Supplementary Table S1: Characteristics of patients in a clinical trial of intraoperative gemcitabine infusion during surgery

Patient	Sex	Age	Race	Differentiation/Histology
1	female	59	Caucasian	Poor/Adeno
2	female	62	Black	Poor/Adeno
3	female	63	Caucasian	Mod/Adeno
4	male	64	Caucasian	Poor/Adeno
5	female	68	Black	Mod/Adeno
6	female	55	Caucasian	Mod/Adeno
7	female	60	Caucasian	Mod/Adeno
8	male	77	Caucasian	Poor/Adeno
9	male	56	Hispanic	Mod/Adeno
10	male	64	Caucasian	Poor/Adeno
11	female	69	Caucasian	Mod/Adeno
12	female	56	Caucasian	Mod/Adeno

Abbreviations: Mod=moderately differentiated, Poor=poorly differentiated, Adeno=adenocarcinoma

Supplementary Table S2: Patients who underwent surgical resection of PDAC without prior therapy (n = 101)

Characteristic	All patients	High delta	Low delta	P value
Median age (range)	64 (25-85)	65 (25-85)	61 (39-81)	0.05
Sex				0.10
Male	55 (54%)	21 (46%)	34 (62%)	
Female	46 (46%)	25 (54%)	21 (38%)	
Anatomical location of PDAC				0.30
Head	81 (80%)	34 (74%)	47 (85%)	
Body	11 (11%)	6 (13%)	5 (9%)	
Tail	9 (9%)	6 (13%)	3 (5%)	
Pathologic T stage				0.29
T1	1 (1%)		1 (2%)	
T2	1 (1%)		1 (2%)	
T3	98 (97%)	46 (100%)	52 (95%)	
T4	1 (1%)		1 (2%)	
Pathologic N stage				0.09
N0	19 (19%)	5 (11%)	13 (24%)	
N1	82 (81%)	41 (89%)	42 (76%)	
Surgical margin				0.72
Positive	14 (14%)	7 (15%)	7 (13%)	
Negative	87 (86%)	39 (85%)	48 (87%)	
Adjuvant chemotherapy				0.03
Yes	76 (75%)	30 (65%)	46 (84%)	
No	25 (25%)	16 (35%)	9 (16%)	
Adjuvant chemoradiation				0.03
Yes	33 (34%)	10 (22%)	23 (42%)	
No	68 (67%)	36 (78%)	32 (58%)	
Median tumor size in cm (range)	3 (1-8)	3 (1.2-8)	3 (1-7.5)	0.14

Supplementary Table S3: Patients who received neoadjuvant gemcitabine-based chemoradiation for resectable PDAC (n = 106)

Characteristic	Value (range or %)	High delta	Low delta	P value
Median age (range)	63 (44-80)	66 (44-80)	62 (51-78)	0.047
Sex				0.01
Male	61 (58%)	27 (47%)	34 (71%)	
Female	45 (42%)	31 (53%)	14 (29%)	
Surgery				0.12
Yes	76 (72%)	38 (66%)	38 (79%)	
No	30 (28%)	20 (34%)	10 (21%)	
Pathological T stage				0.31
T1	8 (11%)	2 (5%)	6 (16%)	
T2	9 (12%)	5 (13%)	4 (11%)	
T3	59 (77%)	31 (82%)	28 (74%)	
T4	0 (0%)	0	0	
Pathological N stage				0.36
N0	36 (47%)	16 (42%)	20 (53%)	
N1	40 (53%)	22 (58%)	18 (47%)	
Median tumor size in cm (range)	2.5 (0.4-6)	2.8 (0.6-5)	2.2 (0.4-6)	0.20

Supplementary Table S4: Patients with metastatic disease at presentation (n = 84)

Characteristic	Value
Median age (range)	61 (36-86)
Sex	
Male	49 (58%)
Female	35 (42%)
Clinical T Staging	
T1/T2	24 (29%)
T3	18 (21%)
T4	42 (50%)
Cytotoxic regimen	
Gem	5 (6%)
Gem-Cisplatin	13 (15%)
Gem-Abraxane	11 (13%)
FOLFIRINOX	55 (66%)

Abbreviations: Gem=gemcitabine

Supplementary Table S5: Univariate and multivariate overall survival analyses of patients with metastatic disease at presentation (see Supplementary Table S4 for patient characteristics)

Characteristic	No. of patients	Univariate Hazard ratio (95% CI)	Univariate P value	Multivariate Hazard ratio (95% CI)	Multivariate P value
Delta with cut-off of 40	84				
High delta (delta≥40)	65	--		--	
Low delta (delta<40)	19	0.47 (0.23-0.88)	0.016	0.45 (0.22-0.87)	0.016
Tumor size (cm)	84	1.18 (1.05-1.3)	0.007	1.22 (1.06-1.39)	0.004
Chemotherapeutic regimen	84				
Gem	5	--		--	
Gem-Cisplatin	13	0.58 (0.13-1.86)	0.38	1.18 (0.25-4.01)	0.81
Gem-Abraxane	11	1.25 (0.27-4.34)	0.74	2.14 (0.45-7.81)	0.31
FOLFIRINOX	55	0.89 (0.21-2.48)	0.85	1.50 (0.36-4.34)	0.53

Supplementary Table S6: Univariate and multivariate overall survival analyses of patients who underwent upfront surgery for resectable PDAC (see Supplementary Table S2 for patient characteristics)

Characteristic	No. of patients	Univariate Hazard ratio (95% CI)	Univariate P value	Model A: Hazard ratio (95% CI)	Model A: P value	Model B: Hazard Ratio (95% CI)	Model B: P value	Model C: Hazard Ratio (95% CI)	Model C: P value	Model D: Hazard Ratio (95% CI)	Model D: P value
Delta with cut-off of 40	101										
High delta (delta≥40)	46	--		--		--				--	
Low delta (delta<40)	55	0.50 (0.32-0.79)	0.003	0.61 (0.39-0.98)	0.040	0.63 (0.39-1.02)	0.059			0.63 (0.39-1.03)	0.065
Surgical margin	101										
Positive (R1)	14	1.57 (0.83-2.98)	0.166	1.41 (0.73-2.73)	0.30						
Negative (R0)	87	--		--							
Pathologic N stage	101										
N1	83	2.61 (1.34-5.10)	0.005	2.73(1.36-5.48)	0.005	2.84 (1.41-5.69)	0.003	3.17 (1.59-6.32)	0.001	2.84 (1.41-5.72)	0.004
N0	18	--		--		--		--		--	
Adjuvant chemotherapy	101										
Yes	76	0.54 (0.33-0.90)	0.017	0.51 (0.29-0.89)	0.018	0.50 (0.29-0.85)	0.011	0.46 (0.27-0.77)	0.003	0.50 (0.29-0.85)	0.011
No	25	--		--		--		--		--	
Adjuvant chemoradiation	101										
Yes	33	0.65 (0.40-1.05)	0.07	0.79 (0.48-1.30)	0.35						
No	68	--		--							
CA19-9 (per 100 units)	101	1.00 (0.98-1.02)	0.96					0.99 (0.98-1.01)	0.70	1.00 (0.98-1.02)	0.98
Gender	101										
Male	55	0.69 (0.45-1.08)	0.102			0.77 (0.49-1.21)	0.25	0.70 (0.45-1.10)	0.13	0.77 (0.48-1.22)	0.26
Female	46	--									
Volumetric AUC	101	0.34 (0.11-0.99)	0.047								
Anatomical location of PDAC	101										
Head	81	--									
Body	11	1.11 (0.54-2.01)	0.7549								
Tail	9	2.16 (1.00-4.17)	0.0513								
	C-index (SE)			**0.677(0.037)**		**0.679 (0.036)**		**0.667 (0.037)**		**0.673 (0.037)**	

Abbreviations: No.=number, CI=confidence interval, AUC= area under the enhancement curve
Note: Models B, C, and D were constructed using AIC backward selection approach and combined with the Delta and CA19-9 to determine effects on the C-index.

Supplementary Table S7: Subgroup overall survival analysis of patients with stage T3 disease

	Multivariate model with Delta classification		Multivariate model with baseline CA19-9	
	HR (95% CI) p-value	C-index(se)	HR (95% CI) p-value	C-index(se)
T3 N0 (n=24)	0.209 (0.070, 0.622) 0.005	0.666 (0.064)	1.000 (1.000, 1.000) 0.471	0.572 (0.08)
T3 N1 (n=35)	0.194 (0.582, 2.446) 0.629	0.552 (0.052)	1.000 (1.000, 1.000) 0.857	0.544 (0.064)

Note: the multivariate model included adjuvant chemotherapy and gender, which were selected using the AIC backward selection approach (Model B in Table S6)
Abbreviations: se = standard error

Supplementary Table S8: Univariate and multivariate overall survival analyses of patients who received gemcitabine-based chemoradiation for potentially resectable pancreatic cancer (see Supplementary Table S3 for patient characteristics)

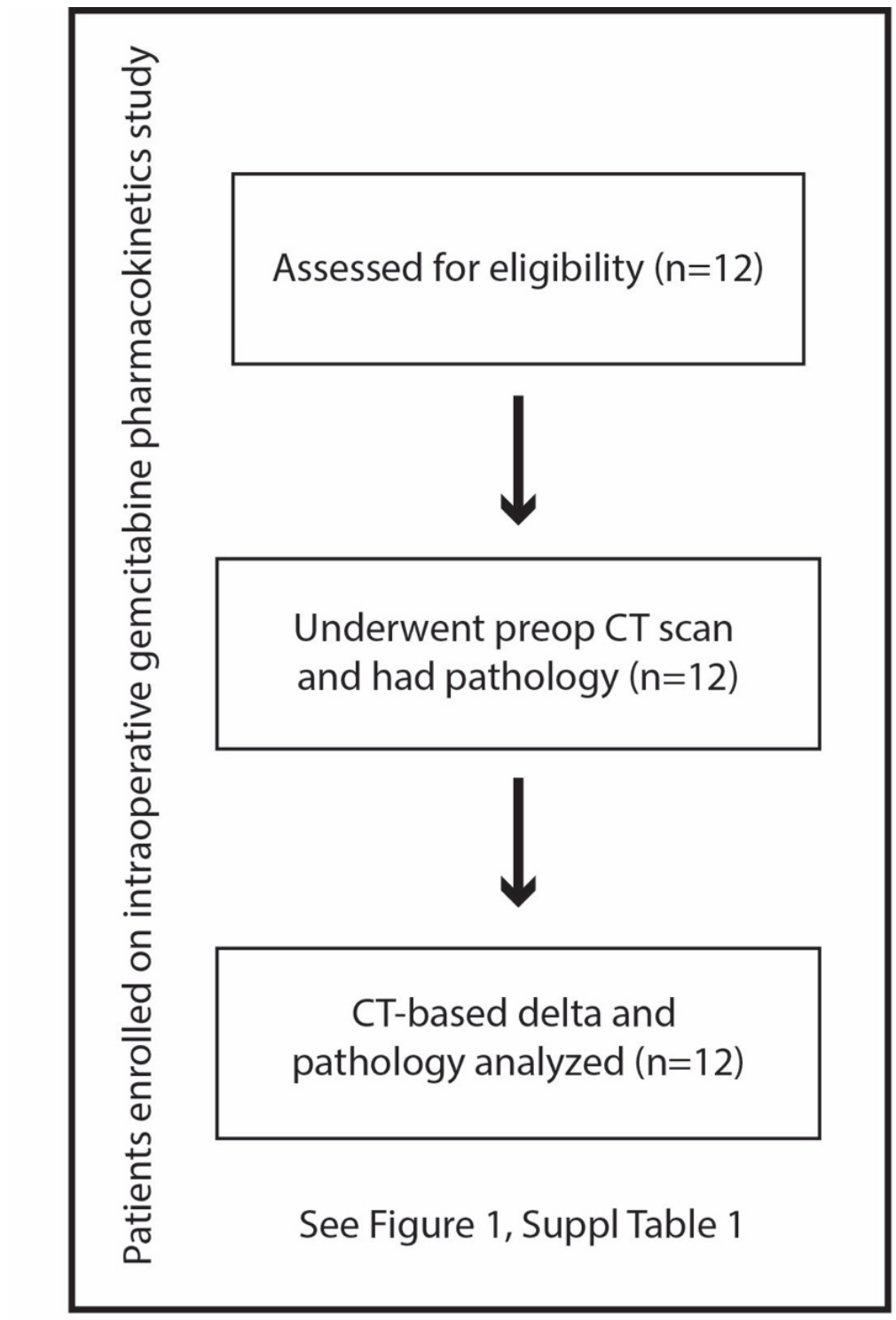
Characteristic	No. of patients	Univariate Hazard ratio (95% CI)	Univariate P value	Model A: Multivariate Hazard ratio (95% CI)	Model A: Multivariate P value	Model B: Multivariate Hazard ratio (95% CI)	Model B: Multivariate P value	Model C: Multivariate Hazard ratio (95% CI)	Model C: Multivariate P value
Delta with cut-off of 40	106								
High delta (delta≥40)	58	--		--				--	
Low delta (delta<40)	48	0.46 (0.29-0.70)	0.0004	0.49 (0.31-0.76)	0.001			0.49 (0.31-0.76)	0.002
Underwent curative-intent resection	106								
Yes	76	0.12 (0.07-0.21)	<0.0001	0.12 (0.07-0.22)	<0.0001	0.11 (0.06-0.19)	<0.0001	0.11 (0.06-0.20)	<0.0001
No	30	--		--		--		--	
Volumetric AUC	106	0.43 (0.18-1.05)	0.06						
Baseline CA19-9 (per 100 units)	102	1.01 (0.99-1.02)	0.50			1.01 (0.99-1.02)	0.18	1.01 (0.99-1.03)	0.14
C-index (SE)				0.717 (0.032)		0.708 (0.035)		0.735 (0.035)	

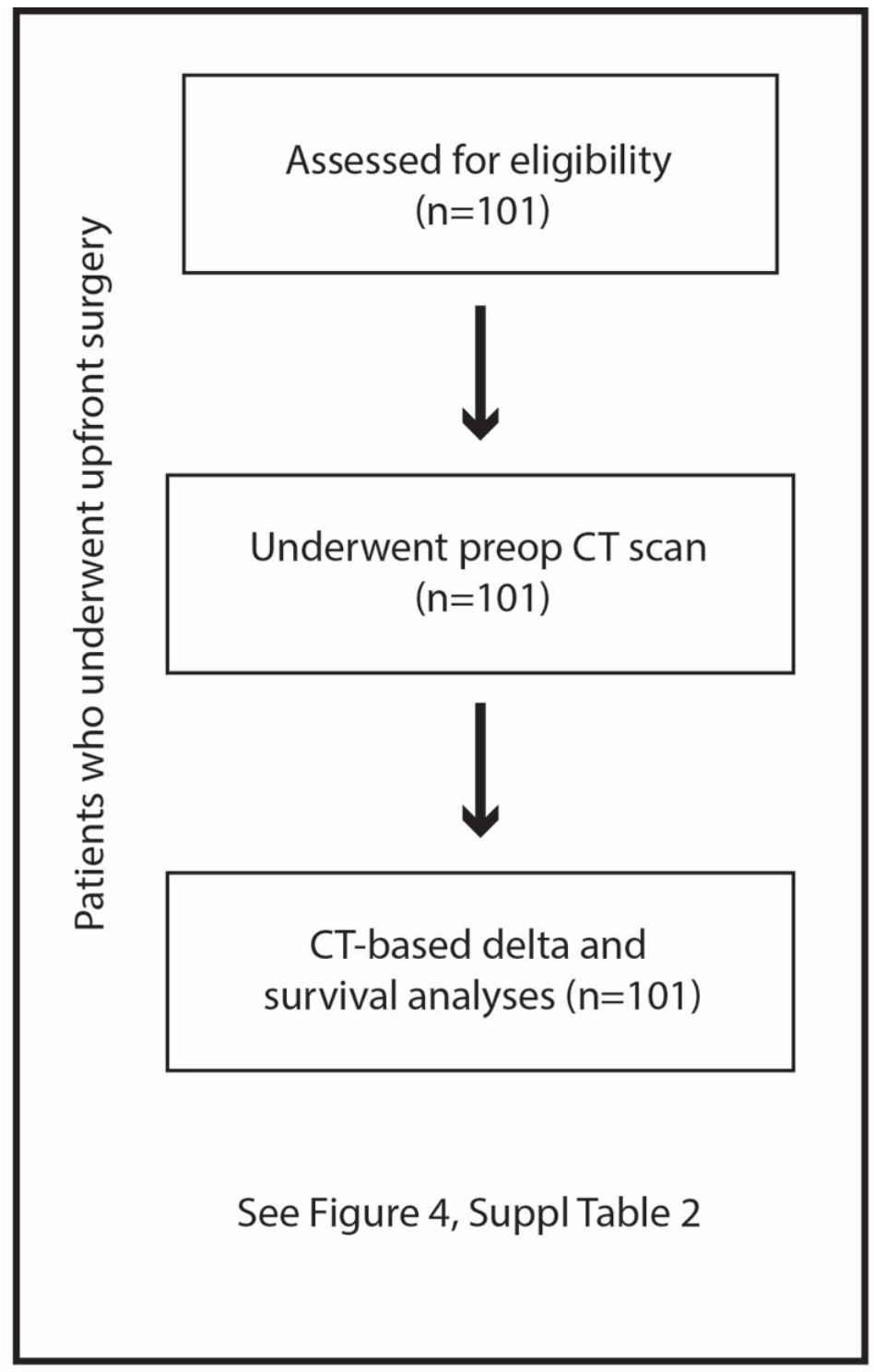
Abbreviations: se = standard error

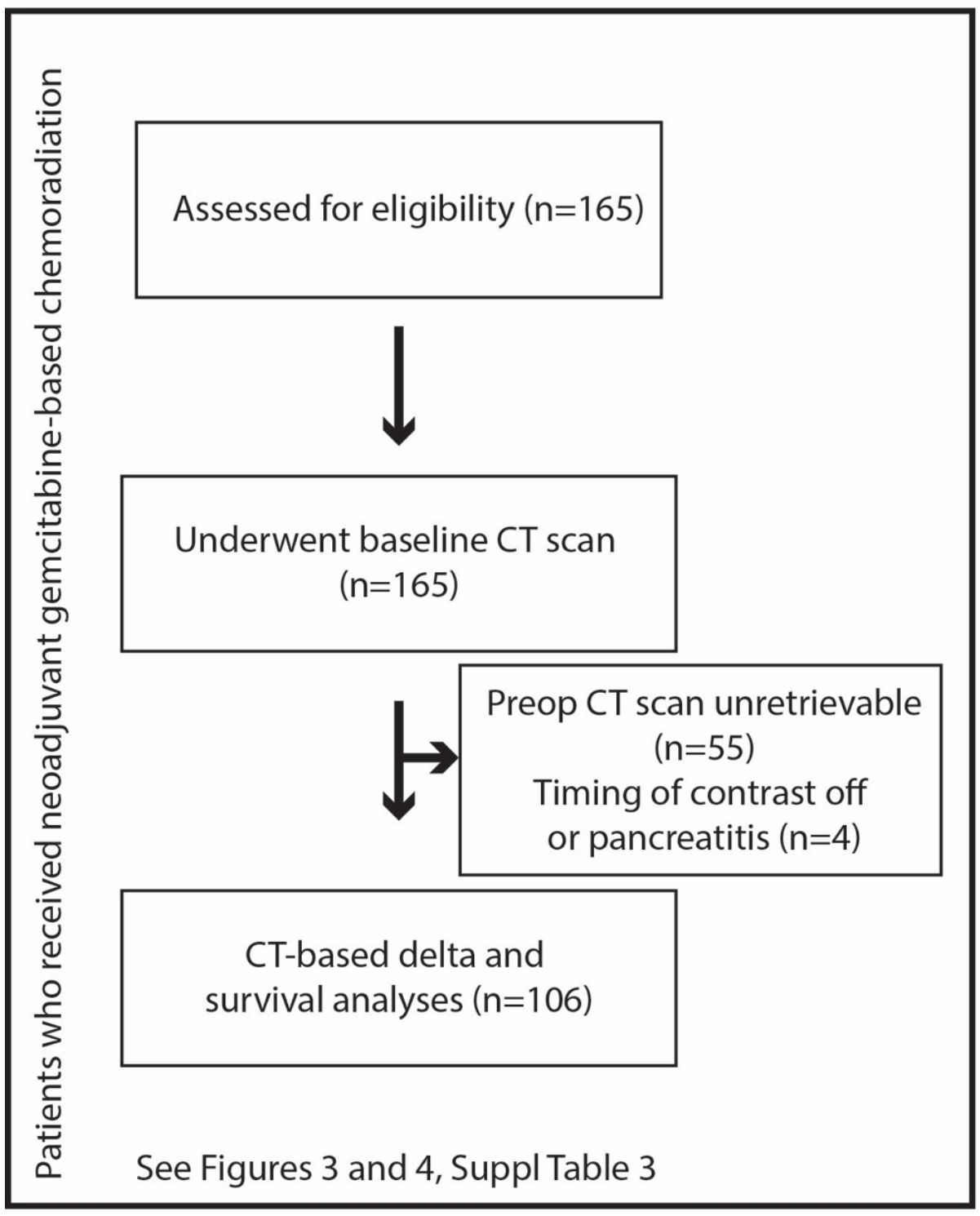
Supplementary Table S9: Univariate and multivariate overall survival analyses of patients who received neoadjuvant gemcitabine-based chemoradiation and underwent resection (see Supplementary Table S3 for patient characteristics)

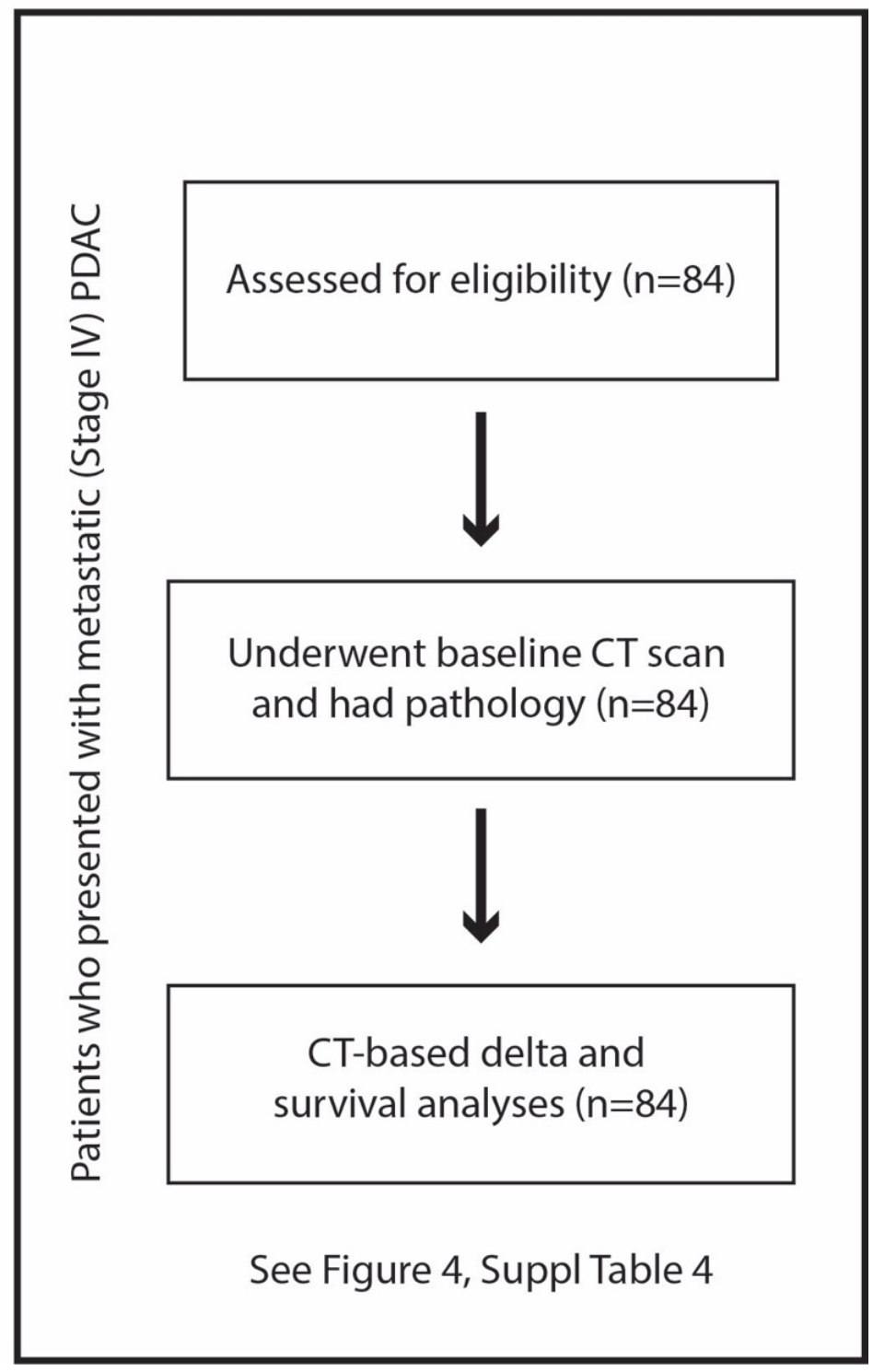
Characteristic	No. of patients	Univariate Hazard ratio (95% CI)	Univariate P value	Multivariate Hazard ratio (95% CI)	Multivariate P value
Delta with cut-off of 40	76				
High delta (delta≥40)	38	--		--	
Low delta (delta<40)	38	0.46 (0.27-0.77)	0.0032	0.49 (0.27-0.84)	0.0104
Surgical margin	76				
Positive (R1)	2	1.44 (0.24-4.64)	0.63	1.10 (0.17-3.92)	0.90
Negative (R0)	74	--		--	
N stage	76				
N1	40	1.42 (0.87-2.36)	0.17	1.18 (0.69-2.03)	0.56
N0	36	--		--	
Volumetric AUC	76	0.36 (0.12-1.06)	0.06		

Supplementary Fig. S1: Consort flow chart for all cohorts



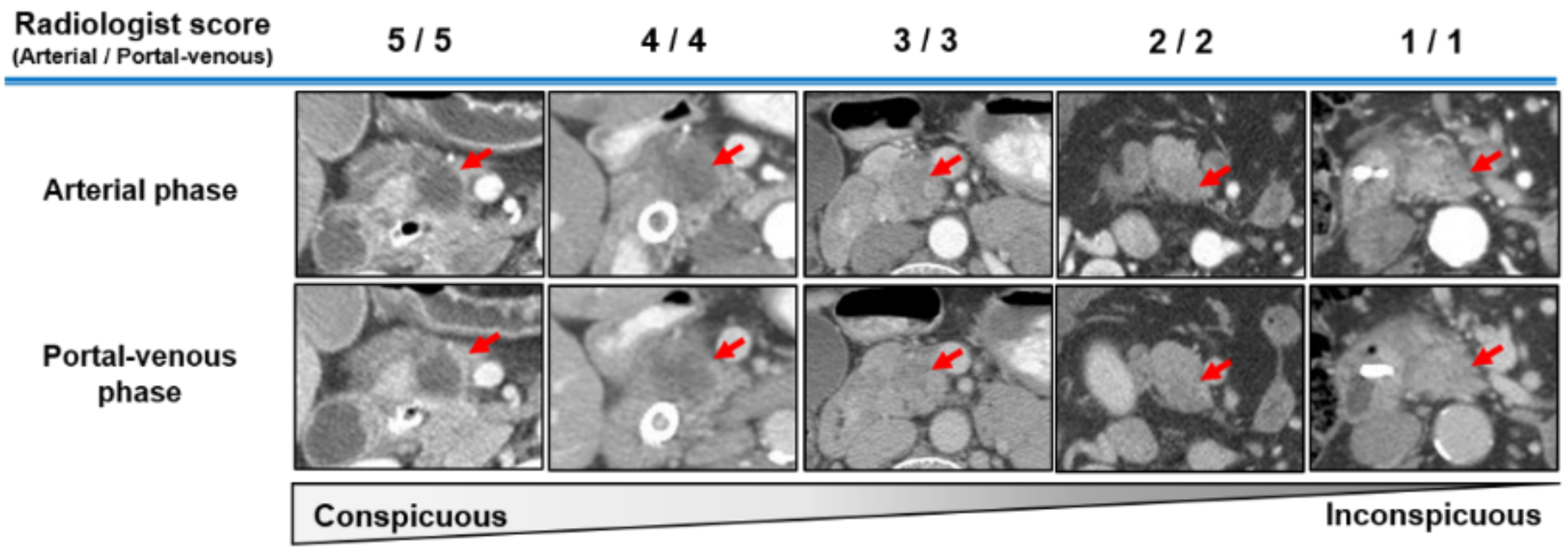


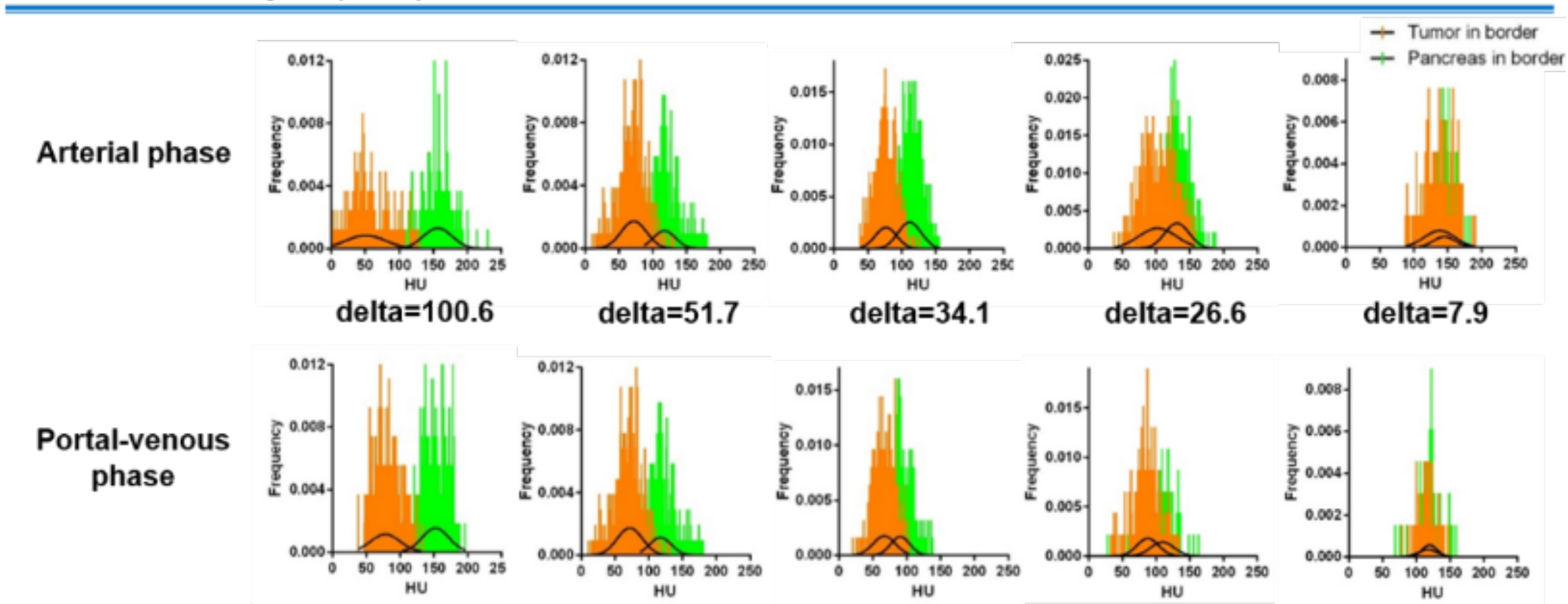




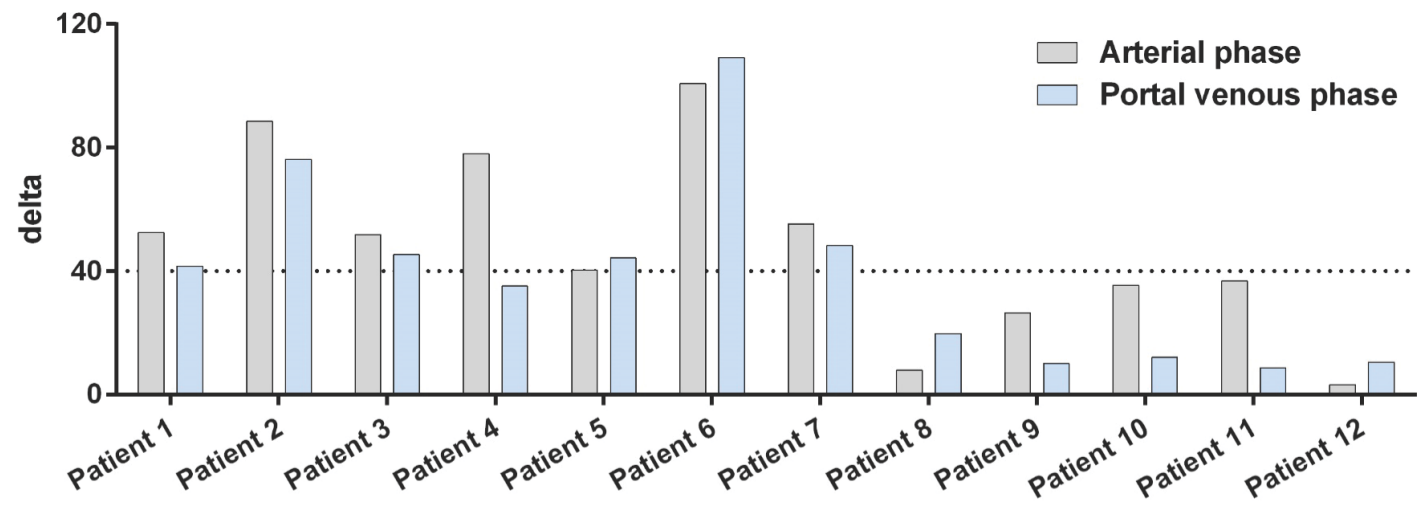
Supplementary Fig. S2: Five-point scoring system for the conspicuity of PDAC tumors on diagnostic CT scans

5: Very conspicuous; 1: Very inconspicuous (top). Corresponding HU histogram and delta values (bottom).

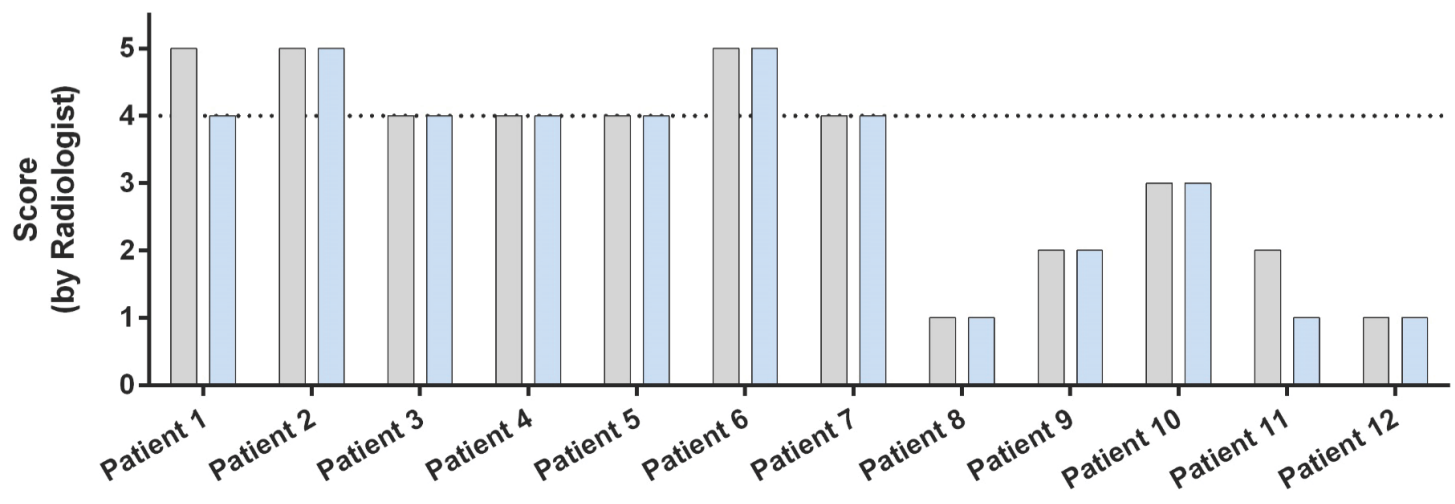




Delta values obtained from 12 patients (Table S1) who were enrolled on a prospective protocol of intraoperative gemcitabine infusion during PDAC resection.

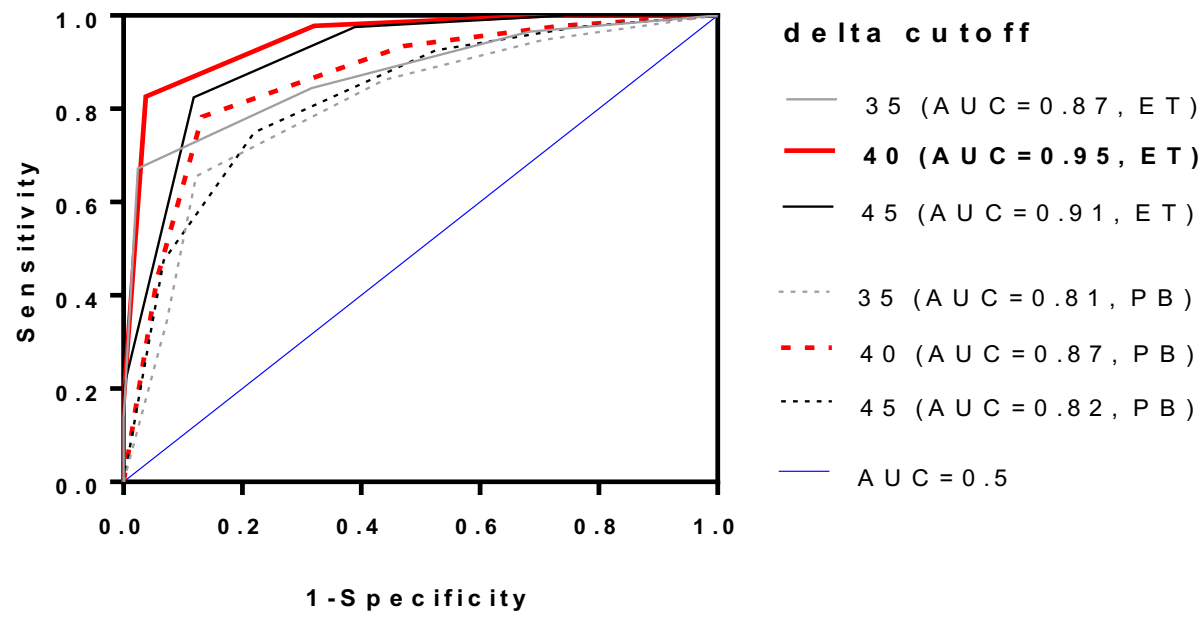


Score determined by two radiologists.

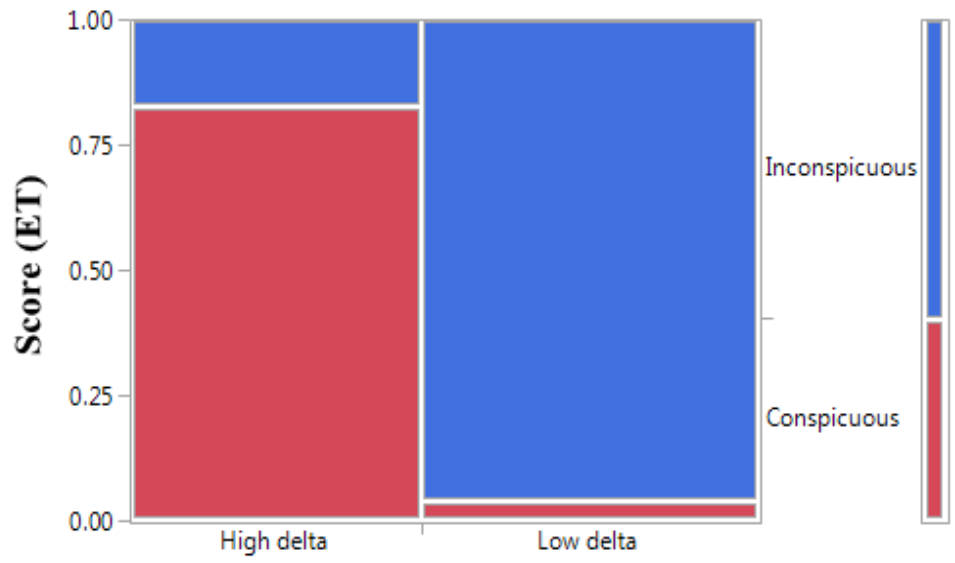


Supplementary Fig. S3: ROC analysis to identify cutoff for delta measurement for patients in Supplementary Table S2. (A) Comparison of area under the receiver operating characteristic (ROC) curves for the delta in the arterial phase. (B, C) The similarity was substantial between the conspicuity score (Fig. S1) of two radiologists (ET, PB) and the delta measurement (cutoff of 40) ((B) kappa coefficient: 0.8; (C) kappa coefficient: 0.7) (D) The two radiologists (ET, PB) had moderate agreement for the conspicuity scoring (kappa coefficient: 0.6) (E) The determination of the delta score for patients who had pancreatic protocol CT scans at baseline at an outside facility (OSF) had high concordance with MD Anderson Cancer Center (MDACC) scans.

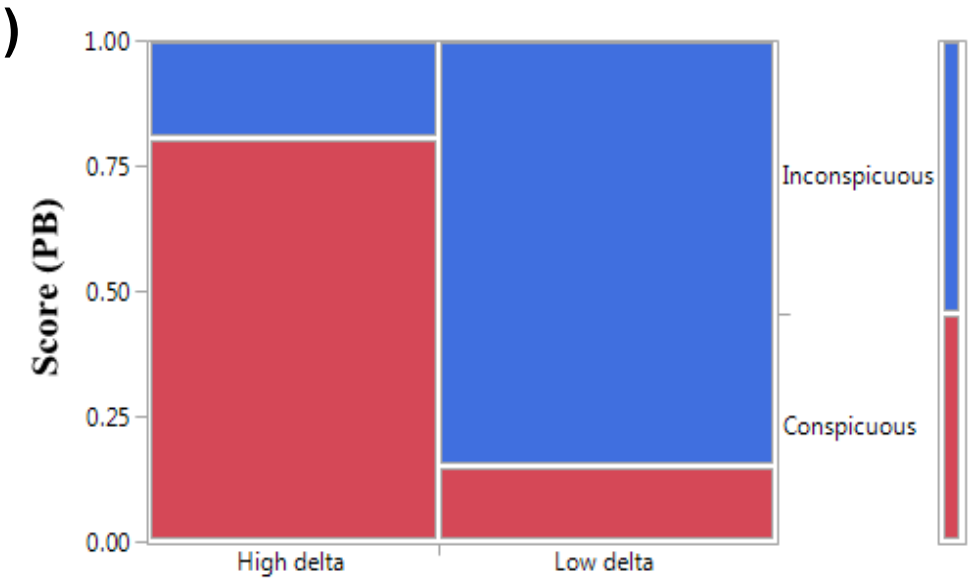
(A)



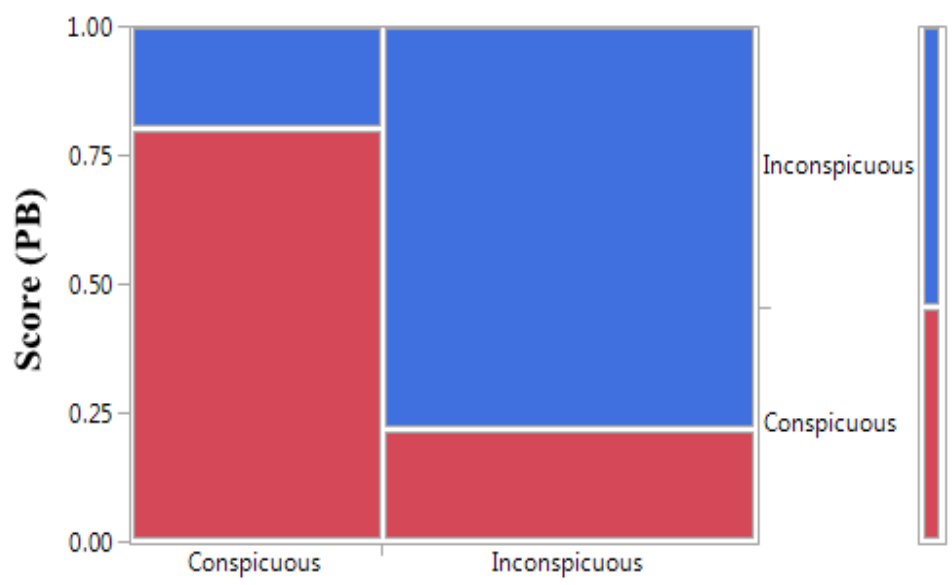
(B)



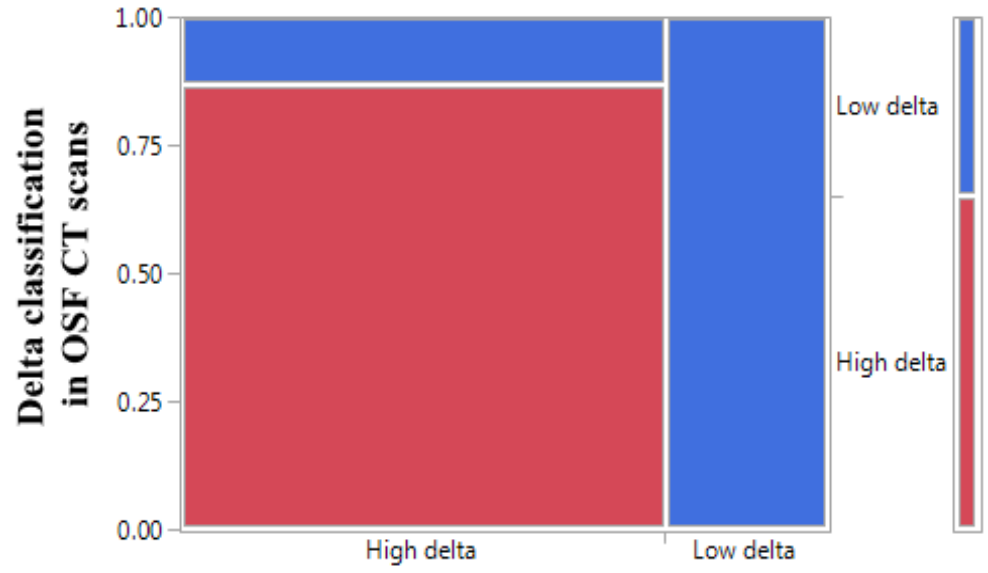
(C)



(D)



(E)

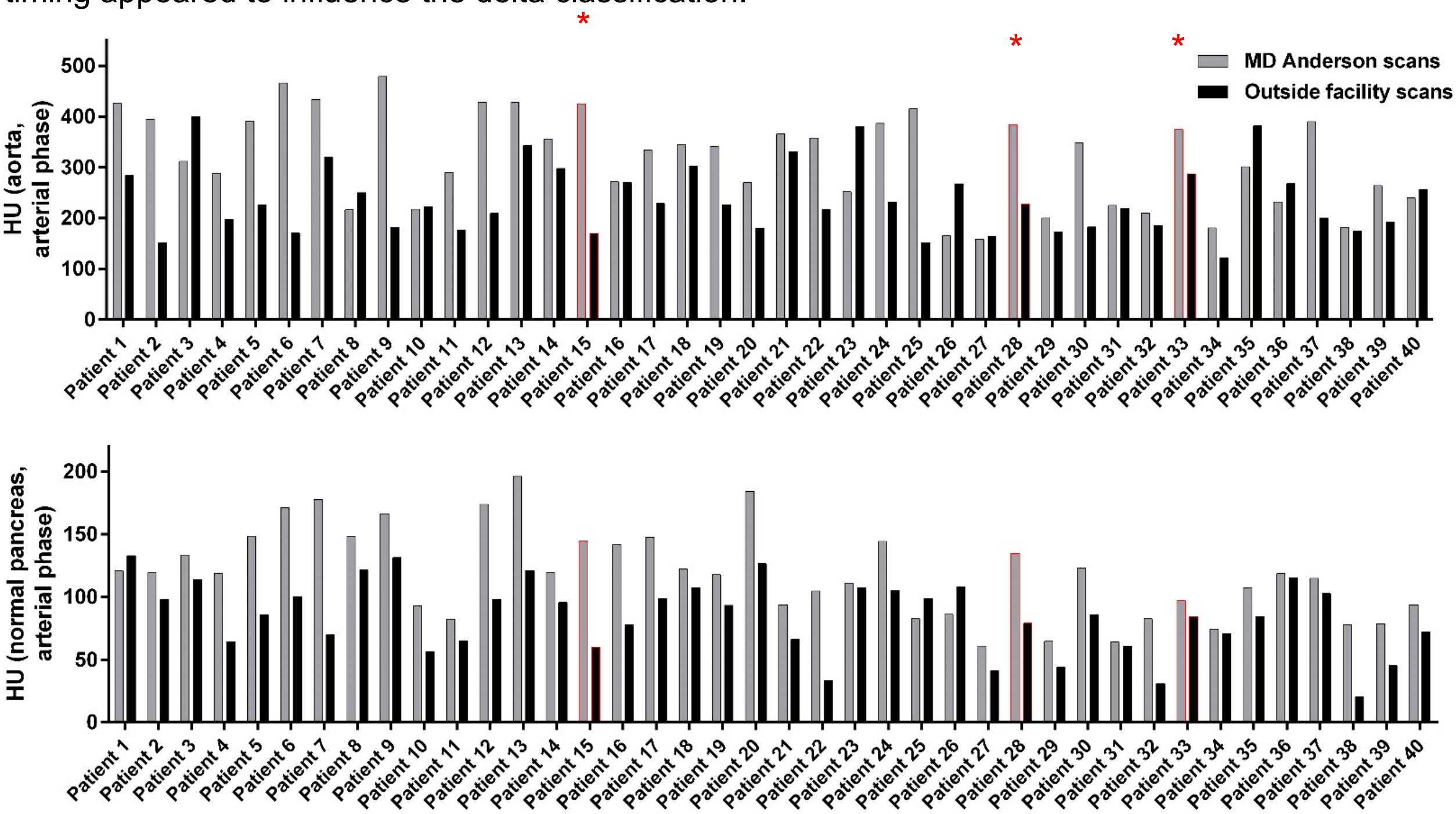


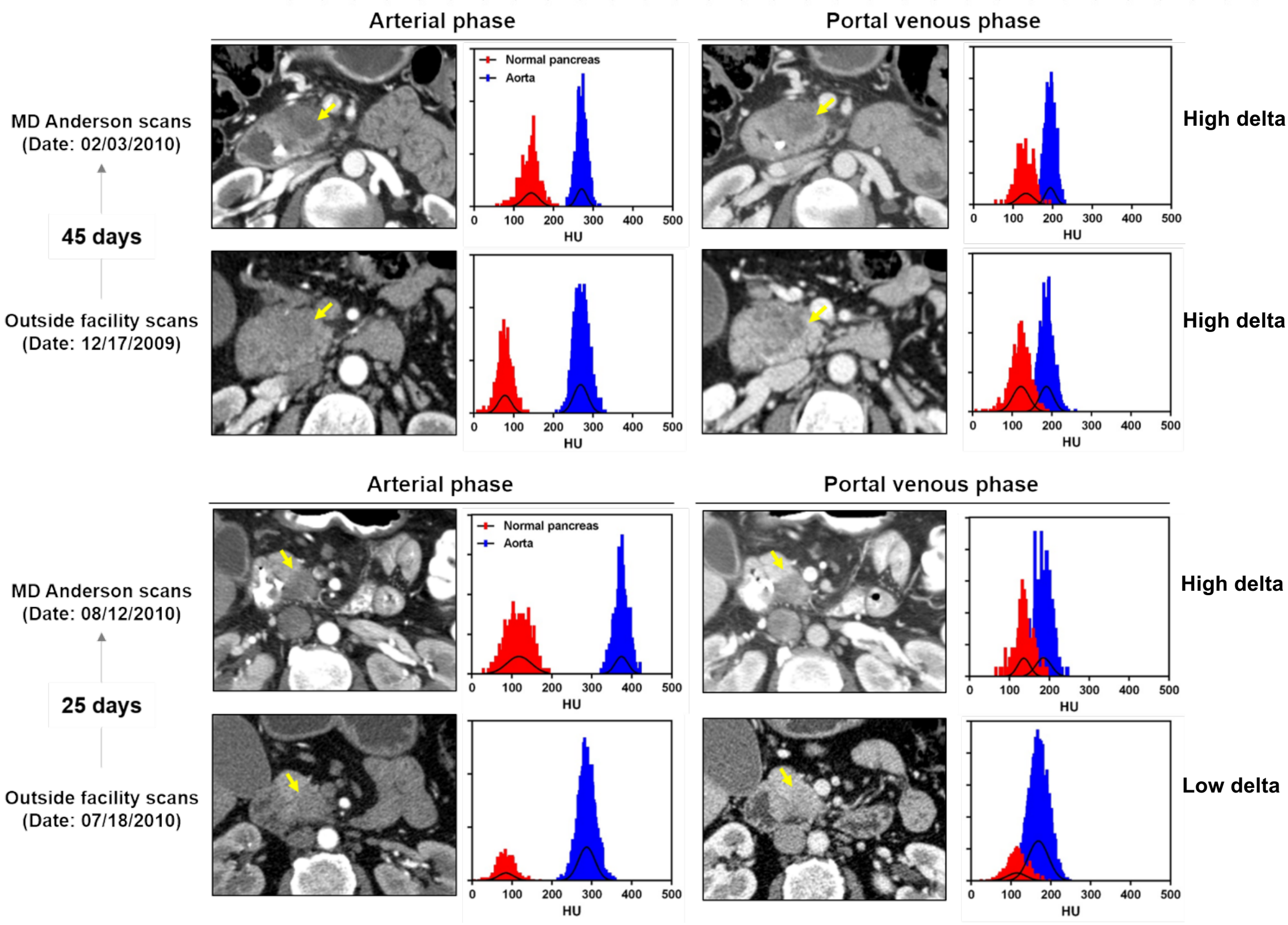
Score (ET)

Delta classification in MDACC CT scans

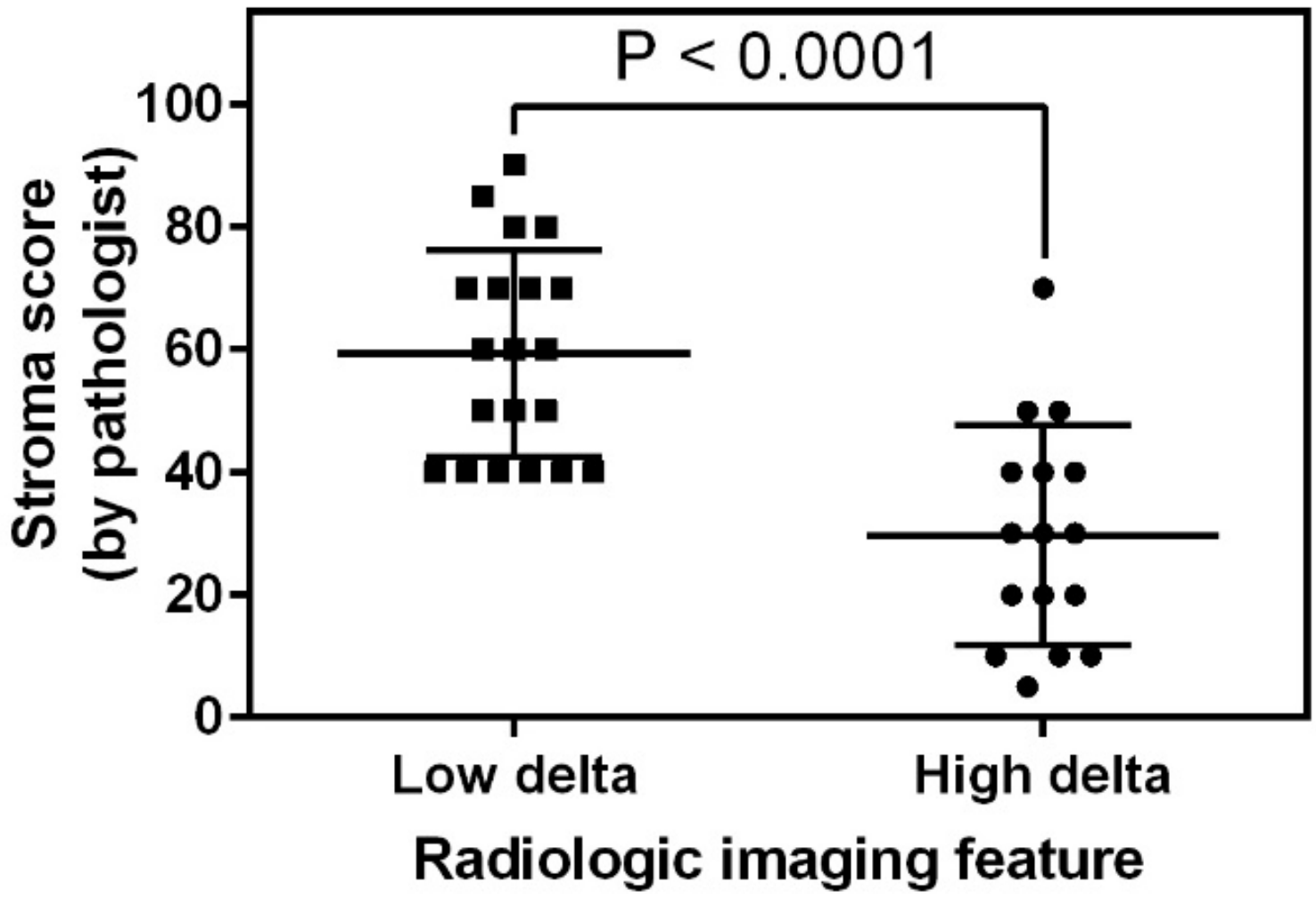
Supplementary Fig. S4: Delta classification between internal and external CT scans.

The top graphs show the three discordant cases (red star). The figures at the bottom of the page show examples of concordant cases and discordant cases. The technique of contrast bolus and timing appeared to influence the delta classification.

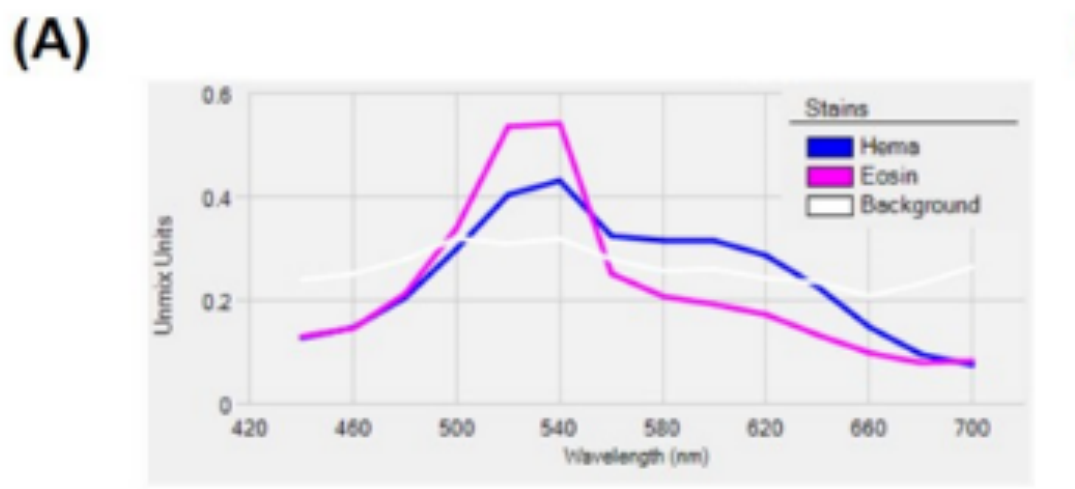


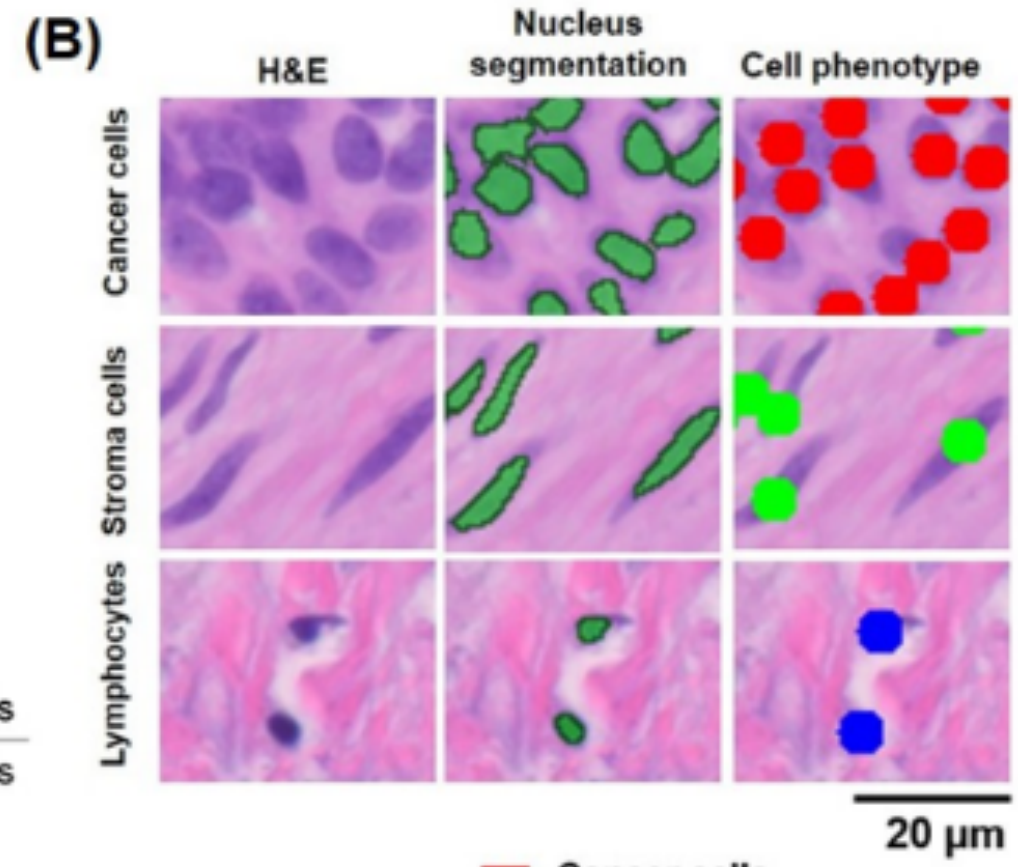


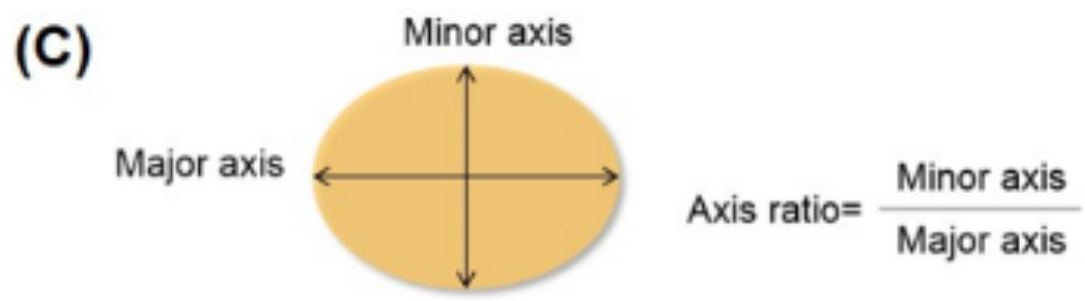
Supplementary Fig. S5: Validation of association between stroma and delta measurement in 33 patients who underwent upfront surgery (part of the patients in Supplementary Table S2).

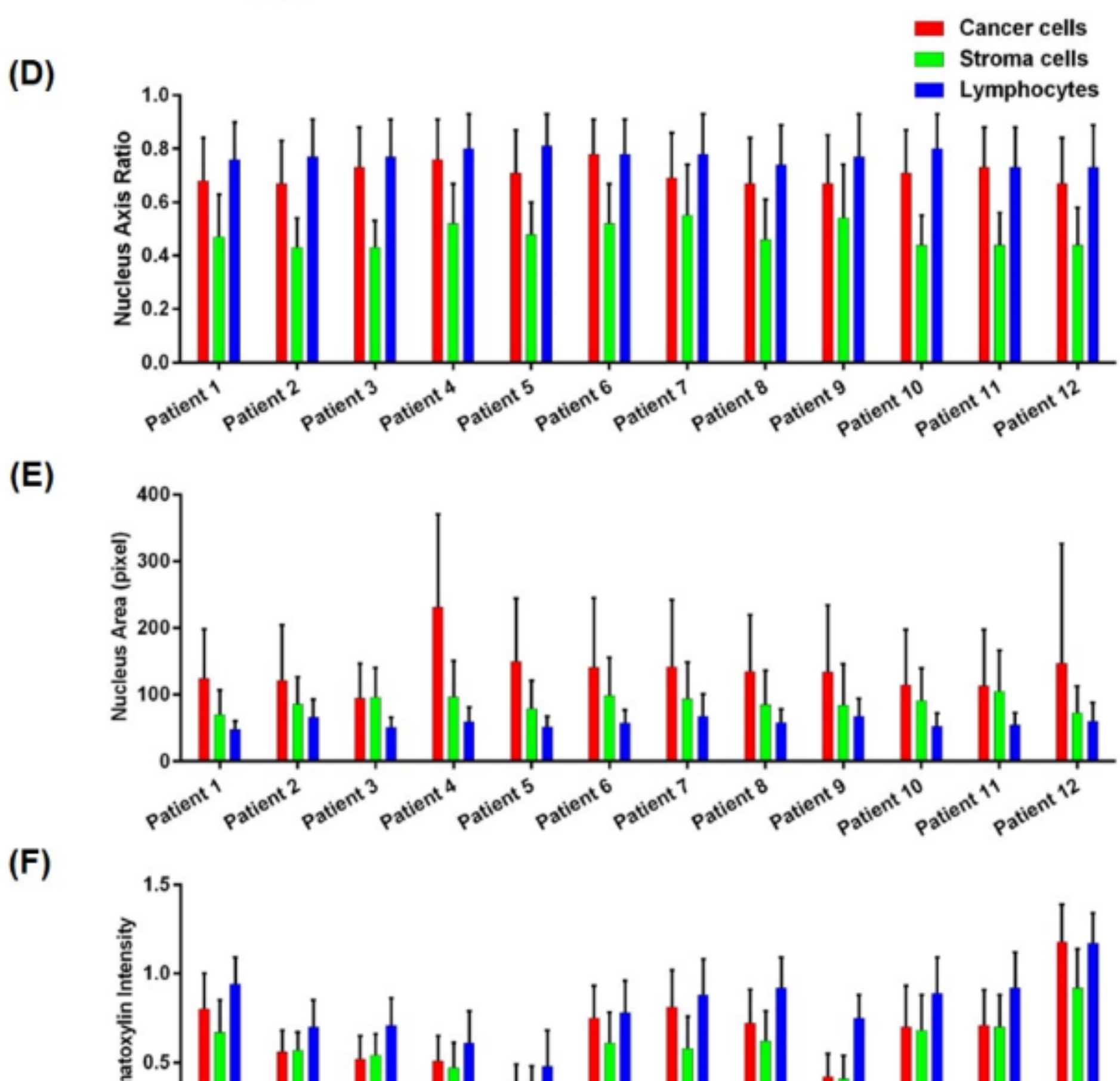


Supplementary Fig. S6: Cell type identification with machine learning algorithm. (A) Spectral library obtained from H&E stained slides. (B) Example of nucleus segmentation and cell type identification analysis of cancer, stroma cells, and lymphocytes. (C) The axis ratio is defined by the ratio of the lengths of the minor and major axis of objects. (D, E, F) Quality control of 12 slides. Note: Only images with cancer cells were selected for this analysis (see Methods).

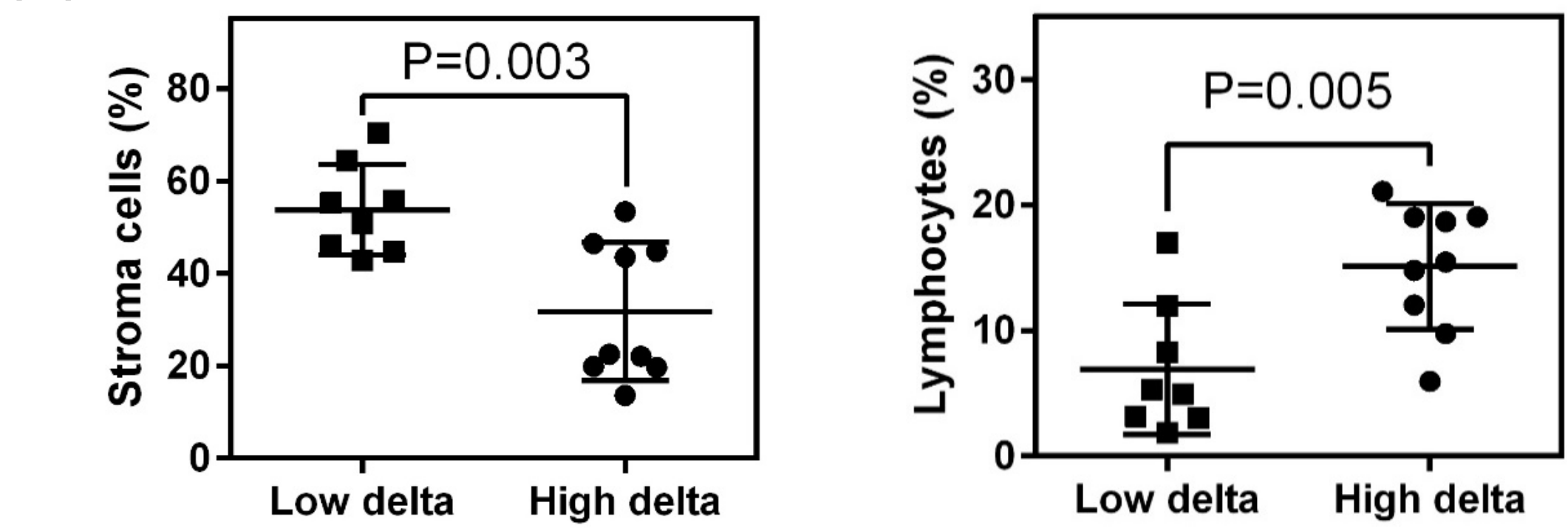




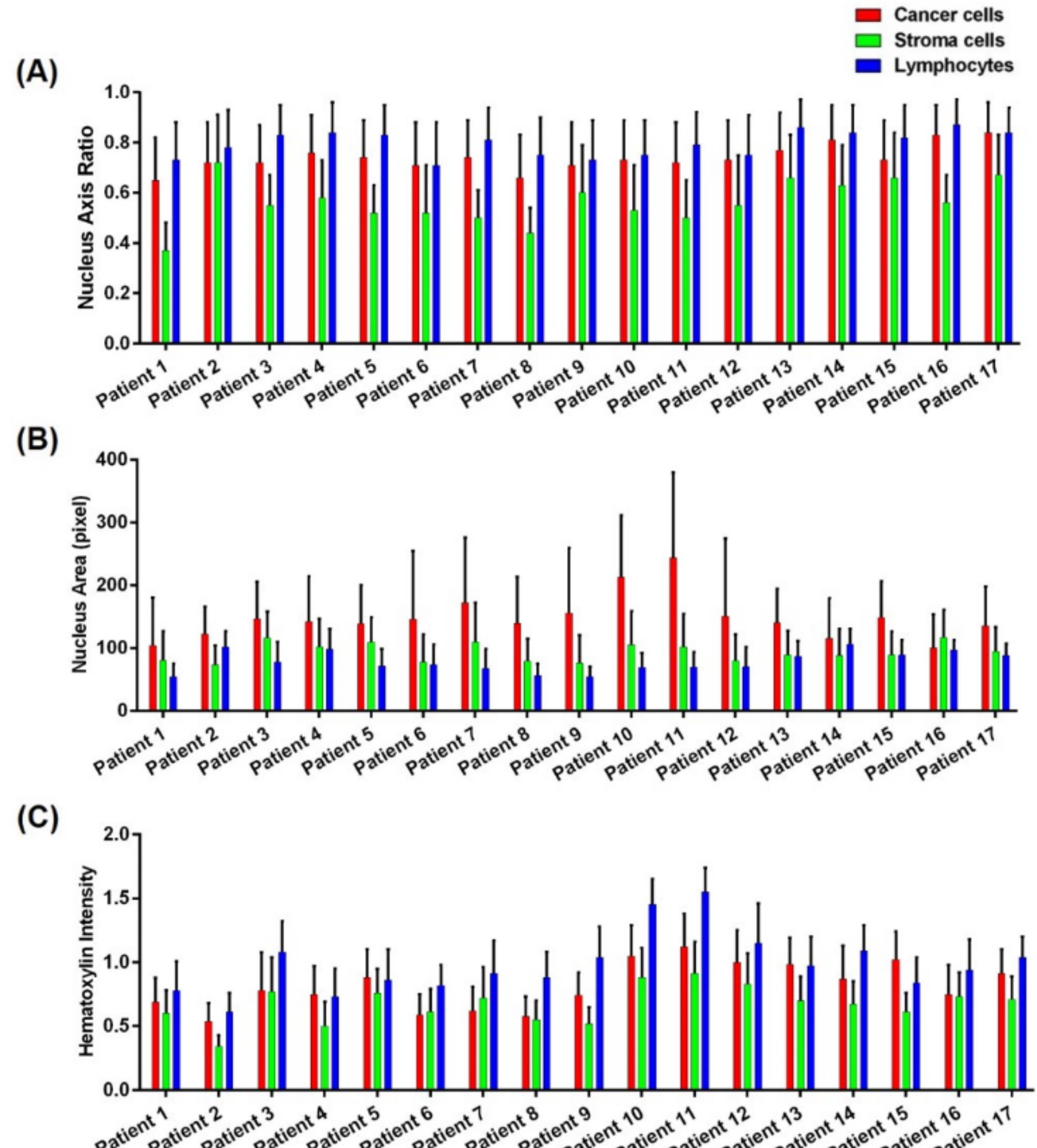




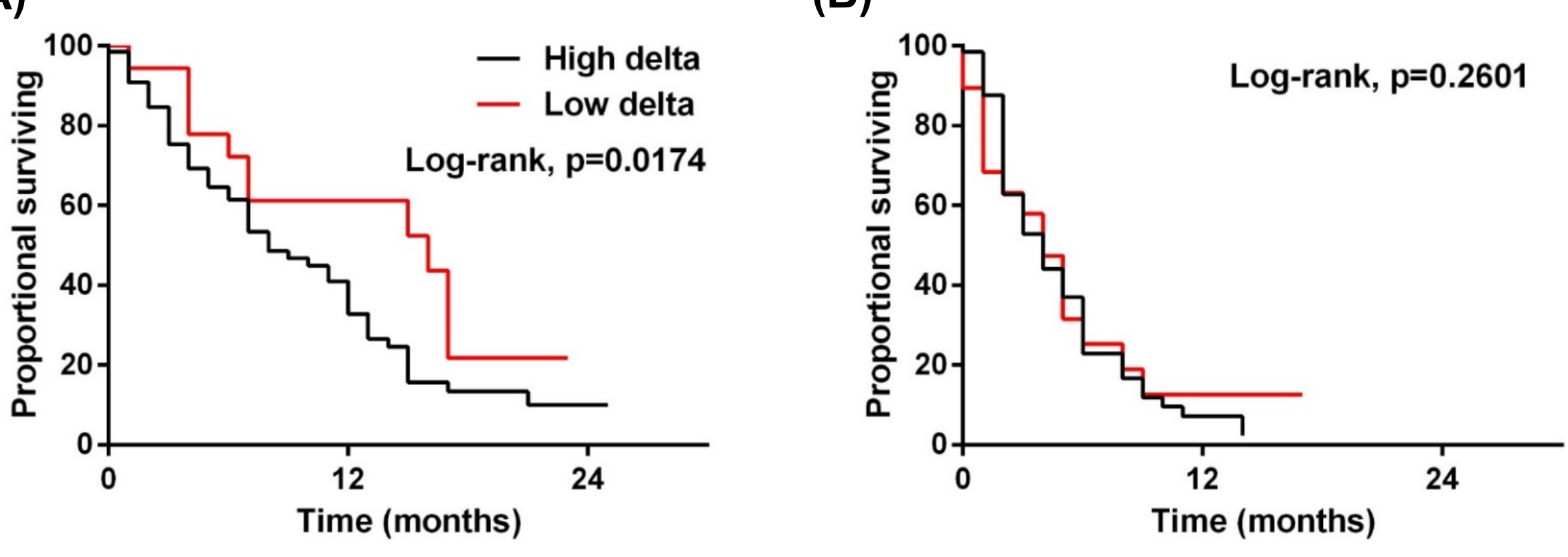
Supplementary Fig. S7: Validation of the proportions of cellular subtypes (A,B) and nucleus axis ratio (C) from pathology specimens from 17 more patients who underwent upfront resection for pancreatic cancer (i.e., no neoadjuvant therapy, part of the patients in Supplementary Table S2).



Supplementary Fig. S8: Validation of machine learning algorithm in 17 additional patients who underwent upfront resection for pancreatic cancer (part of Supplementary Table S2). Note: Only images with cancer cells were selected for this analysis (see Methods).

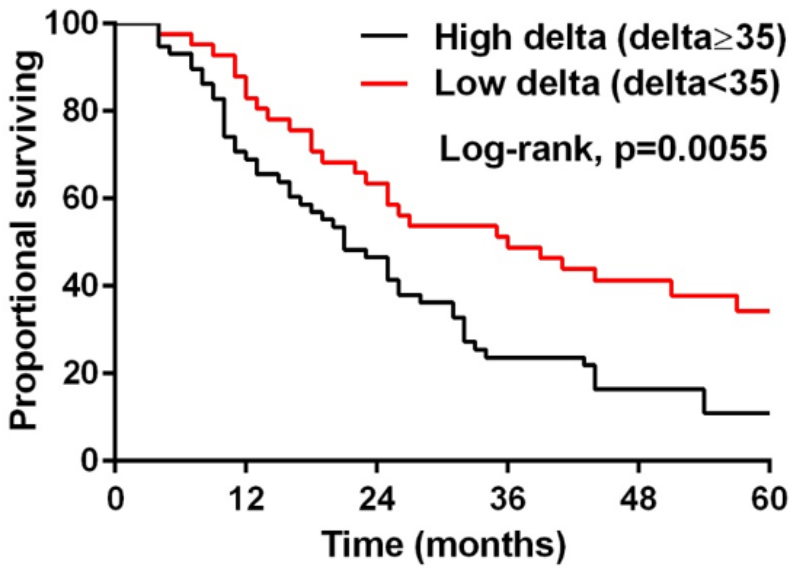


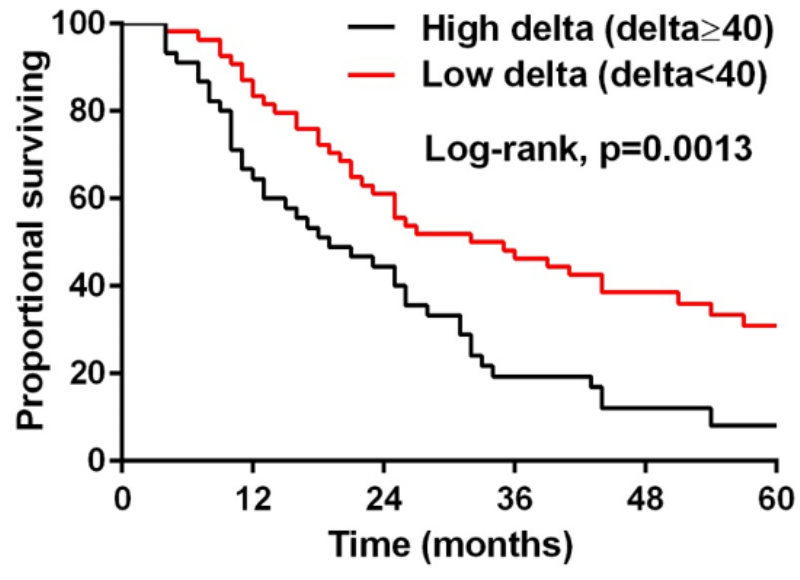
Supplementary Fig. S9: Outcomes of patients with newly diagnosed stage IV PDAC by delta score. (A) OS and (B) PFS (progression free survival) stratified by delta measurement for patients in Supplementary Table S4.

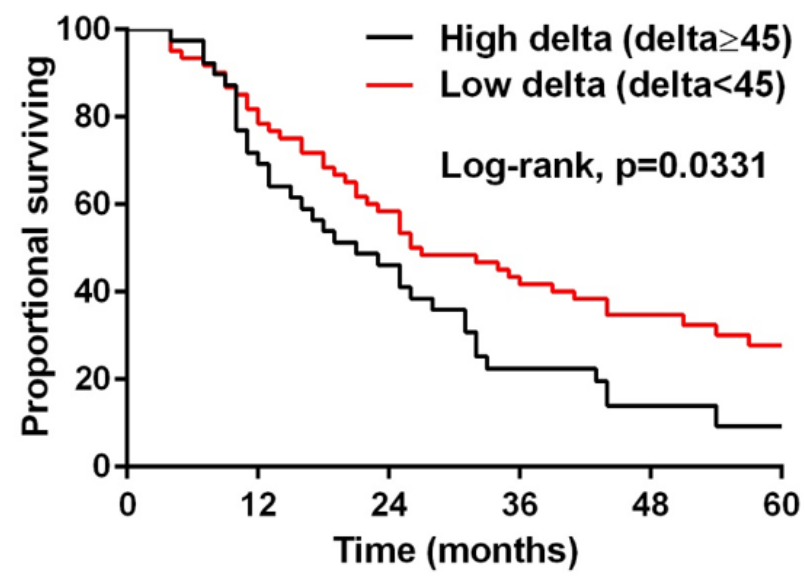


Supplementary Fig. S10: Sensitivity analysis for delta measurement for patients with resectable PDAC.

Comparison of overall survival of subjects having high delta (Left: ≥35; Middle: ≥40, Right: ≥45) or low delta tumors determined by quantitative analysis.







Supplementary Fig. S11: Sensitivity analysis for visual score for PDAC conspicuity. Comparison of overall survival of subjects having conspicuous tumor (A,C: ≥3, B, D: ≥4) or inconspicuous tumors determined by two radiologists (A,B by ET; C,D by PB). See Supplementary Table S2 for patient characteristics. A cutoff of 4 in the visual classification (High delta ≥4) best classified the delta measurements with AUC values of 0.93 in arterial phase and 0.80 in portal venous phase for ET's visual score and 0.83 in arterial phase and 0.82 in portal venous phase for PB's visual score.

Supplementary Fig. S12: Combined classification using delta and VAUC measurements. See Supplementary Table S3 for patient characteristics. (A) Proportions of low and high delta tumors achieving a near pathologic complete response to neoadjuvant therapy (≤10% viable tumor cells; Fisher's Exact test, p=0.07), (B) Proportions of high and low VAUC achieving a near complete response to neoadjuvant therapy (Fisher's Exact test, p=0.03), (C) Proportions of tumors classified according to delta and VAUC (Class 1 Low delta/High VAUC; Class 2 Low delta/Low VAUC; Class 3 High delta/High VAUC; Class 4 High delta/Low VAUC), (Fisher's Exact test, p=0.06), (D) Overall survival stratified by 4 classes for patients in Table S3 (n=106).