

Advanced presentation of Gallbladder cancer: Epidemioclinicopathological study to evaluate the risk factors and assess the outcome

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Abstract

Objective: To evaluate the risk factors and assess the short-term prognosis and independent prognostic factors of cases of gallbladder cancer.

Methods: A retrospective analysis of the data of 52 patients of gallbladder cancer was done. Clinical presentation, laboratory investigations, treatment given, operative findings and histopathological findings were reviewed.

Results: Forty-four patients were unresectable at presentation. A 2-year survival rate for early gallbladder cancer was 100% while it was only 29.2% in the advanced stage group.

Conclusion: The overall 2-year survival rate was 39.58%. The TNM stage was the most important factor affecting the survival (JPMA 60:217; 2010).

Introduction

Gallbladder disease is an important health problem in India.¹ Gallbladder has been the site for a variety of lesions ranging from gallstones to different reparative and proliferative diseases to malignancy. Gallbladder cancer is the fifth most common cancer of gastrointestinal tract and the most common cause of death from biliary malignancies.² In USA, it is an uncommon cancer with an incidence of 2.5 per 100,000 population. In contrast, Chile has a much higher incidence of 7.5 per 100,000 population.³ The Indian Council of Medical Research Cancer Registry has recorded an incidence of 4.5 and 10.1 per 100,000 males and females respectively in the northern parts of India, and 1.2 per 100,000 population in females in southern parts of India.¹ Although different associations have been described, gallstones are found to be associated in 70% to 90% of the cases of gallbladder cancer and approximately 0.4% of all patients affected with gallstones eventually develop carcinoma of the gallbladder.⁴ An autopsy study had shown that the overall incidence of carcinoma of gallbladder is 1% to 3% in patients with cholelithiasis.⁵ Although the exact progression of mucosal changes to carcinoma gallbladder is not elucidated, the suggested sequence is intestinal metaplasia to dysplasia to carcinoma in situ to invasive carcinoma.⁶ Most tumours appear as focal or diffuse thickening of the gallbladder wall, a raised mucosal plaque, a polypoid growth or an infiltrating grey white mass. Early detection and radical surgery may contribute to better survival, but early detection continues to be poor. Resectional surgeries give best chance of survival.⁷⁻⁹ Besides this, tumour (T) status, local tissue and vascular infiltration, lymph node status (N), metastasis (M) and grade

of the tumour also influence the survival. Beneficial effects of intraoperative and/or postoperative radiotherapy and chemotherapy has been suggested.^{10,11} In recent years, a large number of gallbladder cancer patients have reported to the surgical out-patient department of this hospital. Although the subject of gallbladder cancer is well explored, there is relative paucity of clinicopathological studies. The present study evaluates the risk factors, short term survival and prognostic factors in gallbladder cancer.

Patients and Methods

The present study consisted of 52 patients of gallbladder cancer who were being followed up in departments of surgery and/or radiotherapy. A retrograde evaluation of patients' epidemiological background along with assessment of complete history with reference to age, sex, cholelithiasis, associated medical problems, dietary habits, use of cholestatic drugs, any occupational exposure, and history of enteric fever was done. The findings of physical examination, sonographic results and laboratory investigations were studied. Final TNM scoring (after imaging and operative intervention) was also recorded. Per-operative findings like gallbladder size, shape, thickness of the gallbladder wall, its relation to surrounding structures, presence or absence of stones, number of stones and gross picture of mucosa, serosa, and growth was noted. Involvement of lymph nodes and metastasis were also searched. The pathological findings that includes epithelial ulcerations, dysplasia changes, and malignant changes were noted. In inoperable cases, only fine needle aspiration cytology (FNAC) was done and diagnosis was made on predominant cell-type, anisocytosis pattern and other cytological alterations. To determine prognostic factors,

univariate and multivariate analysis was done with respect to the presence of jaundice, weight loss, presence of palpable mass, TNM staging, lymph node status, metastasis, histological type, nature of surgical treatment and any beneficial effects of radiotherapy and chemotherapy.

Results

The median age of all enrolled patients was 61 years (range 30 to 76 years); 5 (9.63%) were men and 47 (90.37%) were women. The most common presenting complaint was pain (n=44, 84.62%). Palpable lump was present in 42 (81.13%) patients. Other signs and symptoms are shown in Table-1. Dietary history revealed that the majority (n=35,

Table-1: Presenting signs and symptoms.

Signs and Symptoms	Number	Percentage
Pain right hypochondrium	44	84.62
Nausea and Vomiting	28	53.84
Dyspepsia	26	50.00
Loss of weight and appetite	38	73.07
Jaundice	18	34.61
Tenderness	15	28.84
Palpable lump	42	81.13

84.62%) were using mustard oil as cooking media and the average fat intake was 80 g/day. Eleven patients were addicted to smoking, 19 were addicted to tobacco chewing and 15 were addicted to both. Only one patient was addicted to alcohol. Seven patients had a documented history of enteric fever and among them three had multiple episodes of illness. A detailed reproductive history of female patients revealed that 32 (68.08 %) of them were multipara with a history of intake of oral contraceptive pills in 13 patients. Biochemical findings revealed that 32 patients had obstructive jaundice. Other findings are shown in Table-2. Sonographic evaluation of hepatobiliary system revealed that 50 patients (96.15%) had cholelithiasis. Gallstones were multiple in all the cases except in three patients and there was evidence of bilobar hepatic metastasis and periportal lymph node enlargement along with gallbladder mass in 39 patients (75%). During laparotomy, tumour was found to be unresectable in 5 patients and bilobar hepatic involvement was seen among three of them. The disease was localized in the remaining 8 patients. These patients were operated for cholelithiasis with chronic cholecystitis but histopathology revealed carcinoma in situ in 2 patients and T1a in 6 patients. Features of chronic cholecystitis were present in all 52 cases. Adenocarcinoma was the most common type and was affecting 94.23% (n=49) of the cases. Undifferentiated carcinoma was seen in two patients (3.84%) while in one case adenosquamous carcinoma was seen. By univariate analysis, significant variables affecting prognosis were found to be as presence of jaundice, weight loss, palpation of gallbladder lump at diagnosis, TNM

Table-2: Laboratory data in patient with gallbladder cancer.

Laboratory Findings	Number	Percentage
Anemia	49	94.23
Abnormal LFT*	23	44.23
Leucocytosis	8	15.38
Hyperbilirubinemia with Serum		
Alkaline phosphatasemia	32	61.83

*LFT: Liver Function Test.

stage, gross pathology and histology of the tumour. In multivariate analysis, the variables which affected the survival were number, size, depth and histology of primary tumour and lymph node metastasis. Out of 52 cases of gallbladder cancer, 48 used to come regularly in surgical and/or radiotherapy OPD. Median follow-up was 8 months. Patients were given external beam radiation therapy and 5-FU and were evaluated for quality of life, relief from pain, appetite and subjective sense of well being or worsening of symptoms. Among the 44 patients of advanced unresectable stage group (Stage 3 and 4) three were lost so that only 41 of them presented regularly in the follow up. The survival rate of two years was calculated separately for early stage and advanced stage groups. In the early stage group, there were 7 patients at the beginning of a two year follow up and all remained alive at the end of the study. So 2-year survival rate for early gallbladder cancer was 100%. In the advanced stage group, there were 41 patients at the beginning. Out of those, only 12 remained alive at the end of two-year follow up. Therefore 2-year survival rate for advanced gallbladder cancer was 29.2%. The overall 2-year survival rate in both group of patients was 39.58%. Median survival of the patients in advanced stage group was 7 months.

Discussion

The main sufferers of the disease were elderly females as compared to the males with median age of 61 years. Out of the 52 cases, only 5 were males (9.62%) having male to female ratio of 1:9.4. The difference may be the result of high incidence of early pregnancy and childbirth in India as compared to the western countries. Since pregnancy and childbirth have a definite influence on biliary tract diseases, by causing bile stasis, hypercholesterolaemia as well as weight gain, there is a high incidence of the disease among females. In our study 68.08% of the patients were multiparous. Since the majority (90.38%) of patients in our study were females, it was reasonable to think that females are at an increased risk, as postulated by an earlier study that linked exogenous estrogens to cholelithiasis having a major predilection for females.⁴ The duration of ailment ranged from 1 month to 5.8 years. The duration of symptoms noted by Arnaud et al varied between 8 days and 5 years.¹² In our country, usually patients especially among females generally do not care much about

vague symptoms like dyspepsia, flatulence, pain and they report to hospitals only after other indigenous methods of treatment fail or the disease really becomes troublesome. This might be the reason for the prolonged duration and advanced stage of presentation in our patients. The main presenting complaint of pain in right hypochondrium was seen in 84.61% of the cases. There were 8 cases of incidental carcinoma of gallbladder who were primarily operated for a benign disease but subsequent histopathological examination revealed malignant changes. In other studies, the incidence of occult carcinoma of gallbladder varied from 1% to 2.5%.^{1,12-14} Gallstones were present in 96.15% of our patients. There were multiple stones in all patients except in three cases. Similar statistics were reported by Tyagi et al who found that 85.7% of the gallbladder cancer patients had associated gallstones.¹⁴ Physical trauma produced by the stone might have resulted in epithelial dysplasia and ultimately the progression to carcinoma. None of our patients was found to be affected with chronic typhoid carrier state. This association of chronic typhoid infection and development of gallbladder cancer needs to be evaluated further in subsequent studies in which fresh bile could be cultured and sera can be analyzed using specific immunologic tests. The majority of our patients were using mustard oil for cooking. A positive association of high fat intake with gallbladder cancer risk was found in a case-control study by Rizvi et al.¹⁵ Prognosis in our study group was very poor especially in advanced stages. Systemic therapy in the form of EBRT and 5-FU did not provide any survival advantage. Although a 2-year survival rate was 100% in the early stage group it requires a longer follow up period to determine prognosis. The poor prognosis in this study is largely due to late stage presentation along with palpable gallbladder lump, jaundice, TNM stage, gross pathology and histology of the tumour.

Conclusion

The prognosis of gallbladder cancer is thus poor mainly because of the delayed presentation. Besides other factors, TNM stage remains the most imperative prognostic

factor affecting the survival. It is desirable to search for any factor which can be linked to gallbladder cancer or which can help in diagnosis of the disease in early stages making surgical intervention possible and ultimately resulting good prognosis. Moreover, to positively affect the outcome of patients in advanced stage of the disease, newer cancer treatment strategies need to be adopted.

References

1. Indian Council of Medical Research (ICMR), Annual report of population based cancer registries of the National Cancer Registry Programme (1993). New Delhi: ICMR 1996; 18.
2. Schauer RJ, Meyer G, Baretton G, Schildberg FW, Rau HG: Prognostic factors and long-term results after surgery for gallbladder carcinoma: a retrospective study of 127 patients. *Langenbeck's Arch Surg* 2001; 386: 110-7.
3. Samad A. Gallbladder carcinoma in patients undergoing cholecystectomy for cholelithiasis. *J Pak Med Assoc* 2005; 55: 497-9.
4. Malik IA, Aziz Z, Zaidi SH, Sethuraman G. Gemcitabine and Cisplatin is highly effective combination chemotherapy in patients with advanced cancer of the gallbladder. *Am J Clin Oncol* 2003; 26: 174-7.
5. Kimura S, Shamada H, Kurada A, Monoka Y. Carcinoma of the gallbladder and extrahepatic biliary ducts in autopsy cases of the aged with special reference to relationship to gallstones. *J Gastroenterol* 1989; 84: 386-90.
6. Albores-Saavedra J, Alcantra-Vasquez A, Cruz-Ortiz H, Herrera-Goepfert R. The precursor lesions of invasive gallbladder carcinoma: hyperplasia, atypical hyperplasia and carcinoma in situ. *Cancer* 1980; 45: 919-27.
7. Koga A, Watanabe K, Fukuyama T, Takiguchi S, Nakayama F. Diagnosis and the operative indications of the polypoid lesions of the gallbladder. *Arch Surg* 1988; 123: 26-9.
8. Nakamura S, Sakaguchi S, Suzuki S, Muro H. Aggressive surgery for the carcinoma of the gallbladder. *Surgery* 1989; 106: 467-73.
9. Pradeep R, Kaushik SP, Sadiq SK, Bhattacharya BN, Pandey CM, Kapoor VK. Predictors of survival in patients with carcinoma of the gallbladder. *Cancer* 1995; 76: 1145-9.
10. Houry S, Schlienger M, Huguier, Lacaine F, Penna F, Laugier A. Gallbladder cancer: Role of radiation therapy. *Br J Surg* 1989; 76: 478-50.
11. Todorki T, Iwasaki Y, Orii K, Otsuka M, Ohara K, Kawamoto T. Resection combined with intraoperative chemotherapy for stage 4 (TNM) gallbladder cancer. *World J Surg* 1991; 15: 357-66.
12. Arnaud JP, Gramfort J L, Adloff M. Primary Carcinoma of the gallbladder: review of 25 cases. *Am J Surg* 1979; 138: 403-6.
13. Bhansali SK. Management of cholelithiasis and cholecystitis. *Ind J Surg* 1976; 38: 436-53.
14. Tyagi SP, Tyagi N, Maheshwari V, Ashraf SM, Sahoo P. Morphological changes in a diseased gallbladder: A study of 415 cholecystectomies at Aligarh. *J Ind Med Assoc* 1992; 90: 178-81.
15. Rizvi TJ, Zuberi SJ. Risk factors for gallbladder cancer in Karachi. *J Ayub Med Coll Abbottabad* 2003; 15: 16-8.