REVIEW ARTICLE

Neoadjuvant Chemotherapy for Advanced Gallbladder Cancer: Do We have Enough Evidence—A Systematic Review

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Abstract

Background: Recently for advanced gallbladder carcinoma, neoadjuvant chemotherapy has emerged as an important strategy in place of adjuvant chemotherapy with the hope that it will help to improve the resectability and survival.

Aim: The goal was to conduct a systematic review of published publications on the benefits of neoadjuvant chemotherapy for advanced gallbladder cancer treatment.

Methods: This systematic review followed the Meta-analysis Of Observational Studies in Epidemiology standards. The clinical benefit rate of neoadjuvant chemotherapy, curative resectability rate, and R0 resection were the major outcomes of interest. The secondary outcomes of interest were overall and disease-free survival.

Results: Six published papers were included (n = 420). One-hundred and twenty-eight cases (30.47%) despite receiving neoadjuvant chemotherapy had disease progression. Although 67.38% of patients (283 of 420) in this systematic review showed good response to the neoadjuvant chemotherapy, just 51.66% (217 of 420 cases) were operated, out of which only 171 cases were deemed to be feasible for surgical resection and had curative resection. Out of the cases that underwent curative surgery, 91.81% had R0 resection (157 out of 171 patients). The overall survival rate was found to be 18.5–50.1 months for patients in whom curative surgery was done and 5.0–10.8 months for nonsurgery patients.

Conclusions: No sufficient data exist to advocate the regular use of neoadjuvant chemotherapy in advanced gallbladder carcinoma, as data showed that only 1/3 of patients benefited and had a R0 resection. Further research should be the randomized controlled trials to further quantify the benefit of neoadjuvant chemotherapy in advanced gallbladder carcinoma.

Keywords: Advanced gallbladder cancer, Downstaging, Neoadjuvant chemotherapy, Survival.

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Introduction

Carcinoma gallbladder is known to be fast-growing malignancy having a very dismal prognosis and about 5% 5-year survival. The only potential chance for survival is the radical surgery especially if patients are operated in the early stage.[1,2] The gallbladder carcinoma incidence is highest in Eastern parts of Europe, some parts of East Asia and Latin America.[3] As the gallbladder carcinoma incidence in the Western world is low, there is a difference in the treatment approach and no standard protocol is available for the management.[4,5] As the incidence of gallbladder cancer is low, the longitudinal studies reported in literature have included data of gallbladder carcinoma in combination with intra- and extrahepatic biliary tract malignancies, which did not allow for precise data interpretation.[6,7]

As survival is poor in patients if they have a recurrence, the benefit for adjuvant treatment options plays a role. Data from observational studies, few randomized controlled trials, and few meta-analyses have proven the benefit of postoperative adjuvant chemotherapy in biliary tract malignancy.[8–11] There is enough evidence from a randomized controlled trial based on which patients in whom curative resection of biliary tract cancer has been done should receive postoperative capecitabine-based chemotherapy for 6 months. Level I evidence is lacking, and thus it is difficult to formulate the multimodal treatment protocol as gallbladder carcinoma is rare. In the previous decade, four randomized phase III clinical trials on the use of adjuvant therapy for biliary tract malignancies have been published: ABC-02, PRODIGE-12/ACCORD-18, BILCAP, and BCAT, as well as a single-arm phase II trial (SWOG0809). They contributed to the formulation of the recommendation for adjuvant capecitabine in curatively resected biliary tract cancer patients.[12] Landmark phase III BILCAP trial was the basis on which the ASCO expert panel advocates the use of postoperative adjuvant capecitabine in all curatively resected

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gallbladder cancer patients and use of adjuvant chemoradiation in cases with positive resection margins.[13] The clinical value of these adjuvant therapy modalities is still limited, as the BILCAP study failed to meet its primary endpoint of increased survival on an intention-to-treat basis, highlighting the need for more randomized controlled trials.[14] There is an opportunity to research the role of chemotherapy in the neoadjuvant setting. The Optimal Perioperative Therapy for Incidental Gallbladder Cancer (OPT-IN/EA2197) trial is an ongoing, randomized, phase II/III clinical trial in patients with stage II–III gallbladder carcinoma, which compares between neoadjuvant chemotherapy with gemcitabine/cisplatin and upfront radical cholecystectomy followed by adjuvant chemotherapy.[14] Retrospective data on the benefit of neoadjuvant chemotherapy in locally advanced gallbladder carcinoma in the past decade have produced conflicting results.[15–22]

As we expect neoadjuvant chemotherapy to improve resectability rate and probably survival, the pitfall is that it may lead to postponing of surgical resection and thus may cause the disease to progress. As a result, the value of neoadjuvant chemotherapy in the treatment of advanced gallbladder cancer is unknown. Our goal is to conduct a systematic evaluation of the available research on the use of neoadjuvant chemotherapy in advanced gallbladder cancer treatment.

Materials and Methods

A search as per the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines and previous recommendations for the conduction of systematic reviews of prognostic variables were developed.[23] A search of Medline, EMBASE, Cochrane Library, PubMed, and Google scholar was conducted using the following keywords: "Gallbladder", "Gallbladder cancer", "Chemotherapy", "Neoadjuvant chemotherapy", "Preoperative chemotherapy", "Pre-operative chemotherapy", "Biliary malignancy", "Biliary cancers," and "Advanced". The studies which were published only in abstract form were excluded from the analysis. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidance was utilized.[24]

Definitions

We measured the effect of neoadjuvant chemotherapy in these papers and the response as per the World Health Organization (WHO) or Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[25] WHO criterion is bidimensional in which it takes the summation of two longest diameters perpendicular to one another and RECIST criterion is unidimensional as it measures the summation of longest diameters.[26] Complete response (CR) to neoadjuvant chemotherapy is described as the no disease left for at least 4 weeks. Partial response (PR) is described as >50% disappearance of disease for 4 weeks (≥30% in RECIST criteria) and no new disease. Stable disease (SD) is when both partial response and progressive disease criteria are not met. Progressive disease (PD) is described as >25% (≥20% for RECIST) increase in the already existing lesions or if the new lesion appears. Clinical benefit rate (CBR) is defined as the total percentage of cases that had complete response, partial response, and stable disease after neoadjuvant chemotherapy.

Inclusion Criteria

These papers analyzed the benefit of neoadjuvant chemotherapy with an aim to downstage the disease and maximize curative surgical resection in locally advanced gallbladder carcinoma. We carefully evaluated these studies for any data, which was overlapping. If a center published two papers, we took the study which was of superior quality or the one which was more recently published. Among the studies including all biliary tract cancers, we included only those studies that had subgroup analysis done on gallbladder cancer cases.

Exclusion Criteria

- We did not include those studies in which the cohort of patients was small.
- If the malignancy was early stage (T1/T2).
- Where ever there was overlap of published studies within the same center.
- If the histology was not adenocarcinoma.

Outcomes

Primary Outcomes

- That how efficiently the tumor was downstaged which was measured as CBR and
- The curative resection rate and R0 resection.

Secondary Outcomes

- Overall survival.
- Disease-free survival.

Data Extraction

Extraction of data was done using a standardized proforma. The following clinical and demographic characteristics were noted: study characteristics, population characteristics (number of patients studied, patient demographics, follow-up duration, and loss to follow-up), and outcomes of interest.

Quality Assessment

The level of evidence was determined separately using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) standards and quality assessment guidelines that have previously been published particularly for systematic reviews of prognostic studies.[27]

The following quality standards were established:

A sufficient baseline data set was recorded, as was the length of follow-up and the number of patients lost to follow-up, as well as a clear mention of the use of downstaging neoadjuvant chemotherapy or surgical resection with the goal of curative surgery.

Statistical Analysis

We tabulated the data. Data were extracted from the main text and from the tables provided. Kaplan Meier survival curves were studied, from which overall survival and disease-free survival were extracted. As there was heterogeneity of the included studies and no data were available to compare, the pooled analysis was not feasible.

Results

We identified six published papers in this literature review (Fig. 1). We excluded the duplicate studies, review articles, letter to the editor, and case reports. After that, 12 papers were short-listed to review the full text. Out of these 12 papers, 6 were excluded after reviewing the complete article as required data were not available, overlap with earlier published studies from the same center, and no separate subgroup analysis for carcinoma gallbladder cases.

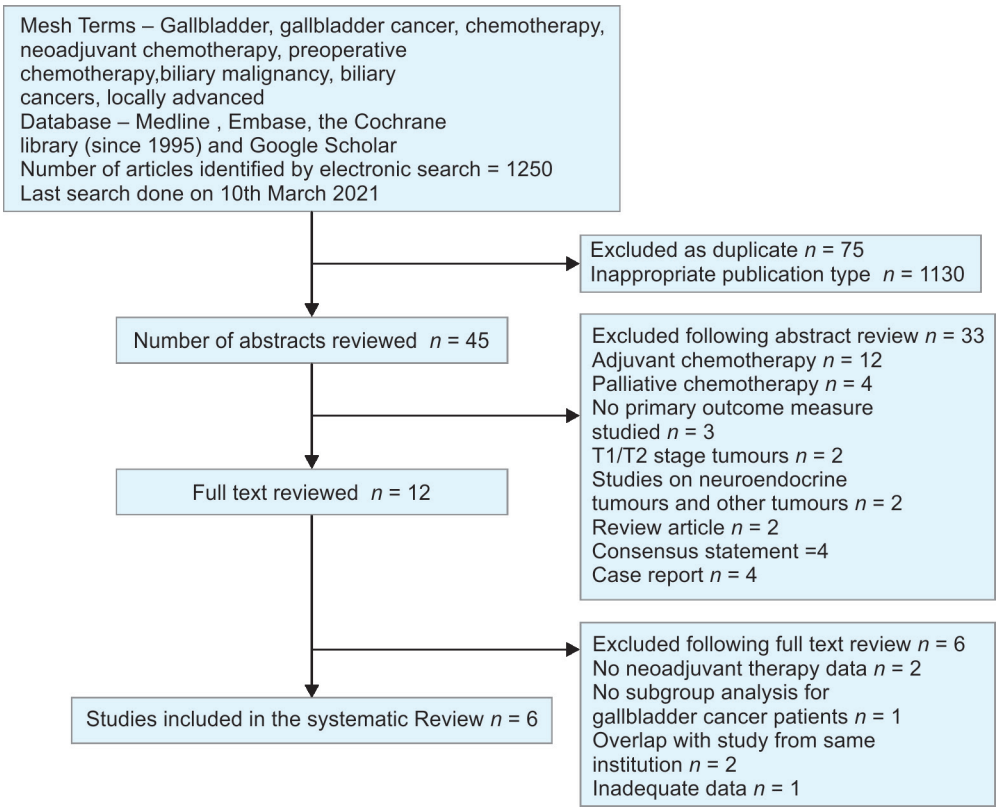

Fig. 1: PRISMA Flowchart depicting the search strategy and selection of articles for the review

Table 1: Demographic features and methodological quality of included studies

	Year	*Period of study*	*Study design*	*No. of patients who had neoadjuvant therapy*	*Consecutive patients*	*Median age (years)*	*Female gender (%)*	*Median follow-up duration (months)*	*Loss to follow-up*	*GRADE score*
Chaudhari et al.[15]	2018	2010–2016	Restrospective	160	Yes	52.0	118 (74%)	33	Yes 6 (3.8%)	Low
Creasy et al.[16]	2017	1992–2015	Restrospective	74	Yes	65.0	38 (51.4%)	36	No	Low
Gangopadhyay et al.[19]	2015	2011–2014	Restrospective	121	Yes	42.0	72 (59.2%)	NM	No	Low
Selvakumar et al.[20]	2015	2004–2010	Restrospective	21	Yes	55.8	NM	4–60	No	Low
Kato et al.[21]	2013	2004–2010	Restrospective	7	Yes	65.3	4 (57.1%)	NM	No	Low
Sirohi et al.[22]	2015	2009–2013	Restrospective	37	Yes	54 (30–73)	24 (64.9%)	11.9 (6.64–58.2)	No	Low

We were left with 6 papers which we included in our review, involving 420 patients.[15,16,19–22] Out of the 399 patients where gender data were available, most of them were females (n = 256, 64.16%). One of the published papers did not mention the gender.[20] The median age from these studies ranged from 42.0–65.3 years. The median follow-up for the cohort of patients ranged from 4–60 months. In two of these studies, the median follow-up was not mentioned (Table 1).[19,21]

Study Quality

All the six studies were retrospective studies (Table 1). All of the studies were assigned a level 4 evidence rating by the Oxford Center for Evidence-based Medicine.[28]

According to GRADE, all of the studies were of low quality and were prone to selection bias. In five of the six investigations, no patients were lost to follow-up, while six patients were lost to follow-up in one research (Table 1).[15]

Neoadjuvant Strategies

Only patients who had locally advanced stage III A or greater were selected in these studies for neoadjuvant chemotherapy. The patients in whom there was vascular or biliary involvement that was not amenable to resection and who had radiologically positive node in the regional nodal basin were considered as the locally advanced disease. American Joint Committee on Cancer (AJCC) classification was used to stage the patients.[29] Some

centers used specific criteria in selecting cases that would have to take neoadjuvant chemotherapy.[15,16,21] Gemcitabine and Cisplatin were the common neoadjuvant chemotherapeutic agents used. The neoadjuvant chemotherapy was tolerated well by the patients of these included studies with 411 out of the 420 patients (97.85%) completing the chemotherapy (Table 2).

Primary Outcomes

Clinical Benefit Rate

Out of 420 patients, 128 (30.47%) showed progressive disease (PD) even after receiving neoadjuvant chemotherapy (NACT). The progressive disease rate in the studies of our review was from 0–51.2%. The CBR (CBR = CR + PR + SD) was 67.38% (283 of the 420 patients). The CBR was as low as 48.8–100% in the reviewed papers (Tables 3 and 4).

Resectability Rate and R0 Resection

About 67.38% of patients (283 of 420) in six studies of our review showed clinical benefit after neoadjuvant chemotherapy, only 51.66% (217 of all 420 patients in the review) were operated, out of which only 171 patients were resectable and thus had curative resection. The resectability rate in these studies was 13.5–66.7%. R0 resection rate was 91.81% (157 out of 171 patients) among patients who underwent surgical resection. R0 resection rates were as low as 25.0% in one study[21] to 100% in two of the papers.[16,20]

Secondary Outcomes

Overall Survival and Disease-free Survival

Patients who underwent curative resection after neoadjuvant chemotherapy had a median overall survival of 18.5–50.1 months, which was considerably better than patients who did not have surgery after neoadjuvant chemotherapy (range 5.0–10.8 months). Furthermore, patients who underwent curative surgical resection had a higher rate of event-free survival than those who did not (median 25.8 vs 5.0 months).[15] Table 4 shows the important survival outcomes from these trials.

Discussion

Gallbladder carcinoma is one of the very lethal intra- and extrahepatic bile duct malignancies having very short-median survival.[2] Although there has been improvement in the management of gallbladder carcinoma, long-term survival is still poor. Long-term survival in these patients is still dependant on curative surgical resection.[1] Radical curative surgery has been shown to improve the survival of gallbladder carcinoma.[30] In locally advanced cancers (T3/T4 and nodal disease), to improve the survival, adjuvant chemotherapy after curative resection is a recommended treatment strategy.[31,32] In patients with advanced gallbladder cancer with R1 resection, a recent multi-institutional research found that postoperative adjuvant therapy was independently related with improved long-term outcomes.[33] In a meta-analysis, Ma et al.[34] came up with the same conclusions. The use of cisplatin/gemcitabine as a surgical adjuvant treatment for people with advanced galactosemia is now supported by new research.[6]

Applicability of neoadjuvant chemotherapy in advanced gallbladder carcinoma is being pursued as a promising treatment option. It has been proposed that it would be prudent to start neoadjuvant chemotherapy in locally advanced gallbladder carcinoma patients as it would help in understanding the tumor biology and also helps to downstage the disease thus chances to increase the resectability rate and survival. There is a lack of evidence for neoadjuvant chemotherapy in advanced gallbladder carcinoma although it has been shown to improve survival for other malignancies.[34] The literature was reviewed, and six studies which had a total of 441 cases with advanced gallbladder carcinoma were analyzed. All the studies were retrospective and of low quality and subject to selection bias. The most common neoadjuvant chemotherapy drugs used were gemcitabine and cisplatin, well tolerated by the patients. The CBR was 67.38% for the patients in these six studies to neoadjuvant chemotherapy, and most of these cases were then considered for surgical resection. Among those patients who were surgically explored, the rate of R0 resection was 91.81% (157 out of 171 cases). These published papers concluded that there was significant increase in the median overall survival for those cases that had curative surgical resection after receiving neoadjuvant chemotherapy vs compared to those patients who did not have curative surgery.

Because locally advanced gallbladder cancer is such a diverse population, proper interpretation of the results is impossible. The American Joint Committee on Cancer (AJCC, 8th edition) and the Union for International Cancer Control (UICC) classifications of gallbladder carcinoma do not provide a detailed assessment of geographical characteristics related with resectability.[29,35] This issue was addressed to some extent by different surgical societies and institutional classifications who tried to include loco-regional factors, which determine unresectability. The Japanese Society of Biliary Surgery Classification includes liver invasion, extend of hepatoduodenal ligament invasion, and presence of liver metastasis and peritoneal disease.[36] The Tata Memorial Hospital (TMH) criteria were proposed by Tata Memorial Hospital, and they highlight high-risk factors for disease recurrence based on clinicoradiologic aspects, as well as the requirement for neoadjuvant treatment in advanced gallbladder cancer cases.[15]

Studies in the past decade have shown that neoadjuvant chemotherapy will only benefit those patients with advanced gallbladder carcinoma that will ultimately have an R0 resection.[15–17,20,21] In our systematic review, out of 420 cases with advanced gallbladder carcinoma treated with neoadjuvant chemotherapy, only 40.71% of them (171 of 420 patients) underwent curative surgical resection. Creasy et al. have reported that 61% of patients with stable disease or partial response did not proceed to surgery for various reasons.[16] Our review showed that 2.82% (8 out of 283) of the cases with clinical benefit from neoadjuvant chemotherapy were found to be inoperable on surgical exploration. Assessment of response to neoadjuvant chemotherapy differed between institutes. In their work, Creasy et al. used contrast-enhanced computed tomography (CECT) to measure chemotherapy response after 8 weeks of treatment.[16] The majority of the studies in our systematic review[18–21] used a similar technique for assessing the response to neoadjuvant chemotherapy. Chaudhari et al., on the contrary, used CECT and PET to measure the response after three to four cycles of chemotherapy.[15]

Also there is a difference between locally advanced and unresectable gallbladder carcinoma that has to be kept in mind. Many surgeons would favor upfront surgery for patients who have a resectable, locally advanced gallbladder carcinoma. R0 resection is believed to be one of the most important prognostic factors for gallbladder carcinoma.[37] Still the radicality of resection in locally advanced gallbladder carcinoma that would give some survival benefit remains undefined. Data reported from Eastern Countries point

Table 2: Type of neoadjuvant therapy and response to therapy

Reference	*Total no. of patients*	*Type of neoadjuvant therapy*	*Neoadjuvant therapy dose and duration*	*Tumor response assessed*	*Number of patients completed therapy*	*Response rates (CR/PR)*	*Stable disease (SD)*	*Progressive disease (PD)*	*Clinical benefit rate (CBR = CR + PR + SD)*
Chaudhari et al.[15]	160	NACT	GEMCIS: Gem 1000 mg/m^2 30-minute infusion on day 1 and 8 and Cis 25 mg/m^2 on day 1 and 8 of a 21-day cycle. GEMOX: Gem 1000 mg/m^2 100-minutes infusion on day 1 and Ox 100 mg/m^2 on day 2 over 2 hours every 14 days.	GEMCIS: after 3 cycles GEMOX: after 4 cycles	151 (94.3%) (9 patients did not complete NACT = 3 patients died and 6 lost to follow-up)	CR = 16 (10.0%) PR = 68 (42.5%)	28 (17.5%)	39 (24.4%)	112 (70.0%)
Creasy et al.[16]	74	NACT	Gem (n = 64, 86.5%) and Gem + platinum-based chemotherapy (n = 42, 56.7%).	Median 64 (22–215)	74 (100%) (7 patients died prior to re-staging scan and are included in PD patients)	CR = 0 (0.0%) PR = 19 (25.7%)	38 (51.4%)	17 (23.0%)	57 (77.0%)
Gangopadhyay et al.[19]	121	NACT	Gem 1000 mg/m^2 on day 1 and 8; Cis 70 mg/m^2 on day 1 for 3 weekly cycles	6 cycles	121 (100%)	NM	NM	62 (51.2%)	59 (48.8%)
Selvakumar et al.[20]	21	NACT	5-FU group: oxaliplatin 85 mg/m^2 day 1, 5-FU 400 mg/m^2 bolus day 1 and 2 and 600 mg/m^2 infusion day 1 and 2 and Leucovorin 200 mg/m^2 day 1 and 2. Gem group: Gem 1000 mg/m^2 day 1 and 8 and cis 35 mg/m^2 or carboplatin.	3 cycles	21 (100%)	CR + PR = 21 (100%)	0 (0.0%)	0 (0.0%)	21 (100%)
Kato et al.[21]	7	NACT	Gem 1000 mg/m^2 once a week for 3 weeks with 1 week respite.	2 cycles	7 (100%)	PR = 1 (14.4%)	3 (42.8%)	3 (42.8%)	4 (57.1%)
Sirohi et al.[22]	37	NACT	On day 1 and 8 and cisplatin 25 mg/m^2 on day 1 and 8 of a 21-day cycle or Gem–Ox (gemcitabine 1000 mg/m^2 on day 1 as a 100-minute infusion and oxaliplatin 100 mg/m^2 on day 2 over 2 hours every 14 days).	After 3 (Gem–Cis) or 4 (Gem–Ox) cycles after completion of chemotherapy.	37 (100%)	CR 5 (13.51%) PR 20 (54.05%)	5 (13.51%)	7 (18.91)	30 (81.08%)

CBR, clinical benefit rate; CR, complete response; Cis, cisplatin; 5-FU, 5-fluorouracil; Gem, gemcitabine; Gy, gray (SI units of radiation dose); NACT, neoadjuvant chemotherapy; NACRT, neoadjuvant chemoradiotherapy; Ox, oxaliplatin; PD, progressive disease; PR, partial response; SD, stable disease

Table 3: Curative surgical resection following neoadjuvant therapy and surgical outcomes in included studies

Reference	*CBR but not operated*	*Number of patients operated*	*Resection rate (curative)*	*R0 resection*	*Final histological stage*	*Operation performed*	*Surgical complications*	*Adjuvant treatment*	*Follow-up postresection*
Chaudhari et al.[15]	CBR = 112 (70.0%) Not operated = 19 (11.8%) (Inoperable stable disease = 10 defaulted/refused prior to surgery = 14)	93/160 (58.0%)	66/160 (41.2%)	63 (98.4%)	ypT0–2 (*n* = 34, 51.0%) ypT3–4 (*n* = 32, 49.0%) ypN0 (*n* = 42, 63.0%) ypN+ (*n* = 24,37.0%)	RC (48, 30%) CRC (18, 11%) RC + organ resection (3, 4.5%) EHBDE (3, 4.5%)	Bile leak (5, 7.5%) Bleeding (1, 1.5%) Postop death (1, 1.5%)	51 (77.0%) (48—ACT 3—ACRT)	33 months
Creasy et al.[16]	CBR = 57 (77.0%) Not operated = 35 (47.3%) (progression on a second scan while receiving continued treatment = 15, clinical deterioration = 13, unresectable with continued biliary or vascular involvement or enlarged N2 nodes = 7)	22/74 (29.7%)	10/74 (13.5%)	10 (100%)	T3N0–2 (7, 70.0%) T0–2N0–1 (3, 30.0%)	S4/5 resection (6), RHH (2) and EHH (2); one PDD and one partial duodenal resection	NM	NM	36 months
Gangopadhyay et al.[19]	CBR = 59 (48.8%) All CBR patients operated.	59/121 (48.8%)	59/121 (48.8%)	52 (88.1%)	T1N0–1 = 12 T2N0–1 = 25 T3N0–1 = 22	RC	Wound infection (5), bile leak (3), UTI (1)	NM	
Selvakumar et al.[20]	CBR = 21 (100%) All CBR patients operated.	21/21 (100%)	14/21 (66.7%)	14 (100%)	Advanced = 14	RC (12), RHH (1), RC + metastatectomy (1)	NM	ART (3) ACT(10)	4–60 months
Kato et al.[21]	CBR = 4 (57.1%) All CBR patients operated.	4/7 (57.1%)	4/7 (57.1%)	1 (25.0%)	Advanced (all T4N1)—stage IVA	RHH with CL and BDR (2), CIH (S4a + S5) and BDR (2)	NM	NM	48 months
Sirohi et al.[22]	CBR = 30 (81.08%)	18/37 (48.64%)	18 (48.64%)	17 (94.44%)	NM	RC R1 14 RC R2 1 RC + Colectomy 1 RC + Colectomy + D1 1 RC + Colectomy + pyloroduodenal 1	NM	NM	

ACT, adjuvant chemotherapy; ACRT, adjuvant chemoradiotherapy; ART, adjuvant radiotherapy; BDR, bile duct resection; CIH, central inferior hepatectomy; CL, caudate lobectomy; CPR, complete pathological response; CRC, completion radical cholecystectomy; EHBDE, extrahepatic biliary duct excision; EHH, extended hemihepatectomy; NM, not mentioned; PDD, pancreatoduodenectomy; RC, radical cholecystectomy; RHH, right hemihepatectomy; RT, radiotherapy; R0, margin negative resection; S4/5, segment 4/5 liver; UTI, urinary tract infection. 112 patients attained CBR and 93 were operated. But according to the report, 10 patients were inoperable stable disease and 14 refused operation (so total of 24)

Table 4: Median overall survival and progression-free or disease-free survival in those underwent curative resection vs no resection following neoadjuvant therapy

	Median overall survival			*Median event-free or progression-free survival*	
Reference	*All patients in the study*	*Neoadjuvant therapy followed by surgery*	*Neoadjuvant therapy with no surgery*	*Neoadjuvant therapy followed by surgery*	*Neoadjuvant therapy with no surgery*
Chaudhari et al.[15]	NM	49.0	7.0	25.0	5.0
Creasy et al.[16]	NM	50.1	10.8	NM	NM
Gangopadhyay et al.[19]	NM	NM	NM	NM	NM
Selvakumar et al.[20]	38.1	42.8	6.6	NM	NM
Kato et al.[21]	NM	18.5	5.0	NM	NM
Sirohi et al.[22]	13.4	40.9 (mean OS median not achieved)	9.5	25.8	5.6

CR, complete response; DFS, disease-free survival; EFS, event-free survival; HR, hazard ratio; MVA, multivariate analysis; NM, not mentioned; OS, overall survival; PR, partial response; RTDI, reduced total dose intensity; R0, margin negative resection

toward improved 5-year survival rate of 30–42% after radical resection, like major hepatectomy, pancreaticoduodenectomy, and hepaticopancreatoduodenectomy.[17] The presence of an advanced T stage does not rule out the possibility of curative resection. Higuchi et al. showed 274 consecutive surgically treated cases of advanced gallbladder cancer with a R0 resection rate of 61.3% and a 5-year survival rate of 52.4% without the use of preoperative chemotherapy.[37] Similar data of a retrospective study of 338 patients from a single center treated for advanced gallbladder cancer revealed a high rate of upfront curative-intent resections (39.6%).[38] R0 resection was found in 116 of the 134 individuals in this study (86.6%). Curative resection patients had significantly higher overall survival rates than noncurative resection patients (1-, 3-, 5-year survival rate and mean survival time: 59.0, 47.3, and 44.3% and 22.0 months vs 12.7, 8.3, and 7.7% and 3.0 months) (p <0.001). The extent of liver resection and decision of whether bile duct resection is done or not do not have a bearing on the prognosis as long as R0 resection is done.[38]

On directly comparing the two protocols for advanced gallbladder carcinoma, neoadjuvant chemotherapy (current study) vs an adjuvant chemotherapy (largest cohort)[38]—among those patients who had achieved R0 resection—the rate was 91.81% (157 out of 171) and 86.6% (116/134), respectively. Also, the R0 resection rate for whole cohort was 37.38% (157/420) and 34.3% (116/338), respectively.[38] So we could decipher that two treatment protocols had similar R0 resection rates. There are certain limitations to the current systematic review, as all of the papers in it received a GRADE of "low" on the quality evaluation. Furthermore, due to the limited sample size and selective reporting, subgroup analysis is not possible to rule out potential confounding factors. Because the treatment protocols in this research differed, it was impossible to make a fair comparison of outcomes. Furthermore, the scheduling of surgery after neoadjuvant treatment differed among published studies, and the time between the end of chemotherapy and surgery was not specified.

Prior to any nonsurgical procedure, an attempt at establishing a histological diagnosis should be done.[39] But this is not essential in patients who are planned for curative surgery where radiological features are diagnostic of malignancy. There have been reports of seeding of biliary cancer along the fine-needle aspiration,[40] with the level of risk being not clear, but seems to be low. Histological diagnosis by biopsy was obtained before starting neoadjuvant chemotherapy in the majority of the published papers in our current review. In certain cases, however, neoadjuvant chemotherapy was initiated based on radiological imaging that indicated locally progressed illness.

Conclusion

The use of neoadjuvant chemotherapy in advanced gallbladder carcinoma should not be a routine as at present, we do not have enough evidence to recommend it. The subgroup of patients among advanced gallbladder carcinoma who may benefit from neoadjuvant chemotherapy are those who may achieve an R0 resection, which in the present analysis accounted for about a third of the whole cohort. Further research in the form of randomized controlled trials needs to be done to study the potential role of neoadjuvant chemotherapy in advanced gallbladder carcinoma. Future study should standardize the classification of advanced gallbladder carcinoma, define the indications for neoadjuvant chemotherapy, and follow a uniform treatment procedure so that findings may be interpreted more meaningfully.

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