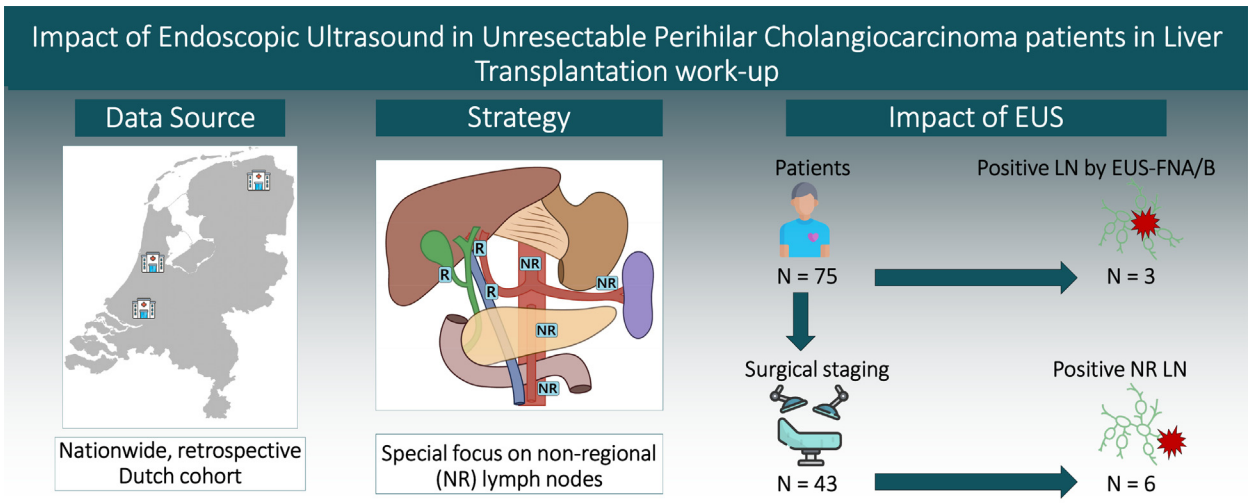
Impact of EUS in liver transplantation workup for patients with unresectable perihilar cholangiocarcinoma

David M. de Jong, BSc,[1] Caroline M. den Hoed, MD, PhD,[1,2] Francois E. J. A. Willemssen, MD,[3] Maarten G. J. Thomeer, MD, PhD,[3] Marco J. Bruno, MD, PhD,[1] Bas Groot Koerkamp, MD, PhD,[4] Jeroen de Jonge, MD, PhD,[2,4] Ian P. J. Alwayn, MD, PhD,[5] Jeanin E. van Hooft, MD, PhD, MBA,[6] Frederik Hoogwater, MD, PhD,[7] Frans van der Heide, MD, PhD,[8] Akin Inderson, MD,[6] Frederike G. I. van Vilsteren, MD, PhD,[8] Lydi M. J. W. van Driel, MD, PhD[1]

Rotterdam, Leiden, Groningen, The Netherlands

GRAPHICAL ABSTRACT



Background and Aims: For a highly selected group of patients with unresectable perihilar cholangiocarcinoma (pCCA), liver transplantation (LT) is a treatment option. The Dutch screening protocol comprises nonregional lymph node (LN) assessment by EUS, and whenever LN metastases are identified, further LT screening is precluded. The aim of this study is to investigate the yield of EUS in patients with pCCA who are potentially eligible for LT.

Methods: In this retrospective, nationwide cohort study, all consecutive patients with suspected unresectable pCCA who underwent EUS in the screening protocol for LT were included from 2011 to 2021. During EUS, sampling of a "suspicious" nonregional LN was performed based on the endoscopist's discretion. The primary outcome was the added value of EUS, defined as the number of patients who were precluded from further screening because of malignant LNs.

Results: A total of 75 patients were included in whom 84 EUS procedures were performed, with EUS-guided tissue acquisition confirming malignancy in LNs in 3 of 75 (4%) patients. In the 43 who underwent surgical staging according to the protocol, nonregional LNs with malignancy were identified in 6 (14%) patients. Positive regional LNs were found in 7 patients in post-LT-resected specimens.

Conclusions: Our current EUS screening for the detection of malignant LNs in patients with pCCA eligible for LT shows a limited but clinically important yield. EUS with systematic screening of all LN stations, both regional and nonregional, and the sampling of suspicious lymph nodes according to defined and set criteria could potentially increase this yield. (Gastrointest Endosc 2024;99:548-56.)

(footnotes appear on last page of article)

Perihilar cholangiocarcinoma (pCCA) is an uncommon malignancy originating from the bile ducts.[1] At presentation, only 30% to 40% of the tumors are resectable by partial hepatectomy.[2] Resectability depends on the tumor stage, vascular involvement, and presence of liver fibrosis or cirrhosis so that an adequate liver volume and function remain after resection. Primary sclerosing cholangitis (PSC) is an established risk factor for pCCA and also limits liver function. For a select group of patients with unresectable pCCA, liver transplantation (LT) is a treatment option with curative intent. The Mayo Clinic has reported favorable results using a strict protocol for these patients, which includes pre-LT neoadjuvant chemotherapy and radiotherapy.[3] It is, however, unclear whether these results are attributable to the strict selection protocol or the neoadjuvant treatment scheme.[4]

Other centers have also reported on the feasibility of LT for pCCA, without the neoadjuvant treatment scheme.[5-9] LT for unresectable pCCA was introduced in The Netherlands in 2011, without the addition of neoadjuvant chemotherapy and radiotherapy.[10] The Dutch screening protocol involves EUS; cross-sectional imaging, such as CT, magnetic resonance imaging (MRI), and fluorodeoxyglucose positron emission tomography–computed tomography (PET-CT); and a staging laparotomy to detect peritoneal metastases and metastatic lymph nodes (LNs). The protocol also includes strict eligibility criteria, as shown in Table 1, with the absence of LN metastases being particularly important. Nonregional LNs, such as those near the aorta, vena cava, superior mesenteric artery, and celiac artery, are considered a contraindication for LT when malignancy is confirmed during EUS or explorative laparotomy. Regional LNs, such as those near the liver hilum, cystic duct, common bile duct, hepatic artery, and portal vein, are not routinely evaluated by EUS but only through frozen section analysis in the same session as the LT and not during staging laparotomy. Whenever no LNs positive for malignancy are identified before the hepatectomy, the LT is completed.

Adequate LN staging in patients with pCCA is essential to exclude patients with positive nonregional LN findings from invasive treatments, such as laparotomy or LT. However, cross-sectional imaging has a limited accuracy in differentiating between malignant and benign LNs.[11] Additional EUS with tissue acquisition (EUS-TA) can potentially detect unidentified positive LNs. Preoperative EUS staging is routinely used for esophageal, gastric, and pancreatic cancer with high accuracy and influence on clinical decision making.[12-17] The Mayo Clinic has used EUS staging for pCCA in its LT protocol for multiple years, and 17% of patients were excluded as LT candidates after identification of metastases by EUS-TA.[18] In another recent study, surgical exploration was precluded in 20 of 141 (14%) patients with resectable pCCA.[19] EUS staging has a high accuracy in all cholangiocarcinoma subtypes as well, detecting LNs in 86% of patients compared to 47% on imaging only ($P < .001$).[20]

The aim of this study is to investigate the effectiveness and accuracy of EUS staging in patients with unresectable pCCA who are being evaluated for LT.

METHODS

Study population

This retrospective national multicenter study included all patients with suspected unresectable pCCA who underwent EUS between 2011 and 2021 as part of the nationally approved LT protocol for pCCA in The Netherlands.[10] Inclusion in this study did not depend on further workup after EUS or final treatment. Patients were eligible from the start of this screening protocol for LT: 2011 for both the Erasmus MC University Medical Center and the University Medical Center Groningen and 2016 for the Leiden University Medical Center. The eligibility criteria for LT for pCCA in this protocol are specified in Table 1. Patients were identified through prospectively collected databases and local endoscopy databases of all 3 Dutch LT centers. The study adhered to the guidelines in the Declaration of Helsinki and was approved by the local ethics committees.

LT workup

The protocolled workup for LT in this patient population consists of staging of the tumor by tumor markers (carbohydrate antigen [CA] 19.9 and carcinoembryonic antigen [CEA]), cross-sectional imaging (CT, MRI/MRCP, and PET-CT), and EUS. ERCP is only performed when biliary drainage is necessary. The indication and purpose of the EUS is to assess the presence of nonregional LN metastases. The protocol dictated that when a nonregional LN was deemed suspicious, EUS-TA was indicated, and regional LNs were not targeted to avoid needle tract tumor seeding because of the tumor's proximity. Whether or not an LN was deemed suspicious was not further specified and was left to the discretion of the endoscopist. Linear EUS endoscopes were used to evaluate LN status (Fujifilm EG-580UT, Tokyo, Japan, and Pentax EG-38J10UT and Pentax EG-3870UTK, Pentax Medical, Tokyo, Japan). The procedure was performed with conscious sedation or propofol, depending on local practice.

The following locations were screened: periaortic, pericaval, superior mesentery artery, and celiac artery (Fig. 1). Regional LNs were not screened routinely. During the majority of the study period, the American Joint Committee on Cancer (7th edition) staging system for LNs was used.[21] This staging system defined regional (or N1) LNs as LNs located at the hilum, common bile duct, cystic duct, hepatic artery, or portal vein. LNs farther from the hepatoduodenal ligament were defined as nonregional (or N2). There was a low threshold to perform a biopsy on nonsuspicious, nonregional LNs. Biopsy was performed using fine-needle aspiration (FNA) or fine-needle biopsy (FNB) based on the endosonographer's preference. Suspicious LNs on EUS were defined as having 1 or more of the following characteristics: short-axis diameter of >10 mm, hypoechogenic, round shape, and sharp demarcation. EUS-FNA was performed by using a 22- or 25-gauge FNA-type needle, and EUS-FNB was performed by using a 22- or 25-gauge FNB-type needle. Rapid onsite evaluation (ROSE) was used in a small number of patients at 2 study sites to confirm if an

TABLE 1. Eligibility criteria for LT protocol for unresectable perihilar cholangiocarcinoma, according to the 2011 Dutch Guidelines[10]

Patients were eligible for LT if
1. No previous percutaneous tumor biopsy
2. Tumor size of <30 mm (radial axis) on computed tomography or magnetic resonance imaging
3. No previous surgical exploration with direct contact on the tumor location
4. No nonregional LN metastases identified with EUS
5. No nonregional LN, peritoneal, or intrahepatic metastases identified during staging laparotomy
6. No distal tumor growth necessitating an eventual pancreatoduodenectomy
7. No general contraindications for LT

LN, Lymph node; *LT*, liver transplantation.

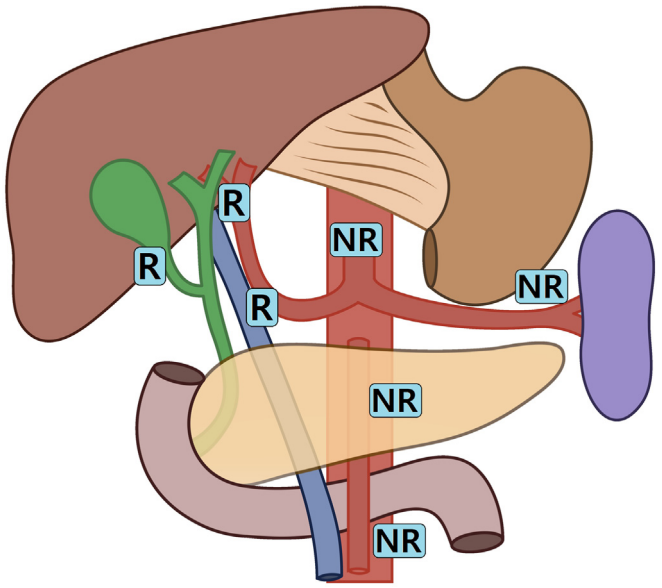


Figure 1. Overview of the locations of lymph nodes (LNs) defined as regional and nonregional according to the American Joint Committee on Cancer. Regional LNs included LNs at the liver hilum, common bile duct, cystic duct, hepatic artery, and portal vein. Nonregional LNs included periaortic, pericaval, superior mesenteric artery, and celiac artery/trunk LNs. *NR*, Nonregional; *R*, regional.

adequate tissue sample was obtained. In summary, LN assessment by EUS was not standardized in the Dutch LT screening protocol for patients with unresectable pCCA and was therefore mostly left to the endosonographer's preference.

After imaging and EUS were performed, the results were reviewed in a multidisciplinary meeting at all 3 centers. At least 2 of the 3 centers had to agree with the criteria for transplantation. Differences in agreement were, for example, caused by a high probability of benign stenosis, such as autoimmune cholangiopathy, for which prednisolone treatment was suggested instead, but also because the tumor was deemed resectable by partial liver resection instead. In the Dutch protocol, pathologic proof is pursued but is not required.

If the audit reached consensus and imaging and EUS-TA did not show any metastases, a diagnostic laparoscopy or open laparotomy was performed with excision of LNs located from the distal hepatoduodenal ligament and along the common hepatic artery to the celiac trunk. The abdominal cavity and liver were also inspected for metastases. If no LN metastases were found, the patient was placed on the national waiting list for LT with a nonstandard exception with 38 Model for End-Stage Liver Disease points, aiming for transplantation at <3 months after surgical staging. During this waiting period, patients were closely monitored with cross-sectional imaging. All LTs started with an explorative laparotomy with reinspection of the abdominal cavity and biopsy of suspicious regional and nonregional LNs. If frozen section analysis identified metastases in the liver, peritoneum, or LNs, the LT was aborted.

Outcomes

The primary outcome of this study was the impact of EUS on the workup of the LT protocol, defined as the number of patients precluded from further workup because of positive for malignancies identified by EUS-TA. The secondary outcomes were (1) the number of patients in whom EUS failed to detect malignant LNs by EUS, (2) EUS-associated adverse events, and (3) post-LT survival.

Data collection and analysis

Each individual patient record was systematically reviewed. Data collected included patient demographics, clinical information (American Society of Anesthesiologists classification and performance status), imaging studies (CT, MRI/MRCP, PET-CT, and information about any LNs present), EUS characteristics (like LN status and biopsy outcomes), and surgical outcomes (type of resection and LN status). Factors that might affect imaging quality or suspiciousness of LNs, such as recent cholangitis or a biliary stent, were also collected. Follow-up time was based on data availability in individual medical records and calculated from time of presentation, EUS, and LT. Continuous variables are reported as mean with standard deviation or median with interquartile range (IQR), depending on the distribution. Survival was analyzed using Kaplan-Meier estimates and log-rank tests, with a 2-sided P value of <.05 considered statistically significant.

RESULTS

Baseline characteristics

A total of 75 patients were evaluated for LT by EUS. Forty-seven (63%) patients were male, with a median age of 56 years (IQR, 43-65) (Table 2). Nearly half (52%) had a prior diagnosis

TABLE 2. Baseline and staging characteristics of the included patients undergoing EUS for liver transplantation workup

Variable	Total cohort (n = 75)
Age, y	56 (43-65)
Male sex	47 (63)
PSC	39 (52)
ASA	
1	4 (5)
2	39 (52)
3	32 (43)
Eastern Cooperative Oncology Group/World Health Organization performance status	
0	58 (78)
1	13 (17)
2	3 (4)
3	1 (1)
Imaging	
Computed tomography and/or PET-CT	74 (99)
Magnetic resonance imaging/magnetic resonance cholangiopancreatography	53 (71)
Cholangitis <30 days before imaging	26 (14)
Stent in situ at time of imaging	93 (49)
Nonregional lymph node described at imaging	41 (55)

Values are n (%) or median (interquartile range).
ASA, American Society of Anesthesiologists physical status classification system; *ECOG*, Eastern Cooperative Oncology Group; *PET-CT*, positron emission tomography–computed tomography; *PSC*, primary sclerosing cholangitis.

of PSC. Imaging showed nonregional lymphadenopathy in 55% of the patients.

EUS characteristics

The 75 included patients underwent 84 EUS procedures. The first EUS was performed 7 days (IQR, 2-18) after the last imaging, with a second EUS performed in 8 patients for various reasons, such as incomplete visualization or unsuccessful procedure (n = 4), Tissue Acquisition of specific LNs (n = 3), TA of distal Common Bile Duct (CBD) mass indicated (n = 1), or for unspecified reasons (n = 1). A total of 65 nonregional LNs in 34 patients were described (Table 3). EUS-TA was performed in 35 of 65 (54%) nonregional LNs; in 30 of 33 (91%) of the suspicious LNs, and in 5 of 32 (16%) nonsuspicious LNs. Malignancy was found in 2 of 35 (6%) biopsy specimens in 2 different patients. These specific LNs were not described on imaging and were suspicious on EUS. Although not conform the protocol, biopsy by EUS-TA was performed on 11 regional LNs, with 1 showing malignancy. There was no specific information available on needle type or other puncture characteristics. Figure 2 shows 2 examples of identified LNs. In 25 of 75 (33%) patients, no LNs were identified during EUS. There were no procedure-related adverse events associated with the EUS or EUS-TA.

The yield of EUS

LT workup was precluded in 3 of 75 (4%) patients because of confirmation by EUS-TA of LNs positive for malignancy. In the 43 patients who underwent surgical LN staging according to the LT protocol, LT was precluded because of the identification of nonregional LNs during explorative laparotomy or robot-assisted LN sampling in 6 of 43 (14%) patients. In the patient with proven malignancy in a regional LN, an extended hemihepatectomy with pancreatoduodenectomy was performed instead without a staging procedure, outside of the LT protocol. Multiple nonregional LNs positive for malignancy were identified on postoperative histopathology. This resulted in a total of 7 malignant nonregional LNs that were missed with EUS in 7 of 54 (13%) patients who underwent any form of surgical procedure, in or outside of the LT protocol. Regarding these missed LNs at EUS, in 4 patients, no LNs were described; in 2 patients, the LN was described as suspicious, but EUS-TA failed to confirm malignancy; and in 1 patient, the LN was identified, but EUS-TA was not performed because the LN was described as not suspicious. At cross-sectional imaging, these missed LNs were described as suspicious in 3 patients and not suspicious in 1 patient and were not described in 3 patients. The median time period between EUS and surgical staging was 47 days (IQR, 16-51).

LT workup

As shown in Figure 3, 21 of 75 (28%) patients did not undergo LT or any other form of surgery after initial LT workup for several reasons. Of the remaining 54 (72%) patients, 43 (80%) were worked up for LT according to the LT protocol with 36 (84%) patients undergoing explorative laparotomy and 7 (16%) patients undergoing robot-assisted diagnostic laparoscopy with LN sampling. These procedures were performed after a median period of 36 days after EUS (IQR, 23-50). In 6 of 43 (14%) procedures, malignant nonregional LNs were identified, precluding LT workup in 6 (14%) patients. In 7 (16%) patients, workup for LT was precluded by other reasons. The final pathology results are detailed in Table 4.

Of the remaining 37 patients in whom staging investigation findings remained negative, 28 (76%) underwent LT, and 1 (3%) was still on the waiting list. In 5 of 28 (18%) patients, an additional pancreatoduodenectomy was performed because the distal frozen section margin was positive for malignancy in 2 patients and showed atypia in 3 patients. One patient's LT was stopped during the surgery because of the discovery of ingrowth in the retroperitoneal space and positive findings on distal bile duct frozen section analysis. In the 28 patients with an LT, final surgical resection specimens showed ≥1 regional LN positive for malignancy in 7 (25%) patients. In 6 of the 28 (21%) patients, no malignancy was identified in the explant.

Patients treated outside of the LT protocol

Eleven of 54 (20%) patients did not proceed in further workup according to the LT protocol after the EUS. Of these

TABLE 3. LN and pathology outcomes of EUS staging in 84 EUS procedures

	Described LNs	Short axis (mm)	EUS-TA		Malignancy
			FNA	FNB	
Total LNs described	98	9 (5.6-12.8)			
Regional	33				
Suspicious	13	10 (9-13.3)*	8 (62)	1 (8)	1 (11)
Not suspicious	20	12 (8.8-15)†	1 (5)	1 (5)	0 (0)
Nonregional	65				
Suspicious	33	7.8 (5-12.5)‡	28 (85)#	3 (9)#	2 (7)
Not suspicious	32	6 (4.1-8)**	5 (16)	0	0 (0)

Values are n, n (%), or median (interquartile range).
EUS-TA, EUS-guided tissue acquisition; *FNA*, fine-needle aspiration; *FNB*, fine-needle biopsy; *LN*, lymph node.
*Missing in 1 LN.
†Missing in 12 LN.
‡Missing in 8 LN.
#In 1 LN, both FNA and FNB were performed.
**Missing in 10 LNs.

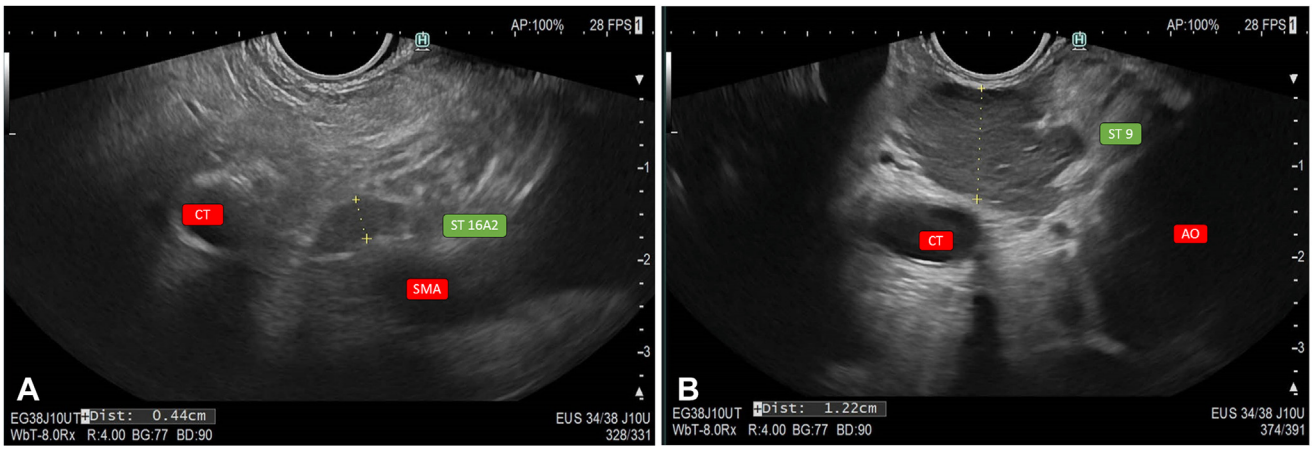


Figure 2. Two examples of identified LNs. **A,** An unsuspicious LN located at station 16A2. A biopsy was not performed. **B,** A suspicious LN located at station 9. Biopsy showed malignancy. *AO*, Aorta; *CT*, celiac trunk; *SMA*, superior mesenteric artery; *ST*, station.

11 patients, 9 (82%) underwent an LT for the indication of PSC cirrhosis because the diagnosis of pCCA was not confirmed or was deemed less probable preoperatively. In 3 patients, pCCA was identified in surgical resection specimens, with 1 patient having multiple regional LNs positive for malignancy. The other 2 (18%) patients were deemed to have resectable pCCA and underwent a hemihepatectomy; 1 of these patients had multiple regional LNs positive for malignancy. These 10 procedures were performed after a median period of 100 days after EUS (IQR, 65-222).

In total, positive regional and/or nonregional LNs were identified during workup, at explorative surgery, or in surgical resection specimens in 16 of 75 (21%) patients. Of these 16 patients, LNs were found with EUS-TA (n = 3), at explorative surgery (n = 6), and in resection specimens (n = 7).

Survival after LT

In total, there were 22 patients with confirmed pCCA in surgical resection specimens who underwent an LT. In those patients, the overall median survival time was 37 months (95% confidence interval, 20.2-not applicable). Positive regional LNs were identified in 7 of 22 (32%) patients. There was a trend toward better survival for patients without regional LN in surgical resection specimens (log-rank P = .054).

DISCUSSION

In this retrospective, multicenter, nationwide cohort study, we found that in patients undergoing a staging EUS aiming at the detection of nonregional LN metastases in the setting of LT screening for suspected unresectable pCCA, EUS-TA detected nonregional LN metastases in only 3%. These patients were precluded from invasive surgical treatments, such as explorative laparotomy or LT. However, in 7 (13%) additional patients, nonregional LNs were identified during these invasive surgical treatments that were not identified by EUS. Combining the yield of EUS and surgery,

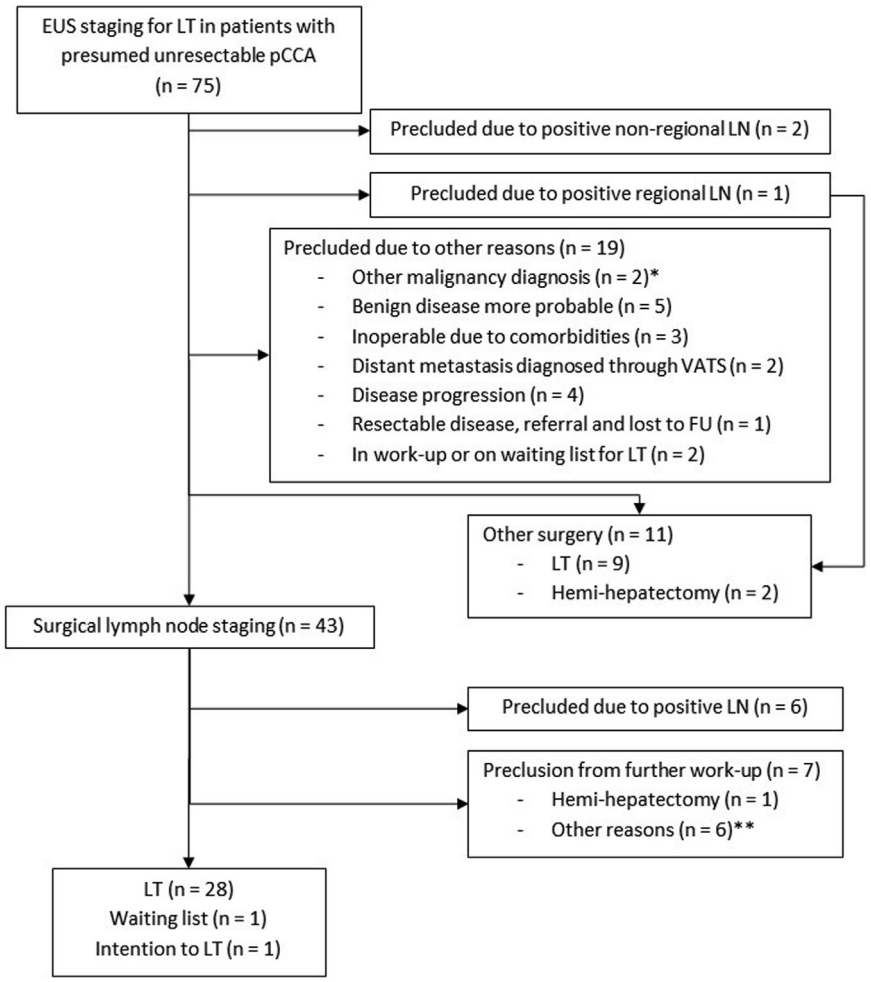


Figure 3. Flowchart of patients undergoing EUS in LT workup for unresectable perihilar cholangiocarcinoma. *Breast cancer in 1 patient and rectal carcinoma in 1 patient. **Lost to follow-up (n = 2), benign disease more probable (n = 1), tumor spill caused by gallbladder cancer (n = 1), gallbladder cancer diagnosis during waiting period (n = 1), and death caused by adverse events after explorative laparotomy (n = 1). *FU*, follow-up; *LT*, liver transplantation; *LN*, lymph node; *pCCA*, perihilar cholangiocarcinoma; *VATS*, video-assisted thoracoscopic surgery.

TABLE 4. Pathology findings for patients with presumed CCA who underwent surgical staging or treatment (n = 54)

Variable	Total patients who underwent surgery (n = 54)	Patients who underwent LT conforming to LT protocol (n = 28)	Other patients (n = 26)
Final pathology diagnosis available*	50 (93)	28 (100)	22 (85)
Pathology diagnosis			
pCCA	32 (64)	19 (68)	13 (59)†
Benign	12 (24)	6 (21)	6 (27)
Intrahepatic CCA	3 (6)	2 (7)	1 (5)
MT-HCC/CCA	1 (2)	1 (4)	–
Gallbladder cancer	2 (4)	–	2 (9)

Values are n (%).
CCA, Cholangiocarcinoma; *MT-HCC*, mixed type-hepatocellular carcinoma/cholangiocarcinoma; *pCCA*, perihilar cholangiocarcinoma; –, not applicable.
*Final pathology was not available in 4 patients who underwent a form of surgery: still on waiting list (n = 1), died after complicated laparotomy (n = 1), lost to follow-up after laparotomy (n = 1), and wait-and-see period after laparotomy (n = 1).
†In 3 of 8 (38%) patients who underwent LT outside the pCCA LT protocol because benign disease was more probable, pCCA was still confirmed in surgical specimens.

regional and/or nonregional LNs positive for malignancy were identified in 16 of 75 (21%) patients.

Previous studies have reported higher rates of surgery preclusion after the identification by EUS of LNs positive for malignancy.[18-20,22] For example, Gleeson et al[18] precluded 8 of 47 (17%) patients from neoadjuvant chemoradiation therapy and surgery after identification of metastases by EUS. Another study[22] not specifying the EUS method precluded 1 of 17 (6%) patients. A follow-up study from the Mayo Clinic using standardized EUS found that EUS identified LNs in 89% of the patients with pCCA and that EUS-TA found malignancy in 16%, precluding surgery.[20] However, in our study, surgery was precluded in only 4% of patients. Our results do not align with these previous studies, which may be attributable to differences in screening methods and patient selection. Our semistandardized method consisted of screening for nonregional LNs with EUS-TA only when an LN was deemed suspicious, whereas the Mayo Clinic assessed all LN locations, with a low threshold for EUS-TA.[18]

In our current protocol, EUS-TA is performed only when an endosonographer deems a nonregional LN suspicious. Out of the 28 suspicious nonregional LNs on which biopsies were performed, malignancy was found in 2 (7%) LNs across 2 patients. Some studies have suggested that EUS features of LNs are not predictive of malignant involvement in the setting of pCCA.[18] Because of inadequate reporting, we were unable to analyze specific LN characteristics on EUS with regard to pathology outcome. Other studies, such as that by Gleeson et al,[18] had a low threshold for performing EUS-TA and also had a cytopathologist present during the EUS to perform ROSE if requested. This allowed for repeat EUS-TA in the same LN if inadequate material was obtained. It is important to note that our study did not follow this strategy, and this difference in approach may have led to an underestimation of the potential yield of EUS-TA. There still is some debate about the additional value of ROSE for EUS-TA of LNs.[23-25]

The median time between the last EUS and first surgical procedure was 36 days for patients following the LT protocol and 100 days for patients receiving surgical treatment outside the LT protocol. These time periods reflect both the strict protocol and the waiting period for an LT or curative-intent resection outside the protocol. Nonregional LNs positive for malignancy were identified in 13% of the patients who underwent surgery. This is similar to findings from the Mayo Clinic studies, but it should be interpreted with caution because there are some important differences.[18,20] In these studies, it is possible that some LNs that were positive for malignancy were ablated by neoadjuvant chemoradiation therapy before staging laparotomy. Also, the time period between EUS and staging laparotomy was significantly longer than in our study, primarily because of the omission of neoadjuvant chemoradiation therapy. It is possible that the "missed" nonregional LNs were not present at the time of EUS and developed in the time period between EUS and surgery.

Unfortunately, imaging has poor performance in detecting LN involvement in cholangiocarcinoma, with a sensitivity of only 53%.[11] In current practice, radiologists base lymphadenopathy primarily on the short-axis criterion of >10 mm, but specific cross-sectional imaging characteristics for malignant LNs in pCCA are lacking. Lymphadenopathy at imaging is significantly associated with positive EUS-TA findings compared to no lymphadenopathy (24% vs 11%).[20] We were unable to validate this finding because of the limited number of patients with positive LN findings. In the 7 patients with nonregional LNs confirmed positive for malignancy at surgery, these were described at cross-sectional imaging in 4 patients, with 3 of them being defined as suspicious. The 2 nonregional LNs that were identified with EUS-TA as positive for malignancy were not described at cross-sectional imaging.

We were unable to find a significant difference in survival for patients with and without malignant regional LNs identified in patients with pathologically confirmed pCCA, likely because of the limited power of our analysis. However, in a recent report by Dondorf et al,[26] the median survival for patients with no LN showing malignancy after LT was 46.7 months, compared to 7.1 months for patients with positive LN findings ($P < .001$). Similarly, in patients treated by partial liver resection, 5-year overall survival was 47% in patients with nodal-negative disease, whereas only 9% of the patients with nodal-positive disease were alive ($P < .001$).[27]

This is the largest retrospective multicenter study on the value of preoperative EUS in patients with presumed unresectable pCCA in the workup for LT. However, this study has several limitations. First, because of the retrospective nature of the study, data regarding LN characteristics and locations were not reported in a standardized or complete manner, both at cross-sectional imaging and EUS, and could therefore not be analyzed. Second, the EUS procedures were not performed in a standardized manner, and some nonregional LN locations were not described. There was a high threshold to perform EUS-TA. EUS-TA was primarily performed in nonregional LNs that were deemed suspicious by the endosonographer, whereas in some other series, all LNs, both suspicious and nonsuspicious, were sampled. This nonstandardized method most likely resulted in underestimation of the yield of EUS. Third, it is possible that nonregional LNs that were positive for malignancy were still "negative" at the time of EUS but turned "positive" in the time between EUS and surgery because of disease progression, although this is unlikely given the relatively short period between EUS and surgery. Both the nonstandardized manner of EUS procedures and tumor progression could have contributed to the missed malignancy-positive LNs, but it is unclear which one is dominant based on our data and the current literature. Finally, regional LNs were not systematically checked during the EUS procedures, in line with the Mayo protocol. The Dutch protocol was changed after the results were discussed internally, with regional LNs as additional targets during EUS.

Regarding the discussion of whether regional LNs should be targeted during EUS, more research is needed. On the one side, LT outcomes for patients with regional LNs positive for malignancy is significantly worse, and preoperative identification could preclude a surgical procedure. On the other side, there is a risk of needle-tract seeding in hilar LNs whenever the pCCA is located close by. In the light of the 8th American Joint Committee on Cancer edition, we believe that the benefits of highly standardized EUS screening of both regional and nonregional LNs outweighs the very low risks of needle-tract seeding and EUS-TA–associated adverse events. Regarding EUS-TA of regional LNs, care should be taken to not pass the tumor mass itself to lower the risk of needle-tract seeding. With the implementation of the standardized EUS screening method, only performed by experienced endosonographers, more patients are spared from explorative surgery, and more prognostic information will be provided to patients earlier in the disease course, resulting in more time to explore palliative treatment options.

In summary, the current approach with EUS-TA in the workup for LT for unresectable pCCA in The Netherlands has a relatively low yield. This study, in line with the current literature, suggests that a more standardized EUS screening method, visualizing all LN locations before LT regardless of prior imaging findings, should be considered. These LN locations should also be described according to the classification of the Japanese Society of Hepato-Biliary-Pancreatic Surgery.[28] Prospective registration studies are currently being performed and are eagerly awaited (NCT05678218).

DISCLOSURE

The following authors disclosed financial relationships: M. J. Bruno: Research funding for industry-initiated studies from Boston Scientific and Cook Medical; research funding for investigator-initiated studies from Boston Scientific, Cook Medical, Pentax Medical, Interscope, Mylan, and 3M; and consultant for Boston Scientific, and Cook Medical. J. E. van Hooft: Lecture fee from Cook Medical, Boston Scientfic, Falk, and Abbvie. Consultant for Olympus. All other authors disclosed no financial relationships.

REFERENCES

1. Amin M. AJCC cancer staging manual. 8th ed. USA: Springer; 2017.
2. 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.
3. Rosen CB, Heimbach JK, Gores GJ. Surgery for cholangiocarcinoma: the role of liver transplantation. HPB (Oxford) 2008;10:186-9.
4. Vugts JJA, Gaspersz MP, Roos E, et al. Eligibility for liver transplantation in patients with perihilar cholangiocarcinoma. Ann Surg Oncol 2021;28:1483-92.
5. Ahmed O, Vachharajani N, Chang SH, et al. Single-center experience of liver transplantation for perihilar cholangiocarcinoma. HPB (Oxford) 2021;24:461-9.
6. Darwish Murad S, Kim WR, Harnois DM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. Gastroenterology 2012;143:88-98.e3.
7. Duignan S, Maguire D, Ravichand CS, et al. Neoadjuvant chemoradiotherapy followed by liver transplantation for unresectable cholangiocarcinoma: a single-centre national experience. HPB (Oxford) 2014;16:91-8.
8. Loveday BPT, Knox JJ, Dawson LA, et al. Neoadjuvant hyperfractionated chemoradiation and liver transplantation for unresectable perihilar cholangiocarcinoma in Canada. J Surg Oncol 2018;117:213-9.
9. Cambridge WA, Fairfield C, Powell JJ, et al. Meta-analysis and meta-regression of survival after liver transplantation for unresectable perihilar cholangiocarcinoma. Ann Surg 2021;273:240-50.
10. Porte RJ; Landelijk Overleg Levertransplantatie. Indicatiestelling en selectie voor levertransplantatie bij patiënten met perihilair cholangiocarcinoom: UMCG. 2011. Available at: https://www.transplantatievereniging.nl/wp-content/uploads/2023/03/Protocol-levertransplantatie-voor-perihilair-cholangiocarcinoom-april-2022.pdf. Accessed February 4, 2024.
11. Ho Yun L, Se Hyung K, Jeong Min L, et al. Preoperative assessment of resectability of hepatic hilar cholangiocarcinoma: combined CT and cholangiography with revised criteria. Radiology 2006;239:113-21.
12. Vazquez-Sequeiros E, Norton ID, Clain JE, et al. Impact of EUS-guided fine-needle aspiration on lymph node staging in patients with esophageal carcinoma. Gastrointest Endosc 2001;53:751-7.
13. Vazquez-Sequeiros E, Wiersema MJ, Clain JE, et al. Impact of lymph node staging on therapy of esophageal carcinoma. Gastroenterology 2003;125:1626-35.
14. Han C, Lin R, Shi H, et al. The role of endoscopic ultrasound on the preoperative T staging of gastric cancer: a retrospective study. Medicine 2016;95:e4580.
15. Tsendsuren T, Jun SM, Mian XH. Usefulness of endoscopic ultrasonography in preoperative TNM staging of gastric cancer. World J Gastroenterol 2006;12:43-7.
16. Kurita A, Kodama Y, Nakamoto Y, et al. Impact of EUS-FNA for preoperative para-aortic lymph node staging in patients with pancreatobiliary cancer. Gastrointest Endosc 2016;84:467-75 e1.
17. Nawaz H, Fan CY, Kloke J, et al. Performance characteristics of endoscopic ultrasound in the staging of pancreatic cancer: a meta-analysis. JOP 2013;14:484-97.
18. Gleeson FC, Rajan E, Levy MJ, et al. EUS-guided FNA of regional lymph nodes in patients with unresectable hilar cholangiocarcinoma. Gastrointest Endosc 2008;67:438-43.
19. de Jong DM, van de Vondervoort S, Dwarkasing RS, et al. Endoscopic ultrasound in patients with resectable perihilar cholangiocarcinoma: impact on clinical decision-making. Endosc Int Open 2023;11:E162-8.
20. Malikowski T, Levy MJ, Gleeson FC, et al. Endoscopic ultrasound/fine needle aspiration is effective for lymph node staging in patients with cholangiocarcinoma. Hepatology 2020;72:940-8.
21. Edge SB. AJCC Cancer Staging Manual. 7th ed. USA: Springer; 2010.
22. Welling TH, Feng M, Wan S, et al. Neoadjuvant stereotactic body radiation therapy, capecitabine, and liver transplantation for unresectable hilar cholangiocarcinoma. Liver Transpl 2014;20:81-8.
23. Chen L, Li Y, Gao X, et al. High diagnostic accuracy and safety of endoscopic ultrasound-guided fine-needle aspiration in malignant lymph nodes: a systematic review and meta-analysis. Dig Dis Sci 2021;66:2763-75.
24. Polkowski M, Jenssen C, Kaye P, et al. Technical aspects of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) Technical Guideline—March 2017. Endoscopy 2017;49:989-1006.
25. Kappelle WFW, Van Leerdam ME, Schwartz MP, et al. Rapid on-site evaluation during endoscopic ultrasound-guided fine-needle

aspiration of lymph nodes does not increase diagnostic yield: a randomized, multicenter trial. Am J Gastroenterol 2018;113:677-85.
26. Dondorf F, Utebeta F, Fahrner R, et al. Liver transplant for perihilar cholangiocarcinoma (Klatskin tumor): the essential role of patient selection. Exp Clin Transplant 2019;17:363-9.
27. Giuliante F, Ardito F, Guglielmi A, et al. Association of lymph node status with survival in patients after liver resection for hilar cholangiocarcinoma in an Italian multicenter analysis. JAMA Surg 2016; 151:916-22.
28. Miyazaki M, Ohtsuka M, Miyakawa S, et al. Classification of biliary tract cancers established by the Japanese Society of Hepato-Biliary-Pancreatic Surgery: 3rd English edition. J Hepatobiliary Pancreat Sci 2015;22:181-96.

Abbreviations: EUS-TA, EUS-guided tissue acquisition; FNA, fine-needle aspiration; FNB, fine-needle biopsy; IQR, interquartile range; LN, lymph node; LT, liver transplantation; MRI, magnetic resonance imaging; PET-CT, positron emission tomography–computed tomography; pCCA, perihilar cholangiocarcinoma; PSC, primary sclerosing cholangitis; ROSE, rapid onsite evaluation; TA, tissue acquisition.

DIVERSITY, EQUITY, AND INCLUSION: The author list of this paper includes contributors from the location where the research was conducted who participated in the data collection, design, analysis, and/or interpretation of the work.

Presented as an oral presentation at the Dutch National Transplant Congress, 2022, Leiden, The Netherlands, and the European Society of Gastrointestinal Endoscopy Congress, 2023, Dublin, Ireland, and presented as a moderated abstract at the United European Gastroenterology Congress, 2022, Vienna, Austria.

0016-5107
https://doi.org/10.1016/j.gie.2023.10.047

Received July 16, 2023. Accepted October 20, 2023.

Current affiliations: Department of Gastroenterology and Hepatology, Erasmus MC Cancer Institute University Medical Center, Rotterdam, The Netherlands (1), Erasmus MC Transplant Institute, Rotterdam, The Netherlands (2), Department of Radiology and Nuclear Medicine, Erasmus MC Cancer Institute University Medical Center, Rotterdam, The Netherlands (3), Department of Surgery, Erasmus MC Cancer Institute University Medical Center, Rotterdam, The Netherlands (4), Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands (5), Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands (6), Department of Hepato-Pancreato-Biliary Surgery and Liver Transplantation, University Medical Center Groningen, Groningen, The Netherlands (7), Department of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, The Netherlands (8).

Reprint requests: Lydi M.J.W. van Driel, MD, PhD, Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Dr. Molewaterplein 40, 3015 GD, Rotterdam, The Netherlands. E-mail: l.m.j.w.vandriel@erasmusmc.nl.