



# Adjuvant therapy for resected gallbladder cancer

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**Abstract:** Gallbladder cancer, one of the family of biliary tract cancers, has a poor prognosis. Adjuvant therapy comprising radiotherapy, chemotherapy plus radiation therapy and systemic chemotherapy may all play a role in improving survival. Most extant data on adjuvant therapy are retrospective studies or meta-analyses based on these studies. Recently, a phase III study demonstrated that capecitabine is a standard treatment option for biliary tract cancers, including gallbladder cancer. Ongoing studies investigating chemotherapy, novel surgical strategies, immunotherapy, molecular-targeted therapies using molecular profiling have been developed. This review summarises current status and future perspectives of adjuvant therapy for gallbladder cancer.

**Keywords:** Gallbladder cancer; adjuvant therapy; capecitabine

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## Introduction

Gallbladder cancer, one of the family biliary tract cancers, including intrahepatic, extrahepatic, and hilar cholangiocarcinoma. It is an uncommon and aggressive cancer with a 5-year survival rate of 5% (1). Although surgical resection is the only cure, the number of patients who can have curative surgery is small and the relapse is frequent (2). Adjuvant therapy plays a crucial role in improving survival.

Prospective data on adjuvant therapy in gallbladder cancer have been limited. In addition to its rarity, gallbladder cancer patients are often frail following major surgery, making enrolment of patients with gallbladder cancer to clinical trials difficult.

In this review, the current status of adjuvant therapy, including radiotherapy, chemotherapy with or without radiation, has been summarised and future perspectives have been discussed.

## Candidates for adjuvant therapy

The primary role of adjuvant therapy is to reduce the

recurrence rate by eliminating micrometastatic disease that cannot be detected with imaging. The toxicity profile must be favourable to permit effective delivery (3). Simple cholecystectomy can be used for the treatment of gallbladder cancer, and long-term survival has been observed if the tumour is within the lamina propria (4,5). However, at stage I with tumours invading the mucosal layer, the 5-year survival rate decreased rapidly to 62.5% (6). Therefore, adjuvant therapy is recommended for every tumour stage according to the National Cancer Center Network guideline (7). The effect of adjuvant therapy differs among cancer stages, including tumour and lymph node stages. A meta-analysis by Horgan *et al.* involving 6,712 patients with gallbladder cancer (66.2%) revealed that adjuvant therapy is associated with nonsignificant improvement ( $P=0.06$ ), with no difference between tumour sites, and provided the greatest benefit for lymph node-positive patients ( $P<0.01$ ) (8). Another meta-analysis by Ma *et al.* also showed the survival benefits of adjuvant therapy in patients with gallbladder cancer with R1 who were lymph node positive and had stage II or more cancer (9). Due to the lack of randomised controlled trials, these meta-analyses are mainly based on retrospective studies (3).

**Table 1** Retrospective and prospective studies of adjuvant radiotherapy and chemotherapy plus radiation therapy for resected gall bladder cancer

First author (reference)	Method	Study arm	Number of patients	R0, %	Lymph node (+) %	OS (M) or survival rate
Bosset (10)	Retrospective	RT	7	NR	NR	5 out of 7 patients alive
Lindell (11)	Retrospective	CRT vs. Obs	10 vs. 10	NR	30 vs. 20	28 vs. 20
Itoh (12)	Retrospective	RT vs. Obs	5 vs. 13	NR	NR	13 vs. 34 (P=0.33)
Wang (13)	Retrospective	RT vs. Obs	760 vs. 3,420	NR	34 vs. 19	15 vs. 8 (P<0.01)
Mojica (14)	Retrospective	RT vs. Obs	395 vs. 1,930	NR	NR	14 vs. 8 (P<0.01)
Todoroki (15)	Retrospective	RT vs. Obs	48 vs. 39	NR	NR	5-year survival 9% vs. 3%
Muller (16)	Retrospective	RT/CRT	46	NR	41	5-year survival rate 51%
Czito (17)	Retrospective	CRT	22	NR	45	23
Gold (18)	Retrospective	CRT vs. Obs	25 vs. 48	100 vs. 100	70 vs. 30	58 vs. 50 (P=0.56)
Kresel (19)	Retrospective	CRT	21	57	67	31
Gu (20)	Retrospective	CRT vs. Obs	44 vs. 50	100	NR	26 vs. 15 (P=0.11)
Lee (21)	Retrospective	CRT vs. Obs	62 vs. 83	NR	NR	46 vs. 46
Balachandran (22)	Retrospective	CRT vs. Obs	73 vs. 44	NR	42 vs. 57	24 vs. 11 (P<0.01)
Mahe (23)	Retrospective	RT	11	100	>27	48
Ben-Josef (24)	Prospective	CRT	25	76	40	2-year 56%

OS, overall survival; RT, radiation therapy; CRT, chemotherapy plus radiation therapy; Obs, observation; NR, detail not reported.

### Adjuvant radiation therapy

Radiation therapy had been used as the only gallbladder cancer method available before the introduction of effective anti-cancer drugs. Its main purpose was to control the local recurrence but not distant metastasis. To the best of our knowledge, only retrospective studies have been conducted and no prospective studies are available (Table 1). These retrospective studies were conducted mainly based on the Surveillance, Epidemiology, and End Results (SEER) programme. Mojica *et al.* analysed 3,187 patients with adjuvant radiation therapy (17%) and demonstrated its survival benefit compared with non-radiation therapy (14 vs. 8 months) (14). Wang *et al.* also showed similar results using a subgroup analysis of 4,187 patients and identified adjuvant radiation therapy as well as age, sex, papillary histology and stage as prognostic factors according to the multivariate analysis (13). A survival benefit was particularly observed for the T2 or higher category, in addition to being lymph node positive. It should be considered that SEER data has no information on concurrent chemotherapy and that radiation regimens varied widely.

Essentially, radiation therapy is limited by micrometastasis, the majority of the first recurrence (85%) of gallbladder

cancer occurring at distant sites (25). Horgan *et al.* showed that radiation therapy is less effective than chemotherapy plus radiation therapy or chemotherapy (8).

### Adjuvant chemotherapy plus radiation therapy

Chemotherapy plus radiation therapy has been expected to yield a synergetic activity with chemotherapy and radiation therapy. In preclinical studies, some anti-cancer drugs have demonstrated radiosensitivity (26–28). Table 1 summarises the series of data of adjuvant chemotherapy plus radiation therapy.

The retrospective data available were limited and a large retrospective data had been obtained from SEER. Due to the lack of randomised trials, chemotherapy plus radiation therapy has not been established as a standard of care. Using the SEER data of 1,137 patients with chemotherapy plus radiotherapy (11%), Wang *et al.* showed the survival benefit of chemotherapy plus radiation therapy, especially for those with T2–4 and/or those who were lymph node positive (29). Mantripragada *et al.* analysed the National Cancer Database (4,775 patients) and suggested a 0.25-year survival benefit in patients with gallbladder cancer receiving chemotherapy plus radiation therapy compared with the observation group (P<0.01) (30).

**Table 2** Retrospective and prospective studies of adjuvant chemotherapy for resected gallbladder cancer

First author (reference)	Method	Study arm	Number of patients	R0, %	Lymph node (+), %	Chemotherapy regimen	OS (M) or survival rate
Mantripragada (30)	Retrospective	Chemo/CRT vs. Obs	727/646 vs. 3,402	69 vs. 80	48 vs. 25	NR	No difference (HR1.01) (propensity matching score)
Kayahara (32)	Retrospective	Chemo vs. Obs	1,231 vs. 2,093	NR	NR	NR	5-year survival rate 33% vs. 45% (P<0.05)
Bergquist (33)	Retrospective	Chemo vs. Obs	T2: 389 vs. 2,090	76 vs. 85	35 vs. 15	NR	25 vs. 28 (P=0.44)
Bergquist (33)	Retrospective	Chemo vs. Obs	T3/4: 578 vs. 1,316	42 vs. 51	47 vs. 55	NR	11 vs. 8 (P<0.01)
Takada (34)	Prospective	Chemo vs. Obs	69 vs. 43	45 vs. 47	91 vs. 98	5FU and MMC	5-year survival rate 27% vs. 14 (P=0.04)
Edeline (5)	Prospective	Chemo vs. Obs	BTC 95 vs. 99	86 vs. 88	37 vs. 36	GEM and oxaliplatin	76 vs. 51 (P=0.74)
Primrose (36)	Prospective	Chemo vs. Obs	BTC223 vs. 224	62 vs. 63	48 vs. 46	Capecitabine	51 vs. 36 (P=0.10) (intent to treat); 53 vs. 36 (P=0.03) (per protocol)

OS, overall survival; Chemo, chemotherapy; CRT, chemotherapy plus radiation therapy; Obs, observation; MMC, mitomycin C; GEM, gemcitabine; BTC, biliary tract cancer; NR, detail not reported.

Recently, one arm phase II chemotherapy plus radiotherapy study conducted by the South West Oncology Group (SWOG) evaluated gemcitabine plus capecitabine, followed by concurrent radiation (45 Gy to regional lymphatics, 54–59.4 Gy to the tumour bed) and capecitabine for cholangiocarcinoma and gallbladder cancer. In addition, the 2-year survival rate, which was the primary end-point, was 65% in biliary tract cancers and 56% in gallbladder cancer (24).

Based on the SWOG S0809 data, the American Society of Clinical Oncology (ASCO) Clinical practice guideline described that patients with gallbladder cancer with R1 resection may undergo chemotherapy plus radiation therapy (3). A randomised study should be conducted to establish the standard treatment.

### Adjuvant chemotherapy

Chemotherapy has been the main treatment procedure in most malignancies. In 2010, cisplatin and gemcitabine were established as the first-line treatment for advanced biliary tract cancers, including gallbladder cancer (31). Moreover, gallbladder cancer has also been recognised as a chemosensitive cancer.

Table 2 shows the adjuvant chemotherapy data. As previously described, Horgan *et al.* published a meta-analysis that showed the survival benefit in the chemotherapy group (8) and Ma *et al.* also showed similar results (9). Conversely, another study that used the National Cancer Database in the U.S. did not demonstrate the survival benefit (30), and the Japanese data (n=4,700) on the adjuvant chemotherapy did not reveal any improvement in survival (32). These inconsistent data were likely to have been due to a patient heterogeneity in retrospective studies and ineffective drugs.

The first phase III trial published in 2002 by Takada *et al.* was a randomised study on biliary tract cancers and pancreatic cancer, including gallbladder cancer (34). Among 438 patients, 112 with gallbladder cancer were evaluated in this study, and the chemotherapy group (mitomycin and 5-FU) demonstrated a significant survival with a 5-year survival rate of 26% compared with the 14% in the observation group (P=0.04). This subgroup analysis suggested the survival benefits of adjuvant chemotherapy. The second phase III study (PRODIGE 12) examined the effects of gemcitabine and oxaliplatin in the chemotherapy group in comparison with those of the observation group (35). This study included 194 patients with gallbladder cancer (20%) with a performance status of 0–2.

**Table 3** Ongoing phase III clinical trial

Study title	Regimen	Reference	Number of patients	Year of completion	Clinical trial number
ASCOT	S-1	Observation	440	2021	UMIN000011688
ACTICCA-1	GEM and CDDP	Capecitabine	440	2023	NCT02170090
AdBTC-1	GEM	Capecitabine	460	2023	NCT03779035

GEM, gemcitabine; CDDP, cisplatin.

The primary endpoint was relapse-free survival and health-related quality of life (HRQL). Although no difference in HRQL was observed between the two groups, the chemotherapy group did not show survival benefits (median, 30.4 months in the chemotherapy arm *vs.* 18.5 months in the observation arm;  $P=0.48$ ). In addition, a subgroup analysis showed no favourable outcomes, including the tumour site, stage and lymph node.

The BILCAP was the third randomised phase III study that evaluated adjuvant chemotherapy with capecitabine (36). This study included 447 patients with gallbladder cancer (18%), regional lymph node positive (54%) and R0 resection (62%) with a performance status of 0 and 1, and the primary endpoint was overall survival. Although no significant difference was observed in an unadjusted intent-to-treat analysis, a per-protocol analysis revealed significant results (median, 53 months in the chemotherapy arm *vs.* 36 months in the observation group;  $P=0.028$ ) and a pre-specified intent-to-treat (ITT) analysis adjusted for nodal status, disease grade and sex also showed significant difference between the two groups. Because capecitabine can improve the overall survival, the ASCO recommends adjuvant capecitabine monotherapy for 6 months (3).

### Ongoing trials and future perspective

Even in the era of systemic chemotherapy, only three randomised phase III trials on adjuvant therapy have been conducted (*Table 3*). The ACTICCA-1 study (NCT02170090) is currently recruiting patients with resected biliary tract cancers to examine the efficacy and safety of gemcitabine and cisplatin. According to the result of the BILCAP study, the referential arm has changed from observation to capecitabine. The ASCOT trial (UMIN000011688) compared chemotherapy group (S-1, a fluoropyrimidine drug similar to capecitabine) with the observation group. A group in China planned a phase III

trial (AdBTC-1, NCT03779035) comparing gemcitabine with capecitabine and opened to accrual in 2018 (37). Besides these studies, a randomised phase II study comparing gemcitabine with capecitabine has completed the enrolment and is awaiting results.

Recently, an immune checkpoint inhibitor has been widely available for the treatment of lung cancer, melanoma, lymphoma, stomach cancer, renal cell cancer, and head and neck cancer. In resected biliary tract cancers, the cluster group had a higher expression of immune checkpoint genes as well as hypermutated genes with poor prognosis and became candidates for immune checkpoint inhibitor (38). A subgroup analysis of KEYNOTE 28 revealed that the use of pembrolizumab in patients with biliary tract cancers showed a 17%-response with manageable tolerability (39).

The progress of genomic sequence has shown genetic alteration of ERBB2 (16%), PIK3CA (14%), KRAS (11–19.2%), CDKN2A/B (19%), ARID1A (11–13%), and BAP (4–13%) in patients with gallbladder cancer (2). Although the first phase III study on advanced biliary tract cancers, using erlotinib, has reported negative results (40), many studies that have used a molecular-targeted therapy have been recruited and are expected to yield positive results. An adjuvant treatment setting is planned after the examination in advanced gallbladder cancer.

### Conclusions

The current status of adjuvant therapy for the treatment of gallbladder cancer is summarized in this study. With the acceptance of chemotherapy as the active treatment by the results of the BILCAP study, chemotherapy has been the main treatment procedure in adjuvant therapy. The results of ongoing phase III studies of adjuvant chemotherapies may connect with improving outcome for gallbladder cancer. The further investigation by the well designed and randomized study will be required to examine the effect of chemotherapy plus radiation therapy.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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