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RESEARCH COMMUNICATION

Clinical Presentation and Outcomes of Patients with Biliary Malignancies: the Aga Khan University Experience

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Abstract

Background: Gall bladder cancer (GBC) is a common malignancy in our country; very limited data exist on this malignancy in Pakistan. **Methods:** This is a retrospective analysis of all the admitted patients diagnosed with GBC or cholangiocarcinoma in between 1st January 1995 to 31st December 2007. **Results:** A total of 245 patients were admitted with diagnosis of GBC or cholangiocarcinoma. Sixty seven percent were females. Right hypochondrial pain (70.6%) and jaundice (49.8%) were the commonest symptoms, followed by nausea and vomiting (11.8%), weight loss (13%), fever (18.8%), anorexia (9.8%) and ascites (3.3%). Gall stones were seen in 132 (53.9%) patients. Pathological diagnosis was confirmed in 155 (63.2%) patients, adenocarcinoma (94.83%) being the predominant type. Metastasis was seen in 204 (83.3%) patients, with liver and abdominal lymph nodes being the frequent sites of metastasis. Most of the patients presented to the surgeons (42.9%) and gastroenterologists (35.9%) at their first visit. Only 89 (26.3%) patients were referred to medical oncologists and 42 (16.7%) of the patients actually received chemotherapy. The patients who received chemotherapy cisplatin and gemcitabine demonstrated partial responses (40%). Common bile duct stricture was seen in 78 patients and stenting was successful in 73 patients. Fourteen (5.7%) patients are alive to date, one is receiving chemotherapy, and another is alive with advanced disease while 10 patients had incidental diagnosis after surgery. Of all 53.9% of patients have died and 38% are lost to follow up. **Conclusion:** Most of the patients with biliary cancers present late with advanced disease at our referral tertiary care hospital. Minority of the patients received chemotherapy and most of responses were observed with cisplatin and gemcitabine combination or capecitabine based therapy.

Key Words: Gallbladder cancer - symptoms - clinical details

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Introduction

Gallbladder cancer (GBC) is considered to be a rare malignancy in the west but its incidence and prevalence is high in South-East Asia (Rizvi and Zuberi 2003; Batra et al., 2005; Rand et al., 2006). Unfortunately no tumor registry exists in Pakistan, sporadic hospital based studies and data from Karachi cancer registry suggest that GBC is common malignancy in Pakistan especially in females. In a study conducted by Bhurgri et al it was 3rd most common malignancy in females and ninth common cancer overall in Karachi south (Bhurgri et al., 2002). GBC was found to be the second most common malignancy in females, in a hospital based cancer registry (Zahir et al., 2000).

GBC is more common in females and gallstones are considered to be number one risk factor for this malignancy. Other associated risk factors are obesity, female sex, high number of pregnancies and age at first child, family history, anomalous pancreaticobiliary ductal

junction and chronic infections with *Salmonella typhi* and *S. paratyphi* and *Helicobacter pylori* and *H. bilis* (de Groen et al., 1999; Rizvi and Zuberi, 2003; Batra et al., 2005; Randi et al., 2006).

Our hospital is a leading tertiary care facility of the area and patients not only from across the Pakistan but from Afghanistan, Iran and United Arab Emirates come to this centre for the treatment of different diseases, malignant or nonmalignant. Keeping in view the prevalence of the GBC in our country we decided to assess our data of patients who were diagnosed with biliary cancers.

Materials and Methods

This is a retrospective analysis of all patients who were diagnosed to have biliary cancers during last 12 years from 1st January 1995 to 31st December 2007. Case records were reviewed and data was entered in a self made well structured performa regarding age, gender, symptoms at

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presentation, association of gallstones, mode of diagnoses (radiological or pathological), stage at presentation, treatment offered, palliative procedure undertaken. Patients who were lost to follow-up were called on phone if possible. The data was analyzed using SPSS V 16.

Results

A total of 245 patients were diagnosed to have biliary cancer during this period. GBC was diagnosed in 214 (87.3%) and cholangiocarcinoma in 29 (11.8%) patients. Mean age at presentation was 57.7 years (range 30-86 years) and 165 (67.3%) were females while 80 (32.7%) patients were male with female to male ratio of 2:1.

Clinical Features

Right upper quadrant pain was found to be the commonest presenting symptom, seen in 173 (70.6%) patients followed by jaundice in 122 (49.8%) patients. Other symptoms noticed at presentation were fever, perhaps secondary to cholangitis 46 (18.8%), weight loss 32 (13.1%), nausea and vomiting 29 (11.8%), anorexia 24 (9.8%) and ascites in 8 (3.3%) patients.

Imaging studies

Ultrasound and CT scan were used as imaging modalities to assess the disease status and in fact in 90 (36.7%) patients, a diagnosis was made only on radiological findings. The main radiological finding was gallbladder mass. Gallstones were visible in 132 (53.9%) patients.

Pathology

Histopathological confirmation of cancer was obtained in 155 (63.3%) patients. Adenocarcinoma was the most common pathological type found in 147 (94.83%) patients. Other pathologies seen were squamous cell carcinoma 4 (2.58%), neuroendocrine tumor 3 (1.93%) one patient had a positive cytology of ascetic fluid (0.64%). Pathological grading was available in only 59 patients. In 13 (22.03%) patients tumor was well differentiated while in 26 (44.06%) and 18 (30.5%) patients tumor was moderately differentiated and poorly differentiated respectively while in 2 (3.38%) patients it was undifferentiated (Table 1).

Stage at presentation

All but 41 (16.7%) patients presented with the metastatic disease. Liver was the commonest site of metastasis. In 77 (31.4%) liver was the only site of metastasis, in other 77 (31.4%) patients liver and regional lymph nodes were involved by the disease, 10 (4.1%) patients had liver and gut metastasis and in 7 (2.9%) patients liver was involved by the disease along with the lung and regional lymph nodes. Other sites of metastatic disease are shown in Table 1.

Interventions/Procedures

Most of the patients required some sort of intervention for diagnoses or as palliative procedure. In 37 (15.1%) patients a biopsy was done under CT scan or ultrasound guidance, 44 (21.9%) required endoscopic retrograde

Table 1. Pathology, Type, Grade, Size (T) and Metastasis Sites

Pathological Diagnosis	155	(63.3%)
Adenocarcinoma	147	(94.8%)
Squamous cell cancer	4	(2.6%)
Neuroendocrine cancer	3	(1.9%)
Ascitic Cytology	1	(0.6%)
Radiological Diagnosis	90	(36.7%)
Grade	59	
Well Differentiated	13	(22.0%)
Moderately Differentiated	26	(44.1%)
Poorly differentiated	18	(30.5%)
Undifferentiated	2	(3.38%)
Site of metastasis		
Liver only	77	(31.4%)
Liver and Lymph nodes	77	(31.4%)
Serosal surface of Gut	13	(5.3%)
Liver and Gut	10	(4.1%)
Lymph nodes	10	(4.1%)
Lung	7	(2.9%)
Liver + Lungs + Lymph nodes	7	(2.9%)
Diaphragm	1	(0.4%)
Adrenal gland	1	(0.4%)
Bone	1	(0.4%)

cholangiopancreatography (ERCP), 39 (15.9%) patients required percutaneous transhepatic cholangiography (PTC), palliative surgery was performed in 66 (26.9%) patients, laproscopic/open cholecystectomy was done on 10 (4.1%) patients. To relieve obstruction stenting of common bile duct was performed in 73 (29.8%) patients, with ERCP in 34 (13.9%) and with PTC in 39 (15.9%) patients. In 1 patient en bloc resection of the tumor and involved liver was carried out.

Patient's first encounter and referrals

Surgeons were to see the most of patients at their initial presentation, to whom 105 (42.9%) patients made their first visit, followed by gastroenterologists 88 (35.9%) and general physicians 27 (11%). Of all 89 (36.3%) patients were referred to the medical oncologist while in 120 (49%) patients no referral was suggested. Rest of the patients were referred to the surgeons 8 (3.3%), gastroenterologists 22 (9%) for interventional or palliative procedures.

Chemotherapy

Of 88 (36.3%) patients seen by the medical oncologists 42 (47.19%) patients were offered chemotherapy and 1 out of those 42 patients refused to take chemotherapy. In remaining 41 patients different chemotherapeutic agents were used. Cisplatin and gemcitabine as combination therapy was used in 13 (31.7%) patients, capecitabine as single agent in 10 (24.4%) patients, flouorouracil with leucovorin in 15 (36.6%) patients, gemcitabine as single agent in 2 (4.9%), etoposide with cisplatin in 2 (4.9%) and gemcitabine with flouorouracil were used in 1 (2.4%) patient. Out of all these, better responses were witnessed with either gemcitabine and cisplatin or capecitabine. All responses were partial responses (53.8% with gemcitabine and cisplatin and 40% with capecitabine) while rest of the chemotherapeutic agents did not show objective clinical

response. With continuous therapy all patient noticed progressive disease after some time except one whose disease remain stable after 10 months of treatment.

All types of chemotherapy were tolerated fairly well especially gemcitabine and cisplatin in combination or capecitabine as a single agent.

One patient who was subjected to enbloc resection of gall bladder mass along with involved liver and hepatic flexure of colon later received concurrent radiation with 5-Flourouracil and Leucovorin followed by 4 more cycles of same chemotherapy remain free of disease for 11 months and now being treated with gemcitabine and cisplatin after recurrence in the abdominal wall and mass along the duodenum.

Survival

Of all 245 patients only 14 (5.7%) patients are alive till today, 132 (53.9%) patients have died while 99 (40.4%) patients have lost to follow up and we do not have information for these patients. Of surviving 14 patients, an incidental diagnosis of gallbladder cancer was made in 10 patients after laproscopic/open cholecystectomy while remaining 4 patients are alive with the disease and one patient is receiving chemotherapy after recurrence of the disease. Median survival observed with gemcitabine and cisplatin combination was 3.3 months while with capecitabine it was 2.4 months.

Discussion

GBC along with cholangiocarcinoma carry a grim prognosis and usually are diagnosed at late stages. Established factors are chronic infections/inflammatory conditions, gallstones, female gender, obesity, congenital anomalies of hepatobiliary tract, molecular/genetic defects, family history and multiple pregnancies (Nawaz 2000; Kapoor and McMichael, 2003; Rizvi and Zuberi, 2003; Barakat et al., 2006; Kumar et al., 2006; Randi et al., 2006; Roa et al., 2006).

Here we have reported the 13 years of experience of biliary cancer at our hospital. Most common symptoms at presentation were right upper quadrant pain in 70.6% patients and jaundice in 49.8% patients and these findings are similar to the local, regional as well as international literature (Chih Jung Shieh 1981; Shukla et al., 1985; Nawaz, 2000; Batra et al., 2005; Malik, 2006). Batra et al (2005) have reported that 81% of patients in their study had upper quadrant abdominal pain and 73% had jaundice at presentation while in series reported by Nawaz et al (2000) 90% patients presented with upper abdominal pain and 60% had jaundice.

The mean age at the presentation in our study seems to be different only for female population (57 years) which is higher than mean age observed in other studies from Pakistan (Nawaz, 2000; Zahir et al., 2000; Rizvi and Zuberi, 2003) and India (Shukla et al. 1985; Batra et al., 2005) but younger than the western population (Chih Jung Shieh, 1981). The gender distribution found in our study however matches the literature published from our region as well as from west (ratio 2:1) (Chih Jung Shieh, 1981; Shukla et al., 1985; Nawaz, 2000; Zahir et al., 2000; Rizvi

and Zuberi, 2003; Batra et al., 2005).

Due to non specificity of symptoms most patients get diagnosed at advanced stage of the disease when less is left to offer and majority of patients end up having palliative treatment. In our study we observed that 83.3% patients presented when disease was already metastatic. Liver was the common site of metastasis. Other affected sites were regional lymph nodes, lungs, serosal surface of the gut, diaphragm, adrenal gland and bone. Our findings are almost similar to the findings of Batra et al (2005) and Shukla et al (1985).

Pathological confirmation of GBC is not necessary for the diagnosis, clear radiological appearance along with suggestive symptoms are usually all that is required for making a diagnosis, Pathology is however required in patients with suspicion of malignancy without typical radiological findings and / or absence of symptoms. In our study population 63.3 % patients had to undergo procedures for pathological diagnosis. Pathological diagnosis was confirmed in 155 (63.3%) patients while in 90 (36.7%) radiological findings were suggestive of the gall bladder cancer and due to advanced nature of the disease and poor performance status of all these patients, no intervention was done to confirm pathological diagnosis. Among 155 patients in whom pathological diagnosis was confirmed, adenocarcinoma was the most common histological type found in 147 (94.83%) patients.

Gall stones are believed to be associated with development of gallbladder cancer. This association has been also found in other studies as well (Chih Jung Shieh 1981; Kapoor and McMichael, 2003; Rizvi and Zuberi, 2003; Batra et al., 2005). In our study 53.9% patients were found to have gall stones, a common association of this disease and considered to be a risk factor for the development of gall bladder cancer.

Majority of patients required some intervention, either for the diagnosis, treatment or for palliation. In 10 (4%) patients diagnosis of GBC was made after cholecystectomy (laproscopic/open) performed due to gall stone associated acute cholecystitis and all of them had disease at earlier stage. Incidental GBC finding after cholecystectomy is well reported in literature and is in range from 1% to 2%, but in different series 2 to 10% patients were found to have incidental GBC (Batra et al., 2005). Survival for patients with incidental diagnosis of GBC is generally good as disease is usually found at earlier stages, and after median follow-up of more than 60 months all of these patients are alive without disease recurrence.

One patient subjected to enbloc resection of gall bladder mass invading the liver and hepatic flexure of colon with resection of regional lymph nodes. To relieve the obstruction stenting of the common bile duct or hepatic ducts was carried out in 29.8% patients. In 26.93% patients, some kind of palliative surgery was done.

Most of the patients were entertained by general surgeons or gastroenterologists while 89 (36.3%) patients were referred to the medical oncologists and out of those 42 patients were offered chemotherapy among which 1 patient refused to take the chemotherapy while remaining 41 (46.06%) patients received chemotherapy with different agents. Patients treated with 5-flourouracil did

not show any significant response while partial responses (PR) were observed with combination of gemcitabine and cisplatin (mean number of cycles 5.3 with range of 1-12, PR = 53.84%) or capecitabine (mean number of cycles 3 with range of 1-8, PR = 40%) at reasonable toxicities of grade I to II gastrointestinal disturbances or cytopenias. Literature also suggests the efficacy of gemcitabine with cisplatin for the treatment of biliary cancer with over all response rates of 64% reported by Malik et al (2003), 27.5% by Thongprasert et al (2005) and 50% response rate with capecitabine as single agent (Patt et al., 2004). Median overall survival is very poor in our patients as compare survival reported in other series (Malik et al., 2003; Patt et al., 2004; Thongprasert et al., 2005). The reason for this seems to be early loss of follow-up and most of patients who were given chemotherapy died after receiving 1 or 2 cycles so that may be the confounding factor for poor survival. Most of our patients lost to follow-up and of among remaining 146 (59.6%) patients only 14 patients are alive till today while 132 patients have died.

Biliary cancer has a dismal outcome and most of the patients present at very advanced stage of the disease. Clinical symptoms are not very useful to pick the disease at early stage and extensive surgery is most of the time is not possible either because of debilitated condition of the patient or due to lack of expertise. Chemotherapy has very little role to offer and capecitabine as a single agent or gemcitabine with cisplatin are useful options.

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