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JAUNDICE IN PATIENTS WITH GALL BLADDER CANCER- A SURROGATE MARKER OF ADVANCED DISEASE

GALLBLADDER CANCER WITH JAUNDICE

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ABSTRACT

Background: Gall bladder cancer (GBC) is most common cancer of biliary tract. R0 resection is the most important predictor of survival. Patients with GBC and jaundice do worse than those without jaundice.

Methods: Retrospective analysis of prospectively kept data of patients with GBC admitted to the department of Surgical Gastroenterology at a tertiary care hospital in northern India over10 years from 2011 to 2020. Data on patient demography, clinical profile, imaging characteristics, clinical course, staging, and operative procedures was extracted and analyzed to compare the experience of patients with GBC with jaundice and GBC without jaundice.

Results: There were 401 patients with GBC; 75 with jaundice and 326 without jaundice. Patients with GBC and jaundice had a significantly higher incidence of pain abdomen, loss of appetite, loss of weight and presence of an abdominal lump, gastric outlet obstruction and hypoalbuminemia, a shorter duration of symptoms, more number of hospital admissions, a less frequent (4% vs 10.7%) incidental diagnosis of GBC and a higher incidence of GB neck tumors (80% vs 20%). In patients with GBC and jaundice detection of metastatic or locally advanced unresectable disease on imaging (31%), laparoscopy (11%) or laparotomy (31%) precluded resection in majority of patients. Only 2.6% patients with GBC and jaundice could undergo definitive surgery as compared to 71.2% of patients without jaundice.

Conclusion: Patients with GBC and jaundice are very likely to have advanced, unresectable disease. Chances of complete resection are slim even after extensive preparation requiring more extensive, time-consuming, costly, multidisciplinary interventions.

Keywords: Gall Bladder Cancer, Jaundice, Resection

1. INTRODUCTION

Gallbladder cancer (GBC) is the most common malignancy of the biliary tract. Diehl (1980) It is the most frequently encountered malignant lesion of the gastrointestinal tract and the most common cause of malignant obstructive jaundice in northern India. Sikora et al. (1994) Obstructive jaundice occurs in up to 30 to 50% of patients with GBC. Hawkins et al. (2004), Dwivedi et al. (2000) Very few studies address the issue of jaundice in patients with GBC specifically. Surgeons who routinely manage large number of patients with GBC are aware that patients with GBC and jaundice are unlikely to undergo a curative resection, which offers the only chance of cure in GBC, and the overall prognosis is poor, but there is scant documentation of this. We present our experience with patients with GBC and jaundice, comparing it to patients with GBC and no jaundice.

2. METHODS

A retrospective review of prospectively maintained database of all patients of GBC admitted to the department of Surgical Gastroenterology, in a tertiary care teaching hospital in northern India between January 2011 – 2020, was done. Data on patient demography, clinical profile, imaging characteristics and clinical course was extracted and analyzed to compare the experience of patients with GBC with jaundice and GBC without jaundice. The study was approved by the Institute Ethics Committee.

Inclusion criteria:

- Radiologic evidence of GBC
- Patients with missed GBC or incidental GBC following cholecystectomy referred for a possible surgical resection.

Exclusion criteria:

- Patients whose imaging findings raised possibility of hilar cholangiocarcinoma (mass lesion at hilum not contiguous with the GB mass)

GBC was defined as mass protruding into GB lumen or filling it completely, a focal or diffuse thickening of GB wall or a mass in GB fossa with the GB itself being indiscernible with or without adjacent liver infiltration and /or suspected lymph nodal involvement. Jaundice was defined as serum Bilirubin >2mg%. All the patients were taken in a sequential manner through a predefined path which has been developed in the department to identify upfront patients with locally advanced and /or metastatic disease and thus avoid unnecessary laparotomy while ensuring no patient is denied a surgical resection, the only definite curative option.

At admission, all patients underwent a triple phase CT scan of the abdomen for radiological staging according to the eighth edition of the AJCC/UICC staging system. In patients with GBC and jaundice, in the absence of metastatic disease on CT scan, an MRCP was done to better assess the nature and extent of biliary obstruction and choose the best drainage procedure - ERCP and stenting or endoscopic naso-biliary drainage (ENBD) or percutaneous trans-hepatic biliary drainage (PTBD) to alleviate the jaundice. Endoscopic stenting was done if there was clear communication between the right and left ductal systems at the hilum (Type I, II or III biliary

stricture); PTBD was done for patients with hilar separation of right sectoral and or left ductal systems.

Endoscopic Ultrasound (EUS)/ Ultrasound (US)/ CT- guided Fine needle aspiration (FNA) of any suspicious periaortic, para-caval or inter-aorto-caval lymph nodes (LNs) identified on triple phase CT scan was done to rule out metastatic disease. Patients with high clinical suspicion of harboring metastatic disease (T4 GBC or enlarged par-aortic/inter-aorto-caval LNs not amenable to EUS FNA) underwent FDGPET evaluation. Once EUS FNA or PET scan were negative for metastatic disease, the patients were planned for potential surgical resection.

Our standard surgery for GBC is extended cholecystectomy (EC) which involves resection of 2cm of liver wedge along with intact gallbladder specimen (with common bile duct resection in selected cases) and lymphadnectomy in the hepatoduodenal ligament (HDL) and around head of pancreas with limited resection of involved organs such as the stomach, duodenum, or transverse colon when the involvement is focal. If tumor extension to other organs is extensive, EC is combined with gastrectomy, colectomy or pancreatoduodenectomy. In the cohort of patients with jaundice, all patients had involvement of bile ducts (extrahepatic region or hilar region) with or without adjacent visceral (duodenum / colon) and vascular (hepatic artery / portal vein) involvement. Each of these played an important role in surgical plan. With respect to arterial invasion, aggressive surgery was considered when the tumor had invaded only the right hepatic artery, but not when invasion had spread to the proper and/or left hepatic artery. Involvement of left hepatic artery or left portal vein and main portal vein was considered a contraindication for surgical resection.

Focal involvement of extra-hepatic bile duct (EHBD) by direct tumor extension or involvement of EHBD by peri-choledochal LNs was dealt by EC with EHBD excision and Roux-en-Y hepaticojejunostomy (RYHJ). A tumor extending into the hepatic hilum and/or right Glissonian pedicle was an indication for right hepatectomy (RH) with segment 4b resection. Any patient needing RH with 4b resection and inadequate FLR on CT volumetry was subjected to percutaneous right portal vein embolization (PVE) (ipsilateral/contralateral with or without Segment IV branches) in an effort to augment the FLR. A staging laparoscopy was done before PVE to identify peritoneal metastatic disease upfront. A triple phase CT scan was repeated in all these patients after 4 weeks to document adequate hypertrophy of the FLR and repeated after 2 weeks in event of inadequate hypertrophy. In presence of FLR > 40%, good nutritional and performance status and absence of disease progression on cross sectional imaging, patients were planned for RH with 4b. All patients were subjected to staging laparosopy and in absence of peritoneal or liver surface metastasis underwent surgical exploration followed by IAC sampling before proceeding with surgical resection. Hepatopancreatoduodenectomy was indicated when a tumor had invaded the middle bile duct or there was extensive LN disease around the pancreatic head.

3. RESULTS

There were 401 patients with GBC; 75 with jaundice and 326 without jaundice. The demographic and clinical profile of the two groups is compared in Table 1.

Table 1

Table 1 Demographic Characteristics, Presenting Symptoms, Imaging Findings

		Gall bladder Carcinoma (GBC) with jaundice (N=75)	Gall bladder Carcinoma (GBC) without jaundice (N=326)	P value
Age (Years)	Range	34 to 92	21 to 88	0.605
	Median	59	55	
Gender	Male: Female	39:36	98:247	<0.001
Presenting symptoms	Pain	42	321	<0.001
	Abdominal lump	24	5	<0.001
	Gastric outlet obstruction	6	2	<0.001
	Loss of appetite and weight/asthenia	71	112	<0.001
	Albumin(mean)	3.6	4	<0.001
	Nutritional ascites	9	0	NA
Duration of symptoms (days)	Mean	62	167	<0.001
	Median	60	120	
Number of hospital admissions (Days)	Mean ± S.D	2.41± 1.29	1.13± 0.39	<0.001
	Median	2.0	1.0	
Location of malignancy in gall bladder	Neck/Neck & body	60	27	<0.001
	Body, fundus	9	118	<0.001
	Fundus	5	146	<0.001
	Gall bladder replaced by mass	1	3	0.708

Patients with GBC and jaundice had a M:F ratio of 1:1 in contrast to a M:F ratio of 3:1 in the non-jaundiced group. Patients with GBC and jaundice had a significantly higher incidence of pain abdomen, loss of appetite, loss of weight and presence of an abdominal lump, gastric outlet obstruction and hypoalbuminemia. The duration of symptoms was significantly shorter in patients with GBC and jaundice (Table 1). In 3(4%) of patients with GBC and jaundice and 35(10.7%) of patients with GBC without jaundice the diagnosis of GBC was made incidentally on histopathology after cholecystectomy and before referral to our center.

Majority of the tumors (80%) in patients with GBC and jaundice were present in the neck of the gall bladder while in patients with GBC without jaundice only 8% tumors were in the gall bladder neck and majority (80%) were in the fundus or fundus and body of the gall bladder (Table 1).

Majority of the patients with jaundice required pre-operative biliary drainage (endoscopic in 44 and percutaneous in 30 patients). 8 patients in this group also underwent pre-operative portal vein embolization (PVE) but none of these patients could undergo resection because of various reasons which are summarized in Table 2.

Table 2

Table 2 Reasons for Abandonment of Surgical Resection in Patients of GBC with Jaundice Who Underwent PVE (n=8)	
Inadequate hypertrophy of FLR	2
Metastasis on staging laparoscopy	2
Worsening of nutritional status/inadequate control of cholangitis	1
Development of systemic metastasis	1
Locally advanced disease on surgical exploration	1
Developed intraoperative instability (Ventricular premature complexes)	1

Locally advanced and metastatic disease was much more common and resection rates significantly lower in patients with GBC and jaundice as compared to those without jaundice. In patients with GBC and jaundice detection of metastatic or locally advanced unresectable disease on imaging (31%), laparoscopy (11%) or laparotomy (31%) precluded resection in the vast majority of patients. Ultimately only 2 (2.6%) patients with GBC and jaundice could undergo definitive surgery as compared to 232(71.2%) of the patients without jaundice (Table 3).

Table 3

Table 3 Discovery of Unresectable Disease During the Clinical Course in Patients with GBC and Jaundice			
	GBC with Jaundice (N=75)*	**GBC without Jaundice (N=326)**	**P value**
On imaging	23(30.7%)	4(1.2%)	<0.001
At laparoscopy	11(14.7%)	23(7%)	0.019
At laparotomy	26(34.7%)	67(20.5%)	<0.001
Underwent Definitive surgery	02(2.6%)	232(71.2%)	<0.001

*13 patients in the SOJ group could not undergo surgery because of various reasons like poor general condition, lack of finances, development of metastasis on follow up or not consenting for extensive surgery.

The surgical procedures performed in the two groups are summarized in Table 4.

Table 4

Table 4 Surgical Procedures	
GBC without jaundice (n=242)	**GBC with jaundice (n=2)**
Definitive procedures- 232 Extended cholecystectomy- 199 Extended cholecystectomy with CBD excision- 18 Extended cholecystectomy with visceral resection- 14 Hepatopancreaticoduodenectomy- 01	**Definitive procedures-2** Extended cholecystectomy with CBD excision- 2
Palliative procedures- 10 Palliative cholecystectomy-5 Palliative bypass-4 Liver metastatectomy-1	

4. DISCUSSION

GBC is an aggressive malignancy with majority of the patients being in advanced stage of the disease at presentation. Surgical resection with complete removal of the primary tumor along with the loco-regional spread offers the only chance of cure. Jaundice in patients with GBC is most often due to direct infiltration of the common hepatic duct (CHD) or common bile duct (CBD), usually by a tumor in the gall bladder neck or cystic duct or sometimes a large tumor involving the body and neck or whole of the gall bladder. At times it is the involved, large lymph nodes in the hepatoduodenal ligament (HDL) causing extrinsic compression of the CHD/CBD that is responsible for jaundice. Behari et al. (2003) Involvement of HDL increases the likelihood of vascular involvement of the hepatic pedicle and increases the complexity of the surgical procedure required for complete resection, including the need for preoperative biliary drainage and PVE.

Most surgeons who manage large number of patients with GBC are aware that presence of jaundice in patients with GBC portends a markedly reduced chance of a curative resection and poor prognosis overall. Hawkins et al. (2004), Mishra et al. (2017)

In one of the earliest studies focusing on the presence of jaundice and its impact on likelihood of resection and overall prognosis Hawkins et al reported resectability rates of 7% in patients with GBC and jaundice (only 5% were R0 resections) compared to 39% margin negative resections in those without jaundice. Hawkins et al. (2004) The disease-specific survival of patients with jaundice was a dismal 6 months compared to 16 months in patients without jaundice. There were no disease-free survivors in the patients with GBC and jaundice as opposed to 21% in the non-jaundiced group. Hawkins et al. (2004) Mishra et al reported presence of gastric outlet obstruction, lump abdomen, and jaundice in patients with GBC to be significant negative predictors of respectability. Mishra et al. (2017) Respectability rates in patients with jaundice and those without jaundice were 15% and 52% respectively. Mishra et al. (2017) In the experience of Varma et al abdominal lump and jaundice were signs of advanced disease but not of unrespectability. Varma et al. (2009) Miyazaki et al in an earlier report on aggressive surgery for advanced GBC reported a significantly lower resection rates and significantly higher rates of need for portal vein resection and higher morbidity and mortality in patients with tumors infiltrating both the liver and the hepatic hilum as opposed to tumors which had no involvement of the hepatic hilum, thereby emphasizing the importance of the location of the tumor and its mode of spread in overall respectability and prognosis. Miyazaki et al. (1996)

In our experience even at the time of initial imaging, patients with GBC and jaundice had a higher chance of having metastatic or locally advanced disease. There was a higher rate of attrition at all stages of clinical course- imaging (31%), staging laparoscopy (15%), laparotomy (35%) due to detection of either metastatic or locally advanced, unresectable disease.

The extensive liver resection, required in tumors close to or infiltrating the liver hilum, may require PVE to address the problem of insufficient FLR. In our experience none of the 8 patients who underwent PVE could proceed to surgical resection; either because of disease progression during the waiting period or due to deterioration in the clinical condition because of sepsis and malnutrition. In a similar experience, a study by Mohapatra et al reported that 17 patients with GBC and jaundice underwent PVE but despite technical success and increase in FLR, only 2 patients could undergo definitive surgical resection; disease progression, main

portal vein thrombosis, persistent sepsis or poor performance prevented surgical resection in 8, 2 and 3 patients respectively. Mohapatra et al. (2018) In a recent report, better (7/14,50%) respectability rates were attained after adding neoadjuvant chemotherapy (NACT) to PVE. Singh et al. (2021) If replicated in larger numbers this could be a valuable addition to management of this group of patients.

Ultimately, in our experience, a dismal 2.6% of patients with GBC and jaundice ended up having a definitive surgical procedure as compared to 71.2% of GBC without jaundice.

The poor prognostic significance of jaundice in a patient with GBC has not been stressed enough in the published literature. While reports of possibility of complete resection in some patients with GBC and jaundice continue to appear intermittently, curative resections are exceptions rather than the norm in patients with GBC and jaundice. Feng et al. (2012), Yang et al. (2014) This is borne out by the absence of large series of curative resections in this subgroup of patients from most countries, including India, where GBC is seen very commonly.

Several factors which may contribute to jaundice being a surrogate marker of poor prognosis include a higher likelihood of the tumor being in a more unfavorable location in an anatomically busy area close to the hepatic hilus, lympho-vascular permeation of tissue of HDL making R0 resection unlikely Kaneoka et al. (2003), the overall deleterious effect of jaundice on the general physiology and performance status of the patient, need for more extensive, time-consuming, multidisciplinary interventions (which add to the hospital stay as well as cost of treatment) and the likelihood of tumor progression in the waiting period. We have reviewed the issue of GBC and jaundice in an earlier publication. Behari et al. (2003)

5. CONCLUSION

Patients with GBC and jaundice are very likely to have advanced, unresectable disease. Chances of complete resection are slim even after extensive preparation; the need for more extensive, time-consuming, costly, multidisciplinary interventions and the likelihood of tumor progression in the waiting period further complicates the management issues. More experience with alternative approaches like neo-adjuvant therapy is required to make conclusions about their efficacy in this group of patients.

6. AUTHOR CONTRIBUTIONS

Conception and design of study: Anu Behari, Supriya Sharma

Acquisition of data: Vijay Kumar Sharma

Analysis and/or interpretation of data: Anu Behari, Supriya Sharma, Vijay Kumar Sharma

Drafting the manuscript: Anu Behari, Supriya Sharma

Revising the manuscript: Anu Behari, Supriya Sharma, Rajneesh Kumar Singh, Ashok Kumar Gupta, Ashish Singh, Rahul, Ashok Kumar, Rajan Saxena.

CONFLICT OF INTERESTS

None.

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