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Gallbladder Cancer in Sudan: A Two-centre Study

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Abstract Poor prognosis of gallbladder cancer (GBC) is due to delayed presentation. Female gender and gallstones are important risk factors. Surgical resection offers significant improvement in 5 year actuarial survival. In Sudan, proper imaging modalities and professional multi-disciplinary teams are available but, inter-disciplinary management protocols haven't been established. This paper aims to delineate the patterns of presentation, possible risk factors and the natural history of GBC to guide management practices in resource-limited settings. The records of 106 patients from two tertiary referral centres were examined. Inclusion criteria included: radiological features of gallbladder mass in addition to one of the following: liver metastasis, porta hepatis lymphadenopathy and/or ascites. The majority of patients were females (70.5%) with a mean age of 64.27±11.39 years with median duration of symptoms of 3 months. The main presenting symptoms were: loss of weight (39.2%), abdominal swelling (35.8%), obstructive jaundice (31.1%) and vomiting (17.6%). Cholelithiasis as detected by ultrasound/CT/MRI was reported in most cases (75.4%). Liver metastasis, biliary dilatation and lymphadenopathy were seen in 67.2%, 40.3% and 39% respectively. Open simple cholecystectomy was performed in a quarter of the patients (24.5%), none had re-resection after postoperative diagnosis of GBC. No significant 3 and 6 months survival benefits were observed in the simple cholecystectomy group compared to those who didn't (p=0.8 and 0.2 respectively). More than fifty per cent (51.1%) of patients received chemotherapy, with no 3 and 6 months survival benefits. The main causes of death were obstructive jaundice complicated by cholangitis and gastric outlet obstruction in 69.5% and 30.5% of patients respectively. The overall survival of CBC patients was 4.96±12.5 months. Most patients presented late, the majority had unrespectable disease, very short duration of symptoms and poor survival. Patients with advanced disease should have holistic palliative approach via a multi-discilpinary team together with systemic chemotherapy.

Keywords: *gall bladder cancer, simple cholecystectomy, chemotherapy, cholelithiasis*

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1. Introduction

The prognosis of gall bladder cancer (GBC) is the worst due to delayed presentation. Patients harbouring gallstones are at an increased risk of developing gall bladder cancer. Other factors include: cholecysto-enteric fistula, typhoid bacillus infection and an anomalous pancreatico-biliary junction [1,2]. Most patients present late in the course of their disease and 75% of patients present with un-resectable disease. Two-thirds of patients present with abdominal pain or biliary colic. Approximately one third of patients presents with jaundice and 10% will have significant weight loss [3].The diagnosis of GBC could be made pre-operatively in the majority of patients and carries the worst prognosis or postoperatively and occasionally intra-operatively where the prognosis is good with cure rates of 84-100% [4,5]. Adequate surgical expiration of the disease carries the only hope of cure compared to other modalities of treatment e.g. chemotherapy. Bartlett and colleagues [5] reported that complete surgical radical resection yielded an actuarial 5-year survival of 83% for stage II, 63% for stage III and 25% for stage IV. It is well documented that a significant increase in 5 years actuarial survival could be achieved following surgical resection, with marked differences in disease free survival and 5-years actuarial survival rates between centres [6,7,8].

Although proper imaging modalities and professional multi-disciplinary team (MDT) members are available, inter-disciplinary referral and management protocols haven't been established in Sudan. This study aimed to understand the patterns of presentation, possible risk factors and the natural history of GBC to guide practice at national Liver Surgery and Transplantation Centres.

2. Methods and Patients

This was a two institutes retrospective study from November 2004 to December 2015. A total of 104 patients were enrolled from The National Institute of Gastroenterology and Liver Diseases, Ibn Sina Hospital, Khartoum, Sudan [n=61] and Aljazeera Institute of

Oncology, Wad Medani, Central Sudan [n=45]. Inclusion criteria: all patients with radiological features of gall bladder cancer (gall bladder mass in addition to one of the following: liver metastasis, lymph nodes enlargement around the hepato-duodenal ligament or ascites.

3. Results

The risk factors assessment for GBC showed that the majority were females (70.5%, 70/106) with a mean age of 64.27±11.39 years. The Median duration of symptoms was 3 months. The main presenting symptoms were loss of weight (39.2%, 46/106), abdominal swelling (35.8, 38/106), obstructive jaundice (31.1%, 33/106) and vomiting (17.6%, 19/106) (Table 1). Cholelithiasis was detected by the ultrasound, CT and MRI in most cases (75.4%, 80/106). Liver metastasis, biliary dilatation and lymph nodes enlargement were seen in 67.2% (67/106), 40.3% (45/106) and 39% (42/106) respectively. Open simple cholecystectomy was carried out in about a quarter of the patients (24.5%, 26/106) before referral to the study centres. No patient had re-resection after the postoperative diagnosis of GBC. No significant 3 and 6 months survival benefits (p=0.8 and p=0.2 respectively) were observed in simple cholecystectomy group compared to those how didn't. About half of the patients (51.1%, 54/106) received chemotherapy, with no significant survival rate differences at 3 and 6 months compared to those who had no chemotherapy. The majority (69.6%, 74/106) of patients died of obstructive jaundice/cholangitis, while 37.8% (40/106) died of gastric outlet obstruction. Two patients with advanced GBC and obstructive jaundice had palliative endoscopic retrograde cholangio-pancreatgrophy (ERCP).

Table 1. Patients' presentations, radiological findings and histopathology patterns

Presentation-radiological and pathological staging	Patient No	Frequency
Loss of weight	46/106	**39.2%**
Obstructive Jaundice	33/106	**31.1%**
Abdominal swelling	38/106	**35.5%**
Vomiting	9/106	**17.6%**
Gallbladder Stones [Radiology]	80/106	**66.0%**
Liver metastasis	67/106	**72.5%**
Biliary dilatation	42/106	**43.0%**
Lymph node enlargement	45/106	**40.3%**
Histopathology:		
Available	37 / 106 patient	
Adenocarcinoma:	28	**58.3%**
Papillary Subtype:	5	**10.4**
adenosquamous	1	**2.1%**
Squamous	2	**4.2**
Leimyosarcoma	1	**2.1**

4. Discussion

Most patients with GBC in this study presented late with the majority having unrespectable disease, very short duration of symptoms and poor survival. The late presentation is most probably due to the vagueness of presenting symptoms that is usually seen in a number of benign conditions. Patients and doctors alike play parts in delayed diagnosis. Cholelithiasis is the main culprit of GBC in our patients concordant with the results of previous reports. This risk factor has been observed to be inversely related to the rate of cholecystectomy especially in the era of laparoscopic cholecystectomy. [9,10,11,12]. Most of our patients benefited from imaging (Ultrasound, CT, MRI) to reach a diagnosis, in agreement with previous reports that showed that imaging is more valuable compared to biopsy/cytology in doubtful cases in early stages of disease [13]. On the other hand, staging laparoscopy is accurate in detecting peritoneal carcinomatosis and liver metastasis missed by imaging and is highly recommended in T3 and T4 to avoid unnecessary laparotomy. The postoperative diagnosis of incidental GBC has increased substantially due to the increase in the number of cholecystectomy especially in developed countries. Disease stage and patient performance status help to triage patients for simple cholecystectomy [stage T1a], extended cholecystectomy and lymph nodes dissection [T1b and T2] or aggressive surgery [T3 and T4].

The mortality was high among the study patients who received palliative chemotherapy, but this is most probably due to delayed presentation and limited accessibility to cancer diagnosis/treatment in agreement with previous reports [14-20].

5. Conclusions

The natural history of gall bladder cancer is dismal. Most patients present late with the majority having unrespectable disease, very short duration of symptoms and poor survival. Adequate staging of patient and early multidisciplinary involvement might yield good result. Patients with advanced disease should have holistic palliative approach by a multi-disciplinary team together with systemic chemotherapy.

Authors Disclosures

Authors declare no conflict of interest.

Authors' Contribution

WE and KAE contributed to the writing of the manuscript and the management of the patients. WE, KAE, MEA and EAGK have contributed to writing, revision and editing of the manuscript. All authors read and approved the final manuscript.

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