Ann Med Res 2020;27(5):1415-21

Annals of Medical Research

DOI: 10.5455/annalsmedres.2019.12.828

Original Article

Our surgical experience in cholangiocellular carcinoma

Ahmet Gokhan Saritas, Abdullah Ulku, Ugur Topal, Kubilay Dalci, Erdi Aydin, Atilgan Tolga Akcam

Cukurova University, Faculty of Medicine, Department of General Surgery, Adana, Turkey

Abstract

Aim: Cholangiocellular carcinomas are rare bile duct tumors. They are categorized as intrahepatic(iCCA), perihilar(pCCA) or distal(dCCA) cholangiocarcinomas according to their anatomical location. In this study, we aimed to present our clinical experience in patients with cholangiocellular carcinoma.

Material and Methods: Patients who underwent curative surgery with the diagnosis of cholangiocellular carcinoma between 2010 and 2019 were retrospectively reviewed. Demographic and clinical characteristics, surgical procedures, tumor characteristics, short- and long-term results and survival of the patients were analyzed.

Results: Twentynine patients were included in the study. The mean age of the patients was 63.3(±10.8) years, and 52% of the patients were older than 65 years. Male sex was 79.3%. Percutaneous biliary drainage was performed in 52% of the patients before the operation. Tumor localizations were distal (dCCA) in 12 (41.4%) patients, perihilar (pCCA) in 11 (38%) patients, and intrahepatic (iCCA) in 6 (20.6%) patients. Only biliary resection was performed in 69%, hepatic + biliary resection in 27.6%, and only hepatic resection in 3.4% of the patients. The mean tumor size was 3.08 cm (±1.91), tumor stage was commonly stage II (58.6%) and postoperative complication was seen in 13.8% of the patients. Ninety-day unplanned readmission was observed in 31.3%, postoperative mortality in 6.9%, and recurrence during postoperative follow-up in 24.2% of the patients. The mean survival time was 22.82(±13.72) months.

Conclusion: The type of surgical approach to be performed in cholangiocellular carcinoma is related to the localization of the tumor. With the right patient selection, curative surgical treatment can be performed at low morbidity and mortality rates.

Keywords: Cholangiocarcinoma; extrahepatic bile duct resection; liver resection

INTRODUCTION

Cholangiocarcinoma was first reported by Durand Fardel in 1840(1).Cholangiocarcinoma (CCA) is an epithelial cell malignancy that may be caused by the differentiation of cholangiocytes, which may result from different locations within the biliary tract. CCA has different clinical, morphological and epidemiological features depending on the anatomical region it is located. It is divided into three different types as Intrahepatic (iCCA), Perihilar (pCCA) and Distal (dCCA) cholangiocarcinoma, according to their anatomic localization (2,3).

Cholangiocarcinoma accounts for 3% of all gastrointestinal cancers worldwide and is the second most common primary hepatic tumor (4). Epidemiological profiles of cholangiocarcinoma subtypes vary depending on different risk factors and genetic characteristics, but they are rare tumors with an incidence of less than 2/100,000 (5).

Etiological factors blamed in the development of cholangiocarcinoma are Primary Sclerosing Cholangitis (PSC), biliary cystic diseases, parasitic infections (Clonorchis and Opisthorchis), hepatolithiasis, toxin exposure, Lynch Syndrome, chronic liver disease, non-viral chronic liver disease, Diabetes Mellitus, obesity, and HIV infection (1-5).

Because of the relatively low incidence and difficulties in the management of the treatment, the treatment of the disease is usually performed in experienced centers (6,7). Surgical resection with negative margins is the only treatment option for all subtypes of cholangiocarcinoma. Considering the involvement of vascular structures, lymph nodes and surrounding tissues, many cases do not have a disease suitable for treatment at the time of diagnosis. Therefore, only 25-35% of all patients may undergo surgical treatment (8).However, aggressive surgical resection with extended hepatectomy, lymphadenectomy and vascular reconstruction may increase the chance of treatment in selected cases (9,6).

Due to late diagnosis, curative surgical resection cannot be performed in the presence of locally advanced or metastatic disease, and high recurrence rates after palliative resection lead to poor prognosis (8).However,

Received: 12.12.2019 **Accepted:** 08.05.2020 **Available online:** 23.05.2020
Corresponding Author: Ugur Topal, Cukurova University, Faculty of Medicine, Department of General Surgery, Adana, Turkey
E-mail: sutopal2005@hotmail.com

the 5-year survival rate reported in large series is 20-30% after resection, which is far from encouraging in terms of surgical treatment (7).

In this study, we aimed to investigate the short-term and long-term results of cholangiocarcinoma patients who underwent hepatobiliary resection in the last 10 years in our clinic, which is a tertiary referral center, and discuss our results in light of the literature.

MATERIAL and METHODS

The study included 29 patients who underwent surgical treatment for cholangiocarcinoma between 2010 and 2019 at the General Surgery Clinic of Cukurova University Faculty of Medicine. Approval numbered 2019/93-4 was obtained from the Ethics Committee of Cukurova University Faculty of Medicine. Patient files, hospital information system records, surgical reports, pathology records and anesthesia notes were examined. The cases were analyzed retrospectively. Follow-up data were supported by telephone interviews with the patients. Patients who were diagnosed as inoperable cholangiocarcinoma and underwent palliative stenting, cases accepted as irresectable during laparotomy and therefore not undergoing surgical resection, patients under the age of eighteen, and patients whose records could not be reached were excluded from the study.

The demographic characteristics, Body Mass Index (BMI), American Society of Anesthesiologists (ASA) score, comorbid diseases, presenting symptoms, preoperative laboratory values, tumor markers, preoperative percutaneous biliary drainage, preoperative Endoscopic Retrograde Cholangio-Pancreatography (ERCP) stent history, neoadjuvant treatment conditions, tumor localization, surgical treatment procedures, intraoperative complications, operation duration, tumor diameter, number of dissected lymph nodes, number of metastatic lymph nodes, postoperative complications, postoperative hospital stay, reoperations, postoperative 90-day mortality, 90-day unplanned re-admission to the hospital, recurrence, mean follow-up, survey and current clinical status of the patients were analyzed.

Most of the patients treated in our clinic were referred from another center after initial investigations such as Computed Tomography (CT) and Endoscopic Retrograde Cholangio-Pancreatography (ERCP). Preoperative evaluation was performed with one or more Doppler ultrasonography (USG), high resolution spiral CT, magnetic resonance cholangiopancreatography (MRCP), percutaneous transhepatic cholangiography (PTC) and endoscopic ultrasonography (EUS) to determine the tumor stage and its resectability. Positron Emission Tomography (PET) screening was performed to evaluate the presence of extrahepatic metastasis.

Patients with cholangitis or pancreatitis after previous biliary intervention were treated preoperatively. The patients who needed to have their existing biliary stent replaced and/or who needed stent for decompression of the biliary tree were decompressed with PTC or ERCP in our center. Plastic stents were converted to metal stents in patients with advanced stage disease who were not suitable for surgery.

Tumors with peritoneal spread on imaging findings, metastatic involvement in the liver parenchyma outside the resection site, and/or macroscopic paraaortic lymph node metastasis were accepted as irresectable. All samples were examined by the same pathologist. If there was suspicion of involvement in the surgical margin, Frozen section examination was performed.

American Joint Committee on Cancer 2010 and 2016 were used for tumor staging.

All surgical resections were performed to microscopically reach the negative surgical margin. In laparotomy, after thorough examination to exclude metastatic disease, in cases where pancreaticoduodenectomy would not be performed, bile duct resection was advanced from the level where the bile duct enters the pancreas to the location of the tumor-free bile duct in the liver hilum. During the operation, frozen section evaluation of the surgical margins of the proximal and distal bile ducts was performed. Resection limits were extended in patients with positive surgical margins. Biliary continuity was repaired with Roux-en-Y biliary-enteric anastomosis. From the Treitz Ligament, the 25 cm distal jejunum loop was cut by staples and the distal end of the jejunum was passed through the Transverse Mesocolic area. In biliary anastomosis with Roux loop; After enterotomy, the posterior wall was first formed with 5/0 prolene sutures as a contine and then the front wall was repaired with 5/0 prolene single sutures. Manual anastomosis was performed between the 60 cm distal of Roux pin and the pin coming from Trietz, and jejunojejunostomy was completed side by side.

Partial hepatectomy (hemi-hepatectomy, extended hepatectomy with or without caudate lobe resection) was also carried out with bile duct resection when the right or left hepatic ducts were involved. All extended right hepatectomies and left hepatectomies included caudate lobectomy. Radiological evaluation was performed in preoperative period in order to determine remnant liver volume in patients undergoing lobectomy. After laparotomy in patients undergoing lobectomy, demarcation line was determined after Portal vein and Hepatic artery ligation of the side to be applied lobectomy. Short hepatic veins between the Retrohepatic Vena Kava Inferior and the Liver were ligated and cut. Resection was performed from the demarcation line created. Clamp-crush technique was used in parenchymal resection. Vascular and bile ducts were ligated with clip or suture techniques. The bile duct and hepatic vein belonging to the side to be resected were tied and cut and lobectomy was completed.

The Whipple Procedure group was included in the biliary resection group.Pancreaticoduodenectomy (Whipple Procedure) was performed for tumors located inferior to the cystic canal.

Following laparotomy, the choledoch was cut just above the cystic duct choledoch junction (until the negative surgical margin was reached).Then, the pancreas was rotated and cut from the Superior Mesenteric Vein border in the posterior of the pancreas.

From the proximal of the pylorus, the distal stomach was freed, rotated and cut. The Treitz ligament was freed, and about 10 cm distal from the jejunum was cut. Ductajejunal anastomosis between the pancreatic duct and jejunum was completed with the help of 5/0 vicryl and 5/0 prolene in end-to-side form. To the proximal of this anastomosis, biliary tract jejunum anastomosis was completed first with 5/0 prolene sutures as the posterior wall continue, and then the anterior wall was completed with 5/0 prolene single sutures.. The lymph node dissection was advanced from the lymphatic tissue in the hepatoduodenal ligament to the level of the celiac trunk.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA). Categorical measurements were summarized as numbers and percentages, and continuous measurements were summarized as mean and standard deviation (median and minimum-maximum where necessary). Kaplan-Meier analysis and Log Rank test were used for survival analysis.

RESULTS

Twenty-nine patients were included in the study. The mean age of the patients was 63.3 (± 10.8) years and 52% of the patients were older than 65 years. Male sex was dominant with 79.3% of the patients included. The most common ASA score was ASA 2 (58.6%) and the most common comorbid disease was hypertension (52%). Presenting complaints were abdominal pain in 48% and jaundice in 52% of the patients. Percutaneous biliary drainage was performed in 52% and endoscopic stenting in 44.8% of the patients. Demographic and clinical characteristics are shown in Table 1.

The mean preoperative total bilirubin level was 7.55 mg/dl, the mean level of direct bilirubin was 4.48 mg/dl, and mean Ca19,9 level was 2422. The laboratory parameters are shown in Table 2.

Tumor localizations were distal (dCCA) in 12 (41.4%), perihilar (pCCA) in 11 (38%), and intrahepatic (iCCA) in 6 (20.6%) patients. Only biliary resection was performed in 69%, hepatic + biliary resection in 27.6%, and only hepatic resection was performed in 3.4% of the patients. The mean operation duration was 295 min. Intraoperative features are shown in Table 3.

The mean tumor size was 3.08 (± 1.91) cm, the mean number of dissected lymph nodes was 6.03, the mean number of metastatic lymph nodes was 0.51, and the most common tumor stage was Stage II (58.6%). The pathological features are shown in Table 4.

Table 1. Demographic and Clinical Characteristics

Variable	(n=29)
Mean age (years)	63.3+10.8 (28-85)
Age (years)	
<65	14(48%)
>65	15(52%)
Sex	
Male	23(79.3%)
Female	6(20.7%)
BMI	25.9+3.94(20.9-37.25)
ASA Score	
1	5(17.2%)
2	17(58.6%)
3	7(24.2%)
Comorbidity	
Hypertension	15(52%)
Diabetes mellitus	3(10.3%)
COPD	6(20.7%)
ASHD	7(24.2%)
None	7(24.2%)
Symptoms	
Abdominal Pain	14(48%)
Jaundice	15(52%)
Biliary Percutaneous Drainage Before the Operation	15(52%)
Endoscopic Stent Before the Operation	13(44.8%)

COPD: Chronic Obstructive Pulmoner Disease, ASHD: Atherosclerotic Hearth Disease

Table 2. Laboratory values

Variable	(n=29)
WBC count mm^3/L	12.14+6.12(5.25-31)
Neutrophil count mm^3/L	9.16+6.15(3.34-27.8)
Lymphocyte counts mm^3/L	2.02+1.51(0.8-8.8)
Platelet counts mm^3/L	292+90.05(129-516)
Hemoglobin gr/dl	12.44+2.02(9.4-16)
Albumin gr/dl	2.92+0.79(1.4-4.4)
CRP	15.92+31.3(0.23-170)
Total bilirubin gr/dl	7.55+7.12(0.38-25.4)
Direct bilirubin mg / dL	4.48+4.35(0.07-15.9)
AST u/l	142.8+138(18-537)
ALT u/l	156.4+172(13-648)
ALP u/l	299.6+203.2(47-804)
GGT u/l	322.6+337.1(30-1703)
CEA (CarcinoembryonicAntigen)	12.9+32.1(0.59-137)
CA 19.9	2422.27+5356(1.6-20270)

Table 3. Intraoperative Characteristics

Variable	(n=29)
Tumor location	
Intrahepatic (iCCA)	6(20.6%)
Perihilar(pCCA)	11(38%)
Distal (dCCA)	12 (41.4%)
Surgery Performed	
Biliary Resection	20(69%)
Hepatic Resection	1(3.4%)
Hepatic + Biliary Resection	8 (27.6 %)
Vascular Invasion	
Portal vein	1(3.44%)
Superior mesenteric vein	1(3.44%)
Right hepatic artery	1(3.44%)
Intraoperative complication	
Iatrogenic small intestine perforation	1(3.44%)
Operation duration (min)	295.4+116.01(165-525)
Intraoperative erythrocytetransfusion (unit)	1.31+1.73(0-7)

Table 4. Pathological Characteristics

Variable	(n=29)
Tumor diameter	3.08+1.91(0.53-8)
Number of dissected lymph nodes	6.03+5.22(0-18)
Number of metastatic lymph nodes	0.51+1.42(0-6)
Tumor Stage	
I	1(3.4%)
II	17(58.6)
IIIA	5(17.2%)
IIIC	5 (17.2%)
IV	1 (3.4%)

The mean postoperative hospital stay was 17 days and the postoperative complication rate was 13.8%. Two patients were repeated and the unplanned re-admission rate was 31.3% in the 90-day period. Postoperative mortality occurred in two patients. Postoperative features are shown in Table 5.

The recurrence rate was 24.2% in the postoperative follow-up. When the current clinical status of the patients was examined, it was found that 24.2% of the patients were still alive and 75.8% of them had died. The mean survival duration was 22.82 months. Oncological outcomes and survival data are shown in Table 6 and Figure 1.

Table 5. Postoperative Characteristics

Variable	(n=29)
Postoperative duration of hospitalization	17+6.03 (4-32)
Postoperativecomplication	4 (13.8%)
Reoperation	2 (6.9%)
90-day readmission	9 (%31.3)
Wound site infection	3 (10.3%)
General condition disorder, oral intake disorder	6 (21%)
Postoperative mortality	2 (6.9%)

Table 6. Oncological Outcomes

Variable	(n=29)
Recurrence	7 (24.2%)
Peritoneal carcinomatosis	2 (6.9%)
Liver	2 (6.9%)
Local recurrence	3 (10.3%)
Current Clinical Condition	
Alive	7 (24.2%)
Exitus	22 (75.8%)
Average Survival	22.82±3.72 (15.52-30.11)
Median Survival	17.30±4.11 (9.24-25.35)

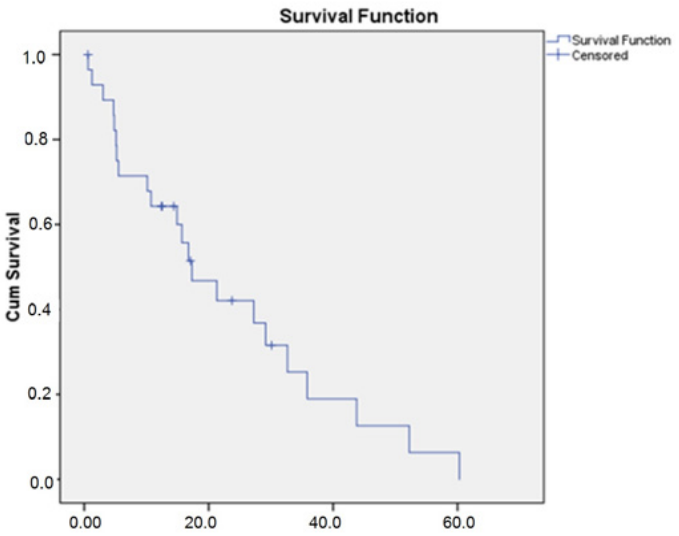

Figure 1. Survival Analysis

DISCUSSION

Of all cholangiocarcinomas diagnosed in the USA, 50-70% is composed of pCCA, 20-30% of dCCA, and the remaining 5-20% of iCCA (11,12).In the series in the literature, the risk of CCA increases with age and the typical incidence is

between 60-70 years(11,13,14).Incidence is 40% higher in men than women, according to data from the Surveillance of Rare Cancers in Europe (RARECARE) project (15). In our series, the mean age was 63.3, similar to the literature, and the number of male patients was 4 times higher than the number of female patients. Tumors were frequently localized in the perihilar and distal regions, in accordance with the literature.

The presenting complaint of cholangiocarcinoma is related to tumor localization. Patients with extrahepatic tumors usually present with painless jaundice resulting from biliary obstruction, while patients with intrahepatic tumors usually present with pain. Patients with early-stage cholangiocarcinoma are usually asymptomatic. Common complaints include itching (66%), abdominal pain (30% - 50%), weight loss (30% - 50%), and fever (up to 20%). In some cases, darkening of the urine color, weight loss and acholic stool complaints are also present (14,16). In our series, similar to the literature, presenting complaints were abdominal pain and jaundice.

Preoperative biliary drainage (PBD) is recommended in the presence of obstructive cholangitis. Biliary drainage is still controversial in patients without cholangitis, since biliary drainage itself may cause cholangitis. Therefore, the indication for PBD should be carefully evaluated. Obstructive jaundice is associated with proinflammatory status, and previous series have shown a relationship between serum bilirubin levels and postoperative complications (7,17). Patients with resectable CCA and bilirubin levels below 15 mL / dL may undergo surgery without preoperative biliary drainage. Preoperative biliary drainage can be provided by percutaneous or endoscopic techniques. In a study in the literature with patients undergoing hepatobiliary resection, postoperative morbidity and mortality rates were significantly higher in patients who underwent preoperative percutaneous intervention compared to endoscopic intervention (18). Although the appropriate preoperative bilirubin value has been reported as 15 mL/dL in the literature, surgery is performed in our clinic on patients who recovered to levels below 7-8 mL/dL and whose cholangitis presentation has improved. In our study, bile duct drainage was performed preoperatively in patients with cholangitis and in patients with high levels of bilirubin. Percutaneous biliary drainage was performed in 52% of our patients and endoscopic biliary drainage was performed in 44% of our patients. The mean preoperative total bilirubin level was 7.55.

Cancer antigen 19–9 (CA 19–9) is the primary serum biomarker used for the diagnosis of cholangiocarcinoma, and CA 19–9 levels >1,000 U/ml have been associated with the presence of metastatic disease (19). In our series, the mean CA 19–9 level was found to be 2224 U/ml, and biliary interventions and the presence of cholangitis were thought to be one of the factors affecting this high level of CA 19–9.

Radiological and endoscopic advances in the preoperative management of cholangiocellular cancer have led to a better evaluation and staging of cholangiocarcinoma. Technical advances in hepatobiliary surgery have also increased the chance of curative resection in this patient group (7). Despite current technological advances, the evaluation of resectability in the preoperative period is still an important problem.

It is known that surgical treatment provides the only chance for the treatment of CCA. Hepatobiliary resection can be performed in anatomically and physiologically appropriate cases. The aim of surgical treatment is to achieve R0 resection while preserving the function of remnant liver tissue. Considering its close relationship with the portal vein and hepatic artery, vascular resections can be performed to perform R0 resection during surgery (10).According to our clinical experience, the level of biliary intestinal reconstruction after biliary resection near the hilar region is an important factor in preventing long-term biliary intestinal anastomosis stenosis.

In the study conducted by Lee et al., patients were divided into two groups as extrahepatic cholangiocarcinoma and intrahepatic cholangiocarcinoma. While bile duct resection was performed in 11% of 302 patients operated for extrahepatic cholangiocarcinoma, other extrahepatic cholangiocarcinoma patients underwent additional hepatic resection. Hepatic resection was performed in all patients with intrahepatic tumors. Portal vein resection was performed in 13% of patients with extrahepatic cholangiocarcinoma and hepatic artery resection was performed in 1.7%, and pancreaticoduodenectomy was performed in seven patients (9).In our series, biliary resection was performed in 69% of patients, while hepatic resection was added to 27.6% of these patients. One patient each underwent vascular resection for portal vein, superior mesenteric vein, and hepatic artery invasion. The choice of resection procedures was based on tumor localization, tumor size, and invasion of adjacent anatomic structures in the bile duct. The mean operation duration was found to be 295 min and the reason for this long duration is the performing of hepatic resection. During the operation, an average of 1.3 units of erythrocyte suspension transfusion was performed, and these cases were usually hepatic resections.

In the literature, tumor diameter has been reported to be higher for iCCA than other localizations. This has been associated with later onset of symptoms in iCCA. De Oliveira M. L et al. reported that tumor diameters were 2.5 cm in pCCA, 2 cm in dCCA and 5.5 cm in iCCA, in their 564 case cholangiocarcinoma series. The tumor diameter of half of all patients in the series was found to be larger than 2 cm (11). In our series, the mean tumor diameter was 3 cm and the most common tumor pathological stage was II.

DeOliveira, M. L et al., in their 564 case cholangiocarcinoma series, found the overall complication rate as 35%and these complications were superficial wound infection (13.1%), and biliary leak (4.0%). The perioperative mortality rate was 4.0% (14). The postoperative mortality rate is around 10%

in major Western centers, but varies from 2% to 15% in the literature (20,21). Nakeeb A. Pitt et al found that the mean postoperative hospital stay was 20 ± 0.9 days in their 294 case cholangiocellular carcinoma series. They found that the duration of hospitalization in patients with perihilar cholangiocarcinoma was significantly longer than patients with distal or intrahepatic cholangiocarcinoma (22). In our series, the duration of hospitalization was found to be 17 days and this was thought to be caused by postoperative complications. Three patients developed wound infection and one patient developed a biliary leak. Two patients were re-operated due to wound problem and anastomotic leakage. One third of our patients re-admitted to the hospital within 90 days. The most common reason for re-admission was general condition disorder and decreased oral intake. Two patients developed postoperative mortality due to pulmonary and cardiac causes.

Survival in cholangiocarcinoma depends on many prognostic factors. Prognostic factors of the tumor are local spread of the tumor, tumor differentiation, lymphovascular or perineural invasion, and lymph node involvement. In addition, factors such as whether the operation is performed by hepatobiliary surgeons and whether radical (R0) resection is performed are also effective in survival (10).

Survival in cholangiocellular carcinoma depends on tumor localization (11). In the literature, the average survival duration was found to be 15 months, in a large series of cholangiocellular carcinomas in the 2000s. This period was 14 months for pCCA, 18 months for dCCA, and 25 months for iCCA (11). Although a standard adjuvant treatment for locally advanced cholangiocarcinoma has not yet been defined, improvements in oncology and transplantation have led to an increase in survival (10,16). The 3-year and 5-year survival rates reported after resection for pCCA are around 45% and 30-40%, respectively (9,23,24). The 5-year survival rate for iCCA has been reported to be 30% and the average survival time as 30 months (25). dCCA, on the other hand, has a similar survival duration to pancreatic head cancers(10).

In our series, the mean survival was 22 months. Three patients had local recurrence and two had liver recurrence. Two patients had peritoneal carcinomatosis. During follow-up, 75.8% of the patients died due to tumor and tumor related causes.

The limitations of the present study were its retrospective design, relatively small sample size, and therefore its inability to compare various parameters between groups. The low number of cases was due to the late presentation of the cases and exclusion of inoperable cases from the study.

CONCLUSION

In conclusion, cholangiocarcinoma is a rare tumor that continues to present difficulties in diagnosis and treatment. Careful preoperative planning, potential biliary drainage, and extended surgery should be performed to ensure a negative margin in patients with potentially resectable tumors. Patient selection and proper surgical management are essential for long-term survival.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: Approval numbered 2019/93-4 was obtained from the Ethics Committee of Çukurova University Faculty of Medicine.

REFERENCES

1. Olnes MJ, Erlich R. A reviewandupdate on cholangiocarcinoma.Oncology 2004;66:167-79
2. Razumilava N, Gores GJ. Cholangiocarcinoma. The Lancet 2014;3832168-79.
3. Lewis HL, Rahnemai-Azar AA, Dillhoff M, et al. Current management of perihilar cholangiocarcinoma and future perspectives. Chirurgia 2017;112:193-207.
4. Khan SA, Thomas HC, Davidson B R, et al. Cholangiocarcinoma. The Lancet 2005;366:1303-14.
5. Bergquist A, vonSeth E. Epidemiology of cholangiocarcinoma. Best Pract Res Clin Gastroenterol 2015;29:221-32.
6. Hidalgo E, Asthana S, Nishio H, et al. Surgeryforhilarcholangiocarcinoma: the Leeds experience. Eur J Surg Oncol 2008;34:787-94.
7. Silva MA, Tekin K, Aytekin F, et al Surgery for hilar cholangiocarcinoma; a 10 year experience of a tertiary referral centre in the UK. Eur J Surg Oncol 2005;31:533-9.
8. Neumann UP, Schmeding M. Role of surgeryin cholangiocarcinoma: from resection to transplantation. Best Pract Res Clin Gastroenterol 2015;29:295-308.
9. Lee SG, Song GW, Hwang S, et al. Surgical treatment of hilar cholangiocarcinoma in the new era: the Asan experience. J Hepatobiliary Pancreat Sci 2010;17: 476-89.
10. Cillo U, Fondevila C, Donadon M, et al. Surgery for cholangio carcinoma. Liver Int 2019;39:143-55.
11. DeOliveira ML, Cunningham SC, Cameron JL,et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. Ann Surg 2007;245:755-62.
12. Ahrendt SA, Pitt HA. Biliary tract. In: Townsend C, editor.Sabiston Textbook of Surgery. Philadelphia: W.B. Saunders Company 2001:1076-11.
13. Everhart JE, Ruhl CE. Burden of digestive diseases in the UnitedStates Part III: Liver, biliary tract, and pancreas. Gastroenterology 2009;136:1134-44.
14. Anderson CD, Pinson CW, Berlin J, et al. Diagnosis and treatment of cholangiocarcinoma. The oncologist 2004;9:43-57.
15. 1RARECARE project, Surveillance of Rare Cancers in Europe. Incidence (1995–2002)in Europe by sex, age, and EU region with expected new case in EU (27) in 2008 Available at: http://dcnapp4. dcn.ed.ac.uk/

rcnet/searchpage.aspx.
16. Squadroni M, Tondulli L, Gatta G, et al. Cholangiocarcinoma. Crit Rev Oncol Hematol 2017;116:11-31.
17. Kimmings AN, van Deventer SJ, Obertop H, et al. Inflammatory and immunologic effects of obstructive jaundice: pathogenesis and treatment. J Am Coll Surg 1995;181:567-81.
18. Hu QL, Liu JB, Ellis RJ, et al Association of preoperative biliary drainage technique with postoperative outcomes among patients with resectable hepatobiliary malignancy. HPB 2019.
19. Rizvi S, Khan SA, Hallemeier CL, et al. Cholangiocarcinoma—evolving concepts and therapeutic strategies. Nat Rev Clin Oncol 2018;15:95-111.
20. Farges O, RegimbeauJm, Fuks D, et al. Multicentre European study of preoperative biliary drainage for hilar cholangiocarcinoma. Br J Surg 2013;100:274-83.
21. Nuzzo G, Giuliante F, Ardito F, et al. Improvement in perioperative and long-term outcome after surgical treatment of hilar cholangiocarcinoma results of an Italian multicenter analysis of 440 patients. Arch Surg 2012;147:26-34.
22. Nakeeb A, Pitt HA, Sohn TA, et al. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg 1996;224:463-75.
23. Nagino M, Ebata T, Yokoyama Y, et al. Evolution of surgical treatment for perihilar cholangiocarcinoma: A single center 34-year review of 574 consecutive resections. Ann Surg 2013;258:129-40.
24. Bhardwaj N, Garcea G, Dennison AR, et al. The surgical management of klatskin tumours: has anything changed in the lastdecade? World J Surg 2015;39:2748-56.
25. Groot Koerkamp B, Fong Y. Outcomes in biliary malignancy. J SurgOncol 2014;110:585-91.