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Original Research Article

Carcinoma of the gall bladder: 8 year experience from a tertiary care centre, Punjab, India

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ABSTRACT

Background: Gall bladder carcinoma is the most common malignancy of biliary tract and one of the most aggressive gastrointestinal malignancies. The present study was conducted to know the clinical aspects, results and survival patterns after therapeutic interventions in patients of gall bladder cancer.
Methods: The study is retrospective analysis of prospectively collected data of gall bladder cancer patients.
Results: In 288 gall bladder cancer patient's median age was 60 yrs. There were 219 females, 69 males (F:M=3.2:1). Median number of days from the onset of symptoms to presentation was 24.5 days. Majority of patients were stage IVB 162 (56.3%), least were stage I 3(1%). 192 (66.7%) patients received palliative treatment because of unresectable malignancy. 39 (13.5%) patients underwent noncurative surgical intervention. 57 (19.8%) patients underwent extended cholecystectomy. The median number of lymph nodes detected on histopathological examination was 4.5 (range 3-12). 21 patients (36.8%) had positive lymph nodes. Median follow up of all patients was 6 months (1-66 months). 27 (9.4%) patients survived till last date of follow up. Median survival time in groups undergoing extended cholecystectomy, noncurative surgery, chemotherapy alone was 12, 8 and 4 months respectively. The difference in median survival time between the groups was statistically significant, Log rank (Mantel-Cox) χ^2=109.78, p=0.00.
Conclusions: Carcinoma of the gall bladder predominately affects females. Majority of patients had delayed presentation, stage IVB. Extended cholecystectomy is the only effective treatment to achieve long term survival.

Keywords: Gallbladder cancer- Punjab- India, Extended cholecystectomy, Outcomes, Survival analysis

INTRODUCTION

Gall bladder carcinoma is the most common malignancy of biliary tract and one of the most aggressive gastrointestinal malignancies. Prognosis of gall bladder cancer remains poor with less than 5% survival in 5 year.[1] Various factors responsible for overall poor prognosis are: Lack of specific clinical features, advanced stage at the time of diagnosis and propensity of early dissemination.[2] Complete surgical resection remains the only potential curative treatment option for gall bladder cancer. Incidence of gall bladder cancer varies geographically with higher incidence in Latin America, Eastern Europe, Japan and Northern India. There are only few studies published on epidemiology of gall bladder cancer in Punjab (India) and very scanty literature is available on therapeutic intervention and subsequent follow up.[3,4] Aim of our study is to know the clinical aspects of disease in our patients of gall bladder cancer and to study the result and survival patterns after therapeutic interventions. Various aspects of gall bladder cancer such as clinical presentation, stage of malignancy at presentation, therapeutic intervention and outcome were studied and analysed.

METHODS

The study is retrospective analysis of prospectively collected data of gall bladder cancer patients managed in a surgical unit of a tertiary care institute. Inclusion criteria- only cases with histopathologically proven gall bladder cancer were included in the study. Exclusion criteria- cases with clinic-radiological suspicion of gall bladder cancer, but negative for malignancy on histopathology were excluded from the study. The study period in which data was collected was from June 2010 to May 2018. Data regarding age, gender, clinical features at the time of presentation, biochemical, radiological, pathological workup and details of management done was retrieved. Classification of gall bladder cancer was done as per American joint committee on cancer (AJCC) 7th edition. The duration of follow up was calculated from the date of admission to the date of last follow up or death. Patients who did not report for follow up were contacted by telephone. The case was declared a dropout in case of failure to trace patient. Outcome of all cases in terms of survival was noted. All statistical evaluations were performed using SPSS version 20.0. Kaplan Meir survival was used for survival analysis.

RESULTS

From July 2010 to May 2018, 334 patients with clinic-radiological suspicion of gall bladder cancer were managed in a surgical unit of tertiary health care centre, Punjab, India. Of these 334 patients, 30 patients were lost to follow up, 10 patients left the hospital without any treatment. In 6 patients histopathology was reported as xanthogranulomatous cholecystitis. These 46 patients were therefore excluded from the analysis. In the remaining 288 patients median age at time of presentation was 60yrs (range 28-79 yrs). There were 219 females and 69 males. Female to Male ratio was 3.2:1. Median number of days from the onset of symptoms to presentation was 24.5 days. Abdominal pain was the most common presenting symptom present in 249 (86.5%) patients. 99 patients (34.9%) were jaundiced at the time of presentation. Hepatomegaly and palpable gall bladder mass was present in 114 (39.6%) and 102 (35.4%) cases respectively. In 39 (13.5%) cases, gall bladder cancer was diagnosed incidentally. Associated gall stones were present in 198 (68.8%) patients. Distribution of patients as per AJCC 7th edition classification was as follows, stage I 3 (1%), stage II 18 (6.3%), stage IIIA 48 (16.7%), stage IIIB 24 (8.3%), stage IVA 33 (11.5%), stage IVB 162 (56.3%) (Table 1). 192 (66.7%) patients had unresectable disease, and were offered palliative treatment in form of percutaneous biliary drainage, stenting and chemotherapy. 39 (13.5%) patients underwent noncurative surgical intervention- staging laparoscopy 9, laparotomy 15, simple cholecystectomy 9 and palliative gastrojejunostomy in 6 cases. Definitive surgery was abandoned in these cases because either the disease was found to be metastatic or primary tumour was locally advanced requiring major hepatectomy or pancreaticoduodenectomy. 57 (19.8%) patients underwent definitive procedure i.e. Extended cholecystectomy. In definitive procedure group, extended cholecystectomy alone was done in 51 patients, extended cholecystectomy plus segmental resection of colon plus sleeve resection of duodenum in 6 patients (Table 2). The median number of lymph nodes detected on histopathological examination was 4.5 (range 3-12). 21 patients (36.8%) had positive lymph nodes on pathological examination with a median of 3 positive nodes per patient (range 1-6 positive nodes per patient). R0 resection status was achieved in all patients. Postoperative complications occurred in 7 (5.26%) patients. Surgical site infection was the most common complication-3 patients. Bile leak occurred in 2 patients, faecal fistula in 1 case and incisional hernia in 1 case. 30 day hospital mortality was in 1 (1.75%) patient secondary to bile leak, sepsis and multiorgan failure.

Table 1: TNM staging of the patients (n=288).

Stage	No of patients (%)
I	3 (1)
II	18 (6.3)
IIIA	48 (16.7)
IIIB	24 (8.3)
IVA	33 (11.5)
IVB	162 (56.3)

Table 2: Surgical procedures.

	Procedure	No of patients
	Simple cholecystectomy	9
	Staging laparoscopy	9
Non curative surgery	Laparotomy	15
	Palliative gastrojejunostomy	6
Definitive procedure	Extended cholecystectomy	51
	Extended cholecystectomy+ segmental colon resection+ duodenal sleeve resection	6

Follow up and survival

All patients were followed up regularly. Median follow up of all patients was 6 months (1-66 months). 27 (9.4%) patients survived till last date of follow up. 3 from stage I, 12 (stage II), 3 (stage IVA), 9 (stage IVB). Median survival time in Stage IIIA, IIIB, IVA and IVB was 7, 5.5, 6 and 4 months respectively (Figure 1). On analysis of survival pattern based on intervention, Median survival time in groups undergoing extended cholecystectomy, noncurative surgery, chemotherapy only was 12, 8 and 4 months respectively Table 2 and Figure 1. The difference in median survival time between the groups was statistically significant, Log rank (Mantel-Cox) χ^2=109.78, p=0.00.

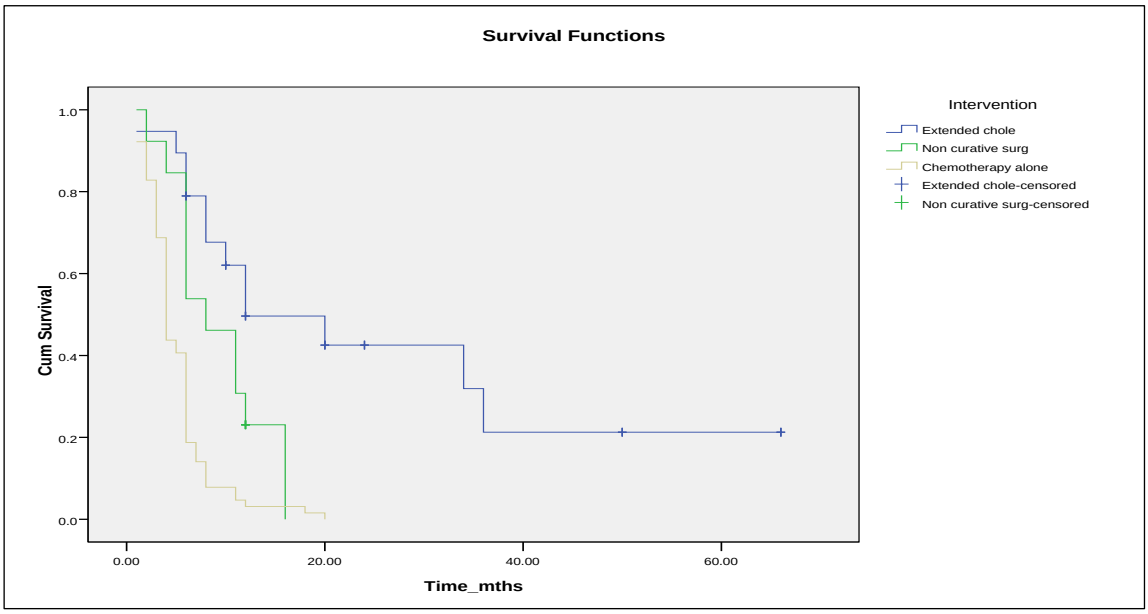

Figure 1: Stage wise survival.

DISCUSSION

Gall bladder cancer is the fifth most common gastrointestinal malignancy following colon, pancreas, stomach and oesophagus.[5] Murthy et al has reported increase in incidence of gall bladder cancer throughout India.[6] This increase in incidence rate was observed across all age groups. However an epidemiological study from Chandigarh revealed gall bladder cancer to be the third most common gastrointestinal malignancy with decreasing incidence rate.[3]

In our study median age at the time of presentation was 60 years (range 28-79). A clinco pathological study from East India reported mean age of 55 years.[7] Similarly results from other centres of India shows that disease predominately affects individuals in 5th decade.[5,8,9] In our present study results showed that gall bladder cancer is more common in females; female to male ratio was 3.2:1. These results were consistent with results of other studies in India.[5,7,8,10]

The presence of gall stones is a common factor implicated in pathogenesis of gall bladder cancer. In the current study gall stones are associated with gall bladder cancer in 198 (68.8%) patients. Pandey et al has reported 70% incidence of gall stones in gall bladder cancer.[5] An epidemiological study from east India has reported 86% incidence of gall stones in gall bladder cancer.[7] A study from Rajasthan reported 52.1% incidence of gall stones.[11] In contrast a study from southern India has shown that only 19% of gall bladder cancer patients have associated gall stones.[12]

Gall bladder cancer usually present with very nonspecific symptoms. There is usually considerable delay between the onset of symptoms and diagnosis of disease. In our experience there was median delay of 24.5 days between onset of symptoms and presentation; abdominal pain was the most common presenting symptom in our study 249 patients (86.5%). Jaundice was present in 99 patients (34.9%). Consistent results were reported from other studies.[7,9]

Incident of incidental gall bladder cancer is 25-41% of all the gall bladder cancers.[13] However in our series it is 13.5%.

Advanced stage at the time of diagnosis is one of the factors contributing to the poor prognosis. Early detection and extended cholecystectomy may result in better survival, however early detection continues to be low.[14,15] In our study only few patients 21 (7.3%) presented at early stage I & stage II disease. Similar experience was reported by other authors.[9,16,17] Majority of our patients 192 (66.7%) had unresectable disease at presentation. These patients were offered palliative care with stenting and chemotherapy. Only a small proportion of patients were eligible for definitive surgery 57 (19.8%); extended cholecystectomy 51, extended cholecystectomy plus segmental resection of colon plus duodenal sleeve resection in 6 patients. R0 resection status was achieved in all patients.

Carcinoma of the gall bladder is characterized by early lymph node involvement; overall 45-85% of patients with gall bladder cancer will have metastases in lymph nodes.[18,19] Lymph node involvement is important predictor of survival.[16,20,21] Median number of lymph nodes dissected in present study is 4.5 (range 3-12); whereas lymph node positivity was detected in 36.8% (21) of patients undergoing extended cholecystectomy

with a median of 3 positive nodes per patient. The issue of optimal number of lymph nodes required to accurately stage N status is debatable. Our policy is to do standard lymph node dissection comprising cystic, pericholedochal, hilar, proper hepatic artery, peri-portal, posteriosuperior pancreaticoduodenal and common hepatic artery lymph nodes. The AJCC 6th edition states that minimum 3 lymph nodes should be resected to accurately stage disease; however 7th edition is silent about the issue. Korean association of hepatobiliary and pancreatic surgery guidelines propose that more than three lymph nodes should be retrieved for histopathologic examination of resected gall bladder cancer specimen.[22] Ito eta al has recommended minimum 6 lymph nodes removal for accurate staging.[23] However Tewari et al in an analysis of radical cholecystectomy patients has shown that total lymph node count (median=3) remains poor despite standard lymph node dissection.[24]

The median overall survival in our series was 6 months; it was poor because majority of our patients presented at advanced stage. 27 (9.4%) survived till last date of follow up; range (1-66 months). Median survival time in Stage IIIA, IIIB, IVA and IVB was 7, 5.5, 6 and 4 months respectively. Goyal et al has shown survival rate for stage II, stage IIIa, stage IIIb, stage IVa and stage IVb was >12, 10, 8.75, 4.5 and 1.5 months respectively.[11] In a retrospective analysis of 99 gall bladder cases; Pandey et al has shown similar stage wise survival. On analysis of survival pattern based on intervention, median survival time in groups undergoing extended cholecystectomy, noncurative surgery, chemotherapy alone was 12, 8 and 4 months respectively.[5] The difference in median survival time between the groups was statistically significant, Log rank (Mantel-Cox) χ^2=109.78, p=0.00. Batra et al in a retrospective analysis of gall bladder cancer patients has shown median survival of 12 months after radical surgery which was significantly better than survival range of 1 to 3 months after non radical surgery.[9] Similarly Pradeep et al has shown that median survival of 16.3 months after resection surgery was significantly better than survival of 4.8 months and 1.6 months after biliary and or gastric bypass surgery and laparotomy alone respectively.[16]

The role of adjuvant therapy after curative surgery remains to be defined. Patkar et al in analysis of 400 gall bladder cancer cases has suggested that addition of perioperative systemic therapy to surgery may improve outcome in stage II /III patients.[25] Two studies have shown that addition of adjuvant radiotherapy to chemotherapy improves survival as compared to adjuvant chemotherapy alone.[26,27] Data is sparse regarding role of Neoadjuvant therapy in locally advanced carcinoma gall bladder. However two recent studies; one from Tata memorial, Mumbai and another from SGPGI, Lucknow has shown that use of Neoadjuvant Chemoradiotherapy benefitted the locally advanced carcinoma gall bladder patients in facilitating the resectability rate with a chance of improved survival.[28,29]

With the current approach of extended cholecystectomy and chemotherapy regimen it is unlikely that further improvement in survival will be achieved. Development of targeted agents based on understanding of molecular biology has the potential for further improvement in survival.

CONCLUSION

In conclusion carcinoma of the gall bladder predominately affects females. Majority of patients had delayed presentation, stage IVB. Extended cholecystectomy is the only effective treatment to achieve long term survival.

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