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Scientific Article

Predictors of Toxicity in a Randomized Study of Consolidation Chemoradiation Versus Observation After First Line Chemotherapy in Advanced Gall Bladder Cancers

Sushma Agrawal, MD,[a,*] Anshika Gupta, MD,[a] Vishwas Kapoor, PhD,[b] Rahul Rahul, MCH,[c] Ashish Singh, MCH,[c] Prabhakar Mishra, PhD,[b] and Rajan Saxena, MS[c]

[a]Departments of Radiotherapy, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India; [b]Biostatistics, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India; and [c]Surgical Gastroenterology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India

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Purpose: Gall bladder cancers (GBC) usually presents in advanced stage. First-line chemotherapy (CT) is the standard of care, and there is no other option for responders than to wait for disease progression. We conducted a randomized study of consolidation chemoradiation (CTRT) versus observation in responders to first line CT (NCT05493956), which showed an improvement in overall survival by 6 months and therefore is practice changing. We are reporting the toxicity and factors predicting toxicity due to CTRT so that it informs appropriate patient selection.

Methods and Materials: Responders to first line CT (partial response, stable disease) were randomized to CTRT versus observation after 4 cycles. CTRT was delivered by 3D conformal radiotherapy (along-with concurrent capecitabine at 1250 mg/m^2) to a dose of 45 Gy in 25 fractions to GBC and lymphatics followed by a boost of 9 Gy in 5 fractions to the GBC. Toxicities documented during CTRT were recorded using the Radiation Therapy Oncology Group criteria. Dose volume data were correlated with the radiation induced side effects.

Results: Among 135 patients enrolled both arms are well balanced demographically, and 58% patients had T4 tumors, 42% had N2 and 15% had paraaortic lymph node, and 27% underwent upfront stenting. Grade 3 adverse events, such as anemia, dyspepsia, hepatotoxicity (Child Pugh B), and gastrointestinal bleed due to CTRT was observed in 9%, 1.5%, 13%, and 5.8%, respectively. Age >58 years (P = .02), planning target volume (PTV) 1 volume (>919 cc, P = .02), PTV2 volume (>380 cc, P = .01), mean liver dose (>28 Gy, P = .07), and liver V40 (>50%, P = .02) predicted radiation-induced liver disease. A receiver operating curve analysis revealed a cut-off value of PTV1 volume of 800 cc (sensitivity and specificity of 75% and 54%) and PTV2 volume of 300 cc (sensitivity and specificity of 81% and 65%) for prediction of hepatotoxicity. Duodenum V45 >45% (P = .02) predicted grade 3 anemia. Numerically high V15 duodenum (98%, P = .11), large PTV2 volume >484 cc (P = .06) and prior stenting had predilection for gastrointestinal bleed.

Conclusions: Consolidation CTRT is tolerable in those with PTV1 volume less than 800 cc.

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Data has not been shared but can be provided if asked by the editor.

*Corresponding author: Sushma Agrawal, MD; Email: sushmaagrawal@yahoo.co.uk

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Introduction

Gall bladder cancers (GBC) usually presents in advanced stage, which is a heterogenous entity including locally advanced, retroperitoneal lymphadenopathy (RPLN), oligo-metastases, omental metastases, or distant metastases. The standard treatment of this heterogenous entity is a combination of cisplatin and gemcitabine which yields a median survival of 9 months.[1] Recently maintenance durvalumab and combination of pembrolizumab, chemotherapy (CT) has shown to improve survival by 1 to 3 months in biliary cancer, but its outcome in GBC is less convincing.[2,3] Durvalumab at a dose of 1500 mg 3 weekly is not a cost-effective option. Responders to CT if left untreated progress within a few months. Based on retrospective literature that consolidation consolidation chemoradiation (CTRT) in responders to CT yields an improvement in overall survival from 9 to 15 months we conducted a phase 3 open label randomized study where responders to 4 cycles CT were randomized to observation versus consolidation CTRT to a dose of 45 Gy to GBC and lymphatics and a boost to GBC up to 54 Gy.[4-6] The median overall survival after randomization in the CTRT arm was 10 months versus 4 months in the observation arm (HR, 0.47 [95% CI, 0.33-0.68] $P = .001$) and the actual overall survival because accrual was 13 versus 7 months, which is practice-changing.[7]6 We are reporting the toxicity endpoints due to consolidation CTRT and its predictors. This trial is the first of its kind to investigate consolidation CTRT in a phase 3 study in responders to CT in a population of advanced GBC. The primary endpoint of this study was improvement in overall survival and the secondary endpoints were improvement in progression free survival and toxicity due to CTRT.

Methods and Materials

Trial design and conduct

The study Protocol was approved by the institutional ethics committee. The study was prospectively registered at the ClinicalTrial.gov website (NCT05493956).

Participants

This is a single-center open-label randomized study in a low middle-income country setting, where patients with advanced GBC (ie, T3, T4, N1, N2, nodes in retroperitoneal region), with good performance status, body mass index >15, with normal organ and marrow function and weight loss not exceeding 10% in the preceding 3 months were included in this trial. Due to COVID-19, we faced difficulty in patient accrual; hence, the inclusion criteria were modified to inclusion of patients with liver metastases limited to segment IV and V, and oligometastatic disease (<3 metastases in the present study). Patients with multiple liver metastasis, ascites, and evidence of significant clinical disorder or laboratory finding that makes it undesirable for the patient to participate in the trial were excluded. After confirmation of the diagnosis by an fine needle aspiration cytology and a CT scan abdomen for ascertaining the stage of disease, patients were taken up for first line CT.

Interventions

After completion of 4 cycles CT (cisplatin, gemcitabine combination) they were evaluated for response with CT scan abdomen. If resectable, they were taken up for surgery. If unresectable (those with partial response and stable disease), they were randomized to consolidation CTRT versus Observation (Fig. 1, consort diagram). CTRT was delivered by 3D conformal radiotherapy technique. The target dose of RT was 45 Gy in 25 fractions to GBC and lymphatics (GBC, liver infiltration, periportal, coeliac, superior mesenteric, and retroperitoneal lymphnodes until L2) followed by a boost of 9 Gy to the GBC mass. Concurrent capecitabine at 1250 mg/m^2 (Monday-Friday) was administered along-with RT. Patients in observation arm were observed until disease progression.

Contouring

GB mass along-with liver infiltration was gross target volume (GTV), and a 5 mm margin around it was clinical target volume (CTV). Liver metastases within adjacent segment and encompass able in RT portal were also delineated as GTV. Nodal CTV was delineated after drawing and combining portal vein, coeliac artery, superior mesenteric artery, and aorta as per the guidelines for biliary cancers.[8] A Boolean of CTV and nodal CTV was designated final CTV. The planning target volume (PTV) 1 margin around final CTV was 1 cm (Fig. 2) and PTV boost margin was 7 mm beyond CTV. DVH constraints were mean liver dose <30 Gy (liver was delineated after subtracting GTV), mean kidney dose <18 Gy (combining both kidneys). Other OAR delineated were stomach, duodenum, bowel, kidney, spinal cord, and their doses were noted (Supplement).

Treatment planning

After the generation of International Commission on Radiation Units and Measurements target volumes GTV, CTV, PTV, and organs at risk the classical plan template of 3 fields were placed (1 anterior and 2 laterals). Plans

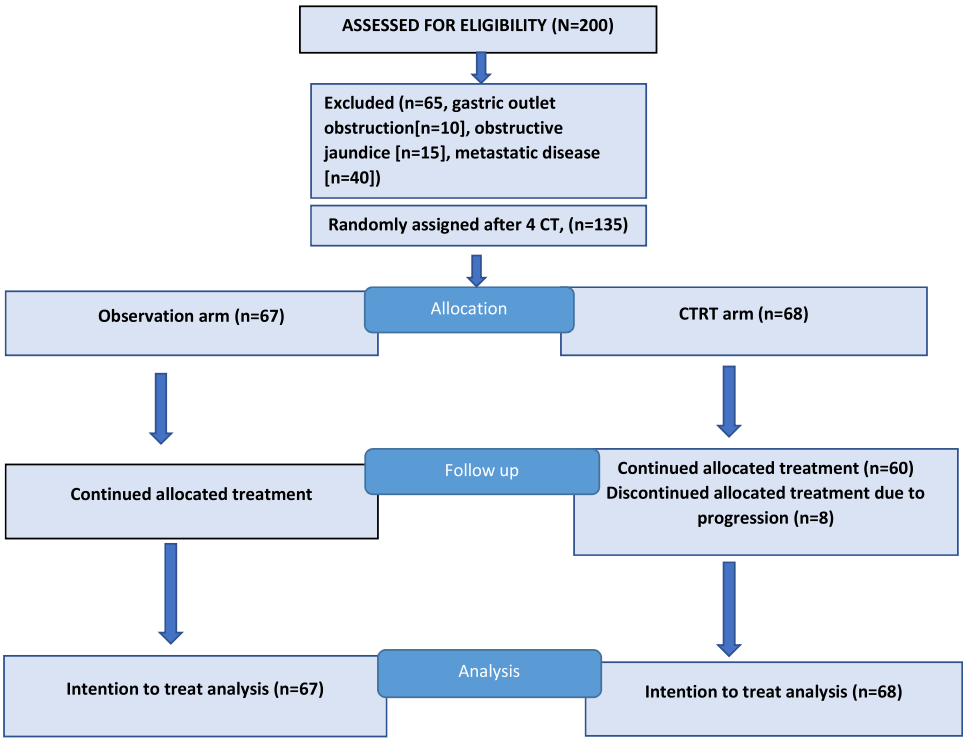

Figure 1 Consort diagram. *Abbreviation:* CTRT = consolidation chemoradiation.

are created using in-homogeneity calculation algorithms (AAA or CCC) and optimized choosing mixed energies 6 MV and 15MV along with enhanced dynamic wedges (mostly wedge angles between 15 and 45 degree were used) and target conformation was done with multileaf collimator (Millennium 120 or Agility 160); 15 MV beam was mostly preferred to avoid lateral edge effect when the lateral separation is more about 35 cm. To improve dose

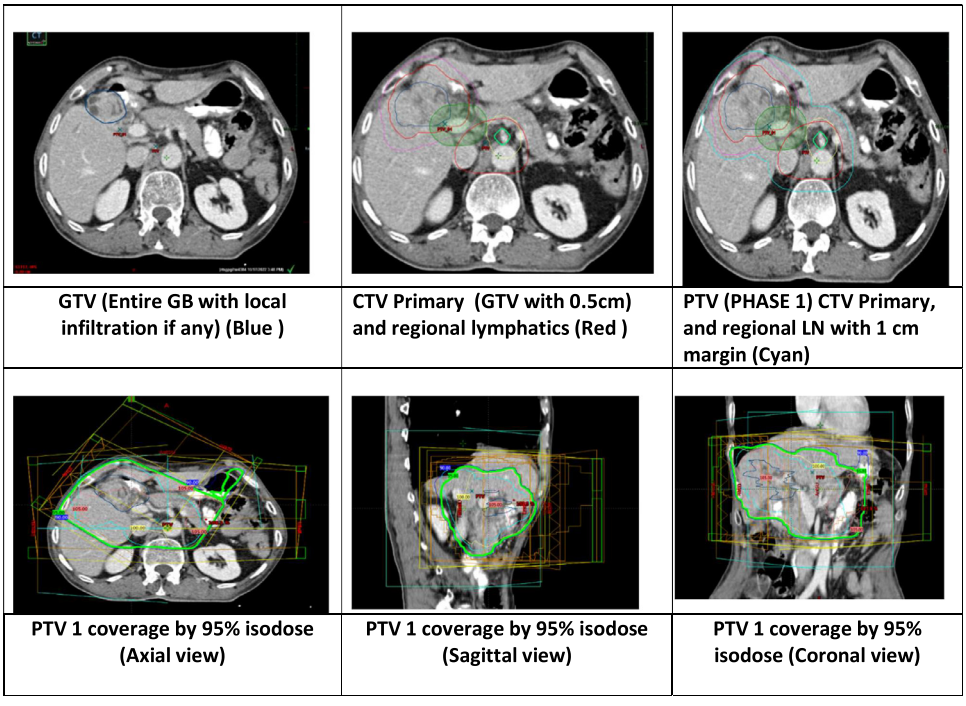

Figure 2 Target delineation and plan for phase 1. *Abbreviation:* CTV = clinical target volume; GTV = gross target volume; PTV = planning target volume.

homogeneity in the intersection area of beams in and around the target the field in field approach was considered. Quantitative and qualitative analysis are considered for plan acceptance (the minimum and maximum dose to the target coverage as per International Commission on Radiation Units and Measurements 50 and 62 recommendations, ie, 95% isodose coverage to PTV and 107% dose envelope volume should not be >1.5 cm diameter). When 107% dose area was >1.5 cm diameter, field in field technique was used for reducing high dose volumes. Once plan was finalized electronic chart was prepared for treatment execution through record and verify module at the treatment console with first day verification protocol (orthogonal setup fields of field size 20 × 20 cm^2 for setup verification).

Treatment delivery and monitoring

All patients were prescribed prophylactic antacids and mucosal coating agents from day 1 of radiation as a measure to prevent duodenal toxicity. Hematological, hepatic, and renal functions, as well as tolerance to the treatment, were assessed weekly. Toxicities documented during CT were recorded using the Common Terminology Criteria for Adverse Events version 3.0 (National Cancer Institute 2006 scale). Toxicities arising during and within 90 days since the completion of radiation therapy and attributed to radiation were assessed according to Radiation Therapy Oncology Group criteria.[9] Hepatotoxicity was classified as classic or nonclassic radiation induced liver disease.[10]

Efficacy and safety assessments

Six weeks after completion of CTRT, response assessment was done with CT angiography of abdomen. If there were signs of considerable downstaging and resect ability, a positron emission tomography/computed tomography was done to rule out distant disease before referral to a surgeon.

On evidence of disease progression in either arm, patients were treated with salvage second line CT [CAPIRI (irinotecan at 180 mg/m^2 and capecitabine at 1650 mg/m^2 × 14 days , 3 weekly) or CAPOX or single agent capecitabine (at 1650 mg/m^2 × 14 days for 3 weeks)] depending on the performance status of patients.

Sample size

Assuming 2-year survival probability of the patients were 0.25 and 0.08 in the treatment (group1) and control (group 2), at minimum 2-sided 95% confidence interval and 80% power of the study, overall sample size came out to be 132 subjects (66 in the group 1 and 66 in the group 2) using a 2-sided log-rank test. The proportion dropping out in each of the treatment and control group was 0.10 (ie, 10%). The number of events required to achieve a power of 0.8 with an assumed hazard ratio of 2 was estimated as 67. Assuming a lost to follow-up of 10%, a sample size of 140 would result in more than 67 events sufficient to achieve 80% power at 0.05 alpha. All analysis in the present article is intent to treat analysis.

Statistical analysis

Categorical variables were summarized with proportion while the median and IQR was calculated for continuous variables. Normality of quantitative data were examined using Shapiro Wilk's test. Parametric data were represented as mean ± SD, whereas skewed data as median (IQR). Association between categorical data were tested using χ^2 or Fisher's exact test. Comparison between groups was done by independent sample *t* test or Mann-Whitney *U* test.

Results

The trial opened for accrual on January 1, 2019, and the last patient was accrued in August 2022. Among 200 patients of GBC registered, 65 patients progressed (gastric outlet obstruction [n = 10], obstructive jaundice [n = 15], metastatic disease [n = 50]), and those who did not progress (n = 135) were inducted into the study. The data analysis was done in April 2023. The median follow-up time in surviving patients was 7 months (IQR, 4-11 months).

A total of 135 patients were recruited (68 in CTRT and 67 in observation). The demographic features are well balanced in both the arms (Table 1). Eight patients progressed in experimental arm after randomization and before initiation of CTRT. Hence, only 60 patients received CTRT. Sixty percent patients were women, 95% had T3, T4 disease, 80% had node positive disease (10% vs 20% had RPLN in observation vs experimental arm), 10% patients had omental involvement (without ascites), 3% had oligometastatic disease (vertebra only), 10% had liver metastases restricted to adjoining segment of liver. Twenty-four percent versus 31% in observation versus experimental arm presented with obstructive jaundice and underwent stenting (plastic stent) before commencement of CT.

Treatment compliance

The analysis suggests that chemotherapy was well tolerated (Data Supplement, Table E1a, b The only significant grade 3 adverse effect due to CT was anemia (12% vs 19%) in observation versus experimental arm respectively ($P = .015$).

Out of 60 patients who were initiated on CTRT, 7 could not complete RT (2 were >65 years and developed grade 3 hepatotoxicity or gastrointestinal (GI) bleed, 1

Table 1 Demographic features of both arms

Characteristics	Observation (n = 67) (%)	CTRT (n = 68) (%)	*P* value
Age (median, IQR), y	54 (IQR, 46-64)	52 (IQR, 45-62)	
Male	27 (40)	24 (35)	
Female	41 (60)	43 (63)	.6
Mean Charlson Comorbidity index	1.63	1.5	.6
Stenting	16 (24)	21 (31)	.3
T2	3 (3)	4 (6)	
T3	27 (48)	26 (38)	
T4	37 (55)	38 (56)	.6
N0	15 (22)	14 (20)	
N1	17 (25)	15 (22)	
N2	28 (42)	25 (37)	
Para-aortic lymphadenopathy	7 (10)	14 (20)	.6
M stage			
Liver (limited)	0	7 (10)	
Bone (solitary)	1 (1.5)	1 (1.5)	.04

Abbreviation: CTRT = consolidation chemoradiation.

developed fatal GI bleed at 45 GY, 1 had large PTV and developed hepatotoxicity at 45 Gy, 1 had treatment interruption due to COVID-19 and she progressed thereafter, 1 had dilated cardiomyopathy and contracted dengue, and she succumbed due to thrombocytopenia and the rest 2 had disease progression while on CTRT. There was no treatment delay in the rest of the patients. Hepatotoxicity (Child Pugh A) due to CTRT was observed in 12% (Fig. 3, Supplement Table). Grade 3 adverse events like anemia, dyspepsia, and hepatotoxicity (Child Pugh B) due to CTRT was observed in 9%, 1.5%, and 13%, respectively. All GI bleeds (5.8%) were fatal. No patient experienced treatment-related bowel perforation or fistula.

The median PTV1 volume was 832 cc (IQR, 674-999 cc) and the median PTV2 volume was 282 cc (IQR, 196-374 cc). The median dose to 95% of PTV1 was 98% (IQR, 98%-99%). Compliance to the predefined radiation dose constraints was high for all reported parameters in this study. The median achieved dose to liver was 29.5 Gy (IQR, 25.7-33.3 Gy), kidney 16.2 Gy (IQR, 13-18 Gy), V15 Duodenum was 50%, V45 duodenum was 43%, and V45 stomach was 30%. The median Dmax to liver was 56

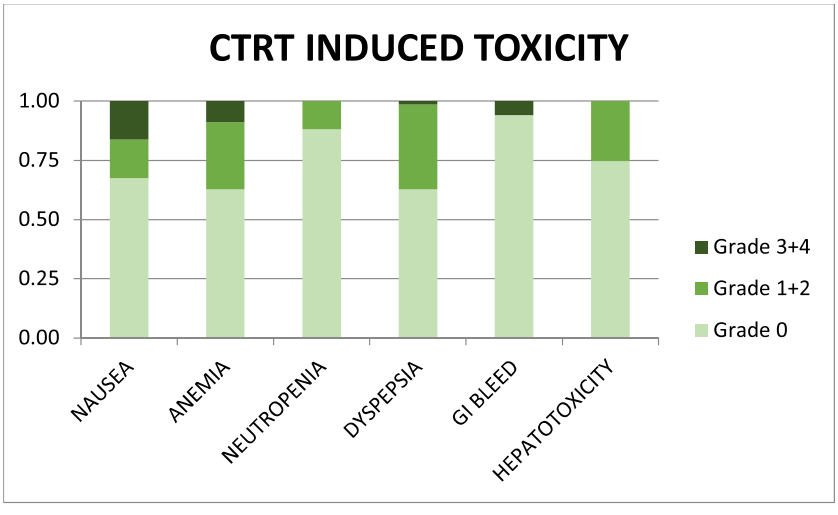

Figure 3 CTRT induced toxicities. *Abbreviations:* CTRT = consolidation chemoradiation; GI = gastrointestinal.

Table 2 Factors predicting chemoradiation induced liver disease

Radiation induced liver disease	Yes	No	*P* value
PTV1 volume	919 (775-1148)	738 (657-905)	.02
PTV2 volume	388 (286-660)	209 (196-321)	.01
Liver mean	30 (28-35)	28 (25-32)	.073
Liver V10	88 (71-91)	80 (70-90)	.363
Liver V20	71 (59-79)	60 (54-71)	.102
Liver V30	58 (50-70)	52 (43-60)	.127
Liver V40	50 (40-56)	39 (35-48)	.021
Liver V50	21 (11-28)	22 (11-28)	.573
Liver Dmax	55 (51-57)	57 (53-57)	.777
SGOT in last week RT (IU/mL)	63 (42-104)	42 (29-60)	.059
SGPT in last week RT (IU/mL)	36 (22-73)	31 (25-48)	.644
Alkaline phosphatase (IU/mL)	289 (159-369)	213 (145-402)	.952
Total bilirubin mg%	2 (1-3)	1 (0-1)	.01
Albumin gm%	3 (3-4)	4 (3-4)	.191

Abbreviations: RT = radiation therapy; SGOT = serum glutamic-oxaloacetic transaminase.
Liver enzymes and biochemistry levels are those in last week of RT.

Gy (IQR, 51-57 Gy) and duodenum 52 Gy (IQR, 48-55 Gy; Supplement Table).

Factors predicting toxicity

The median PTV1 was 919 cc (IQR, 775-1148 cc) in patients who developed hepatotoxicity (classic radiation induced liver disease [RILD]) compared with 738 cc (IQR, 657-905 cc) in those who did not (P = .02; Table 2; Fig. 4). Similarly, the median PTV2 was 388 cc (IQR, 286-660 cc) in patients who developed RILD compared with 209 (IQR, 196-321 cc) in those who did not (P = .01). A receiver operating curve analysis revealed a cut-off value of PTV1volume of 800 cc with a sensitivity and specificity of 75% and 54% and a value of PTV2 volume of 300 cc with a sensitivity and specificity of 81% and 65% to predict hepatotoxicity. Mean liver dose and V40 liver was 30 Gy (28-35 Gy) and 50% (IQR, 40%-56%) in those who developed RILD compared with 28 Gy (25-32 Gy) and 39% (IQR, 35%-48%) in those who did not (P = .07, P = .02). Patients more than 65 years age had a significantly higher incidence of hepatotoxicity (P = .03). The mean age of patients who developed RILD was 58 versus 51 years in those who did not (P = .045). Those who developed RILD also had a significant rise in serum glutamic-oxaloacetic transaminase by last week of CTRT (median level of 63 IU/mL [IQR, 42-104 IU/mL] vs 42 [IQR 29-60 IU/mL], P = .059). Similarly, those who developed RILD also had a significant rise in total bilirubin level by last week of CTRT (median level of 2 mg% [IQR, 1-3 mg%] vs 1 mg% [IQR, 0-1 mg%], P = .01). In terms of ALBI score, the mean value was −2.7 in those who did not develop hepatotoxicity, and −2.1 in those who developed (P = .004).

None of the dosimetry factors showed significance for GI bleed. Even though presentation with obstructive jaundice and subsequent stenting did not reach statistical significance for GI bleed, 60% patients who developed GI bleed had prior stenting (Table 3, Fig. 4, Supplement Table). Similarly, the median PTV2 volume was numerically larger in those who developed GI bleed than those who did not. V15 duodenum was also numerically higher (98%) in those who bled compared with 50% in those who did not. Similarly gastric V45

V15 and V45 duodenum was significantly higher in those who developed anemia 51% (IQR, 43%-92%) and 45% (IQR, 41%-57%) compared with 43% (IQR, 34%-54%) and 38% (IQR 20%-46%; P = .007 and 0.028, Table 4) in those who did not.

It was difficult to discriminate the cause of pain abdomen (dyspepsia) in patients on CTRT, whether it was due to hepatotoxicity or gastritis. None of the dosimetric factors predicted for the development of dyspepsia (Supplement Fig. E2).

Discussion

GBC usually presents in advanced stage hence strategies are needed to improve outcomes in responders to first-line CT. The results of this study revealed clinically

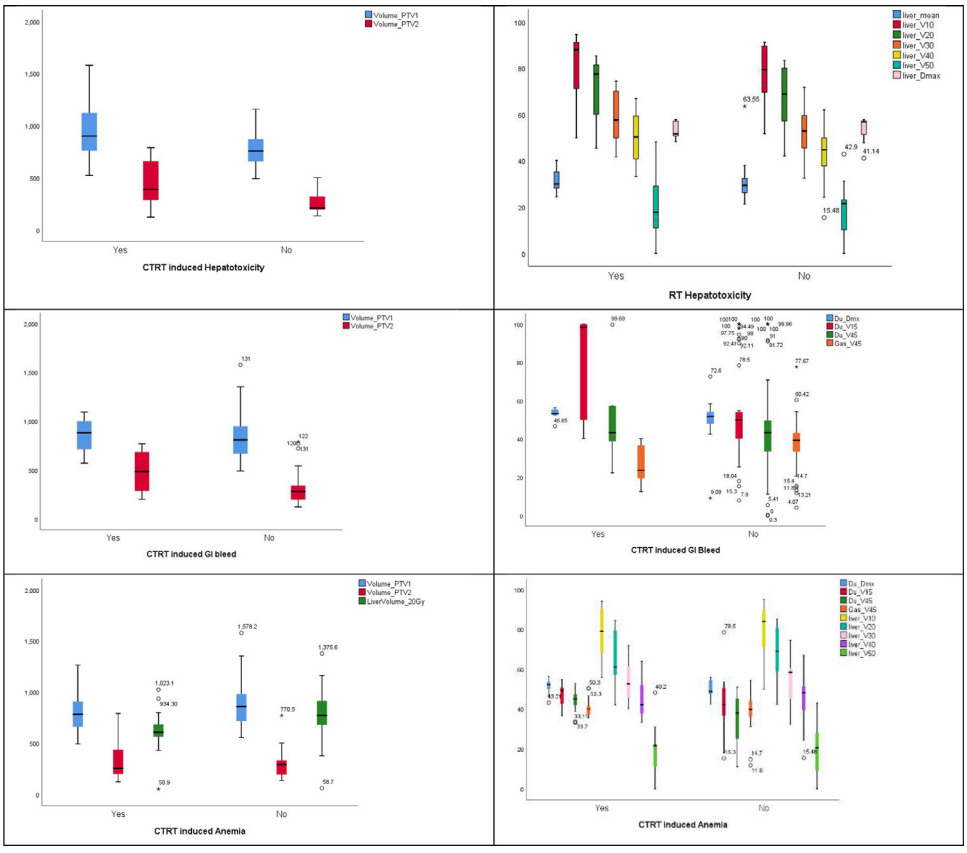

Figure 4 Box plot showing factors affecting consolidation chemoradiation induced toxicities. *Abbreviations:* CTRT = consolidation chemoradiation; PTV = planning target volume.

significant gain in overall survival from 4 to 10 months after randomization and 7 to 13 months after accrual and 2-year OS of 4% versus 13%.[7] Hence it is important to identify predictors of toxicity due to CTRT to practice it safely. Although the literature on toxicity and its predictors are available for hepatocellular cancers and cholangiocarcinoma, toxicity due to consolidation CTRT in postneoadjuvant setting in GBC is not available.

Based on our results grade 3 hepatotoxicity (classic RILD) due to CTRT was observed in 13% patients (Child Pugh B) and grade 2 (Child Pugh A) in 12%. Patients 58 years or older developed RILD, perhaps boost RT may

Table 3 Factors predicting GI bleed

	GI bleed		
	Yes	**No**	***P* value**
PTV1 volume	915 (±228)	842 (±252)	.5
PTV2 volume	484 (±250)	308 (±168)	.06
Duodenum D max	53 (53-55)	52 (48-54)	.361
Duodenum V15	98 (50-100)	50 (40-55)	.112
Duodenum V45	43 (39-57)	43 (33-50)	.701
Gastric V45	24 (19-37)	39 (33-43)	.073
SGOT in last week RT (IU/mL)	34 (23-44)	51 (33-67)	.117
SGPT in last week RT (IU/mL)	31 (16-37)	34 (25-67)	322
Alkaline phosphatase in last week RT (IU/mL)	99 (90-237)	253 (159-422)	.062

Abbreviations: GI = gastrointestinal bleed; RT = radiation therapy; SGOT = serum glutamic-oxaloacetic transaminase.
Liver enzymes are median values in last week of RT.

Table 4 Factors predicting chemoradiation induced anemia

	CTRT induced anemia		
	Yes	No	*P* value
Duodenum Dmax	53 (50-54)	50 (47-54)	.235
Duodenum V15	51 (43-92)	43 (34-54)	.078
Duodenum V45	45 (41-57)	38 (20-46)	.028
Gastric V45	38 (33-41)	37 (25-43)	.88
PTV1 volume	830 (662-999)	832 (674-948)	.865
PTV2 volume	254 (198-436)	290 (192-332)	.678
Liver V10	79 (67-90)	84 (70-90)	.945
Liver V20	61 (54-76)	69 (57-80)	.486
Liver D20 (cc)	605 (563-704)	747 (621-871)	.022
Liver V30	53 (46-62)	58 (43-61)	.758
Liver V40	38 (35-51)	46 (35-51)	.678
Liver V50	22 (11-24)	21 (11-28)	.954

Abbreviation: CTRT = consolidation chemoradiation.

be avoided in elderly after prospective evaluation of tolerance of consolidation CTRT without boost in elderly. We had to include elderly patients in our study due to low accrual in COVID-19 times. Based on these findings we propose that if V40 is 50% or more in phase 1 due to large PTV, then further boost may be avoided. Mean liver dose and V40 should be less than 28 Gy and 50% to avoid hepatotoxicity while using 3D CRT techniques and this data are similar to that reported in literature for liver cancers.[11,12] Although we did not find a correlation of hepatotoxicity with V30, there was correlation with V40 >50%. Studies of 3D conformal radiotherapy in liver cancer have shown a correlation of RILD with V30 >28%, V35 >25%, and V40 >20%. The same study also found a correlation of GTV >1000 cc with 27% incidence of hepatotoxicity, and we observed 25% incidence of hepatotoxicity with median PTV1 of 919 cc and median PTV2 of 388 cc.[13] Based on the receiver operating curve analysis we propose PTV1 volume and PTV2 volume should be less than 800 and 300 cc to avoid hepatotoxicity. Risk stratification of patients to reduce PTV1 volume is likely to result in better tolerance, that is avoiding RPLN irradiation in patients without RPLN involvement. Ideally, risk stratification would be possible only with a positron emission tomography/computed tomography before initiation of CTRT. All patients had normal baseline liver function before initiation of CTRT and patients who developed hepatotoxicity showed a rise in bilirubin and alkaline phosphatase levels toward end of CTRT. The ALBI score has been found to predict hepatic function decline compared with the CP score in patients with HCC and in our series, it was found to distinguish between patients with or with RILD.[14]

All GI bleeds (5.8%) were fatal. Even though none of the dosimetric factors predicted GI bleed in the index study, the mean Duodenum V15 was numerically much higher in patients who bled compared with those who did not (Table E1). Sixty percent of patients who developed GI bleed had prior obstructive jaundice and stenting. Duodenal erosions and ulcers have been reported in patients with pancreato-biliary obstruction.[15] The odds of developing ulcers in patients with obstruction was 4.4 and this was more so in those in whom the degree of obstruction multiplied by duration of jaundice was higher. The PTV2 volume was also higher in patients who bled (484 cc) versus 308 cc in those who did not. To minimize incidence of GI bleed and RILD in patients presenting with obstructive jaundice, boost RT may be omitted as these patients have already compromised liver function and the incidence of GI bleed has been reported to be higher in patients who receive CTRT after stenting. The incidence of stomach or small bowel ulceration was 2%, small bowel obstruction 2%, or GI bleed 15% in a retrospective series of locally advanced extrahepatic biliary cancer where the median RT dose was 50.4 Gy in 28 fractions.[15]

The incidence of all grade and grade 3 anemia was 35% and 9% in the index study. Abdominal CTRT may cause all grades anemia in 80% patients as reported in a series of gastric cancer.[16] Another cohort study observed 11% grade 3 anemia with 45 Gy CTRT. [17] Only duodenal dose predicted occurrence of anemia in our study.

Treatment discontinuation due to adverse events was seen in 11.6% patients in the present study and 8% in a series of unresectable extrahepatic biliary cancer.[14] PTV 2 volume emerged as significant predictor of toxicity for grade 3 hepatotoxicity and GI bleed. Because this is the first randomized study to evaluate the effect of CTRT in responders to first-line CT, we do not know whether there is an advantage with boost. We included boost in our protocol to escalate radiation doses for superior survival as mentioned by Krishan and others where survival benefit was observed with dose escalation.[15,18]They commented that BED >59.5 Gy, elective lymph node irradiation was associated with improvement in OS, and brachytherapy after external RT was associated with inferior OS. The FFCD 9902 trial also suggested a potentially meaningful palliative role for RT with a lower rate of biliary complications (28% vs 44%), such as obstruction with cholangitis, in the cohort receiving CRT compared with chemotherapy alone.[19]The utility of RT, with a suggestion for 2- to 3-year survival benefit has been supported by various authors in retrospective series of biliary cancers.[20]

Limitations

Due to difficulty in accrual of patients due to COVID-19 the inclusion criteria were modified to include elderly patients, those with limited liver metastases in segment

IV and V (encompass able in the treatment portal) or oligo-metastatic disease. Use of IMRT and VMAT is likely to decrease the incidence of adverse effects due to CTRT.

Conclusion

Based on our results, we can conclude that consolidation CTRT is well tolerable in those with PTV1 volume less than 800 cc and PTV 2 volume less than 300 cc. The present study informs us that liver mean dose and V40 should be below 28 Gy and 50% and duodenum V15 should be below 50% to minimize incidence of grade 3 adverse events.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2024.101468.

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