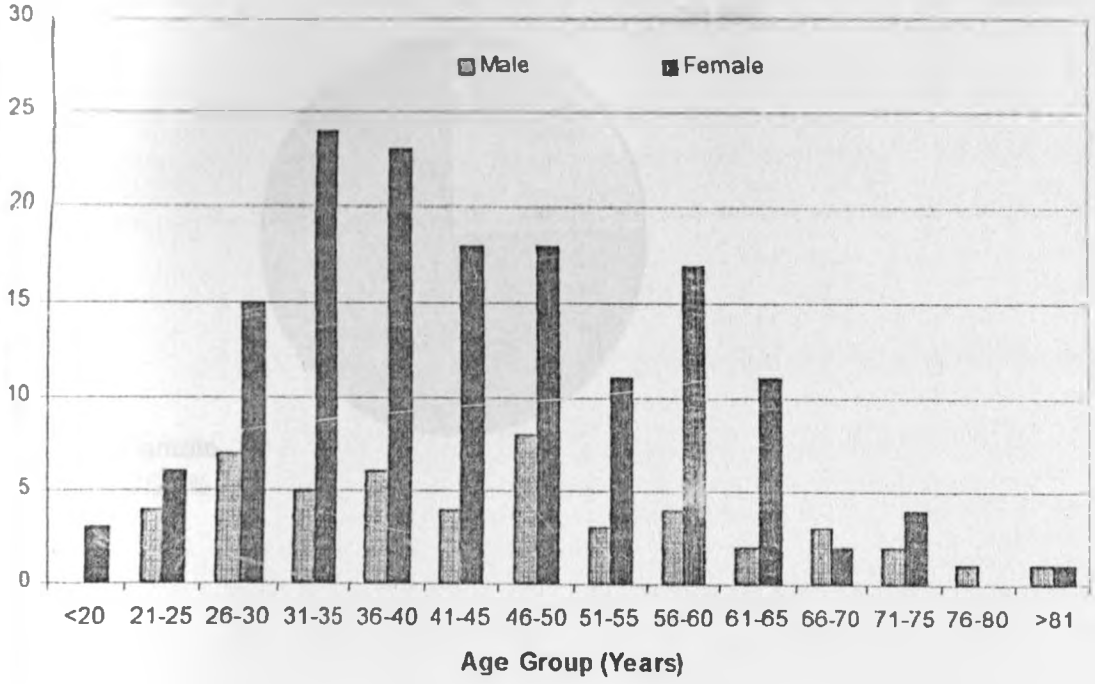


Figure 10: Pie Chart Showing Sex Ratio of Cholecystectomies done at KNH 1988 – 2000.

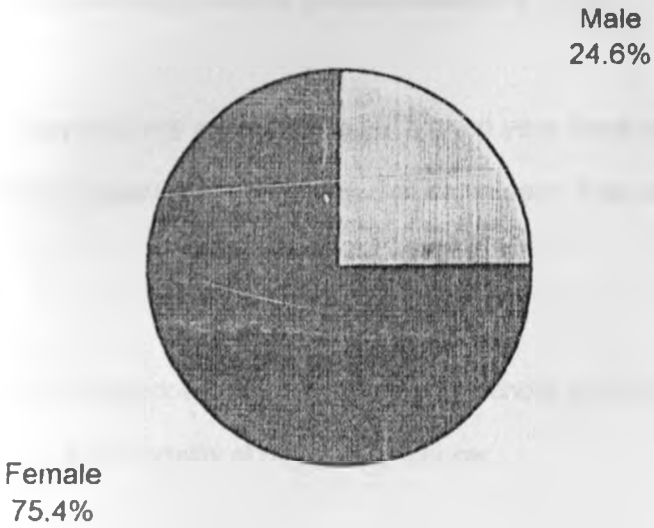


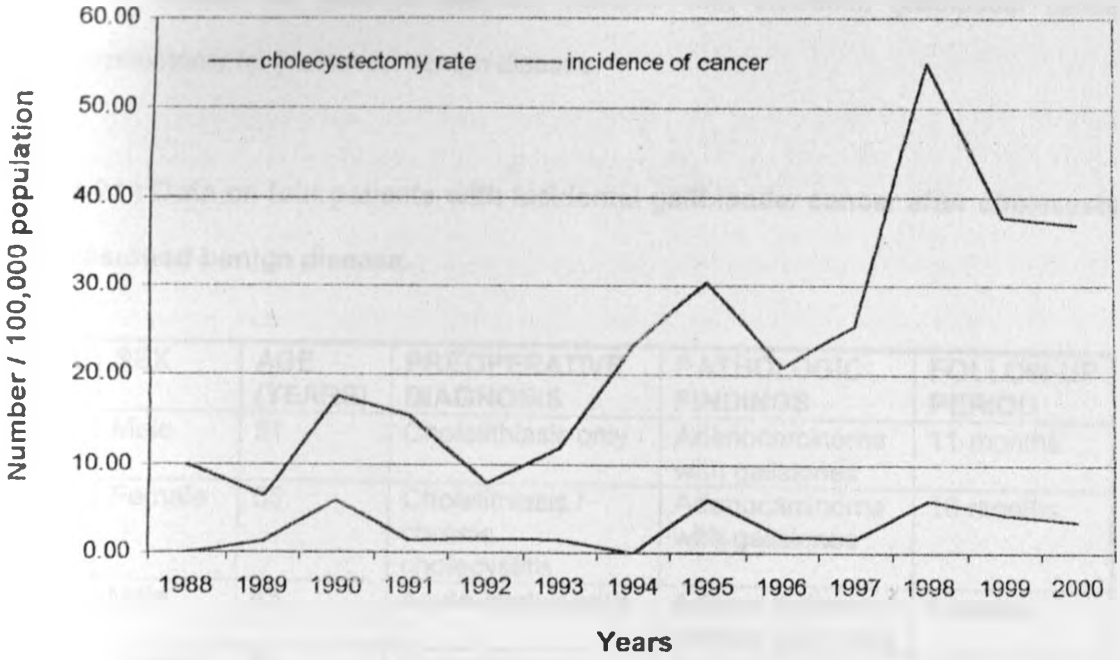
Figure 11 shows the comparison between the cholecystectomy rate and the incidence of gallbladder cancer as seen at Kenyatta National Hospital during the study period.

A sharp increase in the number of cholecystectomies performed was noted in 1998 and most likely attributable to the introduction of laparascopic surgery at KNH that year. A total of 17 patients underwent laparascopic cholecystectomy in 1998.

As the cholecystectomy rate increases in a given year there was also a comparative increase in the incidence of gallbladder cancer in that same year. See illustrations in Table 20 and Figure 11.

No significant correlation was seen between the cholecystectomy rate in the preceding year and the incidence and mortality of gallbladder cancer.

Figure 11 : Comparison between Cholecystectomy Rate and Incidence of Gallbladder Cancer.



Incidental Gallbladder Carcinoma

In this study, carcinoma of the gallbladder was diagnosed first at microscopic examination of the resected gallbladder by the pathologist, after cholecystectomy for presumed benign disease, in 4 of the 24 patients (16.7%). Thus, the incidence of gallbladder cancer in cholecystectomy specimens at Kenyatta National Hospital is 1.97%.

Table 21 shows the data on the four patients with incidental gallbladder cancer after cholecystectomy for presumed benign disease.

Table 21 : Data on four patients with incidental gallbladder cancer after cholecystectomy for presumed benign disease.

YEAR	SEX	AGE (YEARS)	PREOPERATIVE DIAGNOSIS	PATHOLOGIC FINDINGS	FOLLOW-UP PERIOD
1990	Male	51	Cholelithiasis only	Adenocarcinoma with gallstones	11 months
1993	Female	55	Cholelithiasis / chronic cholecystitis	Adenocarcinoma with gallstones	18 months
1998	Male	43	Acute cholecystitis	Adenocarcinoma without gallstones	6 weeks
2000	Female	82	Cholelithiasis / chronic cholecystitis	Adenocarcinoma with gallstones	17 days

There were two females and two males, with a mean age of 57.8 years and a range of 43 to 82 years.

The preoperative diagnosis was chronic cholecystitis with cholelithiasis in 2 patients, acute cholecystitis in one patient and cholelithiasis in only 1 patient. The histopathological findings showed adenocarcinoma in all 4 patients. Stones were found in three (75%) of the patients.

All the patients with incidental gallbladder carcinoma underwent cholecystectomy. None of the patients was re-operated after the histologic diagnosis of carcinoma was proved. One patient received postoperative radiation therapy after the histologic diagnosis of gallbladder cancer was confirmed.

SURGICAL MANAGEMENT

All 24 patients with gallbladder cancer reviewed had surgical procedures performed. The surgical procedures undertaken are listed in table 22.

Table 22 : Surgical procedures performed for gallbladder cancer at KNH 1988 – 2000.

SURGICAL PROCEDURE PERFORMED	NUMBER OF PATIENTS	PERCENTAGE (%)
Exploratory laparotomy and biopsy only	8	33.3
Cholecystectomy only	7	29.1
Cholecystectomy plus right hepaticoloop jejunostomy	1	4.2
Cholecystectomy plus Roux-en-Y choledocho jejunostomy	1	4.2
Biopsy plus cholecysto-jejunostomy	3	12.5
Biopsy plus hepaticoloop jejunostomy	1	4.2
Partial cholecystectomy	1	4.2
Partial cholecystectomy plus retrocolic gastrojejunostomy	1	4.2
Partial cholecystectomy plus cholecystojejunostomy and jejunojejunostomy	1	4.2
TOTAL	24	100.0

Eight patients (33.3%) had exploratory laparatomy and biopsy only. Cholecystectomy was carried out in 7 patients. In four (16.7%) of these patients, the diagnosis was not suspected until it was demonstrated on histologic examination of the resected gallbladder for presumed benign disease.

In the other 3 patients, the gallbladder tumour was an intraoperative finding and cholecystectomy was performed as a palliative procedure, as evidence of tumour spread beyond the gallbladder was noted at operation.

The other patients (37.6%) in this study underwent various palliative procedures. Cholecystectomy combined with biliary-enteric bypass was performed in 2 patients. One patient had a cholecystectomy plus a right hepatico-loop jejunostomy, while one patient had cholecystectomy combined with choledocho-Roux-en Y jejunostomy.

4 patients had a biliary-enteric bypass performed after biopsy of the tumour.12.5% of the patients had cholecystojejunostomy, and one patient had hepatico-loop jejunostomy. Three patients underwent partial cholecystectomy, and in two of these patients it was combined with a biliary-enteric or gastrointestinal bypass procedure. A retrocolic gastrojejunostomy combined with partial cholecystectomy was performed in one patient.

None of the patients with gallbladder tumour in this study had any radical surgical procedures, such as lymphadenectomy, liver resection or pancreaticoduodenectomy performed.

The organs involved by tumour spread detected at the time of surgery are listed in table 23.

The most common areas of spread were the liver (54.2%), extrahepatic bile ducts (33.3%), stomach (29.2%), regional lymph nodes (20.8%), colon (20.8%) duodenum (20.8%), pancreas (12.5%), omentum and mesentery (8.3%).

Table 23: Organs involved by tumour spread and metastasis.

LOCATION	NUMBER OF PATIENTS	PERCENTAGE (%)
Liver	13	54.2
Extrahepatic bile ducts	8	33.3
Stomach	7	29.2
Lymph nodes	5	20.8
Colon	5	20.8
Duodenum	5	20.8
Pancreas	3	12.5
Omentum	1	4.2
Mesentery	1	4.2

Adjuvant Postoperative Therapy

Only three patients with gallbladder cancer received postoperative adjuvant therapy in this study. One patient received intravenous chemotherapy with vincristine after laparotomy and biopsy of the tumour, whereas two patients received postoperative radiation therapy.

One patient with incidental gallbladder carcinoma diagnosed after cholecystectomy for presumed gallstone disease received postoperative radiotherapy.

Table 24 shows the outcome in patients who received postoperative adjuvant chemotherapy or radiation therapy. All the three patients who received postoperative adjuvant therapy were alive at a mean follow up duration of 7.5 months.

Table 24: Outcome in patients who received postoperative adjuvant therapy.

MANAGEMENT	NUMBER OF PATIENTS	OUTCOME
Cholecystectomy plus postoperative radiotherapy	1	Alive at 11 months
Exploratory laparotomy, biopsy plus postoperative chemotherapy	1	Alive at 10 weeks
Partial cholecystectomy plus cholecystojejunostomy / jejunojejunostomy and postoperative radiotherapy	1	Alive at 9 months

Follow-up Results

The results of follow-up for the 24 cases of gallbladder cancer studied are shown in table 25. The duration of follow-up was determined from the time of operation to the last follow-up clinic visit in the case notes.

The follow-up of three patients was not documented in the case notes after the operation, and will be assumed to have been lost for follow-up.

Table 25: Duration of follow-up.

DURATION (MONTHS)	NUMBER OF PATIENTS	PERCENTAGE (%)
<1	6	25.0
1 – 2	4	16.7
3 – 4	2	8.3
9 – 10	1	4.2
11 – 12	1	4.2
17 – 18	1	4.2
Lost to follow-up	3	12.5
Died during follow-up	6	25.0
Total	24	100.0

41.7% of the patients were followed up for less than two months after the surgery. The mean duration of follow-up was 2.3 months. The longest duration of follow-up was 18 months in a patient with incidental cancer after cholecystectomy for presumed benign disease.

Of the 24 patients seen with cancer of the gallbladder, 6 patients died within the first month postoperatively. Patients with incidental gallbladder carcinoma detected after cholecystectomy for presumed benign disease, and those patients who received postoperative adjuvant therapy had a better outcome with a mean follow-up period of 7.8 months and 7.5 months respectively.

DISCUSSION

Cancer of the gallbladder is an uncommon, but not a rare neoplasm. It is the commonest malignant tumour of the biliary tract and the fifth most common malignancy of the gastro-intestinal tract, after the cancers of the rectum, colon, pancreas and stomach [1,2]. The estimated annual incidence of gallbladder cancer is reported to be 2.5 - 2.7 per 100,000 [2,3] and the reported hospital admission rate is between 0.01 and 0.02 percent [90].

In this retrospective study covering a thirteen year period, 24 cases of histologically confirmed gallbladder cancer were seen at Kenyatta national Hospital. Gallbladder cancer accounted for 0.09% of all malignancies and 0.003% of all admissions over the same period. The average number of cases seen per annum was 1.9. The incidence of cancer of the gallbladder was 2.76 per 100,000 of the patients who were seen at KNH during the study period.

Age and Sex Distribution

Cancer of the gallbladder predominates in the elderly females [1]. Over 90% of the patients are over 50 years and the peak age of incidence is in the 65 to 75 year group, with a mean age of 65.2 years [1,6]. The female to male ratio in various series has been 3.2 : 1 [1], 3.38 :1 [6], 1.4 : 1 [90].

In this study, the ages of the patients ranged from 27 and 82 years with a mean age of 52.0 years. The peak age of incidence was in the 51 to 55 year group. 62.5 per cent of the patients were above 51 years of age. The female to male ratio in this study was 2:1. These findings compare well with other series, however it would appear that gallbladder cancer may be presenting at an earlier age in this hospital compared with other centres.

Parity

Increased parity, which is a risk factor for gallstones, has been shown to increase the risk of gallbladder cancer [23]. The average parity of female patients with gallbladder carcinoma in this

study was 6. Thus, increased parity may possibly be a risk factor for gallbladder cancer in patients seen at Kenyatta National Hospital.

Geographical Distribution

Majority of the patients with gallbladder cancer seen at Kenyatta National Hospital were from districts within Central Province, such as Muranga (29.2%), Kiambu (12.5%) and Nyeri (12.5%). This could probably be attributed to the proximity of these districts to Nairobi, or could reflect the large population of the province. Another possibility is that the ethnic groups found within the Central Province may have a higher predisposition to developing gallbladder cancer, and possibly gallstones. The Kikuyu, Meru and Embu are the major ethnic groups found in the Central Province.

Only 4.2% of the patients were from Nairobi despite its proximity to the hospital. The low figures under Nairobi could be explained by the fact that most of the residents of Nairobi do not consider it as its province of origin. Being the national referral hospital, some of the patients seen at KNH were from far flung districts such as Lamu.

Occupation

Some workers have found that a high incidence of gallbladder cancer is seen in people who worked in rubber, automobile, wood finishing and metal fabricating industries [1,17]. The occupation does not seem to affect the causation of gallbladder cancer in our population, as none of the patients with gallbladder cancer seen in KNH had worked in any industry associated with a higher incidence of cancer.

33.3% of the patients were housewives, 16.7% were traders, 12.5% were farmers, 8.3% were teachers, 4.2% were cooks, 4.2% were waiters and 20.8% were unemployed.

PATHOLOGY

The gross appearance of carcinoma of the gallbladder is of either a diffusely or a localized polypoid, nodular, plaque-like or papillary lesion, often with local involvement of adjacent structures [11,17,61]. Gallbladder cancer most frequently occurs in the fundus but can occur in other parts of the gallbladder as well, including the cystic duct [61,62].

Histologically, in this study, the majority of the gallbladder tumours were adenocarcinomas (87.5%). Three of the patients had unclassified histology as per report but with features of cancer of the gallbladder. These findings were similar to the studies done elsewhere in which adenocarcinomas were the most common histological type accounting for 80 to 95% of the malignant primary tumours of gallbladder [11, 61,63].

33.3% (7) had well differentiated adenocarcinomas, 28.6% (6) of the patients had poorly differentiated adenocarcinomas, 19.0% (4) had adenocarcinomas but the degree of differentiation was not elaborated on. Patients with papillary or well differentiated carcinoma had been reported to have a higher survival than poorly differentiated carcinoma [64]. In this study, no correlation was found between the degree of differentiation and survival as the followup of the patients was poor.

The other histological subtypes of gallbladder cancer such as squamous cell carcinoma, adenocanthoma, undifferentiated carcinoma, carcinosarcoma, sarcomas, malignant melanoma or malignant lymphomas were not encountered in the series.

The most common areas of spread in this study were the liver (54.2%), extrahepatic bile ducts (33.3%), stomach (29.2%), regional lymph nodes (20.8%), colon (20.8%), duodenum (20.8%), pancreas (12.5%), omentum and mesentery (8.3%). The apparently low incidence of nodal metastases in our set-up despite the advanced presentation of most of the patients could be explained by the inadequate documentation of lymph node metastases in the operative notes.

Lymph drainage of the gallbladder is primarily to the nodes along the common bile duct and not to the hilus of the liver, and so nodal metastasis can occur in the absence of liver involvement.

Although the exact cause of carcinoma of the gallbladder is unknown, the most commonly implicated aetiologic factors are cholelithiasis and chronic inflammation of the gallbladder [1, 8, 10, 23, 40]. 41.7% of the patients with gallbladder cancer in this study had associated gallstones, despite the fact that gallstone disease has been reported to be rare in the African population. One patient had cholelithiasis with histological features of chronic cholecystitis present in the resected specimen, in association with adenocarcinoma of the gallbladder.

Benign tumours of the gallbladder [50, 51, 52, 53], porcelain gallbladder [41, 42], anomalous pancreaticobiliary ductal junction [43, 44], chronic inflammatory bowel disease [56, 57], previous gallbladder surgery [6, 60] and chronic typhoid infection [50, 58] are other aetiologic factors associated with gallbladder cancer. None of these features seem to affect causation of cancer of the gallbladder in our population as none of the patients had any of these conditions.

CLINICAL PRESENTATIONS

The signs and symptoms of gallbladder cancer are generally non-specific, often resembling benign gallbladder disease. The lack of specific signs or symptoms prevents detection of carcinoma of the gallbladder at an early and resectable stage. Clinical diagnosis of a gallbladder carcinoma is usually only possible in the advanced and invasive stages, when the tumour became symptomatic [1, 5, 10, 11, 12, 13].

The most common initial symptoms in patients with gallbladder cancer is pain, which occurs in 75% [1]. In over half, the pain is localized to the right upper quadrant. In their collective review, Piehler and Crichlow found 76% of symptomatic patients had pain, 38 % had jaundice, 32% had nausea and vomiting and 39% had weight loss [1].

In this study, the most common presenting symptoms were abdominal pain (79.2%), followed by jaundice (62.5%), pruritus (58.3%), nausea and vomiting (41.7%), anorexia (33.3%), abdominal distension or mass (25%), and weight loss (25%).

One patient presented with haematemesis. Clinically evident gastrointestinal tract bleeding in the presence of carcinoma of the gallbladder can occur at varying stages of evolution of the neoplasm, and can result from haematobilia, from direct invasion of stomach, duodenum, colon or from altered coagulation from hepatic failure as a terminal manifestation of the disease [1].

The findings upon physical examination of patients with carcinoma of the gallbladder are generally non-specific. Piehler and Crichlow (1978) found right upper quadrant mass in 42% of patients, hepatomegaly in 41% and upper abdominal tenderness in 38% of the patients [1].

Wanebo in 1982 found that the major clinical signs included tenderness in the right upper quadrant and epigastrium (57%), mass in the same area (54%), hepatomegaly (37%), jaundice (37%), cachexia and fever (10-16%) and ascites (7%) [6]. Hamrick in 1982 noted hepatomegaly in 45% of the patients, representing the most common physical finding. Jaundice was present in 40% of patients and tenderness to palpation was noted in 36% of patients [70].

Common findings on examination in this study were abdominal tenderness (79.2%), jaundice (70.8%), hepatomegaly (66.7%), pallor (33.3%), palpable gallbladder (29.2%), ascites (8.4%) and fever (4.2%).

A notable finding in this study is the high percentage of the patients presenting jaundice. Jaundice is usually found in 30 – 60% of patients with gallbladder cancer and is usually the result of common bile duct obstruction. Widespread liver metastases are responsible for jaundice less often [17]. Jaundice is a poor prognostic sign. Gradisar and Kelly found that 35% of the patients with jaundice have unresectable carcinoma at operation [7].

Duration of Symptoms

The duration of symptoms ranged from 2 weeks to over one year, with the majority of patients (87.5%) in this study reporting symptoms for less than one year. Half the patients had symptoms for two months or less.

From the literature, 80% of patients with gallbladder cancer had symptoms for less than six months prior to their presentation [6, 70]. This correlates well with the findings of this study. Patients with gallbladder cancer have a long duration of symptomatology attributable to benign gallbladder disease, with between 20 and 60 per cent of symptomatic patients having a definite recent change in symptoms, usually relating to change in the quality or frequency of pain, and occasionally to development of new symptoms, such as jaundice, weight loss [1].

Associated Conditions

Carcinomas of the gallbladder have occasionally been associated with paraneoplastic syndromes such as Cushing's syndrome, acanthosis nigricans, pemphigoid skin lesions and Zollinger – Ellison syndrome. None of the patients with gallbladder cancer in this study had any associated paraneoplastic syndrome.

Associated conditions occurred in a minority of patients in this study. Three patients in this study had peptic ulcer disease, with two of them having symptomatology for more than 10 years prior to diagnosis. One patient had an associated liver abscess. One patient had an umbilical hernia in association with gallbladder cancer, an association that has not been reported before, although umbilical metastasis has been reported in patients with carcinoma of the gallbladder.

INVESTIGATIONS

Laboratory and radiological investigations are seldom helpful in the diagnosis of gallbladder cancer, usually because of lack of specificity of findings. The use of new imaging techniques

combined with a high index of clinical suspicion should lead to a preoperative diagnosis in the majority of advanced cases [73].

Laboratory findings, although abnormal, are non-specific and are not diagnostic of neoplasms of the gallbladder. The serum alkaline phosphate level is increased in over three fourths of the patients. Hyperbilirubinaemia and leukocytosis are present in about half. Anaemia of a mild degree is common [1, 4, 5, 6, 90].

Mild anaemia was a common finding in the study. 61.9% of the patients had haemoglobin level below 12.0%. The white blood counts of 13 of the patients fell within the normal range, while only 4 patients (23.5%) had an elevated count.

Liver function testing was carried out in 18 patients. The frequent abnormalities seen were elevated alkaline phosphate (77.8%), hypoalbuminaemia (80%), and hyperbilirubinaemia in 66.7% of the patients. Hepatic enzyme levels were mostly elevated in all cases with obstructive jaundice.

An array of radiological studies are available in the investigation of gallbladder cancer, but most of them are of little aid in establishing the diagnosis of the neoplasm. These include plain radiographs, oral cholecystography, intravenous cholangiography, percutaneous transhepatic cholangiography (PTC), endoscopic retrograde cholangiopancreatography (ERCP), ultrasonography, CT scan, MRI scan and angiography.

Ultrasonography is a non-invasive, non-ionising, less expensive, readily available and may detect the carcinoma at an early and potentially curable stage. Ultrasound is able to establish the diagnosis in approximately 80% of the patients [73].

Ultrasound is operator dependent and thus results vary considerably from one institution to another, and even within the same institution when done by different radiologist. Sonography is particularly limited in the diagnosis of metastasis to the peritoneum and lymph nodes [81]. In recent years, endoscopic ultrasonography has been found to be useful in the diagnosis of the depth of invasion and staging of gallbladder carcinoma [82].

In this study, the most common radiologic study performed preoperatively was ultrasonography. Abdominal ultrasonography was performed in 83.3% of the patients. A mass in the gallbladder and a dilated gallbladder were the findings in 20.8% and 29.2% of the patients respectively. Thickening of the gallbladder wall and collapsed gallbladder were reported in 2 patients each. Ultrasonographic features associated with gallbladder cancer detected in this study included dilated bile ducts (58.3%), gallstones (37.5%), metastatic masses in liver (8.3%) and ascites (4.2%).

Plain abdominal x-rays are of limited value in the assessment of patients with gallbladder cancer, although the radiographs may occasionally show evidence of gallstones, a tumour mass or gallbladder calcification. Plain abdominal x-ray was obtained in 2 patients in this study. One patient had normal radiographic findings while the other was reported as showing gas in the gallbladder. Gas in the gallbladder lumen, biliary tree or liver is suggestive of emphysematous cholecystitis, a fistulous communication with the gastrointestinal tract or a liver abscess.

CT scan was performed in two patients and suggested the diagnosis in both the patients. Percutaneous transhepatic cholangiography (PTC) was performed in one patient with gallbladder cancer and showed dilated main and common hepatic ducts with obstruction at level of origin of the cystic duct. PTC in jaundiced patients may demonstrate several features within the intrahepatic bile ducts highly suggestive of gallbladder cancer including stricturing, distortion

or non-filling of bile ducts and are due to the direct intra hepatic invasion of the bile ducts by the cancer [70].

Barium meal x-ray examination was performed in 2 patients in this study and showed a duodenal ulcer in one of the patients. Oesophago-gastroduodenoscopy was performed in 2 patients and gastritis was identified in both the patients. Oral cholecystography, intravenous cholangiography, MRI, ERCP and angiography were not utilised on any patient in this study. The main reasons were the high cost and the unavailability of some of these modalities.

MODES OF DIAGNOSIS

Most carcinomas of the gallbladder are unexpected findings and the diagnosis is seldom made with conviction preoperatively, because of the relative rarity of carcinoma of the gallbladder and the clinical symptoms and signs commonly mimic benign gallbladder disease.

The preoperative diagnosis of gallbladder cancer at an early and resectable stage is exceptional and difficult because of the non-specific clinical, biochemical and radiological features of the tumour. Once the tumour has become symptomatic the diagnosis is easier[1,5,11,68,72]. In most clinical reviews only 10% of gallbladder cancers were diagnosed preoperatively[10,11,12,13]. In this study, a preoperative diagnosis of gallbladder cancer was made in only 8.3% of the patients who presented clinically with advanced disease. Piehler and Crichlow reported a mean correct preoperative diagnosis of 8.6%[1].

Most carcinomas of the gallbladder are unexpected findings at laparotomy or are initially detected by the pathologist on cholecystectomy specimens removed with presumed diagnosis of symptomatic cholethiasis. Piehler and Crichlow observed that 12% cases of cancer of the gallbladder were discovered by the pathologist on cholecystectomy specimens which were removed for a presumed benign disease [1]. Incidental carcinomas have no characteristic

symptomatology, and the signs and symptoms often resemble those of cholecystitis and cholelithiasis.

In 16.7% of the patients with gallbladder cancer in this study, the diagnosis was made by the pathologist after microscopic examination of the resected gallbladder for presumed benign disease. The diagnosis of gallbladder cancer was established at laparotomy in 75.0% of the patients in this study, in whom there was no preoperative suspicion of the diagnosis.

Nearly all patients with gallbladder cancer usually present as one of the following clinical syndromes:

1) acute cholecystitis
2) chronic cholecystitis
3) obstructive jaundice of undetermined aetiology
4) non-specific symptoms suggestive of a malignant tumour e.g. anorexia, weight loss.

The great overlap between benign and malignant gallbladder disease probably accounts for much of the delays in the diagnosis of gallbladder cancer. The preoperative distinction between benign and malignant gallbladder disease is generally not possible with the present preoperative investigative studies.

About 16% of patients with carcinoma of the gallbladder present with the clinical syndrome of acute cholecystitis preoperatively[1]. These patients have less advanced carcinoma with both a higher incidence of resectability and longer survival [71]. One (4.2%) of the patients in this study presented with the preoperative diagnosis of acute cholecystitis. This low figure can be attributed to the fact that most of the patients with acute cholecystitis in KNH are treated conservatively and interval elective cholecystectomy done after resolution of the acute episode.

The preoperative diagnosis in patients with gallbladder cancer at KNH suggested a benign process in 54.3% of the patients and a malignant process in 45.7%. Chronic cholecystitis and cholelithiasis were the preoperative diagnosis in 37.5% of the patients in this study. Piehler and Crichlow fount that 43% of patients with gallbladder cancer presented with histories consistent with the diagnosis of chronic cholecystitis [1].

Pancreatic cancer, biliary tract cancer and liver cancer were considered the most likely malignant preoperative diagnosis in this study. Three patients presented with the preoperative diagnosis of obstructive jaundice. These findings correlate well with other series.

CHOLECYSTECTOMY AND GALLBLADDER CANCER

In Kenyatta National Hospital, 203 cholecystectomies were performed for benign gallbladder diseases during the years 1988 to 2000, with an average of 15.6 operations per year. Female dominance over males was seen in the ratio of 3.06 : 1 for cholecystectomies with a mean age of 44.5 years. Awasom [118] showed a female preponderance in patients with gallstone disease at KNH with a mean age of 41 years.

A marked increase in the number of cholecystectomies performed was noted in 1998 following the introduction of laparascopic surgery at KNH. One of the patients with unexpected gallbladder cancer was scheduled for a laparascopic surgery with a preoperative diagnosis of chronic cholecystitis. At operation, the cholecystectomy was converted to open procedure due to adhesions.

The diagnosis of cancer of the gallbladder is made in about one-third of cases incidentally at the time of cholecystectomy. Piehler and Crichlow (1978) found 36% of patients of the gallbladder cancer presented with either acute or chronic cholecystitis without suspicion of malignancy. The diagnosis was discovered incidentally either at operation or by the pathologist examining the removed gallbladder [1].

The incidence of carcinoma of the gallbladder found in patients undergoing operations has been reported as 1 to 2 percent in different series [1, 5]. The carcinoma was first diagnosed at microscopic examination of resected gallbladder for presumed benign disease in 4 patients, giving the incidence of gallbladder cancer as 1.97% among cholecystectomy specimens at KNH.

The incidence of gallbladder cancer increases with age, especially in women with cholelithiasis [25]. Nearly 10% of gallbladders removed from patients above 65 years of age will harbour a carcinoma. Over 90% of the patients with cancer of the gallbladder are over 50 years [1, 6]. In this series, 62.5% of the patients with cancer are over 51 years of age whereas 30.5% of patients undergoing non-cancerous cholecystectomy are over 51 years of age.

In some countries, the incidence and mortality from gallbladder cancer is decreasing as a consequence of the concurrent rise in the cholecystectomy rate in the recent years. In 1981, Diehl and Beral estimated that one case of gallbladder cancer is prevented for every 100 cholecystectomies performed for gallstone disease.

In this study, it was noted that as the frequency of cholecystectomies increased in a given year, there was a comparative increase in the incidence of gallbladder cancer in the same year. This could be attributed to the fact that three – quarters of the gallbladder cancers seen at KNH were diagnosed at operation with no preoperative suspicion of the disease. The use of new and extensive diagnostic procedures coupled with improvement in surgical care may result in more persons with cholelithiasis being diagnosed and offered surgery. These may cause a reduction in the prevalence of gallbladder at risk of cancer, with a subsequent decrease in cancer incidence and mortality.

SURGICAL MANAGEMENT

The most effective therapy for carcinoma of the gallbladder is surgical resection of the primary tumour and the most common areas of metastasis. In most series fewer than 25% of tumours are resectable. The vast majority of therapy for gallbladder cancer is palliative. Most lesions cannot be resected with negative margins.

In this series, most of the patients with gallbladder cancer presented clinically with advanced disease or were found at the time of exploration to have advanced disease. At Kenyatta National Hospital, 16.7% of the patients with gallbladder cancer underwent cholecystectomy, 33.3% underwent exploratory laparotomy and biopsy only, and 50.0% underwent various palliative procedures.

If tumour is limited to mucosa, simple cholecystectomy is adequate therapy as the presence of local dissemination or metastatic disease is rare [10, 96]. Most surgical cures have followed a simple cholecystectomy for carcinoma-in-situ or a mucosal lesion and in general the addition of more aggressive surgery has not resulted in improved survival. In this series, 4 patients (16.7%) had potential curative cholecystectomy for unsuspected carcinoma first diagnosed at examination of gallbladders removed for presumed benign disease.

En bloc excision of the gallbladder with wedge resection of adjacent liver and regional lymphadenectomy may prolong survival in selected patients with early, localized disease limited to muscularies or subserosa.

If tumour penetrates the serosa with extension to adjacent organs, surgical therapy with curative intent is impossible and radical surgery in this situation is associated with higher postoperative morbidity and mortality and extremely poor long term prognosis [27, 64, 90]. Although long term survival has occasionally been reported in selected patients with advanced cancer

following more aggressive surgery such as pancreaticoduodenectomy and extensive liver resection [97].

In this study, none of the patients with gallbladder cancer had any radical procedures such as liver resection, lymphadenectomy or pancreatico-duodenectomy performed. This could probably be attributed to the late presentation of patients with gallbladder cancer at KNH at an advanced, unresectable stage of disease.

SURGICAL PALLIATION

Gallbladder tumour cannot be resected in over two thirds of cases and some form of palliative procedure will usually be necessary for biliary or gastrointestinal obstruction. The best approach to non-resectable tumours is usually to document the diagnosis microscopically and perform biliary or gastrointestinal bypass as indicated. The mean survival of the patients with effective biliary bypass even in the best series was only about 10 months [100].

Surgical biliary bypass is not straight forward as the level of tumour obstruction is usually at the common hepatic duct or above. Segment III cholangiojejunostomy has been reported to provide effective long- term decompression of the left biliary tree. Malignant obstruction of the anastomosis will not occur until at a late stage and prolonged relief of jaundice may be obtained [100]. Removal or drainage of the gallbladder may be necessary as a palliative procedure to prevent the subsequent development of acute cholecystitis from cystic duct obstruction related to tumour growth. Gastric outlet obstruction may frequently complicate gallbladder cancer and satisfactory palliation can be achieved in most patients by gastrojejunostomy [100].

50% of the patients with gallbladder cancer in this study had surgical palliative procedures performed. External drainage of the gallbladder or cholecystostomy was not used as palliative procedure in any of the patients. Retrocolic gastrojejunostomy was performed in one patient with gastric outlet obstruction who died two weeks after surgery due to electrolyte imbalance.

In 7 patients with obstructive jaundice, biliary-erteric bypass was performed. Partial cholecystectomy was performed in 3 patients as a palliative procedure. Cholecystojejunostomy was the commonest palliative procedure performed in patients with gallbladder cancer. Two patients had hepatico-loop jejunostomy and one patient had choledocho-Roux-en-Y jejunostomy. The outcome of most of the patients with gallbladder cancer undergoing palliative surgery was poor with 4 of the patients dead within a month of surgery. One patient who underwent partial cholecystectomy with cholecystojejunostomy / jejunojejunostomy had good palliation being alive and symptom-free at 9 months of follow up.

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RADIOTHERAPY AND CHEMOTHERAPY

The effectiveness of chemotherapy and radiotherapy in gallbladder carcinoma is unpredictable and the response is generally poor, whether used separately or in combination both as adjuvant therapy after operation and for palliation of locally advanced and metastatic disease [10].

In this study, one patient received intravenous vincristine after laparatomy and biopsy, and was reported to be alive after 10 weeks of follow-up. There was no difference in the duration of follow-up with the patients who did not receive chemotherapy.

Two patients with gallbladder cancer who received post-operative adjuvant radiotherapy were alive at a mean follow-up duration of 10 months. Houry (1999) commented that gallbladder carcinoma may not be as radio-resistant as was formerly thought. Slight improvement of survival after adjuvant or palliative radiotherapy especially in advanced stage of gallbladder carcinoma has been reported [110].

INCIDENTAL CARCINOMA OF THE GALLBLADDER

In this series, the gallbladder carcinoma was diagnosed first at microscopic examination of gallbladders removed for presumed benign disease in 4 of 24 patients (16.7%). The frequency was about the same in the series of Piehler and Crichlow, or 9 of 48 patients (19%) [1] Berghadl reported a slightly higher frequency (27%) [98]. The mean age was 57.8 years with a range of 43 – 82 years. The age distribution and the frequency of gallstones (75% of patients) was similar to other reported series. The preoperative diagnosis was chronic cholecystitis and / or cholelithiasis in all the patients with incidental adenocarcinoma of the gallbladder. In all the patients with incidental cancer, only cholecystectomy was performed. None of the patients had a radical second operation performed.

Proper management of incidental carcinoma begins with the opening and careful examination of all resected gallbladders at operation. Immediate frozen sections should be done whenever any suspicious lesion is found [11, 70]. When cholecystectomy has been performed for presumed benign disease and the pathologic report indicates carcinoma of the gallbladder, the therapy chosen should also be based on the degree of infiltration of the gallbladder bed.

Cholecystectomy has been considered as an adequate operation for carcinoma confined to the mucosa and submucosa [98]. With deeper involvement of the wall of the gallbladder, the chances of localized recurrence increases demonstrating the inadequacy of reliance upon cholecystectomy alone [14]. Bergadhl (1980) [98] and Shirai (1992) [99] recommended reoperation for delayed hepatic wedge resection and lymph node dissection to increase resection margins, leading to removal of residual tumour and subsequent survival of the patient. With extension of tumour to the serosa or periserosal structures, the decision of reoperation should be individualized since extensive surgery has poor results in this group of patients [44].

Laparascopic cholecystectomy was introduced at KNH in 1998 and is rapidly becoming the surgical procedure of choice over conventional open cholecystectomy for removing the diseased gallbladder. In recent years, there have been an increasing number of case reports of

port-site metastasis and early appearance of peritoneal carcinomatosis following laparascopic cholecystectomy for unsuspected carcinoma of the gallbladder [15, 16].

If malignancy is encountered unexpectedly during laparascopic cholecystectomy, the procedure should be converted to an open resection to allow for appropriate evaluation of the stage of disease and appropriate surgical management.

PATIENT FOLLOW-UP

The prognosis for carcinoma of the gallbladder is bad with less than 5% of the patients still alive after five years post operatively. The majority of patients who live longer than five years are usually those in whom the carcinoma was first diagnosed at microscopic examination of gallbladders which were removed for presumed benign disease [1].

The follow-up period after surgery was short for many of the patients in this study with a mean duration of follow-up of 2.3 months. Most of patients after diagnosis were sent to their district hospitals for follow-up and terminal care. 25% of the patients with gallbladder cancer were dead within the first postoperative month. The longest survivor (who was alive at 18 months) was a patient in whom the tumour was an incidental finding after cholecystectomy for cholelithiasis. Patients treated postoperatively with adjuvant radiation therapy survived longer (mean follow-up 10 months) compared with those not so treated. The various surgical palliative procedures did not prolong survival in this series as most of the patients had advanced disease.

CONCLUSIONS

The following conclusions can be drawn from this study of gallbladder cancer as seen at Kenyatta National Hospital over a thirteen - year period 1988 to 2000.

1. Gallbladder cancer does occur and constitutes 0.[illegible]% of all surgical admissions and 0.09% of all malignant tumours. An average of 1.9 cases are seen per annum.

2. The age range was 27 years to 82 years, with a mean age of 52.0 years. 62.5% of the patients are over 51 years of age. The female to male ratio was 2:1. The average parity of the female patients was 6.

3. 62.5% of the patients with gallbladder cancer in this study were found to have come from Central Province.

4. The incidence of gallbladder cancer in cholecystectomy specimen was 1.97%. An average of 15.6 cholecystectomies per annum are performed at KNH for benign gallbladder disease.

5. An increase in the frequency of cholecystectomies performed was noted after 1998 following the introduction of laparascopic surgery at KNH. The female to male ratio of patients undergoing cholecystectomy for benign gallbladder disease was 3.0 to 1, with 30.5% of the patients over 51.0 years.

6. Most of the cases of carcinoma of the gallbladder present late, with abdominal pain, jaundice, pruritus, nausea / vomiting, anorexia, weight loss and abdominal distension / mass being the commonest presenting symptoms. The common findings on examination were

abdominal tenderness, jaundice, hepatomegaly, pallor and palpable gallbladder. Half of the patients (50%) had symptoms for two months or less.

7. Abdominal ultrasound was the most utilised radiological investigation. The laboratory findings were non-specific and not diagnostic of gallbladder carcinoma. The common abnormalities detected included anaemia, leucocytosis, hypoalbuminaemia, hyperbilirubinemia and elevated alkaline phosphatase.

8. The commonest histological type of gallbladder cancer seen was adenocarcinoma (87.5%). 41.7% of the patients with gallbladder cancer in this study had gallstones.

9. The liver, extrahepatic bile ducts, stomach, regional lymph nodes, colon, duodenum and pancreas were the most common areas of tumour spread in this study.

10. The correct preoperative diagnosis of gallbladder cancer was made in only 8.3% of the patients. In 16.7% of the patients the diagnosis was made by the pathologist after cholecystectomy for presumed benign disease.

11. The diagnosis of gallbladder cancer was established at operation in 75% of the patients. Chronic cholecystitis and cholelithiasis formed the bulk of the preoperative benign diagnosis, whereas pancreatic cancer, biliary tract cancer and liver cancer were considered the most likely preoperative malignant diagnosis.

12. In this study, exploratory laparotomy and biopsy only was done in 33.3% of the patients. 7% of the patients had simple cholecystectomy. No radical surgery was performed.

13. Palliative biliary-enteric and gastrointestinal bypass procedures were performed in one-third of the patients with gallbladder cancer.

14. Only 12.5% of the patients had radiation therapy or chemotherapy after surgery. Adjuvant radiation therapy may improve outcome in patients with gallbladder cancer.

15. The follow-up period after surgery was short, with 25% of the patients dead within the first postoperative month.

RECOMMENDATIONS

1. Gallbladder cancer as seen at KNH is a surgical problem of similar magnitude to that reported in other centres.

2. A high index of clinical suspicion and the use of new imaging techniques may lead to increased pre-operative diagnosis in the majority of advanced cases of gallbladder cancer. There is need to introduce facilities for non-operative palliation in patients with advanced disease, as surgery in these patients is associated with high post-operative morbidity and mortality without prolongation of survival.

3. Approximately 2% of gallbladders resected for benign gallbladder disease at KNH harbour carcinoma. All the gallbladders should be opened and examined carefully at operation in every cholecystectomy, and suspicious lesions should be submitted for immediate histologic examination. There is a need for establishment of facilities for frozen section in KNH for quick diagnosis of any suspicious lesions. The surgeon should ensure that the histology results are available when the patients are reviewed postoperatively.

4. When planning laparascopic cholecystectomy, detailed preoperative evaluation should be undertaken to rule out gallbladder cancer in patients with recognised risk factor e.g. female sex, multiparity, age over 51 years, gallstone disease. When the cancer is identified preoperatively or unexpectedly during laparascopic cholecystectomy, the procedure should be converted to open resection.

5. Strong consideration should be given for more aggressive surgery in selected patients with early localised gallbladder carcinoma in order to improve long term survival.

6. Round ligament approach segment III cholangiojejunostomy should be undertaken as a palliative procedure in patients with malignant obstructive jaundice secondary to gallbladder cancer. It provides excellent palliation and prolonged relief of jaundice.

7. Patients with gallbladder cancer should be subjected to radiation therapy after surgery in order to improve survival, and as a palliative measure in patients with advanced unresectable disease.

8. There is a need to encourage detailed and proper documentation of a patient's hospital records in a legible form. Follow up of patients should be more regular. This makes further reference or academic studies much easier.

APPENDIX

ATA COLLECTION FORM

ICIDENCE, CLINICAL PRESENTATION, MANAGEMENT AND OUTCOME OF GALLBLADDER ANCER AS SEEN AT KENYATTA NATIONAL HOSPITAL (1988 - 2000).

PATIENT PROFILE

IP NO.: _____ SEX : Male ☐ Female ☐

AGE AT PRESENTATION

< 35 years ☐
36 - 40 years ☐
41 - 45 years ☐
46 - 50 years ☐
51 - 55 years ☐
56 - 60 years ☐
> 61 years ☐

ETHNIC GROUP : _____ HOME DISTRICT : _____

PARITY : _____ OCCUPATION :: _____

SMOKING : Yes ☐ No ☐ ALCOHOL USE : Yes ☐ No ☐

DATE OF ADMISSION : i) _____ ii) _____

DATE OF DISCHARGE : I) _____ ii) _____

MODES OF PRESENTATION

INCIDENTAL FINDING AT HISTOLOGY : Yes ☐ No ☐

INTRAOPERATIVE FINDING : Yes ☐ No ☐

CLINICAL PRESENTATION OF ADVANCED DISEASE : Yes ☐ No ☐

PREOPERATIVE DIAGNOSIS

a) Benign - CHOLELITHIASIS : ☐

- CHOLECYSTITIS : ☐

- OTHER : _____

b) Malignant - GALLBLADDER CANCER : ☐

- PANCREATIC CARCINOMA : ☐

- CARCINOMA OF LIVER : ☐

- OTHER : _____

PRESENTING SYMPTOMS			DURATION (MONTHS)
ABDOMINAL PAIN	Yes ☐	No ☐	_____
NAUSEA & VOMITING :	Yes ☐	No ☐	_____
WEIGHT LOSS :	Yes ☐	No ☐	_____
JAUNDICE :	Yes ☐	No ☐	_____
ANOREXIA :	Yes ☐	No ☐	_____
PRURITUS :	Yes ☐	No ☐	_____
ABDOMINAL DISTENSION :	Yes ☐	No ☐	_____
OTHER (SPECIFY) :	_____		_____

CLINICAL SIGNS		
PALLOR	Yes ☐	No ☐
JAUNDICE	Yes ☐	No ☐
FEVER	Yes ☐	No ☐
ABDOMINAL TENDERNESS	Yes ☐	No ☐
HEPATOMEGALY	Yes ☐	No ☐
PALPABLE GALLBLADDER	Yes ☐	No ☐
ABDOMINAL MASS (OTHER THAN LIVER AND GALLBLADDER) :	Yes ☐	No ☐
ASCITES :	Yes ☐	No ☐

OTHER (SPECIFY) : _____

INVESTIGATIONS DONE (Specify Abnormality)

a) LABORATORY

HAEMOGRAM - HAEMOGLOBIN : _____

- WHITE CELL COUNT : _____

- OTHER : _____

LIVER FUNCTION TEST - BILIRUBIN : _____

- ALKALINE PHOSPHATASE : _____

- OTHER : _____

OTHER (SPECIFY) : _____

b) RADIOLOGICAL

PLAIN ABDOMINAL X-RAY : _____

ABDOMINAL ULTRASOUND : _____

ABDOMINAL CT : _____

P T C _____

ORAL CHOLECYSTOGRAPHY : _____

OTHER (SPECIFY) : _____

HISTOLOGY RESULTS

ADENOCARCINOMA : ☐

SQUAMOUS CELL CARCINOMA : ☐

UNDIFFERENTIATED : ☐

ADENOACANTHOMA : ☐

OTHER (SPECIFY) :

DEGREE OF DIFFERENTIATION

WELL DIFFERENTIATED : ☐

MODERATELY DIFFERENTIATED : ☐

POORLY DIFFERENTIATED : ☐

UNKNOWN : ☐

PRESENCE OF GALLSTONES

PRESENT : ☐

ABSENT : ☐

). MODES OF TREATMENT

A) SURGERY

NO OPERATION : ☐

BIOPSY ONLY : ☐

PRIMARY SURGERY - SIMPLE CHOLECYSTECTOMY : ☐

- HEPATIC WEDGE RESECTION : ☐

- LYMPHADENECTOMY : ☐

- SEGMENTAL LIVER RESECTION : ☐

- OTHER (SPECIFY) : _____

B) PALLIATIVE PROCEDURE ☐

C) RADIOTHERAPY ☐

D) CHEMOTHERAPY ☐

1. ORGANS INVOLVED BY TUMOUR AT SURGERY

LIVER : ☐

EXTRAHEPATIC BILE DUCTS : ☐

LYMPH NODES : ☐

STOMACH : ☐

COLON : ☐

DUODENUM : ☐

PANCREAS : ☐

OTHER (SPECIFY) : _____

2. DURATION OF FOLLOW-UP _____

3. OUTCOME _____

4. REMARKS _____

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Ref. KNH/ERC/01/965 Date 14 March 2001

Dr. Al-Ammary A. Yasir
Dept. of Surgery
Faculty of Medicine
University of Nairobi

Dear Dr. Al-Ammary,

RE: **RESEARCH PROPOSAL** "REVIEW OF GALL BLADDER CANCER AS SEEN AT KENYATTA NATIONAL HOSPITAL OVER A THIRTEEN YEAR PERIOD" (P919/9/2000)

This is to inform you that the Kenyatta National Hospital Ethical and Research Committee has reviewed and **approved** the revised version of your above cited research proposal.

On behalf of the Committee I wish you fruitful research and look forward to receiving a summary of the research findings upon completi of the study.

This information will form part of data base that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Thank you.

Yours faithfully,

PROF. A.N. GUANTAI
SECRETARY, KNH-ERC

c.c. Prof. K.M. Bhatt,
Chairman, KNH-ERC,
Dept. of Medicine, UON.

Deputy Director (CS),
Kenyatta N. Hospital.

Supervisor: Prof. G.A. Magoha, Dept. of Surgery, UON

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The Dean, Faculty of Medicine, UON