treated by endoscopic resection only (low-risk T1 CRC). It is however difficult to reliably distinguish low from high-risk invasive carcinomas during colonoscopy. Aim To determine whether endoscopic resection of high-risk T1 CRC followed by surgical resection has a negative effect on lymph node metastasis or recurrence rate compared to primary surgery. Methods: Patients with high-risk T1 CRC treated with primary or secondary surgical resection between 2000 and 2012 from 7 hospitals were identified in the Dutch Cancer Registry. Data on recurrence, polyp characteristics, treatment and follow-up were collected from hospital records, and endoscopy, radiology and pathology reports. Recurrence was defined as the detection of metastasis or local recurrence during follow-up. A T1 CRC was defined as high-risk in the presence of one or more of the following characteristics: poorly differentiated histology, positive resection margins, submucosal invasion depth of > 1 mm or presence of lymphangio-invasion. Patients were subdivided into group A: primary surgical resection or group B: endoscopic resection with additional surgical resection. Results: A total of 388 patients were eligible for analysis (group A: n=206; group B: n=182). Median follow-up was comparable between both groups (A: 50 months IQR 22.3-80.2 vs. B: 56 months IQR 22.2-79.8). Overall recurrence was 23/388 (5.9%). This included 3 local recurrences and 20 distant metastases (9 liver, 6 lung, 4 peritoneum and 1 brain). Of the baseline characteristics, patients treated by primary surgery were more often female and older. Polyps treated by primary surgery were larger in size, more often right-sided and more often had a sessile or flat morphology. Risk analysis was therefore adjusted for the propensity score. No difference was found between primary surgery and secondary surgery for the presence of lymph node metastasis at baseline (9.7% vs. 8.8% respectively; adjusted OR 1.1, 95% CI 0.5-2.5; $P=0.796$) and development of recurrence (A: 7.3%, B: 4.4%; adjusted HR 1.04, 95% CI 0.3-3.2; $P=0.230$). Recurrence rates were 15.9/1000 person-years in group A and 9.5/1000 person-years in group B ($P=0.233$). There was no difference in treatment related mortality, and morbidity between group A and B (1.5% vs. 2.2%, $P=0.584$ and 21.8% vs 29.1%, $P=0.105$). Conclusion: Endoscopic resection of high-risk T1 CRCs followed by surgery had no negative effect on patient outcomes (lymph node metastasis at baseline, recurrence rate, morbidity and CRC-related mortality). These findings justify an attempt to remove polyps suggestive of T1 CRC to prevent surgery of low-risk T1 CRC and polyps containing intra-mucosal carcinomas.

102

International Multicenter IPMN Registry: Role of EUS-FNA Cytology, CEA and Amylase in the Diagnosis of Intraductal Papillary Mucinous Neoplasms

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Background: Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are being diagnosed with increasing frequency. Due to their malignant potential, one of the most challenging decisions is whether to undergo periodic surveillance or perform surgical resection. Cyst fluid analysis obtained by endoscopic ultrasonography (EUS) with fine needle aspiration (FNA) is the most widely recommended strategy to characterize these lesions but has limited accuracy in single center studies. Aim: Determine the accuracy of cytology, CEA and amylase as preoperative diagnosis tests in IPMNs. Methods: An international multicenter IPMN registry was started in 2005 including 3 centers in Europe and 1 in the USA. Each center's database was reviewed to select those patients who underwent surgical resection due to clinically suspected IPMN. Only those with EUS and FNA were finally included in the analysis. Results: From October 1997 to September 2014, 1167 patient with a clinical diagnosis of IPMN were included in the registry. Of these, 237 patients underwent surgery and 180 had both EUS and FNA performed preoperatively. For differentiating benign from malignant IPMNs, cytological analysis showed a high specificity (88%) but a low sensitivity (39%) with a positive predictive value of 76%, a negative predictive value of 60% and an accuracy of 64%.For distinguishing IPMNs from non-mucinous cysts, CEA had a median value of 525.5 ng/ml in IPMNs (n=78) versus 9.7 ng/ml in non-mucinous cysts (n=6), showing an area under the ROC curve (AUC) of 0.87 (Figure 1). The optimal CEA cut-off value for this distinction was 129 ng/ml at which the sensitivity was 76.9% and the specificity 83.3%, yielding a positive predictive value of 95.9% and a negative predictive value of 41.9%. CEA was poor at predicting grade of neoplasia in IPMNs (AUC of 0.55). The accuracy of the combination of CEA and cytology for the diagnosis of IPMNs was also calculated (Table 1). Despite the differences noted in the median amylase levels between IPMNs and MCAs (3210 U/L versus 497 U/L respectively), this test had poor overall accuracy showing an AUC of 0.65. The results for amylase to discriminate all mucinous versus all non-mucinous lesions were also unsatisfactory (AUC of 0.25). Conclusions: In this large multicenter prospective registry, EUS-FNA cytology had a limited role for diagnosing IPMNs due to its lack of sensitivity. We confirm the modest usefulness of CEA to differentiate between mucinous and non-mucinous lesions. However, CEA had limited accuracy to decide grade of malignancy among IPMN-suspected lesions. Amylase, on the contrary, did not show any utility in the diagnosis of IPMN, nor to differentiate between MCAs and IPMNs, nor to recognize malignancy.

Table 1. Accuracy of fluid tests for the diagnosis of intraductal papillary mucinous neoplasms in the study cohort

Test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CEA+	76.9	57.1	90.9	30.8
CEA+, amylase+	46.4	83.3	92.9	25.0
Cytology+, amylase+	21.4	87.5	85.7	24.1
CEA+, cytology+, amylase+	21.4	83.3	85.7	18.5

PPV: Positive predictive value NPV: Negative predictive value
CEA+: ≥129 ng/ml. Cytology+: Intracellular mucin. Amylase+: ≥1326 U/L (IPMN optimal cut-off value)

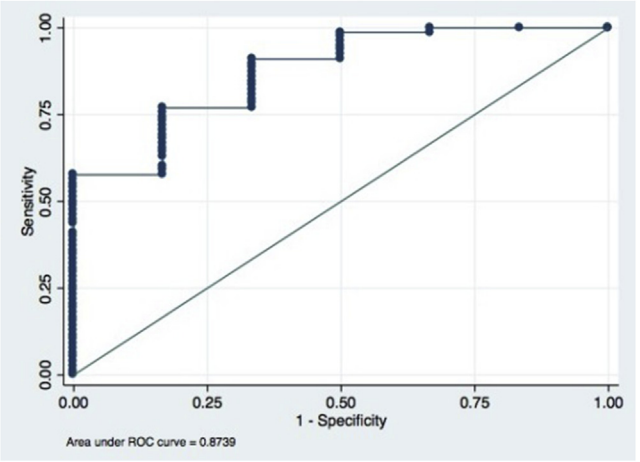

Figure 1. ROC curve of CEA between intraductal papillary mucinous neoplasms and non-mucinous lesions.

103

EUS Guided Ethanol Injection of Pancreatic Cystic Neoplasms: Outcomes of a Prospective Study

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Background: Pancreatic cystic neoplasms (PCN) may require surgical resection. A safe and non-operative treatment of these lesions is desirable. Endoscopic ultrasound (EUS) guided ethanol injection of PCNs has shown to be partially effective but studies are limited. Aim:To assess safety and efficacy of EUS guided ethanol injection of PCNs. Methods: Single center, prospective pilot study conducted between 2007-2014, in which patients ≥ 18 years of age with presumed mucinous cystic neoplasm (MCN) or branch duct intraductal papillary mucinous neoplasm (bIPMN) ≥ 1 cm in maximum diameter were recruited. Patients whose cysts communicated with main pancreatic duct, had imaging evidence of mural nodules or invasive malignancy were excluded. During EUS cyst features were assessed, the cyst was punctured and aspirated and contrast was injected into the cyst under fluoroscopy to exclude ductal communication. Contrast was aspirated from the cyst, which was then filled with an equal volume of 80% ethanol solution. The cyst was repeatedly aspirated and refilled with fresh ethanol solution for a total treatment time of 5 minutes. Follow-up imaging was obtained at 6 & 12 month intervals. Subjects with residual or recurrent lesions were offered additional EUS guided ethanol lavage treatments. Treatment success was defined as a reduction in cyst volume of ≥80%. Results: 23 patients were enrolled and underwent cyst ethanol lavage; treatment was successful in 12 (52%) (Table 1). When comparing responders to non-responders, no significant differences were identified in demographic or clinical features (Table 2). Complete cyst resolution occurred in only 2 patients over a 6 & 7 year follow up period, respectively. One patient had <10% decrease in cyst volume after ethanol lavage and one patient's cyst increased in size during follow-up. 2 adverse events occurred: 1 patient developed acute pancreatitis that resolved with conservative management and another patient developed abdominal pain after ethanol lavage with no evidence of pancreatitis. 4 patients died over the follow-up period, including one patient who developed pancreatic adenocarcinoma 41 months after undergoing ethanol lavage

of a bIPMN lesion. His cancer arose from the treated cyst. Conclusions: EUS guided ethanol injection of PCNs was feasible with an adverse event rate of 9%. Volume of treated cysts decreased by >80% in only half of the participants and one participant subsequently developed pancreatic adenocarcinoma in the treated cyst. This technique is not sufficiently effective for widespread use in presumed MCN and bIPMN lesions. Technical limitations, such as septations blocking flow of ethanol to all parts of the cyst & dilution of ethanol by residual fluid in the cyst may have contributed to the limited effectiveness of ethanol lavage. Further study of EUS guided techniques for ablation of PCNs is warranted.

Table 1. Baseline characteristics of N=23 patients

Variable	Value
Age, yrs (range)	70 (53 - 86)
Sex, N (%)	
Male	13 (57%)
Female	10 (43%)
Location of cystic lesions	
Head/uncinate process	15 (65%)
Neck	2 (9%)
Body	6 (26%)
Tail	0 (0%)
Duration of follow up, months	40 (37; 9-82)
Initial cyst volume as seen on CT or MRI, cm3	9.7 (4.6; 0.93-53)
Initial cyst fluid CEA level, ng/mL*	6742 (377; 0.2-100,560)
Patients that responded to therapy with ≥ 80% change in cyst volume, N (%)	12 (52%)
Patients that underwent more than one EUS guided ethanol treatment, N (%)	5 (22%)

Data presented as means. Medians and ranges shown in parentheses when distributions were skewed.
*Missing data N=2

Table 2. Comparison of patients that achieved ≥ 80% volume reduction in cyst size to patients that achieved < 80% volume reduction in cyst size

Variables	≥ 80% cyst volume reduction (N = 12)	< 80% cyst volume reduction (N = 11)	P-value
Age, yrs (range)	73 (61-86)	67 (53-80)	0.16
Male gender, N (%)	6 (50%)	7 (64%)	1.0
Initial cyst volume as seen on CT or MRI, cm3	7.3 (3.4; 1.2 - 39.5)	12.5 (5; 0.9 - 53)	0.39
Initial cyst fluid CEA, ng/mL¥	10522 (381; 0.2-100,560)	3306 (377; 14.9-31,412)	0.67
Epithelial cells seen in ethanol lavage, N (%)◇	7(78%)	7 (88%)	1.0
Moderate/High cellularity of ethanol lavage, N (%)*	7(78%)	5(63%)	0.89

Data presented as means. Medians and ranges shown in parentheses when distributions were skewed.
¥ Missing data for ≥80% group N=2
◇ Missing data for ≥80% group N=3; for < 80% group N=3
* Missing data for ≥80% group N=3; for < 80% group N=3

104

Is Alcohol Required for Effective Pancreatic Cyst Ablation? the Prospective Randomized CHARM Preliminary Trial Pilot Study

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Background: EUS-guided chemoablation of mucinous type pancreatic cysts with ethanol and paclitaxel has been shown to be an effective intervention; however, a 3-10% rate of pancreatitis, presumably linked to ethanol use, remains an issue. Furthermore, the role and importance of ethanol in the ablation process unclear. In this study we aim to determine: the need for ethanol in the ablation process, whether alcohol free ablation would reduce the rate of pancreatitis, and to evaluate the efficacy of a chemotherapeutic ablation cocktail specifically tailored for pancreatic neoplasia. Methods: This is a prospective, randomized, double-blinded, single center, clinical trial. The initial 22 patients with appropriate pancreatic cystic lesions enrolled are reported here as preliminary results. Inclusion criteria included pancreatic mucinous cystic lesions of 1-5 cm with four or less compartments, no clear communication with the main pancreatic duct, or evidence of pancreatitis. Patients with known or suspected malignancy, pseudocysts, or serous cystadenomas were excluded. Patients underwent EUS-guided fine needle aspiration and then lavage with either 80% ethanol or normal saline. Both groups were then treated with a chemotherapy cocktail of 3 mg/ml paclitaxel and 19 mg/ml gemcitabine. To measure response, cross sectional imaging was obtained at 3, 6, and 12 months for all patients. The primary endpoint was overall reduction in cyst volume with the same definition of response used in previous trials. Results: At six months, patients randomized to the alcohol arm had a 91% average volume reduction, with a 90% reduction noted in the alcohol-free arm over the same time period. Importantly, complete response rates did not differ between groups. Both the alcohol and alcohol-free groups recorded 60% rates of complete ablation at six months which increased to 75% for both groups at the 1 year completion. One patient in the alcohol arm developed acute pancreatitis (10%) requiring a 36-hr. hospital stay with no complications in the alcohol-free arm. Also notable was that the full one-year of surveillance was required to capture complete cyst ablation in several cases. Conclusions: This study revealed no difference in the rate of complete ablation between the alcohol ablation group and the alcohol-free arm. Therefore, in this initial evaluation, alcohol does not appear to be required for effective cyst ablation when a chemoablation cocktail specifically tailored for pancreatic neoplasia is used.

Results

	% Reduction in cyst size after 3 m	% Reduction in cyst size after 6 m	Complete Response after 6 m	Complete Response after 12 m	Major complications	Minor complications
Alcohol arm	74%	91%	3/5 (60%)	3/4 (75%)	1/10 (10%)	3/10 (30%)
Free alcohol arm	81%	90%	3/5 (60%)	3/4 (75%)	0/12 (0%)	0/10 (0%)
Overall in both arms	77.5%	90.5%	6/10 (60%)	6/8 (75%)	1/22 (4.5%)	3/22 (14%)