NATURAL HISTORY OF CARCINOMA OF THE GALLBLADDER AND ITS INFLUENCES ON MANAGEMENT

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ABSTRACT

There were 45 patients (8.8%) of carcinoma of the gall bladder among 506 patients of gall bladder disease admitted during January 1993 to June 1995. Female to male ratio was 4:1 and average age at detection was 52 years. Pain right hypochondrium and jaundice were prominent clinical features. Ultrasonography accurately diagnosed 33 (73.3%) cases while computed tomography was correct in 15/22 (75%) of cases. Cholelithiasis was present in 37 (80%) patients. Sixteen patients were not offered surgery due to either widespread disease or due to poor general health. Cholecystectomy with wedge or segmental resection of liver and lymphadenectomy was performed in 18 out of 29 patients. In 6 patients segmental resection of the contiguous involved organ was performed. Perioperative mortality was 8 per cent. Two patients were alive for more than 24 months, 7 for more than 12 months and 11 were being followed-up for 1 to 12 months. All patients not offered surgery died within 4 months.

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Introduction

The first reported cholecystectomy for carcinoma of the gall bladder was performed in 1887 [1]. In 1894 Ames published a comprehensive review article in which he gave a detailed account of the clinical features and natural history of the disease, stressing its almost universal fatality [2]. In 1962 Fahim et al reviewed 151 cases from the Mayo Clinic who underwent surgical operations between 1909 and 1950. They gave an excellent description of the mode of spread of carcinoma of gall bladder and concluded that the poor prognosis which attended this carcinoma was not necessarily due to the biological nature of the tumour but due to inadequate surgical therapy [3]. In 1976 Nevin et al developed a method of staging the tumour based on the extent of involvement of the gall bladder, and the presence or absence of the tumour in the liver and other organs [4]. In 1991 Sumiyoshi et al [5] carried out a clinicopathological study of 40 cases of carcinoma of the gall bladder and concluded that, in order to improve the prognosis, search for a more rational and effective

radical approach based on the exact understanding of its pathology should be continued. We undertook this clinico-pathological study of carcinoma of the gall bladder with a view to define the extent of surgery necessary for obtaining macroscopic and microscopic clearance and its influence on survival.

Material and Methods

In a prospective, nonrandomised, uncontrolled study, 506 patients of gall bladder disease admitted from January 1993 to June 1995 were taken into the study. Based on clinical and haematological examination, supplemented with ultrasonography (USG), patients having benign gall bladder disease were excluded. Patients suspected to have carcinoma of the gall bladder were subjected to further relevant investigations, viz. computed tomography (CT scan), fine needle aspiration cytology (FNAC), endoscopic retrograde pancreatobiliaryography (ERCP), and percutaneous transhepatic cholangiography (PTC) to arrive at a pre-operative diagnosis. The gall bladder was

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opened and inspected in all patients with benign gall bladder disease undergoing elective cholecystectomy and, if required, subjected to frozen section to arrive at a per operative diagnosis. Patients with gall bladder disease who were subsequently reported to have carcinoma of the gall bladder on histology were subjected to second laparotomy. FNAC was done only in those cases which were not subjected to exploratory laparotomy either due to advanced disease or due to poor performance status.

Surgery performed ranged from cholecystectomy alone to cholecystectomy with wedge resection of liver, clearance of all the lymphoareolar tissue from the suprapancreatic portion of common bile duct (CBD), and segmental resection of certain contiguous organs. Extent of surgery was influenced by preoperative diagnosis, peroperative assessment and loco-regional spread. Twenty nine patients were offered surgery while 16 were found inoperable because of widespread disease or poor performance status.

Results

There were in all 506 patients admitted to surgical wards with the clinical diagnosis of gall bladder disease. The number of patients who were suspected to have carcinoma of the gall bladder based on our protocol were 42. Five patients were proved to have a benign disorder and were excluded from the study. However 5 cases of carcinoma were detected peroperatively after macroscopic examination and frozen section. These 5 patients and 3 more patients who were diagnosed postoperatively after histological examination were included in the study making 45 patients in all.

The age of these 45 patients ranged from 28-79 years. There were 36 females and 9 males with female to male ratio being 4:1. The duration of illness ranged from 10 days to 6 years the average being 12 weeks. Thirty six patients presented with pain. Anorexia was present in 32 patients and weight loss in 25 patients. Icterus was seen in 22 patients, gall bladder mass in 22 and ascites was present in 6 patients. Elevated serum bilirubin level was present in 22 patients and raised serum alkaline phosphatase in 28 patients. USG of the abdomen and pelvis was done in all cases and in 33 patients (73.4%), in whom a mass was demon-

strated on USG, the diagnosis was confirmed at histology/FNAC. CT scan was done in 22 cases and diagnosis was confirmed in 15 (75%) (Table 1).

TABLE 1

Ultrasonography and computed tomography findings in patients with carcinoma of the gall bladder

	USG (n=45)	CT scan (n=22)
Liver		
Enlarged	9	3
Abnormal echotexture	9	10
Dilated IHBR	18	16
Gall bladder.		
Distended	9	3
Mass		22
Fungating	15	—
Lumen filling	13	—
Smooth/raised	—	—
Mucosal thickening	5	—
Stones	37	6
Common duct dilated	12	12
Lymph nodes enlarged	10	12
Ascites	2	2

Twenty nine patients could undergo surgery. Eighteen patients had growth located in the fundus while 11 had growth situated in neck region. In 27 patients the lesion was adenocarcinoma and in remaining 2 it was squamous cell carcinoma and malignant carcinoid respectively. The growth had infiltrated the liver in 12 cases while 17 patients had lymph node involvement. In 12 patients the growth had infiltrated the liver with minimal spread to the CBD and lymph nodes. In 13 cases there was involvement of pericholedochal lymph nodes and creeping sclerosis to the CBD. Involvement of contiguous organs like duodenum, transverse colon and omentum was observed in 6 patients. In 22 patients surgery was performed with intent of cure (radical) and in 7 the procedure was palliative (Table 2).

For staging we have used a simple clinico-pathological classification based on the loco-regional spread of the growth as observed at surgery and histology (Table 3). Three patients were lost to follow-up and 2 patients died in the post-operative period. Four patients of stage IV disease died after

TABLE 2

Types of surgery performed in carcinoma of the gall bladder

Cholecystectomy with CBD clearance	4
Cholecystectomy + lymphadenectomy with wedge/segmental resection of liver and segmental resection of duodenum/ stomach colon/omentum	12
Cholecystectomy and open stenting of CBD	2
Segment III bypass	3
Exploratory laparotomy and biopsy	2

TABLE 3

Staging classification in operated cases (n=29)

Stage	Description	No of patients in present study
Stage I	Primary tumour invades upto muscular layer serosa not involved	3
Stage II	Tumour invades beyond serosa with extension into liver and/or pericholedochal lymph nodes (along hepatoduodenal ligament)	13
Stage III	Tumour extends into adjacent organs (stomach, duodenum, colon, omentum) with or without lymph nodes involvement	6
Stage IV	Peritoneal spread, involvement of left lobe of the liver and spread into more than one contiguous organ and or distant metastasis	7

1-4 months. Two patients (stage I) were alive and symptom free after 2 years of follow-up. Seven patients of stage I and II disease completed 12 months disease-free period and 11 patients (stage II and III) were in different periods (1-12 months) of follow-up. Sixteen patients who were inoperable died within 4 months of diagnosis.

Discussion

Primary carcinoma of the gall bladder is the most common malignancy of the biliary tract and the 5th most common gastrointestinal cancer [6]. In Britain less than 1 per cent of the carcinoma arise in the gall bladder [2]. The condition appears to be more common in the United States and its reported incidence varies from 1-16 per cent [7]. In contrast, owing to the lack of cancer registry, the actual incidence of carcinoma of the gallbladder in India is subject to a variety of opinions. This

series of 45 histologically proved cases over a period of two and half years from a single hospital indicates that the disease is not uncommon in India. We found the incidence to be 8.9 per cent of all gall bladder disease admitted to this hospital. Though this hospital serves a mixed population all patients of carcinoma of the gall bladder were noted to be from northern India. One of the reasons for the predominance among the north Indian population was that benign gall bladder disease in north India far outnumbers the disease in south Indians [8]. Another reason could be that the hospital is located in north India and hence it will draw patients from this region mainly. Other factors responsible for geographical variation are race, environment and dietary factors [9], although none has been confirmed. The aetiological factors most often implicated for primary carcinoma of the gall bladder are gall stones and chronic inflammation. The incidence of gall stones in association with carcinoma of the gall bladder varies from 54-100 per cent [6] and in the present series it was 82 per cent. Gall bladder carcinoma is predominantly a disease of the middle aged or elderly women. The male to female ratio of 4:1 is typical in our study, while average age of 52 years in this series is lower than that mentioned in Western literature [2].

The symptoms of malignancy may be superimposed upon chronic cholecystitis with the transition unnoticed by the patient. At times the patient may not have any symptoms due to malignancy and may present with symptoms of benign biliary tract disease. We observed an incidence of 1.7 per cent of carcinoma of the gall bladder amongst 460 patients operated upon for benign gall bladder disease. In our series duration of illness ranged from 10 days to 6 years with majority giving history of 2-3 months duration. The clinical features in our series were typical of late presentation. Pain in the right hypochondrium, jaundice, anorexia, weight loss, vomiting, mass in the abdomen and low grade fever were the common symptoms noted in our series. A right upper quadrant mass with or without tenderness, hepatomegaly, jaundice and anaemia were the common signs.

In patients with advanced carcinoma of the gall bladder ultrasonography is diagnostic in 70-80 per cent of cases [11]. We had 42 cases beyond stage I

and a correct preoperative diagnosis was possible in 73.3 per cent of the cases. Lymph nodes status was better appreciated by CT scan than by USG. Usually hepatic metastasis in a patient with intra-abdominal tumour is considered to be of haematogenous origin whilst gall bladder carcinoma may spread directly to the liver relatively early, due to the close proximity, without vascular involvement. The liver bed gets involved at even earlier stage than the lymph nodes [12]. We noticed two distinct pattern of spread. An early spread to the liver with minimal spread to the CBD and lymph nodes. This was seen in 12 of 29 operated cases. The other pattern was contiguous creeping sclerosis of the CBD engulfing pericholedochal lymph node and resulting in a mass. This was seen in 13 out of 29 cases. When the spread was towards the CBD there was tendency for contiguous spread to the duodenum, transverse colon and omentum. This was observed in 6 out of 29 patients. Both the patterns subsequently spread to the peritoneum and the distant metastasis. These observations by us and observations by others [13,14] have resulted in our proposing a staging classification for the carcinoma of the gall bladder (Table 3).

Proper management begins with the opening and inspection of the resected gall bladder. Most western authors have a pessimistic view of radical surgery for the gall bladder carcinoma [15,16]. Recently favourable long-term results with radical surgery has been demonstrated [17]. We believe that, except for stage IV disease found at exploration, every attempt must be made to resect the lesion with some form of liver resection, and clearance of lymph nodes along the CBD with the aim of achieving R0 or R1 resection. Surgery is the only form of treatment of any benefit to the patient of carcinoma of the gall bladder as of today. We carried out radical surgery in 22 of 29 patients and in the rest only palliation could be achieved. Standard radical operation employed by Shirai et al [17] included cholecystectomy, wedge resection of the gall bladder bed, resection of the extrahepatic part of the bile duct and *en block* dissection of the lymph nodes. They have reported more than 5 years survival in 9 out of 20 patients with nodal involvement. We have completed follow-up for 1 to 24 months in this study. Two patients died during perioperative period due to cholangitis and

septicaemia and 3 were lost to follow-up. Four patients of stage IV disease died within 4 months of surgery. Two patients completed 2 years of follow-up and 7 patients were disease free for one year. Nakamura et al [18] assessed the effectiveness of hepaticopancreatoduodenectomy in the patients with advanced gall bladder carcinoma directly invading the liver and pancreas, generally considered to be nonresectable, and concluded that there is a potential to improve both the survival and quality of life in carefully selected patients.

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