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Gall Bladder Cancer – The Indian Perspective

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Gall bladder cancer (GBC), uncommon in the West (USA, UK and Australia), is common in north India – the incidence in women in Delhi being more than 9 per 100,000 per year as compared to less than 1 per 100,000 in the West as well as in South India; it is the fourth commonest cancer (following breast, cervix and ovary) and the commonest gastrointestinal cancer in women in Delhi (1). In our experience, it is the commonest cause of malignant surgical obstructive jaundice – as many as 74 (51%) out of 145 patients with malignant surgical obstructive jaundice seen by us between 1989 and 1992 had GBC (2).

The usual and typical clinical presentation of GBC is with dull continous right upper abdomen pain, progressive jaundice, anorexia and weight loss and palpable GB mass. These are, however, features of advanced disease which is usually unresectable. Early – resectable and curable – GBC is an elusive disease – difficult to differentiate clinically from gall stone disease (3) and may not be detected even on ultrasonography (US). Out of 14 patients with early (Stage I) GBC, only 3 were diagnosed preoperatively and another 3 were diagnosed at surgery; GBC was detected incidentally on histology in 8 patients (4). Some patients with GBC present with atypical features eg mucocele, empyema, acute cholecystitis and liver abscess and may have unusual associations eg CBD stones, intestinal obstruction/bleeding (5).

US - the first and commonest imaging modality for biliary disease – may be helpful in diagnosis but was found by us to be a poor investigation for staging of GBC as local infiltration and metastases were often missed (6). CECT is better than US for staging. Laparoscopy is a useful investigation for staging of upper gastrointestinal and pancreatic cancers – it detects surface deposits on liver, peritoneum and omentum and avoids unnecessary laparotomy. Between 1989 and 2001, staging laparoscopy was

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performed in 91 patients with possibly resectable GBC – it detected peritoneal dissemination and avoided unnecessary laparotomy in 35 (38%) patients. Staging laparoscopy improved resectability rate from 43% to 57% (7). Upper gastrointestinal endoscopy (UGIE) detects duodenal infiltration which may be present in about 20% of patients with advanced GBC (8). US/CT guided fine-needle aspiration cytology (FNAC) is a useful method to get preoperative tissue diagnosis – it was positive in more than 85% of 394 patients with GBC. In patients with possible resectable disease on CT, however, we do not go for preoperative tissue diagnosis and perform resection based on imaging or operative suspicion of GBC. With this approach, though, we have ended up performing EC in 9 patients with xanthogranulomatous cholecystitis (XGC).

We recommend a middle path approach for management of GBC – between the pessimistic nihilism of the West and the aggressive radicality of the East (Japan). Procedure of our choice is extended cholecystectomy (EC) which includes GB, 2 cm non-anatomical wedge of liver in GB bed and lymph nodes in hepato-duodenal ligament and behind duodenum and head of pancreas; we do not perform CBD excision as a routine but perform it in only selected cases (9).

Surgical resection is the treatment of choice for GBC. The surgical resection in GBC should aim for R0 resection as it is an important factor for long –term survival. EC was performed between 1989 and 1999 in 42 patients with GBC – R0 resection, achieved in 18 patients, resulted in better survival than R1 resection (median 26 Vs 17 months). R0 resection could be achieved in all T1/ T2, half of T3 and none of T4 patients; it could be achieved in only 15% of node-positive patients. 5-year survival in node - negative patients was 58% but none of the node - positive patients survived for 5 years (10). Out of 117 patients who underwent resections between 1989 and 2000, there were 44 long-term (> 24 months) survivors – they were compared with 73 short-term (< 24 months) survivors. T status and adjuvant chemo-radiotherapy were predictors of long-term survival. Adjuvant therapy improved survival in patients with node-positive and stage III disease and those who had simple cholecystectomy (11).

EC achieves R0 resection in early GBC (14). EC was performed in 76 patients with 4% mortality. More advanced disease may require major resections such as hepatectomy, hepato-pancreatico-duodenectomy, resection of CBD, portal vein and hepatic artery, and retroperitoneal lymphadenectomy as advocated by the Japanese surgeons. These procedures are associated with high mortality and morbidity, prolonged hospital stay and repeated hospitalisations. We feel that GBC is curable, and therefore should be resected,

only when the tumour is confined to GB and nodes are limited to hepato-duodenal ligament (12). We do not, therefore, perform and recommend these major procedures for advanced GBC. In these patients, we perform a non-curative simple cholecystectomy, if technically feasible – this improved survival as compared to biopsy alone (13). Between 1989 and 2003, simple cholecystectomy was performed in 100 patients with stage III and IV GBC. Median survival was longer than those who had biopsy alone (11 Vs 2 months); adjuvant chemo – radiotherapy improved survival after simple cholecystectomy (16 Vs 6 months).

Majority of patients with advanced GBC have unresectable disease and need palliation from jaundice, cholangitis, pruritus and vomiting. Earlier we used to perform surgical biliary bypass in the form of intrahepatic segment III cholangio-jejunostomy. It was performed in 41 patients with stage IV GBC – all had jaundice, 29 had pruritus and 12 had cholangitis. Five patients died within 30 days. The procedures failed in 4 patients, 18 were relieved and 10 had recurrent symptoms after initial relief. We found isotope scan to be useful to predict success/ failure of this procedure (14). Of late, we have changed to endoscopic/ percutaneous stenting. Patients with frank gastric outlet obstruction need therapeutic gastro-jejunostomy (GJ); selective GJ may be performed in patients with duodenal infiltration on imaging and/or at operation but prophylactic GJ is not recommended (15). There is, however, an element of malignant gastroparesis which may not respond to a surgical bypass (8).

TNM staging of GBC proposed by UICC – AJCC has some limitations. We have proposed modifications viz. involvement of muscularis should be classified as T2 (instead of T1b) and staged as II (instead of I) because these patients are best treated with extended cholecystectomy (not simple cholecys-tectomy which is good enough for only T1a – mucosal disease). We also proposed that distant lymph nodes (coeliac, superior mesenteric and para-aortic) should be classified as N3 (instead of N2) and staged as IVB as they behave like metastatic disease (16).

US often reveals a thick-walled GB (TWGB). In prospective study of TWGBs conducted over a 10-month period, 30 had chronic cholecystitis and 28 had XGC; only 2 had GBC (both found incidentally on histological examination). Laparoscopic cholecystectomy could be performed in 40 of these 60 patients (17). XGC - a form of chronic cholecystitis, may be difficult to differentiate from GBC on imaging and even at operation. XGC was present in 453 of about 4,800 cholecystectomies performed by us between 1989 and 2003. GBC was suspected clinically (n=33), radiologically (n=81) and operatively (n=88) in 150 patients. GBC coexisted with XGC in 26/453 (6%) cases with XGC; patients with XGC+GBC were older and more often male (18).

GSD is common in north India. Prophylactic cholecystectomy for asymptomatic GSD to prevent GBC is controversial. Data on natural history of asymptomatic GS from the West does not support prophylactic cholecystectomy. There may, however, be a role for prophylactic cholecystectomy in a young patient with a large stone in an area/ population where GBC is more common (19) though no evidence is yet available to support this view Cholecystectomy for GSD sometimes reveals GBC on histological examination – incidental GBC. Patients with incidental GBC are older (58 Vs 41 years) and have biliary obstruction (jaundice in one-third and raised alkaline phosphatase in half) – cholecystectomy was described as difficult in 85% of these cases. Several reports advocate that nothing more is required and simple cholecystectomy is enough for early GBC but we advocate reoperation to complete EC except in patients with mucosal (T1a) disease (20). This is based on our experience wherein 5 out of 11 patients with T1b disease who underwent simple cholecystectomy had recurrence of disease (4).

It is unfortunate that all GBs that are removed are not subjected to histopathology and some of these patients come back with recurrent GBC which was missed. We strongly advocate that all GBs removed for GSD should be subjected to histological examination which may reveal an incidental GBC which is in early stage and can be cured by EC – tertiary prevention.

Between 1989 and 2004, we have operated upon 543 patients with GBC – biopsy alone could be performed in 157 patients, 155 patients had bypass (biliary and/or gastric) procedures and 231 had resections (155 simple cholecysectomy and 76 EC). Mortality of resections was 6/231 (2.5%). Overall 5-year survival in resected patients was 30% (40% in stage I, 30% in stage II and 15% in stages III and IV); there are 24 actual 5-year survivors.

With one of the highest incidences in the world reported from north India, GBC is an Indian disease (21). We have taken the mantle to accept the challenge of GBC (22) and have joined hands with workers in Japan (23), Chile (24), UK (12, 25, 26) and Australia (19, 21). We have collaborated with colleagues in the University of Tsukuba, Japan to study the cyclo-oxygenase expression in GB. We found significant difference in COX-2 expression between cancerous tissue and adjacent non-cancerous tissue – both in epithelium and parenchyma (23). Mutation in codon 12 of K-ras oncogene was found in 8/21 (28%) FNAC samples from patients with GBC; the incidence of mutation was higher in GBC patients with GSD (46%) as compared to those without GSD (25%) (27). ApoB-Xb gene polymorphism was studied in 153 DNA samples from patients with GBC. Homozygous X - / - genotype was more common in GBC (55%) than in GSD (24%) and normal controls (26%). (28). We are

analysing stones from patients with GBC and GSD by NMR spectroscopy, CT densitometry and bone densitometry to see if they are different. We have described and standardised simple methods of quantification of glycine and taurine conjugated bile acids and cholesterol (30) in human bile using ^{1}H NMR spectroscopy.

Several questions related to GBC need an answer

1. The role of GSD and other factors eg hormones (GBC being one of the few non- genital tract cancers more common in women than men), infections (eg Salmonella, Helicobacter), etc in aetio-pathogenesis of GBC
2. Indians who have migrated to various parts of the world continue to have higher risk of developing GBC. Do (north) Indians, like the native American Indians, have a genetic predisposition for GBC?
3. Natural history of asymptomatic GSD in north India regarding risk of development of GBC.

GBC is an "Indian disease" – answers to these questions will have to come from India – including us.

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