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ORIGINAL ARTICLE

# Neither Neoadjuvant nor Adjuvant Therapy Increases Survival After Biliary Tract Cancer Resection with Wide Negative Margins

**Evan S. Glazer · Ping Liu · Eddie K. Abdalla · Jean-Nicolas Vauthey · Steven A. Curley**

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**Abstract**
*Background* We investigated the role of neoadjuvant/adjuvant therapies on survival for resectable biliary tract cancer. We hypothesized that neoadjuvant and adjuvant therapy should improve the survival probability in these patients.
*Methods* This was a retrospective review of a prospective database of patients resected for gallbladder cancer (GBC) and cholangiocarcinoma (CC). One hundred fifty-seven patients underwent resection for primary GBC ($n$=63) and CC ($n$=94). Fisher's exact test, Student's $t$ test, the log-rank test, and a Cox proportional hazard model determined significant differences.
*Results* The 5-year overall survival rate after resection of GBC and CC was 50.6 % and 30.4 %, respectively. Of the patients, 17.8 % received neoadjuvant chemotherapy, 48.7 % received adjuvant chemotherapy, while 15.8 % received adjuvant chemoradiotherapy. Patients with negative margins of at least 1 cm had a 5-year survival rate of 52.4 % ($p$<0.01). Adjuvant therapy did not significantly prolong survival. Neoadjuvant therapy delayed surgical resection on average for 6.8 months ($p$<0.0001). Immediate resection increased median survival from 42.3 to 53.5 months ($p$=0.01).
*Conclusions* Early surgical resection of biliary tract malignancies with 1 cm tumor-free margins provides the best probability for long-term survival. Currently available neoadjuvant or adjuvant therapy does not improve survival.

**Keywords** Cholangiocarcinoma · Resection · Neoadjuvant · Adjuvant

E. S. Glazer · E. K. Abdalla · J.-N. Vauthey · S. A. Curley (✉)
Department of Surgical Oncology,
The University of Texas M. D. Anderson Cancer Center,
1400 Pressler Street, Unit 1484,
Houston, TX 77030, USA
e-mail: scurley@mdanderson.org

E. S. Glazer
Department of Surgery, The University of Arizona,
Tucson, AZ, USA

P. Liu
Department of Biostatistics,
The University of Texas M. D. Anderson Cancer Center,
Houston, TX, USA

S. A. Curley
Department of Mechanical Engineering and Materials Science,
Rice University,
Houston, TX, USA

## Introduction

There is a growing consensus that the current "standard of care" for unresectable or advanced biliary tract cancers is combination chemotherapy with gemcitabine and cisplatin.[1–3] In addition, small series of patients with resected extrahepatic cholangiocarcinoma treated with neoadjuvant chemotherapy trend towards improved long-term survival, but this has failed to reach statistical significance in recent reports.[4] Furthermore, neoadjuvant chemoradiotherapy for biliary malignancies has demonstrated improved local control rates, but this therapy has not been demonstrated to improve long-term survival.[4,5] Adjuvant chemotherapy is often proposed ad hoc after resection because of the intrinsic poor prognosis in this patient population. However, evidence is lacking that survival is actually increased for the majority of patients who receive adjuvant therapies,[6,7] while surgical resection with negative margins remains the only potentially curative therapy.[8] Finally, liver transplantation as a treatment option has been met with mediocre results,[9] but clinical trials are recruiting patients for both liver transplantation and

adjuvant chemotherapy for patients with resectable cholangiocarcinoma (http://clinicaltrials.gov).

The difficulty in amassing enough patients to power a randomized prospective controlled trial sufficiently to investigate neoadjuvant and adjuvant therapies in resectable biliary tract cancers make it unlikely that the utility of this approach will ever be fully elucidated. Retrospective studies, such as this, are currently the best available research despite significant problems associated with all studies of this type.

We reviewed our experience with neoadjuvant and adjuvant chemotherapy or chemoradiotherapy on the survival in patients seen in a large tertiary referral institution for management of resectable biliary tract cancers. We hypothesized that current neoadjuvant or adjuvant therapies would improve the survival probability after resection of biliary tract cancer with adequate negative margins.

## Patients and Methods

A consecutive series of 174 operations were identified from our prospective hepatobiliary database for gallbladder cancer (GBC) or cholangiocarcinoma (CC). Of these, 17 operations were excluded because they were not the patients' first operation or there was incomplete follow-up data. One hundred fifty-seven patients were then analyzed. The Institutional Review Board approved this study. All patients were diagnosed and underwent resection between 1978 and 2009 at the University of Texas M. D. Anderson Cancer Center in Houston, TX, USA. All patients had confirmation of their disease based on pathologic analysis or classic presentation on radiologic imaging. Patients with GBC and CC were typically identified at outside institutions based on radiologic imaging and referred to our institution. There were no incidental findings of GBC on standard cholecystectomy.

All patients underwent resection with intraoperative ultrasonography during open laparotomy by a hepatobiliary surgeon. Preoperative imaging included chest radiograph or chest computed tomography and abdominopelvic conventional axial imaging (computed tomography or magnetic resonance imaging). The key selection criterion for surgical treatment was probability to achieve complete tumor resection with preservation of sufficient hepatic parenchyma. It should be noted that the quality of the imaging has increased during the study period.

Anatomic resections were based on the segmental anatomy while the surgical goal was to achieve negative margins of at least 1 cm of normal parenchyma. Positive margins were considered those with <0.5 cm of normal tissue between tumor and the transected liver, while marginal margins were between 0.50 and 0.99 cm.

Decisions regarding neoadjuvant and adjuvant therapies were decided upon during multidisciplinary care meetings. Neoadjuvant therapy primarily consisted of gemcitabine/platinum-based chemotherapeutics or 5-fluorouracil for 4–6 months, while adjuvant therapy was primarily gemcitabine or capecitabine-based regimes. The expected surgical delay due to neoadjuvant therapy was 6 months.

Patient demographics, tumor factors, operative factors, pathologic findings, recurrence patterns, and survival were statistically analyzed. Survival time was estimated using Kaplan–Meier methods, and survival was analyzed using the log-rank test. A Cox proportional hazard model was used to evaluate the impact of the risk factors on survival. Hazard ratios and its 95 % confidence interval were calculated as appropriate. Variables (age, operative blood loss, sex, tumor location, margin status, nodal status, neoadjuvant therapy, and adjuvant therapy) that trended towards significance ($p<0.15$) in univariate models were evaluated with the backward elimination (all variables began in the model) method and remained in the model if $p<0.05$ while removing the insignificant variables. Differences in tumor recurrence rates between treatment groups were analyzed using the Fischer's exact and chi-square tests. Aggregated data are presented as means, while the uncertainties are standard deviations unless otherwise noted. Differences were considered to be statistically significant when the $p<0.05$.

## Results

One hundred fifty-seven patients underwent resection for primary GBC ($n=63$) and CC ($n=94$) with 35.7 % of all patients having nodal metastases on final pathology (Table 1). Thirty-four patients (21.7 %) had poorly differentiated carcinomas on histological examination. The average age was 61.1±11.9 years, and 56.1 % ($n=88$) were female. No hepatic lesions were managed with radiofrequency or other thermal ablative techniques. The intraoperative complication rate was 1.9 % ($n=3$: hypotension, splenic capsule tear, and coagulopathy), while the 90-day postoperative complication rate was 31.8 % (Table 2, $n=50$). There were no perioperative deaths. The median length of stay was 7 days (range, 3–74 days, Table 1). Overall survival at the time of data analysis was 55.1 % with a median follow-up of 25.5 months (range, 10 days to 21 years). The 5-year overall survival rate was 50.6 % for GBC and 30.4 % for CC, but the difference did not reach statistical significance ($p=0.059$). Initially, GBC, intrahepatic CC, and extrahepatic CC had similar survival curves (Fig. 1).

**Table 1** Clinical and pathological features of patients in this study

| | | GBC $N=63$ | Extrahepatic CC $N=40$ | Intrahepatic CC $N=54$ | Total $N=157$ |
|---|---|---|---|---|---|
| Age (years) | Mean ± SD | 60.7±10.3 | 62.5±11.6 | 60.4 ±13.8 | 61.1±11.9 |
| Follow up (months) | Median | 29.3 | 18.5 | 20.1 | 25.5 |
| Sex | Male, *n* (%) | 27 (42.9 %) | 19 (47.5 %) | 23 (42.6 %) | 69 (43.9 %) |
| | Female *n* (%) | 36 (57.1 %) | 21 (52.5 %) | 31 (52.4 %) | 88 (56.1 %) |
| Length of stay (days) | Median | 10 | 7 | 7 | 7 |
| Margin status | <0.50 cm | 12 (19.0 %) | 14 (35.0 %) | 20 (37.0 %) | 46 (29.3 %) |
| | 0.50–0.99 cm | 4 (6.3 %) | 1 (2.5 %) | 7 (13.0 %) | 12 (7.6 %) |
| | ≥1 cm | 47 (74.6 %) | 25 (62.5 %) | 27 (50 %) | 99 (63.1 %) |
| Nodal disease | *n* (%) | 44 (69.8 %) | 6 (15.0 %) | 6 (11.1 %) | 56 (35.7 %) |

*GBC* gallbladder cancer, *CC* cholangiocarcinoma

## Neoadjuvant Therapy Does Not Appear to Improve Overall Survival from Diagnosis

Of the patients, 17.8 % ($n=28$) received neoadjuvant chemotherapy, the majority being gemcitabine-based. Two patients received preoperative chemoradiotherapy. Neoadjuvant therapy delayed surgical resection for a mean of 6.8 months ($p<0.0001$). Immediate resection without neoadjuvant chemotherapy was associated with increased median survival from the date of diagnosis from 42.3 to 53.5 months (Fig. 2a, $p=0.01$). On univariate analysis, but not multivariate analysis, patients who received neoadjuvant therapy had a trend towards increased hazards of death (HR=1.66; 95 % confidence interval, 0.97–2.83; $p=0.07$).

## Adjuvant Chemotherapy, but not Chemoradiotherapy, was Associated with Worse Survival

Of the patients, 33.8 % ($n=53$) received adjuvant chemotherapy (majority capecitabine based), while 15.3 % ($n=24$) received postoperative chemoradiotherapy. Adjuvant chemoradiotherapy (majority gemcitabine-based) did not significantly increase the probability hazard of death (Fig. 2b; HR=1.14; 95 % confidence interval, 0.58–2.23; $p=0.71$), whereas adjuvant chemotherapy did significantly increase the probability hazard of death (HR=1.69; 95 % confidence interval, 1.01–2.84; $p=0.04$). However, on multivariate analysis, neither adjuvant chemotherapy nor adjuvant chemoradiotherapy were associated with an effect on overall survival. 59.7 % ($n=46$) of patients receiving adjuvant therapy had negative margins, 5.2 % ($n=4$) had marginal margins, and 35.1 % ($n=27$) had positive margins. Median survival for patients receiving no adjuvant therapy was 5.8 years, while it was 3.8 years for the chemotherapy group and 4.4 years for the chemoradiotherapy group.

## Margins >1 cm are Associated with Improved Survival

Negative margins ($n=99$) of at least 1 cm were associated with a Kaplan–Meier 5-year survival rate of 52.4 % and a median survival of 5.6 years (Fig. 3). Marginal margins ($n=12$) of 0.5–0.9 cm resulted in a HR of 1.51 (95 % confidence interval,

**Table 2** The postoperative complication rate is 31.8 % with an even distribution among multiple organ systems

| Complication | *n* | Percent of complications ($N=50$) | Percent of patients ($N=157$) |
|---|---|---|---|
| Renal insufficiency | 3 | 6.0 | 1.9 |
| Intraabdominal abscess or sepsis | 7 | 14.0 | 4.5 |
| Pneumonia | 2 | 4.0 | 1.3 |
| Pneumonitis/respiratory insufficiency | 4 | 8.0 | 2.5 |
| Biliary obstruction or hepatic insufficiency | 4 | 8.0 | 2.5 |
| Atrial fibrillation or bundle branch block | 8 | 16.0 | 5.1 |
| Biliary cutaneous fistula | 2 | 4.0 | 1.3 |
| Wound infection | 4 | 8.0 | 2.5 |
| Noninfectious intraabdominal fluid collection | 5 | 10.0 | 3.2 |
| Deep venous thrombosis | 1 | 2.0 | 0.6 |
| Other | 10 | 20.0 | 6.4 |
| Total | 50 | 100.0 | 31.8 |

There were no postoperative deaths within 90 days of surgery. "Other" includes urinary tract infections, a deep vein thrombosis, severe postoperative pain, and delirium tremens. The renal and hepatic insufficiencies were temporary in nature

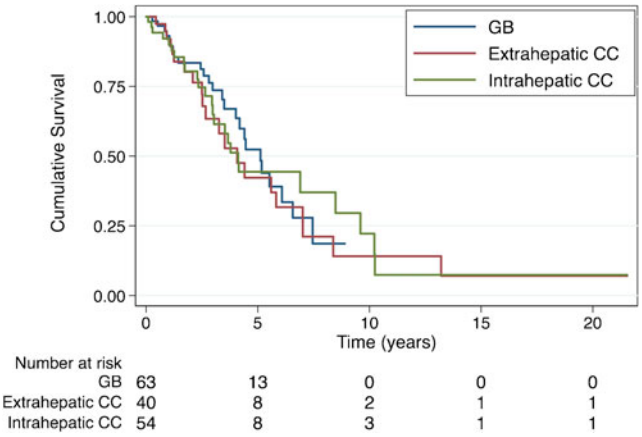


**Fig. 1** Survival of intra- and extrahepatic cholangiocarcinoma (CC) was similar for nearly the first 10 years after resection and not statistically different from each other or gallbladder cancer (GBC) (log rank $p=0.87$)

0.64–3.57; multivariate $p=0.34$) and a median overall survival of 3.0 years. Positive margins <0.5 cm ($n=46$) resulted in a HR of 1.85 (95 % confidence interval, 1.11–3.06; multivariate $p<0.02$) and a median overall survival of 4.1 years. On the multivariate model, margin status was the only significant predictor of long-term survival.

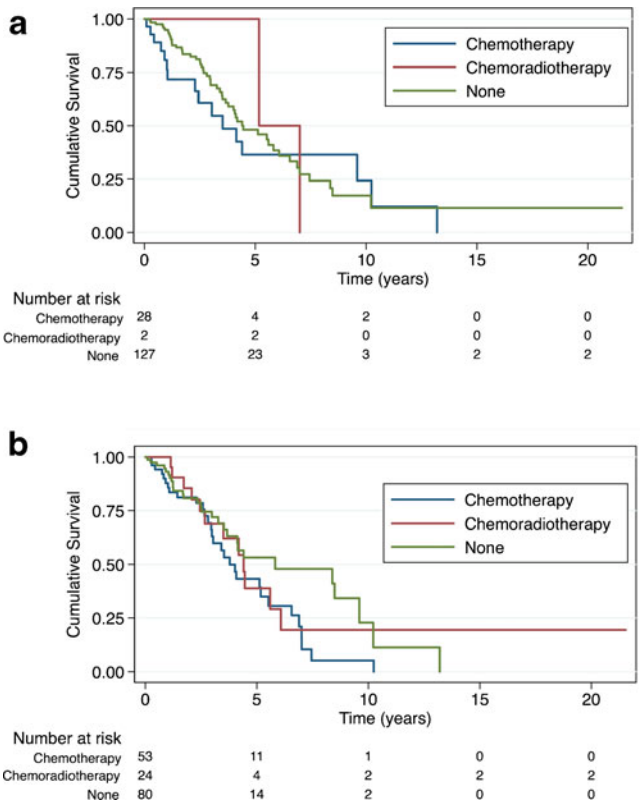


**Fig. 2** Kaplan–Meier analysis demonstrates that neither neoadjuvant (**a** log rank $p=0.59$) nor adjuvant (**b** log rank $p=0.16$) therapy is associated with an improved probability of survival. However, adjuvant chemotherapy is associated with a significant decrease in survival (**b** $p=0.04$)

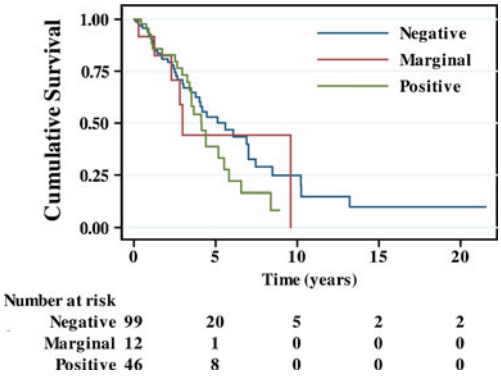


**Fig. 3** Kaplan–Meier analysis of margin status demonstrates similar initial survival after resection of biliary cancer (log rank $p=0.45$). However, on multivariate analysis, margins larger than 1 cm significantly improve survival probability compared to smaller margins ($p<0.01$)

## Discussion

Despite smaller series of patients suggesting that adjuvant therapy may improve survival,[8,10] we found that only adjuvant chemoradiotherapy after resection of biliary tract cancers was not detrimental to survival. Adjuvant chemotherapy was, in fact, statistically associated with decreased survival probability even though nearly 60 % of those receiving adjuvant therapy had negative margins of at least 1 cm. Notably, only 24 of our 157 patients (15.3 %) in this retrospective analysis received adjuvant chemoradiotherapy. We did find that a negative margin of at least 1 cm was associated with improved probability of overall survival. While obtaining a 1-cm margin is not impossible, it is often challenging, especially for proximal extrahepatic bile duct cancer. In our experience, with the use of complex, delicate dissection and reconstruction with wider resection of normal hepatic parenchyma, it is often (but certainly not always) possible to obtain larger margins than simple excision and anastomosis. Finally, nodal status was not statistically associated with survival, but we believe that this is most likely due to low numbers after parsing the study population by disease location and margin status.

Since the 5-year overall survival rate for all stages of patients with biliary tract cancers is <15 %,[8] we felt it was appropriate to investigate overall survival as this is usually the most relevant metric. Despite the appearance of apparent long-term survival differences between GBC and CC, it did not reach statistical significance (Fig. 1), suggesting that despite differences in cancer biology, prognosis may be similar. Therefore, we combined these groups to better power the analysis despite the acknowledged variations in biology. We did not include peri-ampullary cancers, as these cancers not only behave very differently from a biological perspective but carry much higher rates of margin-negative, potentially curative resections (on the order of 95 %).[6] Here, the R0 resection rate was 63.1 % (99/157), a rate similar to other reports.[11]

The higher than expected 5-year overall survival rates described herein relate to a number of potential issues. First, all patients were treated under the guidance of a multidisciplinary care team, which may prove beneficial in patient selection and management. Second, patient selection by the surgeon is greatly enhanced by the multiple imaging that these patients receive: their initial imaging at their home institution and repeat imaging at our center. In doing so, we are selecting for certain tumor biologies more likely to be treated successfully. Finally, the high volume of cases (and other complex operations performed at the same institution) is well accepted to improve short- and long-term survival in most major cancer operations.

Patients in this retrospective series received protocol-based neoadjuvant chemotherapy if they had GBC or centrally located CC lesions with concern about the ability to achieve a margin-negative resection. Tumor cytoreduction with chemotherapy led to operation. Adjuvant chemotherapy was administered for patients with node positive disease, poorly differentiated tumors, or with poor pathologic prognostic findings such as vascular or lymphatic invasion. Adjuvant chemoradiotherapy was delivered on protocol in patients with close or positive resection margins and/or nodal metastases in the porta hepatis.

In reviewing the literature as well as the results presented herein, we strongly discourage use of any neoadjuvant therapy for potentially resectable biliary cancers outside of a clinical trial. While utilizing neoadjuvant chemotherapy to "test" tumor biology is clinically attractive, the data do not suggest that this is appropriate at this time. It is unlikely that lead time bias is skewing the data as neoadjuvant therapy was given when the location of the lesion limited adequate resection. However, adjuvant chemoradiotherapy may benefit selected patients after R1 resections if given with radiosensitizing concomitant chemotherapy.

One of the largest randomized controlled studies to date, by Takada et al.[12], demonstrated a 5-year survival benefit for patients with GBC who received adjuvant chemotherapy after resection. However, there was neither improvement in median survival for these patients nor was there any survival benefit whatsoever for patients receiving chemotherapy after resection of biliary tract cancers. Furthermore, the survival demonstrated in that study with adjuvant chemotherapy was similar to the survival probability found here. In addition, in that study, the primary benefit of adding adjuvant chemotherapy was to patients who underwent noncurative GBC resections. While this study is underpowered for definitive answers, similar results suggest that the survival probabilities described are valid.

Obviously, those patients with positive margins would be expected to have a reduced probability of long-term survival with only surgical treatment. Nonetheless, we theorize that it is possible that some survival benefit is obtained from adjuvant chemoradiotherapy treatment in patients with margin-positive or high-risk (i.e., node-positive) disease as presented here. Ideally, all patients should be entered into a clinical trial with immediate resection and postoperative chemoradiotherapy or active chemotherapy if such is developed. This recommendation is based on the findings of the ABC trials and the nearly universally poor survival even after curative resection.

Retrospective studies, such as this one, often have multiple limitations associated with them a priori. Clearly, we chose to combine GBC and CC in order to maximize the study power to investigate relevant differences, but in doing so, baseline differences in these diseases were ignored. Likewise, extra- and intrahepatic CCs are often considered distinct diseases, both because of the surgical techniques utilized to resect them and the consequences of removing large amounts of normal hepatic parenchyma along with the intrahepatic CC lesion. Interestingly, the main endpoint of this study—overall survival—was not statistically different in the groups (Figs. 1 and 2). However, as seen in the long-term survivors (flat sections on the survival curve), it is likely that statistical significance would have eventually been reached for a much larger sample size or much longer follow-up duration. It is unlikely that these data exist even in high volume centers due to the natural history of the disease. Finally, imaging and surgical techniques have improved greatly over the time period described in this study. This would suggest that survival is improved and morbidity is decreased today compared to 10 years ago. Unfortunately, while this is logical, the small number of patients makes verifying these assertions difficult.

The median follow-up is much shorter than the overall survival because of the large increase in patients treated over time. As hepatic surgery becomes safer, the risks/benefit ratios begin to encourage surgical resection in more patients. As such, studies such as this one have a discordance between the number of patients with relatively short follow-up and fewer patients with very long-term follow-up. Since only a relatively small percentage of biliary cancer patients undergo resection, studies such as this one cover a very long time period. Clearly surgical techniques have changed, typically for the better over this time period.

## Conclusion

The importance of negative margins cannot be over emphasized. Adequate negative margins (>1 cm) provide the best chance for long-term survival. We have demonstrated that even marginal tumor-free margins (0.5–0.99 cm) are equivalent to positive margins. Neither neoadjuvant nor adjuvant chemotherapy seems to rescue patients with marginal margins after surgical resection. Adjuvant chemoradiotherapy

may provide some benefit, but this is unclear and should be investigated in a clinical trial. Finally, if there is no evidence of extrahepatic disease and the negative margin is <1 cm, an additional resection to achieve an adequate margin should be considered if technically feasible.

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**Conflict of interest** The authors declare that there are no conflicts of interest.

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