Endoscopic Ultrasound in Resectable Perihilar Cholangiocarcinoma patients: Impact on Clinical Decision Making

David M de Jong, Sanne van de Vondervoort, Roy S Dwarkasing, Michael Doukas, Rogier P Voermans, Robert C Verdonk, Wojciech G Polak, Jeroen de Jonge, Bas Groot Koerkamp, Marco Bruno, Lydi Van Driel.

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Abstract:

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Accurate assessment of the lymph node (LN) status is crucial in resectable perihilar cholangiocarcinoma (pCCA) to prevent major surgery in patients with extraregional metastatic LN (MLN). This study investigates the added value of preoperative Endoscopic Ultrasound (EUS) with or without Tissue Acquisition (TA) for the detection of MLN in patients with resectable pCCA.

Methods
In this retrospective, multicenter cohort study, patients with potentially resectable pCCA who underwent EUS preoperatively between 2010-2020, were included. The clinical impact of EUS-TA was defined as the percentage of patients who did not undergo surgical resection due to MLN found with EUS-TA. Findings of cross-sectional imaging were compared with EUS-TA findings and surgery.

Results
EUS was performed in 141 patients, of whom 107 (76%) had suspicious LN on cross-sectional imaging. Surgical exploration was prevented in 20 (14%) patients because EUS-TA detected MLN, of which 17 (85%) were extraregional. Finally, 74 (52%) patients underwent surgical exploration followed by complete resection in 40 (28%). MLN were identified at definitive pathology in 24 (33%) patients, of which 9 (38%) were extraregional and 15 (63%) regional.

Discussion
EUS-TA has the promise to be of value in patients with potentially resectable pCCA based on preoperative cross-sectional imaging, regardless of lymphadenopathy at cross-sectional imaging. A prospective study in which a comprehensive EUS investigation with LN assessment and EUS-TA of LN is performed routinely should confirm this promise.

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Key words: Perihilar cholangiocarcinoma, Endoscopic Ultrasound, Lymph node biopsy, Fine-Needle Aspiration, Fine-Needle Biopsy, Tissue Acquisition
List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
</tr>
<tr>
<td>ASA</td>
<td>American Society of Anaesthesiologists (Physical Status Classification System)</td>
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<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<td>ERCP</td>
<td>Endoscopic Retrograde Cholangio-Pancreatography</td>
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<td>EUS</td>
<td>Endoscopic ultrasound</td>
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<td>EUS-TA</td>
<td>EUS with tissue acquisition of the LN through FNA or FNB</td>
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<tr>
<td>FNA</td>
<td>Fine-Needle Aspiration</td>
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<td>FNB</td>
<td>Fine-Needle Biopsy</td>
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<tr>
<td>IQR</td>
<td>Inter Quartile Range</td>
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<td>LN</td>
<td>Lymph node</td>
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<tr>
<td>MLN</td>
<td>Metastatic Lymph Node</td>
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<tr>
<td>MRCP</td>
<td>Magnetic Resonance Cholangio-Pancreatography</td>
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<td>Magnetic resonance imaging</td>
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<td>pCCA</td>
<td>Perihilar cholangiocarcinoma</td>
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<td>PSC</td>
<td>Primary Sclerosing Cholangitis</td>
</tr>
<tr>
<td>PTCD</td>
<td>Percutaneous Transhepatic Cholangiography Drainage</td>
</tr>
<tr>
<td>TA</td>
<td>Tissue Acquisition</td>
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<tr>
<td>WHO</td>
<td>World Health Organisation (Performance Status)</td>
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</table>
1 Introduction

2 Perihilar cholangiocarcinoma (pCCA) is a rare malignancy originating from the second-degree bile ducts up to the insertion of the cystic duct [1]. Survival of all pCCA patients is dismal, with diagnoses often in an advanced stage. The resectability of pCCA depends on biliary tumor extension and vascular involvement. Prognosis however mainly depends on the presence of regional metastatic lymph nodes (MLN) and distant metastases [2, 3].

3 MLN are present in about half of the patients at presentation and associated with poor survival [2-4]. In patients with extraregional MLN, the limited oncological advantage of surgery may not outweigh the substantial surgical risks [4-6]. Therefore, accurate preoperative lymph node (LN) assessment, according to The American Joint Committee on Cancer (AJCC) staging system, is crucial [7-9]. In current practice, Computed Tomography (CT) is recommended to identify MLN and in some guidelines also Magnetic Resonance Imaging (MRI) [10, 11]. Accurate identification of MLN preoperatively on both CT and MRI is challenging since sensitivity and specificity is 61% and 88% respectively for CT and 64% and 68% respectively for MRI [12, 13]. More accurate detection of MLN preoperatively saves more patients from unnecessary invasive surgical treatments.

4 To improve LN staging, Endoscopic Ultrasound with Tissue Acquisition (EUS-TA) of the LN through Fine-Needle Aspiration (FNA) or Fine-Needle Biopsy (FNB) may show benefit [14]. In a study of 47 pCCA patients screened for liver transplantation as curative treatment option, EUS-FNA identified malignant LN in eight (17%) patients, of which only two patients had suspicious LN on cross sectional imaging [15]. On the other hand, a study from the USA showed that CT was more often able to detect malignant LN (4/22 patients, 18%) compared to EUS-FNA (2/23 patients, 9%) [16]. In patients with positive extraregional LN, surgical exploration is almost always precluded. But in patients with only regional MLN, surgery is still an option and only in selected cases is surgery precluded.
In conclusion, data is scarce and inconsistent about the added value and impact of EUS-TA for clinical decision making in the setting of pCCA [14-16]. Therefore, the aim of this study is determine the yield of EUS-TA and the subsequent change in clinical management.
Method

Study population

A retrospective, multi-center cohort study was performed at three Dutch tertiary referral centers for pancreato-biliary diseases. All consecutive patients with potentially resectable pCCA, who underwent EUS preoperatively (with or without EUS-TA) and who were discussed at a multidisciplinary meeting between January 2010 and June 2020, were eligible for inclusion. EUS was not part of the Dutch preoperative surgical work-up guidelines, but at the discretion of the local management team. Exclusion criteria were surgically treated pCCA or unresectable pCCA at time of diagnosis. This study was conducted according to the guidelines in the Helsinki Declaration and IRB approval was obtained in participating centers.

Regional and extraregional LN locations

Regional LN consisted of LN at the liver hilum, cystic duct, common bile duct, hepatic artery and portal vein. Extraregional LN consisted of LN at the peri-aortic region, peri-caval region, superior mesenteric artery and celiac trunk. LN that were not covered by these locations were noted separately and were interpreted as extraregional when located distal to the hepatoduodenal ligament, as described by the EUS. The most important difference between the 7th and the newer 8th edition AJCC staging system is the location of the regional (N1) versus extraregional LN (N2) in the 7th edition, while in the 8th edition extraregional LN locations are considered M1 metastases and the number of MLN determines the N stage (Table 1) [7-9].

EUS procedure and work-up for surgery

EUS procedures were performed using a linear ultrasound endoscope (Olympus GF-UCT-160 or GF-UCT-180 and Pentax EG-3870 UTK, EG-3270 UK or EG38-J10 UT). For FNA and FNB 19-, 20-, 22- or 25-gauge needles were used (Cook Medical). The indication for EUS was categorized in:
assessment of suspicious bile duct mass, LN assessment due to suspicious LN on cross-sectional imaging (e.g., necrotic center and/or short-axis >10 mm), liver transplantation screening, and resectability assessment (e.g., ductal extension). Comprehensive LN assessment and EUS-TA of LN were not an integral part of the procedure. Both LN assessment due to (a specific) suspicious LN on cross-sectional imaging and liver transplantation screening were considered as EUS indications specific for LN assessment. LN were defined as suspicious on EUS based on appearance (short axis diameter >5mm, hypoechoic, round shape and clear margins) according to the opinion of the endosonographer. TA was performed in a low threshold manner, but whenever multiple suspicious LN were identified in a single patient in one EUS procedure, the endosonographer could decide to perform EUS-TA in one or a subset of these LN. Whenever a specific LN was suspicious on cross-sectional imaging, this was often targeted with EUS-TA. Rapid on-site evaluation was not routinely performed. After EUS, patients were re-discussed at multidisciplinary team meetings. For patients with regional MLN surgery could be precluded whenever the patient also had significant comorbidities, negatively affecting post-surgical outcomes. For patients with extraregional MLN surgery is almost always precluded, excluding young patients without comorbidities. Pathology results of the LN were categorized by the pathologist into malignant, suspicious for malignancy, no-malignancy and non-diagnostic. LN were considered as positive for malignancy if EUS-TA results were rated as suspicious for malignancy or malignant. Both regional and extraregional LNs removed during surgery were evaluated by the pathologist.

Outcomes

The primary outcome of this study was the yield of EUS-TA and subsequent change in clinical management, as defined as the number of patients in whom surgery was withheld because of MLN found by EUS-TA.

The secondary outcome was the accuracy of cross-sectional imaging, defined as the number of patients that had confirmed MLN by EUS-TA or surgery, for patients with and without suspicious LN on cross-sectional imaging. Actual accuracy of cross-sectional imaging could not be determined, since LN
status after surgery cannot be considered the gold standard. This is because not all patients undergo surgery, and during surgery in pCCA patients very few extraregional LN are usually assessed and removed.

Data collection

Data was collected on patient demographics, cross-sectional imaging, EUS, surgery and clinical outcomes. On cross-sectional imaging, LN were defined as suspicious based on location, heterogeneity and size criteria according to the objective assessment of reporting radiologists. LN identified at surgical procedures were collected, at staging laparoscopy, explorative laparotomy, and surgical resection.

Statistical analysis

The statistical analysis contained descriptive statistics using medians (with interquartile ranges (IQR)) for continuous not normally distributed variables and using frequencies and proportions for categorical and dichotomous variables. Categorical and dichotomous variables were analyzed using the Chi-square test. The Fisher exact test was used if any categories have a frequency of <5. Subgroup analysis was performed for two patient groups: with or without an EUS with LN assessment as indication. A two-sided p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics version 25.
Results

Baseline characteristics of the patient population

In total, 141 patients were included with potentially resectable pCCA who underwent EUS preoperatively. Table 2 highlights the baseline characteristics of the study population.

EUS characteristics

A total of 169 EUS procedures were performed in these 141 patients (Table 3). In 77/141 (55%) patients, at least one EUS with LN assessment was performed. Across 96/141 (68%) patients, a total of 161 LN locations were described as shown in Table 4. EUS-TA was successfully performed in 67/96 (70%) patients across a total of 88/161 (55%) LN. In suspicious LN identified with EUS, EUS-TA was successfully performed in 81/130 (62%) LN and not successful in 9 (7%) LN due to scope position, intermediary tissue or patient unrest. In non-suspicious LN, EUS-TA was successfully performed in 7/31 (23%) LN. Of these 88 biopsied LN, 23 (26%) were classified as malignant, 53 (60%) as non-malignant, 11 (13%) as non-diagnostic, and one (1%) was missing. FNA was performed in 75/88 (85%), confirming malignancy in 20/75 (27%), FNB in 12/88 (14%) with confirmed malignancy in 3/12 (25%) and both techniques in one (1%) LN showing no malignancy. Cholangitis prior to EUS was not associated with a lower yield (2/8 (25%) vs 21/161 (13%), p=0.3).

Impact of EUS-TA on clinical decision making

In the 141 patients, there were 65 (46%) in whom ≥1 extraregional LN was described at EUS, 31 (22%) in whom only regional LN were described and 45 (32%) in whom no LN were described. In 27/65 (42%) patients in whom ≥1 extraregional LN was described, at the same time ≥1 regional LN
was also described. EUS-TA was performed in 61/97 (63%) extraregional LN, showing malignancy in
18/61 (30%). Regarding regional LN, EUS-TA was performed in in 27/64 (42%) regional LN, showing
malignancy in 5/27 (19%). In two patients EUS-TA proved malignancy in multiple LN. Surgical
exploration was precluded due to positive EUS-TA in 20 (14%) patients; due to extraregional MLN in
17 patients and due to regional MLN in three patients. PSC diagnosis was not associated with a higher
preclusion rate (1/27 (4%) vs 19/114 (17%), p=0.1).

After EUS, six (4%) patients were treated in another hospital and were recorded as loss to follow-up
and 41 (29%) were precluded from surgery due to other reasons (Figure 1). In the remaining patients
the probable diagnosis of resectable pCCA prevailed for which radical resection was the only curative
treatment option. Two patients proceeded to surgical exploration, despite extraregional MLN at EUS-
TA in one and regional MLN at EUS-TA in the other. Finally, explorative surgery was performed in 74
(52%) patients, with complete resection in 40 (28%) patients. In 34 (24%) patients only explorative
surgery was performed, due to regional or extraregional MLN in 13 (38%), advanced or metastatic
disease in 13 (38%) and other reasons in 8 (24%). The median period from last EUS to first surgical
procedure in 74 patients was 49 days [IQR:31–76]. One patient died during explorative laparotomy
and one patient had a missing pathology report. In 24/72 (33%) patients without preoperative
confirmation of MLN by EUS-TA, MLN were identified during explorative surgery or in surgical
resection specimens. These were only regional in 15 (63%) and at least ≥1 extraregional MLN were
described in 9 (38%) patients. These extraregional LN were located at the celiac trunk in three (33%),
peri-aortic region in two (22%), around pancreatic tail and body in two (22%), periduodenal in one
(11%) and the aorta-caval region in one (11%). In the patients undergoing complete resection without
preoperative EUS-TA proven MLN, benign disease was identified in surgical specimens in eleven
(30%) patients.

Differences between the two indication groups

Comparing the clinical impact between the group in which at least one EUS was performed for LN
assessment specifically and the group in which EUS was performed for other reasons, a higher clinical
impact was found for the former (15/77 (20%) vs 5/64 (12%), p=0.048). There was no difference regarding identification of MLN at surgery in these two groups (14/36 (39%) vs 10/34 (29%), p=0.4).

Comparison with cross-sectional imaging

In the entire group of 141 patients, cross-sectional imaging showed suspicious LN in 107 (76%) patients and no suspicious LN in 34 (24%) patients (Figure 2). In these 34 patients, EUS-TA was performed in six patients; five extraregional LN and in one regional LN. Malignancy was identified in 2/34 (6%) patients, both in extraregional LN. In 16 (47%) patients surgery was performed, of whom four (25%) patients had MLN identified. Of these four patients, two had extraregional MLN at the celiac trunk and aorta-caval region respectively, both identified at explorative surgery. Benign disease was confirmed in four (12%) patients in surgical specimens.

In the 107 patients with suspicious LN at cross-sectional imaging, EUS-TA was performed in 61 (57%) patients; 37 extraregional LN, 20 regional LN and in four patients both. Malignancy was identified by EUS-TA in 20/107 (19%) patients, of which 16 (80%) were extraregional. In 54 (51%) patients surgery was performed without preoperative confirmation of MLN, of whom 20 (37%) patients had MLN identified. In eight (40%) patients these were extraregional LN. The yield of EUS-TA was similar for patients with and without suspicious LN on cross-sectional imaging (19% vs 6%, p=0.1). In the patients undergoing surgery, MLN were identified in both groups (37% vs 25%, p=0.37). Benign disease was confirmed in seven (7%) patients.
Discussion

In this multicenter cohort study, we demonstrated that in 14% of patients eligible for surgery with presumed resectable pCCA undergoing EUS, MLN were identified by EUS-TA that prevented surgery. This was primarily influenced by already suspicious LN identified on cross-sectional imaging investigations. Unfortunately, we were unable to confirm nodal status in patients not undergoing any form of surgery, limiting the interpretation on the missed LN with EUS. The accuracy of cross-sectional imaging pertaining LN involvement was limited, as only in 37% of the patients that had suspicious LN on cross-sectional imaging, MLN were confirmed by EUS-TA or surgery. Whenever cross-sectional imaging detected no suspicious LN, EUS-TA still affected clinical decision making in 6% of the patients.

The primary aim of our study was to assess the influence of EUS on clinical decision making in patients with presumed resectable pCCA. We found that in 14% of the patients, surgery was precluded due to positive EUS-TA. As expected, EUS performed to assess LN yielded more MLN than for other EUS-indications (20% vs 12%, \( p = 0.048 \)). Two retrospective studies from the Mayo Clinic reported similar findings [14, 15]. In the study by Gleeson et al., 47 liver transplantation candidates underwent EUS-TA of all identified LN [15]. FNA of 70 LN identified MLN in 9 LN in 8 patients (17%), precluding all of them from transplantation. Similarly, in the more recent study by Malikowski et al., 20 of the 124 (16%) patients with pCCA had MLN precluding them from surgery [14]. This differed from our clinical practice, as for most patients with only regional MLN we find resection a feasible option. Also, we did not check all LN locations systematically. In addition, we did not perform EUS-TA routinely whenever the LN was not suspicious.

MLN were identified during surgery in one out of three patients, more often in patients with lymphadenopathy on cross-sectional imaging. Although not directly comparable, this ‘miss’ rate was higher than in the two studies from the Mayo clinic. Gleeson et al. described 22 patients without preoperative confirmation of MLN by EUS-TA that underwent explorative laparotomy, with
identification of MLN in only 2 (9%) patients [15]. Malikowski et al. did not report the number of missed LN for pCCA, but for all cholangiocarcinoma types [14]. Of the 130 patients without MLN by EUS-TA, 80 (62%) proceeded to staging laparotomy, with identification of MLN in four (5%) patients. This can be due to the non-systematic method we used and high threshold of EUS-TA. Another explanation is that for patients enrolled in pCCA LT work-up at the Mayo Clinic, both regional and extraregional LN are targeted while in patients worked-up for radical resection, primarily extraregional LN are important. It is important to assess LN status preoperatively, as in a recent meta-analysis, MLN were associated with poorer disease free survival [17].

Cross-sectional imaging has limited accuracy regarding LN involvement. In the patients with suspicious LN on cross-sectional imaging, confirmation of MLN was found in 37% during EUS-TA and/or surgery, in comparison to 18% patients without suspicious LN on cross-sectional imaging. This is line with the results from Malikowski et al. describing that presence of lymphadenopathy on cross-sectional imaging was significantly associated with MLN at EUS-TA [14]. In patients without clear lymphadenopathy on cross-sectional imaging, EUS-TA identified MLN in 11% for all cholangiocarcinoma subtypes. Unfortunately cross-sectional imaging has limited performance to adequately define LN involvement in pCCA [14, 15]. PET/CT-scan (Positron Emission Tomography) is not recommended as standard procedure for preoperative LN assessment, since sensitivity is only 33% with a specificity of 97% [18]. In daily practice, radiologists define lymphadenopathy in the upper abdomen primarily on size criteria, a short-axis of >10 mm. However, there are various reports that the size-criterion is not specific enough for various cancers [19, 20]. Cross-sectional imaging could potentially assist in locating LN to facilitate a more targeted approach for EUS-TA. This strategy is probably less useful in PSC patients, as enlarged benign LN are often identified at cross-sectional imaging.

Our study is the largest retrospective multicenter study on the value of preoperative EUS in patients with suspected resectable pCCA. By including all patients with potentially resectable pCCA, instead of pathologically proven pCCA, the actual impact of preoperative EUS is assessed. However, our study
has some limitations. Firstly, due to the retrospective nature, data regarding specific LN locations and
classifications were often reported with little details. Due to this, we were unable to use the 8th AJCC
classification as the number of LN were often inadequately described. Also due to the retrospective
nature, LN evaluation and subsequent EUS-TA was performed differently. In some patients multiple
suspicious LN were identified and EUS-TA was only performed in one LN. In some patients with only
suspicious regional LN no EUS-TA was performed, as resection was still considered an option for
these patients regardless regional LN status. The patients included in our study were discussed in
three different multidisciplinary team meetings, potentially affecting the clinical decision making
success rate. Secondly, since our study focused on the role of EUS and therefore only patients who
had undergone an EUS were included, the accuracy of cross-sectional imaging for LN detection may
have been overestimated. Possibly, we have performed EUS more often in patients with advanced
disease so patients that were not included in our study had a lower prevalence of suspicious LN on
cross-sectional imaging. We were unable to report the total number and or findings of pCCA patients
not undergoing EUS. Thirdly, the yield of EUS may increase with systematic EUS-TA of all LN, which
was not clinical practice at the time of this study. Therefore, our results are most likely
underrepresenting the role of EUS-TA in these patients. In good clinical practice, all LN locations
should be routinely evaluated, sampled and described in the report.

Our study combined with previous evidence show that in patients with presumed resectable pCCA,
clinical decision making can be influenced significantly by EUS-(TA) with far-reaching consequences
for individual patients. Also, our study supports further prospective evaluation of routine
implementation of EUS in patients with potentially resectable pCCA.
Conflicts of interest

M.J. Bruno received research funding for industry initiated studies from Boston Scientific and Cook Medical. He received research funding for investigator initiated studies from Boston Scientific, Cook Medical, Pentax Medical, Interscope, Mylan and ChiRoStim. He is a consultant to Boston Scientific, Cook Medical, and Pentax Medical. R.P. Voermans received research funding for investigator initiated studies from Boston Scientific and Prion Medical. He is a consultant with speakers fee for Boston Scientific. The other authors declare that they have no conflicts of interest.
References

Appendices

Table 1. N staging of the 7th and 8th edition of the AJCC staging system
For both 7th and 8th edition of the AJCC staging system, Nx is defined as ‘Regional LNs cannot be assessed’ and N0 as ‘No regional MLN’. H (Hilar), CD (cystic duct), CBD (common bile duct), HA (hepatic artery), PV (portal vein), PPD (posterior pancreato-duodenal), PA (peri-aortic), PC (peri-caval), SMA (superior mesenteric artery), CO (coeliac), HDL (hepato-duodenal ligament).

Table 2. Baseline characteristics of study population
‡ Missing in one patient
§ Missing in seven patients

Table 3. Characteristics of the 169 EUS procedures across 141 patients
A total of three EUS procedures were performed in four (3%) patients, two EUS procedures in 20 (14%) patients and only one EUS procedure in 117 (83%) patients.

Table 4. Characteristics of all described LN by EUS

Figure 1. Flowchart of patients included in this study
§ In 72 patients, because missing pathology in 1 patient and 1 patient with cardiac arrest during surgery, before any resection. Two patients had preoperative confirmation of MLN by EUS-TA and underwent surgery. The first patient underwent a diagnostic laparoscopy which showed locally advanced disease. The second patient underwent left hemi-hepatectomy with regional MLN. These patients are not taken into account.

Figure 2. Flowchart of patients included in this study, according to imaging findings
§ For patients without preoperative confirmation of MLN by EUS-TA
<table>
<thead>
<tr>
<th>Variable</th>
<th>All resectable pCCA patients with preoperative EUS performed (n = 141)</th>
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<tr>
<td>Age at diagnosis, median [IQR], years</td>
<td>63 [55 - 71]</td>
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<tr>
<td>Male gender – n (%)</td>
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<td>PSC – n (%)</td>
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<td>- 3</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Imaging – n (%)</td>
<td></td>
</tr>
<tr>
<td>- CT only</td>
<td>28 (20%)</td>
</tr>
<tr>
<td>- MRI/MRCP only</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>- Both</td>
<td>108 (77%)</td>
</tr>
</tbody>
</table>

Table 2. Baseline characteristics of study population
‡ Missing in one patient
§ Missing in seven patients
<table>
<thead>
<tr>
<th>Variable</th>
<th>Total number of EUS (n = 169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of EUS – n (%)</td>
<td></td>
</tr>
<tr>
<td>- Tertiary referral center</td>
<td>125 (74%)</td>
</tr>
<tr>
<td>- Referring hospital</td>
<td>44 (26%)</td>
</tr>
<tr>
<td>Drainage prior to EUS – n (%)</td>
<td></td>
</tr>
<tr>
<td>- Stent by ERCP</td>
<td>65 (39%)</td>
</tr>
<tr>
<td>- Percutaneous drain (PTCD)</td>
<td>10 (6%)</td>
</tr>
<tr>
<td>- PTCD and stent by ERCP</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Cholangitis &lt;1 month prior to EUS – n (%)</td>
<td>8 (5%)</td>
</tr>
<tr>
<td>Indication for EUS – n (%)</td>
<td></td>
</tr>
<tr>
<td>- Assessment of suspicious bile duct mass</td>
<td>74 (44%)</td>
</tr>
<tr>
<td>- LN assessment due to suspicious LN on imaging</td>
<td>68 (40%)</td>
</tr>
<tr>
<td>- Liver transplantation screening</td>
<td>17 (10%)</td>
</tr>
<tr>
<td>- Resectability assessment</td>
<td>10 (6%)</td>
</tr>
<tr>
<td>Any LN described at EUS – n (%)</td>
<td>117 (69%)</td>
</tr>
</tbody>
</table>

**Table 3. Characteristics of the 169 EUS procedures across 141 patients**

A total of three EUS procedures were performed in four (3%) patients, two EUS procedures in 20 (14%) patients and only one EUS procedure in 117 (83%) patients.
<table>
<thead>
<tr>
<th>Described LN</th>
<th>#</th>
<th>Successful EUS-TA</th>
<th>EUS-TA Not possible</th>
<th>Pathology results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>FNA</td>
<td>FNB</td>
<td>Both</td>
</tr>
<tr>
<td>Regional</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Suspicious</td>
<td>52</td>
<td>20</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>- Not suspicious</td>
<td>12</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Extraregional</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Suspicious</td>
<td>78</td>
<td>48</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>- Not suspicious</td>
<td>19</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>161</td>
<td>75</td>
<td>12</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4. Characteristics of all described LN by EUS
<table>
<thead>
<tr>
<th></th>
<th>N1</th>
<th>N2</th>
<th>M1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AJCC 7th edition</strong></td>
<td>≥1 MLN in the regional LNs (H, CD, CBD, HA or PV LNs)</td>
<td>≥1 MLN in the regional LNs (PA, PC, SMA or CO LNs)</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td><strong>AJCC 8th edition</strong></td>
<td>1-3 MLN in the regional LNs (H, CD, CBD, HA, PPD or PV LNs)</td>
<td>≥ 4 MLN in the regional LNs described for N1</td>
<td>Distant metastasis (includes MLN distant to the HDL)</td>
</tr>
</tbody>
</table>

**Table 1. N staging of the 7th and 8th edition of the AJCC staging system**

For both 7th and 8th edition of the AJCC staging system, Nx is defined as ‘Regional LNs cannot be assessed’ and N0 as ‘No regional MLN’. H (Hilar), CD (cystic duct), CBD (common bile duct), HA (hepatic artery), PV (portal vein), PPD (posterior pancreato-duodenal), PA (peri-aortic), PC (peri-caval), SMA (superior mesenteric artery), CO (coeliac), HDL (hepato-duodenal ligament).
Resectable pCCA undergoing EUS (n = 141)

- Suspicious LN (n = 107)
  - Positive EUS-TA (n = 20)
    - No surgery (n = 33)
    - Surgery performed (n = 54)*
      - MLN (n = 20)
  - No suspicious LN (n = 34)
    - Positive EUS-TA (n = 2)
    - No surgery (n = 16)
    - Surgery performed (n = 16)§
      - MLN (n = 4)