

SUPPLEMENTARY TABLES

Supplementary Table 1. Baseline and post-treatment, imaging-based prognostic factors for LPFS ($p \leq 0.1$) after univariate analysis in the ITT population

		<i>N</i> events	5-year LPFS (95% CI)	HR (95% CI)	<i>P</i> -value
Baseline factors					
Study	EXPERT EXPERT-C	10/105 5/164	89.3 (83.0 – 95.6) 96.3 (93.2 – 99.4)	1.0 0.32 (0.11 – 0.94)	0.038
Cetuximab	No Yes	14/186 1/83	91.1 (86.6 – 95.6) 98.6 (95.9 – 100)	1.0 0.14 (0.02 – 1.09)	0.061
Post-treatment imaging-based factors					
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Abbreviations: LPFS: local progression-free survival; ITT: intention-to-treat population; HR: hazard ratio; CI: confidence interval.

Supplementary Table 2. Baseline and post-treatment, imaging-based prognostic factors for DPFS ($p \leq 0.1$) after univariate analysis in the ITT population

		N events	5-year DPFS (95% CI)	HR (95% CI)	P-value
Baseline factors					
mrEMVI	Neg Pos	10/75 50/191	86.9 (78.9 – 94.9) 71.4 (64.7 – 78.1)	1.0 2.20 (1.11 – 4.33)	0.023
Tumour grade	1 / 2 3 / 4	46/229 12/27	50.6 (29.6 – 71.6) 78.5 (73.0 – 84.0)	1.0 3.14 (1.66 – 5.94)	<0.001
Post-treatment imaging-based factors					
mrEMVI	Pos at baseline and after treatment Pos at baseline – Neg after treatment Neg at baseline	30/81 12/66 10/75	61.6 (50.8 – 72.4) 81.0 (71.2 – 90.8) 86.9 (78.9 – 94.9)	1.0 0.41 (0.21 – 0.81) 0.31 (0.15 – 0.63)	(0.001) 0.010 0.001
mrT downstaging	No Yes	41/146 10/75	71.4 (63.9 – 78.8) 85.6 (77.4 – 93.8)	1.0 0.43 (0.22 – 0.86)	0.017
mrTRG	3 / 4 / 5 1 / 2	42/134 11/96	67.6 (59.4 – 75.8) 88.1 (81.4 – 94.7)	1.0 0.31 (0.16 – 0.60)	0.001

Abbreviations: DPFS: distant progression-free survival; ITT: intention-to-treat population; HR: hazard ratio; CI: confidence interval; mrEMVI: magnetic resonance extramural venous invasion; mrT downstaging: magnetic resonance T downstaging; Pos: positive; Neg: Negative; mrTRG: magnetic resonance tumour regression grade.

Supplementary Table 3. Baseline and post-treatment, imaging-based prognostic factors for PFS ($p \leq 0.1$) after univariate analysis in the ITT population

		<i>N</i> events	5-year PFS (95% CI)	HR (95% CI)	<i>P</i> -value
Baseline factors					
Age	< 70 yrs ≥ 70 yrs	73/205 34/64	67.9 (61.4 – 74.4) 61.3 (49.1 – 73.5)	1.0 1.63 (1.08 – 2.44)	0.020
T4	No Yes	80/211 27/58	69.2 (62.9 – 75.5) 55.7 (42.8 – 68.6)	1.0 1.46 (0.94 – 2.26)	0.093
N stage	0 1 / 2	27/81 80/188	72.5 (62.7 – 82.3) 63.7 (56.8 – 70.6)	1.0 1.44 (0.93 – 2.23)	0.100
mrEMVI	Pos Neg	21/75 85/191	78.2 (68.8 – 87.6) 61.7 (54.8 – 68.6)	1.0 1.77 (1.10 – 2.85)	0.020
Tumour grade	1 / 2 3 / 4	85/229 18/27	69.2 (63.1 – 75.3) 38.6 (19.8 – 57.4)	1.0 2.74 (1.64 – 4.58)	<0.001
Post-treatment imaging-based factors					
mrEMVI	Yes at baseline and after treatment Yes at baseline - No after treatment No at baseline	37/81 26/66 21/75	57.1 (46.1 – 68.1) 71.0 (60.0 – 82.0) 78.2 (68.8 – 87.6)	1.0 0.68 (0.41 – 1.13) 0.51 (0.30 – 0.86)	(0.038) 0.136 0.013
mrT downstaging	No Yes	61/146 21/75	63.9 (56.1 – 71.7) 79.5 (70.3 – 88.7)	1.0 0.54 (0.33 – 0.89)	0.016
mrTRG	3 / 4 / 5 1 / 2	61/134 23/96	60.6 (52.2 – 69.0) 81.9 (74.1 – 89.7)	1.0 0.40 (0.24 – 0.64)	<0.001

Abbreviations: PFS: progression-free survival; ITT: intention-to-treat population; HR: hazard ratio; CI: confidence interval; mrEMVI: magnetic resonance extramural venous invasion; mrT downstaging: magnetic resonance T downstaging; Pos: positive; Neg: Negative; mrTRG: magnetic resonance tumour regression grade.

Supplementary Table 4. Baseline and post-treatment, imaging-based prognostic factors for OS ($p \leq 0.1$) after univariate analysis in the ITT population

		<i>N</i> events	5-year OS (95% CI)	HR (95% CI)	<i>P</i> -value
Baseline factors					
Age	< 70 yrs ≥ 70 yrs	63/205 31/64	74.6 (68.5 – 80.7) 69.2 (57.6 – 80.8)	1.0 1.62 (1.05 – 2.49)	0.030
Performance status	0 1 / 2	32/112 62/157	75.8 (67.8 – 83.8) 71.6 (64.5 – 78.7)	1.0 1.58 (1.02 – 2.44)	0.040
T4	No Yes	69/211 25/58	75.8 (69.9 – 81.7) 64.6 (52.1 – 77.1)	1.0 1.72 (1.08 – 2.72)	0.021
mrEMVI	Pos Neg	19/75 74/191	82.0 (73.2 – 90.8) 69.6 (62.9 – 76.3)	1.0 1.61 (0.97 – 2.66)	0.066
Tumour grade	1 / 2 3 / 4	73/229 18/27	76.6 (71.1 – 82.1) 41.4 (22.2 – 60.6)	1.0 3.52 (2.07 – 5.97)	<0.001
Post-treatment imaging-based factors					
mrEMVI	Pos at baseline and after treatment Pos at baseline – Neg after treatment Neg at baseline	32/81 23/66 19/75	65.7 (55.1 – 76.3) 78.6 (68.6 – 88.6) 82.0 (73.2 – 90.8)	1.0 0.68 (0.39 – 1.17) 0.55 (0.31 – 0.97)	(0.096) 0.161 0.039
mrT downstaging	No Yes	53/146 19/75	71.3 (63.9 – 78.7) 83.6 (75.2 – 92.0)	1.0 0.60 (0.35 – 1.02)	0.058
mrTRG	3 / 4 / 5 1 / 2	54/134 20/96	68.8 (60.8 – 76.8) 85.1 (77.8 – 92.4)	1.0 0.47 (0.28 – 3.56)	0.004
Tumour response (RECIST)	SD / PD CR / PR	14/33 67/211	66.7 (50.6 – 82.8) 77.6 (71.9 – 83.3)	1.0 0.49 (0.27 – 0.88)	0.018

Abbreviations: OS: overall survival; ITT: intention-to-treat population; HR: hazard ratio; CI: confidence interval; mrEMVI: magnetic resonance extramural venous invasion; mrT downstaging: magnetic resonance T downstaging; Pos: positive; Neg: Negative; mrTRG: magnetic resonance tumour regression grade; SD: stable disease; PD: progressive disease; PR: partial response; CR: complete response.

Supplementary Table 5. Baseline, post-treatment, imaging-based and post-treatment surgical/pathological prognostic factors for LRFS ($p \leq 0.1$) after univariate analysis in the R0/R1 population

		<i>N</i> events	5-year LRFS (95% CI)	HR (95% CI)	<i>P</i> -value
Baseline factors					
Study	EXPERT EXPERT-C	9/95 3/145	90.0 (83.7 – 96.3) 97.6 (94.8 – 100)	1.0 0.22 (0.06 – 0.80)	0.022
Post-treatment imaging-based factors					
-		-	-	-	-
Post-treatment surgical/pathological factors					
ypT	3 / 4 0 / 1 / 2	9/126 3/114	91.6 (86.3 – 96.7) 97.3 (94.4 – 100)	1.0 0.33 (0.09 – 1.21)	0.093
Resection	R1 R0	3/7 9/233	30.0 (0 – 76.8) 95.9 (93.2 – 98.6)	1.0 0.06 (0.02 – 0.23)	<0.001

Abbreviations: LRFS: local recurrence-free survival; ITT: intention-to-treat population; HR: hazard ratio; CI: confidence interval; ypT: pathological T stage; R0: microscopically negative resection margins; R1 microscopically positive resection margins.

Supplementary Table 6. Baseline, post-treatment, imaging-based and post-treatment surgical/pathological prognostic factors for DRFS ($p \leq 0.1$) after univariate analysis in the R0/R1 population

		<i>N</i> events	5-year DRFS (95% CI)	HR (95% CI)	<i>P</i> -value
Baseline factors					
mrEMVI	Pos Neg	9/70 38/167	86.1 (77.7 – 94.5) 76.2 (69.5 – 82.9)	1.0 1.87 (0.90 – 3.86)	0.092
Tumour grade	1 / 2 3 / 4	35/205 11/25	82.3 (77.0 – 87.6) 47.0 (24.5 – 69.5)	1.0 3.90 (1.98 – 7.71)	<0.001
Post-treatment imaging-based factors					
mrEMVI	Pos at baseline and after treatment Pos at baseline – Neg after treatment Neg at baseline	22/74 10/61 9/70	69.1 (58.3 – 79.9) 82.7 (72.9 – 92.5) 86.1 (77.7 – 94.5)	1.0 0.49 (0.23 – 1.04) 0.38 (0.18 – 0.83)	(0.026) 0.063 0.015
mrT downstaging	No Yes	32/134 9/72	75.1 (67.7 – 82.5) 86.6 (82.5 – 94.8)	1.0 0.49 (0.23 – 1.02)	0.057
mrTRG	3 / 4 / 5 1 / 2	34/122 9/93	70.6 (62.4 – 78.8) 89.9 (83.6 – 96.2)	1.0 0.30 (0.14 – 0.63)	0.001
Post-treatment surgical/pathological factors					
ypT downstaging	No Yes	30/104 17/136	69.5 (60.3 – 78.7) 86.9 (81.0 – 92.8)	1.0 0.37 (0.20 – 0.67)	0.001
ypT or ypN downstaging	No Yes	15/49 32/191	67.2 (53.5 – 80.9) 82.5 (77.0 – 88.0)	1.0 0.45 (0.24 – 0.83)	0.011
ypT	3 / 4 0 / 1 / 2	38/126 9/114	67.8 (59.4 – 76.2) 91.7 (86.4 – 97.0)	1.0 0.21 (0.10 – 0.44)	<0.001
ypN	1 / 2 0	26/65 21/175	59.0 (47.8 – 71.2) 87.2 (82.1 – 92.3)	1.0 0.25 (0.14 – 0.44)	<0.001
ypStage	III II I 0	26/65 14/71 5/56 2/48	59.0 (46.8 – 71.2) 78.4 (68.4 – 88.4) 90.5 (82.7 – 98.3) 95.7 (90.0 – 100)	1.0 0.45 (0.23 – 0.86) 0.18 (0.07 – 0.46) 0.08 (0.02 – 0.34)	(<0.001) 0.015 <0.001 0.001
Dworak pTRG	0 / 1 2 3 / 4	20/72 11/61 4/75	70.1 (59.1 – 81.1) 80.5 (70.1 – 90.9) 94.6 (89.5 – 99.7)	1.0 0.58 (0.28 – 1.21) 0.15 (0.05 – 0.45)	(0.002) 0.144 0.001
Resection	R1 R0	3/7 44/233	40.0 (0 – 82.9) 80.3 (75.0 – 85.6)	1.0 0.27 (0.08 – 0.87)	0.028
Complete response (pCR + cCR)	No Yes	45/192 2/48	75.2 (68.9 – 81.5) 95.7 (90.0 – 100.0)	1.0 0.15 (0.04 – 0.63)	0.009

Abbreviations: DRFS: distant recurrence-free survival; ITT: intention-to-treat population; HR: hazard ratio; CI: confidence interval; mrEMVI: magnetic resonance extramural venous invasion; Pos: positive; Neg: Negative; mrT downstaging: magnetic resonance T downstaging; mrTRG: magnetic resonance tumour regression grade; ypT downstaging: pathological T downstaging; ypN downstaging: pathological N downstaging; ypT: pathological T stage; ypN: pathological N stage; ypStage: pathological stage; pTRG: pathological tumour regression grade; R0: microscopically negative resection margins; R1 microscopically positive resection margins. pCR: pathological complete response; cCR: clinical complete response.

Supplementary Table 7. Baseline, post-treatment, imaging-based and post-treatment surgical/pathological prognostic factors for RFS ($p \leq 0.1$) after univariate analysis in the R0/R1 population

		N events	5-year RFS (95% CI)	HR (95% CI)	P-value
Baseline factors					
Age	< 70 yrs ≥ 70 yrs	55/183 28/57	72.8 (66.3 – 79.3) 67.6 (55.3 – 79.9)	1.0 1.60 (1.01 – 2.54)	0.044
Tumour grade	1 / 2 3 / 4	64/205 16/25	75.3 (69.4 – 81.2) 36.6 (16.8 – 56.4)	1.0 3.84 (2.19 – 6.73)	<0.001
Post-treatment imaging-based factors					
mrEMVI	Pos at baseline and after treatment Pos at baseline – Neg after treatment Neg at baseline	31/74 22/61 18/70	61.7 (0.51 – 72.9) 73.5 (62.3 – 84.7) 79.3 (69.7 – 88.9)	1.0 0.60 (0.34 – 1.06) 0.50 (0.28 – 0.89)	(0.043) 0.080 0.019
mrT downstaging	No Yes	51/134 19/72	67.5 (59.5 – 75.5) 79.9 (70.5 – 89.3)	1.0 0.58 (0.34 – 0.98)	0.043
mrTRG	3 / 4 / 5 1 / 2	51/122 21/93	64.3 (55.7 – 72.9) 82.3 (74.5 – 90.1)	1.0 0.47 (0.28 – 0.78)	0.004
Post-treatment surgical/pathological factors					
ypT downstaging	No Yes	49/104 34/136	60.0 (50.6 – 69.4) 80.5 (73.8 – 87.2)	1.0 0.43 (0.27 – 0.66)	<0.001
ypT or ypN downstaging	No Yes	26/49 57/191	54.2 (40.1 – 68.3) 76.0 (69.9 – 82.1)	1.0 0.42 (0.26 – 0.66)	<0.001
ypT	3 / 4 0 / 1 / 2	59/126 24/114	58.8 (50.2 – 67.4) 85.6 (79.1 – 92.1)	1.0 0.32 (0.20 – 0.52)	<0.001
ypN	1 / 2 0	35/65 48/175	53.8 (41.6 – 66.0) 78.3 (72.0 – 84.6)	1.0 0.43 (0.28 – 0.67)	<0.001
ypStage	III II I 0	35/65 27/71 13/56 8/48	53.8 (41.6 – 66.0) 66.6 (55.4 – 77.7) 81.8 (71.6 – 92.0) 91.7 (83.9 – 99.5)	1.0 0.76 (0.45 – 1.26) 0.31 (0.16 – 0.59) 0.23 (0.11 – 0.50)	(<0.001) 0.285 <0.001 <0.001
Dworak pTRG	0 / 1 2 3 / 4	33/72 18/61 12/75	59.3 (47.9 – 70.7) 72.6 (61.0 – 84.2) 90.6 (83.9 – 97.3)	1.0 0.65 (0.36 – 1.15) 0.30 (0.15 – 0.58)	(0.002) 0.140 <0.001
Resection	R1 R0	7/7 76/233	0.0 73.8 (68.1 – 79.5)	1.0 0.15 (0.07 – 0.33)	<0.001
Complete response (pCR + cCR)	No Yes	75/192 8/48	66.6 (59.9 – 73.3) 91.7 (83.9 – 99.5)	1.0 0.33 (0.17 – 0.73)	0.005
Adherence to study treatment					
Treatment completed	No Yes	36/85 47/155	63.6 (53.2 – 74.0) 75.9 (69.0 – 82.8)	1.0 0.61 (0.39 – 0.94)	0.025

Abbreviations: RFS: recurrence-free survival; ITT: intention-to-treat population; HR: hazard ratio; CI: confidence interval; mrEMVI: magnetic resonance extramural venous invasion; Pos: positive; Neg: Negative; mrT downstaging: magnetic resonance T downstaging; mrTRG: magnetic resonance tumour regression grade; ypT downstaging: pathological T downstaging; ypN downstaging: pathological N downstaging; ypT: pathological T stage; ypN: pathological N stage; ypStage: pathological stage; pTRG: pathological tumour regression grade; R0: microscopically negative resection margins; R1 microscopically positive resection margins. pCR: pathological complete response; cCR: clinical complete response.

Supplementary Table 8. Baseline, post-treatment, imaging-based and post-treatment surgical/pathological prognostic factors for OS ($p \leq 0.1$) after univariate analysis in the R0/R1 population

		<i>N</i> events	5-year OS (95% CI)	HR (95% CI)	<i>P</i> -value
Baseline factors					
Age	< 70 yrs ≥ 70 yrs	46/183 25/57	79.2 (73.3 – 85.1) 72.6 (60.6 – 84.6)	1.0 1.68 (1.03 – 2.76)	0.039
Tumour grade	1 / 2 3 / 4	53/205 16/25	81.0 (75.5 – 86.5) 39.8 (19.6 – 60.0)	1.0 4.84 (2.71 – 8.65)	<0.001
Post-treatment imaging-based factors					
mrTRG	3 / 4 / 5 1 / 2	45/122 18/93	70.6 (62.4 – 78.8) 85.5 (78.2 – 92.8)	1.0 0.51 (0.29 – 0.8)	0.015
Post-treatment surgical/pathological factors					
ypT downstaging	No Yes	42/104 29/136	67.3 (58.1 – 76.5) 84.7 (78.4 – 91.0)	1.0 0.44 (0.27 – 0.70)	0.001
ypT or ypN downstaging	No Yes	23/49 48/191	59.5 (45.4 – 73.6) 81.6 (75.9 – 87.3)	1.0 0.38 (0.23 – 0.63)	<0.001
ypT	3 / 4 0 / 1 / 2	52/126 19/114	65.6 (57.2 – 74.0) 89.9 (84.2 – 95.6)	1.0 0.29 (0.17 – 0.50)	<0.001
ypN	1 / 2 0	31/65 40/175	62.7 (50.9 – 74.5) 82.7 (77.0 – 88.4)	1.0 0.46 (0.29 – 0.74)	0.001
ypStage	III II I 0	31/65 23/71 10/56 7/48	62.7 (50.9 – 74.5) 71.9 (61.1 – 82.7) 86.8 (77.6 – 96.0) 93.7 (86.8 – 100)	1.0 0.82 (0.47 – 1.43) 0.31 (0.15 – 0.63) 0.27 (0.12 – 0.62)	(0.001) 0.484 0.001 0.002
Dworak pTRG	0 / 1 2 3 / 4	29/72 16/61 11/75	65.9 (54.7 – 77.1) 75.6 (64.4 – 86.8) 91.8 (85.5 – 98.1)	1.0 0.69 (0.37 – 1.28) 0.34 (0.17 – 0.68)	(0.009) 0.243 0.002
Resection	R1 R0	6/7 65/233	28.6 (0 – 62.1) 78.7 (73.4 – 84.0)	1.0 0.24 (0.10 – 0.55)	0.001
Complete response (pCR + cCR)	No Yes	64/192 7/48	73.0 (66.5 – 79.5) 93.7 (86.8 – 100)	1.0 0.39 (0.18 – 0.86)	0.019
Adherence to study treatment					
Treatment completed	No Yes	34/85 37/155	66.9 (56.7 – 77.1) 82.8 (76.7 – 88.9)	1.0 0.51 (0.32 – 0.81)	0.005

Abbreviations: OS: overall survival; ITT: intention-to-treat population; HR: hazard ratio; CI: confidence interval; mrTRG: magnetic resonance tumour regression grade; ypT downstaging: pathological T downstaging; ypN downstaging: pathological N downstaging; ypT: pathological T stage; ypN: pathological N stage; ypStage: pathological stage; pTRG: pathological tumour regression grade; R0: microscopically negative resection margins; R1 microscopically positive resection margins. pCR: pathological complete response; cCR: clinical complete response.

Supplementary Table 9. Hazard ratios and c-indexes of short-term outcome measures for RFS and OS in R0/R1 patients (N=191)

Outcome measure	RFS			OS		
	HR (95% CI)	P-value	c-index	HR (95% CI)	P-value	c-index
mrTRG post CRT (1/2 vs 3-5)	0.52 (0.30 – 0.91)	0.022	0.5778	0.50 (0.28 – 0.90)	0.022	0.5828
ypT downstage (no vs yes)	0.49 (0.29 – 0.83)	0.008	0.5829	0.56 (0.32 – 0.98)	0.044	0.5679
pTRG (3/4 vs 0-2)	0.37 (0.19 – 0.71)	0.003	0.6065	0.39 (0.20 – 0.79)	0.008	0.6005
CR (no vs yes)	0.39 (0.17 – 0.86)	0.019	0.5776	0.38 (0.16 – 0.89)	0.026	0.5794
ypT (0-2 vs 3-4)	0.34 (0.19 – 0.61)	<0.001	0.6238	0.39 (0.21 – 0.72)	0.003	0.6094
pStage AJCC (0-1 vs 2-3)	0.33 (0.18 – 0.61)	<0.001	0.6252	0.38 (0.20 – 0.71)	0.002	0.6132

Abbreviations: RFS: recurrence-free survival; OS: overall survival; ITT: intention-to-treat population; HR: hazard ratio; CI: confidence interval; mrTRG: magnetic resonance tumour regression grade; CRT: chemoradiotherapy; ypT downstaging: pathological T downstaging; pTRG: pathological tumour regression grade; CR: complete response; AJCC: American Joint Committee on Cancer.

Supplementary figure legends

Supplementary Figure 1. EXPERT and EXPERT-C trial design

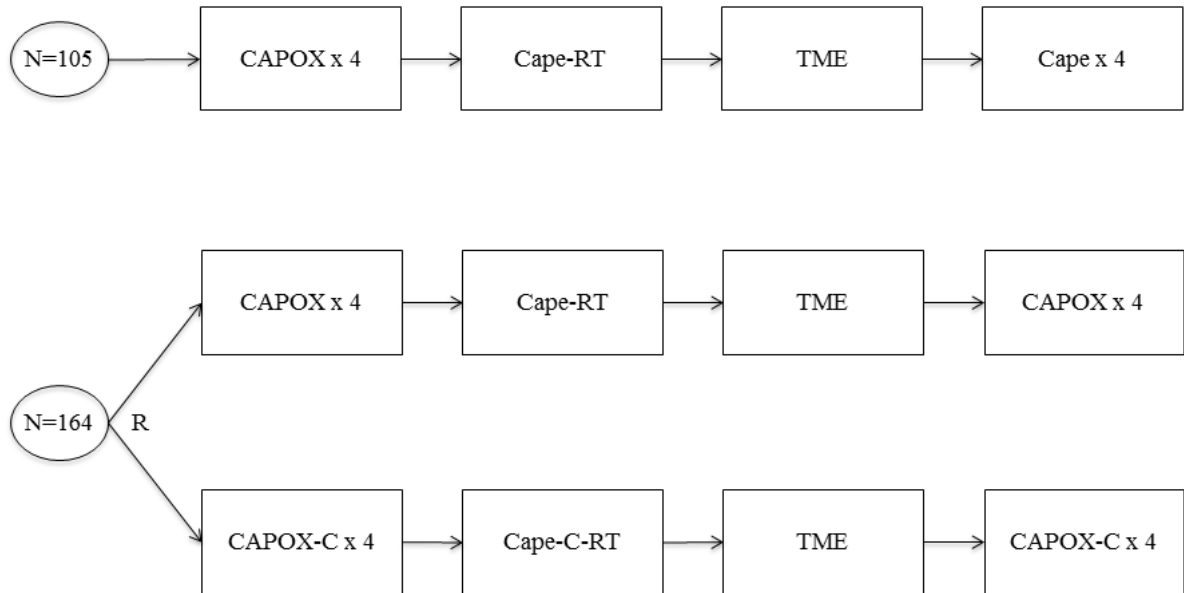
Abbreviations: N: number of eligible patients; R: randomisation; CAPOX: capecitabine and oxaliplatin; C: cetuximab; Cape: capecitabine; RT: radiotherapy; TME: total mesorectal excision

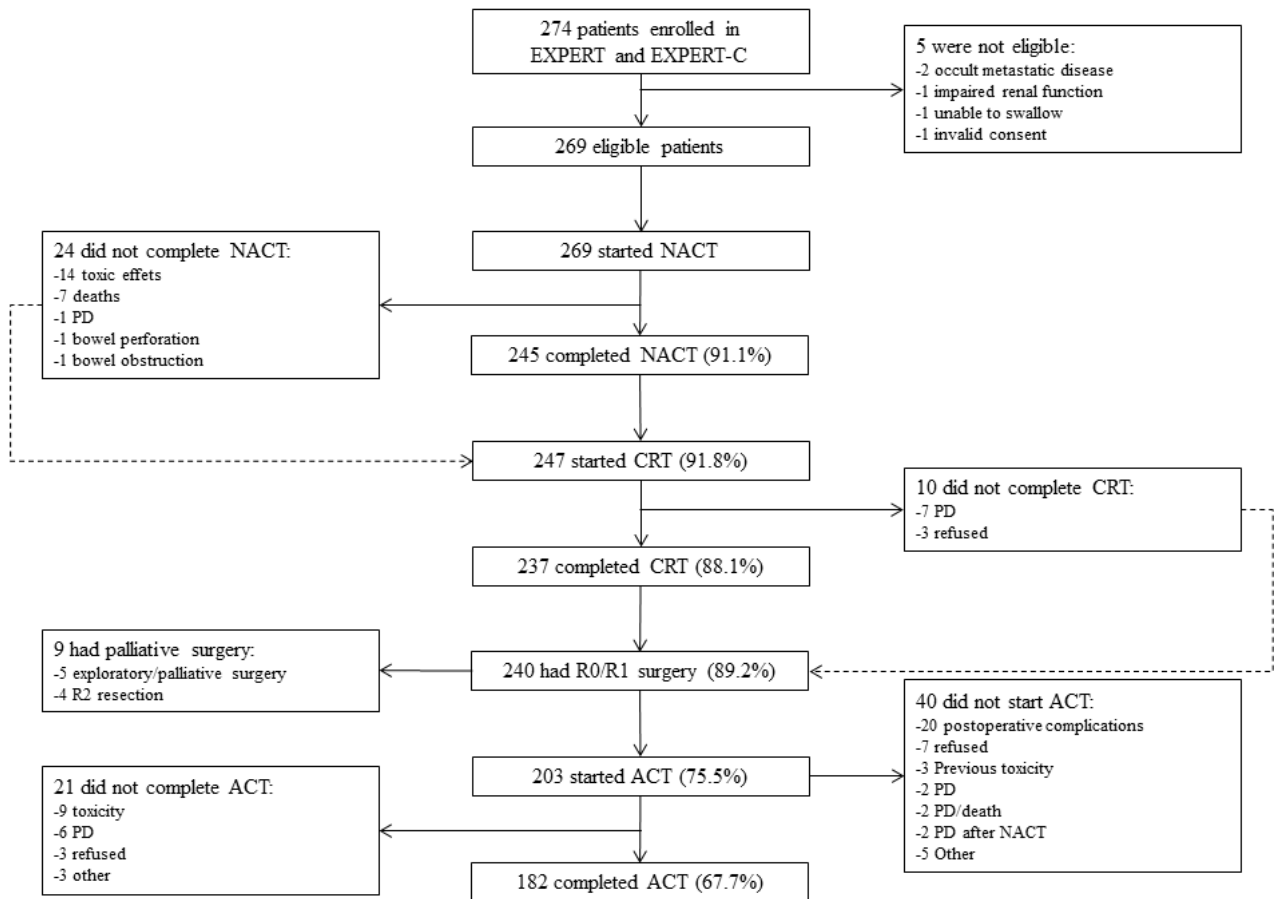
Supplementary Figure 2. PAN-EX study flow diagram.

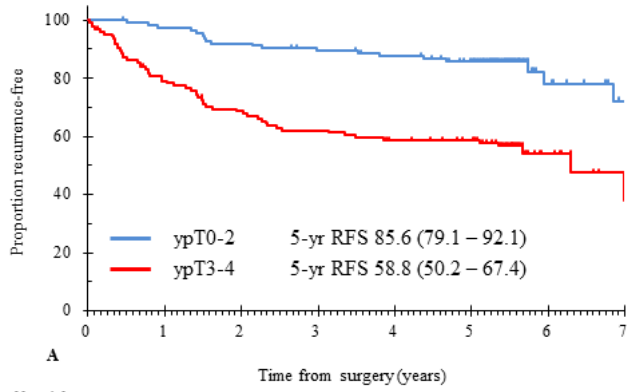
Abbreviations: NACT: neoadjuvant chemotherapy; CRT: chemoradiotherapy; ACT: adjuvant chemotherapy; R0/R1: microscopically radical resection; PD: progressive disease.

Supplementary Figure 3. Recurrence-free survival (A) and overall survival (B) by pathological T stage in the R0/R1 resection population (n=240)

Abbreviations: RFS: recurrence-free survival; OS: overall survival.

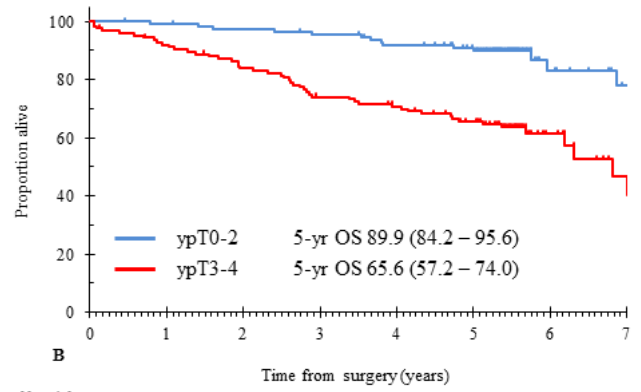






N at risk:

ypT0-2	114	110	104	99	95	85	19	11
ypT3-4	126	98	84	76	70	63	12	4



N at risk:

ypT0-2	114	112	109	106	100	90	22	13
ypT3-4	126	114	103	90	84	71	18	7