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Supplementary Information

Neoadjuvant Treatment Modalities for Rectal Cancer: Independent Correlates of Tumor Response and Sphincter Preservation in a Real-World Cohort

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Supplementary Table S1. Baseline M1 case series (n = 44)

Group	n	Radiotherapy received	Overall downstaging, %	Sphincter preservation, %	Documented recurrence, %
CRT	5	5 (100)	40.0	60.0	60.0
NACT	25	0 (0)	16.0	100	44.0
TNT	14	14 (100)	28.6	85.7	57.1

Descriptive data only; no formal comparisons were performed owing to small numbers. CRT, chemoradiotherapy; NACT, neoadjuvant chemotherapy; TNT, total neoadjuvant therapy.

Supplementary Table S2. Missing-data frequencies in the M0 cohort (n = 298)

Variable	Missing, %
Tumor differentiation	25.2
Neoadjuvant cycles	25.5
MLH1 IHC	34.2
MSH2 IHC	33.6
MSH6 IHC	35.6
PMS2 IHC	35.9
MMR status	37.6
Ki67	48.3
Baseline CRM status	50.0
Baseline EMVI status	65.1
BRAF V600E	70.1
HER2	77.9
KRAS	92.3
NRAS	95.3

All variables entered into the primary regression models (age, sex, BMI, clinical T and N categories, distance from the anal verge, tumor differentiation [unknown as a category]) had no missing values. CRM, circumferential resection margin; EMVI, extramural vascular invasion; MMR, mismatch repair; IHC, immunohistochemistry.

Supplementary Table S3. Two-pathway mechanistic decomposition of sphincter preservation (associative analysis)

Pathway	Variable	OR (95% CI)	P value
Anatomic pathway	Distance from anal verge, per cm	1.56 (1.33–1.84)	**<0.001**
Anatomic pathway	cT4 vs non-cT4	0.27 (0.13–0.53)	**<0.001**
Anatomic pathway	Age, per year	0.97 (0.95–1.00)	0.063
Biologic pathway	T-category downstaging	1.52 (0.81–2.87)	0.194
Biologic pathway	TRG 0–1	5.78 (1.10–30.34)	**0.038**

Firth-penalized logistic regression; outcome was sphincter preservation. These models are associative and do not constitute formal causal mediation. Bold P values indicate statistical significance. OR, odds ratio; CI, confidence interval; TRG, tumor regression grade.

Supplementary Table S4. Predictors of TRG 0–1 (n = 222 with complete cycle data)

Variable	OR (95% CI)	P value
cT3 vs cT1–2	0.50 (0.11–2.16)	0.351
cT4 vs cT1–2	0.26 (0.05–1.20)	0.083
cN1 vs cN0	1.08 (0.39–3.00)	0.889
cN2 vs cN0	1.77 (0.63–4.93)	0.277
Distance from anal verge, per cm	1.15 (1.02–1.30)	**0.024**
Neoadjuvant cycles, per cycle	1.16 (0.92–1.48)	0.212

Firth-penalized logistic regression. Bold P values indicate statistical significance. Abbreviations as in previous tables.

Supplementary Table S5. Low-tumor subgroup (≤5 cm vs >5 cm from the anal verge, M0 cohort)

Outcome	≤5 cm (n = 167)	>5 cm (n = 131)
Sphincter preservation, %	76.6	93.1
APR, %	23.4	6.1
ypStage 0–I, %	27.5	26.7

Descriptive subgroup analysis. APR, abdominoperineal resection.

Supplementary Table S6. Complete age-cutpoint scan for the treatment-mode-by-age-group interaction (TRG 0–1)

Age cutpoint, years	Younger-stratum n	Interaction P value (joint Wald)
36	15	0.947
37	17	0.921
38	23	0.971
39	25	0.828
40	31	0.698
41	38	0.511
42	43	0.471
43	45	0.425
44	51	0.558
45	56	0.596 (probe)
46	63	0.611
47	72	0.788
48	85	0.277
49	95	0.061
50	112	0.012 (prespecified)
51	124	**0.021**
52	134	**0.025**
53	142	0.085
54	150	0.088
55	156	0.201
56	170	0.123
57	175	0.186
58	189	0.137
59	197	0.105
60	207	0.092
61	212	0.144
62	218	0.121
63	225	0.314
64	230	0.238
65	235	0.184

At each cutpoint, age was dichotomized at the indicated value and a Firth logistic model with a treatment-mode-by-age-group interaction was fitted; the joint Wald P value is shown. Cutpoints yielding a stratum of fewer than 15 patients were not evaluated. Bold P values indicate statistical significance.

Supplementary Table S7. Supporting analyses for the early-onset interaction module

Analysis	Joint Wald χ^2 (df)	P value
Continuous age × treatment mode (TRG 0–1)	5.353 (2)	0.069
ypStage 0–I × mode × onset (adjusted; null report)	0.255 (2)	0.880
Mode × onset excluding four dMMR tumors (n = 294)	8.167 (2)	**0.017**

Bold P values indicate statistical significance. dMMR, deficient mismatch repair.

Supplementary Table S8. Surgical procedures among patients achieving TRG 0–1

Group	Procedure	n	%
CRT	Low anterior resection	12	92.3
CRT	Abdominoperineal resection	1	7.7
NACT	Low anterior resection	14	100
TNT	Low anterior resection	16	100

Response-adapted surgery analysis restricted to patients with TRG 0–1.

Supplementary Table S9. Ki67 and treatment response (exploratory)

A. Ki67 by treatment mode (patients with available Ki67, n = 154)

Group	n	Ki67, median	ypStage 0–I, %	TRG 0–1, %
CRT	35	70 (55–80)	28.6	14.3
NACT	67	70 (40–80)	38.8	4.5
TNT	52	60 (50–80)	17.3	7.7

B. Adjusted Firth models (Ki67 per percent)

Endpoint	OR (95% CI) per 1% Ki67	P value
ypStage 0–I	1.00 (0.98–1.01)	0.664
TRG 0–1	0.99 (0.97–1.02)	0.584

Exploratory analyses; Ki67 was not associated with either response endpoint. Abbreviations as in previous tables.