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Surgical Site Infection is Associated with Tumor Recurrence in Patients with Extrahepatic Biliary Malignancies

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Abstract

Background—Surgical site infections (SSI) are one of the most common complications after hepato-pancreato-biliary surgery. Complications may lead to an associated immune-modulatory effect that inhibits the body's response to cancer surveillance. We sought to define the impact of SSI on long-term prognosis of patients undergoing surgical resection of extra-hepatic biliary malignancies (EHBM).

Methods—Patients undergoing surgery for EHBM between 2000 and 2014 were identified using a large, multi-center, national cohort dataset. Recurrence free survival (RFS) was calculated and a multivariable Cox proportional hazards model was utilized to identify potential risk factors for RFS including SSI.

Results—728 patients included in the analytic cohort; 236 (32.4%) patients had perihilar cholangiocarcinoma, 241 (33.1%) gallbladder cancer, and 251 (34.5%) distal cholangiocarcinoma. A major resection liver resection was performed in 205 (28.3%) patients, while 110 (15.2%) patients had a pancreaticoduodenectomy. The overall incidence of morbidity was 55.8%; among the 397 patients who experienced a complication, 161 patients specifically had an SSI. The SSI

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occurred as an infection of the surgical site (n=70, 9.6%) or formation of an abscess in the operative bed (n=91, 12.5%). SSI was associated with long-term survival as patients who experienced an SSI had a median RFS of 19.5 months compared with 30.5 months for those patients who did not have an SSI (HR 1.40, 95% CI 1.08–1.80; p=0.01). Among 279 patients who had EHBM that had no associated lymph node metastases, well-to-moderate tumor differentiation, as well as an R0 resection margin, SSI remained associated with worse RFS (HR 1.84, 95% CI 1.03–3.29; p=0.038), as well as overall survival (HR 1.87, 95% CI 1.18–2.97; p=0.008).

Conclusion—SSI was a relatively common occurrence following surgery for EHBM as 1 in 10 patients experienced an SSI. In addition to standard tumor-specific factors, the occurrence of post-operative SSI was adversely associated with long-term survival.

Keywords

recurrence free survival; cholangiocarcinoma; gallbladder cancer; surgical site infection

Introduction

For patients with extrahepatic biliary malignancies (EHBM) surgical resection is the best potentially curative option.[1–5] Long-term overall survival (OS) after resection can vary, however, ranging from 35–40 months for perihilar cholangiocarcinoma (PHC), 24 months for gallbladder cancer (GBC), and 22–42 months for distal cholangiocarcinoma (DCC).[6–11] Several prognostic factors that impact OS have been identified including lymph node metastases, depth of invasion, poor tumor differentiation, and positive resection margins.[1, 11, 12] Some of these factors have been incorporated into the American Joint Committee on Cancer (AJCC) staging manual, as well as other staging systems and nomograms.[12, 13] While helpful, these prognostic tools are not always adequate or able to stratify patients into distinct prognostic groups. In turn, other clinical determinants have been suggested as relevant factors to prognosis.

One clinical factor that some groups, including our own, have suggested as a relevant prognostic factor is the occurrence of peri-operative complications.[14–17] Most EHBM require a major surgical procedure, which can involve a liver resection, removal of the extrahepatic biliary tree, or a pancreatoduodenectomy.[1] Peri-operative outcomes following these extensive operations can be associated with considerable morbidity, with post-operative complications as high as 30–40% in many centers.[18, 19] When a complication does occur, the long-term prognosis of the patient can be adversely impacted independent of tumor-specific factors. Specifically, complications may lead to an associated immune-modulatory effect that inhibits the body's response to cancer surveillance.[20–22] While the impact of complications on prognosis has been examined among patients with hepatocellular carcinoma and intrahepatic cholangiocarcinoma, the effect on EHBM has not been studied. [14, 17] In addition, many previous studies have only considered complications as an aggregate variable, failing to examine the effect of specific complications on prognosis. Given that surgical site infections (SSI) are one of the most common complications, we sought to define the impact of SSI on long-term prognosis of patients undergoing surgical resection of EHBM using a large, multi-center, national cohort dataset.

Methods

Data Sources and Patient Population

Patients undergoing surgery for EHBM between January 1, 2000 and December 31, 2014 at one of ten institutions participating in the Extrahepatic Biliary Malignancy Consortium were retrospectively identified (Ohio State University, Columbus, Ohio; Johns Hopkins University, Baltimore, Maryland; Emory University, Atlanta, Georgia; Stanford University, Stanford, California; University of Wisconsin, Madison, Wisconsin; Washington University, St. Louis, Missouri; Vanderbilt University, Nashville, Tennessee; New York University, New York, New York; University of Louisville, Louisville, Kentucky; Wake Forest University, Winston-Salem, North Carolina). Only patients with histologically confirmed EHBM who underwent curative intent surgery for their primary tumor were included.

Standard demographic and clinicopathologic data were collected for each patient including age, sex, race, primary tumor size, AJCC 7th Edition T-stage, histologic grade, presence of nodal disease, final resection margin, and the presence of vascular and/or perineural invasion. Tumor size was defined as the largest diameter of the tumor in the resected specimen. If multiple tumors were resected, the largest diameter was used to define tumor size. Histologic grade was defined as well-, moderate-, or poorly-differentiated with the highest histologic grade used to define tumor grade among patients with multiple resected specimens. Margin and nodal status were determined using the final postoperative pathologic report. Margin status was considered to be R1 when microscopic tumor was present at the resection margin; R0 was defined as a microscopically clear pathological margin. Postoperative complications were scored according to the Clavien-Dindo classification.[23] Class I and II (requiring bedside and medical intervention) are considered minor complications, whereas class III and above require reintervention or admission to the intensive care unit. Class V is perioperative death. SSI was defined as clinical symptoms of infection at the surgical site, including severe cellulitis, purulent drainage from either spontaneous dehiscence or intentional opening of the wound, intra-abdominal infection, or an abscess in the operative bed. The institutional review board of each participating institutional approved this study.

Statistical analysis

Summary statistics were provided as whole numbers and percentages for categorical variables and medians with interquartile range (IQR) for continuous variables. The primary outcome of interest was recurrence-free survival (RFS), defined as the time interval between the date of surgery and the date of recurrence or last follow-up/death, as appropriate. Recurrence was defined as either pathological or radiological evidence of disease progression. Estimates for RFS were calculated using the Kaplan-Meier method. Differences in RFS were assessed using the Log-Rank test. OS estimates were calculated in a similar manner from date of surgery to date of death or last follow-up. Patients who died within 30 postoperative days were excluded from the analysis. A multivariable Cox proportional hazards model was utilized to identify potential risk factors for RFS and OS. Specifically, patient and disease factors included age, sex, primary tumor size, T-stage, and tumor invasion (vascular and/or perineural). Factors with a $p < 0.1$ on univariable analysis were

included in the multivariable models. For multivariable analyses, multiple imputations were performed using the *mice* package for R 3.3.3. Results from the Cox models were reported as hazard ratios (HR) and corresponding 95% confidence intervals (CI). All analyses were performed using SPSS 22.0 (IBM, New York) and R 3.3.3. All tests were 2-sided and $p < 0.05$ defined statistical significance.

Results

Among the 728 patients included in the analytic cohort, median patient age was 66.7 years (IQR, 57.2–73.2) and roughly half of the patients were male ($n = 386$; 53.0%) (Table 1). The EHBM diagnosis was evenly distributed; 236 (32.4%) patients had perihilar cholangiocarcinoma, 241 (33.1%) gallbladder cancer, and 251 (34.5%) distal cholangiocarcinoma. Preoperative biliary drainage was performed in 427 (58.7%) patients. Preoperative chemotherapy utilized in only 23 patients (non-SSI group, $n=17$ vs. SSI-group, $n=6$; $p=0.634$). At the time of surgery, a major resection liver resection was performed in 205 (28.3%) patients, while 110 (15.2%) patients had a pancreaticoduodenectomy. Among all patients, 82.8% ($n=601$) had an intraoperative drain placed at the time of surgery. Utilization of an intraoperative drain was slightly higher among patients who developed an SSI versus patients who did not (91.9% vs. 80.2%; $p < 0.001$). On final pathology, 561 (77.1%) patients had R0 microscopically negative margins and 466 patients (70.9%) had a well- or moderately-differentiated tumor. Lymph node metastases were present in 294 (40.4%) patients and 298 (46.8%) patients had either a T3–T4 tumor. In the post-operative period, the overall incidence of morbidity was 55.8%; the average Clavien Dindo class of complications was II, indicating the need of medical treatment of the complication; there were no difference in the average Clavien Dindo class among patients with versus without SSI (all $p > 0.05$). Among the 397 patients who experienced a complication, 161 patients specifically had an SSI. The SSI occurred as an infection of the surgical site ($n=70$, 9.6%) or formation of an abscess in the operative bed ($n=91$, 12.5%). Patients who experienced an SSI were more likely to have more extensive disease at the time of surgical resection (Table 1). In the post-operative setting, over half of patients received chemotherapy ($n=363$, 54.6%). Receipt of chemotherapy was comparable among non-SSI patients ($n=275$, 53.1%) and SSI patients ($n=88$, 59.9%) ($p=0.145$).

After a median follow-up of 18.7 months, 302 (41.5%) patients experienced an EHBM recurrence. Overall median RFS was 26.8 months. Several factors were associated with a worse RFS including resection margin status (HR 1.69, 95% CI 1.31–2.18), lymph node metastasis (HR 1.68, 95% CI 1.34–2.11), and poor tumor differentiation (HR 1.63, 95% CI 1.28–2.07) (all $p < 0.001$). In addition, SSI was associated with long-term survival as patients who experienced an SSI had a median RFS of 19.5 months compared with 30.5 months for those patients who did not have an SSI (HR 1.40, 95% CI 1.08–1.80; $p=0.01$; Figure 1). Of note, most recurrences occurred as distant metastatic disease ($n=227$; 77.4%) rather than a local recurrence ($n=66$; 22.5%); there was no difference in the distribution of recurrences among patients who did or did not have SSI ($p=0.73$). Specifically, 80.0% of SSI patients had distant recurrence ($n=64$), whereas 76.5% of non-SSI patients had distant metastases ($n=163$) ($p=0.23$).

A subset analysis was subsequently performed to examine the impact of SSI on prognosis among patients who had traditionally good prognostic characteristics. Specifically, 279 patients who had EHBM that had no associated lymph node metastases, well-to-moderate tumor differentiation, as well as an R0 resection margin were identified (Table 2). Median survival in this select cohort of patients was 78.8 months. Of note, even among patients with a good prognosis, SSI impacted survival. Specifically, median survival among patients with SSI was 26.3 months versus 83.6 months among patients without SSI ($p=0.04$; Figure 2). Similar to the overall cohort, on multivariable analysis, SSI remained associated with a worse RFS (HR 1.84, 95% CI 1.03–3.29; $p=0.038$; Table 3) and OS (HR 1.87, 95% CI 1.18–2.97; $p=0.008$) (Table 4).

Discussion

EHBM is a malignancy associated with a guarded prognosis even after curative-intent surgery. Surgery can often involve a major resection with attendant post-operative morbidity. [18, 19] While the impact of post-operative complications on long-term survival has been examined for other gastrointestinal and hepatic malignancies, the effect of complications on prognosis following resection of EHBM has not been reported.[14–17] In addition, the specific prognostic impact of SSI, one of the most common post-operative complications, has not been reported among patients with EHBM. The current study was important because we investigated the impact of SSI on RFS among a large, multi-center cohort of patients who underwent curative-intent resection for EHBM. Of note, the occurrence of an SSI in the post-operative setting had an adverse impact on RFS. Specifically, patients who experienced an SSI had a 40% increased risk of recurrence compared with patients who did not have an SSI. Interestingly, the relative adverse effect of SSI was even more pronounced among patients with otherwise good prognostic features. Although patients with SSI tended to have more advanced disease than patients without SSI, SSI remained associated with RFS even on multivariable analysis after controlling for other procedure and tumor specific factors. The independent effect of SSI on OS prognosis was confirmed on multivariable.

Determinants of recurrence-free survival among patients undergoing resection of EHBM have been previously reported.[1, 11, 12] Virtually all studies to date, however, have focused only on tumor specific factors. For example, lymph node metastases, poor tumor differentiation, and positive resection margins have been previously associated with EHBM prognosis.[11, 12, 25, 30] Consistent with previous reports, we similarly noted that these tumor specific factors were associated with RFS among patients undergoing surgery in the current cohort. As such, many of these factors have been incorporated into staging systems for EHBM.[31, 32] Accurate prognostic stratification of EHBM patients is important to help guide adjuvant treatment choices, to inform surveillance, as well as to assist patient counselling. For example a recent meta-analysis demonstrated an oncological benefit for select patients with high-risk EHBM.[33] In addition, the on-going ACTICCA-1 (NCT02170090) trial is currently accruing patients to assess the effect of adjuvant therapy among patients with biliary cancers.

Although pathology clearly has a major impact on recurrence and prognosis, other factors likely play a role in determining long-term outcomes of patients. To this end, known risk

factors have not been able to explain fully the difference among individual patient survival. For example, the AJCC 7th edition staging, as well as proposed tumor-specific nomograms, have not been able to fully differentiate patients into survival categories, and most have not fare well on external validation.[12, 13] As such, in addition to standard tumor-specific factors, immune related considerations have been postulated as being important in the long-term prognosis of cancer patients.[20–22] The immune system may have a vital role in not only the etiology of cancer, but immunologic factors may also have an impact on prognosis after resection.[20] To this end, in a recent systematic review, Wang et al. noted that CD66b+ neutrophils, neutrophil-lymphocyte ratio, intratumoral IL-17+ cells and PD-1+/CD8+ tumor-infiltrating T lymphocytes were all associated with a worse prognosis among patients with EHBM.[20] The authors hypothesized that elevated neutrophil cells and reduced CD8+ lymphocytes may indicate exhaustion of effector T cells, contributing to tumor progression. [20, 34–37] Post-operative complications have been demonstrated to be immunosuppressive and mediate immunological changes.[20] In the current study, we noted an association between post-operative SSI and RFS, as patients with SSI had a worse long-term RFS (Figure 1&2). While the reason for this may be multifactorial, SSI may induce inflammation and thereby alter systemic inflammatory cytokines and chemokines.[38] In experimental studies, TNF α has been associated with SSI and, in turn, has been demonstrated to be potentially pro-tumorigenic.[39] Of note, most recurrences among patients with SSI were distant metastases perhaps suggesting a more systemic impact on the risk of recurrence.

Several limitations should be considered when interpreting results of the current study. Inherent to all retrospective analyses, there may have been a selection bias regarding the diagnosis and treatment of patients. Although there was no difference in receipt of adjuvant chemotherapy among patients with and without SSI, we were unable to determine the impact of timing of chemotherapy receipt. In addition, the use of data from a multi-institutional cohort did not allow for the standardization of the operative and perioperative approach among centers. Given the low incidence of EHBM, the use of data from multiple centers did ensure a large sample size while also making the results more generalizable. Specifically, data used in the current study were derived from high-volume hepatopancreatobiliary surgery centers across the United States. As such, the data were likely a good representation of the current state of treatment of extrahepatic biliary cancers, with a higher level of detail than can be achieved using national databases.[11, 24–29] Finally, data on the degree/severity of the SSI was not available and therefore a “dose effect” of SSI on RFS could not be assessed.

In conclusion, SSI was a relatively common occurrence following surgery for EHBM as 1 in 10 patients experienced an SSI. Standard tumor-specific factors such as T category, lymph node metastasis, and tumor grade were associated with prognosis following resection. In addition, after controlling for these factors, the occurrence of post-operative SSI was adversely associated with long-term survival. These data further strengthen the notion that peri-operative morbidity not only adversely affects EHBM patients in the short-term, but that complications such as SSI can also negatively impact long-term survival.

References

1. Groot Koerkamp B, Fong Y. Outcomes in biliary malignancy. *J Surg Oncol*. 2014; 110(5):585–91. [PubMed: 25250887]
2. Hezel AF, Zhu AX. Systemic Therapy for Biliary Tract Cancers. *The Oncologist*. 2008; 13(4):415–423. [PubMed: 18448556]
3. Dodson RM, et al. Intrahepatic cholangiocarcinoma: management options and emerging therapies. *J Am Coll Surg*. 2013; 217(4):736–750 e4. [PubMed: 23890842]
4. Brito AF, et al. Cholangiocarcinoma: from molecular biology to treatment. *Med Oncol*. 2015; 32(11):245. [PubMed: 26427701]
5. Razumilava N, Gores GJ. Cholangiocarcinoma. *Lancet*. 2014; 383(9935):2168–79. [PubMed: 24581682]
6. Pichlmayr R, et al. Surgical treatment of cholangiocellular carcinoma. *World J Surg*. 1995; 19(1):83–8. [PubMed: 7740815]
7. Matsuo K, et al. The Blumgart preoperative staging system for hilar cholangiocarcinoma: analysis of resectability and outcomes in 380 patients. *J Am Coll Surg*. 2012; 215(3):343–55. [PubMed: 22749003]
8. Groot Koerkamp B, et al. American Joint Committee on Cancer staging for resected perihilar cholangiocarcinoma: a comparison of the 6th and 7th editions. *HPB (Oxford)*. 2014; 16(12):1074–82. [PubMed: 25267346]
9. Igami T, et al. Surgical treatment of hilar cholangiocarcinoma in the “new era”: the Nagoya University experience. *J Hepatobiliary Pancreat Sci*. 2010; 17(4):449–54. [PubMed: 19806294]
10. Postlewait LM, et al. Proposal for a new T-stage classification system for distal cholangiocarcinoma: a 10-institution study from the U.S Extrahepatic Biliary Malignancy Consortium. *HPB (Oxford)*. 2016; 18(10):793–799. [PubMed: 27506989]
11. Buettner S, et al. Changing Odds of Survival Over Time among Patients Undergoing Surgical Resection of Gallbladder Carcinoma. *Ann Surg Oncol*. 2016; 23(13):4401–4409. [PubMed: 27495279]
12. Buettner S, et al. A Comparison of Prognostic Schemes for Perihilar Cholangiocarcinoma. *J Gastrointest Surg*. 2016; 20(10):1716–24. [PubMed: 27412318]
13. Groot Koerkamp B, et al. Survival after resection of perihilar cholangiocarcinoma-development and external validation of a prognostic nomogram. *Ann Oncol*. 2016; 27(4):753. [PubMed: 26920702]
14. Margonis GA, et al. Prognostic impact of complications after resection of early stage hepatocellular carcinoma. *J Surg Oncol*. 2017; 115(7):791–804. [PubMed: 28205284]
15. Pang TC, et al. Complications following liver resection for colorectal metastases do not impact on longterm outcome. *HPB (Oxford)*. 2015; 17(2):185–93. [PubMed: 25158227]
16. Neal CP, et al. Preoperative systemic inflammation and infectious complications after resection of colorectal liver metastases. *Arch Surg*. 2011; 146(4):471–8. [PubMed: 21502458]
17. Spolverato G, et al. Impact of complications on long-term survival after resection of intrahepatic cholangiocarcinoma. *Cancer*. 2015; 121(16):2730–9. [PubMed: 25903409]
18. Abbas S, Sandroussi C. Systematic review and meta-analysis of the role of vascular resection in the treatment of hilar cholangiocarcinoma. *HPB (Oxford)*. 2013; 15(7):492–503. [PubMed: 23750491]
19. Lafaro K, et al. Defining Post Hepatectomy Liver Insufficiency: Where do We stand? . *J Gastrointest Surg*. 2015; 19(11):2079–92. [PubMed: 26063080]
20. Wang Y, et al. Activation or suppression of the immune response mediators in biliary tract cancer (BTC) patients: a systematic review and meta-analysis. *J Cancer*. 2017; 8(1):74–84. [PubMed: 28123600]
21. Tsukagoshi M, et al. Overexpression of natural killer group 2 member D ligands predicts favorable prognosis in cholangiocarcinoma. *Cancer Sci*. 2016; 107(2):116–22. [PubMed: 26608587]
22. Goeppert B, et al. Prognostic impact of tumour-infiltrating immune cells on biliary tract cancer. *Br J Cancer*. 2013; 109(10):2665–74. [PubMed: 24136146]

23. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004; 240(2):205–13. [PubMed: 15273542]
24. Buettner S, et al. Conditional probability of long-term survival after resection of hilar cholangiocarcinoma. *HPB (Oxford).* 2016; 18(6):510–7. [PubMed: 27317955]
25. Buettner S, et al. Survival after resection of perihilar cholangiocarcinoma in patients with lymph node metastases. *HPB (Oxford).* 2017
26. Beal EW, et al. Elevated NLR in gallbladder cancer and cholangiocarcinoma – making bad cancers even worse: results from the US Extrahepatic Biliary Malignancy Consortium. *HPB (Oxford).* 2016; 18(11):950–957. [PubMed: 27683047]
27. Gani F, et al. Assessing the impact of common bile duct resection in the surgical management of gallbladder cancer. *J Surg Oncol.* 2016; 114(2):176–80. [PubMed: 27198742]
28. Ethun CG, et al. A Novel Pathology-Based Preoperative Risk Score to Predict Locoregional Residual and Distant Disease and Survival for Incidental Gallbladder Cancer: A 10-Institution Study from the U.S. Extrahepatic Biliary Malignancy Consortium. *Ann Surg Oncol.* 2017; 24(5): 1343–1350. [PubMed: 27812827]
29. Ethun CG, et al. Association of Optimal Time Interval to Re-resection for Incidental Gallbladder Cancer With Overall Survival: A Multi-Institution Analysis From the US Extrahepatic Biliary Malignancy Consortium. *JAMA Surg.* 2017; 152(2):143–149. [PubMed: 27784058]
30. Petrova E, et al. Survival outcome and prognostic factors after pancreatoduodenectomy for distal bile duct carcinoma: a retrospective multicenter study. *Langenbecks Arch Surg.* 2017
31. Edge, SB., et al. *AJCC Cancer Staging Manual.* 7th. Chicago, IL: Springer; 2009.
32. Groot Koerkamp B, et al. Survival after resection of perihilar cholangiocarcinoma-development and external validation of a prognostic nomogram. *Ann Oncol.* 2015; 26(9):1930–5. [PubMed: 26133967]
33. Horgan AM, et al. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. *J Clin Oncol.* 2012; 30(16):1934–40. [PubMed: 22529261]
34. Kusumanto YH, et al. Platelets and granulocytes, in particular the neutrophils, form important compartments for circulating vascular endothelial growth factor. *Angiogenesis.* 2003; 6(4):283–7. [PubMed: 15166496]
35. Lim YJ, et al. High ratio of programmed cell death protein 1 (PD-1)(+)/CD8(+) tumor-infiltrating lymphocytes identifies a poor prognostic subset of extrahepatic bile duct cancer undergoing surgery plus adjuvant chemoradiotherapy. *Radiother Oncol.* 2015; 117(1):165–70. [PubMed: 26235847]
36. Gu FM, et al. Intratumoral IL-17(+) cells and neutrophils show strong prognostic significance in intrahepatic cholangiocarcinoma. *Ann Surg Oncol.* 2012; 19(8):2506–14. [PubMed: 22411204]
37. Lee BS, et al. Neutrophil-lymphocyte ratio predicts survival in patients with advanced cholangiocarcinoma on chemotherapy. *Cancer Immunol Immunother.* 2016; 65(2):141–50. [PubMed: 26728479]
38. Murthy BL, et al. Postoperative wound complications and systemic recurrence in breast cancer. *British Journal of Cancer.* 2007; 97(9):1211–1217. [PubMed: 17968426]
39. Coffey JC, et al. Excisional surgery for cancer cure: therapy at a cost. *Lancet Oncol.* 2003; 4(12): 760–8. [PubMed: 14662433]

Figure 1.

Recurrence free survival stratified by surgical site infection (p=0.01).

Figure 2.

Recurrence free survival stratified by surgical site infection in patients with otherwise good prognostic characteristics ($p=0.04$).

Table 1

Baseline Characteristics

Characteristic	n (%) / median (IQR)	No Surgical Site Infection	Surgical Site Infection	p-value
Included patients	728 (100.0)	567 (100.0)	161 (100.0)	
Male Gender	386 (53.0)	291 (51.3)	95 (59.0)	0.085
Age, years	66.7 (57.2–73.2)	67.2 (57.9–73.8)	64.9 (55.6–70.6)	0.009
BMI (kg/m ²)	26.3 (23.2–30.2)	26.3 (23.2–30.0)	26.5 (23.5–30.6)	0.427
Preoperative Biliary				
Drainage	427 (58.7)	307 (54.1)	120 (74.5)	<0.001
Minimally Invasive Surgery	18 (2.5)	18 (3.2)	0 (0.0)	0.018
Type of Resection				0.002
Minor	410 (56.6)	336 (59.6)	74 (46.0)	
Major	315 (43.4)	228 (40.4)	87 (54.0)	
Type of Cancer				0.001
Gallbladder cancer	241 (33.1)	207 (36.5)	34 (21.1)	
Distal cholangiocarcinoma	251 (34.5)	190 (33.5)	61 (37.9)	
Perihilar cholangiocarcinoma	236 (32.4)	170 (30.0)	41.0 (41.0)	
Postoperative complication	397 (55.8)	237 (43.1)	161 (100.0)	<0.001
Clavien Dindo grade	II (II–IIIa)	II (II–IIIa)	IIIa (II–IIIa)	0.067
Surgical Site Infection	161 (22.1)	0 (0.0)	161 (100.0)	<0.001
Margin Status				0.019
R0	561 (77.1)	448 (79.0)	113 (70.2)	
R1	167 (22.9)	119 (21.0)	48 (29.8)	
Tumor Size				0.165
2.5 cm	459 (63.0)	365 (64.4)	94 (58.4)	
> 2.5 cm	269 (37.0)	202 (35.6)	67 (41.6)	
Grade				0.298
Well Differentiated	98 (14.9)	74 (14.6)	24 (16.1)	
Moderately differentiated	368 (56.0)	288 (56.7)	80 (53.7)	
Poorly differentiated	188 (28.6)	145 (28.5)	43 (28.9)	
Undifferentiated	3 (0.5)	1 (0.2)	2 (1.3)	
AJCC T-stage				0.007
T1–T2	339 (53.2)	280 (56.0)	59 (43.1)	
T3–T4	298 (46.8)	220 (44.0)	78 (56.9)	
Lymph Node Metastases	294 (40.4)	213 (37.6)	81 (50.3)	0.004
Lymphovascular Invasion	254 (34.9)	187 (33.0)	67 (41.6)	0.043
Perineural Invasion	417 (71.9)	313 (70.8)	104 (75.4)	0.299

Table 2

Patients with good prognostic characteristics (Good or moderate differentiation, R0, N0); R0: Microscopically negative margin, N0: No lymph node metastases

Characteristic	n (%) / median (IQR)	No Surgical Site Infection	Surgical Site Infection	p-value
Included patients	279 (100.0)	241 (100.0)	38 (100.0)	
Male Gender	139 (49.8)	120 (49.8)	19 (50.0)	0.981
Age, years	66.7 (59.7–73.8)	67.2 (56.7–73.8)	62.0 (53.7–74.9)	0.399
BMI (kg/m ²)	26.3 (23.1–30.8)	26.4 (23.2–30.9)	25.9 (22.2–30.5)	0.415
Preoperative Biliary				
Drainage	141 (50.5)	114 (47.3)	27 (71.1)	0.006
Minimally Invasive Surgery	12 (4.3)	12 (5.0)	0 (0.0)	0.381
Type of Resection				0.048
Minor	178 (64.3)	159 (66.5)	19 (50.0)	
Major	99 (35.5)	80 (33.5)	19 (50.0)	
Type of Cancer				0.093
Gallbladder cancer	109 (39.1)	100 (41.5)	9 (23.7)	
Distal cholangiocarcinoma	80 (28.7)	65 (27.0)	15 (39.5)	
Perihilar cholangiocarcinoma	90 (32.3)	76 (31.5)	14 (36.8)	
Postoperative complication	130 (48.3)	92 (39.8)	38 (100.0)	<0.001
Clavien Dindo grade	IIIa (II–IIIa)	II (II–IIIa)	IIIa (II–IIIa)	0.166
Surgical Site Infection	38 (13.6)	241 (100.0)	38 (100.0)	<0.001
Tumor Size				0.449
2.5 cm	198 (71.0)	173 (71.8)	25 (65.8)	
> 2.5 cm	81 (29.0)	68 (28.2)	13 (34.2)	
Grade				0.010
Well Differentiated	53 (23.1)	143 (70.4)	14 (46.7)	
Moderately differentiated	176 (76.9)	60 (29.6)	16 (53.3)	
AJCC T-stage				0.403
T1–T2	157 (67.4)	44 (22.2)	9 (29.0)	
T3–T4	76 (32.6)	154 (77.8)	22 (71.0)	
Lymphovascular Invasion	51 (18.3)	44 (18.3)	7 (18.4)	0.981
Perineural Invasion	111 (58.1)	95 (58.6)	16 (55.2)	0.727

Table 3

Cox regression analysis of RFS in patients with good prognostic characteristics

Characteristic	Univariable			Multivariable		
	HR	95% CI	P	HR	95% CI	P
Male Gender	1.07	0.69–1.66	0.755			
Age, years	1.00	0.98–1.01	0.648			
BMI (kg/m ²)	0.99	0.96–1.03	0.709			
Preoperative Biliary Drainage	1.40	0.90–2.18	0.137			
Type of Resection						
Minor	Ref	–	–	Ref	–	–
Major	1.46	0.94–2.27	0.094	1.10	0.65–1.85	0.733
Type of Cancer						
Gallbladder cancer	Ref	–	–			
Distal cholangiocarcinoma	1.61	0.96–2.70	0.069			
Perihilar cholangiocarcinoma	1.00	0.57–1.75	1.000			
Surgical Site Infection	1.76	1.00–3.09	0.050	1.84	1.03–3.29	0.038
Tumor Size						
≤ 2.5 cm	Ref	–	–	Ref	–	–
> 2.5 cm	1.53	0.97–2.40	0.065	1.48	0.93–2.35	0.096
Grade						
Well Differentiated	Ref	–	–			
Moderately differentiated	1.23	0.68–2.21	0.492			
AJCC T-stage						
T1–T2	Ref	–	–	Ref	–	–
T3–T4	1.81	1.13–2.91	0.013	1.56	0.90–2.73	0.116
Lymphovascular Invasion	1.91	1.19–3.06	0.007	1.78	1.11–2.88	0.018
Perineural Invasion	1.38	0.79–2.43	0.261			

Table 4

Cox regression analysis of overall survival in patients with good prognostic characteristics

Characteristic	Univariable			Multivariable		
	HR	95% CI	p	HR	95% CI	p
Male Gender	1.23	0.86–1.76	0.249			
Age, years	1.02	1.01–1.04	0.011	1.03	1.01–1.04	0.004
BMI (kg/m ²)	0.98	0.95–1.01	0.194			
Preoperative Biliary Drainage	1.92	1.31–2.80	0.001	1.26	0.73–2.16	0.402
Type of Resection						
Minor	Ref	–	–	Ref	–	–
Major	1.69	1.18–2.42	0.004	1.07	0.66–1.73	0.792
Type of Cancer						
Gallbladder cancer	Ref	–	–	Ref	–	–
Distal cholangiocarcinoma	2.49	1.53–4.04	<0.001	1.28	0.58–2.79	0.540
Perihilar cholangiocarcinoma	2.47	1.53–3.99	<0.001	2.13	1.08–4.21	0.030
Surgical Site Infection	2.21	1.42–3.42	<0.001	1.87	1.18–2.97	0.008
Tumor Size						
≤ 2.5 cm	Ref	–	–			
> 2.5 cm	1.28	0.88–1.86	0.203			
Grade						
Well Differentiated	Ref	–	–			
Moderately differentiated	1.04	0.65–1.65	0.886			
AJCC T-stage						
T1–T2	Ref	–	–	Ref	–	–
T3–T4	2.05	1.37–3.06	<0.001	1.91	1.11–3.28	0.019
Lymphovascular Invasion	1.03	0.66–1.59	0.912			
Perineural Invasion	1.59	1.01–2.51	0.047	1.09	0.66–1.81	0.730