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Locally advanced cases of Ca Gall Bladder : Is concurrent CT+RT beneficial in improving survival

Oncology

KEYWORDS: Adjuvant, chemotherapy, gallbladder cancer, radiotherapy

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ABSTRACT

Background: Gall bladder carcinoma (GBC) is considered the fifth most common one of the most aggressive gastro intestinal tract malignancies. Over the years surgical resection has been considered the only curative treatment of these tumours. , even after curative surgery, survivals are dismal and loco-regional failure accounts for 40-86%. Although these are considered radio-resistant, adjuvant radiation, with or without chemotherapy, has been tried to improve loco-regional control and overall survival rates. With an aim to evaluate acute and late toxicity and efficacy of adjuvant chemo-radiation (CRT) after curatively resected GBC.

Materials and Methods: We retrospectively analyzed the cohort of patients diagnosed from 2010 to 2015, treated with adjuvant CRT at our institution. Treatment protocol considered external beam radiation (RT) (45-50 Gy) to tumor bed and regional lymph nodes with concurrent Cisplatin (40mg/m ^{2} /weekly infusion one hour before radiotherapy). Data was obtained from medical records, mortality from death certificates. Survival was estimated by Kaplan- Meier curves.

Results: 46 patients with curatively resected GBC received adjuvant CRT. Median age was 57 years (range 33-76); 42 patients were female. After diagnosis, a second surgery was performed in 42 patients. Cholecystectomy with hepatic segmentectomy and lymphadenectomy was the curative surgery in 41 patients. All patients received RT with a planned dose of 50 Gy in 25 fractions, and 34 patients had concurrent Cisplatin. Therapy was well tolerated. Five patients experienced grade 3 toxicities. No grade 4 or 5 toxicity was observed. No grade >2 late toxicity was observed. Three- and 5-year overall survival (OS) were 51 and 36%, respectively

Conclusions: Adjuvant chemo radiation is well tolerated and might impact favourably on survival in patients with curatively resected GBC.

INTRODUCTION

Globally, the cancers of the biliary tract are relatively rare. Of the various anatomical locations in the biliary tract, Gallbladder cancer (GBC) is the most commonly affected . In India per se it is a rare but northern India has a higher frequency gall bladder cancer, it is the commonest cancer of gastrointestinal tract in Indian women.[1] Delhi, the capital of the country, reports an age adjusted incidence of gallbladder cancer of 10.6 patients per 100,000 population, which is by the way the world's highest rate for women suffering from this cancer.[2] And is a leading cause of cancer related mortality in different parts of the world.[3]

Different risk factors associated with malignancies of gall bladder include chronic cholelithiasis, obesity, female gender, high rates of typhoid fever, and low socioeconomic status.[4,5]

Prognosis is bleak with an overall survival (OS) of only 8.5% at 5 years for all stages, majority of patients being diagnosed at advanced stage. [6] Even after aggressive surgery, cure is achieved in only 35%. [7]

We started this study with an aim to evaluate the efficacy and toxicity of CRT or RT after curatively resected GBC.

MATERIALS AND METHODS

We retrospectively reviewed 46 patients of advanced Ca GB with curative surgeries between January 2011 and December 2015.They received adjuvant RT or CT+RT.

The inclusion criteria were histologically proven carcinoma of the gallbladder who underwent curative surgery and received at least one cycle of postoperative chemotherapy or a course of EBRT with or without concurrent CT. Patients having residual disease post surgery or unresectable tumors, histology other than adenocarcinoma (different variants),or stage IV i.e. metastatic disease were excluded.

We got hold of the data from the medical records. age, sex, performance status (PS), date of diagnosis, type of surgery (recorded the same for second surgery), histological grade, TNM classification and group staging, the date when adjuvant therapy was started, planned and received RT dose, the planned and received dose of chemotherapy, acute and late toxicity, disease free survival, overall survival.

RESULTS

All the patients underwent surgery. On histopathological staging, 10patients (21.7%) had stage II, 21 (45.6%) had stage IIIA, 15 (32.6%) had stage-IIIB. All the patients received adjuvant radiotherapy, 12 (26%) patients received adjuvant RT alone, 34 (73.9%) received post-operative CT+RT.

With a median follow-up of 41 months...Patient, tumor characteristics and the particulars of the treatment used are given in the table below. [Table 1]. The median age was 48years (range 33 - 76), with 42 female patients (91%). The histological grades were well differentiated in 16 patients (34.7%), moderately differentiated 23 (50%), and poorly differentiated 7 (15.2%).

Table 1: Characteristics of patients, tumor and treatment given

Characteristics	
Age	48years
Female	42 (91.3)
ECOG	
0	1 (2)
1	10 (21.7)
2	27 (58.6)
3	7 (15.2)
Histological grade	
Well differentiated	16 (34.7)
Moderately differentiated	23 (50)
Poorly differentiated	7 (15.2)
Stage	
II	10 (21.7)
IIIA	21 (45.6)
IIIB	15 (32.6)

Treatment options	
Cholecystectomy	17 (36.9)
Extended Cholecystectomy	29 (63)
RT	12 (26)
CT+RT	34 (73.9)

Performance status was noted for all the 46 patients using ECOG performance scale. With most patients with PS of 2.All 46 patients received radiotherapy as an adjuvant treatment. The dose of radiotherapy was 50Gy in 25 Fractions in 5 weeks & 34 patients received concurrent weekly Inj Cisplatin 40mg/m^2 infusion with a ceiling dose of 50mg.

Median delay in adjuvant treatment was 96 days (range: 35-200).

Toxicity data are presented in [Table 2]. Therapy was well tolerated. None of the patients receiving RT alone presented with acute grade 3 adverse events. Only seven patients receiving CRT experienced grade 3 acute toxicities, including one grade 3 thrombocytopenia; one each of grade 3 neutropenia, vomitting, fatigue and pain abdomen; two grade 3 elevation of liver enzymes. No grade 4 acute adverse events were observed. Three out of 9 evaluable patients (33%) in the RT alone group presented late toxicity: one hepatic failure with portal hypertension and ascites, one grade 1 diarrhea and 1 gastritis. Seven of 33 evaluable patients in the CRT group (21%) presented late toxicity: one duodenal ulcer, three cases of gastritis and diarrhea each. No grade > 2 late toxicity was reported.

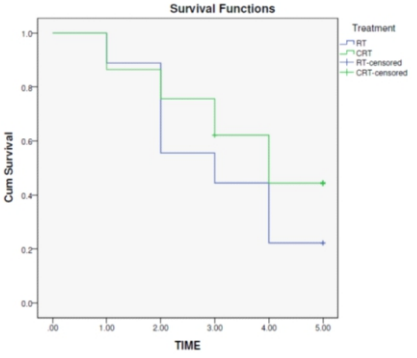
Table 2 : Acute and Chronic toxicity

Acute Toxicity (Grade 3)	No. of patients		Chronic Toxicity	No of patients	
	RT	CRT		RT	CRT
Neutropenia	0	1	Duodenal ulcer	0	1
Thrombocytopenia	0	1	Diarrhea	1	3
Vomitting	0	1	Hepatic failure	1	0
Deterioration of LFT	0	2	Gastritis	1	3
Fatigue	0	1			
Pain abdomen	0	1			
Total	0	7		3	7

As of December 2015, 22 patients died in total, 19 of malignancy and 3 of other than malignancy related causes; 21 presented with recurrent or metastatic disease, more than 5 years after the diagnosis of Ca GB.

Two patient were lost for follow up. The survival curve is shown in [Figure 1]. Three and five year OS rates for the whole series were 43.0% and 24.8%, respectively. Analyzed by the treatment group, a trend toward significant longer survival in the group which received CRT compared with only RT was observed (p= 0.065 by log rank method, Hazard Ratio : 0.81).

Figure 1 : Survival function by Kaplan Meier



Survival after diagnosis of recurrence was low, with a median survival of 4.2 months after diagnosis of recurrence. Only five patients received palliative chemotherapy.

On univariate analysis using log-rank analysis, T-stage, type of adjuvant treatment, and histological grade did not show statistically significant impact on survival, whereas N1 and R1 resection were associated with poor prognosis.

DISCUSSION

A retrospective analysis of patients treated at Acharya Tulsi Regional Cancer Treatment Centre was done to assess the outcome in terms of survival benefits for patientswith locoregionally advanced Ca GB. The median follow up for the patients alive, defined as the time between histological diagnosis and last visit to the hospital was 4 years, which allowed us to report consistent data for late toxicity. The vast majority of our patients had been diagnosed by cholecystectomy performed for cholelithiasis and had to undergo a revision surgery.

Based on the data of the SEER data base implications have been made that CRT leads to potential gain in OS, where as the addition of RT to treatment was associated with a benefit in OS (14 vs. 8 months, $P < 0.0001$)[10] however, no chemotherapy details were available for the analyzed patient population.

Based on this SEER data, a model for predicting the survival benefit of adjuvant radiotherapy has been proposed for Ca GB cases. [11]

The potential benefits of CRT followed by adjuvant CT were explored by Lim *et al.* for patients with radically curatively resected Ca GB cases, and a favourable impact for adjuvant 5FU-based CT could be demonstrated in this non-randomized study (HR 0.429, $P = 0.01$). [12] According to a few available reports most institutions use RT with 5FU-based chemo sensitization. [13,14] One such study has recommended use of adjuvant chemotherapy post R0 resection of Ca GB patients. [15]

Provided that almost half of the patients with recurrance present with distant spread, hence a more comprehensive chemotherapy regimen is clearly required to improve the results of adjuvant treatments in GBC. In the metastatic setting, palliative chemotherapy with GEMOX regimen improved overall survival compared to best supportive care (HR 0.44) whereas 5FU + Folinic Acid did not improve OS but significant improvement in symptomes was noted. [16] Another study showed improved survival with Gemcitabine + Cisplatin compared to Gemcitabine alone (HR 0.61). [17]

Factors affecting the survival include local recurrence inspite of using CRT, and R0 resection is one of the most important favourable pronostic factor, as shown by a few studies[14,15,18] In our study, very few patients with positive surgical margins received adjuvant CRT; inspite of this, nearly half presented with local recurrence.

In our experience, only 20-25% of all GBC patients seen at the tumor board received adjuvant CRT, mostly because of advanced stage at presentation or residual disese even after revision surgery, a study mentions even for potentially resectable GBC submitted to operation, curative surgery was achieved in only 61.3% of the cases. [21]

Neo adjuvant strategies could offer the opportunity to benefit more patients by down staging the tumors and increasing R0 resection, which could translate into survival benefits and should, therefore, be explored.

In the era of genomics and proteomics, great progress has been made in understanding some cancer types. Some of these findings even have opened the field for individualized prognostic and therapeutic assessments.

In contrast, very little is known about carcinogenesis and molecular subtypes in GBC. [22]

Adjuvant treatment with radiotherapy or CRT might improve outcome in terms of OS, as our results compare favourably to series

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reporting outcome with surgery only. The treatment used was well tolerated and CRT with 5FU administered over 120 h in two cycles could be given safely. Although adjuvant CRT showed better OS compared to RT, this difference was not statistically significant and should be confirmed by a randomized trial.

Given the poor prognosis of GBC even at a localized stage, after curative surgical treatment, adjuvant or neo adjuvant strategies with improved systemic treatments should be explored.

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