INTRODUCTION

Carcinoma of gall bladder is the fifth most common cancer of digestive tract and the most common malignancy of the biliary tract. Women are three times more commonly affected than men. Peak incidence of gall bladder carcinoma is observed in 6th and 7th decades of life. Despite advancements in diagnostic and surgical techniques, it is still characterized by late diagnosis and poor prognosis except when incidentally diagnosed at an early stage after cholecystectomy for cholelithiasis. The overall reported 5 year survival rate is about 5%. There is considerable geographical variation in its incidence especially in sub-continent where its incidence is very high. In United States, the overall incidence of gall bladder carcinoma is 2.5 cases per 100,000 residents, where as in United Kingdom it is 1.5 cases per 100,000 population. In Pakistan, different studies show frequency of gall bladder carcinoma with cholelithiasis ranging from 1.15% to 11%. The exact etiology is unknown, but gall stones are present in 75-90% of reported series of carcinoma of gall bladder. However, the 20 year risk of developing cancer for patients with gall stones is less than 0.5% for the overall population and 1.5% for high risk groups. This risk of developing cancer of gall bladder is higher in patients with symptomatic than asymptomatic gall stones. Larger stones (3 cm) are associated with a tenfold increased risk of cancer. Other risk factors include calcified porcelain gall bladder, sessile polyps more than 10 mm, choledochal cysts, sclerosing cholangitis, typhoid carriers and exposure to carcinogens (azotoluene, nitrosamines). The adenocarcinoma is the most common histological type (80%) of gall bladder carcinoma. A variety of other lesions including undifferentiated carcinoma (6%), squamous carcinoma, adenosquamous carcinoma, carcinoid tumors, sarcoma, melanoma and lymphomas have also been found. Early diagnosis of gall bladder cancer is rarely achieved because signs and symptoms of gall bladder carcinoma are generally indistinguishable from those associated with...
cholecystitis and cholelithiasis. These include abdominal discomfort, right upper quadrant pain, nausea and vomiting. Jaundice, weight loss, anorexia, ascites and abdominal mass are less common presenting symptoms. Laboratory findings are not diagnostic, and despite marked advances in biliary tract, imaging diagnostic accuracy is not satisfactory in cases of this cancer. Only 8.6% of pre-operative diagnoses are correct. Ultrasonography often reveals thickened, irregular gall bladder wall or a mass replacing the gall bladder, which may be a false positive result. Surgery remains the only curative option for the gall bladder cancer and there is no proven role of radiotherapy or chemotherapy. Unfortunately, majority of the patients have advanced disease far beyond the surgical resection at the time of diagnosis with poor prognosis. This study was designed to help in the assessment of demographic profile of the population at risk in this part of country, and to establish some policies, or protocols, for early diagnosis of this aggressive disease.

**PATIENTS AND METHODS**

This descriptive study was conducted at Isra University Hospital which is a leading private tertiary care centre catering the health needs of people of Hyderabad and other adjoining districts of Sindh province of Pakistan. This study was carried out from April 2006 to March 2008 and included 200 cases of cholelithiasis who underwent cholecystectomy. Inclusion criteria of study were the patients of both sexes and all age groups. All the patients had symptomatic gall stones, diagnosed by trans-abdominal ultrasonography and underwent cholecystectomy. Inclusion criteria of study were the patients of both sexes and all age groups. All the patients had symptomatic gall stones, diagnosed by trans-abdominal ultrasonography and underwent cholecystectomy. The patients having gall bladder carcinoma in the absence of gall stones and the histo-pathological diagnosis of other than primary gall bladder carcinoma were excluded from study. The diagnosis was made on clinical grounds by correlating history, signs and symptoms and the ultrasonography. A uniform procedure of history taking, clinical examination and necessary laboratory investigations was adopted for each patient. All the patients were managed in the surgical ward and followed up during the study period. The data were noted on a pre-designed proforma. All the specimens of gall bladder were subjected to histo-pathological examination. The biopsy reports were collected from pathology department and the type of gall bladder cancer, part of gall bladder involved and its extent of spread were noted.

**RESULTS**

Out of 200 cases that were operated for gall bladder stone disease, eight were found with carcinoma of gall bladder. Therefore, the frequency of gall bladder carcinoma was 4%. The age of the patients ranged from 35 to 70 years. Mean age of females was 50 ($\pm$ 5.32) and males 56 ($\pm$ 2) years. Most of the patients were in the 6th decade of life. (Table I) Among 08 cases, 06 (75%) were females showing male to female ratio of 1:3. Signs and symptoms of gall bladder carcinoma were generally indistinguishable from those associated with cholecystitis and symptomatic cholelithiasis. (Table II) Liver function tests were deranged in minority of patients. Bilirubin level was slightly elevated in 02 cases and serum alkaline phosphatase level was raised in 03(37.5%) cases. On ultrasound, only three patients with advanced disease had a pre-operative clue of carcinoma. Computed tomography was done in one case with mass but revealed same finding as that of ultrasonography. (Table III) On histo-pathological examination, different parts of the gall bladder were involved. Of 04 (50%) specimens of the fundus, in 03 (37.5%) the body and in 01 (12.5%) whole of the gall bladder was involved. All of the gall bladder cancers in this study were adenocarcinomas and half (50%) of them were well differentiated. (Table IV) The growth was confined to mucosa (Stage - 1) in 02 (25%) cases and in 01 (12.5%) case to muscularis and perimuscular connective tissue with no nodal involvement (Stage - II). Stage III was seen in 03 (37.5%) cases in which the tumor perforated through serosa and there was lymph node involvement. In stage IV, 02 cases were found out of which 01 (12.5%) patient had the inoperable growth due to extensive invasion and secondaries in the liver, omentum and gut.
DISCUSSION

Gall bladder carcinoma is an aggressive disease with late presentation, rapid progression, early recurrence and dismal outcome. A strong association has been reported between gall bladder carcinoma and cholelithiasis with variable incidence among different ethnic groups suggesting various other factors responsible including size of stone, diet, lifestyle, chronic bacterial infections, hepatobiliary anomalies and environmental pollutants. Available literature reveals that 0.3% to 2.85% of the patients who undergo cholecystectomy for presumed benign disease are found to have carcinoma of gall bladder. The proportion of gall bladder carcinoma detected in patients undergoing cholecystectomy for cholelithiasis in this study is 04% which is higher than reported in western literature. In contrast to this, some studies from other areas of Pakistan and India have reported even more higher percentages (i.e. 6% to 11%) of such patients with gall bladder carcinoma. These large differences in the frequencies may be due to differences in the sample size or some geographical and environmental factors. Samad A (2005) in his study conducted at the Aga Khan University Hospital Karachi found the frequency of 1.15%, which is quite comparable with western literature. Carcinoma of the gall bladder occurs in Pakistan at an earlier age and females are more frequently inflicted. Same results are seen in this study with average age being 50 years. But in western countries, incidence is at higher age i.e. seventh
decade.\textsuperscript{16} Carcinoma of the gall bladder is predominately a disease of females. However, there is a regional variation in male to female ratios 1:1.1 to 1:4 in the world literature.\textsuperscript{17} However, in Pakistani and Indian studies the ratio is almost same i.e. 1:2,\textsuperscript{18} 1:3,\textsuperscript{19} 1:3.37,\textsuperscript{20} 1:4.\textsuperscript{21} In this study, the male to female ratio was 1:3, which is approximately similar to regional and other international studies. Carcinoma of the gall bladder does not have typical clinical features and 90% of patients present with syndromes of acute or chronic cholecystitis.\textsuperscript{20,22} In this study, main symptoms in the majority of patients were pain in the right upper quadrant, dyspepsia, nausea, vomiting and weight loss. The most common sign was positive Murphy's sign. All these findings are identical to worldwide and local studies and it seems that the nature of this lethal disease has not changed significantly. Huguet KL (2005)\textsuperscript{23} has reported that abnormal serum alkaline phosphatase and gamma glutamyl transferase may be elevated in the absence of jaundice. In this study, serum alkaline phosphatase level was elevated in 03 (37.50%) patients and serum bilirubin was raised in 2 (25%) patients but was not more than 2.5 mg/dl and the patients were nonicteric. Therefore, the role of laboratory investigations is supportive to detect the associated problems or to diagnose the advanced disease. Despite marked advances in biliary tract imaging, diagnostic accuracy is not satisfactory in cases of gall bladder carcinoma.\textsuperscript{1,2} Ultrasonography may detect advanced disease in up to 70% of cases, but the sensitivity of trans-abdominal ultrasound in detecting early disease is variable.\textsuperscript{24} Computed tomography (CT scan) is better at detecting lesions than ultrasonography (US). CT scan has a low sensitivity for detecting lymph node metastasis. Both US and CT scan may fail to show local gastrointestinal and omental infiltration and peritoneal deposits. In this study, only 37.50% cases were suspected by sonography whereas in 62.50% cases it was not helpful. The same results are also reported in studies from other parts of country.\textsuperscript{25} This might be attributed to the lack of appropriate technology in skilled specialist hands and some cases were in too early stage to be detected by sonography. Recent improvements in hepato-biliary surgery have underlined the importance of an early specific diagnosis, which requires a multidisciplinary approach and when possible, specialized equipment. Ultrasound guided fine needle aspiration cytology has about 90% diagnostic accuracy in evaluation of gall bladder carcinoma.\textsuperscript{26} Endoscopic ultrasonography and percutaneous transhepatic cholecystoscopy are also recent valuable tools for the detection of early gall bladder carcinoma and need to be used in our patients. The pre-operative use of cholangiography, dynamic magnetic resonance imaging and Color Doppler ultrasonography to differentiate benign from malignant disease has been associated with some degree of success. Further refinement of these techniques may lead to better pre-operative detection of malignancy in the future. The pre-operative diagnosis of early gall bladder carcinoma is difficult and majority of these lesions are apparent at cholecystectomy either during the surgical exploration or at histo-pathological examination.\textsuperscript{27} In this study, 03 (37.50%) cases were diagnosed incidentally by histo-pathological report and not suspected during surgery; which is a higher frequency than that reported in literature. Routine and careful intra-operative examination of the specimen can identify carcinoma gall bladder with a sensitivity and specificity of 79% and 93% respectively.\textsuperscript{28} In this study, 05 cases (62.50%) were suspected and identified as carcinoma of gall bladder during surgery and confirmed later on by histo-pathological report. As most of the patients are received in late stages of the disease, curative treatment is not possible. One of the reasons in this regard could be lack of medical facilities. Studies on the natural history and most decision analysis studies do not favor prophylactic cholecystectomy for patients with silent gall stones; because it is presumed that long standing chronic inflammation by cholelithiasis plays a role in carcinogenesis.\textsuperscript{29} It is advised that in gall bladder carcinoma endemic areas patients with symptomatic gall stones must be encouraged to undergo cholecystectomy in order to reduce the risk of malignant change and improve survival rate by early detection. As this study has limitation of smaller sample size, hence, findings shall be interpreted with caution.

CONCLUSION

The frequency of gall bladder carcinoma in our population is much higher than other parts of the world. Females are more affected than males. Ultrasonography can miss malignant lesions and there are no typical clinical features of malignancy.
in early stages. Therefore, present study highlights the importance of careful gross and histopathological evaluation of the gall bladder specimens. In unsuspected cases undergoing laparoscopic cholecystectomy, gentle handling of the gall bladder is critical to avoid port site implantation caused by spillage of bile.

REFERENCES


