



Radiotherapy for Locally Advanced Unresectable Gallbladder Cancer-A Way Forward: Comparative Study of Chemotherapy Versus Chemoradiotherapy

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Abstract

Background: For non-metastatic locally advanced gallbladder cancer (LAGBC) which remain unresectable and nonmetastatic after chemotherapy, there is no consensus on whether to continue chemotherapy or add local radiotherapy for improving outcomes.

Materials and Methods: Forty-five patients of surgically unresectable non-metastatic LAGBC were analysed. Twenty patients did not receive radiotherapy (No RT cohort) and received only chemotherapy, while 25 patients received RT (RT cohort) with conformal techniques along with concurrent gemcitabine based chemotherapy. No RT and RT cohorts were compared for disease related outcomes and toxicities.

Results: Median follow up of the entire cohort was 11.5 months. Two-year progression free survival (18.6% v/s 0, p=0.0001) and overall survival (37.3% v/s 5%, p=0.0001) were significantly better in the RT cohort as compared to a No RT cohort. More number of patients had locoregional progression in the No RT cohort (85% v/s 32%, p=0.0002). Radiation induced acute and late GI toxicity RTOG \geq grade 3 were seen in one and two patients, respectively.

Conclusion: Addition of local radiotherapy to chemotherapy improves the survival outcomes and can be considered as a definite treatment modality for non-metastatic locally advanced gallbladder cancer patients not amenable to surgery who have responded to chemotherapy.

Introduction

Gallbladder Cancers (GBC) are rare but highly aggressive tumours of the extrahepatic biliary tree. As per GLOBOCAN 2018, the worldwide age standardized incidence and mortality (per 1,00,000) for GBC are 2.3 and 1.7, respectively [1]. Approximately 50-60% of the nonmetastatic GBC present at a locally advanced stage (T3/T4 or N+). The median survival for locally advanced gall bladder cancer (LAGBC) in multiple series ranges from 6-16 months with a 2 year survival of < 20% [2,3]. These patients generally receive chemotherapy or chemoradiation followed by an assessment for surgery if optimal response. For patients who receive chemotherapy, and do not achieve optimal downstaging to

undergo R0 resection and continue to be nonmetastatic, there is no consensus, whether they should receive further chemotherapy alone or local radiotherapy (RT) should be added with an aim to achieve better local control and prolong survival. The role of RT has remained a matter of debate for LAGBC, with multiple older series failing to demonstrate any potential benefit of RT in LAGBC [4-6]. Most of these studies include both gall bladder cancers and extrahepatic bile duct cancers together and have utilized conventional RT techniques. However, with the emergence of newer RT techniques (IMRT, IGRT etc.), contemporary data in this regard seems more encouraging with retrospective analysis of two

population database (SEER and NCDB) showing survival benefit with addition of RT to chemotherapy in unresectable localized disease [7,8]. We performed a retrospective comparative analysis to ascertain the benefit of giving local RT in these unresectable LAGBC at our institute.

Materials and Methods

This study is a retrospective analysis of patients of LAGBC patients treated between March 2013 to December 2018 at a single tertiary cancer institute. Institutional Review Board (IRB) approval was obtained for the study (IEC no: 900653).

Inclusion and Exclusion Criteria

All cases of non-metastatic LAGBC who had received neoadjuvant chemotherapy (NACT) as per predefined protocol were considered. Patients who were deemed as unresectable in Multidisciplinary Tumor Board (MDT) after NACT due to local factors like hilar infiltration, non-communicating hilar block, complete encasement of one or more major vessels at porta, involvement of D2 requiring Whipple's procedure or extensive liver infiltration, were considered for the study. Few patients who were deemed as "unlikely to ever come up for curative resection" in MDT due to extensive local factors were not offered NACT and were considered for definitive chemoradiotherapy (CTR). Exclusion criteria were patients who were treated with palliative intent RT (8Gy/ 1 fraction, 20Gy/ 5 fractions or 30Gy/ 10 fractions) for symptomatic relief, patients who did not complete the planned RT schedule and patients in whom no follow up data was available. The patients were classified into two cohorts: patients who received only chemotherapy (No RT cohort) vs patients received a fractionated course of local radiotherapy (RT cohort). As per institutional protocol, patients with spread to regional nodes including coeliac nodes were also treated with RT and hence were considered for analysis. The two cohorts were matched as per age, sex, comorbidities, T and N stage.

Treatment

All patients selected either received few more cycles of chemotherapy or received local radiotherapy followed by chemotherapy as per the decision of the MDT. If the patient had obstructive jaundice, drainage procedure with ERCP or PTBD was performed and self-expanding metal stents placed allowing bilirubin to normalize before the start of the treatment. The chemotherapy regimen used at our institute was either a combination of gemcitabine and cisplatin or gemcitabine and oxaliplatin and has been described in detail in previous publications from our institute [9-11]. Response to therapy was assessed in MDT with a Contrast Enhanced Computerized Tomography (CECT)/ Positron Emission Tomography-Computerized Tomography (PET-CT) as per RECIST 1.1 criteria and Carbohydrate Antigen-19.9 (CA-19.9) levels [12].

Radiotherapy

Patients were simulated using a planning contrast enhanced CT scan. Clinical Target Volume primary and node (CTVp and CTVn) delineation was done as per existing institutional practice already published earlier [10]. The dose prescription to PTVp (Primary) and PTVn (nodes) was 45-50Gy at 1.8-2 Gy per fraction respectively. A dose of 52-57Gy as simultaneous integrated boost (SIB) was given to gross tumor volume (GTV) primary and node (GTVp and GTVn respectively) if feasible. Organs at risk (OARs) were delineated as per standard guidelines [13]. The desired dose volume constraints for target and OARs are given in table 1. Weekly concurrent chemotherapy as gemcitabine (300 mg/ m²) was given to all patients. Treatment planning was with Intensity Modulated Radiotherapy Techniques (IMRT) or related techniques (Helical tomotherapy, Volumetric Modulated Arc Therapy). Treatment verification (Image Guided Radio Therapy) was done by KV-CBCT or MVCT. Further chemotherapy with palliative intent was continued as per MDT discussion.

Table 1: Target volume and Organs at Risk (OARs) dose volume constraints.

Target	Dose/ Volume constraint
PTV (Primary/Node)	95% volume to be covered by 95% dose
Organ at Risk	Dose/ Volume constraint
Duodenum	1 cc < 55Gy
Duodenum	4 cc < 50Gy
Liver	V30Gy < 30%
Liver	Mean dose < 24-26Gy
Bowel Bag	V15Gy < 120cc
Bowel Bag	V45Gy < 195cc
Spinal Cord	Dmax < 45Gy
Kidneys (b/l)	Mean dose < 14Gy

Follow-up/ Toxicity

Patients were followed up post completion of CTRT or chemotherapy at an interval of 2-3 months with CECT/ PET-CT and CA-19.9 for response. Patients were advised for subsequent follow ups after completion of all treatment were at 3-4 monthly interval with subsequent imaging at 6 monthly interval or for rising CA-19.9/ suspected clinical progression. Acute and late radiation toxicity was scored using Radiation therapy Oncology Group (RTOG) morbidity schema [14].

Statistics

The primary end point of the study was progression free survival (PFS). PFS was defined as the time interval in months between the date of diagnosis of malignancy and the date of clinical/ radiological progression or death. The secondary endpoint was

overall survival (OS) and acute/late toxicity. Kaplan-Meier method was used to determine the survival between the two cohorts. Log rank test was used to determine the difference (if any) between the two cohorts. Chi square test was used to ascertain difference between categorical variables.

Results

A total of 69 patients of locally advanced non metastatic adenocarcinoma of the gall bladder were identified who were treated between March 2013 and December 2018. Out of these 24 were excluded as per the exclusion criteria and 45 were available for analysis (figure 1). of these 45 patients, 20 did not received RT (No RT cohort) and 25 received RT (RT cohort). The demographics of both groups are elaborated in table 2. There was no significant difference between the two cohorts with respect to any of the demographic features. The majority had unresectable disease due to extensive liver infiltration (n=14) or duodenal infiltration (n=10)

and a bile duct involvement with hilar Type II non communicating or higher block (n=8). The median follows up of entire cohort was 11.5 months (IQR: 7.5-21.9 months). In the RT cohort 6 patients received upfront CTRT whereas 19 patients received RT after NACT. Post response assessment, 14 out of 20 patients continued to receive 3-4 cycles chemotherapy in the no RT cohort, whereas, in the RT cohort, 22 out of 25 patients received further 3-4 cycles of chemotherapy after the completion of CTRT. The median number of chemotherapy cycles in RT cohort was 5 (range 3-11) and in No RT cohort was 4 (range 3-8). In the No RT cohort, partial response (PR), stable disease (SD) and progressive disease (PD) was seen in 8 (40%), 5 (35%) and 7 (35%) respectively. In the RT cohort 10 (52.6%) patients had PR and 9 (47.3%) had SD (table 4). The median RT dose to the CTV was 50Gy while the median tumor dose was 52Gy. Median RT duration was 36 days (range 32-50 days) with a median of 6 (range 2-7) cycles of concurrent chemotherapy. Post CTRT 14 (56%) patients had a partial response, 5 (20%) had stable disease and 6 (24%) had a progressive disease.

Table 2: Demographic and disease parameters of no RT and RT cohorts.

Parameter	No RT (n=20)	RT (n=25)	Total (n=45)
Median age (range)	49 years (36-65)	54 years (36-72)	52 years (36-72)
Male vs Female	5(25%) vs 15(75%)	10(40%) vs 15(60%)	15(33.3%) vs 33(66.7%)
Comorbidities			
Diabetes	6(30%)	7(28%)	13(28.8%)
Hypertension	8(40%)	10(40%)	18(40%)
T3 v/s T4 stage	11(55%) vs 9(45%)	15(60%) vs 10(40%)	25(55.5%) vs 20(45.5%)
N0 v/s N+ stage	10(50%) vs 10(50%)	16(64%) vs 9(36%)	26(57.2%) vs 19(42.2%)

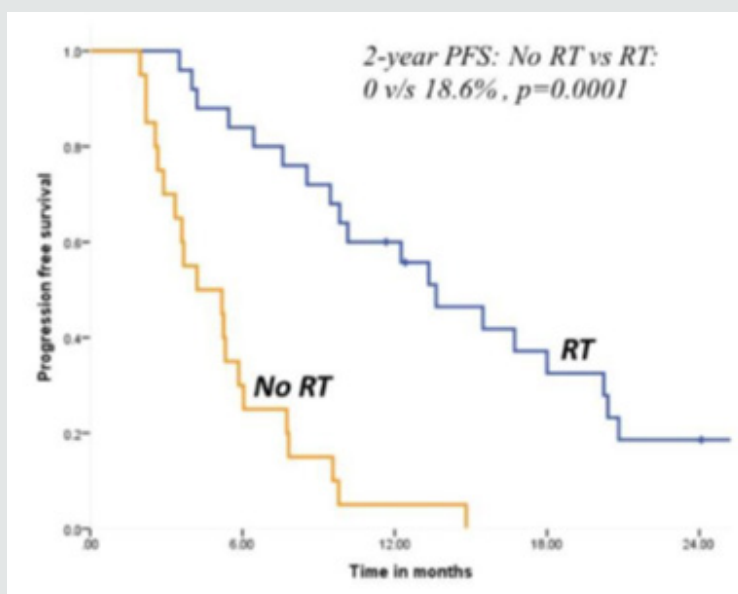


Figure 1: Two year Progression Free Survival (PFS) in No RT and RT cohort.

Treatment outcomes

At last follow-up, all 20 patients in the No RT cohort were dead (100%) whereas 20 out of 25 patients (80%) died in the RT cohort. Five patients were alive at last follow up in the RT cohort with 1 patient having no evidence of disease and 4 having stable disease radiologically. The 2 year PFS was 18.6% vs 0%, p=0.0001 for RT

and No RT cohorts respectively with a median PFS of 12.4 months v/s 4.7 months. The 2 year OS was 37.3% v/s 4.3%, p=0.0001 with a median of 18 months v/s 7.5 months (figure 2). The pattern of failure for both cohorts is shown in Table 3. More number of patients in the No RT cohort had a locoregional failure(85% v/s 32%, p = 0.0002).

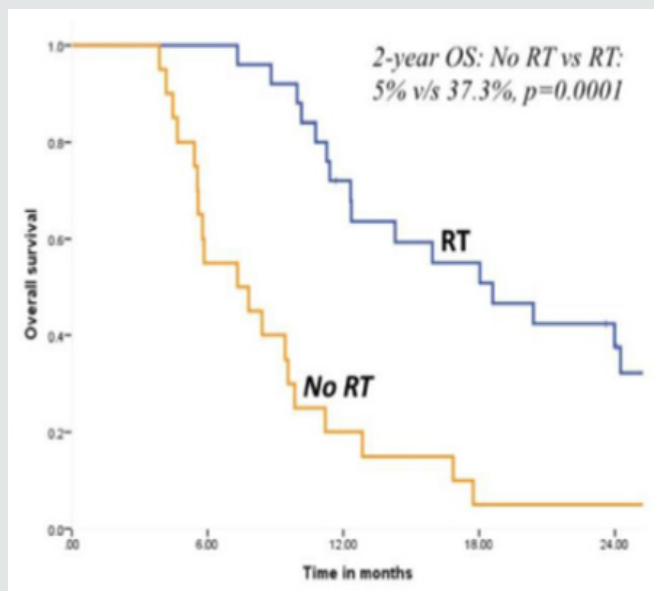


Figure 2: Two year Overall Survival (OS) in No RT and RT cohort.

Table 3: Patterns of failure in no RT and RT cohort.

Type of failure	No RT (n=20)	RT (n=25)
Locoregional	12(60%)	2(8%)
Distant	3(15%)	12(48%)
Locoregional+distant	5(25%)	6(24%)
Stable/ no progression	0	4(16%)
No evidence of disease	0	1(4%)

Toxicity

The acute RT toxicities (skin and GI) are shown in Table 4. Only 1 patient had a grade 3 diarrhoea at RT completion which was

managed conservatively. Additionally, 4 (16%) patients had grade 3 haematological toxicity (neutropenia). Severe late toxicity (≥ grade 2) was seen in 2 patients (1 duodenal stricture and 1 diarrhoea). Two patients had pneumobilia.

Table 4: Response post 3-4 cycles of neoadjuvant chemotherapy in no RT and RT cohorts

	No RT (n=20)	RT (n=19)	P value
Response post 3-4 Cycles NACT			0.01
Complete response/ Partial response/ Stable disease	12(60%)	19(100%)	
Progressive disease	8(40%)	0	
Progressive disease Number of patients receiving any treatment Post 3-4 Cycles NACT	17(85%)	19(100%)	0.73
Number of patients who 16(80%) remained non- metastatic post 3-4 cycles NACT	19(100%)	0.11	
NACT: Neoadjuvant chemotherapy			

Discussion

There exists little if any consensus between various guidelines about the role of RT in LAGBC. Both National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines suggest local RT as a valid option for LAGBC; with NCCN guidelines suggesting concurrent CTRT as a first line treatment option and ESMO guidelines recommending it as an option for patients who have localized disease after chemotherapy (15,16).

In a relatively large surgical series by Birnbaum *et al* of LAGBC (n=78) patients with T3/ T4 disease underwent extended resection (CBD, pancreaticoduodenectomy). The median survival was 16 months with a 2 year overall survival of 21%. The in-hospital mortality rate was 8% (17). Similarly, in our own published series of 160 patients who received NACT to facilitate surgical resection, 66 patients (41.2%) could undergo surgical resection. The median survival for the entire cohort and those who underwent surgical resection was 13 months and 49 months respectively. The peri-op morbidity rate was 17.2% (11). Hence, although surgical resection remains the only curative modality for GBC, the morbidity and mortality of extensive surgical resection cannot be ignored. The encouraging outcome of patients who received RT in our cohort (median survival 18 months, 2 year survival 37%) suggests local RT as a good local treatment modality to extensive surgical resection with high anticipated perioperative morbidity/ mortality.

There is a paucity of literature with regards to the utilization of RT as a definitive modality in the treatment of GBC (18). Most of the older series failed to demonstrate conclusively a benefit of RT in these cancers. This is mainly ascribed to older/ 2D / conventional RT techniques which lead to either delivery of suboptimal RT doses or excessive therapy related morbidity and mortality. Reports with modern RT techniques are more encouraging. A report of National Cancer Database of the USA of 11,190 gallbladder cases showed that receipt of radiotherapy was an independent predictor of improved OS in LAGBC (7). Similarly, in a SEER database review of 453 patients of biliary tract cancers (11% GBC), patients who received RT had an improved survival (HR 0.82, 95% CI:0.72-0.97, p=0.02) (8). Results of this population database analyses are in line with our results.

GBC have traditionally been considered to be as radio-resistant cancers. In 2016, we published our results of neoadjuvant chemoradiotherapy for LAGBC (10). Out of 28 patients, 20 patients (71%) patients had a radiological response. Out of 14 patients who underwent R0 resection, 7 (50%) had tumor regression grade (TRG) grade 0 or grade 1 response. These results provide radiobiological evidence that GBC may have some degree of radio-sensitivity. In agreement with our past results, only 3 (11%) receiving CTRT in the current cohort of patients had an isolated locoregional progression and the overall incidence of locoregional progression was less in

patients receiving RT. With improvements in systemic therapy for biliary tract cancers like immunotherapy and targeted therapy, this fact should be considered in formulating future treatment protocols for nonmetastatic patients.

The severe late toxicity of CTRT (\leq RTOG grade 3) remained low in our series. We ascribe this to our meticulous treatment protocol especially with regards to the delineation of the duodenum by an experienced gastrointestinal radiation oncologist and limiting of doses to the duodenum (19). A meticulous image guidance protocol may also have a role in limiting the late GI toxicity in the current series.

We agree that superior outcomes in CTRT cohort may be due to a selection bias with patients having no progression on chemotherapy being selected for RT (table 4). Nevertheless, the lesser incidence of locoregional failures as well as encouraging disease related outcomes in the CTRT cohort demonstrate that RT should be incorporated into the treatment protocol whenever feasible. Since 8 (18%) patients progressed (4 locally and 4 local with distant metastasis) after few cycles of chemotherapy would they have benefitted with upfront CTRT is matter of speculation. Further randomized studies are required to determine the optimal sequencing of treatment that is chemotherapy followed by CTRT or upfront CTRT followed by chemotherapy.

The current the study is subject to the drawbacks of a retrospective analysis. The number of patients in each cohort are limited owing to the paucity of non-metastatic and unresectable LAGBC. The time duration for response assessment post NACT was not standardized across the cohort with patients receiving a variable number of chemotherapy cycles before assessment for radiotherapy and some patients (n=6) receiving CTRT upfront (depending on the volume of the disease). Also, the criteria for continuing with chemotherapy or giving chemoradiation was not very well defined. However, as mentioned above the treatment protocol was chosen in a multidisciplinary tumor board comprising of dedicated biliary tract surgeons and radiologists, radiation oncologists, and medical oncologists specializing in gastrointestinal cancers. We believe this to be one of the most important factors for our relatively better outcomes in these cancers.

In conclusion, patients with unresectable GBC who have responded to chemotherapy can be considered for CTRT as definitive local treatment.

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