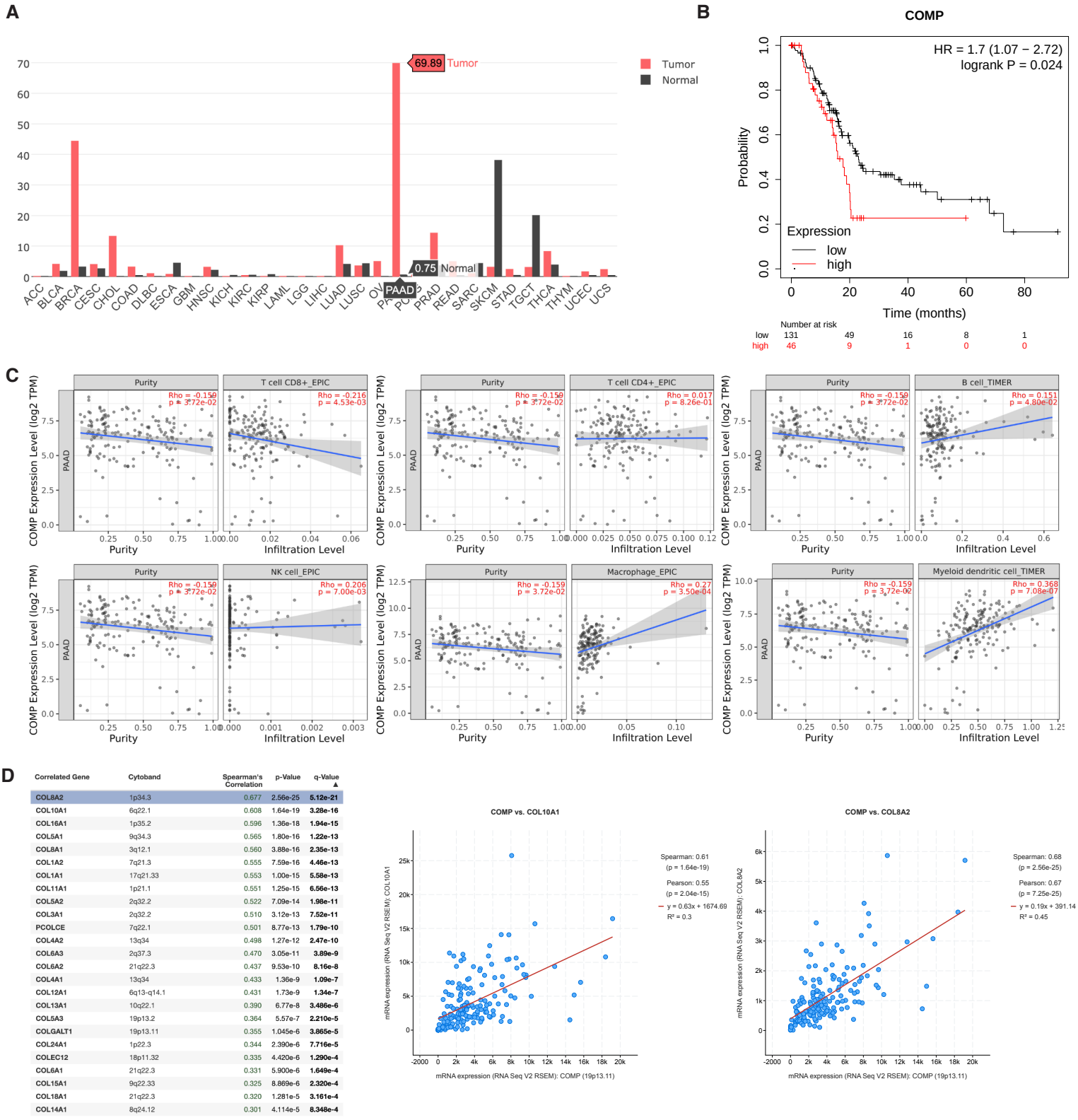
Figure S1



Correlated Gene	Cytoband	Spearman's Correlation	p-Value	q-Value ▲
COL8A2	1p34.3	0.677	2.56e-25	**5.12e-21**
COL10A1	6q22.1	0.608	1.64e-19	**3.28e-16**
COL16A1	1p35.2	0.596	1.36e-18	**1.94e-15**
COL5A1	9q34.3	0.565	1.80e-16	**1.22e-13**
COL8A1	3q12.1	0.560	3.88e-16	**2.35e-13**
COL1A2	7q21.3	0.555	7.59e-16	**4.46e-13**
COL1A1	17q21.33	0.553	1.00e-15	**5.58e-13**
COL11A1	1p21.1	0.551	1.25e-15	**6.56e-13**
COL5A2	2q32.2	0.522	7.09e-14	**1.98e-11**
COL3A1	2q32.2	0.510	3.12e-13	**7.52e-11**
PCOLCE	7q22.1	0.501	8.77e-13	**1.79e-10**
COL4A2	13q34	0.498	1.27e-12	**2.47e-10**
COL6A3	2q37.3	0.470	3.05e-11	**3.89e-9**
COL6A2	21q22.3	0.437	9.53e-10	**8.16e-8**
COL4A1	13q34	0.433	1.36e-9	**1.09e-7**
COL12A1	6q13-q14.1	0.431	1.73e-9	**1.34e-7**
COL13A1	10q22.1	0.390	6.77e-8	**3.486e-6**
COL5A3	19p13.2	0.364	5.57e-7	**2.210e-5**
COLGALT1	19p13.11	0.355	1.045e-6	**3.865e-5**
COL24A1	1p22.3	0.344	2.390e-6	**7.716e-5**
COLEC12	18p11.32	0.335	4.420e-6	**1.290e-4**
COL6A1	21q22.3	0.331	5.900e-6	**1.649e-4**
COL15A1	9q22.33	0.325	8.869e-6	**2.320e-4**
COL18A1	21q22.3	0.320	1.281e-5	**3.161e-4**
COL14A1	8q24.12	0.301	4.114e-5	**8.348e-4**

Figure S1 Analyses of COMP expression reported in various databases confirm that COMP is highly expressed in pancreatic cancer where it correlates with patient survival and low immune cell infiltration. (A) Profile of COMP mRNA expression in cancer tissues and in healthy tissue was retrieved from GEPIA. Notably, high expression of COMP was noted in pancreatic cancer (PAAD) and breast cancer (BRCA). (B) Estimation of survival for pancreatic cancer patients with tumours expressing high and low levels of COMP mRNA using Kaplan-Meier Plotter for Pan-cancer RNA-seq confirmed association of COMP expression with poor survival. (C) Estimation of infiltrating immune cells populations into pancreatic tumours in relation to COMP mRNA expression using algorithms retrieved from TIMER 2.0. (D) Strong correlation of COMP mRNA expression with mRNA expression levels of several types of collagens, data retrieved from cBioPortal analysing data sourced from TCGA, PanCancer atlas.

Figure S2

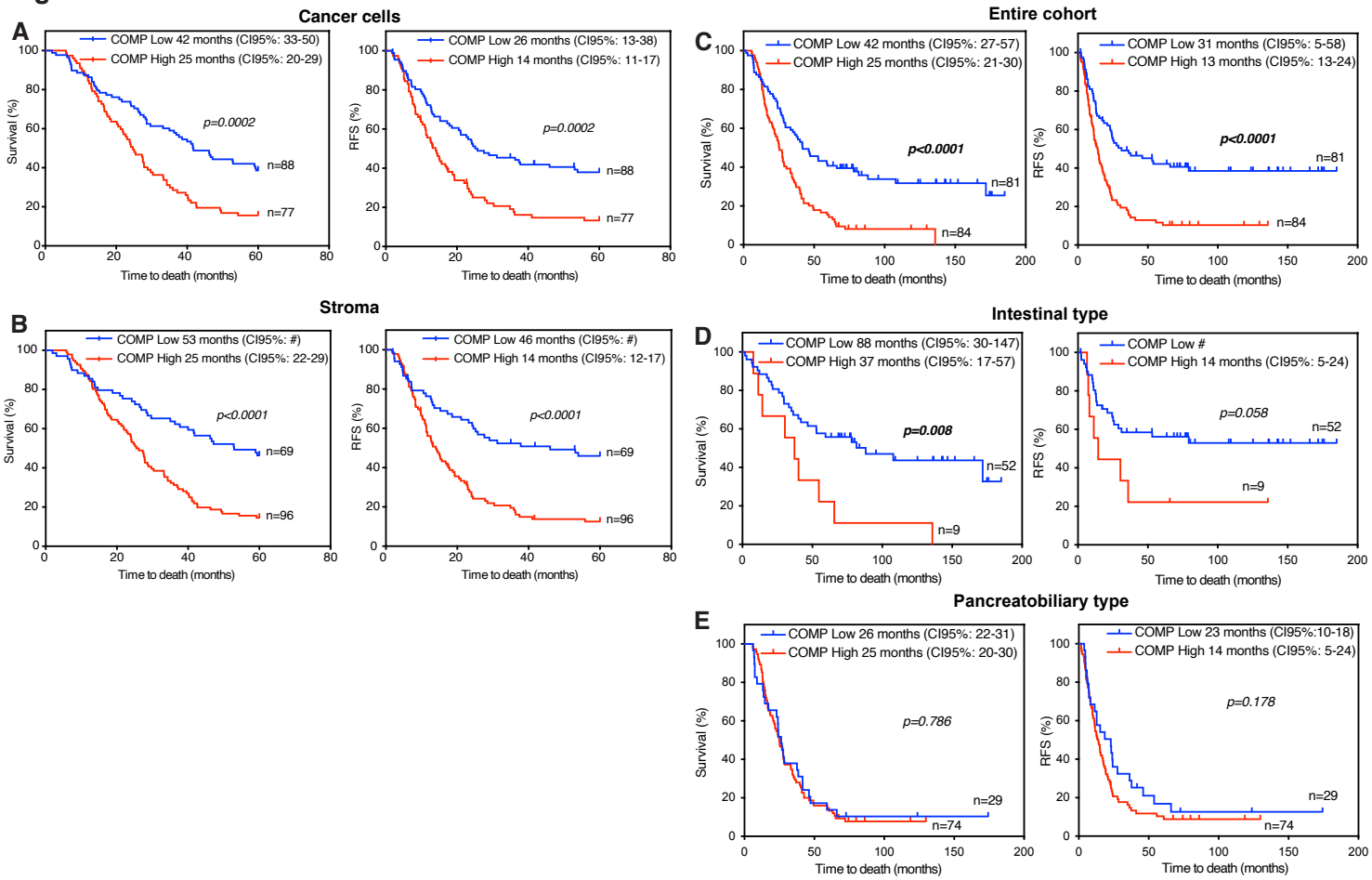


Figure S2 Estimation of OS and RFS and 5-years post-surgery. Patients were stratified according to COMP expression: low (score 0-1) and high (score 2-3), based on immunohistochemical analysis of tissue microarrays. High expression of COMP from the cancer cells (A) or in the stroma (B) was correlated with decreased OS and RFS of the cancer patients at 5-years post-surgery. QuPath open-source software was used to calculate the percentage of COMP positive cells detected collectively in cancer cells and in stroma. Patients were stratified as low or high COMP expressing according to median. OS and RFS were calculated for the entire cohort (C) and the intestinal (D) and pancreatobiliary (E) types of morphology separately. Kaplan Meier estimation of survival and recurrence was used, with log Rank (Mantel-Cox) pairwise comparisons (# stands for incalculable).

Figure S3

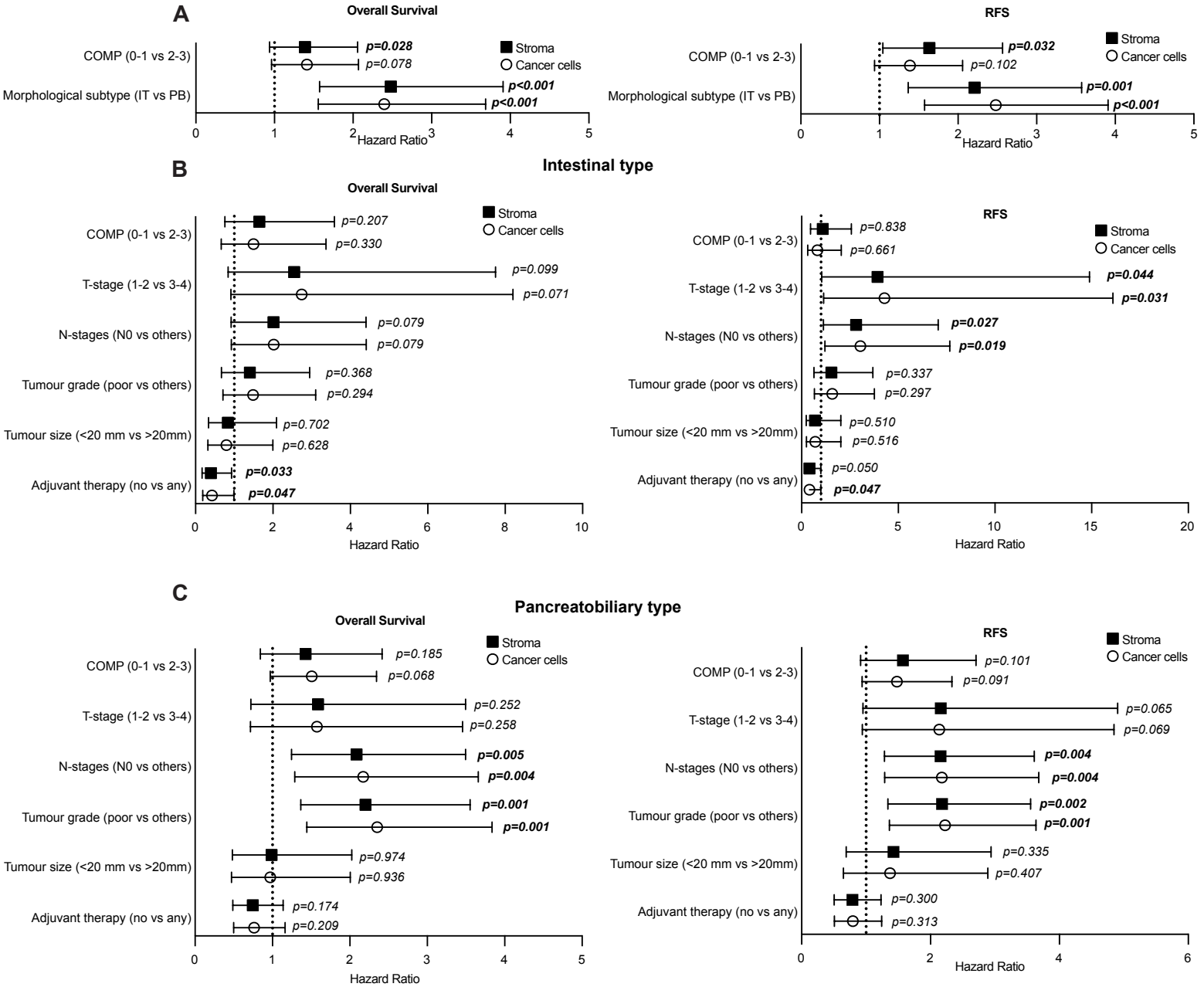


Figure S3 (A) Multivariate Cox analyses of COMP expression by the cancer cells and in stroma together with the type of tumour morphology. Estimation of survival with Cox multivariable analyses for patients with intestinal type (B) and pancreatobiliary type (C) of periampullary adenocarcinoma.

Figure S4

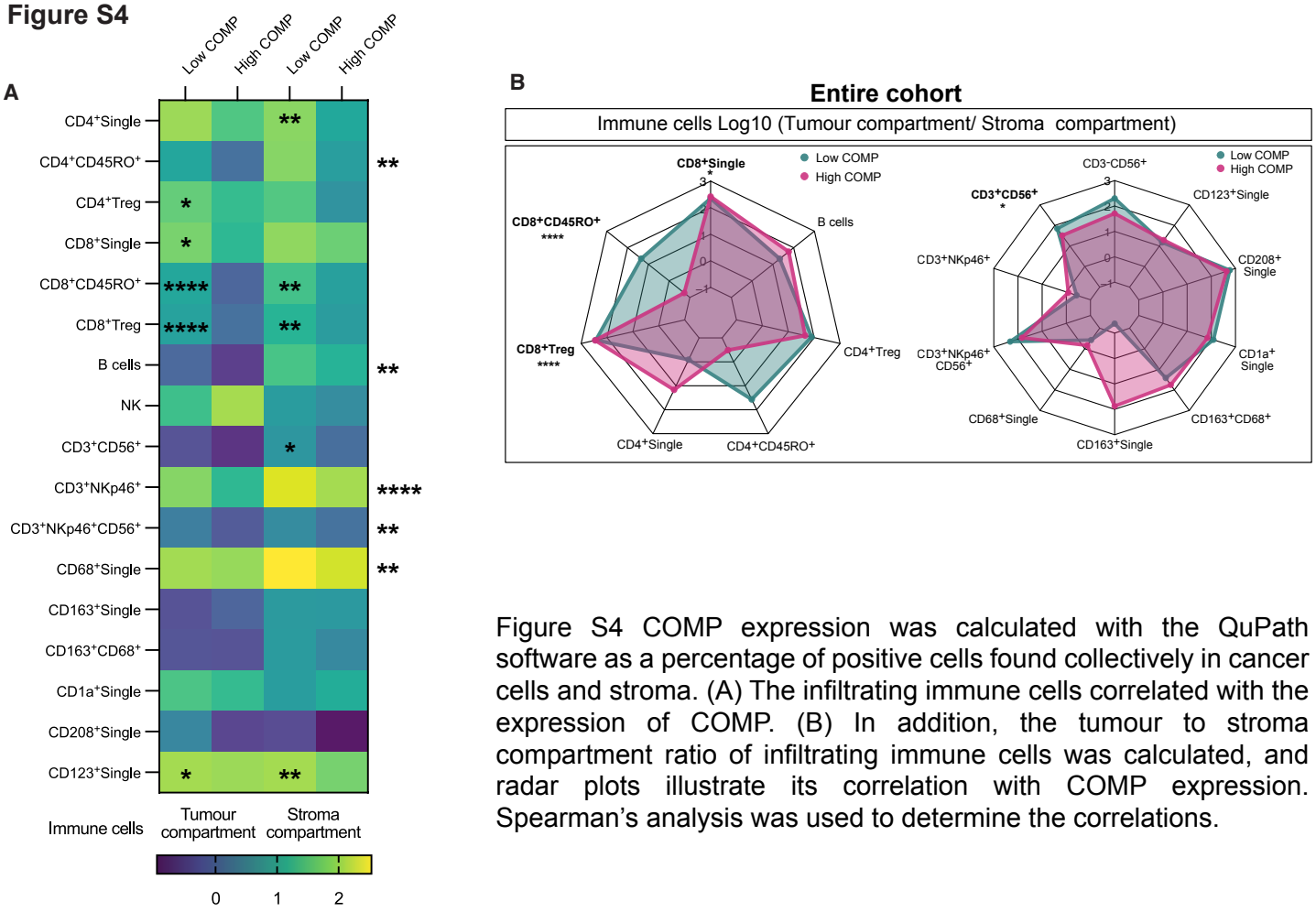


Figure S4 COMP expression was calculated with the QuPath software as a percentage of positive cells found collectively in cancer cells and stroma. (A) The infiltrating immune cells correlated with the expression of COMP. (B) In addition, the tumour to stroma compartment ratio of infiltrating immune cells was calculated, and radar plots illustrate its correlation with COMP expression. Spearman's analysis was used to determine the correlations.

Table S1 Associations of clinicopathological characteristics with COMP expression in patients with intestinal type of tumour morphology.

	Cancer cells					Stroma cells				
Factor	**COMP low**		**COMP high**		***p*-value**	**COMP low**		**COMP high**		***p*-value**
	N	(%)	N	(%)		N	(%)	N	()	
All (N=63)	52	82.54	11	17.46		48	76.19	15	23.81	
Age at surgery					0.746[b]					0.369[b]
<50	6	9.5	2	3.2		5	7.9	3	4.8	
50-70	32	50.8	7	11.1		29	46.0	10	15.9	
>70	14	22.2	2	3.2		14	22.2	2	3.2	
Sex					0.536[a]					0.217[a]
Female	29	46.0	5	7.9		28	44.4	6	9.5	
Male	23	36.5	6	9.5		20	31.7	9	14.3	
Adjuvant vs no adjuvant					**0.037[a]**					**0.016[a]**
No adjuvant	40	63.5	5	7.9		38	60.3	7	11.1	
Adjuvant	12	19.0	6	9.5		10	15.9	8	12.7	
Anatomical tumour origin					0.660 [b]					0.814[b]
Duodenum	11	17.5	3	4.8		11	17.5	3	4.8	
Papilla-Ampulla Intestinal	41	65.1	8	12.7		37	58.7	12	19.0	
Papilla-Ampulla Pancreatobiliary	0	0.0	0	0.0		0	0.0	0	0.0	
Distal Bile Duct	0	0.0	0	0.0		0	0.0	0	0.0	
Pancreas	0	0.0	0	0.0		0	0.0	0	0.0	
Tumour size					**0.039[a]**					**0.034[a]**
≤ 20 mm	22	34.9	1	1.6		21	33.3	2	3.2	
>20 mm	30	47.6	10	15.9		27	42.9	13	20.6	
N-stage					0.069[a]					0.093[a]
pN0	30	47.6	3	4.8		28	44.4	5	7.9	
pN1	22	34.9	8	12.7		20	31.7	10	15.9	
T-stage					**0.043[a]**					**0.014[a]**
pT1-T2	15	23.8	0	0.0		15	23.8	0	0.0	
pT3-T4	37	58.7	11	17.5		33	52.4	15	23.8	
R-margin status					0.473[a]					0.176[a]
R0	15	23.8	2	3.2		15	23.8	2	3.2	
R1 or Rx	37	58.7	9	14.3		33	52.4	13	20.6	
Perineural growth					**<0.0001[a]**					**<0.0001[a]**
No growth	42	66.7	2	3.2		40	63.5	4	6.3	
Perineural growth	10	15.9	9	14.3		8	12.7	11	17.5	
Cancer in lymph vessels					0.967[a]					0.262[a]
No cancer	24	38.1	5	7.9		24	38.1	5	7.9	
Cancer	28	44.4	6	9.5		24	38.1	10	15.9	
Cancer in blood vessels					0.170[a]					0.379[a]
No cancer	49	77.8	9	14.3		45	71.4	13	20.6	
Cancer	3	4.8	2	3.2		3	4.8	2	3.2	
Growth in peripancreatic fat					**0.004[a]**					**0.003[a]**
No growth	38	60.3	3	4.8		36	57.1	5	7.9	
Growth	14	22.2	8	12.7		12	19.0	10	15.9	

Abbreviations: COMP. cartilage oligomeric matrix protein; The bold indicates *p*-values <0.05. [a]Mann–Whitney two-tailed Exact *p*-value. [b]Kruskal-Wallis *p*-value.

Table S2 Associations of clinicopathological characteristics with COMP expression in patients with pancreatobiliary type of tumour morphology.

	Cancer cells					Stroma cells				
Factor	**COMP low**		**COMP high**		***p*-value**	**COMP low**		**COMP high**		***p*-value**
	N	(%)	N	(%)		N	(%)	N	(%)	
All (N=107)	40	37.38	67	62.62		25	23.36	82	76.63	
Age at surgery					0.780[b]					0.252[b]
<50	2	1.9	2	1.9		0	0.0	4	3.7	
50-70	24	22.4	44	41.1		14	13.1	54	50.5	
>70	14	13.1	21	19.6		11	10.3	24	22.4	
Sex					0.982[a]					0.720[a]
Female	18	16.8	30	28.0		12	11.2	36	33.6	
Male	22	20.6	37	34.6		13	12.1	46	43.0	
Adjuvant vs no adjuvant					0.284[a]					0.479[a]
No adjuvant	21	19.6	28	26.2		13	12.1	36	33.6	
Adjuvant	19	17.8	39	36.4		12	11.2	46	43.0	
Anatomical tumour origin					0.337[b]					0.080[b]
Duodenum	0	0.0	0	0.0		0	0.0	0	0.0	
Papilla-Ampulla Intestinal	0	0.0	0	0.0		0	0.0	0	0.0	
Papilla-Ampulla Pancreatobiliary	9	8.4	10	9.3		8	7.5	11	10.3	
Distal Bile Duct	18	16.8	26	24.3		7	6.5	37	34.6	
Pancreas	13	12.1	31	29.0		10	9.3	34	31.8	
Tumour size					0.052[a]					**0.022[a]**
≤ 20 mm	9	8.4	6	5.6		7	6.5	8	7.5	
>20 mm	31	29.0	61	57.0		18	16.8	74	69.2	
N-stage					0.376[a]					0.449[a]
pN0	14	13.1	18	16.8		9	8.4	23	21.5	
pN1	26	24.3	49	45.8		16	15.0	59	55.1	
T-stage					0.651[a]					0.623[a]
pT1-T2	6	5.6	8	7.5		4	3.7	10	9.3	
pT3-T4	34	31.8	59	55.1		21	19.6	72	67.3	
R-margin status					0.513[a]					0.114[a]
R0	3	2.8	3	2.8		3	2.8	3	2.8	
R1 or Rx	37	34.6	64	59.8		22	20.6	79	73.8	
Perineural growth					**0.017[a]**					**0.003[a]**
No growth	14	13.1	10	9.3		11	10.3	13	12.1	
Perineural growth	26	24.3	57	53.3		14	13.1	69	64.5	
Cancer in lymph vessels					0.775[a]					0.887[a]
No cancer	13	12.1	20	18.7		8	7.5	25	23.4	
Cancer	27	25.2	47	43.9		17	15.9	57	53.3	
Cancer in blood vessels					0.944[a]					0.206[a]
No cancer	26	24.3	44	41.1		19	17.8	51	47.7	
Cancer	14	13.1	23	21.5		6	5.6	31	29.0	
Growth in peripancreatic fat					0.100[a]					**0.002[a]**
No growth	12	11.2	11	10.3		11	10.3	12	11.2	
Growth	28	26.2	56	52.3		14	13.1	70	65.4	

Abbreviations: COMP. cartilage oligomeric matrix protein; The bold indicates *p*-values <0.05. [a]Mann–Whitney two-tailed Exact *p*-value. [b]Kruskal-Wallis *p*-value.

Table S3 Cox multivariable analyses of overall and recurrence free survival

Overall urvival		**Cancer cells**			**Stroma**	
Variable	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
COMP (0-1 vs 2-3)	1.487	1.280-2.650	**0.001**	2.018	1.358-2.999	**0.001**
Adjuvant therapy (no vs any)	0.860	0.505-1.053	0.092	0.686	0.474-0.995	**0.047**
Tumour size (≤20 mm vs >20mm)	1.143	0.559-1.717	0.943	0.982	0.569-1.695	0.949
Tumour grade (poor vs others)	1.507	1.258-2.718	**0.002**	1.742	1.188-2.555	**0.004**
N-stages (N0 vs others)	1.812	1.311-3.013	**0.001**	1.910	1.262-2.893	**0.002**
T-stage (1-2 vs 3-4)	2.114	1.087-3.816	**0.027**	1.985	1.058-3.725	**0.033**
Recurrence-free survival		**Cancer cells**			**Stroma**	
Variable	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
COMP (0-1 vs 2-3)	1.596	1.090-2.337	**0.016**	1.795	1.181-2.728	**0.006**
Adjuvant therapy (no vs any)	0.764	0.521-1.121	0.169	0.739	0.502-1.087	0.124
Tumour size (≤20 mm vs >20mm)	1.143	0.631-2.068	0.660	1.173	0.661-2.082	0.586
Tumour grade (poor vs others)	1.661	1.116-2.472	**0.012**	1.612	1.084-2.397	**0.018**
N-stages (N0 vs others)	2.191	1.410-3.404	**<0.001**	2.089	1.348-3.236	**0.001**
T-stage (1-2 vs 3-4)	2.391	1.202-4.758	**0.013**	2.277	1.152-4.499	**0.018**

Abbreviations: COMP, cartilage oligomeric matrix protein. The bold indicates *p*-values <0.05.

Table S4 Distribution of clinicopathological characteristics in patients with and without lymph node metastases.

Factor	**Metastatic patients**		**Non-metastatic patients**	
All (N=170)	N	(%)	N	(%)
Age at surgery				
<50	7	0.04	5	0.03
50-70	69	0.41	38	0.22
>70	29	0.17	22	0.13
Sex				
Female	45	0.26	37	0.22
Male	60	0.35	28	0.16
Adjuvant vs no adjuvant				
No adjuvant	49	0.29	45	0.26
Adjuvant	56	0.33	20	0.12
Anatomical tumour origin				
Duodenum	6	0.04	8	0.05
Papilla-Ampulla Intestinal	24	0.14	25	0.15
Papilla-Ampulla Pancreatobiliary	16	0.09	3	0.02
Distal Bile Duct	26	0.15	18	0.11
Pancreas	33	0.19	11	0.06
Tumour size				
≤ 20 mm	13	0.08	25	0.15
>20 mm	92	0.54	40	0.24
T-stage				
pT1-T2	12	0.07	17	0.10
pT3-T4	93	0.55	48	0.28
R-margin status				
R0	9	0.05	14	0.08
R1 or Rx	96	0.56	51	0.30
Perineural growth				
No growth	25	0.15	43	0.25
Perineural growth	80	0.47	22	0.13
Cancer in lymph vessels				
No cancer	27	0.16	35	0.21
Cancer	78	0.46	30	0.18
Cancer in blood vessels				
No cancer	74	0.44	54	0.32
Cancer	31	0.18	11	0.06
Growth in peripancreatic fat				
No growth	22	0.13	42	0.25
Growth	83	0.49	23	0.14

Table S5 Panel of antibodies utilised to detect the different populations of immune cells.

Target	Supplier	Catalogue number	Dilution
CD4	DAKO	M7310	1:200
CD8α	Thermo Fisher Scientific	MA5-13473	1:500
FoxP3	Cell Signalling Technology	12653	1:100
CD20	DAKO	GA604	1:3000
CD45RO	Thermo Fisher Scientific	MA1-19452	1:200
CD68	Dako, Agilent Technologies	M0876	1:100
CD163	Atlas Antibodies	HPA046404	1:100
NKp46	Thermo Fisher Scientific	PA5-79720	1:150
CD56	Dako, Agilent Technologies	M730429-2	1:100
CD3	Dako, Agilent Technologies	M725429-2	1:80
CD1a	Dako, Agilent Technologies	M357101-2	1:400
CD208	Thermo Fisher Scientific	PA5-84069	1:50
CD123	Sigma	198M-14	1:20
CD15	Sigma,	M3631	1:100
E-cadherin	BD Biosciences	610182	1:5000
pan Cytokeratin	Abcam	ab7753	1:1000
pan Cytokeratin Type I/II	Thermo Fisher Scientific	MA5-13156	1:500