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Original Article

Oncology Section

Impact of Adjuvant Therapy on Survival in Curatively Resected Gallbladder Carcinoma

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ABSTRACT

Background: Gallbladder carcinoma (GBC) has the propensity to fail at loco-regional (LR) and distant sites despite aggressive radical surgery. Adjuvant therapy in the form of radiotherapy (RT), systemic chemotherapy (CT) and chemoradiation (CRT) is the usual practice. Due to rarity of this disease, there is limited evidence to suggest the type of adjuvant treatment which should be offered to the patients.

Aim: The study was conducted to evaluate the impact of adjuvant treatment on curatively resected GBC patients.

Settings and Design: Histological proven patients of GBC registered between June, 2008 and July, 2014 were identified from our hospital database and retrospective analysis was done.

Materials and Methods: Patients of GBC who had curative resection followed by adjuvant treatment as RT alone, CT alone or CRT were included in the study.

Statistical Analysis: Adverse prognostic factors and the effect of adjuvant treatment on overall survival (OS) and disease free survival (DFS) were evaluated using Cox Regression Method and Kaplan Meier plot.

Results: We identified 33 patients of which 23 were Stage I or II disease (Early disease) and the remaining 10 were Stage III or IV disease (Advanced disease). All except one patient had adenocarcinoma. A total of 5 patients were treated with RT alone while 16 patients received CT alone. The remaining 12 patients were treated with CRT. Median follow-up period was 8.5 months. At analysis 4 were alive while the remaining 29 were dead due to disease. With regard to "Early disease" patients who had RT alone, CT alone and CRT, the median OS was 22.3, 10.3 and 15.2 months respectively (p = .440). Cohort of patients with "Advanced disease" who were treated with CT alone and CRT the median OS was 7.5 and 7.0 months respectively (p = .643). On multivariate analysis none of the prognostic factors had an adverse impact on survival.

Conclusion: The impact of adjuvant treatment in the form of RT, CT or CRT after curative resection in GBC patients was seen in terms of improved survival but was not statistically significant.

Keywords: Chemoradiation, Chemotherapy, Gallbladder cancer, Radiotherapy

INTRODUCTION

Carcinoma of the gallbladder (GBC) is an extremely fatal disease with a very dismal survival outcome despite aggressive surgical resection. The reported 5-year survival rates are as follows: stage I, 33-100%; stage II, 9-33%; stage III, 0-25%; and stage IV, 0-5% [1,2].

Due to multiple vague symptoms mimicking cholecystitis, it is diagnosed incidentally following laparoscopic simple cholecystectomy in 1-2% of cases. For very early stage disease wherein the depth of invasion is short of muscularis propia, simple cholecystectomy is adequate. However, if the tumour has invaded the muscularis propria (T2 and beyond), a radical cholecystectomy involving removal of gallbladder along with at least 2 cm of gallbladder bed and regional lymphadenectomy should be attempted.

Even after an optimal surgery, GBC is known to have a very high risk of loco-regional (LR) failure and distant metastases. Therefore, adjuvant radiotherapy (RT) to the surgical bed and regional lymphatic seems a very rational and attractive therapeutic option. Unfortunately there is no substantial evidence which suggests adjuvant RT improves LR control or survival outcomes. Owing to the lack of randomized controlled trials, no standard of chemotherapy (CT) exists in the treatment of GBC. Based on retrospective analysis and phase II trials, gemcitabine combined with platinum compounds represents the current standard of CT in GBC.

The aim of our study was to evaluate the role of adjuvant treatment following curative surgery in GBC patients and to look for factors which affect the survival outcomes.

MATERIALS AND METHODS

We searched our patients' database that had been registered in our outpatient department between June, 2008 and July, 2014. We identified those who had histological proven gallbladder cancer for which they had curative surgery. We chose to study only those patients who had received adjuvant treatment in the form of RT or CT or chemoradiation (CRT). We excluded patients who had metastatic disease at presentation. It was imperative that the patients' records had surgical and histopathological details. The medical records of these 33 patients were examined in detail for patient, tumour and treatment characteristics, patterns of failure and survival.

Patients had computerized tomography based simulation and planning was done on "ASHA" treatment planning system. Patients were treated on Tele-cobalt unit using wedge pair antero-lateral fields with conventional fractionation schedule. Most of the patients received 2-3 cycles of CT before RT and the remaining 3-4 cycles were given after completion of RT. Patients were treated with either gemcitabine and platinum combination or 5-FU & LV regime. Patients were treated with RT, CT or CRT.

Ethics Committee approval

This being a retrospective study, approval of ethics committee was not required.

STATISTICAL ANALYSIS

Primary end points were disease-free survival (DFS) and overall survival (OS). Survival was calculated from the date of surgery. DFS and OS were estimated using Kaplan & Meier survival plot. A comparison of survival curves was done using log-rank test. Log-rank tests were used in the univariate analysis of prognostic factors, and multivariate analysis was performed using Cox regression model. A p-value of 0.05 was considered statistically significant. Data analysis was done using SPSS 16 software.

RESULTS

We could identify 33 patients of GBC who could meet the criteria of inclusion into the study. Patient and tumour characteristics are presented in [Table/Fig-1]. Median patient age was 55 years (range 28-73). Most of the patients were female (n = 29; 87.9%). One patient suffered with small cell carcinoma while the rest had

adenocarcinoma (n = 32; 97%). Most patients had intermediate to poorly differentiated tumours on histology (n = 17; 51.5%). About half the patients in both the groups had GB calculus. We grouped Stage I &II patients into "Early disease" (n =23) while stage III & IV were grouped as "Advanced disease" (n = 10). Treatment profile of Early and Advanced disease is presented in [Table/Fig-2].

It was observed that most of the patients underwent open radical cholecystectomy (n = 29; 87.9%) while the rest had laparoscopic simple cholecystectomy (n = 4; 12.1%). Only one patient had an involved resection margin. RT was offered to almost half of the cohort of patients (n= 17; 51.5%). Most of patients received CT (n = 28; 84.8%). Gemcitabine based CT was used in most of the patients (n = 22; 78.6%). The median CT cycle was six. The majority of the patients were treated with either RT or CT (n = 21; 63.6%) while the remaining received combined treatment with CRT (n = 12; 36.4%). The median RT dose was 45 Gy in 25 fractions. One patient could not complete the planned dose of RT and had to be stopped after 10 Gy due to poor RT tolerance.

Characteristics	Value
Age (years) Median Range	 55 28-73
Female	29 (87.9)
Gallbladder calculus Present	 17 (51.5)
Histologic findings Adenocarcinoma Small cell carcinoma	 32 (97) 1 (3)
Grade of tumour WD MD PD Unknown	 12 (36.4) 11 (33.3) 6 (18.2) 4 (12.1)
Pathological stage I II IIIA IIIB IVB	 12 (36.4) 11 (33.3) 8 (24.2) 1 (3) 1 (3)
Early disease Advanced disease	23 (69.7) 10 (30.3)
Lymphovascular invasion Present	 5 (15.1)
Perineural invasion Present	 3 (9.1)
Resection margin Positive	 1 (3)

[Table/Fig-1]: Patient characteristics (n = 33)

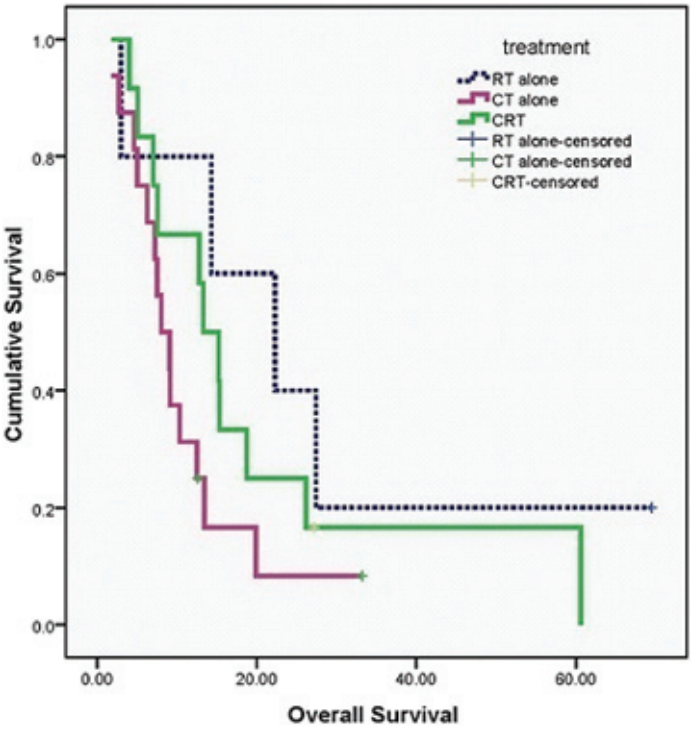
Treatment type	Early disease (n = 23)	Advanced disease (n = 10)
Surgery type Laparoscopic cholecystectomy Open cholecystectomy	 4 (17.4) 19 (82.6)	 0 10 (100)
RT alone	5 (21.7)	0
CT alone	9 (39.1)	7 (70)
CRT	9 (39.1)	3 (30)
CT regime Gemcitabine based Non-gemcitabine based	 13 (56.5) 5 (21.7)	 9 (90) 1 (10)

[Table/Fig-2]: Treatment characteristics

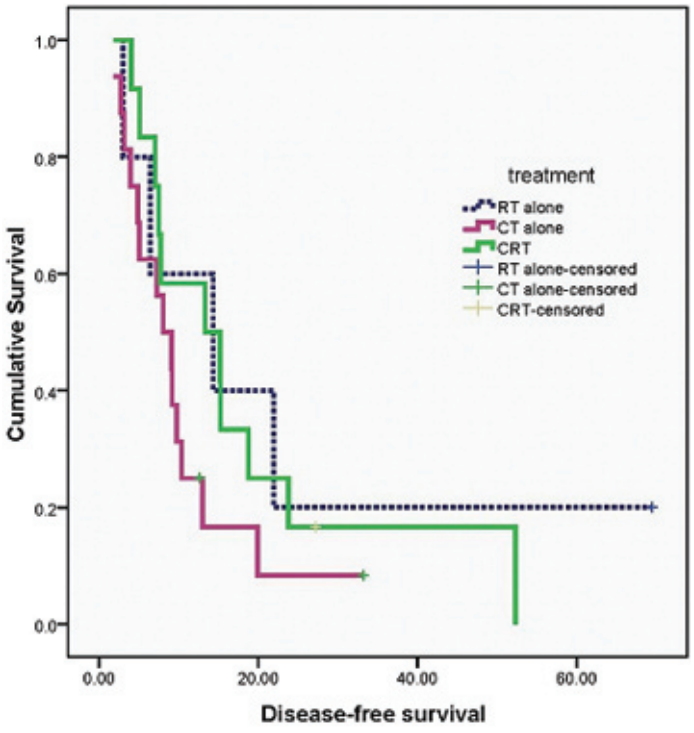
Analysis was done on 01.03.2015. The median follow-up was 8.5 months in all patients and 28.3 months in survivors. At analysis 4 patients were alive while the remaining 29 were dead. The cause of death was disease specific. The median survival time for the entire cohort of patients was 12.5 months. The OS at 1, 2 and 3 years was 52%, 20% and 12%.

Recurrence was observed in 18 patients. The first site of relapse was LR in 14 patients and distant in 4. Of the 5 patients who were treated with RT alone, 2 had failure (1 distant, 1 LR). Sixteen patients were treated with CT alone of which 8 relapsed (1 distant, 7 LR). Out of 12 patients who were treated with CRT 8 had failure (2 distant, 6 LR). The median OS of patients who were treated with RT alone, CT alone and CRT was 22.3, 8.0 and 13.3 months respectively (p = 0.133) [Table/Fig-3]. The median DFS of patients who were treated with RT alone, CT alone and CRT was 14.3, 8.0 and 13.3 months respectively (p = 0.284) [Table/Fig-4].

Cumulative median OS for "Early disease" and "Advanced disease" was 14.3 and 7.2 months respectively (p = 0.06). With regard to "Early disease" patients who had RT alone, CT alone and CRT the median OS was 22.3, 10.3 and 15.2 months respectively (p = 0.440) [Table/Fig-5]. Cohort of patients with "Advanced disease" who were treated with CT alone and CRT the median OS was 7.5 and 7.0 months respectively (p = 0.643) [Table/Fig-6].



[Table/Fig-3]: Kaplan Meier plot for OS comparing RT vs. CT vs. CRT



[Table/Fig-4]: Kaplan Meier plot for DFS comparing RT vs. CT vs. CRT

Median survival for patients who underwent laparoscopic cholecystectomy for asymptomatic GBC was 22.3 months while it was 10.3 months in those who had open cholecystectomy for symptomatic GBC (p = .076).

The results of the univariate analysis of prognostic factors for OS are listed in [Table/Fig-7]. No adverse prognostic factors for OS were found statistically significant on univariate analysis, but trends were noted for RT vs. no RT, "Early disease" vs. "Advanced" disease and Laparoscopic surgery vs. open cholecystectomy. Factors showing trends toward statistical significance on univariate analysis were incorporated into the multivariate analysis for OS [Table/Fig-8]. None of these factors significantly affected OS.

Factor	Hazard ratio (95% CI)	p
Age (< 50 vs. >50 years)	0.753 (0.35-1.60)	.462
Gender (female vs. male)	1.068 (0.32-3.57)	.915
Stone (present vs. absent)	1.019 (.49-2.14)	.961
Early disease vs. advanced disease	0.458 (0.20-1.06)	.068
Laparoscopic cholecystectomy vs. Open cholecystectomy	0.286 (0.07-1.24)	.094
RT vs. No RT	0.489 (0.23-1.06)	.069
CT vs. No CT	0.469 (0.16-1.38)	.169
Gemcitabine based CT vs. Non-gemcitabine based CT	1.712 (0.63-4.70)	.295

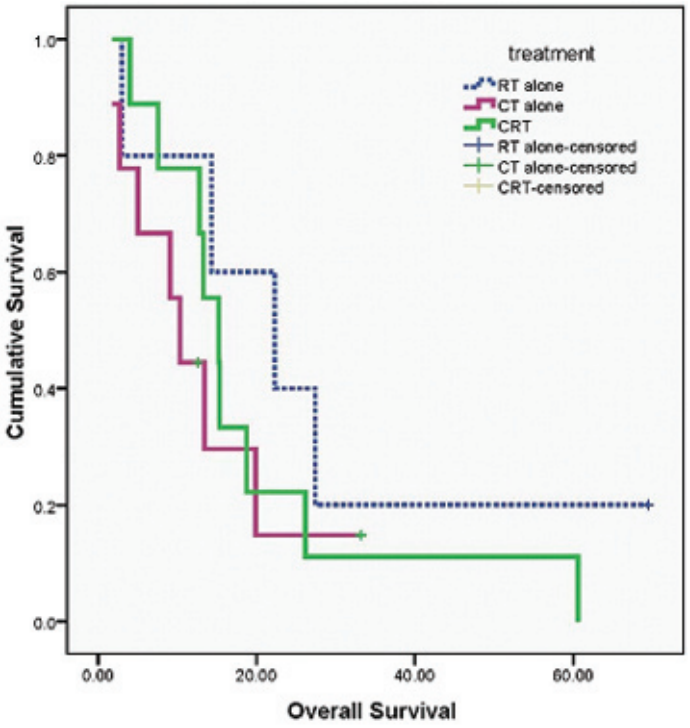
[Table/Fig-7]: Univariate analysis of prognostic factors for overall survival

Factor	Hazard ratio (95% CI)	p
Laparoscopic cholecystectomy vs. Open cholecystectomy	0.395 (0.09-1.82)	.233
RT done vs. No RT	0.626 (0.28-1.40)	.254
Early disease vs. advanced disease	0.563(0.24-1.33)	.189

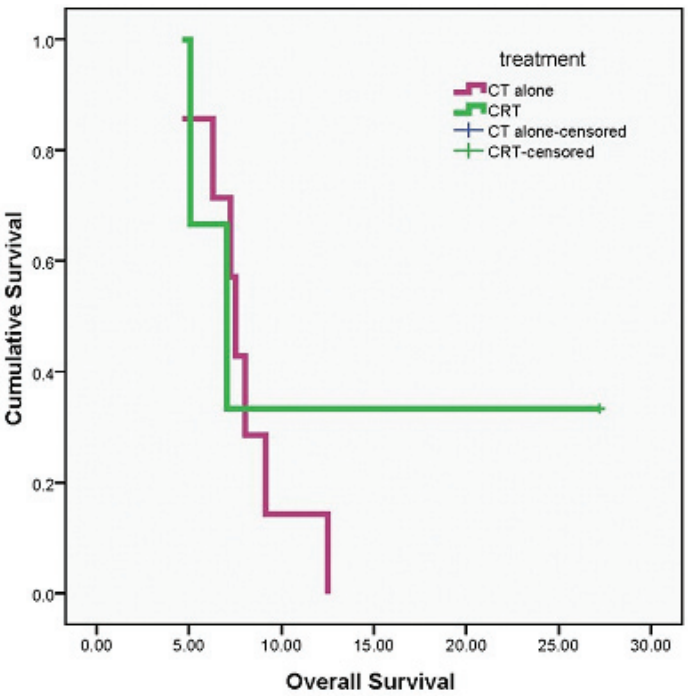
[Table/Fig-8]: Multivariate analysis of prognostic factors for overall survival

DISCUSSION

GBC has a potential for LR and distant relapse even after a curative surgery. Local invasion into adjoining organs is high due to thin muscular layer of gallbladder. For patients with T2 lesions, the incidence of nodal metastases ranges from 40-60%. When GBC involves the covering serosa or adjacent organs, nodal metastases rates is 70-80%. The primary lymph nodes are along the cystic and common bile duct. Secondary spread occurs to the pancreatico-duodenal nodes and later to the peri-aortic nodes [3].



[Table/Fig-5]: Kaplan Meier plot for OS in early disease comparing RT vs. CT vs. CRT



[Table/Fig-6]: Kaplan Meier plot for OS in advance disease comparing CT vs. CRT

The survival of GBC patients correlates with the extent of tumour penetration through the gallbladder wall as well as nodal involvement. Overall survival at 5 years for all stages is about 5% [4]. The median survival for suspected GBC is 9.2 months, and for incidental carcinomas is 26.5 months [5].

Based on the pattern of failure it seems very rational and lucrative to treat GBC patients with RT to the tumour bed and draining lymph node regions. CT, when added, probably reduces the risk of distant spread. CT, when given concurrently with RT, acts as a radio-sensitizing agent and also tends to take care of subclinical metastatic disease. However, due to rarity of GBC incidence we do not have robust clinical data to support the use of adjuvant RT, CT or CRT in GBC.

In a recent retrospective analysis of database of Surveillance, Epidemiology, and End Results, by Omar Hyder et al., [6] 5011 patients with GBC who underwent surgical resection were identified. Most of the patients (75%) had T2 disease; T3 and T4 disease were found in 11.4% and 13.6%% respectively. A total of 899 patients (17.9%) received RT whereas 4,112 patients did not. The 1-year survival of patients who underwent surgery plus RT was 68.2% versus 58.0% for patients who underwent surgery alone (p = .03). Patients with node positive and those with moderate-to-poorly differentiated tumours benefited the most from RT.

Brian et al., had done retrospective analysis of 22 patients of GBC who had radical surgical resection followed by RT [7]. Eighteen patients received concurrent 5-FU. The 5-year actuarial OS, DFS were 37% and 33%. Median survival of all patients was 1.9 years. The study suggested that an approach of radical resection followed by RT with concurrent 5-FU in patients with locally advanced, non-metastatic GBC may improve ultimate outcome.

Douglas et al., had retrospectively evaluated the role of adjuvant CRT in early stage (I & II,) GBC who had R0 resection [8]. Of the total 73 patients, 25 received adjuvant CRT while the rest had no adjuvant therapy. Patients who were treated with adjuvant CRT had a median OS of 4.8 years. Median OS in the surgery alone arm was 4.2 years. The difference in OS was not significant. The authors noted that adjuvant CRT had a significant impact on OS when T and N stage where taken into account.

Adjuvant CRT was compared with RT in patients of GBC who had curative surgery in a recently published retrospective trial by Bettina et al., [9]. Of the 46 patients, 12 were treated with adjuvant RT while in the remaining concurrent 4 weekly continuous infusion of 5-FU was given. Three- and 5-year OS were 57% and 51% respectively.

Kresl et al., reported on 21 patients who underwent resection followed by concurrent chemoradiation with 5-FU [10]. Intraoperative RT was used along with external beam RT. The 5-year survival rate of patients with Stage I-III disease was 65% vs. 0% for those with Stage IV disease (p = 0.02).

A retrospective trial was reported from MSKCC [11] wherein 435 patients of GBC were identified of which 123 had curative resection. Of the 123 patients 8 had adjuvant CT, 8 had CRT and 8 were treated with CRT and CT. Median survival for the entire cohort of 435 patients was 10.3 months while it was 23.4 months for those who had adjuvant treatment. The authors had concluded that the number of patients who received adjuvant therapy was small with marked heterogeneity in clinical and therapeutic details due to which any definite conclusion could not be drawn.

Kim et al., had reported a retrospective study of 166 patients who had radical cholecystectomy with R0 resection [12]. Almost 25% of patients received some form of adjuvant treatment. When appropriate surgery was done, neither adjuvant RT, CT or CRT had any impact on DFS. The commonest site for tumour recurrence was regional lymph nodes. This study suggested that rather than advocating for patients with GBC to receive adjuvant treatment to improve survival, it was important for patients to have appropriate radical surgery.

Comparisons of similar trials dealing with curative surgery followed by adjuvant treatment have been illustrated in [Table/Fig-9]. Most of our patients had stage I & II disease. Every patient in our cohort underwent curative surgery. All patients had adjuvant treatment in the form of RT alone, CT alone or CRT. None of the patients in the advanced disease group were treated with RT alone. There was trend towards an increased survival in patients with early disease vs. advanced disease. Similarly, survival was better in those who had asymptomatic disease compared to symptomatic GBC but the difference was not significant. Early disease patients who were treated with RT alone compared to CT alone or CRT had improved OS but the difference was not statistically significant. There was marginal increased survival in patients who were treated with CT alone vs. CRT in patients with "Advanced disease". Overall, the impact of adjuvant treatment in the form of RT alone, CT alone or CRT in patients of GBC who had curative surgery was not observed. The outcome could have been affected due to several fallacies of the study.

STUDY	treatment	outcome
Omar Hyder et al., [6] (all stages)	Curative surgery followed by RT Curative surgery alone	1-yr OS : 68.2% 1-yr OS : 58.0%
Douglas et al., [8] (stage I & II)	R0 resection followed by CRT RO resection alone	Median OS 4.8 years Median OS 4.2 years
Bettina et al., [9] (all stages)	R0 resection followed by RT R0 resection followed by CRT	3-yr OS: 57% 5-yr OS: 51%
Kresl et al., [10] (all stages)	Surgery followed by CRT	Stage I-III: 5-yr OS: 65% Stage IV: 5-yr OS: 0%
Duffy et al., [11]	Curative surgery alone Curative surgery followed by adjuvant RT, CT or CRT	Cumulative median OS: 10.3 months Median OS for those who had adjuvant treatment: 23.4 months
Present study	Curative surgery followed by RT, CT or CRT	Early stage: 1-yr OS: 65% Advanced stage: 1-yr OS: 20%

[Table/Fig-9]: Comparison with recent trials of curative resection followed by adjuvant treatment.

The most important caveat was its retrospective nature. The database could not explain the basis on which a particular adjuvant treatment was used for a certain patient. The results did not achieve statistical significance due to insufficient power of the study. In addition, there was marked heterogeneity in the tumour and treatment characteristics, precluding any definite conclusions being drawn from the analysis. Our study also suggests that there is a definite need for prospective randomized controlled trials so as to establish a clear cut treatment guideline for this extremely lethal disease.

CONCLUSION

The impact of adjuvant treatment in the form of RT, CT or CRT after curative resection in GBC patients was observed in terms of survival but was not statistically significant. A well powered prospective randomized trial is required to conclusively establish the impact of adjuvant therapy in curatively resected GBC.

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