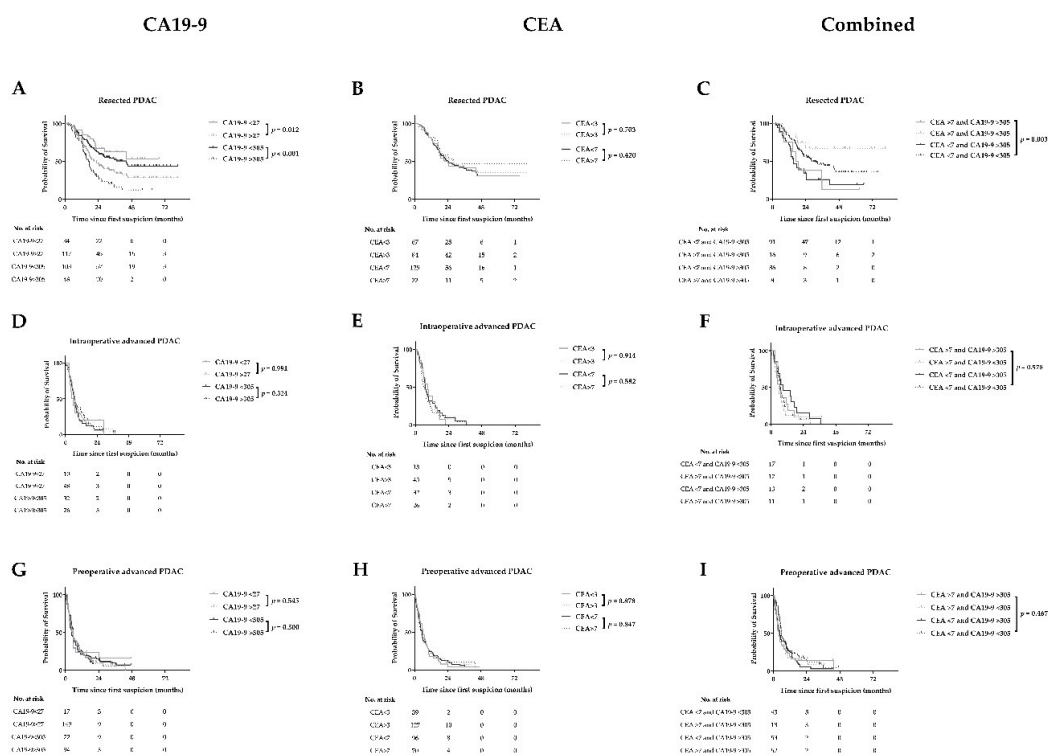


Article

# Stage-Specific Value of Carbohydrate Antigen 19-9 and Carcinoembryonic Antigen Serum Levels on Survival and Recurrence in Pancreatic Cancer: A Single Center Study and Meta-Analysis

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**Figure S1.** Survival curves for CA19-9 and CEA serum levels stratified by resected PDAC (A–C), intraoperative advanced PDAC (D–F) and preoperative advanced PDAC (G–I) patients.

**Table S1.** Multivariable cox regression analysis for overall survival including combined CA19-9 and CEA levels.

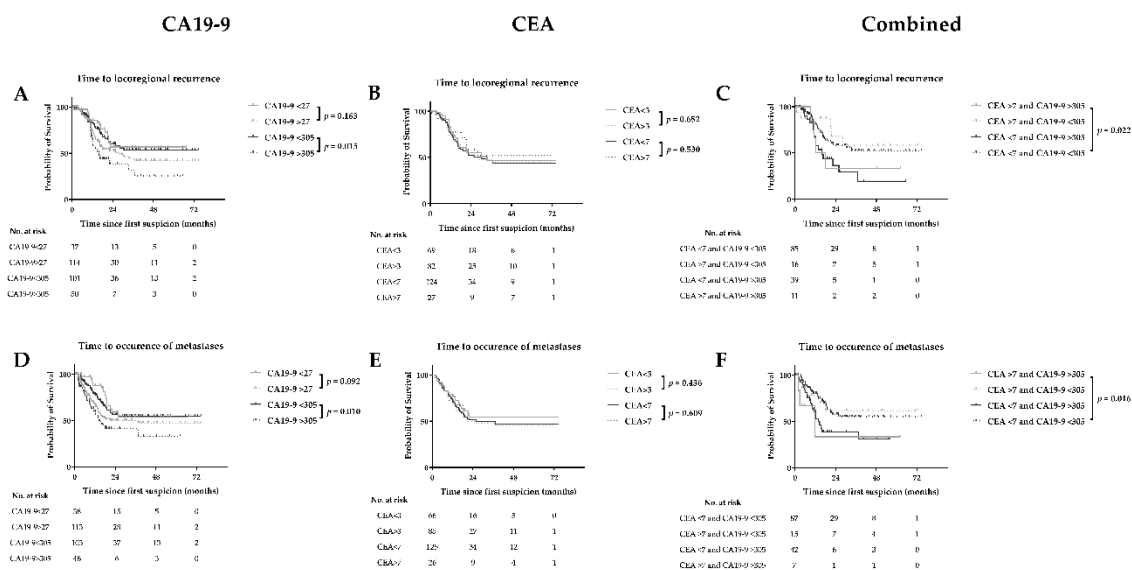
Parameter	Entire Cohort (n = 375)			Resected Cohort (n = 151)			Advanced PDAC Cohort (n = 224)		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
<b>Tumormarkers</b>									
CA19-9 < 305 kU/L and CEA < 7 µg/L	1.00	1.00–1.00	1.000	1.00	1.00–1.00	1.000	1.00	1.00–1.00	1.000
CA19-9 < 305 kU/L and CEA > 7 µg/L	1.24	0.72–2.12	0.439	0.40	0.11–1.38	0.145	1.30	0.76–2.21	0.337
CA19-9 > 305 kU/L and CEA < 7 µg/L	1.71	1.21–2.42	0.003	2.23	1.24–4.01	0.007	1.00	0.65–1.54	0.992
CA19-9 > 305 kU/L and CEA > 7 µg/L	2.17	1.46–3.23	<0.001	2.74	0.86–8.70	0.088	0.99	0.62–1.58	0.967
<b>Age (yr)</b>									
>65 yr	1.28	0.98–1.67	0.070	1.03	0.65–1.64	0.889	1.02	0.72–1.44	0.917
<b>Sex, n (%)</b>									
Female	0.84	0.65–1.08	0.167	0.98	0.62–1.57	0.943	0.65	0.47–0.88	0.006
<b>ASA score, n (%)</b>									
I	1.00	1.00–1.00	1.000	1.00	1.00–1.00	1.000	1.00	1.00–1.00	1.000
II	1.13	0.78–1.65	0.526	1.69	0.73–3.91	0.224	1.61	1.03–2.52	0.038
III-IV	1.75	1.15–2.67	0.010	3.85	1.53–9.69	0.004	2.23	1.31–3.79	0.003
<b>Bilirubin</b>									
>17 µmol/L	0.78	0.61–1.01	0.063	0.79	0.48–1.30	0.351	1.09	0.80–1.51	0.581
<b>Tumor size</b>									
>20 mm	2.36	1.48–3.75	<0.001	1.60	0.82–3.13	0.170	2.73	1.36–5.50	0.005

Abbreviations: CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen.

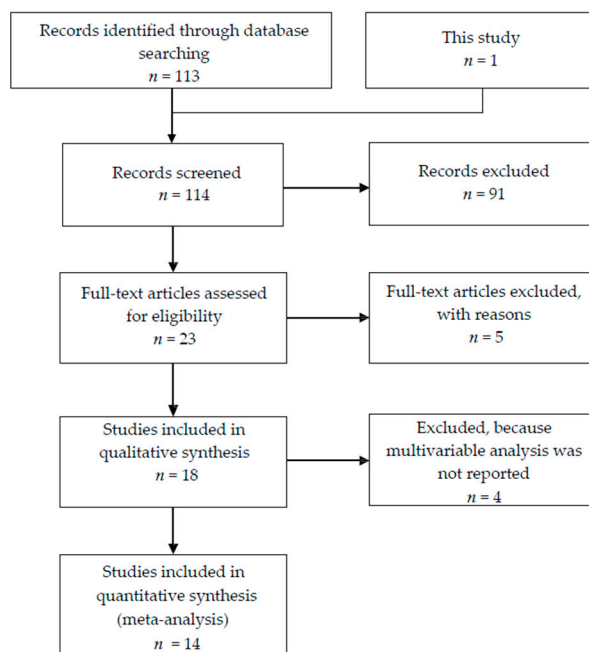
**Table S2.** Multivariable cox regression analysis for recurrence in resected PDAC cohort including combined CA19-9 and CEA levels.

Parameter	General Recurrence ( <i>n</i> = 84) *			Locoregional Recurrence ( <i>n</i> = 55) *			Distant Recurrence ( <i>n</i> = 61) *		
	HR	95% CI	<i>p</i> -value	HR	95% CI	<i>p</i> -value	HR	95% CI	<i>p</i> -value
Tumormarkers									
CA19-9 <305 kU/L and CEA <7 µg/L	1.00	1.00–1.00	1.000	1.00	1.00–1.00	1.000	1.00	1.00–1.00	1.000
CA19-9 <305 kU/L and CEA >7 µg/L	0.62	0.23–1.70	0.354	0.66	0.17–2.60	0.551	0.65	0.21–2.00	0.449
CA19-9 > 305 kU/L and CEA < 7 µg/L	1.63	0.93–2.86	0.091	1.70	0.83–3.48	0.149	1.65	0.85–3.21	0.140
CA19-9 >305 kU/L and CEA >7 µg/L	1.41	0.40–5.00	0.591	1.44	0.51–4.02	0.491	1.49	0.31–7.09	0.614
Tumor size									
>20 mm	1.97	1.03–3.76	0.041	1.79	0.83–3.83	0.136	1.77	0.84–3.74	0.135
Perineural invasion									
Present	1.26	0.77–2.07	0.353	1.13	0.62–2.06	0.692	1.41	0.78–2.53	0.257
Margin status									
R1	1.48	0.94–2.32	0.092	1.40	0.80–2.46	0.242	1.61	0.95–2.71	0.075
Differentiation grade									
Well	1.00	1.00–1.00	1.000	1.00	1.00–1.00	1.000	1.00	1.00–1.00	1.000
Moderate	1.88	0.91–3.86	0.088	1.61	0.73–3.53	0.234	2.04	0.82–5.08	0.125
Poorly	1.66	0.51–5.41	0.109	1.06	0.46–2.44	0.895	2.18	0.88–5.39	0.091
Undifferentiated or unknown	1.66	0.51–5.41	0.405	0.65	0.14–3.18	0.599	2.67	0.73–9.76	0.138

Abbreviations: PDAC: pancreatic ductal adenocarcinoma; HR: Hazard Ratio; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen. \* Some patients had both locoregional recurrence and distant metastases.



**Figure S2.** Recurrence patterns (locoregional (A–C) vs metastatic recurrence (D–F)) by CA19-9 and CEA serum levels.



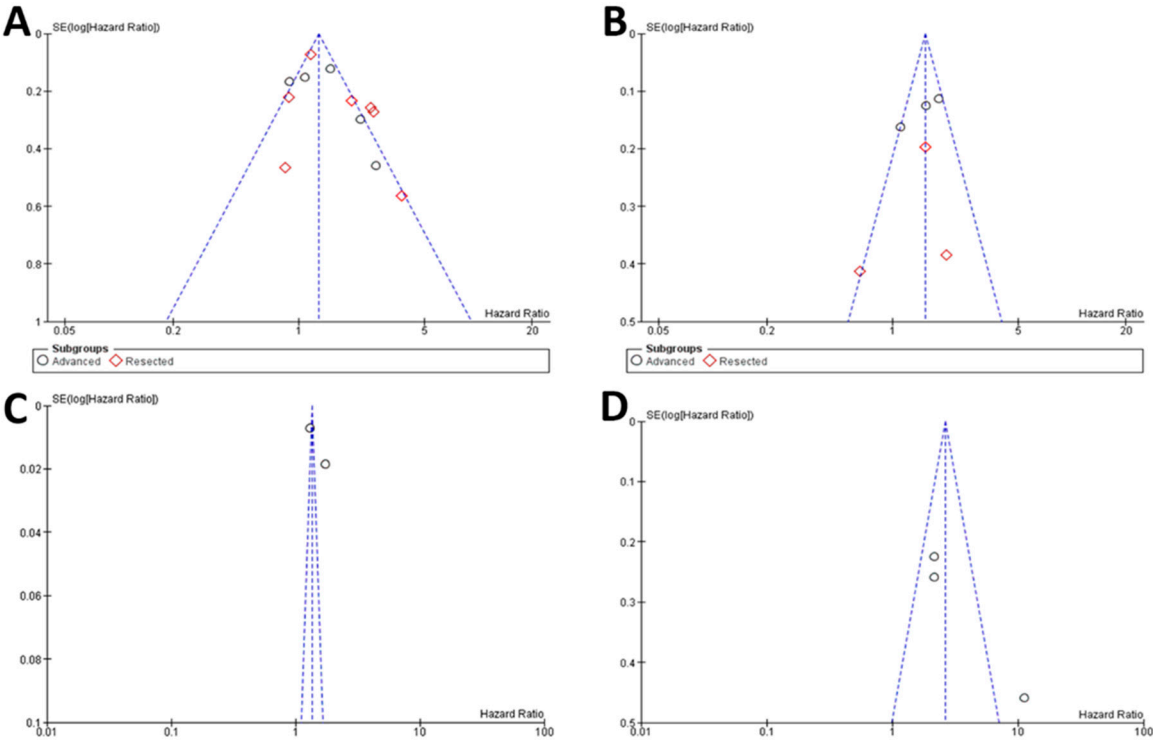
**Figure S3.** Flowchart of study selection.

**Table S3.** Studies that report on prognostic value of serum CA19-9 and CEA on overall survival in PDAC patients.

Study	Country	Study Population (No. of Patients)	Cut-off Level (CEA: $\mu\text{g/L}$ ; CA19-9: kU/L)	Fraction above Cut-off (%)	Median OS (95% CI) below Cut-off (Months)	Median OS (95% CI) above Cut-off (Months)	Performance of Multivariable analysis
CA19-9							
Ni et al., 2005 [1]	China	Resected and advanced PDAC ( $n = 105$ )	1,000	37.8	9	6	No
Ferrone et al., 2006 [2]*	United States	Resected PDAC ( $n = 111$ )	37 200 1000 2000	NR	28 28 28 22	19 14 12 13	No
Smith et al., 2008 [3]	United Kingdom	Resected PDAC ( $n = 109$ )	150	58.7	22.1	10.4	Yes
Martin et al., 2012 [4] *	United States	Resected ( $n = 30$ ) and advanced ( $n = 93$ ) PDAC	37	Resected: 50 Advanced: 72	Resected: 36 Advanced: 32.3	Resected: 20 Advanced: 11.3	No
Hartwig et al., 2013 [5] *	Germany	Resected PDAC ( $n = 1543$ )	<5	6.4	-	26.8	No
			5–37	18.2		28.5	
			37–100	14.0		26.9	
			100–250	16.0		22.5	
			250–500	13.2		20.1	
			500–1,000	11.9		15.4	
1000–2,000	8.2		12				
2000–4,000	6.0		12.3				
$\geq 4000$	6.1		14.4				
Lee et al., 2013 [6]	Korea	Resected PDAC ( $n = 187$ )	376	75.4	12.4	13.5	Yes
Dong et al., 2014 [7]	China	Resected PDAC ( $n = 139$ )	339	43.3	24.9	11.9	Yes
Reitz et al., 2015 [8]	Austria	Resected and advanced PDAC ( $n = 393$ )	931	47.1	10	5	Yes
Asaoka et al., 2016 [9]	Japan	Resected PDAC ( $n = 46$ )	230	30.4	NR	15.8	Yes
Imaoka et al., 2016 [10]	Japan	Resected PDAC ( $n = 119$ )	37	68.0	55.9	44.9	Yes
Imaoka et al., 2016 [11]	Japan	Metastatic PDAC ( $n = 433$ )	37	84.8	8.9	7.8	Yes

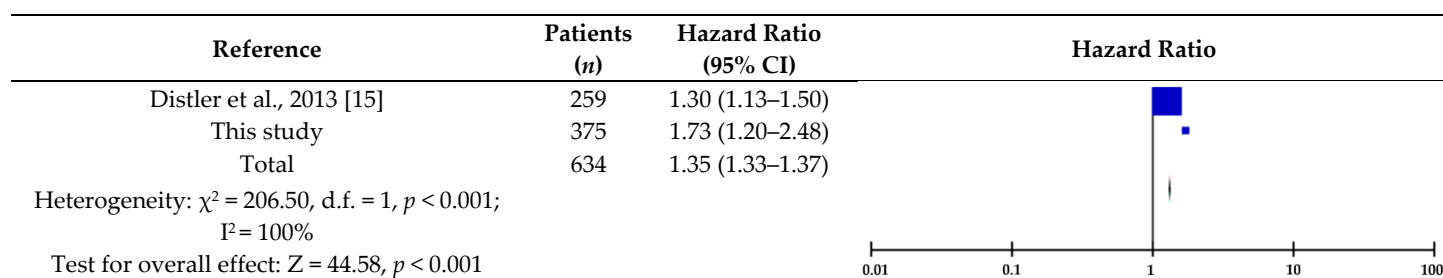
Kondo et al., 2017 [12]	Japan	Resected PDAC ( <i>n</i> = 198)	300	32.2	18.8	46.7	Yes
Tingle et al., 2018 [13]	United Kingdom	Advanced PDAC ( <i>n</i> = 115)	770	NR	15.1	7.7	Yes
Song et al., 2018 [14]	China	Metastatic PDAC ( <i>n</i> = 59)	626	57.6	NR	NR	Yes
This study	The Netherlands	Resected and advanced PDAC ( <i>n</i> = 375)	305	44.3	13	8	Yes
<b>CEA</b>							
Ni et al., 2005 [1]	China	Resected and advanced PDAC ( <i>n</i> = 105)	5	47.6	11	6	No
Lee et al., 2013 [6]	Korea	Resected PDAC ( <i>n</i> = 187)	5	39.0	16.1	10.2	Yes
Reitz et al., 2015 [8]	Austria	Resected and advanced PDAC ( <i>n</i> = 393)	6.9	33.6	10	4	Yes
Asaoka et al., 2016 [9]	Japan	Resected PDAC ( <i>n</i> = 46)	4	23.9	NR	NR	Yes
Imaoka et al., 2016 [11]	Japan	Metastatic PDAC ( <i>n</i> = 433)	5 20	57.3 30.3	10.3 NR	6.8 6.1	Yes
This study	The Netherlands	Resected and advanced PDAC ( <i>n</i> = 375)	7	32.3	13	7	Yes
<b>CA19-9 and CEA combined</b>							
Distler et al., 2013 [15]	Germany	Resected PDAC ( <i>n</i> = 259)	75 (CA19-9) 3 (CEA)	35.1	33.3	23.9	Yes
This study	The Netherlands	Resected and advanced PDAC ( <i>n</i> = 375)	305 (CA19-9) 7 (CEA)	18.4	7	5	Yes

CA 19-9: cancer antigen 19-9, CEA: carcinoembryonic antigen, OS: overall survival, PDAC: pancreatic ductal adenocarcinoma, HR: Hazard Ratio, NR: not reported. \* Multiple cut-off values have been used.



**Figure S4.** Funnel plots of included studies in meta-analysis, determining the prognostic value of CA19-9 on overall survival (A) CEA on overall survival (B) both CA19-9 and CEA on overall survival (C) and CA19-9 on recurrence (D) in PDAC patients.



**Table S4.** Forest plot of prognostic value of CA19-9 and CEA combined on overall survival in PDAC patients.

CA 19-9: cancer antigen 19-9; CEA: carcinoembryonic antigen; d.f.: degrees of freedom.

**Table S5.** Studies that report on prognostic value of preoperative serum CA19-9 and CEA for early recurrence in resected PDAC patients.

Study	Country	Marker	Study Population (No. of Patients)	Cut-off Level (CEA: $\mu\text{g/L}$ ; CA19-9: $\text{kU/L}$ )	Fraction above Cut-off (%)	Median time-to-Recurrence (95% CI) below Cut-off (Months)	Median time-to-Recurrence (95% CI) above Cut-off (months)	Performance of Multivariable Analysis
Waraya et al., 2009 [16]	Japan	CA19-9	Resected PDAC ( $n = 117$ )	37	56.4	30.6	12.7	Yes
Sugiura et al., 2012 [17]	Japan	CA19-9	Resected PDAC ( $n = 154$ )	100	47.4	22	6	Yes
Asaoka et al., 2016 [9] *	Japan	CA19-9	Resected PDAC ( $n = 46$ )	230	30.4	12.7	5.8	No
Imaoka et al., 2016 [10] *	Japan	CA19-9	Resected PDAC ( $n = 119$ )	37	68.0	24.8	17.9	No
This study	The Netherlands	CA19-9	Resected PDAC ( $n = 151$ )	27	76.8	22	15	Yes
		CEA	Resected PDAC ( $n = 151$ )	3	53.0	18	15	No
				7	19.9	21	16	

CA 19-9: cancer antigen 19-9, CEA: carcinoembryonic antigen, PDAC: pancreatic ductal adenocarcinoma.

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