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ORIGINAL ARTICLE

Role of Adjuvant Chemotherapy in Resected T2N0 Gall Bladder Cancer

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Abstract

Background Management of operable gall bladder cancer (GBC) is closely related to its tumor (T) and nodal (N) status. The magnitude of benefit with adjuvant chemotherapy in completely resected, node negative T2 cancers is not completely defined.

Materials and Methods Retrospective analysis of patients diagnosed with pathological T2N0 (stage II, 7th edition AJCC) GBCs from January 2011 to June 2016 was evaluated for adverse risk factors, adjuvant treatment received, recurrence-free survival (RFS), and overall survival (OS). Survival analysis was done using Kaplan-Meier and Cox regression tools.

Results Of the 88 patients included, 30 received adjuvant chemotherapy while 58 were observed. The OS and RFS in the entire cohort were 82.9% and 62.7%, respectively, at a median follow-up of 44.18 months. The OS and RFS in the chemotherapy group were 85.1% and 76.4% while it was 81.4% and 55.5% in the observation group ($p = 0.50$). Recurrent disease was seen in 30.7%.The presence of lymphovascular invasion predicted inferior RFS ($p = 0.031$).

Conclusions Adjuvant chemotherapy may reduce distant failure rates but did not improve OS in completely resected T2N0 GBC patients in this study. LVI predicted inferior RFS in T2N0 patients. An evaluation of adverse prognostic factors would help design personalized treatment strategies for this select cohort of T2N0 GBC.

Keywords Gall bladder cancer · Adjuvant chemotherapy · T2N0 · Lymphovascular invasion (LVI)

Introduction

Gall bladder cancer (GBC) is the commonest biliary tract malignancy which accounts for 80–95% of all biliary tract cancers. It is also the 6th most common gastrointestinal cancer worldwide[1] with an incidence of 2 per 1000,000.[2] The survival outcomes are dismal and can be often fatal despite aggressive surgical resection.[3] The 5-year overall survival rate is around 5–10%, all stages combined[1] with 80% survival in stage I, 30–40% in stage II, and around 10% in stage III disease.

Recurrences in gall bladder cancer, after a standard resection which includes a radical cholecystectomy and periportal lymphadenectomy, can be nodal, distant (liver, peritoneum, lungs), or a combination of both. Adjuvant treatment (chemotherapy/chemoradiotherapy) is thought to likely diminish the risk of both local and distant recurrences. This forms the basis for administering adjuvant therapy even after curative resections.[3]

Adjuvant chemotherapy has shown maximal benefits in cases where there is nodal positivity, R+ resections, or tumors with stages above pathological (p)T2.[4] Literature supporting adjuvant chemotherapy includes small retrospective studies that quote incremental survival benefit, although other studies have not replicated the same. Furthermore, gall bladder cancers are usually combined with biliary tract cancers that lead to ambiguity in interpretation of results.[5] Adjuvant chemoradiation, on the other hand, has been used for margin positive or node positive resections and rarely for R0 resections.[2,4] Since the majority of benefit of adjuvant therapy for GBC is in node

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positive and R+ resections, there is a possibility that lower disease stages need exploration of factors which may or may not influence the need for adjuvant therapy. Patients with T2N0 GBC comprise such a niche subset and the current study aims to explore possible prognostic factors as well as outcomes in such a subset.

Materials and Methods

This was a retrospective analysis of a prospectively maintained database from January 2011 till June 2016 done at Tata Memorial Hospital, Mumbai. The medical records of patients with pathological stage T2N0 were retrieved from our database of gall bladder patients treated surgically. Patients who had received any form of chemotherapy prior to surgery were excluded from analysis. Demographic, surgico-pathological, and oncological outcomes including survival were measured. The decision to administer adjuvant chemotherapy was at the discretion of a multi-disciplinary team, on a case to case basis. Gemcitabine with cisplatin (or oxaliplatin) was the standard adjuvant chemotherapy. The surgery undertaken was radical cholecystectomy (involving resection of the gall bladder with liver wedge/segment IVB, V excision, and periportal lymphadenectomy) in upfront cases and revision cholecystectomy (involving gall bladder bed excision with periportal lymphadenectomy) in those patients presenting with incidental gall bladder cancers after a simple cholecystectomy. The decision to administer chemotherapy or observe was taken in multidisciplinary (joint) clinic after reviewing the histopathology report. Young patients with aggressive histologies and/or poor prognostic features (perineural invasion/lymphovascular invasion) generally received chemotherapy whereas older patients with significant comorbidities were generally kept under observation.

All patients were followed 3 monthly for the first 2 years and 6 monthly for the next 3 years and yearly thereafter. At each follow-up, thorough clinical examination with ultrasound abdomen and CA 19-9 levels were measured. Patients in whom recurrence was suspected underwent further evaluation using contrast-enhanced computerized tomography (CECT) scans of thorax, abdomen, and pelvis or positron emission tomography (PET)-CT scans. Biopsies were done to confirm disease recurrences when indicated. Locoregional recurrence was defined as disease recurring at the porta, gall bladder fossa, or periportal nodes. Distant recurrence was defined as the development of liver, retroperitoneal nodal, or peritoneal metastases.

All the data were analyzed using the SPSS ver. 25 software (IBM Corporation, NY; formerly SPSS Inc. Chicago, IL). Descriptive statistics including median, frequency, and percentage for categorical variables was used. Kaplan-Meier method with Cox logistic regression analysis was used to calculate survival. Statistical significance was defined as p value < 0.05. In the initial explorative data analysis, factors likely to be of prognostic significance were included in the univariate analysis and subsequently in the multivariate analysis if p value < 0.05. Overall survival (OS) was defined as the time period from the date of surgical resection till date of last follow-up or death while recurrence-free survival (RFS) was defined as the time period from the date of surgical resection till the detection of recurrent disease.

Results

Baseline Clinical, Surgical, and Pathological Characteristics

Eighty-eight patients (out of 334 patients curatively treated for GBC which included 0.3% of Tis tumors, 4.5% of Tx tumors, 1.8% of T1a tumors, 4.8% of T1b tumors, 31.4% of T2 tumors, 28.1% of T3 tumors, 1.8% of T4 tumors with 27.2% having no tumor identified on final histopathology: implying no residual tumor) with pathological T2N0M0 satisfied the inclusion criteria and were included for analysis.

The median age of patients was 52 years (range: 29–76 years) with a female predominance (73.9%). The median preoperative CA 19-9 levels were 10.61 IU/ml (range: 2–428). Details are as shown in Table 1. Fifty-eight patients (65.91%) underwent revision cholecystectomy and 30 patients (34.09%) underwent radical cholecystectomy. A concomitant extra-hepatic biliary tree excision (EHBTE) was performed in 4.5% ($n = 4$ patients) (in view of coexistent choledochal cysts in two patients, cystic duct margin positive on frozen section intra-operatively which needed EHBTE in one patient and common bile duct exploration during the first surgery with unknown margin status in one patient). All except two patients (both robotic cholecystectomy) underwent open surgery. In one patient, an en–bloc antrectomy had to be performed in view of adhesions to gastric antrum. Intra-operative gall stones were identified in seven patients (8%).

Adjuvant Therapy and Survival Outcomes

Thirty patients (34.09%) received adjuvant therapy with three patients receiving additional radiotherapy. Among the patients who received adjuvant chemoradiation, one patient had MANEC (mixed adeno- and neuroendocrine) histology and another had a small soft tissue tumor deposit at the porta. Fifty-eight patients (65.9%) received no further treatment (observation group).

The median follow-up was 44.18 months (range: 20–82 months). The OS and RFS of the entire cohort were 82.9% and 62.7%, respectively. Median OS was not reached. In the adjuvant chemotherapy group, OS was 85.1% while in

Table 1 Clinical, surgical, and pathological characteristics of patients

Parameters	Total ($n = 88$)	Observation arm ($n = 58$)	Chemotherapy arm ($n = 30$)
Median age (range)	52 (29–76)	54 (30–76)	48 (29–66)
Gender			
• Males	23 (26.1%)	19 (32.76%)	4 (13.33%)
• Females	65 (73.9%)	39 (67.24%)	26 (86.67%)
Complaints			
• Pain abdomen	51 (58%)	26 (44.83%)	25 (83.33%)
• Incidental	32 (36.4%)	28 (48.28%)	4 (13.33%)
• Dyspepsia	2 (1.1%)	1 (1.72%)	1 (3.33%)
Prior simple cholecystectomy			
• Laparoscopic	40 (45.5%)	32 (55.17%)	8 (26.67%)
• Open	18 (19.3%)	12 (20.69%)	6 (20.00%)
Type of surgery			
• Radical cholecystectomy	30 (34.09%)	14 (24.14%)	16 (53.33%)
• Revision cholecystectomy	58 (65.91%)	44 (75.86%)	14 (46.67%)
• Extra-hepatic biliary tree excision	4 (4.5%)	2 (3.45%)	2 (6.67%)
Histology			
• Adenocarcinoma, NOS	75 (85.22%)	51 (87.93%)	24 (80.00%)
• Papillary adenocarcinoma	5 (5.68%)	4 (6.9%)	1(3.33%)
• Adenosquamous carcinoma	2 (2.27%)	1 (1.72%)	1 (3.33%)
• Mucinous adenocarcinoma	1 (1.13%)	–	1 (3.33%)
• Mixed adeno- neuroendocrine tumor	1 (1.13%)	–	1 (3.33%)
• Signet ring differentiation	2 (2.27%)	2 (3.45%)	–
• Adenocarcinoma with squamous differentiation	2 (2.27%)	–	2 (6.67%)
Median nodal retrieval	7	6	8
Median blood loss (range) in ml	450 (100–3000)	450 (50–1800)	475 (150–3000)
Perineural invasion			
• Present	12 (13.7%)	4 (6.9%)	8 (26.67%)
• Absent	54 (61.4%)	39 (67.24%)	15 (50%)
• Not known	22 (24.9%)	15 (25.86%)	7 (23.33%)
Tumor differentiation			
• Well differentiated (WDAC)	12 (13.7%)	7 (12.07%)	5 (16.67%)
• Moderately differentiated (MDAC)	57 (64.77%)	40 (68.97%)	17 (56.67%)
• Poorly differentiated (PDAC)	13 (14.77%)	7 (12.07%)	6 (20%)
Lymphovascular invasion			
• Present	7 (8%)	3 (5.17%)	4 (13.33%)
• Absent	63 (71.6%)	41 (70.69%)	22 (73.33%)
• Not known	18 (20.4%)	14 (24.14%)	4 (13.33%)
Post-operative complications ($n = 5$)			
Biliary leak	5.5%	3	1
Wound infection	1.1%	1	0
Median hospital stay (range): days	6 (4–25)	6(4–24)	5.5 (4–25)

the observation group, it was 81.4% ($p = 0.50$). The RFS in the chemotherapy group was 76.4% whereas it was 55.5% in the observation group ($p = 0.22$).

Recurrent disease was found in 27 patients (30.7%). The pattern of recurrences is shown in Table 2. The median time to tumor recurrence was 19 months. Nineteen patients with documented recurrent disease received palliative chemotherapy (21.6%). Death due to disease occurred in 11 patients (12.5%): 2 patients in the adjuvant chemotherapy group (2/30; 6.67%) and 9 patients in the observation group (9/58; 15.5%). At the time of analysis, 64 patients were disease free, 13 were alive with disease, and 11 were dead due to disease progression.

Table 2 Patterns of recurrences in both groups

Recurrences	Local ($n = 7$) (25.92%)	Regional ($n = 2$) (7.4%)	Distant ($n = 18$) (66.67%)
Adjuvant group ($n = 6$) (22.22%)	2 (7.41%)	1 (3.7%)	3 (11.11%)
Observation group ($n = 21$) (77.78%)	5 (18.51%)	1 (3.7%)	15 (55.56%)

Prognostic Factors

LVI, PNI, degree of differentiation, and adjuvant therapy were evaluated as factors predicting for outcomes on univariate analysis (Table 3). None of these factors showed any statistical significance in predicting for RFS or OS except in patients with positive LVI who showed better RFS ($p = 0.031$) in adjuvant group compared to observation group.

Discussion

The T2 N0 category fits into stage II disease. These patients have a favorable 5-year survival rate that ranges from 69 to 90% (after a radical oncological resection) that drastically plummets to 10–40% after a simple cholecystectomy alone, thereby underlining the importance of complete oncological excision in these patients.[6] Lymphadenectomy must be included as a component of the surgery as there may be a 40–60% risk of lymph nodal positivity in these patients.[3,6]

The treatment of non-metastatic GBC is closely related to the tumor and nodal status. For early T stage tumors (T1b and T2a/T2b), surgery remains the treatment of choice which includes radical cholecystectomy or revision cholecystectomy (for incidentally detected GBCs). Adjuvant therapy is often instituted for T3/select T4 tumors and in the setting of node and/or margin positivity. The role of adjuvant therapy in the setting of node negative completely resected T2 cancers remains contentious. In addition, there is a paucity of level I evidence related to adjuvant therapy restricted to retrospective analysis or expert statements. Two important caveats must be borne in mind while interpretation of these results: firstly, studies usually include cholangiocarcinomas and periampullary carcinomas along with GBC to summarize their results and secondly, suboptimal surgeries (like simple cholecystectomy with or without nodal clearance) performed in these patients confound the very benefit of administrating adjuvant therapy.[7] Tables 4 and 5 depict a list of trials that have studied the role of adjuvant therapy viz. chemotherapy and chemoradiotherapy in resectable GBCs. As evident from the table, few studies have shown survival[1,11–13] benefit while others have not.[4,8–10]

In our study, there was no difference in OS in patients who received adjuvant chemotherapy over observation alone although RFS was better only in a subset of patients who had positive LVI and had received chemotherapy ($p = 0.031$). Pathological risk factors had no effect on OS. Presence of lymphatic and vascular emboli potentially help tumor cells disseminate via the lymphatic and blood stream which can increase risk of failures especially regional and distant failures. Also, a higher percentage of patients in the observation group had recurrences especially distant recurrences. Both these observations hint that adjuvant chemotherapy may act against any micro-metastases in the blood/lymphatic channels, thereby preventing distant seeding of tumor cells.

Around 30% of patients had disease recurrences locally, regionally, distantly, or as a combination of the above. Only 70% of these recurrences were amenable for palliative chemotherapy emphasizing that recurrent gall bladder cancers have a very poor prognosis and first chance at resection/

Table 3 Relationship of prognostic factors on recurrence and survival

Prognostic variables	Number	Recurrences	Comments
Positive lymphovascular invasion (LVI)			RFS better in adjuvant group compared to observation ($p = 0.031$) OS: no difference
• Adjuvant group	4	0	
• Observation group	3	2	
Positive perineural invasion (PNI)			No difference in RFS ($p = 0.103$) or OS ($p = 0.157$) in both groups
• Adjuvant group	8	2	
• Observation group	4	3	
Poorly differentiated tumors			No differences in RFS ($p = 0.335$) or OS in both groups
• Adjuvant group	6	0	
• Observation group	7	1	
Other histologies (e.g., signet ring etc)			No differences in RFS ($p = 0.317$) or OS in both groups
• Adjuvant group	6	0	
• Observation group	7	1	

Table 4 Studies showing absence of survival benefit from adjuvant therapy in gall bladder cancer

Author/year	Time period	Number (*n*)	Adjuvant therapy	% Received	Stages	F/U (months)	Survival (OS/DFS) adjuvant vs. observation	Recurrences	Comments
Go[8]/2016	1999–2014	363	CT CRT	10.74% 12.4%	I-III	60.4 and 53.4	OS: 66.2% vs. 79.5%	23.41%	Lower RFS in adjuvant arm; no benefit of chemotherapy in R0 resected patients
Wang[9]/2011	1995–2005	1137	CT CRT	11% 11%	I-IV	NR	Median OS:16 months	NR	In T2N0, no benefit from chemotherapy5; CRT: small benefit
Park[10]/2010	2000–2009	43/ 61	CT CRT	65.11% 34.88%	I-III	27.3	OS:78% vs. 64% DFS:69% vs. 56%	NR	No improvement in OS; only DFS benefit
Glazer[4]/2012	1978–2009	63	CT CRT	48.7% 15.8%	All	25.5	3.8 years vs. 5.8 years	NR	Chemotherapy increased probability of death
Present study/2018	2011–2016	88	CT	34.0%	T2N0	44.18	OS:85.1% vs 81.4% RFS: 76.4% vs. 55.5%	30.7%	No RFS or OS benefit from chemotherapy

CT chemotherapy, *CRT* concurrent chemoradiation, *DFS* disease-free survival, *OS* overall survival, *NR* not reported

Table 5 Studies showing some survival benefit from adjuvant therapy in gall bladder cancer

Author/year	Time period	Number (*n*)	Adjuvant therapy	% Received	Stages	F/U (months)	Survival (OS/DFS) adjuvant vs. observation	Recurrences	Comments
Mc-Namara[11]/2015	1987–2011	296	CT CRT	16.52% 9.8%	II:36%	22.3	Median DFS: 13.7 vs. 14.8 months Median OS: 23.6 vs. 22.1 months	60% L:18% D:59% Both: 23%	Adjuvant chemotherapy associated with improved overall survival; R1 resections benefit
Kasumova[1]/2017	2004–2014	6825	CT	31.8%	pT2: 48%	30–40	Median OS: 23.3 vs. 10.7 months	NR	Adjuvant chemotherapy improves survival
Siebenuner[12]/2018	2008–2014	30	CT	100%	T2:5% N0: 67%	31.4	Median OS:40.6 months Median DFS:14.9 months	L:9 D:3 Both:6	Chemotherapy resulted in promising survival
Lee[13]/2012	1994–2011	218	CT CRT	34% 28%	T2 (45%)	200	OS:56%	NR	Adjuvant therapy improves survival

CT chemotherapy, *CRT* concurrent chemoradiation, *DF* disease-free survival, *OS* overall survival, *NR* not reported, *L* local recurrence, *D* distant recurrence

treatment remains the best chance to offer potential cure in these patients. Disease-related mortality was seen in 12.5% patients: higher in the observation group (15.5% vs 6.67%) compared to adjuvant therapy group. All patients died due to disease progression.

All patients in our study underwent as standard oncological surgery (radical or revision cholecystectomy) with R0 resection and an adequate lymph node yield obviating any 'pseudo' benefit that could have arisen from an incomplete or inappropriate resection.

A similar study[14] on the role of adjuvant chemotherapy in resected T2N0 periampullary cancers showed limited benefit with the use of adjuvant chemotherapy. This was a retrospective analysis of 105 patients with 3-year OS and DFS of 94.2% and 81.9% in the observation group and 100% and 90.9% in the chemotherapy group, respectively ($p = 0.33$ and 0.47 for OS and DFS), though the authors suggest that adjuvant chemotherapy could improve survival.

Chemotherapy may be administered as combination or single agent chemotherapy. Single agent 5-fluorouracil (5-FU) has a 20% response rate while gemcitabine has a response rate of 36%.[15] Two meta-analyses have studied the role of adjuvant chemotherapy in GBC. The first study by Horgan et al.[16] reported a non-significant improvement in overall survival in patients receiving chemotherapy over surgery alone in patients with GBC (pooled OR: 0.74). This meta-analysis included 20 studies with a little over 6700 patients. Patients who received adjuvant chemotherapy or chemoradiation did better than those who received adjuvant radiotherapy, though maximum benefit was noted in node positive and R1 resected cancers. The next study by Ma et al.[17] involved 10 studies with around 3100 patients. Again, there was a non-significant improvement in OS in adjuvant therapy group (HR: 0.76). But patients with node negative or R0 resected cancers did not seem to enjoy this benefit.

Two phase III trials have also been published in this regard. In the PRODIGE 12 study[18] which evaluated adjuvant gemcitabine and oxaliplatin versus observation alone in patients with biliary tract cancers demonstrated no difference in relapse-free survival (RFS) in both the groups. Patients with non-curative, macroscopically positive (R2) resections were excluded in this trial. The BILCAP study[19] used adjuvant capecitabine and reported a longer median survival in treated patients, although the study failed to demonstrate a significant improvement in overall survival in the intention to treat analysis. This was accounted for the fact that there was more number of node positive patients in this study. Importantly, both the above mentioned studies had only 18% and 20% of patients with GBC from non-high endemic areas which could limit the generalization of this to GBC.

One of the major strengths of the current study is an attempt to identify nuances in the treatment of stage II GBC beyond T stage alone. Factors like LVI (as predicting for inferior RFS in this study) can be used in larger cohorts for validation as markers of prognosis. Whereas available data from larger RCTs (e.g., BILCAP) suggest that adjuvant treatment should be used, the current study suggests that application of adjuvant treatment on the basis of (or lack thereof) high risk features is worth considering. Despite such hypothesis generating data, multiple caveats exist with the study. The retrospective nature of the study means that it has an inherent bias with regard to non-uniform selection of adjuvant treatment for patients. The small numbers of patients which have been evaluated in this study also have to be factored when considering the implications of our results.

Conclusions

Adjuvant chemotherapy reduced the risk of distant failures but did not improve OS in completely resected T2N0 GBC patients, although a subset of patients with positive LVI showed RFS benefit. Specific large studies should be systematically conducted to identify a cohort of high-risk T2 N0 GBC where a decision for administration of adjuvant chemotherapy can be made based on identification of high-risk factors (like LVI). The recent 8th edition of the AJCC does attempt to subdivide T2 into T2a and T2b which may aid stratification of patients into high-risk and low-risk groups for administering adjuvant chemotherapy in the future.

Authors' Contribution AKK and SP have contributed equally towards concept, design, data collection and analysis, interpretation and final approval of the manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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