

RESEARCH ARTICLE

Radiological Downstaging with Neoadjuvant Therapy in Unresectable Gall Bladder Cancer Cases

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Abstract

Background: Gall bladder cancer (GBC) usually presents as unresectable or metastatic disease. We conducted a feasibility study to evaluate the effect of neoadjuvant therapy (NAT) on radiologic downstaging and resectability in unresectable GBC cases. **Materials and Methods:** Patients with locally advanced disease were treated with chemoradiotherapy [CTR] (external radiotherapy (45Gy) along with weekly concurrent cisplatin 35mg/m² and 5-FU 500 mg) and those with positive paraaortic nodes were treated with neoadjuvant chemotherapy [NACT (cisplatin 25mg/m² and gemcitabine 1gm/m² day 1 and 8, 3 weekly for 3 cycles). Radiological assessment was according to RECIST criteria by evaluating downstaging of liver involvement and lymphadenopathy into complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). **Results:** A total of 40 patients were evaluated from January 2012 to December 2014 (CTR=25, NACT=15). Pretreatment CT scans revealed involvement of hilum (19), liver infiltration (38), duodenum involvement (n=22), colon involvement (n=11), N1 involvement (n=11), N2 disease (n=8), paraaortic LN (n=15), and no lymphadenopathy (n=6). After neoadjuvant therapy, liver involvement showed CR in 11(30%), PR in 4 (10.5%), SD in 15 (39.4%) and lymph node involvement showed CR in 17 (50%), PR in 6 (17.6%), SD in 4 (11.7 %). Six patients (CTR=2, NACT=4) with 66.6 % and 83% downstaging of liver and lymphnodes respectively underwent extended cholecystectomy. There was 16.6 % and 83.3% rates of histopathological CR of liver and lymph nodes. All resections were R0. **Conclusions:** Neoadjuvant therapy in unresectable gall bladder cancer results in a 15% resectability rate. This approach has a strong potential in achieving R0 and node negative disease. Radiologic downstaging (CR+PR) of liver involvement is 40.5% and lymphadenopathy is 67.5%. Nodal regression could serve as a predictor of response to neoadjuvant therapy.

Keywords: Radiologic downstaging - neoadjuvant therapy - unresectable gallbladder cancer

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Introduction

Gall bladder cancer is endemic in northern India and often presents as locally advanced or metastatic disease (Randi et al., 2006). Complete surgical resection is the only treatment modality with curative potential. It has a median survival of 9 months after simple cholecystectomy, and 19 months after extended cholecystectomy in patients who are apparently resectable. The clinical diagnosis of gallbladder cancer is challenging due to the lack of specific signs and symptoms and consequently, the diagnosis is often not made until the disease is unresectable. Down-staging these tumours by neoadjuvant therapy could possibly render these tumours resectable and allow standard surgery to be carried out, as has been attempted and demonstrated by few investigators (Aretxabala et al., 1999; Kato et al., 2013).

Unresectable GBC are those which are involving the portal vein, hepatic artery, common bile duct, adjacent organs and those with distant nodal disease or metastases. The proximity of the gallbladder neck to the right portal

pedicle and right hepatic duct poses limitations on the surgical margins in this area without compromising the integrity of the right liver - these tumors more often than not, end up receiving only palliation (Saxena et al., 1995). The preoperative identification of gross bulky hilar lymphadenopathy is a strong relative contraindication to surgery.

Given the very poor prognosis of gallbladder cancer in the setting of bulky radiologically evident adenopathy, some investigators have advocated preoperative therapy in order to downstage and render these patients resectable. The earliest published phase II report by Aretxabala et al. (1999) reported 86% resectability rate with neoadjuvant 5-fluorouracil and radiation in 18 potentially resectable gall bladder cancers. At a median follow-up of 24 months, 46% were alive. Amongst those who died only one patient had a local recurrence. This kind of optimistic response in a disease like gall bladder cancer, with nihilistic five year survival figures overall, merits addressing de-novo gall bladder cancers at primary stage rather than as incidental gall bladder cancers, which are biologically early lesions

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as compared to locally advanced gall bladder cancers. The other published study of neoadjuvant chemotherapy in locally advanced GBC from Japan demonstrated 36.5% resectability rate (Kato et al., 2013).

We report radiologic downstaging in a cohort of unresectable GBC patients who received neoadjuvant therapy as a part of our prospective feasibility study.

Materials and Methods

This is a prospective feasibility cohort study approved by institute ethics committee. Patients with GBC, proven cytologically or histologically with TNM Stages IIIa, IIIb, IVa were included in this study. The inclusion criteria for patients was involvement of right branch of the hepatic artery or portal vein or common bile duct, common hepatic duct and primary biliary confluence or liver, duodenum and colon involvement and lymphadenopathy in hepato-duodenal, peri-pancreatic, common hepatic artery regions (N1). Jaundiced patients were to be included in this trial only after endoscopic palliation of jaundice. Patients with recognizable metastasis (M1) and having following criteria: age > 70 years, untreated surgical obstructive jaundice (SOJ), ascites, history of prior chemotherapy for locally advanced or metastatic disease, uncontrolled co-morbidities (like diabetes mellitus, coronary artery disease, chronic renal failure, chronic lung disease) making them unfit for chemoradiotherapy or anesthesia and major surgical undertaking, ECOG performance status >1, Platelets <100.000 X10⁹/L, serum creatinine >1.5 X institutional upper limit of normal (IULN), serum bilirubin >1.5X IULN, serum ALT>2.5 X IULN, history of weight loss >15%, inadequate dietary intake (at least 1500 cal/day) were excluded from this study. After an year patient recruitment was below the expectations and patients more often presented with enlarged paraaortic lymphnodes, hence the inclusion criteria was relaxed to include these patients with advanced disease as well.

Primary objective

To assess the radiological downstaging of locally advanced carcinoma gallbladder with neoadjuvant therapy as per RECIST criteria (Therasse et al., 2009).

Treatment schedule

Patients underwent basic diagnostic investigations (complete history, physical examination, triple phase CT scan abdomen, chest X-ray, routine hematology, and serum chemistry and FNAC). A diagnostic laparoscopy to rule out presence of disseminated disease was desirable in all patients. In jaundiced patients, laparoscopy was performed after palliation of jaundice, prior to induction into study.

For patients undergoing chemoradiation a treatment planning scan was done on Somatom Sensation Open CT scanner (M/s Siemens Medical System, Germany) and the data was imported into Eclipse planning system. Radiotherapy was delivered by a linear accelerator to gallbladder tumour and enlarged lymphnodes with 1.5 cm margin using at least 6 MV photons or a combination with 15 MV photons by 3DCRT technique upto a dose of 45Gy/25#/5weeks along with concurrent chemotherapy

consisting of weekly injection 5-Fluorouracil 325 mg/m² and injection cisplatinum 35mg/m² with adequate hydration and antiemetic cover. Prophylactic irradiation of unenlarged periportal, peripancreatic, retroportal, coeliac, superior mesenteric and paraaortic lymphnodes upto L2 vertebral level upto 45 Gy was also mandatory. For those presenting with enlarged or suspicious coeliac, superior mesenteric or paraaortic lymph nodes (N2 or more), neoadjuvant chemotherapy (NACT) was administered for 3 cycles (cisplatin 25mg/m² and gemcitabine 1gm/m² day 1 and 8, 3 weekly). If patients had adequate downstaging after 3 cycles they were subjected to surgery and if not, then further 3 cycles were given before a restaging triple phase CT scan was done for evaluation for resectability. Weekly toxicity assessment using NCI-CTC criteria for haematological and non-haematological toxicity during chemoradiation or chemotherapy was also done (ctc version 2003).

Evaluation of efficacy of treatment

Radiological assessment of disease status prior to neoadjuvant treatment was as per the AJCC 7th edition (AJCC 7th Edition Cancer Staging Manual). A triple phase CT scan 4-6 weeks after completion of treatment (chemoradiation or 3-6 cycles chemotherapy) was done to evaluate radiological downstaging. Radiological downstaging was graded into complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) according to Response Evaluation Criteria in Solid Tumours (RECIST) for extent of liver infiltration and lymph node size. Indentation or loss of fat plane with duodenum and colon was considered involvement of these structures and complete restoration of fat plane was considered as complete response, partial resolution as partial response, no resolution as stable disease and progression of infiltration was considered as progressive disease. Irregularity of the vessel wall or narrowing was considered as vessel involvement. Resolution of vessel wall abnormality or restoration of its patency was considered as response to neoadjuvant therapy.

Surgery

All patients showing radiological signs of resectability 4 weeks after completion of CRT or NACT were considered for surgical resection. The surgical procedure were classified as microscopically radical (R0), macroscopically complete but microscopically non-radical (R1) or macroscopically incomplete (R2).

Follow-up

Patients with R0 disease were kept only on follow-up and those with R1 disease were offered postoperative radiotherapy (in those who received neoadjuvant chemotherapy). Thereafter patients were followed up every 3 months for 2 year and then every 6 months until local progression, death, loss to follow-up or until 36 months after study inclusion in radiation oncology and surgical gastroenterology OPD.

Statistical considerations

A sample size of 50 was taken assuming 10-20%

resectability rate after chemoradiation. This is an interim analysis of radiological downstaging in 40 patients with this approach. Conversion of radiological downstaging to resectability rate and conversion of radiological response to pathological response is also being reported. Treatment compliance, morbidity, mortality and survival will be reported separately after adequate follow-up. Analysis of the study was according to intent to treat.

Results

Forty patients have been inducted into this study from January 2012 to December 2014. The median age of patients was 52 years (interquartile range 35-57 years), male: female ratio is 9:31. Only 50 % patients underwent diagnostic laparoscopy due to logistic reasons. 19 presented with obstructive jaundice and underwent stenting prior to neoadjuvant therapy. 7.5% (n=3) patients progressed on treatment and 15% (n=6) deteriorated on or after completion of treatment and hence 2 sets of CT scans for response assessment were available for 31 patients only. 62.5% patients (n=25) were treated by CTRT and 37.5% (n=15) by NACT. 10% patients with obstructive jaundice treated with CTRT were radiologically suitable for further surgical evaluation, but succumbed to gastrointestinal bleeding after completion of treatment.

Radiological downstaging

The pretreatment CT scans revealed involvement of hilum in 47.5% (n=19), liver infiltration (any) in 95% (n=38), liver infiltration > 2cm in 70% (n= 28), duodenum involvement in 55% (n=22), colon involvement in 27.5% (n=11), N1 station involvement (periportal lymphadenopathy) in 27.5% (n=11), N2 disease (coeliac and superior mesenteric lymphadenopathy) in 20% (n=8), paraaortic lymphadenopathy in 37.5% (n=15), no lymphadenopathy in 15% (n=6). Right hepatic artery was involved in 30% (n=12), common hepatic artery was involved in 12% (n=5), portal vein was involved in 25% (n=10).

After neoadjuvant therapy (CTRT=25, NACT=15), the overall radiological response rate (CR+PR) was 40.5 % in any liver involvement, 24.9% in liver infiltration > 2cm, 76.8% in duodenum and 62.5% in colon (Table 1). There was 36.3% partial response in 22 patients who presented with vessel involvement (any). Radiological resolution of hepatic artery or portal vein involvement was seen in 25% and 12.5% patients and the rest had static disease. Out of 34 patients who presented with lymphadenopathy 67.6% showed overall radiological response (CR+PR). 36.3% with N1 lymphadenopathy, 62.5% with N2 lymphadenopathy and 53.3% with paraaortic lymphadenopathy revealed radiological CR (Table 2).

Resectability rate

6 patients underwent extended cholecystectomy (CTRT=2, NACT=4). All resections were R0. All resected patients had preoperative liver infiltration (n=6), 2 had colon involvement and 3 had duodenal wall abutment. All had lymphadenopathy (N1=1, N2=3, paraaortic LN=2). Four patients (66.6%) showed radiological CR at primary but the histopathological CR was seen in one patient only

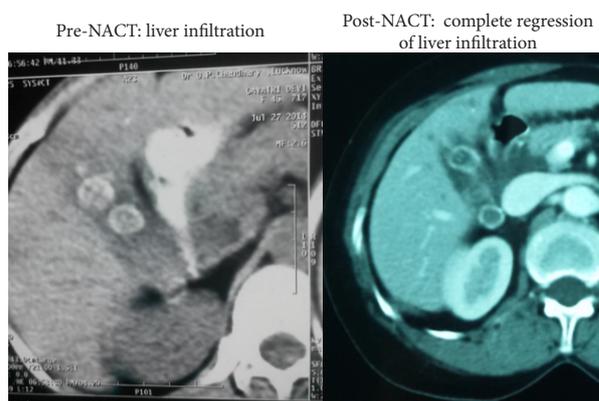


Figure 1. Illustration of Radiological CR Liver Infiltration, on Histopathology: pathological CR of Gallbladder and Liver

Table 1. Radiological Downstaging of Liver, Colon, Duodenum and Vessels

	Radiological CR % (n)	Radiological PR % (n)	Radiological Static disease % (n)	Radiological progressive disease % (n)	Not evaluable % (n)
Liver infiltration (n=38, 95%)	30 (11)	10.5 (4)	39.4 (15)	-	21 (8)
Liver infiltration >2cm (n=28, 70%)	21.4 (6)	3.5 (1)	50 (14)	-	25 (7)
Duodenum (n=22, 55%)	45.4 (10)	31.8 (7)	2.5 (1)	-	18.1 (4)
Colon (n=12, 30%)	54.5 (6)	8 (1)	16.6 (2)	-	25 (3)
Arterial involvement *(n=12, 30%)	-	25 (3)	75 (9)	-	-
Venous involvement (n=10, 25%)	-	12.5 (5)	12.5 (5)	-	-

*Involvement of common hepatic artery and right hepatic artery clubbed together.

Table 2. Radiological Downstaging of Various Stations of Lymph Nodes

	Radiological CR % (n)	Radiological PR % (n)	Radiological Static % (n)	Radiological progressive disease % (n)	Not evaluable % (n)
N1 (n=11, 27.5%)	36.3 (4)	36.3 (4)	4 (1)	0	8 (2)
N2 (n=8, 20%)	62.5% (5)	12.5 (1)	0	0	2
Paraaortic (n=15, 37.5%)	8 (53.3)	1 (6.6)	3 (20%)	1 (6.6%)	13.3 (2)
Overall	17 (50%)	6 (17.6%)	4 (11.7%)	1 (2.9%)	12 (30%) (6 had no upfront lymphadenopathy)

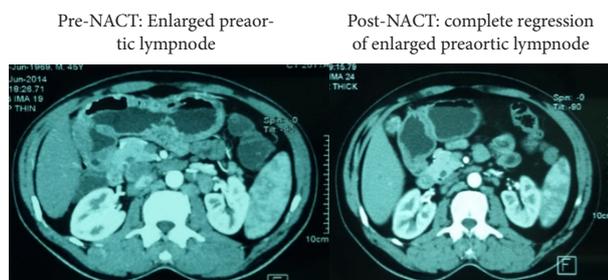


Figure 2. Illustration of Radiological CR Preaortic Lymphnode, R0 Resection, on Histopathology: Pathological CR of Lymphnode

(16.6%) (Figure 1). 83.3% (5/6) showed radiological CR at lymphnodes and all had histopathological CR (Figure 2). At a median follow-up of 18 months, four out of 6 patients are alive till date. One patient expired in the immediate postoperative period and the other developed liver metastases after a 24 months disease free period and succumbed after a course of secondline chemotherapy.

Discussion

To the best of our knowledge this is the first detailed report on radiologic response assessment to neoadjuvant therapy in unresectable gall bladder cancer. Neoadjuvant therapy results in high overall radiological response rate (CR+PR) in these patients. It is 40.5 % in patients with any liver involvement, 24.9% in liver infiltration > 2cm, 76.8% in duodenum and 62.5% in colon involvement. Some 30% of patients with any liver involvement and 20% with liver infiltration > 2cm achieved radiological CR, this also being the case in 45% of patients with duodenum involvement and 54% with colon involvement. The histopathological CR at primary site was 2.5%.The conversion rate of radiological CR to histopathological CR for liver infiltration was 9%.

Similarly radiological response rates in downstaging of lymphadenopathy is also very encouraging. The overall radiological response rate is 67.6% for lymphadenopathy at any site.72.6% of patients with N1 disease,75% with N2 and 59.9 % with paraaortic lymphadenopathy. 36.3% with N1 lymphadenopathy, 62.5% with N2 lymphadenopathy and 53.3% with paraaortic lymphadenopathy showed radiological CR. The histopathological CR was 12.5%.The conversion rate of radiological CR to histopathological CR is 29.4% in this series and is very promising for unresectable GBC.

Aretxabala reported 55.5% pathologic CR in liver and lymphnodes in a potentially resectable subset of GBC who underwent neoadjuvant chemoradiation (Aretxabala et al., 1999). Their study included patients with disease limited to gallbladder bed and N1 station lymphadenopathy while in our study patients had N1, N2 and paraaortic lymphadenopathy. Kato reported 13.6% PR and 50% SD with neoadjuvant gemcitabine in a series of 22 unresectable GBC patients and the pathologic CR rate for GB and liver was not seen while it was 22% for lymphadenopathy and this is comparable to our series (Kato et al., 2013). Radiological resolution of vascular

involvement was seen in only a quarter of patients and none of them were rendered resectable. Similar results were observed in the Japanese series (Kato et al., 2013).

Neoadjuvant therapy in our series resulted in 15% resectability rate, 36.3% in Japanese series and 57.4% and 47% in Indian series of 122 and 17 patients respectively (Sirohi et al., 2012; Gangopadhyay et al., 2015). All resected patients in our series had R0 resection, while 18% in Japanese series underwent R0 resection and 18% underwent R1 resection (Kato et al., 2013). Our low resectability rates could be explained by disease progression or morbidity in 22.5% patients presenting with obstructive jaundice.

There is no known predictor of response to chemotherapy in GBC. The results of this study demonstrate that lymphnode regression with neoadjuvant therapy is a good predictor of histopathological response.

The limitations of this study were non uniform protocol of treatment due to low accrual and the compliance for diagnostic laparoscopy was 50% due to logistic reasons.

In conclusion, neoadjuvant therapy in unresectable gall bladder cancer results in 15% resectability rate. This approach has a strong potential in achieving R0 and node negative disease. Radiologic downstaging (CR+PR) of liver involvement is 40.5% and lymphadenopathy is 67.5%. Nodal regression could serve as a predictor of response to neoadjuvant therapy.

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