

Potential for adjuvant treatment after radical resection in carcinoma gallbladder: A tertiary care experience from India

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ABSTRACT

Context: Gallbladder cancer represents the most common among the biliary tree cancers. Complete surgical resection offers the best chance for cure. Adjuvant chemotherapy and radiotherapy have increasing role in adjuvant management of carcinoma gall bladder, particularly in subgroup patients with high risk features. **Aims:** To analyze and identify the risk factors for role of adjuvant chemoradiotherapy in resectable patients of carcinoma gallbladder. **Materials and Methods:** The study designed as retrospective analysis of 40 postoperative patients of carcinoma gallbladder treated in our institute from 2008 to 2011. Patients treated with curative intent were included in this analysis. Clinical characteristic and treatment in form of surgery, radiotherapy, and chemotherapy were evaluated. For statistical analysis, data was arranged using SPSS 19 version. Descriptive studies were done for all parameters and Kaplan-Meier analysis used for survival analysis. $P < 0.05$ is considered as statically significant. **Results:** Forty patients were available for final analysis. Median age of patients was 51 years there were 10 male and 30 female patients. Eleven patients received only adjuvant radiotherapy, 16 patients received adjuvant chemotherapy, and 13 patients received both chemotherapy and radiotherapy. At end of treatment, 85% patients had no evidence of disease and 15% had recurrence. Patients on combined chemotherapy and radiotherapy had better 2-year disease free survival (DFS). Liver infiltration by tumor was found to be a bad prognostic factor with DFS at 1-year of 0.8 vs. 0.5 patients with no liver infiltration ($P = 0.06$). **Conclusion:** The present analysis reveals better overall survival in patients who received chemotherapy and radiation rather than single modality treatment. Liver infiltration and adequate lymph node dissection have been found to be two important prognostic factors for considering this subgroup of patients for adjuvant chemotherapy as well as radiotherapy.

Key words: Adjuvant, cancer gall bladder, chemoradiotherapy, chemotherapy, radiotherapy

INTRODUCTION

Gallbladder carcinoma is showing an increase in incidence in the Indian subcontinent. It is one of malignancy associated with a poor survival. Five-year survival rates of 5% or less are seen in majority of patients present with unresectable or metastatic disease.^[1] Resection remains the only potentially curative treatment for patients with

gallbladder carcinoma. Approximately 10-35% of patients are candidates for resection at presentation.^[2] For patients undergoing resection, survival is associated with extent of tumor invasion in the gallbladder wall and the presence or absence of nodal involvement. When the disease is confined to gallbladder wall, the reported 5-year survival rate ranges from 10 to 30%. With tumor invasion to the gallbladder serosa, local lymph nodes, or adjacent liver; 5-year survival rates drop to 5%.^[3,4] For patients undergoing resection with curative intent, locoregional failure is common and a major cause of mortality.^[5] Adjuvant therapy is rational in the light of the patterns of failure and poor survival. However, the use of radiation therapy and chemotherapy in resected patients remains poorly defined. Adjuvant treatment are indicated in subgroup of patients presenting with high risk feature like lymph node positive, margin positive, advance T-stage, and liver and adjacent structure infiltration. This

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study reports a single institution experience of using adjuvant radiation therapy with or without chemotherapy after resection in patients with gallbladder carcinoma.

MATERIALS AND METHODS

Forty postoperative patients of adenocarcinoma of the gall bladder were evaluated [Table 1]. In this retrospective analysis of treated patients in our institute between 2008 and 2011, all patients underwent curative surgery with simple cholecystectomy or with radical cholecystectomy. Radical resection consists of removal of the gallbladder and the gallbladder bed with adjacent hepatic resection and or formal lymphadenectomy. In patients presenting high risk features, on postop histopathology, adjuvant chemotherapy, and/or radiotherapy was given. For postop radiotherapy, patients planned using 3D conformal radiotherapy. For radiotherapy planning, image was acquired using dedicated CT simulator with a slice thickness of 2.5 mm, then image transfer to eclipse planning system. Clinical target volume includes the tumor bed and locoregional lymph nodes (portahepatis, pericholedochal, celiac, and pancreaticoduodenal). Planning target volume (PTV) generated by giving margin of 0.5 cm. Dose to PTV was 45 Gy in 25 fraction; 1.8 per fraction daily, 5 days a week; radiation portal included anterior/posterior, anterior/posterior/posterior/anterior, anterior/posterior/posterior/anterior

with opposed lateral fields, and anterior/posterior with opposed lateral fields. Beam energies included 6 and 15 MV photons, patients underwent three-dimensional treatment planning. Adjuvant chemotherapy using gemcitabine (1.2 gm/m²) and oxaliplatin (80 mg/m²) repeated twice weekly; gemcitabine (1.2 mg/m²) d1 and d15 and cisplatin (70 mg/m²) d1 repeated thrice weekly; and gemcitabine (1.2 mg/m²) d1 and d15 and carboplatin (AUC 6) d1 repeated thrice weekly. Total six cycle was given. Patients were followed-up every 3 months for physical examination and radiological examination was included as it was clinically indicated. Response evaluation was done using response evaluation criteria in solid tumors (RECIST criteria) version 1.1. For statistical analysis, data was arranged using SPSS 19 versions. Descriptive studies were done for parameter, survival, disease free survival (DFS), and local control rates for the entire cohort. The logrank test was used to analyze prognostic factors for the entire cohort^[6] and Kaplan-Meier analysis used for survival analysis. *P* < 0.05 is considered as statically significant.

RESULTS

Patient characteristics are summarized in Table 1. Median age of patients was 51 years there were ten male and 30 female patients. Stage-wise distribution showed stage I, II, III, patients to be 15, 50, and 35% respectively. A total of 25% patients had undergone simple cholecystectomy and 75% underwent extended cholecystectomy. Eleven patients received only adjuvant radiotherapy, 16 patients received adjuvant chemotherapy, and 13 patients receive both chemotherapy and radiotherapy. At end of treatment, there were no evidence of disease (85%) and 15% had recurrence. Patients on combined chemotherapy and radiotherapy had better 2-year DFS compared to those who did not receive single modality treatment with a 2-year DFS of 60% [Figure 2]. Also at 2 years, patients receiving adjuvant chemotherapy had better DFS compared to those who did not receive chemotherapy, that is, DFS 70 vs. 50% [Figure 1]. Liver infiltration in surgical specimen was found to be a bad prognostic factor with DFS at 1 year of 80 vs. 50% in those with no liver infiltration [Figure 3]. Extended cholecystectomy had better survival than simple cholecystectomy with 40% 2 years DFS. Age, sex, and chemotherapy regime were not significant prognostic factor in this present analysis.

DISCUSSION

Carcinoma of the gallbladder is an uncommon but lethal malignancy. Collective tumor registry data of over 2,500 cases in the United States between 1985 and 1995 showed 5-year survivals of 15, 5, and 1% for stages II, III, and IV patients, respectively. Approximately 70% of

Table 1: Patients characteristics

Characteristics	RT only	RT+CCT	CCT only
Age			
<50 years	2	3	6
≥50 years	9	10	10
Sex			
Male	4	4	6
Female	7	9	10
KPS			
100 to>80	10	12	12
80-70	1	1	4
Stage			
I	0	4	2
II	5	6	9
III	6	3	5
IV	0	0	0
Charlson index			
0	8	11	12
1	3	2	4
2	0	0	0
3	0	0	0
Surgery			
Cholecystectomy	5	3	2
Extended cholecystectomy	6	10	14
HB			
>10	5	8	12
≤10	6	5	4
Bilirubin			
<1	10	10	12
≥1 to <1.5	1	3	4
Creatinine			
≤1	9	8	14
>1 to <1.5	2	5	2

RT: Radiotherapy, CCT: Chemotherapy, KPS: Karnofsky performance status, HB: Hemoglobin

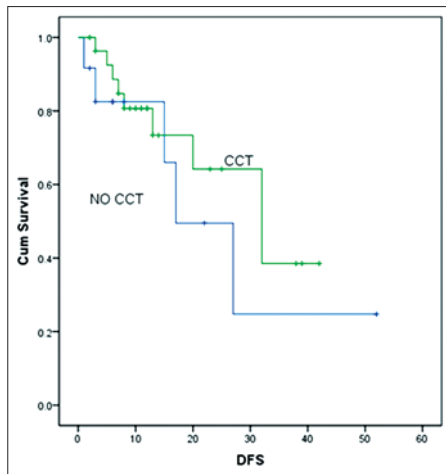


Figure 1: Kaplan-Meier estimation of survival of patients who received chemotherapy had better survival than who did not receive chemotherapy

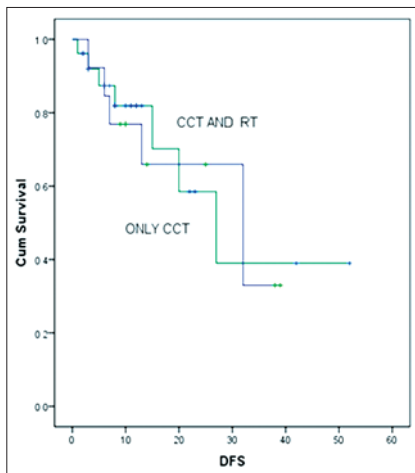


Figure 2: Kaplan-Meier estimation of survival of patients who received both chemotherapy (CCT) and radiotherapy (RT) had better survival than RT and CCT alone

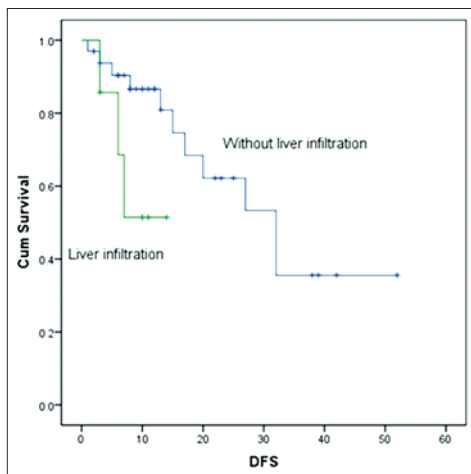


Figure 3: Kaplan-Meier estimation of survival of patients in whom liver infiltration in surgical specimen was found to be a bad prognostic factor

patients present with stage III or stage IV disease.^[3] In tumors confined to the gallbladder wall, 5-year survival rates after

resection only range from 10 to 30%.^[1,7-9] Most patients with gallbladder carcinoma present with more advanced disease (i.e., adjacent organ or metastatic involvement). Local invasion into surrounding tissue and liver is facilitated by thin muscular gallbladder wall as well as continuum of the perimuscular connective tissue with the interlobular connective tissue of the liver.^[10] Hepatic infiltration by gallbladder cancer has been observed in 60-70% of patients on collective review and autopsy series.^[1,11] Lymphatic spread by gallbladder cancer is also common. Overall regional nodal involvement has been reported in 40-80% of patients.^[1,11] For patients with T2 lesions (confined to the gallbladder wall), the incidence of nodal metastases ranges from 40 to 62%.^[12-15] When disease invades the covering serosa or adjacent organs, nodal metastases rates rise to 70-80%.^[14,15] The primary draining nodal groups are along the cystic and common bile ducts. Retrograde spread to hilar nodes can occur, particularly in more advanced disease.^[16] Secondary spread occurs to the pancreaticoduodenal nodes and later to the periaortic nodes, both of which usually go undissected, even in more radical procedures. With either lymph node involvement or hepatic infiltration (stage III/IV), prognosis is poor, with reported 5-year survivals of 5% or less.^[7] Inadvertent, simple cholecystectomy is the most common surgical procedure for resection of primary carcinoma of the gallbladder,^[3] as the diagnosis is not usually suspected preoperatively. Even in early stage disease, positive margins after resection are common, given that the plane of dissection at simple cholecystectomy is subserosal.^[17] Therefore, many hepatobiliary surgeons advocate radical resection or re-resection (wedge resection of the gallbladder bed/hepatic resection, excision of regional nodes) in the treatment of stage T2 or higher disease, although less than 10% of patients undergo such procedures.^[3,18,19] Although limited by small patient numbers, our data suggests radical resection of gallbladder carcinoma affords a better survival (5-year survival 51 vs. 15%, $P = 0.10$). Differing surgical series have also reported that survival may be improved in patients with stage T2N0 or higher disease by more radical operations.^[19-23] Nonetheless, the role of more radical resection versus simple cholecystectomy remains controversial. Patients with microscopically positive margins after gross total resection have a statistically worse outcome compared with those with negative margins. Margin negative resection had a superior survival vs. patients with positive margins.^[24] However, we consider achieving margin negative resection an important end point. The role of persistent locoregional disease contributing to the development of distant metastases is controversial, although in other disease sites, uncontrolled local disease appears to be a source of distant metastases.^[25] Reports that describe patterns of failure after surgery are limited. Available data suggests that locoregional recurrence is common and ultimately leads to death, usually from

complications of biliary obstruction and liver failure. Literature review indicates that local recurrence occurs in up to 86% of patients after cholecystectomy. In long-term survivors after surgery, local recurrence rates remain high, even beyond 5 years.^[26-28] A likely explanation for this finding is that occult nodal involvement is common and localized invasion of the liver is not recognized and resected. This high incidence of residual microscopic disease has been reported in autopsy series.^[29] Even in patients treated with radical cholecystectomy locoregional recurrence has been reported to be as high as 75%.^[26] A recent large study from Memorial Sloan-Kettering Cancer Center showed that in patients who undergo radical resection of gallbladder cancer, 45% of relapse occurs locoregionally.

In many of these series, local failure rates are likely underestimated. In our series, 7 of 20 patients (35%) experienced locoregional failure, despite adjuvant therapy. Given the patterns of failure and poor overall prognosis in gallbladder cancer, consideration of adjuvant treatments is appropriate. Only an estimated 20% of patients receive radiotherapy or chemotherapy after resection, and fewer than 10% of all presenting patients undergo surgery, radiotherapy, and chemotherapy.^[3] Therefore, reports that described the use of adjuvant radiochemotherapy in the setting of resected gallbladder carcinoma are limited. Recent series have suggested that locoregional control and possibly ultimate outcome can be improved by the use of adjuvant therapy. Kresl *et al.*,^[24] reported on 21 patient who underwent resection followed by adjuvant chemoradiotherapy with 5-fluorouracil (5-FU). They reported a 5-year survival rate of 33% and a 5-year survival of 64% in patients treated with margin negative resection followed by adjuvant chemoradiotherapy in a cohort that consisted primarily of stage III/IV patients.^[24] A large National Cancer Database collective report has suggested that patients who undergo trimodality therapy may have a superior survival when compared with patients who undergo surgery alone.^[3] Advancement in radiation delivery technique like intensity modulated radiation therapy, image guided radiation therapy, etc., and with availability of better chemotherapy drug; the practice of adjuvant chemotherapy will likely benefit patients with high risk features.

CONCLUSION

In summary, carcinoma of the gallbladder remains a lethal malignancy. In the minority of patients that are resectable for cure, locoregional recurrence remains a major cause of morbidity and mortality. Our survival and local control rates are similar to those reported in the limited radiotherapy literature and are generally better than those reported with surgery alone in patients with stage III/IV disease. Although patient selection for extended surgery

may have biased our results, our patients tended to benefit from more radical resections when compared with simple cholecystectomy patients. Our series suggests that an approach of radical resection followed by external beam radiotherapy or chemotherapy and or both. Our data also highlight the need for prospective clinical trials in this disease, where improvements in treatment are still urgently needed. In present analysis liver infiltration and inadequate lymph node dissection were identified as bad prognostic factors and probably need both chemotherapy as well as radiotherapy for better survival outcomes.

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