Impact of preoperative endoscopic ultrasound-guided fine needle aspiration on postoperative recurrence and survival in cholangiocarcinoma patients

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Background and study aim: Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is frequently performed for suspected biliary tumors for diagnosis and staging but carries a theoretical risk of needle-track seeding. We aimed to evaluate the impact of preoperative EUS-FNA on long-term outcomes for patients with cholangiocarcinoma (CCA).

Patients and methods: In a retrospective single-center study of consecutive patients with CCA with preoperative EUS-FNA, main outcome measures were overall survival and progression-free survival.

Results: In 150 patients with confirmed CCA, 61 underwent preoperative FNA. Median overall survival was 18.5 months (95 % confidence limits [CL] 15.4, 25.7): 111 patients died and 39 survived. Of the 150 patients, 119 underwent curative-intent surgical resection, with median progression-free survival of 17.8 months (95 %CL 14.5, 22.8); 89/119 patients had tumor recurrence or died, and 30/119 remained alive and disease-free. On multivariable analysis, overall survival was associated with: undergoing curative-intent surgery (hazard ratio [HR] 5.79, $P=0.001$), lack of lymph node involvement (HR 1.89, $P=0.011$), younger age (HR 1.51 for every 10 years, $P<0.0015$), and small tumor size (HR 1.11 for every 1 cm, $P=0.029$). For patients undergoing curative-intent surgery, on multivariable analysis, improved progression-free survival was associated with: lack of lymph node involvement (HR 1.88, $P=0.010$), smaller tumor size (HR 1.16 for every 1 cm smaller, $P=0.003$), and younger age (HR 1.53 for every 10 years, $P<0.001$). Number of needle passes showed no statistically significant impact on overall survival.

Conclusion: Preoperative EUS-FNA in patients with CCA does not appear to adversely affect overall or progression-free survival.

Introduction

Cholangiocarcinoma (CCA) results from malignant transformation of biliary epithelium and may occur anywhere along the biliary tract. Anatomically, CCA can be classified into intrahepatic and extrahepatic tumors. Extrahepatic tumors are further categorized as perihilar and distal CCA [1]. The incidence of CCA is estimated at 1 – 2 cases per 100 000/year and has increased (particularly for the intrahepatic type) over the past two decades [2 – 8]. In untreated patients, the median survival is approximately 5 – 8 months [9]. Among eligible patients, curative intent via surgical resection remains the only substantive treatment and improves median survival by 15 – 40 months [10, 11].

Accurate preoperative evaluation is aimed at distinguishing CCA from metastatic cancer or benign diseases and at assessing surgical resectability. Endoscopic ultrasound (EUS) and EUS-guided fine needle aspiration (EUS-FNA) are accurate tools for the diagnosis and staging of CCA [12 – 20]. Nevertheless, some experts have discouraged the use of FNA in patients with CCA because of possible tumor seeding along the needle track [21 – 27]. The aim of this study is to investigate the impact of preoperative EUS-FNA on the overall survival and progression-free survival in patients with CCA who underwent curative-intent surgery.

Methods

Study population

This is a retrospective, single-center study that was approved by the Institutional Review Board at Indiana University Health Medical Center.

Two databases were utilized to identify a potential study population. First, prospectively maintained cytology and EUS electronic databases

were searched between May 2003 and December 2009 for patients with CCA who underwent EUS-FNA as part of the initial diagnostic and/or staging workup. Second, a surgical database was examined to identify a control group of patients who had either no preoperative EUS or preoperative EUS without FNA. Patients were included if they had either histopathologic confirmation of CCA from surgical resection, or cytologic confirmation of CCA from FNA of biliary mass or stricture with a clinical picture consistent with this diagnosis for patients with unresectable disease. Patients with any other primary malignancy at the time of CCA diagnosis or with insufficient endoscopic, surgical, or pathologic data in our medical records were excluded.

EUS-FNA was performed using a curvilinear array echoendoscope (GF-UC140P; Olympus America, Center Valley, Pennsylvania, USA) with a 22- or 25-gauge needle (EchoTip Ultra; Cook Medical, Bloomington, Indiana, USA) attached to suction in at least one pass. All tumors were accessed from the first or second part of the duodenum. Nine surgeons and six endosonographers performed surgical resections and EUS, respectively. The number of passes performed and choice of needle size were left to the discretion of the endosonographer.

Data collection

A comprehensive review of computerized medical records was conducted and data were recorded according to the variables in **Table 1.** The time of CCA diagnosis was defined as the date of first identification of a bile duct stricture or mass. Primary tumor location and extent within the bile duct were determined using data from EUS, endoscopic retrograde cholangiopancreatography (ERCP), abdominal imaging (computed tomography [CT] or magnetic resonance imaging/magnetic resonance cholangiopancreatography [MRI/MRCP]), and surgical pathology.

On the basis of preoperative assessment, patients underwent either curative-intent surgery if their cancer was resectable or nonoperative palliative treatment when it was deemed unresectable. Unresectability of cancers was determined preoperatively, based on radiographic/EUS findings that were defined as presence of any of the following: distant noncontiguous liver nodules consistent with metastasis, malignant-appearing nonregional lymph nodes, ascites, peritoneal carcinomatosis, or vascular invasion (portal vein, bilateral portal vein branches, or hepatic artery) [12, 28, 29]. Curative-intent surgeries were classified into five categories: pancreatoduodenectomy, left hepatectomy, right hepatectomy, en bloc resection of extrahepatic bile ducts and gallbladder and regional lymphadenectomy with Roux-en-Y hepaticojejunostomy, and orthotopic liver transplantation.

Survival data were stratified by chemotherapy into categories: no chemotherapy, partial adjuvant chemotherapy (when chemotherapy was discontinued prior to completion), complete adjuvant chemotherapy, and neoadjuvant chemotherapy which was used exclusively prior to orthotopic liver transplantation according to the Mayo experience [30].

Tumor staging was based on the pathologic examination of resected specimens when these were available and based on EUS and other imaging studies for those deemed unresectable. Staging was performed according to the classification of the American Joint Committee on Cancer (AJCC) manual (6th edition) [31]. Tumor recurrence was confirmed by cytopathologic confirmation whenever available, or imaging (CT and/or positron emission tomography [PET] scan), done during follow-up or when indicated by evidence of recurrence, either clinical (jaundice, abdominal pain, weight loss) or laboratory (significant elevation of CA19 – 9 from baseline).

Date of death was obtained by querying the Social Security Death Index in March 2011. Patients who died within 30 days of surgery because of postoperative complications were excluded from the survival analysis.

Statistical analysis

Patient and disease characteristics were compared between patients who did and did not undergo FNA, using chi-squared/Fisher's exact test analyses or two-sample t tests, as appropriate.

The Kaplan – Meier method was used to determine median overall survival from date of diagnosis to date of death among all patients and among patients with resectable cancers. Patients who were still alive were censored in March 2011. Similarly, the Kaplan–Meier method was used to determine median progression-free survival from date of diagnosis to either date of recurrence or date of death for patients who underwent curative-intent surgery. Patients without recurrence or who had not died were censored at their last known disease-free date, given that most patients had routine follow up with their oncologist.

Univariate Cox proportional hazards models were used to investigate the association the following variables with overall survival and progression-free survival: gender, tumor location (proximal, distal), T stage (T0 – T2 vs. T3 – T4), N stage (N0 vs. N1 – N2), EUS (yes vs. no), FNA (yes vs. no), chemotherapy (none, partial adjuvant, complete adjuvant), age, and tumor size. Surgical margins (positive vs. negative) were tested for association with overall and progression-free survival in patients with resectable tumors.

Those of the above variables that showed $P < 0.25$ on univariate analysis, and also the variables tumor location and tumor size, were entered into multivariable Cox proportional hazards models. Location and size were always included in the initial multivariable analysis regardless of the univariate P value since they are important factors in determining eligibility for FNA. Backwards elimination was used to determine the final model. The Cox proportional hazards model was used to test for an association between number of needle passes and overall survival in patients with FNA.

A P value of < 0.05 was used for statistical significance. Statistical analyses were done using SAS for Windows 9.3.

Results

Between May 2003 and December 2009, CCA was diagnosed in 176 patients at our institution. A total of 26 patients were excluded from the study for the following reasons: 23 had insufficient data in our medical records, 2 underwent surgery at other institutions, and one had widely metastatic melanoma in addition to CCA. Our study population therefore comprised 150 patients (56.0 % men; mean age 64.3 years, range 29 – 87) including 61 who underwent preoperative EUS-FNA, 10 who underwent preoperative EUS without FNA, and 79 who had neither preoperative EUS nor FNA (**Fig. 1**).

Table 1 summarizes the clinical, operative, and pathologic characteristics of patients, grouped by preoperative EUS-FNA status. All 71 patients in the EUS (with/without FNA) group successfully underwent transpapillary biliary drainage during ERCP prior to surgery. The median number of needle passes performed during FNA to make the diagnosis was 5 (range 1 – 12).

Table 1 Preoperative endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) in patients with cholangiocarcinoma. Patient and disease characteristics for all patients and tumor and treatment characteristics for those who underwent curative-intent surgery Data for all patients and for those who did or did not have FNA. .Data are n (%), except where indicated otherwise.

Variable	All patients (n = 150),				Patients with curative-intent surgery (n = 119).			
	n	FNA (n = 61)	Non-FNA (n = 89)	*P* value	n	FNA (n = 39)	Non-FNA (n = 80)	*P* value
Age at diagnosis, mean (SD), years		67.1 (11.0)	62.5 (13.1)	0.026		66.4 (9.8)	63.1 (12.6)	0.157
Gender				0.698				0.878
Male	84	33 (39 %)	51 (61 %)		69	23 (33 %)	46 (67 %)	
Female	66	28 (42 %)	38 (58 %)		50	16 (32 %)	34 (68 %)	
Chemotherapy				0.341[1]				0.168*
None	74	26 (35 %)	48 (65 %)		62	17 (27 %)	45 (73 %)	
Partial adjuvant	33	11 (33 %)	22 (67 %)		29	8 (28 %)	21(72 %)	
Complete adjuvant	22	12 (55 %)	10 (45 %)		21	11(52 %)	10 (48 %)	
Neoadjuvant	4	1 (25 %)	3 (75 %)		4	1 (25 %)	3 (75 %)	
Missing information	17	11 (65 %)	6 (35 %)		3	2 (67 %)	1 (33 %)	
Tumor location				< 0.001				< 0.001
Intrahepatic	18	0 (0 %)	18 (100 %)		17	0 (0 %)	17 (100 %)	
Hilar	79	21 (27 %)	58 (73 %)		61	10 (16 %)	51 (84 %)	
Distal	53	40 (75 %)	13 (25 %)		41	29 (71 %)	12 (29 %)	
Type of surgery				< 0.001				
Curative-intent	119	39 (33 %)	80 (67 %)					
Palliative	31	22 (71 %)	9 (29 %)					
Surgical margins								0.096
Negative					81	30 (37 %)	51 (63 %)	
Positive					37	8 (22 %)	29 (78 %)	
Missing					1	1 (100 %)	0 (0 %)	
Tumor recurrence								0.708
No					30	9 (30 %)	21 (70 %)	
Yes[2]					89	30 (34 %)	59 (66 %)	
T staging				0.278[3]				0.267[3]
T0	1	0 (0 %)	1 (100 %)		1	0 (0 %)	1 (100 %)	
T1	22	9 (41 %)	13 (59 %)		21	9 (43 %)	12 (57 %)	
T2	32	10 (31 %)	22 (69 %)		31	10 (32 %)	21 (68 %)	
T3	56	15 (27 %)	41 (73 %)		54	15 (28 %)	39 (72 %)	
T4	7	1 (14 %)	6 (86 %)		7	1 (14 %)	6 (86 %)	
Unknown	32	26 (81 %)	6 (19 %)		5	4 (80 %)	1 (20 %)	
N staging				0.633[4]				0.715§
N0	58	18 (31 %)	40 (69 %)		55	18 (33 %)	37 (67 %)	
N1	47	16 (34 %)	31 (66 %)		46	16 (35 %)	30 (65 %)	
N2	1	1 (100 %)	0 (0 %)		1	1 (100 %)	0 (0 %)	
Unknown	44	26 (59 %)	18 (41 %)		17	4 (24 %)	13 (76 %)	

[1] Missing excluded from analysis.
[2] Includes pathologically confirmed recurrence as well as death as endpoint of recurrence.
[3] T0 – T2 vs. T3 – T4.
[4] N0 vs. N1 – N2.

In the study population, 53 patients (35.3 %) had intrapancreatic tumors, 79 (52.7 %) had hilar tumors, and 18 (12.0 %) had intrahepatic tumors. Of these, 119 patients (79.3 %) underwent curative-intent surgical resection and 31 (20.7 %) underwent palliative procedures for unresectable disease.

Of the patients who underwent curative-intent resection, 42 had pancreaticoduodenectomy, 33 had left hepatectomy, 25 had right hepatectomy, 14 had en bloc resection of the extrahepatic bile ducts and gallbladder, and 5 had orthotopic liver transplantation. In this same group of 119, surgical margins were tumor-free in 81 patients (68.1 %), tumor-positive in 37 patients (31.1 %), and not specified in 1 patient (0.8 %). Regarding chemotherapy in the patients who underwent curative-intent surgery (n = 119), this was not given to 62 (52.1 %). Adjuvant chemotherapy was completed in 21 patients (17.6 %), and only partially completed in 29 patients (24.4 %) because of intolerance or major adverse events. Neoadjuvant chemotherapy was given to only 4 patients (3.4 %), none of whom received adjuvant chemotherapy, and chemotherapy status could not be confirmed in 3 patients (2.5 %).

Of the 31 patients who had unresectable disease, 14 underwent surgical biliary bypass, 16 underwent endoscopic biliary stenting and 1 was treated only with palliative chemotherapy.

Overall survival

The median overall survival from date of diagnosis was 18.5 months (95 %CL 15.4, 25.7) for the entire study population. Patients who underwent curative-intent surgery had a median overall survival of 24.5 months (95 %CL 17.3 – 35.1), compared with 12.5 months (95 %CL 6.3 – 17.6) for the palliative group. A total of 111 patients had died and 39 were alive as of March 2011.

Hazard ratios (HRs) for overall survival are shown in **Table 2**. Among patients who underwent FNA, number of needle passes was not significantly associated with overall survival (HR 0.93, *P* = 0.322).

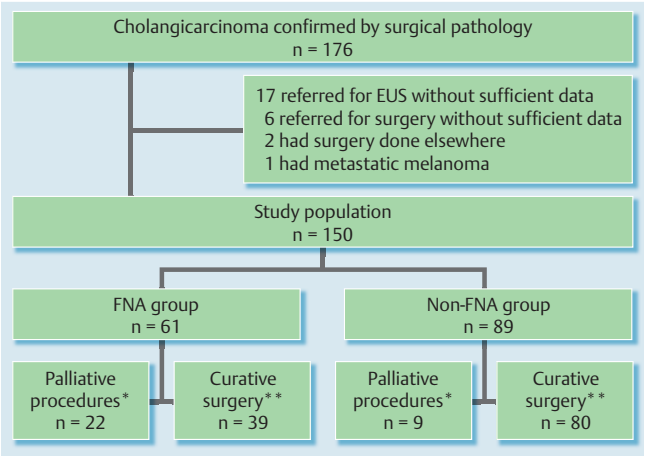

Fig. 1 Impact of preoperative endoscopic ultrasound (EUS)-guided fine needle aspiration (EUS-FNA) in cholangiocarcinoma: patient flow. * Palliative procedures included biliary bypass surgery (n = 14), endoscopic retrograde cholangiopancreatography (ERCP) with biliary stenting (n = 16) and palliative chemotherapy (n = 1). ** Curative surgery included pancreaticoduodenectomy (n = 42), left hepatectomy (n = 33), right hepatectomy (n = 25), en bloc resection of the extrahepatic bile ducts and gall bladder (n = 14), and orthotopic liver transplantation (n = 5).

Recurrence and progression-free survival

There was radiologically and/or pathologically confirmed tumor recurrence in 38 patients: 11 in the EUS-FNA group and 27 in the non-FNA (control) group.

The most common location for recurrence was the liver, in 25 patients, while 2 patients had recurrence in or around the pancreatic resection margin. In the 11 EUS-FNA group patients, the locations were as follows: liver n = 8, thoracic spine n = 1, lungs n = 1, and retroperitoneal mass n = 1.

Recurrence was confirmed on EUS or CT-guided FNA in 22 patients, and in the remaining patients recurrence was determined based on imaging and rising tumor markers.

Regarding the patients with curative-intent surgery (n = 119), the median progression-free survival from the date of diagnosis was 17.8 months (95 %CL 14.5, 22.8), with 89 patients having tumor recurrence or dying and 30 patients alive and remaining disease-free. **Table 3** shows HRs for progression-free survival in this group, by patient and disease characteristics.

Multivariable analysis of survival

Regarding overall survival, on multivariable analysis, patients who underwent curative-intent surgery had significantly longer overall survival compared with the palliative group (HR 5.79, P = 0.001). Lack of lymph node involvement (N0) (HR 1.89, P = 0.011), younger age (HR 1.51 for every 10 years, P < 0.001), and tumor size (HR 1.11 for every 1 cm, P = 0.029) were also significantly associated with longer overall survival in all of the 150 study patients. No other patient or disease characteristics, including preoperative FNA, were significantly associated with overall survival on multivariable analysis (**Fig. 2**). The same three variables of size, lymph node involvement, size, and age remained significantly associated with overall survival in the curative-intent resection group.

Regarding progression-free survival, on multivariable analysis, this was significantly longer in patients with negative lymph node involvement (N0) (HR 1.88, P = 0.010), smaller tumor size (HR 1.16 for every 1 cm, P = 0.003), and younger age (HR 1.53 for every 10 years, P < 0.001). Preoperative FNA status was not found to be significantly associated with progression-free survival (**Fig. 3**).

Discussion

Cholangiocarcinoma is characterized by its difficult diagnosis, aggressive biological behavior, limited treatment options, and poor prognosis. Radical resection remains the only potential cure but must be preceded by a detailed workup including localization of the tumor, pathologic confirmation whenever possible, and assessment of tumor resectability. EUS-FNA is less invasive than

Table 2 Overall survival among all study patients (n = 150) and among those with resectable tumors (n = 119).

	All patients (n = 150)				Patients with curative-intent resection (n = 119)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Hazard ratio (95 %CL)	*P* value	Hazard ratio (95 %CL)	*P* value	Hazard ratio (95 %CL)	*P* value	Hazard ratio (95 %CL	*P* value
Gender (male vs. female)	1.23 (0.84, 1.79)	0.286			1.29 (0.83, 2.00)	0.267		
Location (distal vs. proximal)	1.12 (0.76, 1.65)	0.560			1.06 (0.67, 1.67)	0.806		
T stage (3/4 vs. 0–2)	1.42 (0.92, 2.19)	0.116			1.46 (0.94, 2.29)	0.095		
N stage (N1/N2 vs. N0)	1.34 (0.85, 2.13)	0.210	1.89 (1.15, 3.09)	0.011	1.42 (0.89, 2.29)	0.145	2.14 (1.29, 3.55)	0.003
EUS (yes vs. no)	1.37 (0.94, 2.00)	0.105			1.06 (0.68, 1.66)	0.801		
FNA (yes vs. no)	1.36 (0.93, 1.99)	0.112			1.09 (0.69, 1.73)	0.700		
Chemotherapy								
None vs. partial	1.57 (0.97, 2.54)	0.065			1.57 (0.93, 2.67)	0.094		
None vs. complete	1.54 (0.87, 2.73)	0.138			1.41 (0.77, 2.57)	0.266		
Partial vs. complete	0.98 (0.51, 1.87)	0.953			0.90 (0.45, 1.77)	0.750		
Type of surgery (palliative vs. curative)	2.16 (1.40, 3.32)	< 0.001	5.79 (1.99, 16.79)	0.001				
Surgical margins					1.41 (0.89, 2.21)	0.143		
Age (for every 10 years)	1.26 (1.07, 1.47)	0.005	1.51 (1.22, 1.88)	< 0.001	1.33 (1.09, 1.62)	0.005	1.61 (1.28, 2.01)	< 0.001
Size (for every 1 cm)	1.02 (0.96, 1.09)	0.480	1.11 (1.01, 1.22)	0.029	1.04 (0.97, 1.11)	0.257	1.12 (1.02, 1.23)	0.023

CL, confidence limits; FNA, fine needle aspiration; EUS, endoscopic ultrasound.

Table 3 Progression free survival among cholangiocarcinoma patients with resectable tumors (n = 119).

	Univariate analysis			Multivariate analysis		
	HR	95 %CL	*P* value	HR	95 %CL	*P* value
Gender (male vs. female)	1.20	(0.79, 1.84)	0.399			
Location (distal vs. proximal)	0.92	(0.59, 1.44)	0.719			
T stage (3 /4 vs. 0 – 2)	1.56	(1.01, 2.41)	0.043			
N stage (N1 /N2 vs. N0)	1.32	(0.84, 2.07)	0.231	1.88	(1.17, 3.04)	0.010
EUS (yes vs. no)	0.91	(0.59, 1.41)	0.675			
FNA (yes vs. no)	0.98	(0.63, 1.53)	0.944			
Chemotherapy						
None vs. partial	1.36	(0.83, 2.23)	0.223			
None vs. complete	1.55	(0.87, 2.78)	0.139			
Partial vs. complete	1.14	(0.60, 2.18)	0.687			
Surgical margins	1.96	(1.25, 3.05)	0.003			
Age (for every 10 years)	1.35	(1.11, 1.64)	0.003	1.53	(1.23, 1.90)	< 0.001
Size (for every 1 cm)	1.04	(0.97, 1.11)	0.257	1.16	(1.05, 1.28)	0.003

HR, hazard ratio; FNA, fine needle aspiration; EUS, endoscopic ultrasound.

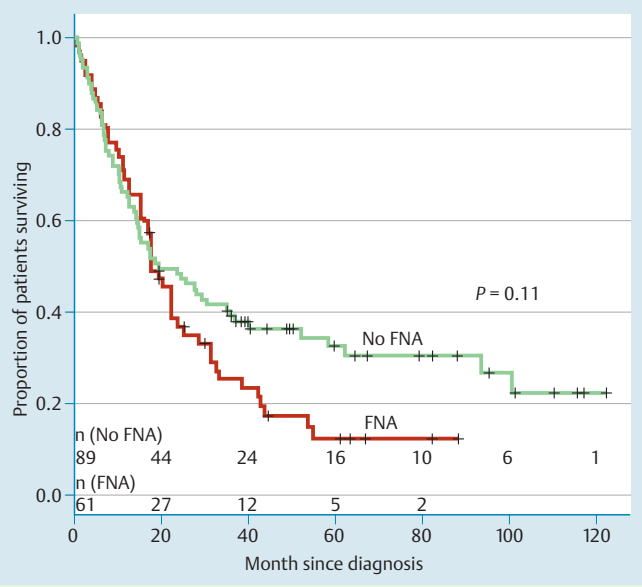

Fig. 2 Disease-specific overall survival in cholangiocarcinoma patients with preoperative endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) vs. no FNA: Kaplan–Meier curve.

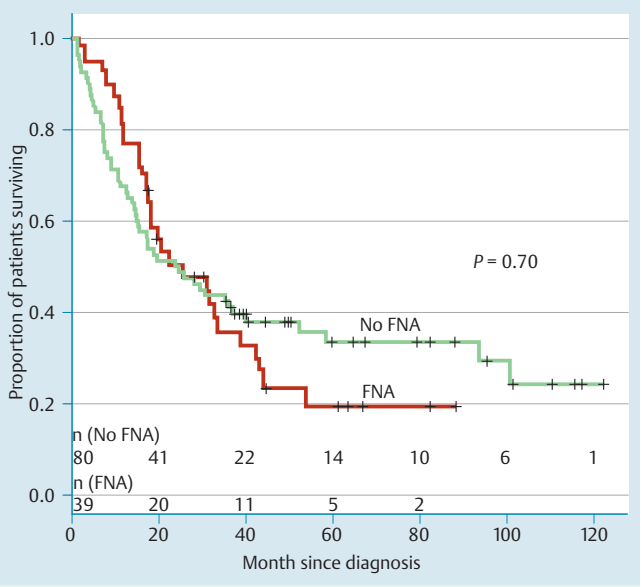

Fig. 3 Progression-free survival (progression-free survival) in cholangiocarcinoma patients with preoperative endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) vs. no FNA: Kaplan–Meier curve.

other sampling techniques yet appears more accurate compared with other modalities [12, 14, 18]. Real-time visualization of the lesion, and the close proximity to the lesion makes EUS well-suited for the diagnosis and staging of CCA. Nevertheless, performance of FNA for tissue diagnosis in patients with potentially resectable tumors has been discouraged because of the risk of needle-track seeding [21 – 23, 25, 26, 32 – 38]. Microscopic tumor cell dissemination along the needle track of percutaneous FNA has been reported to have a frequency as high as 75 % in some older reports [31, 38 – 41], while the incidence of clinically significant tumor seeding and growth is estimated to be below 0.009 % in radiological literature [38]. However, the literature lacks large-scale studies definitely linking needle-track seeding during EUS-FNA to early postoperative recurrence [39].

Our study is one of the largest reported CCA cohorts and the first to investigate the impact of EUS-FNA on overall survival and progression-free survival in patients who mostly underwent a curative-intent surgical resection. We found that performance of preoperative EUS-FNA did not impact overall survival or progression-free survival in the FNA group compared with those without FNA (the control population). We also showed that a higher number of needle passes, theoretically increasing the risk for tumor dissemination [32], was not associated with decreased overall survival. We hypothesize that microscopic tumor implantation from EUS-FNA takes a long time to develop into a clinically detectable disease which is of limited importance in an aggressive cancer characterized by limited survival. Moreover, we demonstrated that patients who underwent EUS-FNA without chemotherapy had comparable progression-free survival and overall survival to those who did receive chemotherapy of any type. This observation again supports the hypothesis that tumor dissemination not subsequently eradicated by chemotherapy is likely not clinically significant and does not affect survival. Survival and postoperative recurrence in patients with hilar CCA were evaluated in our study since the FNA track is not typically removed surgically as in patients with distal CCA. Our study demonstrates no

survival difference between those groups. This outcome could be related to multiple factors including the small size of needles used, limited number of passes, and shorter needle track compared with the percutaneous approach [24]. In our literature search, we came across only three reported cases of tumor seeding and secondary implantation possibly associated with EUS-FNA, showing the scarcity of such a complication [22,25,26]. Our results are in agreement with other recent studies evaluating the impact of EUS-FNA on patient outcomes. In a study from our institution [39], preoperative EUS-FNA was performed on 230 patients including 63 patients with pancreas cancer who subsequently underwent distal pancreatectomy. No differences in overall or recurrence-free survival were noted between cancer patients in the EUS groups, and patterns of tumor recurrence were not associated with EUS-FNA. In another study by Ikezawa et al. [40], EUS-FNA was not found to be associated with the development of peritoneal carcinomatosis on imaging and/or cytology on follow-up.

We found that younger patients and those undergoing curative-intent surgery have a significantly better overall survival. An improved survival in the younger population could reflect the ability to apply aggressive resection protocols in younger patients with fewer co-morbidities. The improved survival seen with curative-intent surgery could be explained by earlier disease stages based on preoperative assessments. Interestingly, the extent of lymph node involvement (N stage) but not tumor invasion (T stage) significantly correlated with overall survival and progression-free survival. This could be a reflection of the limited prognostic power of the T-staging system adopted by the AJCC. This is partly because of the vague definition of histologic boundaries of the extrahepatic bile ducts that was endorsed by the AJCC when distinguishing between T1 and T2 stages [41,42]. Hong et al. [43] and, more recently, de Jong et al. [44] showed that the depth of tumor invasion (which is not accounted for by the AJCC) is a better tool than T staging to determine prognosis. Also, the AJCC system blends proximal and distal extrahepatic CCA into one T-stage scheme disregarding the fact that there is a strong biologic heterogeneity between the two tumor sites [39, 40,45,46]. In fact recent literature has shown no significant difference in survival among different T subgroups in all CCA types staged according to the classification in the AJCC 6th edition manual [43,44]. Despite the update of the CCA staging system in the new AJCC 7th edition, a similar approach continues to be adopted for T staging [44,47].

Previous literature has suggested that surgical resection with an attempt to achieve tumor-free margins whenever possible improves survival in CCA [11,48–52]. In the population that we studied, negative surgical margins were significantly associated with longer progression-free survival but not with overall survival. This is could be related to the several co-morbidities in such a fragile population that ultimately impacted the overall survival and that we could not take into account in our retrospective study. Nevertheless, the improved progression-free survival in patients with negative surgical margins justifies the effort to obtain negative margins during curative surgeries.

Very few studies compared prognosis of CCA according to anatomic locations within an homogeneous population and their results were conflicting. Older studies showed a worse prognosis with proximal and intrahepatic lesions [53,54], while more recent ones showed no significant survival difference [55–57]. This trend is likely accounted for by the evolution of surgical techniques by which full resection of proximal lesions became more feasible [55]. Our results are in agreement with recent studies showing by multivariate analysis that tumor location does not affect overall survival or progression-free survival in the curative and/or the palliative group. This is another piece of evidence that tumor location is not a major independent factor in CCA staging, and that a very complicated interaction of multiple biologic factors is what dictates the prognosis of CCA.

We acknowledge several limitations in our study arising from its retrospective design. Referral bias could be present since the study was conducted in a single tertiary center with a wide referral basis, often treating patients with several co-morbidities and advanced disease stage. Because of the retrospective nature of the study, it was difficult to obtain data on co-morbidities or performance status and this was not taken into account in the analysis. Another limitation relates to the under-representation of patients with intrahepatic CCA who underwent FNA. This is the result of the technical difficulty in visualizing and sampling such lesions during EUS. On the other hand, that EUS-FNA was performed mostly in distal lesions in our population adds to the accuracy of our results since the sensitivity and specificity of visualization and sampling are highest with distal lesions [12]. Also, the radiological and clinical expertise available at our referral center may not be available in the community, potentially limiting the generalizability of our results. We have tried to compensate for the above deficiencies by investigating a relatively large homogeneous cohort of patients and controls who were followed regularly at one center with consistent care by surgeons, oncologists and gastroenterologists.

In summary, while tumor cell dissemination likely occurs along the needle track during EUS-FNA, its clinical significance is probably small. We have shown that preoperative EUS-FNA has no impact on the overall survival and progression-free survival. Thus the incorporation of EUS-FNA for preoperative diagnosis and staging of CCA appears to be safe. However, until further prospective larger studies become available, endosonographers should continue to be conservative by using smaller size needles, minimizing the number of passes, and utilizing on-site cytology interpretation whenever possible.

Competing interests: None

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