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Research Article

Cyst Fluid CEA Concentration Discriminates Between Benign and Premalignant/Malignant Pancreatic Cystic Lesions. A Prospective Cohort Study

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Abstract

Background: The objective was to evaluate cyst fluid carcinoembryonic antigen (CEA) as a putative marker of malignant potential in cystic pancreatic lesions (CPLs).

Methods: Prospective observational cohort study from October 2008 to September 2013. A total of 190 patients with CPL were included after signed informed consent. Endoscopic ultrasound and fine needle aspiration (EUS-FNA) of cyst fluid for analysis of CEA was performed as part of the multimodal preoperative workup. The diagnostic performance of cyst fluid CEA value for the selection of the right patients for surgery was evaluated by histological diagnosis as endpoint in operated patients. Diagnostic accuracy of cyst fluid CEA was assessed by receiver operating characteristics (ROC) analysis.

Results: Surgical resection was performed in 65 patients (34.2%) after evaluation by the multidisciplinary team (MDT). Lesions with malignant potential or invasive carcinomas were found in 46 (70.8%) of resected cases. Area under the ROC curve (AUC) for cyst fluid CEA was 0.71 (95% CI 0.61 - 0.81). The optimal cut-off value was 36.3 ng/mL (sensitivity 74%, specificity 62%, PPV 51%, NPV 81%, accuracy 66%). A total of 125 patients (65.8%) were never operated, 15 because of unresectable carcinoma. None of the 110 patients undergoing conservative management developed malignancy at a median follow-up of 46.5 months (range 4 - 86 months).

Conclusion: There is a significant diagnostic yield of cyst fluid CEA determination, when the indication for surgical exploration is focused.

Keywords: *Carcinoembryonic Antigen (CEA); Cystic Pancreatic Lesion (CPL); Mucinous Cystic Neoplasm; Serous Cystic Neoplasm; Pancreatic Resection; Pancreatic Adenocarcinoma; Intraductal Papillary Mucinous Neoplasm; Diagnostic Accuracy*

Introduction

Cystic pancreatic lesions (CPL) are identified in increasing numbers due to widespread use of cross sectional imaging together with an aging population [1]. This has generated important clinical questions: First, is it a CPL, and second, if yes, is the CPL malignant, or is there a potential for malignancy in the future? The indication for surgical resection depends on the latter question, which puts the subject of diagnostic accuracy in focus as the risk of malignancy varies significantly between different histological entities of CPLs. Improved imaging quality, endoscopic ultrasound with fine needle aspiration (EUS-FNA) for biochemical analysis of cyst fluid and the introduction of new guidelines, may contribute to better patient selection. However, the evidence in the literature behind all recommendations is limited [2,3], which implies significant uncertainty in the prediction of clinical outcome. The heterogeneity of data concerning the risk of

malignancy in branch duct IPMN (BD-IPMN) illustrates the problem facing clinicians [4-6]. One reason for the wide perspective of differing opinions may be that numerous reports on potential for malignancy in CPLs derive from retrospective studies, typically combining histological diagnoses with re-evaluations of imaging data, resulting in illusory and misleading diagnostic accuracy which is unaffordable during the preoperative workup. The present investigation was initiated to conduct a prospective analysis of the diagnostic accuracy and clinical consequences of a revised diagnostic algorithm, introduced in our department in 2008. Thus, transition to a selective approach was imperative, but only partly based on the Sendai criteria [7]. In cyst fluid, carcinoembryonic antigen (CEA) is the tumor marker of choice for distinguishing mucinous from serous neoplasms [8,9]. The clinical core question is when to recommend surgical removal, and our analysis is focused on this objective. The main methodological problem in this research field is that histological diagnoses can mainly be obtained from patients undergoing surgical exploration, whereas the potential diagnostic yield of cyst fluid CEA applies to the whole patient cohort [3].

The main objective of the present study was therefore to analyze prospectively the diagnostic performance of CEA values in preoperative patient selection, applied on the whole heterogeneous cohort of patients, referred with CPL. End points were histological diagnosis in operated patients.

Methods

In October 2008, our institution established a multidisciplinary research program, including all patients referred to our tertiary HPB center with solid or cystic pancreatic and periampullary lesions [10]. The program was approved by the Regional Ethical Committee. All patients gave written informed consent and underwent prospective registration of clinical and biochemical data.

New Management Algorithm

Our management algorithm for CPLs was revised before study initiation, based on the Sendai criteria. The preoperative workup was based on imaging with multidetector CT angiography, using a triphasic pancreas protocol [11]. MRI/MRCP was performed if necessary for clarification of duct anatomy or when the cystic nature of the lesion was questioned. EUS-FNA and biochemical analysis of cyst fluid was performed whenever feasible, and the main focus was the aspiration of cyst fluid for CEA analysis. If a patient underwent more than one EUS, the primary investigation was recorded for this study. A CEA value above 192 ng/mL was considered indicative of a mucin-producing neoplasm, in line with data from the Cooperative Pancreatic Cyst Study Group [12]. EUS was generally not performed if the cyst was very small (approx. 10 mm), the patient refused or the patient was deemed a candidate for surgical exploration at the initial evaluation. The flow chart for CPL patients after the revision is illustrated in Figure 1. Our Multidisciplinary Pancreatic Team (MDT) evaluated clinical, radiological and EUS-based data, focusing on the indication for surgery. A small, but significant group had cystic lesions with solid components, which was locally advanced or metastatic carcinomas (n = 15). All these lesions were histologically verified, and the patients were subsequently referred to palliative chemotherapy. After supplementary investigations 65 patients were selected for surgery. The remaining cohort (n = 110) were managed conservatively.

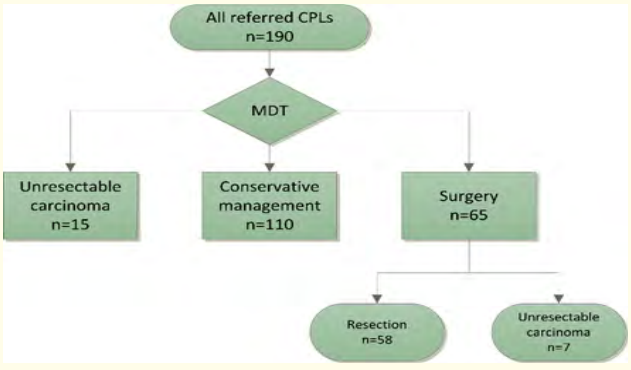

Figure 1: *Patient management flow chart for CPLs.*

Indications for surgery were symptomatic lesions and assumed mucin-producing lesions with risk of malignancy according to the Sendai consensus. Thus, the indication for surgery was based on clinical, radiological and biochemical parameters, with special emphasis on CEA in cyst fluid. The focus of the MDT meeting was to conclude on treatment modality: Surgery or conservative management.

Statistics

Descriptive statistics are given as median and range. Median regression was used to estimate the median (with 95% confidence interval) cyst fluid CEA values within the resected and unresected groups, and to test for between group differences in medians. The diagnostic performance of cyst fluid CEA was evaluated by plotting a receiver operating characteristic (ROC) curve to illustrate the extent to which cyst CEA values are able to distinguish lesions with malignant potential from those without. The predictive value of CEA was summarized by the area under the curve (AUC) with a 95% confidence interval. Sensitivity and specificity was plotted for the measured CEA values. CEA cut-off level was determined by optimizing the accuracy with the prerequisite of a clinically relevant sensitivity, set to a minimum of 0.70. The statistical analyses were performed with Stata 14 (StataCorp LP, College Station TX, USA).

Results

From October 2008 to September 2013 a total of 572 patients were referred to our tertiary HPB center suspected of pancreatic or periampullary neoplasms, 190 (33.2%) with cystic pancreatic lesions.

Surgically explored patients (n = 65)

In surgically explored patients, EUS was performed in 53 of 65 patients. CEA in cyst fluid could be obtained in 44 patients. During the surgical resection cyst fluid was collected from two additional patients. Accordingly, cyst fluid CEA values were obtained from 46 patients (70.8%) pre- or peroperatively. EUS-FNA for CEA analysis was successful in 44/53 procedures, with no difference related to cyst size and location, see table 1. There were no significant complications from the EUS-FNA. In one patient cyst fluid was collected both pre- and peroperatively. CEA ranges in each subgroup are given in Table 2.

		Diameter of the largest cyst, mm		
	n	< 20	20 - 30	> 30
Surgery, frequency (per cent)	65	13	14	38
Location				
Head	29	5	8	16
Body	10	2	3	5
Head and body	3	2	1	0
Tail	13	3	0	10
Head and tail	1	0	0	1
Body and tail	6	0	2	4
All segments	3	1	0	2
Multifocality	13	3	3	7
EUS	53	11	13	29
CEA	44	10	10	24
EUS-CEA, success rate		91%	77%	83%

Table 1: *Size and location of operated cysts.*

Diagnostic status	Subjects (♂/♀)	Age (median, range)	Cyst fluid CEA obtained (%)	CEA value (median, range; ng/mL)
All patients	190 (72/118)	69 (21 - 87)	120 (63.2)	42 (0.2 - 54824)
Surgical exploration	65 (27/38)	66 (21 - 83)	46 (70.8)	224 (2.1 - 15000)
Unresectable carcinoma, histologically verified	15 (9/6)	67 (53 - 83)	9 (60)	251 (0.2 - 54824)
Unoperated – conservative follow-up	110 (36/74)	70 (25 - 87)	65 (59.1)	21.8 (0.2 - 2363)

Table 2: *Patient characteristics and CEA values in selected subgroups.*

Surgically explored patients have significantly (p = 0.004) higher median cyst fluid CEA levels (median 224 [95% CI 115 to 333] ng/mL) than unoperated (median 21.8 [-58.4 to 10] ng/mL). The selection of lesions in need of surgical resection resulted in 110 patients managed conservatively and 65 undergoing surgical exploration. Surgical procedures are summarized in Table 3. There was no postoperative 90-day mortality.

	N
Total number of patients	65
Male/female	27/38
Surgical procedure	
Pancreaticoduodenectomy	23
Pancreaticoduodenectomy and distal resection	1
Distal pancreatectomy	26
Enucleation	3
Total pancreatectomy	5
Peroperatively unresectable	7

Table 3: *Surgical procedures.*

Final histological diagnoses and cyst fluid CEA values in all explored patients are shown in Table 4. Carcinomas were found in 25 patients, and premalignant mucin-producing neoplasms in 21, altogether 70.8% of resected patients. The relationship between preoperative diagnoses and final histology is illustrated in Table 5. In 26 patients expected to have BD-IPMN, the final histological diagnosis matched the preoperative diagnoses in only 9 cases (34.6%). Four of these patients with mistaken preoperative diagnosis had invasive ductal adenocarcinoma. Three tumors were recognized as probable carcinomas during the first MDT meeting, and then operated without delay, but found unresectable because of locally advanced or metastatic disease. One patient with an assumed retention cyst insisted on surgery. The lesion removed was a cystic neuroendocrine neoplasm.

	Histology	Malignant	Cyst fluid CEA	CEA value (median/range)
◀MD-IPMN	6	3	2	11 - 281
◀Mixed type-IPMN	7	1	6	622 (12 - 49399)
◀BD-IPMN	10	1	8	289 (61 - 1971)
◀MCN	4	1	3	27 (3 - 539)
Pancreatic ductal adenocarcinoma	12	12	9	405 (25 - 15000)
Cholangiocarcinoma	1	1	1	537
Acinar cell carcinoma	1	1	0	n/a
Solid pseudopapillary neoplasms	2	2	1	49
Neuroendocrine neoplasm	3	3	3	0.9 (0.4 - 2.2)
Retention cyst	5	n/a	4	1261 (198 - 54824)
Pseudocyst	4	n/a	2	346 - 518
Multicentric acinar cell adenoma	1	n/a	1	23710
Serous cystic neoplasm	9	0	6	0.7 (0.2 - 9828)
Total	65	25	46	

Table 4: *Histological diagnoses and CEA values in cyst fluid.*

◀Lesions with malignant potential

	Preoperative diagnosis									
Final pathology	**MD-IPMN**	**Mixed type IPMN**	**BD-IPMN**	**MCN**	**SPPN**	**Cancer**	**SCN**	**Retention cyst**	**NET**	**SUM**
MD-IPMN	6									6
Mixed type IPMN	2	3	2							7
BD-IPMN			9			1				10
MCN			1	2			1			4
SPPN				1	1					2
DAC	4		4	1		2	1			12
SCN			4			1	4			9
Retention cyst			4	1						5
NET								1	2	3
Pseudocyst	1		1			2				4
Acinar cell carc.			1							1
Cholangiocarc.	1									1
Multicentr. acin.	1									1
SUM	15	3	26	5	1	6	6	1	2	65

Table 5: *Preoperative diagnoses related to final histology.*

Footnote: Left column gives final histological diagnosis.
Head row shows what preoperatively was supposed to be the condition, representing the indication for surgery.

Clinical consequences of misdiagnoses among operated patients

The clinical importance of delayed surgery in the four patients with unresectable pancreatic carcinoma is uncertain, as the advanced tumor stage might already have been present at the initial presentation 4-6 months earlier. Furthermore, the uncertainty associated with the preoperative diagnoses resulted in resection of patients with asymptomatic SCNs, pseudocysts, retention cysts and Sendai negative and benign BD-IPMNs, altogether 14 cases and in additional four patients delayed surgical procedures. Accordingly, misdiagnoses were clinically relevant in 18 patients (27.7%).

Clinical consequences of misdiagnoses among patients followed conservatively

There are no final histological diagnoses in these patients, except in the 15 cases with unresectable carcinoma, recognized at the first MDT. The residual 110 patients were conceived to have CPL without (e.g. SCN) or with low malignant potential at baseline (e.g. Sendai negative BD-IPMN). The majority were followed with serial imaging. The observation time was median of 46.5 months (range 4-86 months), investigated for expansive growth, intramural nodules and development of CPL-related symptoms including recurrent episodes of pancreatitis until further follow-up was found unnecessary, or follow-up is ongoing.

Predictive value of cyst fluid CEA

The potential clinical benefit of determining cyst fluid CEA is to improve patient selection between surgical exploration and observation. If all unexplored patients (n = 110) are conceived as correctly diagnosed, the ROC is 0.71 (95%, CI 0.61 - 0.81), illustrating that cyst fluid CEA value has acceptable diagnostic value when applied on the whole patient cohort (Figure 2). The best cut-off value in this series was 36.3 ng/mL, resulting in sensitivity 74%, specificity 62%, positive predictive value (PPV) 51%, negative predictive value (NPV) 81% and accuracy 66% (Figure 3).

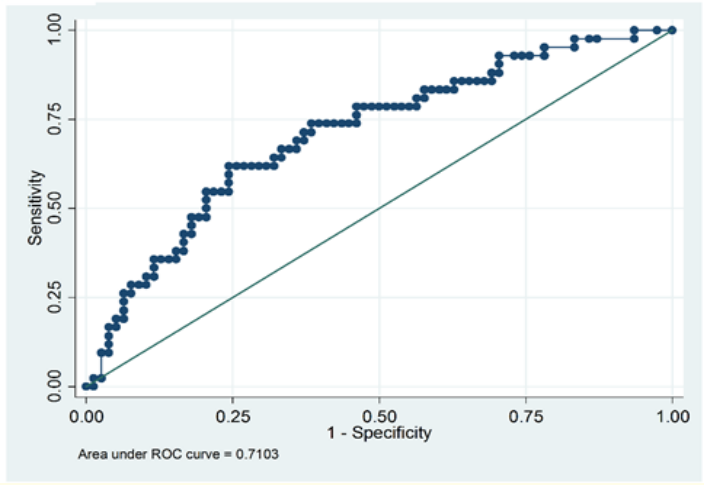

Figure 2: *ROC curve for patients with measured cyst fluid CEA level (n = 120): Separation of CPL patients who need surgical exploration from those who only need conservative follow-up.*

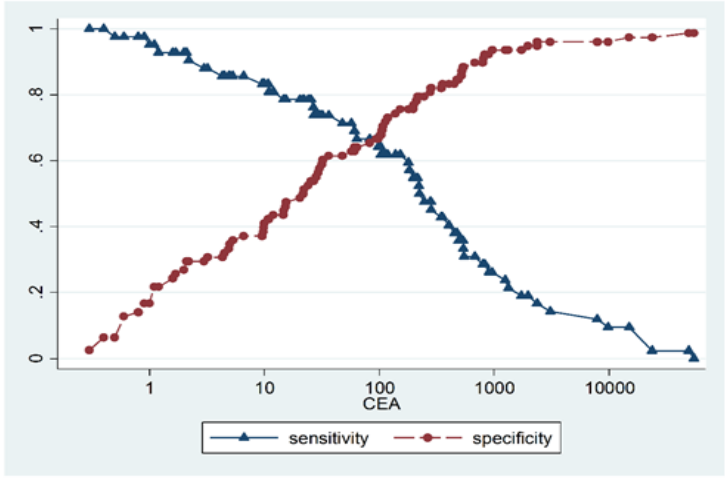

Figure 3: *Corresponding sensitivity and specificity curves of cyst fluid CEA levels.*

Discussion

The limited accuracy of preoperative diagnoses of CPL in a heterogeneous patient cohort with significant numbers of invasive carcinoma is clearly illustrated in this series. The most important clinical concern and the focus of this study is to identify patients who already have or are going to develop a malignant lesion. The accuracy of preoperative diagnosis of 44.6% and clinical impact of misdiagnosis in 27.7% of the patients is inferior to a recent study from Sweden reporting corresponding rates of 60.9% and 8.5%, respectively [13]. The reason for this difference is not apparent, but the retrospective selection of resected, verified CPL in the Swedish study cohort limits the histological heterogeneity observed in the present prospective patient cohort, and may explain part of the discrepancy. The difference is even greater when the present data are compared with an Italian cohort [14], reporting that the preoperative diagnosis of BD-IPMN was always confirmed by the final pathological diagnoses. However, the same group reports an inaccurate preoperative diagnosis of CPL in 22% of the patients when all subgroups are included [15]. The present data emphasize the uncertainty of recommendations based on consensus based guidelines, when applied to a heterogeneous patient cohort of all histological CPL entities. Expectations of the high diagnostic accuracy of studies which reassess radiology retrospectively in light of histological diagnoses [5,13,15] is probably dangerous in this situation, as it may result in observation of patients with invasive carcinoma. The 4-6 months delay of surgery in four of the present patients illustrates the potential serious clinical consequences of misdiagnoses. The proportion of malignant tumors was 21.1% recognized during the first MDT or shortly thereafter, is high in this series. Half underwent surgical exploration, the other half were only histologically verified. High proportions of pancreatic ductal adenocarcinoma among patients referred with CPL have been reported also by others [16,17].

A selective approach for surgery in CPL patients is mandatory [18] and the present preoperative workup included EUS-FNA for cyst fluid CEA analysis. Selection for surgery was partly based on the original Sendai criteria. But these guidelines only apply to MCN and IPMN, which constituted 41.5% of the patients. Sendai validation studies have confirmed that the criteria have a high sensitivity, but the specificity is low [19]. In spite of this, overall the modified management algorithm reduced the frequency of lesions without malignant potential among resected patients from 61% to 29.2%, which is in line with the expected clinical benefit of EUS with/without FNA in other recent reports [20-22]. However, the present patient selection has been far from optimal, and the main problem in the resected group seems to be the high frequency of lesions with malignant potential or invasive carcinoma operated too late. This fact raises concern also for the 110 patients managed conservatively, as they lack histological confirmation of the diagnoses. However, no pancreatic cancers developed during a median of 4 years follow-up. Accordingly, we conclude that patient selection has so far been correct in these cases.

The prevalence of malignancy in subgroups of IPMNs has recently been reported in the range of 19 - 42% [9], and several investigators underline that BD-IPMN is not an aggressive entity [14,23,24]. This is contradicted by the Heidelberg and Tampa groups [4,25]. The present series emphasize the risk of long-term observation of BD-IPMN lesions, even though this is part of current guidelines [26]. Similarly, MCN lesions are reported not to be an aggressive entity [27]. However, the frequency of carcinoma in situ and invasive carcinoma in MCN lesions have been reported as high as 44% [28]. This is another illustration of the limited evidence behind current concepts.

Cyst fluid CEA is the predictor of choice for separation of mucinous versus serous CPL [29,30]. An early report [12] recommended CEA cut-off value 192 ng/mL for prediction of mucinous lesions, which was part of the present algorithm. However, significantly lower values have been advocated [31], and a recent report from Philadelphia describes best accuracy for discrimination between mucinous and serous CPLs by CEA cut-off value 30 ng/ml [9]. However, we included patients with CPLs prospectively, and our study design did not allow a post-hoc selection of serous and mucinous lesions. Actually, only 66% of the patients who underwent surgery harbored a cystic lesion which would have been included by the definition from the original CEA study [12]. Accordingly, the present analysis is not focused on the differentiation between serous and mucinous lesions, but the use of cyst fluid CEA as marker of malignant or premalignant CPLs. In this regard, we found that the best cyst fluid CEA cut-off was 36.3 ng/mL, and the analyses seems helpful in patient selection for surgery even though is cannot predict final histological diagnosis in this study. Even molecular analyses of cyst fluid DNA did not increase performance characteristics in 48 patients with mucinous pancreatic cysts [32], but the combination of cyst fluid gene mutations and clinical features have recently been found to classify CPL type correctly with sensitivity 90-100%, specificity 92 - 98% in 130 operated patients [33]. In the near future significantly improved preoperative selection of CPL patients seems affordable.

There are similarities between preoperative workup for CPL and cancer screening, recently analyzed by the High Value Care Task Force of the American College of Physicians (ACP). Their work resulted in new guidelines [34,35] with components relevant for the present discussion. First, the best management algorithm depends critically on the clinical setting in which it is applied. The perspective of the HPB referral center cannot be transferred to health care first line and vice versa. Second, it is essential for every health care institution to be aware that incidental findings can lead to a cascade of decisions that bring about benefit or harm [36]. This raises uncertainty on one of the recent recommendations of the latest AGA guidelines: Cysts with at least 2 high-risk stigmata, such as cyst size > 3 cm, dilated main pancreatic duct or presence of an associated solid component, should be examined by EUS-FNA [3,37]. Based on the present study, this set of data should rather lead to surgery without further investigation. Moreover, the recent observation that functional outcome and quality of life (QoL) after surgery is equal to healthy references [38], justify surgical resection of more patients with CPL in the future.

The diagnostic yield of cyst fluid CEA as preoperative indicator for surgery in the whole patient cohort is acceptable. However, CEA level from cyst aspirate should form a part of the evaluation including clinical data, imaging and serum markers. A careful evaluation of every single patient managed conservatively should be performed.

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