# Resectable Cholangiocarcinoma: Reviewing the Role of Adjuvant Strategies

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**ABSTRACT:** Cholangiocarcinoma is a very heterogeneous and rare group of neoplasms originating from the perihilar, intra-, or extrahepatic bile duct epithelium. It represents only 3% of gastrointestinal cancers, although their incidence is increasing as its mortality increases. Surgical resection is the only potentially curative option, but unfortunately the resectability rate is low. Overall, these malignancies have got a very poor prognosis with a five-year survival rate of 5–10%. Although the five-year survival rate increases to 25–30% in the cases amenable to surgery, only 10–40% of patients present with resectable disease. Therefore, it is necessary to optimize the benefit of adjuvant strategies after surgery to increase the rate of curability. This study reviewed the role of adjuvant chemotherapy in resectable bile duct cancers.

**KEYWORDS:** cholangiocarcinoma, bile duct carcinomas, adjuvant chemotherapy

## Introduction

Cholangiocarcinoma is a very heterogeneous and rare group of neoplasms originating from the perihilar, intra-, or extrahepatic bile duct epithelium.[1] It represents only 3% of gastrointestinal cancers, although their incidence is increasing.[1]

Surgical resection represents the only potentially curative option, but unfortunately the resectability rate is low. Overall, these malignancies have got a very poor prognosis with a five-year survival rate of 5–10%. Although in those cases amenable to surgery, the five-year survival rate increases to 25–30%, only 10–40% of patients present with resectable disease.[2,5]

In any case, the treatment has improved the survival rate, which may result in a better outlook for patients nowadays.[6] But efforts are needed to optimize the benefit of adjuvant strategies after surgery to increase the rate of curability.

The present study reviewed the role of adjuvant chemotherapy in resectable bile duct cancers.

## Brief Epidemiology

Cholangiocarcinoma represents only less than 2% of all human neoplasms,[7] but it is the second most common primary hepatic malignancy after hepatocellular carcinoma, accounting for 10–15% of liver malignancies.[8]

The peak age for cholangiocarcinoma is the seventh decade, with a slightly higher incidence in men. Given the poor prognosis, mortality and incidence rates are similar.[8]

In the European Union, intrahepatic cholangiocarcinoma (ICC) is 3.2 and 5.4/100,000 per year for males and females, respectively, whereas the ICC is increasing and it is estimated as 0.9–1.3 and 0.4–0.7/100,000 for males and females, respectively.

Its prevalence and incidence are geographically heterogeneous, with the highest rates in Asia, especially Southeast Asia.[8] The incidence rate varies significantly between different regions from 5% in Japan to 20% in Korea or even more significant with a 90% incidence in Thailand.[9]

In high-risk areas in Europe (such as the south of Italy), the incidence is 4.9–7.4/100,000 and 2.9–4.3/100,000 for males and females, respectively. In Crete, Greece, it has increased from 0.998/100,000 in 1992–1994 to 3.327/100,000 in 1998–2000.[10]

## Classification

Cholangiocarcinomas are classified according to their anatomic location as intrahepatic and extrahepatic (Table 1). The extrahepatic tumors include those involving the confluence of the right and left hepatic ducts. These account for 80–90%, and the intrahepatic neoplasms represent between 5 and 10% of all cholangiocarcinomas.

Histopathologically, adenocarcinoma is the most frequent type, accounting for 90% of cases.

Other types include papillary or intestinal type adenocarcinoma, clear cell adenocarcinoma, signet ring cell carcinoma, adenosquamous carcinoma, squamous cell carcinoma, and oat cell carcinoma.[11]

Extrahepatic cholangiocarcinomas can be subdivided according to the Bismuth classification (Table 2). Other classifications are based on macroscopic appearance of both intra- and extrahepatic tumors (Table 3).

**Table 1.** Classification of cholangiocarcinomas.

| INTRAHEPATIC CHOLANGIOCARCINOMA | EXTRAHEPATIC CHOLANGIOCARCINOMA |
|---|---|
| Intrahepatic bile duct carcinoma | Biliary confluence (Klatskin tumour) |
| Peripheral cholangiocarcinoma | Distal bile duct |
| Cholangiocellular carcinoma | – |

## Methods

The structure of this systematic review followed the PRISMA guidelines.[13]

**Information sources and search strategy.** For all studies, a literature search was conducted using MeSH keyword search on PubMed (MEDLINE), which matched the eligibility criteria as mentioned earlier. An additional manual search of OVID (MEDLINE) was carried out. All identified articles discussing about adjuvant strategies for cholangiocarcinoma were retrieved from those databases.

These studies were restricted to those in English language. The search period was restricted to be more representative of modern postoperative outcomes.

**Treatment of localized cholangiocarcinomas: resection first.** The establishment of the exact criteria for resectability in patients with cholangiocarcinoma has several limitations. Many factors should be taken into account: the patient's clinical condition and comorbidities, the biology of the neoplasia, the technical expertise of the surgeon, local involvement of the major vessels and bile ducts at the hilum, future liver remnant, etc.[14]

Although the establishment of resectability criteria has many limitations, the patient must be medically fit for resection, the presence of metastatic disease should be ruled out, and the local involvement of the main tumor mass should be assessed very carefully with attention to vascular inflow, outflow, hepatic parenchyma, and the biliary tree. If the portal vein, hepatic artery, or secondary biliary tree is involved, the tumor is considered as not resectable. In some cases, minimal portal vein involvement can be resected and cleared if far enough away from the umbilical fissure.[15]

Surgical resection generally includes cholecystectomy, en bloc hepatic resection, and lymphadenectomy with or without bile duct excision, depending on the location of the tumor. If cancer is found incidentally at the time of surgery for other reasons, resectability is not clearly established, then delayed open laparotomy is appropriate, as there is no survival deficit compared to immediate resection.[16,17]

In all the cases, the liver remnant should be at least 30% of the liver volume of relatively normal nonatrophied parenchyma that should have a good vascular inflow, outflow, and biliary drainage.

The decision about resectability for patients with distal cholangiocarcinoma is more straightforward than that for those with perihilar and peripheral tumors.[15]

For the peripheral tumors, if the lesion is away from the hilus of the liver and does not involve a significant proportion of parenchyma, the determination of resectability would be less complicated than for central or very large tumors.[17]

Generally for cholangiocarcinomas, the overall rate of resectable disease is only 10–40%[2,5] and an operative mortality of 4% has been reported for peripheral cholangiocarcinomas.[15]

For hilar cholangiocarcinoma, the 30- and 90-day operative mortalities have been shown to be 10 and 12%, respectively. The overall incidence of postoperative morbidity was 69%. In all, 68% of them were described as major. No difference in operative blood loss or perioperative transfusion rates was observed for patients with major versus minor or no postoperative morbidity. Patients with major postoperative morbidity received adjuvant chemotherapy in less number of cases when compared with those with minor postoperative morbidity or no complications 29 versus 52%.[19]

Although removal of clinically suspicious nodal disease is mandatory, the role of routine lymphadenectomy is not well defined. Lymph node dissection is not routinely performed at the time of ICC resection in most Western countries as opposite to many Japanese hospitals. In Western series, only 50% of the patients had at least one lymph node examined, and more relevant was the fact that among these patients, metastatic nodal disease was found in up to 30% of patients.[18]

This is the reason why some researchers have defended the role of routine lymphadenectomy as this will impact on prognosis.[20]

Many surgeons will pursue resection, despite local lymph node metastases, whereas distant lymph node metastases are a contraindication to surgery.

Despite this finding, Shimada et al concluded that routine lymphadenectomy was not necessary if lymph node involvement was not clinically apparent. Their

**Table 2.** Extrahepatic cholangiocarcinomas classification.

| TYPE | TUMOUR EXTENSION OR INVASION |
|---|---|
| I | Common hepatic duct distal to the biliary confluence |
| II | Biliary confluence |
| IIIa | Biliary confluence and the right hepatic duct |
| IIIb | Biliary confluence and the left hepatic duct |
| IV | Biliary confluence and both the right and left hepatic ducts or multifocal |

**Table 3.** Classification based on macroscopic appearance.[12]

| EXTRAHEPATIC | INTRAHEPATIC |
|---|---|
| Sclerosing | Mass forming |
| Nodular | Periductal infiltrating |
| Papillary | Intraductal |

study showed that among those patients who underwent lymphadenectomy, there were no differences in survival if lymph node was not involved regardless of the use of lymph node dissection.[21]

Rate of recurrence is about 50–60%, and the median disease-free survival has been documented as 26 months. Five-year survival and overall survival (OS) after surgical resection of ICC range from 15 to 40% in most series.[21,22]

Liver is the most common site of recurrence (50–60%), but recurrence in regional lymph nodes or the peritoneum has also been documented in 20–25%.[23–25] Other series mention 23–63%.[26–28]

One of the factors associated with an increased risk of recurrence include lymph node metastasis and also tumor size, multiple tumors, and vascular invasion.[29]

The ICCs are relatively rare, but their incidence and mortality are increasing worldwide.[30]

The only potentially curative treatment option for patients who have resectable disease is surgery as for the rest but again and unfortunately, the five-year survival rate is about 20–35%.[31,32]

Moreover, the role of adjuvant therapies, including systemic chemotherapy and radiotherapy, remains poorly defined and has been reported to have only a modest therapeutic effect.

Routine staging laparoscopy has been proposed because high incidence of metastatic disease has not been detected by conventional imaging.[33]

Lymphadenectomy is also not routinely performed in most Western countries, despite data suggesting that lymph node status may provide considerable prognostic information.[34,35]

**Adjuvant therapies for resectable cholangiocarcinomas.** The role of adjuvant chemotherapy/chemoradiation in patients with resected biliary tract cancer is poorly defined. Although it is widely used and recommended in guidelines from expert groups, the survival benefit of any adjuvant strategy has been proven mainly in retrospective studies rather than designed randomized clinical trials.

The benefit of adjuvant therapy for biliary tract cancer continues although being unclear. Available literature mainly consists of uncontrolled institutional series and registry analysis with conflicting results, although these seem to favor an adjuvant approach.[36]

This uncertainty led Horgan et al to carry out a systematic review and meta-analysis in an attempt to determine the impact of adjuvant treatments on survival.[37]

This included 20 studies (including 6,712 patients) assessing the results of chemotherapy, radiotherapy, or chemoradiotherapy as adjuvant approaches to a radical surgery for these patients.[37]

The pooled analysis showed nonsignificant benefit in unselected patients in OS with any adjuvant treatment compared with surgery alone, but in those with node positivity or margins involved, adjuvant therapy seemed to provide advantages in the same parameter. Those receiving chemotherapy or chemoradiotherapy had more significant benefit than radiotherapy alone.[37]

Horgan et al concluded that adjuvant therapy is supported for resected disease in patients with high-risk features, particularly in cholangiocarcinoma. Prospective randomized trials are needed to provide better rationale for this strategy. The above-mentioned authors also suggested two active comparators rather than a no-treatment arm among patients with lymphadenopathy (LN) positive or R1 disease.[37]

**Adjuvant chemotherapy.** For node-positive disease, the evidence supports chemotherapy as an adjuvant approach.

Two randomized clinical trials have examined its benefit following resection. Takada et al carried out a randomized controlled trial comparing the benefit of postoperative adjuvant chemotherapy with surgery alone in patients with resected pancreatobiliary carcinoma.[38]

Patients were randomized to surveillance only or to receive mitomycin C and 5-fluorouracil (5-FU) followed by 5-FU until disease recurrence. Primary end point was OS. Although the five-year survival rate in gallbladder cancer was significantly better with chemotherapy (26 vs. 14%, $P = 0.0367$), this was not statistically significant in the intention-to-treat analysis. Those patients had a benefit in disease-free survival (20.3 vs. 11.6%). The study did not show any benefit with chemotherapy in patients with bile duct carcinomas (five-year survival, 27 vs. 24%). Unfortunately, this trial was underpowered to prove definitively a treatment benefit.[38]

A single-center retrospective analysis showed a benefit in survival when gemcitabine-based adjuvant treatment was administered in cholangiocarcinoma patients.[39]

Another clinical trial evaluated the role of 5-FU or gemcitabine in patients with resected periampullary adenocarcinomas.

Four hundred and twenty-eight patients were randomly assigned to one of three arms: observation, 6 months of leucovorin-modulated 5-FU, or 6 months of gemcitabine. Adjuvant chemotherapy produced a benefit though not statistically significant (median 43 vs. 35 months, hazard ratio 0.86, 95% confidence interval: 0.66–1.11). However, multivariable analysis adjusting for prognostic variables demonstrated a statistically significant survival benefit associated with adjuvant chemotherapy, specifically for gemcitabine.[40]

Whether single-agent versus doublet chemotherapy show better results remains to be determined.

Other clinical trials are either still recruiting patients or awaiting presentation of results.

ACTICCA-1 is a randomized, multidisciplinary, and multinational phase III trial. It will evaluate the efficacy of gemcitabine and cisplatin versus observation alone in terms of disease-free survival in patients with bile tract carcinomas after complete surgical resection. Two different cohorts will be included, cholangiocarcinomas and gallbladder carcinoma.

The French PRODIGE-12 evaluating gemcitabine and oxaliplatin and the British BILCAP using capecitabine are two clinical trials from which we are still expecting the results.

BILCAP is a multicenter prospective, randomized phase III trial examining the role of adjuvant chemotherapy with oral fluoropyrimidine (capecitabine) in patients following potentially curative surgical resection of a biliary tract cancer. It has already completed the accrual, and results are expected to be reported soon.[41]

There are two further ongoing studies in Japan. The BCAT (registration UMIN-CTR; ID UMIN000000820) evaluating gemcitabine monotherapy versus surgery alone, and this study is already closed. The other trial is the ASCOT (registration UMIN-CTR; ID UMIN000011688) evaluating the role of S-1 versus surgery alone, and this study is still open, recruiting participants.

Their results will give more light to the questions about the adjuvant chemotherapy for this disease.

**Adjuvant chemotherapy dosages.** Surgery for biliary tract cancer, including pancreatoduodenectomy and major hepatectomy, is very aggressive and does not allow postoperative chemotherapy to be administered in the usual dosage due to adverse events, which may be caused by insufficient liver function.

Fujiwara et al performed a study of dose finding of adjuvant gemcitabine in patients with biliary tract cancer who underwent a surgical resection with major hepatectomy. These authors evaluated the pharmacokinetics and pharmacodynamics of gemcitabine in these patients after administration at a dose of 800–1,000 mg/m$^2$. The authors concluded that major hepatectomy did not affect the pharmacokinetics of gemcitabine.[42]

Other authors determined the recommended dose for gemcitabine and S-1 after major hepatectomy in patients with biliary tract cancers, concluding that the recommended dose is 1,000 mg/m$^2$ of gemcitabine every two weeks and 80 mg/m$^2$/day of S-1 on days 1–28 every six weeks.[43]

Yamanaka et al studied the benefit of adjuvant gemcitabine with different dosages depending on the aggressiveness of the surgery. In those who underwent major hepatectomy, gemcitabine was administered at a dose of 800 mg/m$^2$ biweekly. Otherwise 1,000 mg/m$^2$ for three weeks every month. These authors concluded that adjuvant gemcitabine may be effective, especially for patients with stage III and ICC.[44]

Kobayashi et al hypothesized that the feasibility of three-weekly protocol (days 1 and 8, every three weeks) of adjuvant gemcitabine may be superior to the four-weekly treatment (days 1, 8, and 15 for every four weeks). Their study enrolled 27 patients, and the authors concluded that the three-weekly protocol did not yield superior completion as the rate of adverse events or recurrence-free survival was similar to the four-week regimen.[45]

The study by Kainuma et al assessed the feasibility and the efficacy of gemcitabine plus cisplatin (CDDP) for biliary tract cancer in the adjuvant setting. Gemcitabine at 1,000 and 25 mg/m$^2$ of CDDP on days 1 and 8 was repeated for every three weeks. They concluded that this treatment is tolerable in patients who underwent curative resection with or without major hepatectomy.[46]

Toyoda et al studied a phase I study to determine the maximum tolerated dose and recommended dose of a combination with gemcitabine and cisplatin in the adjuvant setting for this cancer. The starting dose was the standard: gemcitabine (1,000 mg/m$^2$) and cisplatin (25 mg/m$^2$) on days 1 and 8, every three weeks. These authors defined the standard dose as the recommended dose for adjuvant chemotherapy for biliary tract cancer treated by curative resection without major hepatectomy, but they recommended further study to clarify the safety and efficacy of this regimen for all patients.[47]

**Radiotherapy and chemoradiotherapy.** Retrospective studies suggest that adjuvant radiotherapy following resection had a survival benefit in ICC patients with regional lymph node metastasis.[48]

Gwak et al carried out a study with adjuvant radiotherapy compared to surgery alone in extrahepatic bile duct carcinomas. The study showed a benefit in five-year survival following adjuvant radiotherapy (21 vs. 11.6%).[49]

However, Gonzalez et al used combinations of pre- and postoperative external beam radiotherapy, and no impact on survival was observed.[50]

Newer radiation therapy techniques, such as intraluminal transcatheter brachytherapy, intraoperative, or intensity-modulated radiation therapy, and three- and four-dimensional treatment planning, permit radiation dose escalation without significant increment in normal tissue toxicity, thereby increasing the effective radiation dose. Preliminary results of studies with hepatic transplantation and radiation therapy are encouraging, but prospective trials are needed in order to get solid evidence.[51]

Further prospective studies are needed at this moment as there are no data supporting the use of adjuvant radiotherapy in patients with negative resection margins.

Horgan et al in their meta-analysis conclude that radiation therapy seems to benefit only patients with R1 resections, with possible harm in R0 disease.[37]

Their meta-analysis included Takada et al's trial, two SEER registry analyses, and 17 retrospective series. This includes 6,712 patients, of whom 1,797 received some form of adjuvant therapy.

There were eight studies of radiotherapy plus chemotherapy, three of chemotherapy alone, and nine of RT alone. Only one study included ICC.

The authors conclude an improvement in five-year survival with any adjuvant therapy. Although not statistically significant compared with surgery alone, the benefit became significant if data from the two large series were excluded.[37]

A combined analysis of gallbladder and bile duct cancers showed a significant survival benefit for chemotherapy and chemoradiotherapy but not for radiation alone.

In patients with nodal positivity, this meta-analysis showed a benefit in OS for any adjuvant therapy. Most of

these patients had received chemotherapy alone (77%), and the remainder received chemoradiotherapy.

In patients with margin positivity, adjuvant therapy showed also a benefit.

The addition of radiation to chemotherapy may be associated with a deleterious effect in the R0 population.[37]

There are only a few studies evaluating the benefit of adjuvant chemoradiotherapy in cholangiocarcinomas.

Two studies support the use of chemoradiotherapy as adjuvant approach in cholangiocarcinoma. Kim et al evaluated its role in 72 patients with extrahepatic cholangiocarcinoma, among them 25 patients had positive margins. The patients underwent postoperative external beam radiotherapy (40 Gy) and concomitant boluses of 5-FU. Five-year survival rates were 36% after R0 resection, 35% in R1, and 0% following R2.[52]

Another small study showed again improved survival with chemoradiotherapy in hilar cholangiocarcinoma.[53]

SWOG trial, a phase II, single-arm, using chemoradiotherapy in node or margin positive patients, has shown good tolerance and promising efficacy.

Patients received four cycles of a combination with gemcitabine and capecitabine followed by concurrent capecitabine and radiotherapy.[54]

Ramirez-Merino et al concluded in their review that patients with localized and locally advanced cholangiocarcinomas must be treated in a multidisciplinary team, being surgery the main therapeutic option. However, it is necessary to improve survival but it is still difficult to clarify the role of adjuvant treatment.

Adjuvant therapy is widely recommended for intrahepatic or extrahepatic cholangiocarcinomas with microscopically positive resection margins and for those with a complete resection but node-positive disease.

Gemcitabine plus cisplatin has been shown to be superior to gemcitabine alone, but this regimen has not been compared head to head with other gemcitabine-based combinations.[55]

**Others: conventional transarterial chemoembolization.** A retrospective analysis has reported that adjuvant conventional transarterial chemoembolization (cTACE) after curative surgery did not delay recurrence but may prolong the OS of patients with early recurrence.[56]

A prospective study has evaluated the feasibility, safety, and efficacy of conventional cTACE with mitomycin-C and of irinotecan-eluting beads (iDEB-TACE) and to retrospectively compare them with conventional chemotherapy with oxaliplatin and gemcitabine.

These authors report that the treatment with iDEB-TACE is safe in patients with normal liver function, prolongs progression-free survival (PFS) and OS. Local tumor control, PFS, and OS are similar to those achieved by chemotherapy with oxaliplatin and gemcitabine but superior to cTACE.[57]

**Photodynamic therapy.** Photodynamic therapy is a local ablative method of treating dysplasia or neoplasia. It consists of selective accumulation of a photoactive drug (photosensitizer) in tumor tissue followed by light activation of the retained photosensitizer. This results in tumor necrosis mediated by cytotoxic radicals, mainly singlet oxygen.[58]

In an uncontrolled study, adjuvant photodynamic therapy of residual tumor after surgical resection in a few patients was promising.[59]

Tumor ablation with photodynamic therapy combined with biliary stenting reduces cholestasis and significantly improves median survival in selected patients with bile duct cancers.[60]

Further studies are necessary to get solid conclusions about the real role of this therapy in the adjuvant setting.

## Conclusion

Despite significant advances in the treatment of patients with cholangiocarcinoma, radical surgical excision remains the only treatment with curative intent. Unfortunately, the rates of resection are very low, and adjuvant therapies only provide a limited benefit in survival.

The current practice recommends adjuvant therapies in patients with node or margins positive. We await results of several clinical trials to help draw the adjuvant management. Although for patients at high risk of recurrence, the benefits seem to be clear, further clinical trials are needed to assess the benefit in low-risk patients. It will be also necessary to know what would be the best regimen to settle as standard, and further research with biological agents seems to be relevant.

For node-positive disease, the evidence supports chemotherapy as an adjuvant approach.

What it is not clear is whether the addition of radiotherapy will provide further advantage.

## Author Contributions

Conceived the concepts: EUC. Analyzed the data: EUC. Wrote the first draft of the manuscript: EUC. Developed the structure and arguments for the paper: EUC. Made critical revisions: EUC. The author reviewed and approved of the final manuscript.

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