

Utility of endoscopic ultrasound for assessment of locoregional recurrence of pancreatic adenocarcinoma after surgical resection



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ABSTRACT

Background and study aims Up to 80% of patients with pancreatic adenocarcinoma develop locoregional recurrence after primary resection. However, the detection of recurrent pancreatic ductal adenocarcinoma (RPDAC) after pancreatic surgery can be challenging because of difficulty distinguishing locoregional recurrence from normal post-operative or post-radiation changes. We sought to evaluate the utility of endoscopic ultrasound (EUS), in detecting pancreatic adenocarcinoma recurrence after surgical resection and its impact on the clinical management of patients.

Patients and methods This was a retrospective study of all pancreatic cancer patients who underwent EUS post-resection at two tertiary care centers between January 2004 and June 2019.

Results Sixty-seven patients were identified. Of these, 57 (85%) were diagnosed with RPDAC, resulting in change in clinical management of 46 (72%) patients. EUS identified masses not seen on computed tomography, magnetic resonance imaging, or positron emission tomography in seven (14%).

Conclusions EUS is useful in detecting RPDAC after pancreatic surgery and can lead to significant impact on clinical management.

Introduction

Pancreatic cancer is diagnosed in more than 50,000 individuals each year [1]. The 5-year survival for pancreatic cancer is approximately 9%. In those who undergo surgical resection, median survival is approximately 1.5 years with median recurrence

at 1 year [2]. Isolated recurrence may be managed with repeat surgical, chemotherapeutic, or radiation treatment, and can lead to increase in survival [3].

Detection of recurrent pancreatic ductal adenocarcinoma (RPDAC) after tumor resection can be challenging because of

difficulty distinguishing locoregional recurrence from normal postoperative changes. Currently, the National Comprehensive Cancer Network recommends postoperative surveillance consisting of semi-annual CA 19–9, chest computed tomography (CT) and pancreas imaging via CT or magnetic resonance imaging (MRI) for at least 2 years [4]. Although there are no standardized CA19–9 goals, some studies have used a single value of CA19–9 as a surrogate predictor for clinical recurrence or response to treatment postoperatively [5]. However, the role of endoscopic ultrasound (EUS) in postoperative surveillance is not clearly defined [6, 7].

We sought to evaluate the clinical utility of EUS in detecting RPDAC after surgical resection. Our secondary aim was to investigate the impact of EUS results on clinical decision making based on the presence and absence of histologic confirmation of recurrence across two institutions.

Patients and methods

This retrospective cohort from a prospectively maintained database included two tertiary care health systems. Patients greater than 18 years old were included if they had surgical resection of biopsy proven pancreatic adenocarcinoma from January 2004 to June 2019 and at least one postoperative EUS. Patients were considered to have pathologic recurrence if they had cytologically or histologically proven recurrence on EUS-guided sampling. If no malignant cytology was available, patients were considered to have recurrence if they had a combination of disease progression on non-invasive imaging (CT, MRI, and/or positron emission tomography [PET]) and rising serum CA19–9 (“composite recurrence”). Patients were excluded if they did not have any adenocarcinoma or had recurrent distant metastases.

Patients were categorized as “mass” group if they had a discrete mass or cyst on any imaging or “non-mass” group if they had any abnormalities, such as nonspecific soft tissue thickening, lymphadenopathy, and/or vessel involvement manifested by hypochoic cuffing (extravascular migratory metastasis) in the absence of a discrete mass. Cysts were included in the mass group because they are distinct lesions offering a more defined target for sampling than other abnormalities, such as soft tissue thickening. The latest CA19–9 value was collected within 3 months prior to resection. Cytology was classified as malignant, benign, atypical or indeterminate. The latest CT, MRI, and PET findings within 3 months of the patients’ first post-op EUS were analyzed. EUS and cross-sectional imaging were interpreted by the performing endoscopist and radiologists at each study site, respectively. Endoscopists in the study had greater than 5 years of EUS experience. Tumor staging, serial CA19–9 values prior to surveillance EUS, and data on neoadjuvant or adjuvant chemoradiation were also collected. Values less than 37 U/ml were considered normal range for CA 19–9 [6].

The secondary outcome of impact on the clinical management was defined as a change in medical management (addition, subtraction, or dose change of chemotherapy or radiation), repeat surgery, palliative withdrawal of care, further diag-

nostic imaging following EUS or continued routine surveillance. Dates of death were based on queries of the US Social Security Death Index. This study was approved by the institutional review board of each institution and data user agreement was entered.

Data analysis

Data was collected at each institution and deidentified before pooling. Statistics for continuous variables are presented as mean values \pm standard deviation and differences between means were evaluated using a t or F test. Categorical variables were evaluated using either the Chi-Squared test or Fischer’s exact test. All tests were two-tailed. $P < 0.05$ was considered statistically significant. All analyses were performed using SAS version 9.4.

Results

A total of 67 patients with pancreatic adenocarcinoma were included. Patients were predominantly white, male (63%), with mean age at time of surgery of 62.5 years and had received adjuvant chemotherapy (77.6%) (► **Table 1**). There was no significant difference in tumor staging (► **Table 1**). Forty patients (60%) had cross-sectional imaging for routine surveillance, and the remainder had imaging prompted by weight loss, abdominal pain, diarrhea or an increasing CA19–9. The mass group contained 49 patients (73%) and non-mass included 18 patients (27%) (► **Table 1**).

EUS findings

EUS identified a mass or cyst in 41 of 49 patients (83.6%) in the mass group (► **Table 1**, ► **Table 2**). Among these, a mass or cyst was seen in seven patients (14%) on EUS not previously identified by recent CT, MRI, or PET ($P > 0.2$, ► **Table 3**). The seven patients in this group had the following interventions: four surveillance, two initiation or a change in chemotherapy or radiation, and one was lost to follow-up. Two of the seven patients had malignant cytology on fine-needle aspiration, of which one was medically treated and the other was lost to follow-up. In nine patients (18%), a mass or cyst was seen only on CT, MRI, or PET and not seen on EUS exam. EUS agreed with CT, MRI, and PET findings in 41 of 67 patients (61%) (► **Table 3**).

Recurrence

Of those surveilled, 57 patients (85%) had RPDAC: 42 (64.6%) had pathologic recurrence and 15 patients (23%) had composite recurrence (► **Table 4**). Two patients did not have pathologic recurrence status available. Overall, FNA was performed in 50 patients (74%), 42 (63%) in the mass group and eight (12%) in non-mass group (► **Fig. 1**, ► **Table 3**, ► **Table 5**). Of all FNAs in the presence of a mass on both cross-sectional and EUS imaging, 23 (56%) had cytology consistent with malignancy. Notably, three patients (12%) who had an abnormality on EUS but did not have a mass on cross-sectional imaging had malignant cytology (► **Table 5**). In the patients with pancreatic cysts and recurrence, one cyst found on EUS and CT was malignant, two patients had cysts found on MRI but not on EUS which were ma-

► **Table 1** Baseline patient characteristics.

Factor	Total (N=67)	Non-mass group (N=18)	Mass group (N=49)	P value
Age at time of surgery (yr)	62.5 ± 10.3	61.7 ± 8.4	62.8 ± 11.0	0.71 ¹
Time between surgery and EUS (yr)	2.1 ± 1.8	2.2 ± 1.7	2.0 ± 1.9	0.71 ¹
Time between surgery and recurrence (yr)*	2.7 ± 2.7	3.7 ± 3.9	2.4 ± 2.0	0.091 ¹
Gender				0.87 ²
▪ Male	42 (62.7)	11 (61.1)	31 (63.3)	
▪ Female	25 (37.3)	7 (38.9)	18 (36.7)	
Race				0.64 ³
▪ Black	2 (3.0)	1 (5.6)	1 (2.0)	
▪ Hispanic	3 (4.5)	1 (5.6)	2 (4.1)	
▪ White	59 (88.1)	16 (88.9)	43 (87.8)	
▪ Other	3 (4.5)	0 (0.0)	3 (6.1)	
Primary tumor staging				0.99 ³
▪ T1	4 (6.0)	1 (5.6)	3 (6.1)	
▪ T2	18 (26.9)	5 (27.8)	13 (26.5)	
▪ T3	42 (62.7)	11 (61.1)	31 (63.3)	
▪ T4	3 (4.5)	1 (5.6)	2 (4.1)	
Node staging				0.60 ²
▪ N0	30 (44.8)	9 (50.0)	21 (42.9)	
▪ N1	37 (55.2)	9 (50.0)	28 (57.1)	
Metastasis staging				
▪ M0	67 (100.0)	18 (100.0)	49 (100.0)	
Chemo type				0.42 ³
▪ None	6 (9.0)	0 (0.0)	6 (12.2)	
▪ Neoadjuvant	1 (1.5)	0 (0.0)	1 (2.0)	
▪ Adjuvant	52 (77.6)	15 (83.3)	37 (75.5)	
▪ Both	8 (11.9)	3 (16.7)	5 (10.2)	
Radiation type				0.51 ²
▪ None	32 (47.8)	7 (38.9)	25 (51.0)	
▪ Neoadjuvant	7 (10.4)	3 (16.7)	4 (8.2)	
▪ Adjuvant	28 (41.8)	8 (44.4)	20 (40.8)	
Imaging indication				0.89 ²
▪ Surveillance	40 (59.7)	11 (61.1)	29 (59.2)	
▪ Suspect recurrence	27 (40.3)	7 (38.9)	20 (40.8)	

Statistics presented as mean ± SD, median [P25, P75], median (min, max) or N (column %).

P values:

¹ ANOVA

² Pearson's chi-square test

³ Fisher's Exact test

* Data not available for all subjects. Missing values: Time between surgery and recurrence=4.

► **Table 2** Imaging findings suggesting recurrence.

		No. patients with abnormal imaging findings*	
		Mass group (N=49)	Non-mass group (N=18)
CT N=65	Mass	28	
	Cyst	1	
	Lymphadenopathy		5
	Soft tissue thickening		10
	Vessel involvement		3
	Other		3
MRI N=18	Mass	2	
	Cyst	4	
	Lymphadenopathy		1
	Soft tissue thickening		0
	Vessel involvement		0
	Other		3
PET N=33	Mass	15	
	Cyst	0	
	Lymphadenopathy		2
	Soft tissue thickening		4
	Vessel involvement		1
	Other		0
EUS N=67	Mass	34	
	Cyst	7	
	Lymphadenopathy		6

* Number may exceed N if a patient had multiple different findings on same modality.

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; EUS, endoscopy ultrasonography.

lignant, and one patient had imaging of a cyst on EUS and MRI with atypical cytology clinically deemed to be recurrence. CA19–9 trends over time were graphed (► Fig. 2). There was no significant correlation between CA19–9 trends and recurrence, nor was there a statistically significant association between surgery type and recurrence (► Fig. 2, ► Table 6).

EUS impact on clinical management

Overall, 46 patients (72%) had a change in clinical management from routine surveillance following EUS (► Table 5). In 15 patients (21%) who did not have CT, MRI, or PET findings of a mass but did have an abnormality on EUS, five (33%) had a change in medical management or underwent surgical intervention (► Table 5). Of the 16 patients with FNAs negative for RPDAC, four (25%) had a change in management (► Table 5).

► **Table 3** EUS concordance with CT, MRI, and PET abnormalities.

	Mass group	Non-mass group	Total
N	49	18	67
Findings only on CT/MRI/PET	9	7	16
Findings only on EUS	7	0	7
Both EUS & CT/MRI/PET agree	33	8	41
Agreement between EUS & MRI			61.2%

Comparing among groups as well as concurrent vs exclusive imaging detection showed no significant difference between groups after Bonferroni correction ($P>0.2$).

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; EUS, endoscopic ultrasonography.

► **Table 4** Type of recurrence by mass category.

	Mass group (N=47)	Non-mass group (N=18)	% total patients (N=65)
Pathologic+ (N=42)*	34	8	42 (64.6%)
Composite+ (N=15)	8	7	15 (23.08%)
Pathologic-/composite- (N=8)	5	3	8 (12.31%)

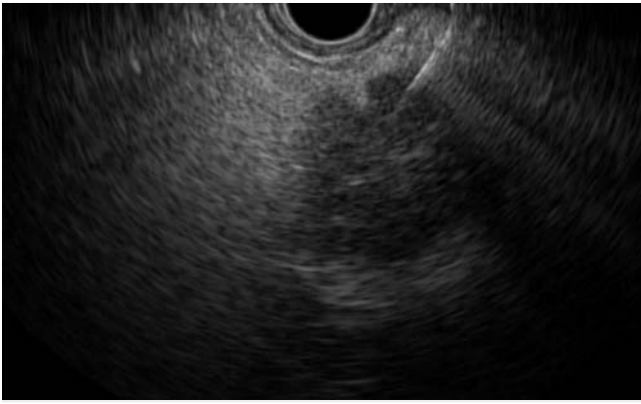
FNA, fine-needle aspiration.

* Two patients did not have records of pathologic recurrence status. If FNA was not performed or inconclusive, pathologic recurrence was based on biopsy of metastatic lesion, surgical biopsy or brushings (n=15).

In the event that FNA was not performed or results were unknown, eight of 17 patients (47%) patients had a change in management from routine surveillance. Two patients had lesions not amenable to FNA, one patient was discharged from oncology after both CT and EUS were unremarkable for signs of recurrence, and three patients had non-diagnostic FNA. One patient had a sudden hospitalization within 5 days of EUS and expired, so impact of EUS could not be established.

Discussion

Currently, pancreatic adenocarcinoma surveillance after surgical resection does not include the use of EUS. We sought to understand the contribution of EUS to clinical decision making when recurrence is suspected and compare this with current surveillance methods including cross-sectional imaging and serum CA19–9. Studies have compared test characteristics of EUS to CT for the diagnosis of pancreatic ductal adenocarcinoma masses but few have evaluated the performance of EUS against other cross-sectional imaging in detecting RPDAC [7, 8]. Our health system performs approximately 150 pancreatic surgeries annually for malignancy, and rates of locoregional recurrence approach 15% at 1 year after surgery. We found that EUS identified masses not seen on CT, MRI, or PET in up to 14% of patients ($P>0.2$). This rate is similar to a previous study in



► **Fig. 1** Fine-needle aspiration of hypoechoic mass in the remnant pancreas.

which three of eight patients (38%) had a pancreatic mass mischaracterized as a cyst on CT or undetected and later found on EUS for RPDAC [9].

Following EUS, 46 patients (73%) had a change in their management from continued surveillance. About one-half (52%) initiated or changed a chemotherapy/radiation regimen, six (13%) had a repeat surgery, and seven (15%) entered hospice or palliative care. EUS was especially helpful in further evaluating equivocal cross-sectional imaging findings and serum oncologic markers. Interestingly, 25% of patients with negative FNA also had a change in their clinical management; the majority of these patients had an abnormality on diagnostic EUS. The overall clinical presentation of the patients and high rate of RPDAC likely influenced decisions to change treatment in patients with abnormal EUS in spite of FNA results. Technical concern for FNA sampling error in the setting of altered postsurgical anatomy may also have been a consideration for variations in management; notably, there was no difference in pathologic or composite recurrence among patients with different types of resection (► **Table 6**). In this study, EUS was performed in response to abnormal surveillance imaging or symptoms; however, more studies are needed to determine whether regular EUS surveillance is warranted following pancreatic adenocarcinoma resection.

Most patients with recurrence had a mass on imaging. Chemotherapy and radiation at the time of initial diagnosis and surgery of pancreatic ductal adenocarcinoma did not appear associated with the later manifestation of recurrence as a mass. FNA in the absence of a discrete mass was less likely to have malignant cytology compared to patients with a discrete mass (3 vs 26 patients, ► **Table 5**). In another study, FNA of soft tissue around an artery was only 55% sensitive for RPDAC [10]. This may be due to lack of an adequate target for FNA, leading to sampling error. Alternatively, patients without a mass may be at lower risk for recurrence; this idea is corroborated by the role of tumor size as a risk factor for disease progression. This may suggest that EUS with FNA should be more strongly considered if a mass is present and less so if a mass is absent, given low yield. Only eight patients had neither evidence of composite or pathologic recurrence, and they lived an average of 5

years after surgery. Future studies could evaluate the role of normal appearing EUS as a complement to normal appearing cross-sectional imaging in deescalating therapy or exiting surveillance.

Other studies have evaluated declining CA19–9 as a surrogate for response to chemotherapy and to detect locoregional recurrence [5, 11]. A post-resection CA19–9 value >90 has been associated with nearly 3-fold risk of locoregional recurrence [11]. In the current study, this cutoff would capture most patients with pathologic recurrence, but several patients with baseline post-resection CA19–9 >90 would prove difficult to stratify. No one CA19–9 trend correlated well with findings of recurrence. Observing different trends may be due to a subgroup of our patients with non-secreting pancreatic tumors or negative for Lewis blood group antigens *a* and *b*, as these patients typically do not have abnormal levels of CA19–9 [6]. There may be selection bias in choosing CA19–9 trends that correlate with EUS findings, as patients rarely are referred for EUS with down-trending or neutral CA19–9 alone. The lack of significant associations between CA19–9 trends and cytology may speak to the small sample size in this study or to the limited number of data points used to define the visual trends or both. This absence of strong associations corroborates the need for research into more specific or sensitive biomarkers, such as s-pancreas antigen-1 (SPan-1) [6].

Limitations of this study include its retrospective design, and inconsistent intervals between labs, EUS and cross-sectional imaging. As postoperative EUS surveillance is not currently standard of care, the number of patients undergoing routine EUS surveillance was limited. EUS for suspicion of recurrence may have introduced selection bias, thereby increasing rates of recurrence detection; however, a comparison of patient indications for EUS did not show a significant difference in EUS findings. Additionally, imaging was interpreted by various endoscopists and radiologists, which predisposes radiologic interpretation to interobserver bias while mimicking real world practice. The current study includes the use of neoadjuvant chemotherapy, whose use has significantly increased over the study period due to improved survival benefit; the evolving use of neoadjuvant chemotherapy may require further studies to reflect its potential impact on EUS detection of locoregional recurrence [12]. More CA19–9 data points would be needed to better assess longitudinal trends. This study was conducted at tertiary referral centers, and some patients may have resumed follow-up locally after EUS, which limited time to observe recurrence.

Conclusions

EUS as an adjunct to cross-sectional imaging and serum markers is useful in diagnosis and management for RPDAC. EUS-FNA is more often diagnostic in patients with a pancreatic mass rather than those patients with nonspecific cross-sectional or EUS findings. Based on our data, CA19–9 is not significantly correlated with EUS findings or cytology of postoperative recurrence.

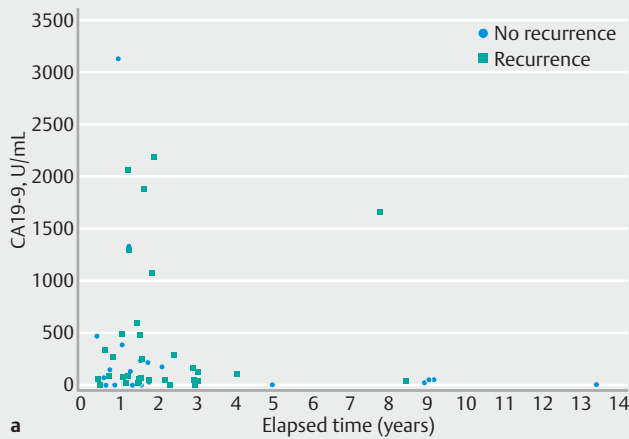
► **Table 5** CT, MRI, PET and EUS findings with subsequent cytology and impact on management.

CT findings	EUS findings	FNA cytology	Clinical management	No. patients			
CT/MRI/PET with mass N = 42	EUS abnormality N = 38	FNA malignant N = 23	Medical treatment	16			
			Palliative	3			
			Repeat labs	1			
			Surgery	1			
			Other	2			
			Lost to follow-up	1			
		FNA indeterminate N = 3	Surveillance	1			
			Surgery	1			
			Other	1			
		FNA atypical N = 2	Medical treatment	1			
			Surgery	1			
		FNA negative N = 8	Surveillance	3			
			Palliative	2			
			Repeat labs	1			
	Other		1				
	Lost to follow-up		1				
	FNA not performed/unknown N = 2	Medical treatment	1				
		Surveillance	1				
	EUS no abnormality N = 4	FNA malignant N = 0	FNA indeterminate N = 0	FNA atypical N = 0	FNA negative N = 0		
						FNA not performed/unknown N = 4	Medical treatment
Repeat labs							1
Other							2
CT/MRI/PET without mass N = 25		EUS abnormality N = 15	FNA malignant N = 3	Medical treatment	2		
	Lost to follow-up			1			
	FNA indeterminate N = 1		Surveillance	1			
			FNA atypical N = 1	Surveillance	1		
	FNA negative N = 7		Medical treatment	1			
			Surveillance	6			
			FNA not performed/unknown N = 3	Medical treatment	1		
	Palliative			1			
	Surgery	1					
	EUS no abnormality N = 10	FNA malignant N = 0	FNA indeterminate N = 0	FNA atypical N = 1	Surgery	1	
					FNA negative N = 1	Surveillance	1
FNA not performed/unknown N = 8		Medical treatment	1				
		Surveillance	4				
		Surgery	2				
Other		1					

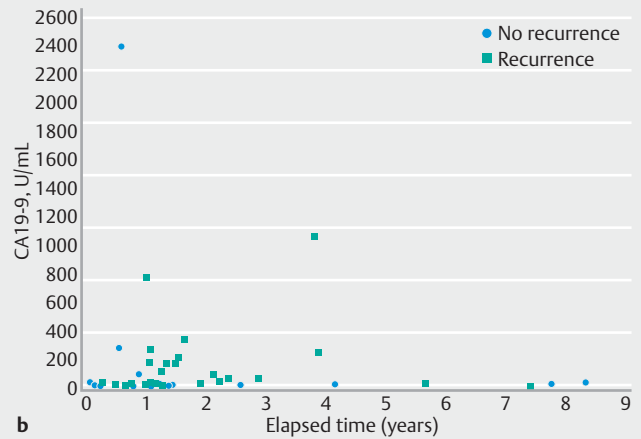
Medical treatment: Initiation or change in chemotherapy regimen. Surveillance: Routine monitoring by CA19–9 or CT/MRI/PET imaging or both. Repeat lab: Repeat imaging and/or serum markers earlier than next surveillance diagnostics.

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; EUS, endoscopic ultrasonography.

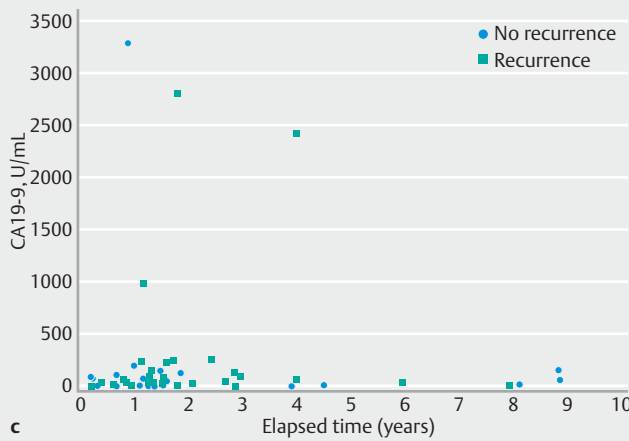
Pre-endoscopic ultrasound CA 19-9 vs elapsed time from surgery



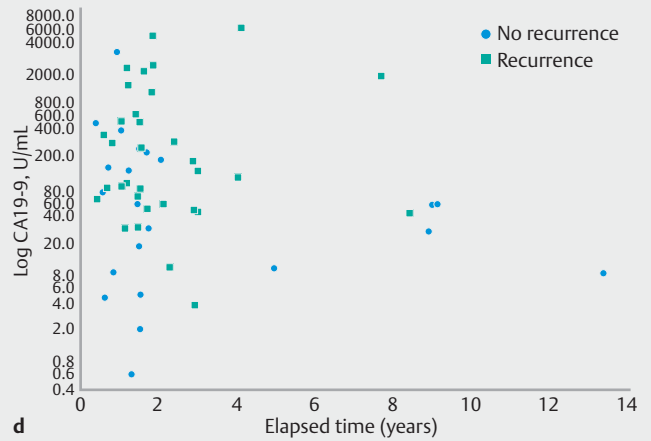
1st post-operative CA 19-9 vs elapsed time from surgery



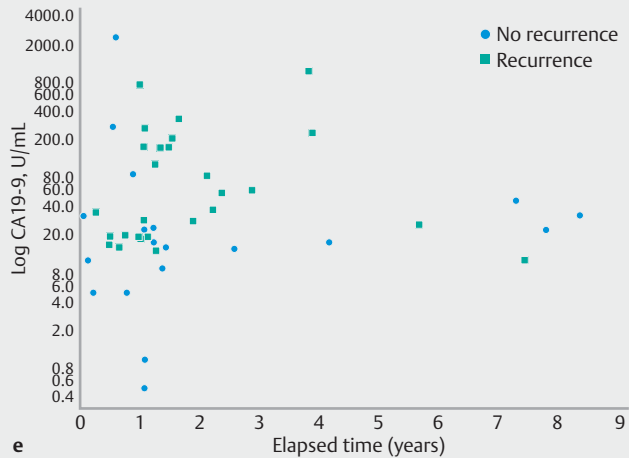
2nd post-operative CA 19-9 vs elapsed time from surgery



Log pre-endoscopic ultrasound CA 19-9 vs elapsed time from surgery



Log 1st post-operative CA 19-9 vs elapsed time from surgery



Log 2nd post-operative CA 19-9 vs elapsed time from surgery

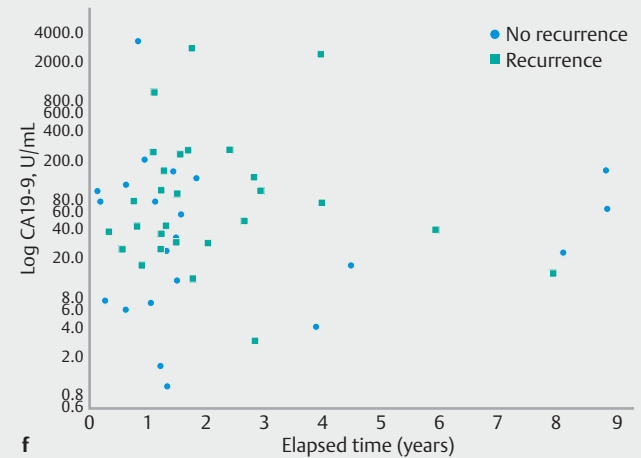


Fig. 2 Pre EUS and postoperative CA19-9 values vs elapsed time from surgery. **a** Pre EUS CA19-9 vs elapsed time from surgery. **b** First post-operative CA19-9 vs elapsed time from surgery. **c** Second postoperative CA19-9 vs elapsed time from surgery. **d** Log pre EUS CA19-9 vs elapsed time from surgery. **e** Log first postoperative CA19-9 vs elapsed time from surgery. **f** Log second postoperative CA19-9 vs elapsed time from surgery.

► **Table 6** Recurrence by surgery type.

Surgery type (n=67)	Total number of patients per surgery type	Pathologic recurrence (%)		Composite recurrence (%)	
Pancreaticoduodenectomy	24	19	(79.17)	15	(62.50)
Pylorus-preserving pancreaticoduodenectomy	24	11	(45.83)	20	(83.33)
Total pancreatectomy	3	2	(66.67)	1	(33.33)
Partial pancreatectomy	16	10	(62.50)	11	(68.75)

Bonferroni corrections applied for multiple comparisons. There are no significant associations between surgery types and recurrence types ($P < .05$).

Competing interests

Dr. Simons-Linares received a grant from Boston Scientific and Food/Beverage from AbbVie, Takeda Pharmaceuticals, and Gilead Sciences. Dr. Pluskota has received food and beverage from Shire North American Group, Covidien LP, AbbVie, Olympus America, Novo Nordisk, and Boston Scientific. Dr. Confer received consulting fee from Merit Medical Systems Inc, speaking fees from Boston Scientific, and food/beverage from Boston Scientific, Cook Medical, Intercept Pharmaceuticals, Olympus America, AbbVie, Allergan Inc, and Covidien. Dr. Khara received consulting fees from CONMED, Aries Pharmaceuticals, Gyrus ACMI Inc, US Endoscopy and Olympus America Inc. He also received speaker fees from Olympus America Inc, Covidien LP, Boston Scientific Corp, and an honorarium from GI Supply, Inc. Travel/lodging stipend from Covidien, Boston Scientific, Aries Pharmaceuticals, Olympus Corporation of the Americas, Olympus America Inc, Gyrus ACMI Inc, US Endoscopy and CONMED. Educational stipend was received from Olympus Corporation of the Americas He received food/beverage from AbbVie, Covidien LP, CONMED, Boston Scientific, Cook Medical LLC, Olympus Corporation of the Americas, and Olympus America. Dr. Johal received consulting fees from Gyrus ACMI Inc and Olympus Corporation of the Americas, speaker fees from Boston Scientific Corporation, Olympus America Inc. He also received food and beverage from Boston Scientific, Olympus America, Gyrus ACMI and AbbVie. Dr. Diehl received consulting fees from Olympus America, Boston Scientific, Cook Medical, Pentax, Endogastric Solutions, Inc, US Endoscopy, and Wilson Cook. He has received honoraria from GI Supply, Inc. He received fees for services other than consulting from Lumendi, ERBE USA Inc, and Covidien. Dr. Walsh received food and beverage from Aesculap, Inc, Ethicon, Davol, Integra LifeScience, Sirtex Medical, Covidien, Abbott Laboratories, and Intuitive Surgical. Dr. Chahal received consulting fees from Boston Scientific. She received food/beverage from Boston Scientific and Covidien.

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