RESEARCH ARTICLE

Editorial Process: Submission:04/19/2025 Acceptance:10/02/2025 Published:10/19/2025

A Phase 2 Prospective Trial of Capecitabine Plus Oxaliplatin as First-Line Therapy for Advanced Gall Bladder Cancers

Vivek Goti, Mohd Waseem Raza*, Archana Singh, Shambhu N Prasad

Abstract

Aim and objective: This study aimed to evaluate the efficacy and safety of Capecitabine plus Oxaliplatin (CapOx) chemotherapy in patients with locally advanced, inoperable, or metastatic adenocarcinoma of the gallbladder. The primary objective of the study was to determine the objective tumour response rates (complete and partial). The secondary objectives included assessment of toxicity, progression free survival, and overall survival. **Material and methods:** A prospective, single-arm, phase II study was conducted at a single center between January 2021 and December 2021. Forty-three patients with histologically confirmed advanced gallbladder adenocarcinoma were enrolled. All patients received CapOx chemotherapy (Capecitabine 1000 mg/m² orally twice daily for 14 days and Oxaliplatin 130 mg/m² intravenously on day 1, every 3 weeks for six cycles). Tumor responses were assessed clinically after each cycle and radiologically after three cycles using RECIST 1.1 criteria. Treatment-related adverse events were graded per NCI CTCAE version 5. Progression-free survival (PFS) and overall survival (OS) were analyzed using SPSS version 29. **Results:** Among the 43 patients, 35 completed three or more cycles, and 19 completed six cycles. The objective response rate (ORR) was 30.2%, and the disease control rate (DCR) was 65.1%. Median OS for all patients was 7.4 months, and PFS was 5.5 months. In patients completing six cycles, median OS was 9.8 months, and PFS was 7.3 months. The most common metastatic site was the liver. Sensory neuropathy was observed in 58.1% of patients, with grade 3/4 toxicity in 16.3%. Other reported toxicities included anemia (grade 3 in four patients), biochemical abnormalities, and gastrointestinal symptoms. **Conclusion:** CapOx chemotherapy demonstrated modest efficacy with a disease control rate of 65.1% in patients with advanced gallbladder cancer. Toxicities were generally manageable, with sensory neuropathy being the most common. Further studies are needed to validate these findings and explore additional therapeutic options.

Keywords: Chemotherapy- CapOx- First-Line Therapy- Advanced Gall Bladder cancer- Metastatic

Asian Pac J Cancer Prev, **26 (10)**, 3761-3767

Introduction

Gallbladder cancer (GBC) ranks 22nd globally in terms of new cases (122,491 annually) and 20th in mortality (89,055 deaths per year), based on GLOBOCAN 2024 data [1]. This cancer displays an unusual and uneven geographical distribution worldwide. In the Mapuche Indian population from Valdivia, Chile, South America, the rates are noted as 12.3 per 100,000 for men and 27.3 per 100,000 for women [2].

India is considered a high-risk region for GBC, accounting for approximately 10% of the global disease burden. Within the country, higher incidence rates are seen in the northern, northeastern, central, and eastern regions, while lower rates are observed in the southern and western parts. The incidence is steadily increasing across both genders. Patients in India often present with advanced stages of the disease, which is associated with a grim prognosis. In contrast to Western countries, GBC in India affects comparatively younger individuals, typically in their 5th and 6th decades of life. Gallstones are identified in 80% of Indian GBC cases, elevating the susceptibility of the gallbladder to mucosal damage [3]. Globally, GBC is the most prevalent malignancy of the biliary tract and ranks as the fifth most common gastrointestinal cancer [4]. Despite being relatively rare, GBC is highly aggressive with a poor survival rate. The disease shows marked geographic, ethnic, and cultural variability, indicating significant genetic and environmental contributions to its development and progression [4, 5]. One major reason for its poor prognosis is the absence of a serosal layer in the gallbladder, which allows direct invasion into the liver and metastatic spread [2].

Various genetic and environmental influences have been associated with the onset of gallbladder cancer. Chronic gallbladder infection (salmonella typhi), exposure to certain chemicals, heavy metals, and dietary factors have all been linked to the disease. The disproportionate prevalence of GBC among women and in specific geographic regions, particularly in developing countries, is

*Department of Oncology, J. K. Cancer Institute, Kanpur, Uttar Pradesh, India. *For Correspondence: waseem.drraza000@gmail.com*

thought to be influenced by hormonal factors, cholesterol metabolism, and salmonella infections, according to existing studies [6, 7].

Apart from genetic and geographical factors, the presence of large gallstones is a key risk factor for GBC. Gallbladder polyps larger than 1.5 cm, especially solitary, sessile, hypoechogenic polyps, have a 50% malignancy risk. Younger individuals and those without gallstones may also develop cancer, often linked to conditions such as porcelain gallbladder, particularly when the mucosa is calcified [8]. Additional risk factors include Mirizzi's syndrome, bile reflux, a family history of gallstones, tobacco use, chemical exposure, residence in the Gangetic belt, high levels of secondary bile acids, and excessive consumption of fried foods (often with reused oil) [9]. While gallstones are strongly associated with GBC, their causative role remains uncertain [10]. Substantial evidence supports their role as a significant factor in the etiology of GBC [11].

The Chinese population has exhibited recurrent mutations in the ErbB pathway [12]. Meanwhile, Javle et al. identified 26 missense mutations, with TP53 and PIK3CA being the most prevalent, in GBC tumors using NGS technology [13]. Among Indian GBC patients, PIK3CA and KRAS mutations are the most common genetic alterations [14].

The variability in results reflects the intratumoral heterogeneity of cancer, a phenomenon where distinct tumor cells exhibit different morphological and molecular characteristics, including varied gene expression, but ultimately converge on a shared phenotype [15]. Gallbladder carcinoma develops through a series of progressive events before becoming an invasive malignancy. Exposure to carcinogens can transform normal gallbladder epithelium into a metaplastic condition, which then advances to dysplasia, carcinoma in situ (CIS), and, after approximately 15 years, invasive carcinoma [16, 17]. To date, there are no reliable tumor markers specifically validated for diagnosing gallbladder cancer. The two markers often elevated in advanced stages, carcinoembryonic antigen (CEA) and carbohydrate antigen 199, have low specificity and are thus rarely used as standalone diagnostic tools [18].

Most GBC cases are diagnosed at advanced stages. Complete surgical resection remains the only curative treatment for early-stage neoplasms, regardless of their location within the biliary system [19]. However, fewer than one-third of cholangiocarcinomas (CCCs) are resectable, and patients with unresectable CCC or UICC stage IV GBC treated with supportive care alone have a poor prognosis, with a median survival time of less than six months [20, 21].

Various cytotoxic agents have been assessed, both as single therapies and in combination chemotherapy regimens [22]. Chemotherapy has been shown to significantly enhance survival and improve quality of life compared to best supportive care [23]. Capecitabine, an oral fluoropyrimidine pro-drug, is preferentially converted to 5-FU in tumor tissues. In a phase I study combining capecitabine with oxaliplatin [24], a patient with GBC who had previously progressed on a regimen of 5-FU and leucovorin experienced a partial response. This finding, along with the efficacy of single-agent 5-FU and 5-FU combined with cisplatin in biliary tract cancers, prompted further investigation into the combination of capecitabine and oxaliplatin as a first-line therapy in biliary tract cancers.

Few randomized trials have explored chemotherapy in advanced biliary-tract cancers. In an analysis of 104 trials involving 2,810 patients, the combination of gemcitabine and platinum-based agents was found to be more effective than gemcitabine alone [25]. The UK ABC-02 phase III trial [26] further confirmed that gemcitabine combined with cisplatin outperformed gemcitabine as a monotherapy. Additional studies, including single-group investigations [27-29] and a randomized trial [30], demonstrated the efficacy of gemcitabine combined with oxaliplatin, showing antitumor activity with a favorable toxicity profile. Despite these advancements, the prognosis for advanced biliary-tract cancer remains poor, with median overall survival rates below one year [25, 26, 30].

The regimen combining gemcitabine and cisplatin is demanding, requiring frequent hospital visits. A phase II trial on biliary tract cancers [31] reported a median progression-free survival of 4.6 months (95% CI: 2.8–6.4 months) and a median overall survival of 7.9 months (95% CI: 5.3–10.4 months). In light of the lack of a definitive regimen, capecitabine and oxaliplatin were explored as a treatment for unresectable advanced gallbladder adenocarcinoma in a prospective phase II trial at our center.

Materials and Methods

This was a prospective single arm, phase II, single-center study. Histologically or cytologically confirmed adenocarcinoma of the gallbladder were included, locally advanced(non-resectable) or metastatic disease. Proper metastatic workup was done and non resectability confirmed by surgical colleagues. Further inclusion criteria were measurable or assessable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Adequate renal and bone marrow functions. Biliary tract obstruction (if any) had to be adequately treated before study entry, with total bilirubin concentrations less than or equal to three times the upper limit of normal range (ULN) and aminotransferase concentrations of less than or equal to five times the ULN. Patients were excluded if they had received previous palliative chemotherapy for biliary-tract cancer, received adjuvant treatment within 6 months before study entry, metastatic disease other than liver, grade 2 or worse peripheral neuropathy, or had additional malignancy within the past 5 years. We included 43 patients treated with Capecitabine plus oxaliplatin for advanced gall bladder cancer between January 2021 and December 2021 at our centre (Figure 1).

All patients gave written consent. The institutional ethics committee reviewed and approved the protocol.

Treatment and response assessment

All patients received capecitabine (1000 mg/m^2 po, twice daily, days 1–14) and oxaliplatin (130 mg/m^2 i.v,

day 1) every 3 weeks for six cycles. Tumor responses were assessed with clinically after each cycle while radiologically after 3 cycles. We assessed the treatment response according to the Response Evaluation Criteria in Solid Tumors (RECIST)version 1.1. [32] whereas, treatment-related adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria version 5 [33]

Statistical analysis

The registration date was considered as the start date of the initial regimen (CapOx) for all patients. Progression free survival was defined as the time from the registration date to the date of disease progression or death from any cause, whichever occurred first. Overall survival was defined as the time from the registration date to death from any cause (Figure 2). The Objective response rate was defined as the complete response (CR) and Partial response (PR) of the disease of the patients. The Disease control rates (DCR) was calculated as CR, PR and stable disease (SD) of the population. SPSS version 29 was used for statistical analysis.

Table 1. Baseline Patient Characteristics

Characteristics	n = 43
Agemedian year (range)	58.5 (35-75)
Sex, male:female	11(25.6%) : 32(74.4%)
ECOG	
0	4 (9.3%)
1	37 (86%)
2	2 (4.7%)
Extent of disease	
Metastatic	35 (81.4%)
Non metastatic locally advanced	8 (18.6%)

Results

In the present study we recruited forty three patients from our center in between January 2021 to December 2021 for CapOx chemotherapy in advanced, inoperable or metastatic gall bladder adenocarcinoma. At the time of the final analysis all patients died. Eight patients received less than three cycles and were lost to follow up (three received 1 cycle and five received two cycles). A total of thirty five patients received three or more than three cycles. Nineteen patients completed 6 cycles of chemotherapy. Eight patients had progressive disease and were planned for second line chemotherapy All patients were analysed as per intention to treat analysis.

A total of 10 patients had tumor progression (34%), of whom 10 died. The median survival in the CapOx group was 8.5 months. Baseline patient characteristics are summarized in Table 1. The median age was 58.5 years (range 35–75 years). Most patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 1 (86%) at the time of start of treatment Capecitabine plus oxaliplatin. The Liver was the most common metastatic site, followed Lung, and Peritoneum.

Objective responses

Complete and partial responses were achieved in one and twelve patients, respectively. Responses were achieved in stable disease and PD in 15 (34.9%) and 8(18.6%) patients, respectively. The Objective Response rate (ORR) and Disease control rate (DCR) were 30.2% and 65.1% in all patients (Table 2).

The median overall survival was 7.4 months and PFS 5.5 months for overall patients. (Figure 3). If we consider patients only who completed 6 cycles of Capox chemotherapy then median survival was 9.8 months and PFS was 7.3 months respectively.

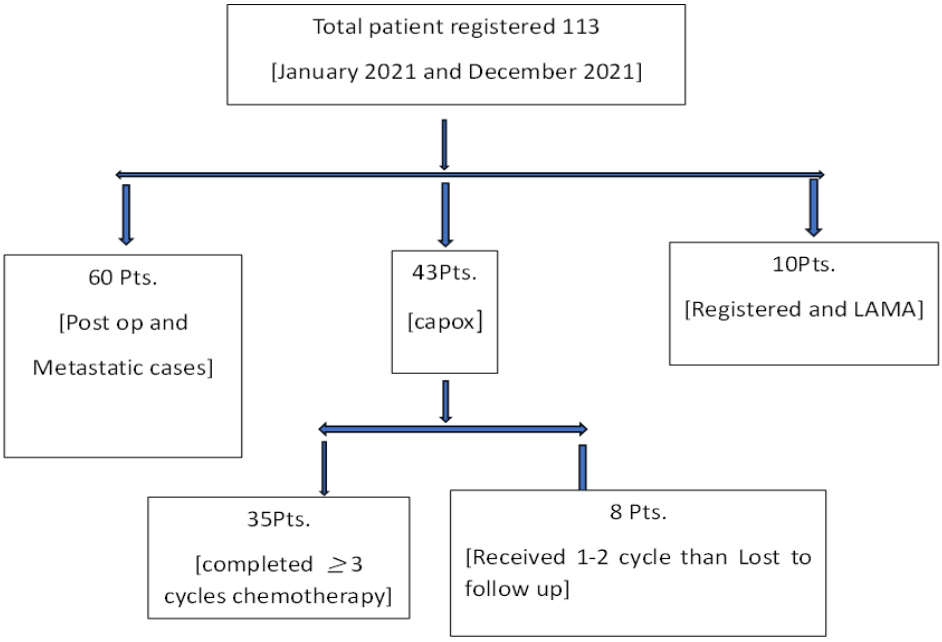

Figure 1.Patient Flow Chart

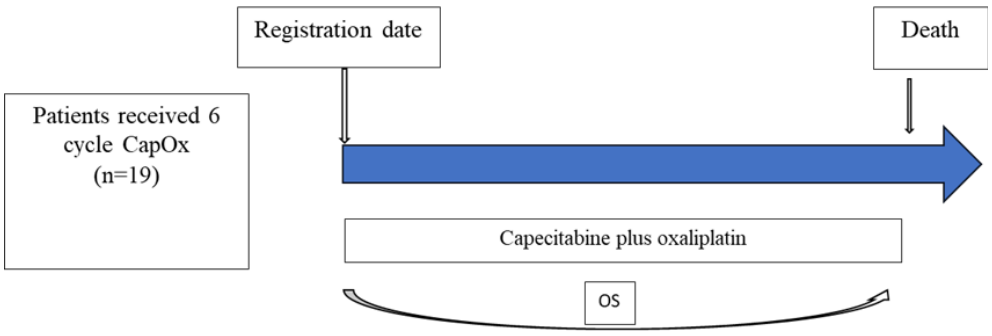

Figure 2. Showing Flowchart for OS

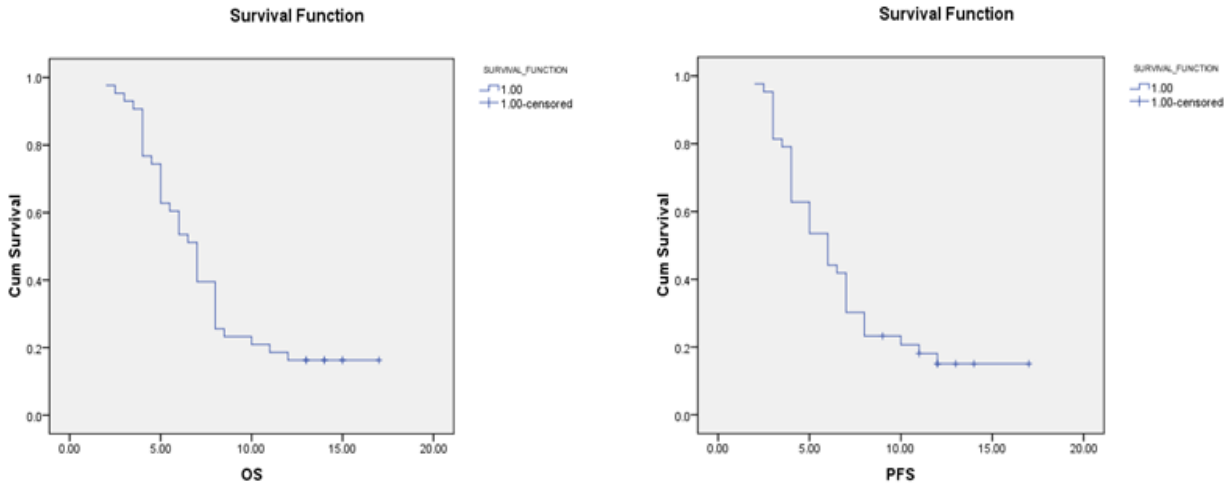

Figure 3. Showing Overall Survival and Progression Free Survival

Table 2. Treatment Response

	Overall (n = 43)
Complete response	1 (2.3%)
Partial response	12 (27.9%)
Stable disease	15 (34.9%)
Progressive disease	8 (18.6%)
Could not be assessed	7 (16.3%)
ORR (OBJECTIVE RESPONSE RATE)	30.2 %
DCR (DISEASECONTROL RATE)	65.1%

Toxicity assessments

As per NCI CTCAE version 5, maximum toxicity was reported and it was seen that maximum haematological toxicity was grade 2 with no grade 3/4 neutropenia or thrombocytopenia. Four patients experienced grade 3 anemia for which packed cell transfusions were done.

Biochemical abnormalities included increased bilirubin in five patients who underwent stenting, elevated alkaline phosphatase in twelve patients, SGOT and SGPT were maximum two times upper limit of normal. Sensory neuropathy was observed in 25 (58.1%) patients,

and was grade 3/4 in 7 (16.3%) patients. Other toxicities included fatigue, nausea, vomiting, diarrhoea, anorexia, abdominal cramps and loose motions of maximum grade 2/3 toxicity.

Discussion

The study primarily aimed to evaluate the objective tumor response rates, including both complete and partial responses. Secondary objectives encompassed analyzing toxicity levels, progression-free survival, and overall survival rates. Oxaliplatin is commonly used in clinical settings as an alternative to cisplatin, displaying clinical efficacy and manageable safety when combined with capecitabine or 5-FU across various cancer types [34, 35]. The combination of capecitabine and oxaliplatin (XELOX) serves as a standard treatment for gastric, colorectal, and other gastrointestinal cancers. A phase II trial conducted by JS Graham et al. recruited 43 patients from July 2003 to December 2005. The overall response rate was recorded at 23.8% (95% CI: 12.05–39.5%). Stable disease was observed in 31% (13 patients), while progressive disease occurred in 28.6% (12 patients). Median progression-free survival reached 4.6 months (95% CI: 2.8–6.4 months), and median overall survival was 7.9 months (95% CI: 5.3–10.4 months). The regimen demonstrated favorable tolerability, with no instances of grade 3/4 neutropenia or thrombocytopenia. Grade 3/4 sensory neuropathy was reported in six patients. XELOX exhibited modest efficacy and an acceptable toxicity profile in biliary tract cancers [31].

In the present study, patients treated with the CapOx regimen achieved a disease control rate (DCR) of 65.1%

and an objective response rate (ORR) of 35.2%. These results highlight the effectiveness of CapOx combination chemotherapy as a first-line treatment for advanced gallbladder cancer.

Another trial conducted by O Nehls et al. included 47 patients, where the response rate for gallbladder cancer (GBC) and extrahepatic cholangiocarcinoma (ECC) was 27%, including 4% complete responses. Stable disease (SD) was observed in 49% (23 patients). Among 18 patients with intrahepatic cholangiocarcinoma (ICC), no objective responses were noted, though 33% (6 patients) exhibited SD. Median survival was calculated at 12.8 months (95% CI: 10.0–15.6 months) for GBC/ECC patients, further subdivided as 8.2 months (95% CI: 4.3–11.7 months) for GBC and 16.8 months (95% CI: 12.7–20.5 months) for ECC. ICC patients demonstrated a median survival of 5.2 months (95% CI: 0.6–9.8 months). Across both groups, the CapOx regimen was well-tolerated, with peripheral sensory neuropathy (grade 3–4) observed in 11 patients as the most common severe toxicity. Their findings suggested that CaPOx is an effective and tolerable treatment for advanced GBC and ECC but may yield less favorable outcomes for ICC [19 O Nehls].

A previous phase II trial conducted by Yong et al. assessed the efficacy of capecitabine combined with oxaliplatin as a second-line chemotherapy for locally advanced gallbladder cancer. The study reported an overall response rate (ORR) of 14% and a disease control rate (DCR) of 52%. With a median follow-up period of 15.6 months, the median overall survival (OS) was eight months. These findings were consistent with our study outcomes, where the progression-free survival (PFS) was 5.5 months, and the OS was 7.4 months.

The ABC-02 trial, another significant study, focused on locally advanced gallbladder cancer. Patients were randomized into two groups: one receiving chemotherapy with gemcitabine and cisplatin, and the other receiving gemcitabine alone. After a median follow-up period of 8.2 months, with 327 deaths recorded, the median OS was 11.7 months for the cisplatin–gemcitabine group (204 patients) and 8.1 months for the gemcitabine-only group (206 patients). These results indicate that the CapOx regimen is less effective compared to gemcitabine combined with cisplatin but on par with gemcitabine alone [23].

In our study, 43 patients were analysed, but only 19 completed more than six cycles of chemotherapy. One notable concern is the higher frequency of hospital visits required for gemcitabine-based regimens. Patients undergoing gemcitabine plus cisplatin required two admissions (Day 1 and Day 8) per cycle, whereas those receiving gemcitabine alone needed three admissions (Day 1, Day 8, and Day 15). In contrast, the CAPOX regimen required fewer hospital visits, highlighting its convenience compared to the other two regimens.

The findings align with a study conducted by S. T. Kim et al. in 2019, which randomly assigned 114 patients to GEMOX (gemcitabine plus oxaliplatin) and 108 patients to XELOX (capecitabine plus oxaliplatin). Median PFS was 5.3 months for GEMOX and 5.8 months for XELOX. The six-month PFS rate was 44.5% for GEMOX and 46.7% for XELOX, with a 95% confidence interval for the difference in PFS rates between the groups ranging from 12% to 16%, satisfying the noninferiority criteria for XELOX compared to GEMOX. There were no significant differences in ORR ($P = 0.171$) or OS ($P = 0.131$) between the two groups. The most frequent grade 3–4 adverse events included neutropenia and thrombocytopenia. Importantly, no treatment-related fatalities occurred, and XELOX demonstrated significantly fewer hospital visits compared to GEMOX ($P < 0.001$) [36].

Overall, the CAPOX regimen is characterized by a favourable safety profile and greater convenience, making it a potential alternative first-line treatment option for advanced gallbladder cancers.

In conclusion, this study shows a promising survival for CapOx over gemcitabine and inferior survival over Gemicitabine plus Cisplatin with a tolerable safety profile in patients with Locally advanced Gall Bladder Cancer. The ORR and DRR is promising so we are planning a phase III randomized study with larger population comparing Gemcitabine cisplatin to CapOx chemotherapy in locally advanced and metastatic gall bladder cancer.

Author Contribution Statement

Patient recruitment and collection of clinical data: MWR, VG, AS, design of study: MWR, AS, data analysis: MWR, VG, final manuscript draft: MWR, VG, AS, SNP. All authors read and approved final manuscript.

Acknowledgements

We thank all participating patients and their families, nursing staff and paraclinical staff involved in the study.

Ethics Approval

Study was a part of MD thesis approved by Institutional Ethics committee.

Conflict of interest

No authors have any conflict of interest.

References

1. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer; 2024. Available from: https://gco.iarc.who.int/today, accessed [12 March 2025].
2. Hundal R, Shaffer EA. Gallbladder cancer: Epidemiology and outcome. Clin Epidemiol. 2014;6:99-109. https://doi.org/10.2147/clep.S37357.
3. Dutta U, Bush N, Kalsi D, Popli P, Kapoor VK. Epidemiology of gallbladder cancer in india. Chin Clin Oncol. 2019;8(4):33. https://doi.org/10.21037/cco.2019.08.03.
4. Misra S, Chaturvedi A, Misra NC. Gallbladder cancer. Curr Treat Options Gastroenterol. 2006;9(2):95-106. https://doi.org/10.1007/s11938-006-0028-1.
5. Andia ME, Hsing AW, Andreotti G, Ferreccio C. Geographic variation of gallbladder cancer mortality and risk factors in chile: A population-based ecologic study. Int J Cancer.

2008;123(6):1411-6. https://doi.org/10.1002/ijc.23662.
6. Shukla R, Shukla P, Behari A, Khetan D, Chaudhary RK, Tsuchiya Y, et al. Roles of salmonella typhi and salmonella paratyphi in gallbladder cancer development. Asian Pac J Cancer Prev. 2021;22(2):509-16. https://doi.org/10.31557/apjcp.2021.22.2.509.
7. Iyer P, Barreto SG, Sahoo B, Chandrani P, Ramadwar MR, Shrikhande SV, et al. Non-typhoidal salmonella DNA traces in gallbladder cancer. Infect Agent Cancer. 2016;11:12. https://doi.org/10.1186/s13027-016-0057-x.
8. Kianmanesh R, Scaringi S, Castel B, Flamant Y, Msika S. Precancerous lesions of the gallbladder. J Chir (Paris). 2007; French.144(4):278-86. doi: 10.1016/s0021-7697(07)91953-5.
9. Jain K, Sreenivas V, Velpandian T, Kapil U, Garg PK. Risk factors for gallbladder cancer: A case-control study. Int J Cancer. 2013;132(7):1660-6. https://doi.org/10.1002/ijc.27777.
10. Shrikhande SV, Barreto SG, Singh S, Udwadia TE, Agarwal AK. Cholelithiasis in gallbladder cancer: Coincidence, cofactor, or cause! Eur J Surg Oncol. 2010;36(6):514-9. https://doi.org/10.1016/j.ejso.2010.05.002.
11. Hsing AW, Bai Y, Andreotti G, Rashid A, Deng J, Chen J, et al. Family history of gallstones and the risk of biliary tract cancer and gallstones: A population-based study in shanghai, china. Int J Cancer. 2007;121(4):832-8. https://doi.org/10.1002/ijc.22756.
12. Li M, Zhang Z, Li X, Ye J, Wu X, Tan Z, et al. Whole-exome and targeted gene sequencing of gallbladder carcinoma identifies recurrent mutations in the erbb pathway. Nat Genet. 2014;46(8):872-6. https://doi.org/10.1038/ng.3030.
13. Javle M, Rashid A, Churi C, Kar S, Zuo M, Eterovic AK, et al. Molecular characterization of gallbladder cancer using somatic mutation profiling. Hum Pathol. 2014;45(4):701-8. https://doi.org/10.1016/j.humpath.2013.11.001.
14. Kumari N, Corless CL, Warrick A, Beadling C, Nelson D, Neff T, et al. Mutation profiling in gallbladder cancer in indian population. Indian J Pathol Microbiol. 2014;57(1):9-12. https://doi.org/10.4103/0377-4929.130849.
15. Sharma A, Sharma KL, Gupta A, Yadav A, Kumar A. Gallbladder cancer epidemiology, pathogenesis and molecular genetics: Recent update. World J Gastroenterol. 2017;23(22):3978-98. https://doi.org/10.3748/wjg.v23.i22.3978.
16. Albores-Saavedra J, Alcántra-Vazquez A, Cruz-Ortiz H, Herrera-Goepfert R. The precursor lesions of invasive gallbladder carcinoma. Hyperplasia, atypical hyperplasia and carcinoma in situ. Cancer. 1980;45(5):919-27. https://doi.org/10.1002/1097-0142(19800301)45:5<919::aid-cncr2820450514>3.0.co;2-4.
17. Roa I, Araya JC, Villaseca M, De Aretxabala X, Riedemann P, Endoh K, et al. Preneoplastic lesions and gallbladder cancer: An estimate of the period required for progression. Gastroenterology. 1996;111(1):232-6. https://doi.org/10.1053/gast.1996.v111.pm8698204.
18. Srivastava K, Srivastava A, Mittal B. Potential biomarkers in gallbladder cancer: Present status and future directions. Biomarkers. 2013;18(1):1-9. https://doi.org/10.3109/1354750x.2012.717105.
19. Nehls O, Oettle H, Hartmann JT, Hofheinz RD, Hass HG, Horger MS, et al. Capecitabine plus oxaliplatin as first-line treatment in patients with advanced biliary system adenocarcinoma: A prospective multicentre phase ii trial. Br J Cancer. 2008;98(2):309-15. https://doi.org/10.1038/sj.bjc.6604178.
20. Pitt HA, Grochow LB, Abrams RA . Cancer of the biliary tree. In Cancer: Principles and Practice of Oncology, DeVita VT, Hellman S, Rosenberg SA (eds) 5th edn. Philadelphia, Pennsylvania/ New York: Lippincott-Raven. 1997; pp 1114–28.
21. Weber SM, DeMatteo RP, Fong Y, Blumgart LH, Jarnagin WR. Staging laparoscopy in patients with extrahepatic biliary carcinoma. Analysis of 100 patients. Ann Surg. 2002;235(3):392-9. https://doi.org/10.1097/00000658-200203000-00011.
22. Hejna M, Pruckmayer M, Raderer M. The role of chemotherapy and radiation in the management of biliary cancer: A review of the literature. Eur J Cancer. 1998;34(7):977-86. https://doi.org/10.1016/s0959-8049(97)10166-6.
23. Glimelius B, Hoffman K, Sjödén PO, Jacobsson G, Sellström H, Enander LK, et al. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. Anna Oncol. 1996;7(6):593-600. https://doi.org/10.1093/oxfordjournals.annonc.a010676.
24. Díaz-Rubio E, Evans TR, Tabemero J, Cassidy J, Sastre J, Eatock M, et al. Capecitabine (xeloda) in combination with oxaliplatin: A phase i, dose-escalation study in patients with advanced or metastatic solid tumors. Anna Oncol. 2002;13(4):558-65. https://doi.org/10.1093/annonc/mdf065.
25. Eckel F, Schmid RM. Chemotherapy in advanced biliary tract carcinoma: A pooled analysis of clinical trials. Br J Cancer. 2007;96(6):896-902. https://doi.org/10.1038/sj.bjc.6603648.
26. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362(14):1273-81. https://doi.org/10.1056/NEJMoa0908721.
27. André T, Reyes-Vidal JM, Fartoux L, Ross P, Leslie M, Rosmorduc O, et al. Gemcitabine and oxaliplatin in advanced biliary tract carcinoma: A phase ii study. Br J Cancer. 2008;99(6):862-7. https://doi.org/10.1038/sj.bjc.6604628.
28. Harder J, Riecken B, Kummer O, Lohrmann C, Otto F, Usadel H, et al. Outpatient chemotherapy with gemcitabine and oxaliplatin in patients with biliary tract cancer. Br J Cancer. 2006;95(7):848-52. https://doi.org/10.1038/sj.bjc.6603334.
29. Jang JS, Lim HY, Hwang IG, Song HS, Yoo N, Yoon S, et al. Gemcitabine and oxaliplatin in patients with unresectable biliary cancer including gall bladder cancer: A korean cancer study group phase ii trial. Cancer Chemother Pharmacol. 2010;65(4):641-7. https://doi.org/10.1007/s00280-009-1069-7.
30. Sharma A, Dwary AD, Mohanti BK, Deo SV, Pal S, Sreenivas V, et al. Best supportive care compared with chemotherapy for unresectable gall bladder cancer: A randomized controlled study. J Clin Oncol. 2010;28(30):4581-6. https://doi.org/10.1200/jco.2010.29.3605.
31. Graham JS, Boyd K, Coxon FY, Wall LR, Eatock MM, Maughan TS, et al. A phase ii study of capecitabine and oxaliplatin combination chemotherapy in patients with inoperable adenocarcinoma of the gall bladder or biliary tract. BMC Res Notes. 2016;9:161. https://doi.org/10.1186/s13104-015-1778-4.
32. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised recist guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47. https://doi.org/10.1016/j.ejca.2008.10.026.
33. Freites-Martinez A, Santana N, Arias-Santiago S, Viera A. Using the common terminology criteria for adverse events (ctcae - version 5.0) to evaluate the severity of adverse events

of anticancer therapies. Actas Dermosifiliogr (Engl Ed). 2021;112(1):90-2. https://doi.org/10.1016/j.ad.2019.05.009.
34. Mathé G, Kidani Y, Segiguchi M, Eriguchi M, Fredj G, Peytavin G, et al. Oxalato-platinum or 1-ohp, a third-generation platinum complex: An experimental and clinical appraisal and preliminary comparison with cis-platinum and carboplatinum. Biomed Pharmacother. 1989;43(4):237-50. https://doi.org/10.1016/0753-3322(89)90003-6.
35. Kim ST, Kang JH, Lee J, Lee HW, Oh SY, Jang JS, et al. Capecitabine plus oxaliplatin versus gemcitabine plus oxaliplatin as first-line therapy for advanced biliary tract cancers: A multicenter, open-label, randomized, phase iii, noninferiority trial. Ann Oncol. 2019;30(5):788-95. https://doi.org/10.1093/annonc/mdz058.