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Chemotherapy for gallbladder cancer (Protocol).
Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD004546.
DOI: [10.1002/14651858.CD004546](https://doi.org/10.1002/14651858.CD004546).

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
BACKGROUND	2
OBJECTIVES	2
METHODS	2
REFERENCES	5
APPENDICES	6
HISTORY	7
CONTRIBUTIONS OF AUTHORS	7
DECLARATIONS OF INTEREST	8
SOURCES OF SUPPORT	8
NOTES	8

[Intervention Protocol]

Chemotherapy for gallbladder cancer

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Editorial group: Cochrane Hepato-Biliary Group.

Publication status and date: Edited (no change to conclusions), published in Issue 9, 2021.

Citation: Pandey M, Chandramohan KN. Chemotherapy for gallbladder cancer (Protocol). *Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No.: CD004546. DOI: [10.1002/14651858.CD004546](https://doi.org/10.1002/14651858.CD004546).

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the beneficial and harmful effects of chemotherapy for gallbladder cancer .

BACKGROUND

Carcinoma of the gallbladder is the commonest malignancy of the biliary tract. It is relatively rare in the west, with United States having an incidence of 1/100,000 (Perkin 1997). High incidences have been noted in the Southwest American Indians in the USA and inhabitants of Chile, Mexico, Bolivia, Poland, and Israel (Waterhouse 1976; Perkin 1997). It is the third most common gastrointestinal malignancy in India (Shukla 1985). The disease clinically mimics benign gallbladder diseases and escapes detection until very late in its course (Piehler 1978). It is also an unexpected histopathological finding in 1 to 3% of the resected specimens after elective cholecystectomy for presumably benign gallbladder diseases (Hamrick 1982). The disease is encountered mainly in sixth and seventh decades of life (Piehler 1978). The overall prognosis of gallbladder cancer has remained dismal with a five-year survival of under 10% (Fields 1987), which is mainly due to the late detection of the disease (Balaroutsos 1971; Piehler 1978; Chao 1991; Kapoor 1996).

Prior to the era of ultrasonography (USG) and computerized tomographic (CT) scanning, the correct pre-operative diagnosis of gallbladder cancer was seldom made (Piehler 1978), now a correct preoperative diagnosis is now achieved in 75 to 88% of the patients (Itai 1980; Palma 1980; Soiva 1987). Still, a preoperative diagnosis of early carcinoma of the gallbladder is seldom made, where the 5-year survival is 91 to 100% (Shirai 1992; Yamaguchi 1992). The patients present with multiple vague symptoms: abdominal pain, anorexia, or weight loss being the commonest (Vaitinen 1970; Piehler 1978; Shukla 1985; Silk 1989; Chao 1991). Jaundice is invariably associated with advanced disease. Owing to the strong association of the gallstones with the disease early cholecystectomy should be considered (Diehl 1980; Pandey 1996). A routine histopathological examination of all cholecystectomy specimens with serial sectioning is a must, specially in patients from high incidence areas, to exclude the possibility of an inapparent carcinoma (Yamaguchi 1992; Kapoor 1996).

In the Surveillance, Epidemiology, and End Results Program (SEER) of the National Cancer Institute (NCI), the five-year survival for 3038 gallbladder cancers of all histological subtypes was less than 10%, with a two-year survival of 13% (Henson 1992). The five-year survival rates were 30% for stage I and less than 5% for stage II-IV gallbladder cancer. Complete surgical resection is often not possible. Metastasis occurs early with or without local dissemination (Piehler 1978; Shukla 1985). Although combined treatment with surgery and radiotherapy has resulted in improved local control, there is only minimal improvement in disease free survival as a result of high incidence of distant metastasis (Todoroki 1997; Todoroki 1999). Chemotherapy in such situations could improve survival by reducing chances for distant metastases and could render radiation more effective in controlling regional disease, after surgical resection (Todoroki 2000).

Chemotherapy has been used for unresectable primary gallbladder cancer and also as an adjuvant to surgical resection mostly in non-randomised cohort or retrospective case-control settings. The majority of studies on single agent chemotherapy have used 5-fluorouracil (5-FU) or mitomycin (MMC), with response rates ranging from 10 to 20% (Falkson 1984; Oberfield 1988; Taal 1993). Other drugs that have been used as single agent

for the systemic treatment include cisplatin (CDDP) (Okada 1994), carmustine (BCNU), streptozotocin (STZ) (Moertel 1973), and paclitaxel (Jones 1996). Only 5-FU, MMC, and CDDP have shown partial response. Various combinations of chemotherapy have been used in unresectable disease with median survival ranging from a low of 2.5 months (Murakami 1998) to a high of 14 months (Murakami 1998). In a retrospective review by Todoroki et al, they reported the overall response rate of combination chemotherapy regimens to be better than single-agent systemic chemotherapy (17.9 compared to 8.7%) (Todoroki 2000). Many of the published reports included data on patients with bile duct, pancreas, and even liver cancers. Hence, using the results of these studies to establish chemotherapy regimens specifically for gallbladder cancer is impossible.

There are no systematic reviews or meta-analyses on use of chemotherapy in gallbladder cancer.

OBJECTIVES

To assess the beneficial and harmful effects of chemotherapy for gallbladder cancer.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomised clinical trials irrespective of blinding, publication status, or language. For the evaluation of rare, serious adverse events we will additionally consider large cohort studies, as such events are rarely captured in randomised clinical trials.

Types of participants

People of all ages and sex fulfilling the cytological or histological diagnosis of gallbladder cancer.

Types of interventions

This review will address:

- (1) chemotherapy versus placebo/no chemotherapy;
- (2) one type of chemotherapy versus another type of chemotherapy.

Co-interventions will be allowed if received by both intervention arms.

Types of outcome measures

Primary outcome measures

- (1) Overall survival.
 - (2) Disease free (event free) survival, if the chemotherapy has been used in adjuvant setting after surgical resection of the tumour.
 - (3) Response to chemotherapy (complete response, partial response, no response, or progressive disease).
- Complete response is described as complete radiological and clinical disappearance of tumour. A regression of greater than 50% in size is recorded as a partial response. Any regression less than that will be recorded as no response. On the other hand an increase in size of the lesion or metastasis is recorded as progressive disease.

(4) Adverse events. They will be defined as any untoward medical occurrence not necessarily having a causal relationship with the treatment, but resulting in a dose reduction or discontinuation of treatment. Severe adverse events will be defined according to the International Committee on Harmonization guidelines (ICH-GCP 1997) as any event that would increase mortality; is life-threatening; requires inpatient hospitalisation; results in a persistent or significant disability; or any important medical event which may jeopardise the patient or require intervention to prevent it.

Secondary outcome measures

(5) Quality of life.

(6) Cost-effectiveness.

Search methods for identification of studies

We will find relevant randomised clinical studies searching *The Cochrane Hepato-Biliary Group Controlled Trials Register*, *The Cochrane Central Register of Controlled Trials (CENTRAL)* in *The Cochrane Library*, *MEDLINE*, and *EMBASE*. Preliminary search strategies are given in [Appendix 1](#).

We will identify further trials by reading the reference lists of the identified studies. We will write to the principal authors of the identified randomised clinical trials and enquire about additional trials of which they might be aware or for additional non-reported information in their trials.

Data collection and analysis

We will conduct the systematic review according to this protocol following the recommendations of *The Cochrane Reviewers' Handbook* (Clarke 2003).

Data extraction

We will extract the following characteristics from each randomised clinical trial: Primary author; number of patients randomised; patient inclusion and exclusion criteria; methodological quality (see below); sample size estimation; intention-to-treat analysis; intervention regimens; mean age; sex; stage of disease; median follow-up; response to treatment; survival; event free survival; cost effectiveness; and adverse events.

Assessment of methodological quality

We will assess separately the methodological quality of the trials by using the four components: patient randomisation (generation of the allocation sequence and allocation concealment) blinding, and completeness of follow-up (Schulz 1995; Moher 1998; Kjaergard 2001). We will use the following definitions in the assessment of the methodological quality:

Generation of the allocation sequence

- Adequate, if the allocation sequence was generated by a computer or random number table. Drawing of lots, tossing of a coin, shuffling of cards, or throwing dice will be considered as adequate if a person who was not otherwise involved in the recruitment of participants performed the procedure.
- Unclear, if the trial was described as randomised, but the method used for the allocation sequence generation was not described.
- Inadequate, if a system involving dates, names, or admittance numbers were used for the allocation of patients. These studies

are known as quasi-randomised and will be excluded from the present review.

Allocation concealment

- Adequate, if the allocation of patients involved a central independent unit, on-site locked computer, identically appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed envelopes.
- Unclear, if the trial was described as randomised, but the method used to conceal the allocation was not described.
- Inadequate, if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised.

Blinding (or masking)

- Adequate, if the trial was described as double blind and the method of blinding involved identical placebo or active drugs.
- Unclear, if the trial was described as double blind, but the method of blinding was not described.
- Not performed, if the trial was not double blind.

Follow-up

- Adequate, if the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.
- Unclear, if the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
- Inadequate, if the number or reasons for dropouts and withdrawals were not described.

Authors of the primary trial reports will be contacted when necessary to clarify data and to provide missing information. The characteristics and outcomes of included trials and details of excluded trials will be entered into RevMan. If there is a disagreement between the reviewers, it will be resolved by discussion. The presence of publication bias will be determined, if required.

Statistical analysis

The analyses will be performed with RevMan Analyses. We will analyse the statistical heterogeneity and assess intervention effects by both fixed and random effects meta-analyses. The principal outcome measure, duration of survival, will be assessed for each trial using the log hazard ratio, a statistic that combines time to event and censoring in survival studies (Parmar 1998). We will carry out survival analysis of the pooled data using the Kaplan Meier method, and we will compare the difference in outcome by using log rank test. We will calculate 95% confidence intervals. We also intend to convert the survival data into binary data and analyse them by using RevMan Analyses relative risks. Analysis for adverse events will be carried out using relative risks, and that for quality of life will be carried out by comparing weighted mean differences if comparable instruments have been used.

Subgroup analyses

We will perform subgroup analyses according to the methodological quality of the trials comparing trials with adequate components to those with unclear and inadequate components.

Publication bias

By using the statistical package 'Stata', we will use the Egger et al. regression asymmetry test ([Egger 1997](#)) to assess funnel plot asymmetry, which indicates the presence of publication bias and other biases.

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APPENDICES

Appendix 1. Search Strategies

Database	Time of search	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	Date given at review stage.	('biliary tract' OR biliary OR gallbladder OR 'gall bladder' OR gall-bladder) AND (malignan* OR tumor* OR cancer OR neoplasm*)
The Cochrane Central Register of Controlled Trials in The Cochrane Library (CENTRAL)	Latest issue.	MP281002#1 GALLBLADDER-NEOPLASMS*:ME#2 CHEMOTHERAPY-ADJUVANT*:ME#3 ((GALLBLADDER or (GALL and BLADDER)) OR GALL-BLADDER)#4 (((CANCER or CARCINOM*) or TUMOR) or NEOPLASM*) or MALIGNAN*)#5 (#3 and #4)#6 ADJUVANT#7 (CHEMOTHERAPY or THERAPY)#8 (#6 and #7)#9 (#1 or #5)#10 (#2 or #8)#11 (#9 and #10)
MEDLINE	1950 to date search is performed.	# 1 explode "Gallbladder-Neoplasms"/ all subheadings #2 explode "Chemotherapy-Adjuvant"/ all subheadings # 3 "gall" # 4 "bladder" # 5 gallbladder # 6 gall-bladder

Chemotherapy for gallbladder cancer (Protocol)

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(Continued)

7 "gall bladder" or gallbladder or gall-bladder
#8 cancer
#9 carcinom*
#10 tumor or tumour
#11 neoplasm*
#12 malignan*
#13 cancer or carcinom* or tumor or tumour or neoplasm* or malignan*
#14 adjuvant
#15 therapy
#16 chemotherapy
#17 adjuvant and (therapy or chemotherapy)
#18 #7 and #13
#19 #1 or #18
#20 #2 or #17
#21 #19 and #20

EMBASE	1980 to date search is performed.	# 1 explode "Gallbladder-Neoplasms"/ all subheadings #2 explode "Chemotherapy-Adjuvant"/ all subheadings # 3 "gall" # 4 "bladder" # 5 gallbladder # 6 gall-bladder # 7 "gall bladder" or gallbladder or gall-bladder #8 cancer #9 carcinom* #10 tumor or tumour #11 neoplasm* #12 malignan* #13 cancer or carcinom* or tumor or tumour or neoplasm* or malignan* #14 adjuvant #15 therapy #16 chemotherapy #17 adjuvant and (therapy or chemotherapy) #18 #7 and #13 #19 #1 or #18 #20 #2 or #17 #21 #19 and #20
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HISTORY

Protocol first published: Issue 1, 2004

Date	Event	Description
23 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

MP selected the topic, wrote the final version of the protocol, decided onto analyses in consultation with The Cochrane Hepato-Biliary Group and edited it.

CM devised the literature search strategies, did a preliminary search, and wrote the draft version of the protocol.

MAP will search the literature, select studies to be included, will perform the analyses, and will write the review.

CK will help in searching the literature, selection of studies, and writing of review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- No sources of support provided

NOTES

The protocol is out of date and does not meet the current methodological standards of Cochrane.