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Review

# The role of neoadjuvant chemotherapy or chemoradiotherapy for advanced gallbladder cancer – A systematic review

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ABSTRACT

*Background:* Neoadjuvant chemotherapy for advanced gallbladder cancer (GBC) has recently been proposed as an alternative to adjuvant chemotherapy, with potential increase in resectability rate and overall survival.
*Aim:* To undertake a systematic review and critical appraisal of available literature on the use of neoadjuvant chemotherapy (NACT) or chemoradiotherapy (NACRT) in the treatment of advanced GBC.
*Methods:* Systematic review carried out in line with the Meta-analysis Of Observational Studies in Epidemiology guidelines. Primary outcomes were clinical benefit rate (CBR) of neoadjuvant therapy, defined as percentage of complete response, partial response and stable disease, resectability rate and R0 resection. Secondary outcomes were overall and disease-free survival.
*Results:* 8 studies met the inclusion criteria (n = 474), of which 398 (84.0%) received NACT and 76 (16.0%) received NACRT. 133 of 434 patients (30.6%) had progressive disease despite NACT or NACRT. The CBR was 66.6%. 17% of the patients who responded to chemotherapy did not proceed to surgery. 50.4% of the patients were considered suitable for surgical resection, of which 191 (40.3%) underwent curative resection. The R0 rate for the whole cohort was 35.4%. Overall survival ranged from 18.5 to 50.1 months for those who underwent curative resection versus 5.0–10.8 months for non-resected group.
*Conclusions:* There is insufficient data to support the routine use of NACT or NACRT in advanced GBC, as this has only benefited a third of whole cohort, who eventually achieved a R0 resection. Future studies should be in the form of randomized controlled trials to investigate the role of neoadjuvant therapy in advanced GBC.



## Introduction

Gallbladder cancer (GBC) is a rare disease accounting for 4% of all gastrointestinal malignancies [1]. There is a higher incidence in countries such as India, Japan, Chile and Mexico [2]. GBC is considered a highly aggressive malignancy with poor prognosis [3]. The low incidence of GBC in the Western world has led to variation in the treatment modalities and lack of standardisation in the approach to management [4,5]. In addition, previous longitudinal studies have included GBC along with other biliary tract malignancies such as cholangiocarcinoma and therefore not allowing for accurate interpretation of data [6,7].

Due to the lack of early symptoms, most of the patients with GBC are diagnosed at an advanced stage, in which the 5-year survival is less than 10% [2,8]. Surgical resection with negative margins remains the only potentially curative therapy [9]. Despite the application of aggressive surgical approach and radical resections, the prognosis of GBC remains dismal [10]. The role of adjuvant chemotherapy for biliary tract cancer has been well established following the results of randomised controlled trials, meta-analysis and retrospective studies [11–14]. Cisplatin plus Gemcitabine is now considered as the standard adjuvant therapies for patients with advanced GBC [6,15]. Recent retrospective studies evaluating the use of neoadjuvant chemotherapy in locally advanced GBC have shown conflicting results [16–23]. While neoadjuvant chemotherapy may increase resectability and survival, there are concerns with regards to delay in the surgical resection and disease progression.

The significance of neoadjuvant chemotherapy in the treatment of advanced GBC has not yet been clarified. Our aim is to critically

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appraise the current literature for the use of neoadjuvant chemotherapy or chemoradiotherapy in the treatment of advanced GBC.

## Materials and methods

### *Search strategy*

A search strategy in line with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines and previous recommendations for the conduction of systematic reviews of prognostic variables was developed [24,25]. An electronic search of Medline (1952-present), EMBASE (1980-), Cochrane Library (1995-), CINAHL (1982-) and Google scholar was conducted independently by authors ARH and MP utilising the following key words: "Gallbladder", "Gallbladder cancer", "Chemotherapy", "Chemoradiotherapy', "Neoadjuvant chemotherapy", "Preoperative chemotherapy", "Pre-operative chemotherapy", "Biliary malignancy", "Biliary cancers" and "Advanced". MeSH (Medical Subject Headings) terms were further explored to identify additional studies. Only human studies were considered for inclusion. Those studies not in English language were included and the text was translated into English using Google translate. Bibliographies of relevant studies and the "related articles" link in PubMed were used to identify additional studies. Any study published only in abstract format or unpublished reports were excluded from the analysis. All citations and abstracts identified were thoroughly reviewed by independent investigators. The National Institute for Health and Care Excellence (NICE) and Health Education England (HEE) provided 'healthcare databases advanced search' (HDAS) software was also used (https://hdas.nice.org.uk). The last date for this search was 10th May 2018. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidance was utilised [26] (Fig. 1).

### *Definitions*

The response to chemotherapy in the included studies was recorded using the World Health Organisation (WHO) or Response Evaluation Criteria in Solid Tumours (RECIST) criteria [27]. WHO criteria uses sum of two longest diameters in perpendicular dimensions (bidimensional), whereas RECIST uses sum of longest diameters (unidimensional) [28]. Complete response (CR) was defined as the disappearance of all known disease for at least 4 weeks. Partial response (PR) was defined as greater than or equal to 50% decrease for at least 4 weeks ($\geq$30% for RECIST) without the appearance of new lesions or progression of any known lesion. Stable disease (SD) is neither PR or PD criteria met. Progressive disease (PD) was defined as greater than 25% ($\geq$20% for RECIST) increase in one or more of the measurable lesions or the appearance of a new lesion(s). Clinical Benefit Rate (CBR) was defined as the percentage of patients that achieved CR, PR and SD following neoadjuvant treatment. Patients with CBR were considered for surgery after at least 4 weeks following completion of neoadjuvant therapy.

### *Inclusion criteria*

Included studies analysed the impact of neoadjuvant chemotherapy (NACT) or chemoradiotherapy (NACRT) in downstaging advanced GBC with an aim to improve curative surgical resection. Observational and comparative studies were considered for inclusion. The studies were carefully evaluated for duplication or overlapping of data. If an institution reported two studies, we included either the one of better quality (primary outcomes studied) or the most recent publication. If the study included all biliary tract cancers, then the study was included if the data was available for GBC patients (i.e.) there is enough subgroup analysis done on this group of patients.

### *Exclusion criteria*

Studies were excluded if they reported data from small patient cohorts (<5 patients), there were only early stage cancers (T1/T2) or there was overlap with institutions or patient cohorts already published in better quality studies. Studies were also excluded if the gallbladder malignancy was other than adenocarcinoma, such as metastatic tumours or malignant neuroendocrine tumours.

### *Outcome measures*

The primary outcome of interest was downstaging of tumours with NACT or NACRT, hence the clinical benefit rate (CBR) of therapy and the resectability rate (i.e.) curative resection rate and R0 resection.

Secondary outcomes of interest are overall survival (OS) and disease-free survival (DFS).

### *Study selection*

Two authors (ARH and MP) independently performed the search strategy. Both the authors reviewed the abstracts identified by the search to exclude those that did not meet our inclusion criteria. When no abstract was available or the abstract details were inadequate, the full article was reviewed. Differences between the two authors (ARH and MP) in selection of the studies were resolved by consensus with the third author (KVM), who independently reviewed all retrieved papers to make the selection of studies as robust as possible. If the selection of the study was still not resolved by consensus between the authors, the lead author's (KVM) decision was considered as final.

### *Data extraction*

Extraction of data was done by the two authors (ARH and MP) independently using a standardised proforma and any disagreement resolved by consensus with the third author (KVM). The following demographic and clinical parameters were recorded: study characteristics (first author, year of publication, study period, study design, country where the study was performed), population characteristics (number of patients studied, patient demographics, follow-up duration, loss to follow-up) and outcomes of interest.

### *Quality assessment*

The level of evidence was independently determined by the two authors (ARH and MP) in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria and the quality assessment guidelines previously published specifically for systematic reviews of prognostic studies [26,29]. The following quality criteria were defined: adequate baseline data reported, length of follow-up reported, loss to follow-up and clear mention on the usage of downstaging neo-adjuvant chemotherapy or chemoradiotherapy with the intention of curative surgical resection.

### *Statistical analysis*

Results were tabulated. The percentages were calculated from the full texts' raw data, if not already available. OS and DFS from the included studies were extracted from the Kaplan-Meier survival

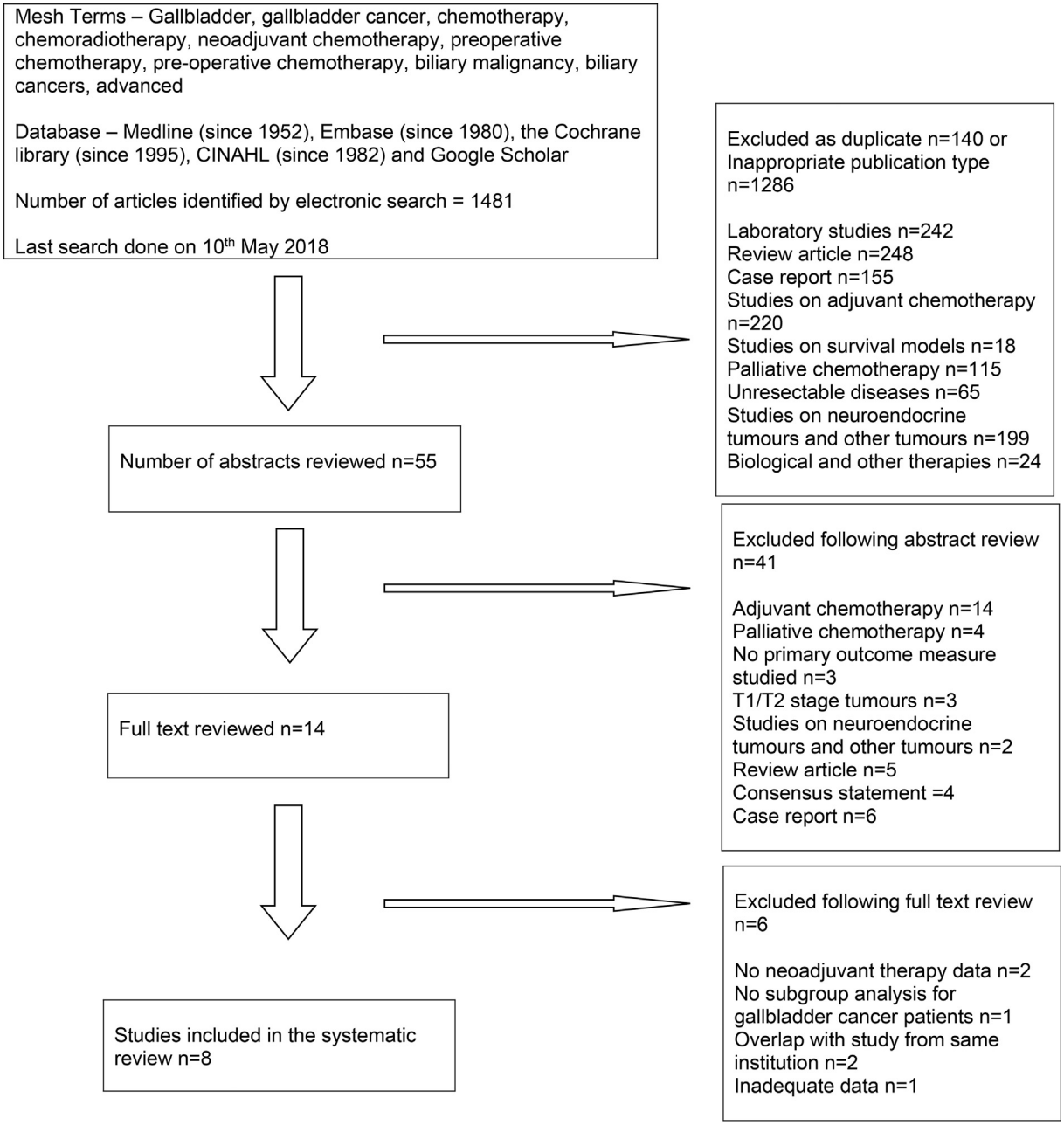


**Fig. 1.** PRISMA Flowchart depicting the search strategy and selection of articles for the review.

curves if not already mentioned in the manuscript. Due to the heterogeneity of the included studies and lack of comparative data, the pooled analysis was not feasible.

## Results

A total of 8 studies were identified by our search strategy (Fig. 1). After exclusion of duplicate publications, laboratory studies, review articles, letters, case reports and studies reporting inappropriate outcome measures, 14 relevant articles were identified for further full text review. Six studies were subsequently excluded after full text review, due to lack of neoadjuvant chemotherapy data [30,31], overlap with previous studies from same institution [32,33], inadequate data [5] and no sub-group analysis for gallbladder cancer patients [7]. This left eight articles for inclusion in this review, involving 474 patients [16–23]. Of the 474 patients, 398 (84.0%) were treated with neoadjuvant chemotherapy (NACT) [16,17,19–23] and 76 patients (16.0%) received chemoradiotherapy (NACRT) [18,19,23]. In one study 25 patients received NACRT and 15 received NACT [19]. Of the 453 patients with gender data available, the majority were female (n = 285, 62.9%). In one study the gender was not mentioned [21]. The median age from the included studies ranged from 42.0 to 65.3 years. The median follow-up for the cohort of patients in 6 studies ranged from 4 to 60 months, with an average of 38 months. In two studies the median follow-up was not mentioned [20,22] (Table 1).

**Table 1**
Demographic features and methodological quality of included studies.

| | Year | Country | 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[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Chaudhari et al. [16] | 2018 | India | 2010 –2016 | Retrospective cohort study | 160 | Yes | 52.0 | 118 (74.0%) | 33 | Yes 6 (3.8%) | Low |
| Creasy et al. [17] | 2017 | USA | 1992 –2015 | Retrospective cohort study | 74 | Yes | 65.0 | 38 (51.4%) | 36 | No | Low |
| Engineer et al. [18] | 2016 | India | 2008 –2013 | Prospective cohort study | 28 | Yes | 53.0 | 21 (75.0%) | 37 | No | Low |
| Agrawal et al. [19] | 2016 | India | 2012 –2014 | Retrospective cohort study | 40 | Yes | 52.0 | 9 (22.5%) | 18 | No | Low |
| Gangopadhyay et al. [20] | 2015 | India | 2011 –2014 | Retrospective cohort study | 121 | Yes | 42.0 | 72 (59.2%) | NM | No | Low |
| Selvakumar et al. [21] | 2015 | India | 2004 –2010 | Retrospective cohort study | 21 | Yes | 55.8 | NM | 4–60[a] | No | Low |
| Kato et al. [22] | 2013 | Japan | 2004 –2010 | Retrospective cohort study | 7 | Yes | 65.3 | 4 (57.1%) | NM | No | Low |
| Aretxabala et al. [23] | 2004 | Chile | 1993 –1999 | Prospective cohort study | 23 | Yes | 58.0 | 23 (100%) | 43.8 | No | Low |

NM = Not mentioned.
[a] Follow-up range.
[b] GRADE Score = Grading of Recommendations Assessment, Development and Evaluation (GRADE) Atkins D et al. *BMJ.* 2004; 328:1490 [29].

*Study quality*

Among the eight included studies, six of them were retrospective studies and two were based on prospective cohorts (Table 1). According to the Oxford Centre for Evidence-Based Medicine levels of evidence, all the included studies were graded as level 4 evidence [34]. GRADE scoring determined that all studies were of LOW quality and subject to selection bias. Seven out of eight studies had no patients lost to follow-up, whereas in one study 6 patients (3.8%) were lost to follow-up [16] (Table 1).

*Neoadjuvant strategies*

The patients selected in the studies for neoadjuvant therapy were those with stage III A or greater, which is locally advanced ± radiologically involving the lymph nodes. The locally advanced disease included those with vascular or biliary involvement precluding resection. Node-positive cancer was defined as radiologically enlarged or biopsy-proven lymph nodes along the cystic duct, common bile duct, portal vein, or hepatic artery (N1) or those involving aortocaval, retro-pancreatic, coeliac or superior mesenteric artery lymph nodes (N2). The staging was based on the American Joint Committee on Cancer (AJCC) classification [35] or in some centres there were specific criteria for selecting patients to have neoadjuvant therapy [16,17,22]. Gemcitabine and Cisplatin were the common neoadjuvant chemotherapeutic agents and the chemotherapy protocol varied widely among the included studies. The NACT and NACRT were well tolerated by the patients with 459 of the 474 patients (96.8%) completing the therapy (Table 2).

*Primary outcomes*

*Clinical benefit rate*

Of the 474 patients included in the review, 133 of 434 (30.6%) had PD despite NACT or NACRT. In one study, the number of patients with PD was not reported [19]. The PD rate in the included studies ranged from 0% to 51.2%. The Clinical Benefit Rate (CBR = CR + PR + SD) was 66.6% (289 of the 434 patients; data available from seven of eight studies). The CBR ranged from as low as 48.8% to as high as 100% in the included studies, with one study not reporting the CBR rate [19] (Tables 3 and 4).

*Resectability rate and R0 resection*

Although 66.6% of patients (289 of 434) in seven included studies showed clinical benefit to the chemotherapy, only 50.4% (239 of all 474 patients in the review) were considered suitable for surgical resection. Out of 239 patients who underwent surgical resection, 191 patients (40.3%) finally had a curative resection. Among those who were operated with a curative intent, 48 patients (20.1%) were deemed to be inoperable on exploration following neoadjuvant therapy. The resectability rate in the included studies ranged from as low as 13.5% to as high as 66.7%. Among those who were subjected to curative resection, the R0 resection rate was 92.5% (160 out of 173 patients in seven studies; R0 resection rate was not reported in one study [23]). R0 resection rates were as low as 25.0% in one study [22] to 100% in three of the included studies [17,19,21]. The R0 resection rate for whole cohort was 35.4% (160 out of 451 patients included). (Tables 3 and 4).

*Secondary outcomes*

*Overall survival and disease-free survival*

The median follow-up in the included studies was 36 months. The median overall survival (OS) for those patients who underwent curative resection following neoadjuvant therapy ranged from 18.5 to 50.1 months, which was significantly better than the survival for those who did not have surgery following neoadjuvant therapy (range 5.0–10.8 months). Similarly, those who underwent curative surgical resection had much better event-free survival rate than those who did not undergo curative resection (median 25.0 vs. 5.0 months) [16]. In keeping with their better overall survival, the disease-free survival (DFS) rate was a median of 30 months for those who underwent curative surgical resection, but only reported in one study [18]. Some of the key survival outcomes from the included studies are listed in Table 4.

## Discussion

GBC is the most aggressive biliary tract malignancy with the shortest median survival from the time of diagnosis [1,3]. Radical resection has been shown to cure GBC [36]. In order to improve survival in patients with locally advanced T3/T4 tumours and lymph node involvement, adjuvant chemotherapy and chemo-radiotherapy following surgical resection is a recommended

**Table 2**
Type of neoadjuvant therapy and response to therapy.

| Reference | Total no. of patients | Type of neoadjuvant therapy | Neoadjuvant therapy dose and duration | Tumour 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. [16] | 160 | NACT | GEMCIS: Gem 1000 mg/m$^2$ 30-min infusion on day 1,8 and Cis 25 mg/m$^2$ on day 1,8 of a 21-day cycle. GEMOX: Gem 1000 mg/m$^2$ 100-min infusion on day 1 and Ox 100 mg/m$^2$ on day 2 over 2 h 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. [17] | 74 | NACT | Gem (n = 64, 86.5%) and Gem + platinum-based chemotherapy (n = 42, 56.7%) | Median 64 (22–215) days | 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%) |
| Engineer et al. [18] | 28 | NACRT | Helical tomotherapy (57 Gy over 25 fractions to the tumour and 45 Gy over 25 fractions to the surrounding nodes) and Gem 300 mg/m$^2$ per week for 5 weeks. | 6 weeks | 25 (89.3%) [3 failed to complete NACRT due to progression in liver metastasis, died due to colonic perforation, recurrent cholangitis] | CR = 9 (32.1%) PR = 4 (14.3%) | 7 (25.0%) | 5 (17.8%) | 20 (71.4%) |
| Agrawal et al. [19] | 40 | NACRT (25) NACT (15) | Locally advanced disease – NACRT: RT (45 Gy) with weekly cisplatin 35 mg/m$^2$ and 5-FU 500 mg. For positive para-aortic nodes - NACT: Cisplatin 25 mg/m$^2$ and gemcitabine 1 gm/m$^2$ day 1,8 and 3 weekly | 3 cycles | 37 (92.5%) [3 patients progressed during chemo-therapy] | CR + PR = 40.5% with liver involvement; 24.9% in liver infiltration >2 cm; 77% in duodenum and 63% in colon. CR + PR = 67.6% with lymphadenopathy; radiological CR – 36.3% N1, 62.5% N2 and 53.3% with para-aortic lymphadenopathy | NM | NM | NM |
| Gangopadhyay et al. [20] | 121 | NACT | Gem 1000 mg/m$^2$ on day 1 and 8; Cis 70 mg/m$^2$ on day 1 for three weekly cycles | 6 cycles | 121 (100%) | NM | NM | 62 (51.2%) | 59 (48.8%) |
| Selvakumar et al. [21] | 21 | NACT | 5-FU group: oxaliplatin 85 mg/m$^2$ day 1, 5-FU 400 mg/m$^2$ bolus day 1,2 and 600 mg/m$^2$ infusion day 1,2 and Leucovorin 200 mg/m$^2$ day 1,2. Gem group: Gem 1000 mg/m$^2$ day 1,8 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. [22] | 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%) |
| Aretxabala et al. [23] | 23 | NACRT | 5-FU 350–500 mg/m$^2$ continuous infusion for 5 days; day 1–5 and 28–32. RT 45 Gy divided into 25 sessions | 4–6 weeks | 23 (100%) | CR + PR = 16 (69.6%) | 0 (0.0%) | 7 (30.4%) | 16 (69.5%) |

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.

treatment strategy [37,38]. In a recent multi-institutional analysis, adjuvant therapies were reported to be independently associated with improved long-term outcomes in patients with advanced GBC, R1 disease and lymph node metastasis [39]. Similar conclusions were also shown by Ma et al. in a meta-analysis [40]. Current evidence would support the use of cisplatin plus gemcitabine as an adjuvant treatment option for patients with advanced GBC [6].

However, the role of neoadjuvant chemotherapy (NACT) or chemoradiotherapy (NACRT) in advanced GBC has been recently investigated as an appealing treatment strategy. It has been proposed that neoadjuvant treatment may give a better insight to the tumor biology, downstage the disease, increase resectability rate and improve overall survival. Although NACT has been successful for other malignancies, its role in advanced GBC is unclear due to paucity of evidence [41]. Review of the current literature revealed eight relevant studies with a total of 474 patients with advanced GBC. Six of them were retrospective studies and two were based on prospective cohorts. All studies are of low quality and subject to selection bias. Gemcitabine and Cisplatin were the most common neoadjuvant chemotherapeutic agents and were generally tolerated well by the patients. Three studies administered chemo-radiotherapy at a dose of 45–57 Gy [18,19,23]. Interestingly, the

**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 post-resection |
|---|---|---|---|---|---|---|---|---|---|
| Chaudhari et al. [16] | CBR = 112 (70.0%) Not operated = 19 (11.8%) [Inoperable stable disease = 10 Defaulted/Refused prior to surgery = 14][a] | 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%) Post-op death (1, 1.5%) | 51 (77.0%) [48 − ACT 3 − ACRT] | 33 months |
| Creasy et al. [17] | 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 |
| Engineer et al. [18] | CBR = 20 (71.4%) Not operated = 2 (7.1%) [Both patients refused surgery] | 18/28 (64.3%) | 14/28 (64.3%) | 14 (77.8%) | CPR = 3 pT0 = 5pT1 = 3 pT2 = 3 pT3 = 3 pN0 = 11 pN1 = 3 | RC with wedge resection (14, 77.8%) | Bile leak (6), two needing interventions | 12 (66.7%) | 37 months |
| Agrawal et al. [19] | CBR not mentioned. Not operated = 34 (85.0%) [3 patients deteriorated during chemotherapy; 6 patients after completion of chemotherapy; no reasons for why other patients were not operated] | 6/40 (15.0%) | 6/40 (15.0%) | 6 (100%) | Histological CR in liver = 1 (16.6%) Histological CR in lymph nodes = 5 (83.3%) | RC | NM | NM | 24 months |
| Gangopadhyay et al. [20] | 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. [21] | 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. [22] | 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 |
| Aretxabala et al. [23] | CBR = 16 (69.5%) All CBR patients operated. | 16/23 (69.5%) | 14/23 (60.9%) | NM | NM | RC | NM | NM | 43.8 months |

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 = Extra-Hepatic Biliary Duct Excision; EHH = Extended Hemi-hepatectomy; NM = Not mentioned; PDD = Pancreato-duodenectomy; RC = Radical Cholecystectomy; RHH = Right hemihepatectomy; RT = Radiotherapy; R0 = Margin negative resection; S4/5 = Segment 4/5 liver; UTI = Urinary tract infection.

[a] Numbers quoted in the manuscript do not match up; 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 24).

CBR was 66.6% for the patients in seven included studies to neo-adjuvant treatment and the majority of those patients were then considered for surgical resection. The rate of R0 resection among those who underwent surgery was 92.5% (160 out of 173 patients). All published studies showed a significant increase in the median overall survival for those patients who underwent curative resection following neoadjuvant therapy versus those who did not have surgery following neoadjuvant therapy.

However if we were to critically appraise the data - the subset of "locally advanced" GBC is a very heterogenous cohort with no firm description, hence not allowing for accurate interpretation of the results. The Union for International Cancer Control (UICC) classification and the American Joint Committee on Cancer (AJCC, 8th edition) of GBC do not include a detailed classification of regional factors associated with resectability [35,42]. This was addressed by individual surgical societies and institutional classifications of gallbladder cancer that tried to incorporate locoregional factors of inoperability and poor surgical outcome. The Japanese Society of Biliary Surgery Classification includes liver invasion, extend of hepatoduodenal ligament invasion and presence of liver metastasis and peritoneal disease [43]. In addition, Tata Memorial Hospital has created the TMH criteria which are considered to be high-risk features for disease recurrence based on clinico-radiologic indications, and suggest the need for systemic chemotherapy in GBC patients [16].

Current studies have shown that neoadjuvant treatment will only benefit those patients with advanced GBC that would go on to have a subsequent R0 resection [16–18,21,22]. In our review, from the 474 patients with advanced GBC treated with neoadjuvant therapy, only 40% of them (191 of 474 patients) underwent curative resection. Although neoadjuvant treatment was correlated with high R0 resection rate (92.5%), only 35.4% of the whole cohort underwent a curative resection with clear resection margins (160 out of 451 patients).

Almost 17% of the patients who responded to chemotherapy did not proceed to surgery (only 239 operated out of 289 with CBR).

**Table 4**
Median overall survival and progression-free or disease-free survival in those curative resection versus no resection following neoadjuvant therapy.

| Reference | Median Overall Survival | | | Median Event-Free or Progression-Free Survival | | Main outcomes from the study |
|---|---|---|---|---|---|---|
| | 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. [16] | NM | 49.0 | 7.0 | 25.0[†] | 5.0[a] | • With 33 months median follow-up, the median OS and EFS of the entire cohort were 13 months and 8 months respectively.<br>• EFS was 13 months in those who has clinically beneficial response and 3 months in those who had progressive disease.<br>• T stage only significant factor affecting OS on MVA (HR 3.53).<br>• T stage and nodal involvement remained significant factors affecting EFS on MVA (HR not available). |
| Creasy et al. [17] | NM | 50.1 | 10.8 | NM | NM | • 22 patients (30%) proceeded to surgery and 10 (45%) of them had definitive curative resection, which were all R0.<br>• Those who had definitive resection had significantly better long-term survival (median 50.1 months) when compared to those who were operated, but did not achieve a curative resection (median 10.8 months) [P = 0.003]. |
| Engineer et al. [18] | 20 | 35 | 10 | 30[b] | NM | • Local actuarial control rate for the patients undergoing R0 resection was 93%<br>• Estimated 5-year survival rate was 24% for all patients and 47% for patients undergoing R0 resection.<br>• Neoadjuvant therapy can facilitate surgical resection in tumours deemed unresectable. |
| Agrawal et al. [19] | NM | NM | NM | NM | NM | • At a median follow-up of 18 months, four of six resected patients were alive<br>• Neoadjuvant therapy led to 15.0% resectability rate.<br>• 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. |
| Gangopadhyay et al. [20] | NM | NM | NM | NM | NM | • Among the patients who underwent resection after chemoradiation, 5 were still alive with a follow-up of 43.8 months.<br>• Treated patients had a worst actuarial survival than those not treated with chemoradiation.<br>• Chemotherapy delayed surgery in 8 patients; reasons were thrombocytopenia (4), leucopenia (2) and both thrombocytopenia and leucopenia (2). The average delay was 3 weeks, with a range between 1 and 6 weeks. |
| Selvakumar et al. [21] | 38.1 | 42.8 | 6.6 | NM | NM | • Among the patients who underwent resection after chemoradiation, 5 were still alive with a follow-up of 43.8 months.<br>• Treated patients had a worst actuarial survival than those not treated with chemoradiation.<br>• Among the patients who underwent resection after chemoradiation, 5 were still alive with a follow-up of 43.8 months.<br>• Treated patients had a worst actuarial survival than those not treated with chemoradiation.<br>• Chemotherapy delayed surgery in 8 patients; reasons were thrombocytopenia (4), leucopenia (2) and both thrombocytopenia and leucopenia (2). The average delay was 3 weeks, with a range between 1 and 6 weeks. |
| Kato et al. [22] | NM | 18.5 | 5.0 | NM | NM | • Two-year overall survival for patients with surgical resection after downsizing chemotherapy versus chemotherapy alone without surgical resection were 45% and 19% respectively (this includes other biliary cancers)[c] |
| Aretxabala et al. [23] | NM | NM | NM | NM | NM | • Among the patients who underwent resection after chemoradiation, 5 were still alive with a follow-up of 43.8 months.<br>• Treated patients had a worst actuarial survival than those not treated with chemoradiation.<br>• Chemotherapy delayed surgery in 8 patients; reasons were thrombocytopenia (4), leucopenia (2) and both thrombocytopenia and leucopenia (2). The average delay was 3 weeks, with a range between 1 and 6 weeks. |

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.
[a] Event-free survival.
[b] Disease-free survival.
[c] This study includes 22 patients − 7 intrahepatic cholangiocarcinoma, 8 extrahepatic cholangiocarcinoma, 7 gallbladder cancers.

Creasy et al. have reported an even higher rate of 61% of patients with stable or partial response who did not proceed to surgery for various reasons [17]. The most common reasons were progression on a second CT scan while receiving continued treatment or clinical deterioration. Neoadjuvant chemotherapy can delay surgical resection for a mean of 6.8 months [7]. In our review, 20% (48 out of 239) of the patients with clinical benefit from neoadjuvant therapy, deemed to be inoperable on exploration. There was no standard

practice among the published studies with regards to the diagnostic tools and preoperative imaging. Assessment of response to neoadjuvant therapy differed between centres. Creasy et al. have used contrast-enhanced computed tomography (CECT) in order to assess chemotherapy response, at approximately 8 weeks from initiation [17]. Similar protocol for the evaluation of the efficacy of treatment was followed by the majority of the studies in our review [19–22]. However, Chaudhari et al. used both CECT and positron emission tomography (PET) with CECT after 3/4 cycles of chemotherapy [16]. Engineer et al. used a combination of PET and CECT prior to NACRT and 6 weeks following completion of CRT [18]. The utility of positron emission tomography (PET)-CT could provide a very useful diagnostic tool for staging and assessment of response to NACT/NACRT. Engineer et al. showed that PET scans were useful in excluding nearly 30% of the screened patients with metastatic disease that was missed on routine triphasic CECT [18].

In addition, there is a difference between locally advanced and inoperable GBC that could be easily overlooked. Many surgeons would advocate for surgery upfront for those patients with resectable, locally advanced GBC. It is widely accepted that R0 resection is one of the most important prognostic factors for GBC [44,45,47,49]. However, the extent of resection in advanced GBC that translates into meaningful outcomes remains undefined. Several reports from Eastern Countries suggest that aggressive surgical approach with radical resections including, major hepatectomy, pancreaticoduodenectomy, hepaticopancreatoduodenectomy and extended lymph node dissection can lead to an improved 5-year survival rate of 30–42% [18,46–49]. It is important to underline that these type of surgical resections have a significant risk of morbidity and mortality and therefore should be only performed in high volume centres following multidisciplinary discussion.

An advanced T stage does not preclude curative resection. Higuchi et al. presented 274 consecutive surgically-treated cases of advanced GBC with an R0 resection rate of 61.3% and a 5 year survival rate of 52.4% without application of neoadjuvant treatment [47]. Similarly, a large retrospective single center study of 338 patients treated for advanced GBC, revealed a high rate of upfront curative intent resections (39.6%) [49] R0 resection was carried out in 116 out of 134 patients (86.6%). The overall survival rates for curative resection patients were significantly greater than those for non-curative resection patients (1-,3-,5-year survival rate and mean-survival time: 59.0%, 47.3%, 44.3% and 22.0 months vs. 12.7%, 8.3%, 7.7% and 3.0 months) ($P < 0.001$). Positive margin, lymph node metastasis, poorly pathological differentiation and the presence of ascites were all independent risk factors for poor prognosis. The range of liver resection and whether common bile duct resection is performed do not influence the prognosis as long as R0 resection is achieved [49].

If we were to compare directly the two strategies for neoadjuvant (current study) versus an adjuvant approach (largest cohort) [49] - among all patients who were subjected to curative resection the R0 resection rate was 92.5% (160/173) and 86.6% (116/134) respectively. Also, the R0 resection rate for whole cohort on intention to treat was 35.4% (160/451) and 34.3% (116/338) respectively [49]. Therefore, the two approaches have similar outcomes in terms of achieving a R0 resection.

There are limitations to the current review as all included studies scored GRADE 'low' on quality assessment. Also, the sample size was small, with very select reporting, thereby precluding subgroup analysis to rule out potential confounding factors. We have to acknowledge that a meta-analysis was not possible as most of the data were from non-comparative observational studies that were predominantly retrospective and therefore are likely to have inherent bias. There was wide variation in all the chemotherapy/chemoradiotherapy protocol in the included studies, thereby precluding any reasonable comparison of outcome. In addition, the timing of surgery following neoadjuvant treatment varied between the published studies and the interval between the completion of chemotherapy and surgery was not clearly mentioned. Based on the current review, surgery should be considered approximately 6–8 weeks after completion of NACT or NACRT and following further staging imaging [16].

Attempt to establish histological diagnosis should be made before any non-surgical treatment modality for patients with advanced GBC [50]. However, this is not essential in patients due to undergo curative surgery where radiological features are diagnostic. Seeding of biliary cancer along the fine needle aspiration (FNA) track has also been reported [51]; with the exact level of risk being uncertain, although this appears to be low. Decisions to undertake biopsy should be made in a multidisciplinary setting, particularly in patients with potentially resectable tumours subjected to neoadjuvant treatment. Data regarding histological diagnosis are not consistent and precise in the studies included in the current review. Histological diagnosis was essential prior to administration of neoadjuvant therapy in the majority of the published studies in the current review. However, there are cases where neoadjuvant treatment was administered only on the basis of imaging indicative of locally advanced disease. In addition, it is not clear whether biopsies were obtained via CT/US guided FNAB or ERCP/EUS.

Future studies should be in the form of randomized controlled trials comparing neoadjuvant treatment followed by surgery (following response to treatment) versus surgery upfront and adjuvant chemotherapy. The studies should also standardize the definition of advanced GBC, define the indication for neoadjuvant therapy and follow standard treatment protocol, that would allow for a more meaningful interpretation of data.

## Conclusion

There is currently not enough data to support the routine use of NACT or NACRT in advanced GBC. The only patients with advanced GBC that may benefit from neoadjuvant therapy are those who will subsequently achieve an R0 resection, accounting for only a third of the whole cohort. Future studies should be in the form of randomized controlled trials to investigate the potential role of neoadjuvant therapy in advanced GBC.

## Author contributions

KVM and ARH conceptualised and designed the study. ARH and MP performed the search strategy, selected studies and extracted data. KVM cross-checked the search strategy and reviewed the data extracted from the included studies. ARH tabulated the information from the included studies and appraised the published literature. ARH and MP wrote the initial draft. KVM made the final corrections to the manuscript and will be the corresponding author.

All authors approved the final version of the manuscript.

## Conflict of interest

None declared.

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## References


[1] Lai CH, Lau WY. Gallbladder cancer–a comprehensive review. Surgeon 2008;6(2):101–10.
[2] Misra S, Chaturvedi A, Misra NC, Sharma ID. Carcinoma of the gallbladder. Lancet Oncol 2003;4(3):167–76.
[3] Zhu AX, Hong TS, Hezel AF, Kooby DA. Current management of gallbladder carcinoma. Oncologist 2010;15(2):168–81.
[4] Aloia TA, Járufe N, Javle M, et al. Gallbladder cancer: expert consensus statement. HPB (Oxford) 2015;17(8):681–90.
[5] Ethun CG, Le N, Lopez-Aguiar AG, et al. Pathologic and prognostic implications of incidental. Am Surg 2017;83(7):679–86.
[6] Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362(14):1273–81.
[7] Glazer ES, Liu P, Abdalla EK, Vauthey JN, Curley SA. Neither neoadjuvant nor adjuvant therapy increases survival after biliary tract cancer resection with wide negative margins. J Gastrointest Surg 2012;16(9):1666–71.
[8] Jin LX, Pitt SC, Hall BL, Pitt HA. Aggressive surgical management of gallbladder cancer: at what cost? Surgery (St Louis) 2013;154(2):266–73.
[9] Zaidi MY, Maithel SK. Updates on gallbladder cancer management. Curr Oncol Rep 2018;20(2):21.
[10] Verslype C, Prenen H, Van Cutsem E. The role of chemotherapy in biliary tract carcinoma. HPB (Oxford) 2008;10(3):164–7.
[11] Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. J Clin Oncol 2012;30(16):1934–40.
[12] Takada T, Amano H, Yasuda H, et al. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. Cancer 2002;95(8):1685–95.
[13] Primrose JN, Fox RF, Palmer DH, et al. Adjuvant capecitabine for biliary tract cancer: the BILCAP randomized study. J Clin Oncol 2017;35. 15_suppl;4006 (Abstract).
[14] Abdel-Rahman O, Elsayed Z, Elhalawani H. Gemcitabine-based chemotherapy for advanced biliary tract carcinomas. Cochrane Database Syst Rev 2018;4: CD011746.
[15] Shukla SK, Singh G, Shahi KS, Bhuvan, Pant P. Staging, treatment, and future approaches of gallbladder carcinoma. J Gastrointest Canc 2018;49(1):9–15.
[16] Chaudhari VA, Ostwal V, Patkar S, et al. Outcome of neoadjuvant chemotherapy in "locally advanced/borderline resectable" gallbladder cancer: the need to define indications. HPB (Oxford) 2018;20(9):841–7.
[17] Creasy JM, Goldman DA, Dudeja V, et al. Systemic chemotherapy combined with resection for locally advanced gallbladder carcinoma: surgical and survival outcomes. J Am Coll Surg 2017;224(5):906–16.
[18] Engineer R, Goel M, Chopra S, et al. Neoadjuvant chemoradiation followed by surgery for locally advanced gallbladder cancers: a new paradigm. Ann Surg Oncol 2016;23(9):3009–15.
[19] Agrawal S, Mohan L, Mourya C, Neyaz Z, Saxena R. Radiological downstaging with neoadjuvant therapy in unresectable gall bladder cancer cases. Asian Pac J Cancer Prev APJCP 2016;17(4):2137–40.
[20] Gangopadhyay A, Nath P, Biswas J. Reduced dose intensity of chemotherapy may not lead to inferior palliation in locally advanced carcinoma of the gall bladder: an experience from a regional cancer centre in eastern India. J Gastrointest Canc 2015;46(3):297–300.
[21] Selvakumar VP, Zaidi S, Pande P, Goel A, Kumar K. Resection after neoadjuvant chemotherapy in advanced carcinoma of the gallbladder: a retrospective study. Indian J Surg Oncol 2015;6(1):16–9.
[22] Kato A, Shimizu H, Ohtsuka M, et al. Urgical resection after downsizing chemotherapy for initially unresectable locally advanced biliary tract cancer: a retrospective single-center study. Ann Surg Oncol 2013;20(1):318–24.
[23] de Aretxabala X, Losada H, Mora J, et al. Neoadjuvant chemoradiotherapy in gallbladder cancer. Rev Med Chile 2004;132(1):51–7.
[24] Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. J Am Med Assoc 2000;283(15): 2008–12.
[25] Altman DG. Systematic reviews of evaluations of prognostic variables. BMJ 2001;323(7306):224–8.
[26] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7), e1000097.
[27] Park JO, Lee SI, Song SY, et al. Measuring response in solid tumors: comparison of RECIST and WHO response criteria. Jpn J Clin Oncol 2003;33(10):533–7.
[28] Choi JH, Ahn MJ, Rhim HC, et al. Comparison of WHO and RECIST criteria for response in metastatic colorectal carcinoma. Cancer Res Treat 2005;37(5): 290–3.
[29] Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328(7454):1490.
[30] Patkar S, Ostwal V, Ramaswamy A, et al. Emerging role of multimodality treatment in gall bladder cancer: outcomes following 510 consecutive resections in a tertiary referral center. J Surg Oncol 2018;117(3):372–9.
[31] Kim BJ, Hyung J, Yoo C, et al. Prognostic factors in patients with advanced biliary tract cancer treated with first-line gemcitabine plus cisplatin: retrospective analysis of 740 patients. Canc Chemother Pharmacol 2017;80(1): 209–15.
[32] Sirohi B, Mitra A, Jagannath P, et al. Neoadjuvant chemotherapy in patients with locally advanced gallbladder cancer. Future Oncol 2015;11(10):1501–9.
[33] de Aretxabala X, Roa I, Burgos L, et al. Preoperative chemoradiotherapy in the treatment of gallbladder cancer. Am Surg 1999;65(3):241–6.
[34] Oxford centre for Evidence-based Medicine – Levels of Evidence. http://www.cebm.net [accessed 20 May 2018].
[35] Chun YS, Pawlik TM, Vauthey JN. 8th edition of the AJCC cancer staging manual: pancreas and hepatobiliary cancers. Ann Surg Oncol 2018;25(4): 845–7.
[36] Åndrén-Sandberg A, Deng Y. Aspects on gallbladder cancer in 2014. Curr Opin Gastroenterol 2014;30(3):326–31.
[37] Verma V, Surkar SM, Brooks ED, Simone CB, Lin C. Chemoradiotherapy versus chemotherapy alone for unresected nonmetastatic gallbladder cancer: national practice patterns and outcomes. J Natl Compr Canc Netw 2018;16(1): 59–65.
[38] Shroff RT, Knox J, Dixon E. Consensus conference on gallbladder cancer. HPB (Oxford) 2015;17(8):664–5.
[39] Kim Y, Amini N, Wilson A, et al. Impact of chemotherapy and external-beam radiation therapy on outcomes among patients with resected gallbladder cancer: a multi-institutional analysis. Ann Surg Oncol 2016;23(9):2998–3008.
[40] Ma N, Cheng H, Qin B, Zhong R, Wang B. Adjuvant therapy in the treatment of gallbladder cancer: a meta-analysis. BMC Canc 2015;15:615.
[41] Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364(19):1817–25.
[42] Sobin LH, Gospodarowicz MK, Wittekind CH. TNM classification of malignant tumors (UICC International Union Against Cancer). http://www.inen.sld.pe/portal/documentos/pdf/educacion/13072015_TNM%20Classification.pdf. [accessed 20 May 2018].
[43] Miyazaki M, Ohtsuka M, Miyakawa S, et al. Classification of biliary tract cancers established by the Japanese Society of Hepato-Biliary-Pancreatic Surgery: 3(rd) English edition. J Hepatobiliary Pancreat Sci 2015;22(3): 181–96.
[44] Araida T, Higuchi R, Hamano M, et al. Hepatic resection in 485 R0 pT2 and pT3 cases of advanced carcinoma of the gallbladder: results of a Japanese Society of Biliary Surgery survey–a multicenter study. J Hepatobiliary Pancreat Surg 2009;16(2):204–15.
[45] Hawkins WG, DeMatteo RP, Jarnagin WR, Ben-Porat L, Blumgart LH, Fong Y. Jaundice predicts advanced disease and early mortality in patients with gallbladder cancer. Ann Surg Oncol 2004;11(3):310–5.
[46] Cong LL, Cai ZQ, Guo P, et al. Decision of surgical approach for advanced gallbladder adenocarcinoma based on a Bayesian network. J Surg Oncol 2017;116(8):1123–31.
[47] Higuchi R, Ota T, Araida T, et al. Surgical approaches to advanced gallbladder cancer: a 40-year single-institution study of prognostic factors and resectability. Ann Surg Oncol 2014;21(13):4308–16.
[48] Dixon E, Vollmer CM, Sahajpal A, et al. An aggressive surgical approach leads to improved survival in patients with gallbladder cancer: a 12-year study at a North American Center. Ann Surg 2005;241(3):385–94.
[49] Chen C, Geng Z, Shen H, et al. Long-term outcomes and prognostic factors in advanced gallbladder cancer: focus on the advanced T stage. PLoS One 2016;11(11), e0166361.
[50] Valle JW, Borbath I, Khan SA, et al. ESMO guidelines committee. Biliary cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27(suppl 5):v28–37.
[51] Razumilava N, Gleeson FC, Gores GJ. Awareness of tract seeding with endoscopic ultrasound tissue acquisition in perihilar cholangiocarcinoma. Am J Gastroenterol 2015;110:200.