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Preoperative Chemoradiotherapy Versus Upfront Surgery for Early-Onset Clinical Stage II–III Rectal Cancer: A Multicenter Asian Registry Study

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Abstract

Background

To compare postoperative survival after preoperative chemoradiotherapy versus upfront surgery in patients with early-onset clinical stage II–III rectal cancer who underwent surgical resection in East and Southeast Asia.

Methods

This retrospective study included patients aged 18–49 years diagnosed during 2013–2023 who underwent resection at 11 East and Southeast Asian institutions. Propensity-score weighting targeted patients receiving preoperative chemoradiotherapy. Disease-free and overall survival from surgery were evaluated using weighted Kaplan–Meier estimates and facility-stratified Cox models with robust variance estimation.

Results

The cohort comprised 415 patients: 270 underwent upfront surgery and 145 received preoperative chemoradiotherapy. Median follow-up was 4.17 years. Disease-free survival was analyzed in 410 patients with 125 events, and overall survival in 411 patients with 37 deaths. Preoperative chemoradiotherapy was not significantly associated with disease-free survival (hazard ratio 1.55, 95% confidence interval 0.95–2.52; P = 0.081) or overall survival (hazard ratio 1.36, 95% confidence interval 0.61–3.01; P = 0.454). Weighted 5-year disease-free survival was 66.4% after upfront surgery and 58.6% after preoperative chemoradiotherapy; corresponding overall survival was 89.8% and 84.9%. Locoregional recurrence was recorded in nine and eight patients, respectively.

Conclusion

Preoperative chemoradiotherapy was not significantly associated with improved postoperative survival among these resected patients; the findings do not establish equivalence. Treatment selection should incorporate pretreatment local tumor risk, and future studies should evaluate treatment completion and functional outcomes.

Introduction

Early-onset colorectal cancer, defined as colorectal cancer diagnosed before 50 years of age, is increasing in multiple countries and regions [1]. Global Burden of Disease (GBD) estimates show that the GBD-defined East Asia region had the highest overall burden of early-onset colorectal cancer in 2021 [2]. Population-based registries in East Asia have also documented increasing young-onset rectal cancer [3].

Young patients face both the risk of cancer recurrence and the lasting consequences of treatment, making the choice of treatment particularly important [4].

Early-onset colorectal cancer has heterogeneous genetic and pathological features. Pathogenic or likely pathogenic germline susceptibility variants were detected in 16% of an unselected early-onset cohort [5], and sporadic, mismatch-repair-proficient tumors can show adverse histological features, including signet-ring cell differentiation and venous or perineural invasion [6]. Studies have also reported age-associated somatic mutation patterns [7] and frequent TP53 mutations in early-onset rectal cancer [8]. However, molecular features vary by anatomical site [9], and a larger study found no significant age-group differences in the examined gene or pathway alterations of microsatellite-stable tumors after adjustment for location [10]. Whether these biological differences translate into differential chemoradiotherapy benefit remains an open question that requires molecular correlative studies rather than clinical outcome data alone.

Preoperative chemoradiotherapy (CRT) is an established option for locally advanced rectal cancer in Western countries, selected to improve local control and support organ-preservation [11]. However, CAO/ARO/AIO-94 showed improved local control with preoperative versus postoperative CRT without a significant overall survival (OS) benefit [12]. Treatment outcome data specifically addressing younger patients remain limited [13]. Notably, in a US National Cancer Database study of stage II–III rectal cancer, guideline-directed treatment including neoadjuvant CRT was associated with better OS among patients aged 50–75 years, but no significant association was observed among those aged 20–49 years [14]. Whether this apparent age-related difference reflects a true difference in treatment benefit or residual confounding cannot be determined from observational data alone, underscoring the need for outcome data specifically focused on young patients with rectal cancer.

Multinational data on treatment patterns and postoperative outcomes in young Asian patients with rectal cancer remain limited. The ESEA CRC-01 registry provides standardized patient-level clinical and treatment information in Asia [15, 16]. We compared postoperative disease-free survival (DFS) and OS after preoperative CRT versus upfront surgery in resected patients aged 18–49 years with clinical stage II–III rectal cancer in East and Southeast Asia, alongside their treatment and pathological characteristics.

Patients and Methods

Study design and population

This retrospective cohort study used the ESEA CRC-01 registry, established by the East and Southeast Asia Colorectal Cancer Research Collaborative. The registry collected standardized clinical, pathological, molecular, and outcome data for patients diagnosed before 50 years of age who underwent primary colorectal tumor resection during 2013–2024 at 11 centers across eight countries and regions. Data were retrospectively abstracted from institutional medical records.

For the present study, adults aged 18–49 years diagnosed during 2013–2023 with rectal adenocarcinoma and clinical stage II–III disease were eligible. Rectal location was based on each institution's recorded tumor classification. Patients undergoing resection without preoperative treatment comprised the upfront surgery group; those undergoing resection after preoperative CRT comprised the preoperative CRT group. Patients receiving preoperative chemotherapy alone, radiotherapy alone, or an unknown treatment were excluded, as were those with familial adenomatous polyposis, multiple primary colorectal cancers, or deficient mismatch repair/high microsatellite instability (dMMR/MSI-H).

Clinical variables and outcomes

Clinical stage was determined from pretreatment T, N, and M assessments at each institution. Clinical T category was grouped as cT1–2, cT3, or cT4, and clinical N category as cN0, cN1, or cN2. Preoperative treatment details, surgical procedures, residual tumor classification, postoperative pathological stage, and postoperative treatment were obtained from the registry.

The primary outcomes were DFS and OS from the date of primary tumor resection. DFS was defined as time to first recurrence or death from any cause, and OS as time to death from any cause. Each survival outcome was analyzed in its corresponding available-data cohort. Median follow-up was estimated using the reverse Kaplan–Meier method in the OS analysis cohort. Recurrence patterns were summarized among patients in the DFS cohort with known recurrence status. Locoregional recurrence included anastomotic recurrence.

Statistical analysis

Continuous variables were summarized as medians with interquartile ranges and categorical variables as numbers and percentages. Propensity scores for preoperative CRT were estimated using logistic regression with age group (18–34, 35–44, or 45–49 years), sex, body mass index, Eastern Cooperative Oncology Group performance status (0, 1–3, or unknown), reason for presentation (medical check-up or symptoms/other), clinical T and N categories, and diagnosis year. Patients lacking required covariates were excluded from weighting.

Average treatment effect among the treated (ATT) weighting assigned a weight of 1 to patients receiving preoperative CRT and PS/(1 − PS) to patients undergoing upfront surgery, where PS denotes the propensity score. This estimand targets the preoperative CRT recipients. Balance was assessed using absolute standardized mean differences, with values < 0.10 considered adequate.

Survival was estimated using ATT-weighted Kaplan–Meier methods. Facility-stratified, ATT-weighted Cox models with robust variance estimation provided hazard ratios (HRs) and 95% confidence intervals (CIs) for preoperative CRT versus upfront surgery. Facility stratification allowed separate baseline hazards for each institution while estimating a common treatment HR from within-institution comparisons. Proportional hazards were assessed using a treatment-by-log-time interaction. Operative, pathological,

postoperative treatment, and recurrence distributions were compared using unadjusted chi-square or Fisher's exact tests as exploratory analyses. Tests were two-sided, with $P < 0.05$ considered statistically significant. Analyses were performed using Stata/SE 14.0 (StataCorp LP, College Station, TX, USA).

Results

Patient selection and baseline characteristics

The final cohort included 415 patients: 270 underwent upfront surgery and 145 received preoperative CRT (Fig. 1). Median age was 45 years. The preoperative CRT group more frequently had clinical stage III disease (84.8% versus 64.4%), cN2 disease (36.6% versus 27.0%), and cT4 disease (28.3% versus 23.0%). After ATT weighting, absolute standardized mean differences were < 0.10 for all patient-level covariates included in the propensity-score model (Table 1).

Table 1
Baseline characteristics and covariate balance.

Characteristic	Overall (N = 415)	Upfront surgery (n = 270)	Preoperative CRT (n = 145)	Absolute SMD before weighting	Absolute SMD after ATT weighting
Age, years, median (IQR)	45.0 (41.0–47.0)	45.0 (41.0–47.0)	44.0 (40.0–48.0)	0.098	0.009
Age group, n (%)					
18–34 years	39 (9.4%)	22 (8.1%)	17 (11.7%)	0.120	0.011
35–44 years	166 (40.0%)	108 (40.0%)	58 (40.0%)	0.000	0.002
45–49 years	210 (50.6%)	140 (51.9%)	70 (48.3%)	0.072	0.005
Sex, n (%)					
Male	243 (58.6%)	151 (55.9%)	92 (63.4%)	0.154	0.025
Female	172 (41.4%)	119 (44.1%)	53 (36.6%)	0.154	0.025
Body mass index, kg/m², median (IQR)	23.2 (20.6–25.8)	22.9 (20.5–25.4)	23.6 (20.7–26.1)	0.249	0.044
ECOG performance status, n (%)					
0	177 (42.7%)	112 (41.5%)	65 (44.8%)	0.068	0.062
1–3	114 (27.5%)	47 (17.4%)	67 (46.2%)	0.650	0.075
Unknown	124 (29.9%)	111 (41.1%)	13 (9.0%)	0.799	0.005
Reason for hospital visit, n (%)					

Values are unweighted n (%) or median (IQR). Absolute SMDs are shown before and after ATT weighting; values < 0.10 indicate adequate balance. The propensity-score model included age group, sex, body mass index, ECOG performance status, reason for presentation, clinical T and N categories, and diagnosis year. Institution was accounted for by stratification in the Cox models. ATT, average treatment effect among the treated; CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; SMD, standardized mean difference.

Characteristic	Overall (N = 415)	Upfront surgery (n = 270)	Preoperative CRT (n = 145)	Absolute SMD before weighting	Absolute SMD after ATT weighting
Medical check-up	69 (16.6%)	60 (22.2%)	9 (6.2%)	0.471	0.013
Symptomatic/other	346 (83.4%)	210 (77.8%)	136 (93.8%)	0.471	0.013
Clinical T category, n (%)					
cT1–2	18 (4.3%)	17 (6.3%)	1 (0.7%)	0.309	0.011
cT3	294 (70.8%)	191 (70.7%)	103 (71.0%)	0.006	0.054
cT4	103 (24.8%)	62 (23.0%)	41 (28.3%)	0.122	0.052
Clinical N category, n (%)					
cN0	118 (28.4%)	96 (35.6%)	22 (15.2%)	0.482	0.047
cN1	171 (41.2%)	101 (37.4%)	70 (48.3%)	0.221	0.066
cN2	126 (30.4%)	73 (27.0%)	53 (36.6%)	0.205	0.027
Clinical stage, n (%)					
Stage II	118 (28.4%)	96 (35.6%)	22 (15.2%)	0.482	0.047
Stage III	297 (71.6%)	174 (64.4%)	123 (84.8%)	0.482	0.047
Institution, n (%)					
Aichi	59 (14.2%)	59 (21.9%)	0 (0.0%)	0.748	0.688
Ajou	71 (17.1%)	35 (13.0%)	36 (24.8%)	0.307	0.229

Values are unweighted n (%) or median (IQR). Absolute SMDs are shown before and after ATT weighting; values < 0.10 indicate adequate balance. The propensity-score model included age group, sex, body mass index, ECOG performance status, reason for presentation, clinical T and N categories, and diagnosis year. Institution was accounted for by stratification in the Cox models. ATT, average treatment effect among the treated; CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; SMD, standardized mean difference.

Characteristic	Overall (N = 415)	Upfront surgery (n = 270)	Preoperative CRT (n = 145)	Absolute SMD before weighting	Absolute SMD after ATT weighting
Beijing	40 (9.6%)	30 (11.1%)	10 (6.9%)	0.148	0.138
China Medical	25 (6.0%)	18 (6.7%)	7 (4.8%)	0.079	0.129
Chulalongkorn	60 (14.5%)	21 (7.8%)	39 (26.9%)	0.522	0.398
Hong Kong	13 (3.1%)	3 (1.1%)	10 (6.9%)	0.298	0.326
NCC Japan	84 (20.2%)	81 (30.0%)	3 (2.1%)	0.823	0.110
Philippine GH	8 (1.9%)	1 (0.4%)	7 (4.8%)	0.283	0.229
Sengkang	5 (1.2%)	2 (0.7%)	3 (2.1%)	0.113	0.128
Singapore GH	37 (8.9%)	15 (5.6%)	22 (15.2%)	0.320	0.092
Songkla	13 (3.1%)	5 (1.9%)	8 (5.5%)	0.195	0.157

Values are unweighted n (%) or median (IQR). Absolute SMDs are shown before and after ATT weighting; values < 0.10 indicate adequate balance. The propensity-score model included age group, sex, body mass index, ECOG performance status, reason for presentation, clinical T and N categories, and diagnosis year. Institution was accounted for by stratification in the Cox models. ATT, average treatment effect among the treated; CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; SMD, standardized mean difference.

Treatment, operative, and pathological characteristics

Capecitabine was the most frequently recorded preoperative chemotherapy regimen (33.1%). The median total radiotherapy dose was 50.0 Gy, and the median number of fractions was 25. A schedule of 45–50.4 Gy in 25–28 fractions was recorded in 82 patients (56.6%), and 25 Gy in five fractions in 16 (11.0%) (Table 2).

Table 2
Details of preoperative chemoradiotherapy.

Characteristic	Preoperative CRT (n = 145)
Preoperative chemotherapy regimen, n (%)	
Capecitabine	48 (33.1%)
XELOX (CAPOX)	32 (22.1%)
Other regimen	32 (22.1%)
UFT/leucovorin	13 (9.0%)
FOLFOX	11 (7.6%)
FOLFOXIRI	4 (2.8%)
FOLFIRI	1 (0.7%)
Unknown	4 (2.8%)
Radiotherapy	
Total dose, Gy, median (IQR)	50.0 (45.0–50.4)
Number of fractions, median (IQR)	25 (25–28)
Dose–fractionation schedule, n (%)	
45–50.4 Gy in 25–28 fractions	82 (56.6%)
25 Gy in 5 fractions	16 (11.0%)
Other schedule	14 (9.7%)
Unknown or incomplete	33 (22.8%)

Values are n (%) or median (IQR). Percentages use all 145 patients; dose and fraction summaries use available data. CAPOX/XELOX, capecitabine plus oxaliplatin; CRT, chemoradiotherapy; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan; IQR, interquartile range; UFT, tegafur–uracil.

The surgical procedure distribution differed between groups (P < 0.001), with abdominoperineal resection (15.9% versus 7.4%) and pelvic exenteration (9.7% versus 3.3%) more frequent after preoperative CRT. R0 resection was achieved in 117/122 assessable patients (95.9%) after CRT and 190/198 (96.0%) after upfront surgery (P = 1.000). Residual tumor status was unavailable in 23/145 patients (15.9%) after CRT and 72/270 (26.7%) after upfront surgery. Postoperative pathological stage distributions also differed (P < 0.001), with stage III less frequent after CRT (31.9% versus 57.6%). Postoperative treatment distributions differed (P = 0.047), with chemotherapy alone administered to 69.7% after CRT and 59.3% after upfront surgery (Table 3).

Table 3
Operative, pathological, and postoperative characteristics.

Characteristic	Upfront surgery (n = 270)	Preoperative CRT (n = 145)	P value
Surgical approach	**Available n = 270**	**Available n = 143**	**0.369**
Open	92/270 (34.1%)	40/143 (28.0%)	
Laparoscopic	131/270 (48.5%)	74/143 (51.7%)	
Robotic	43/270 (15.9%)	24/143 (16.8%)	
Other approach	4/270 (1.5%)	5/143 (3.5%)	
Unknown	0/270 (0.0%)	2/145 (1.4%)	
Surgical procedure	**Available n = 269**	**Available n = 145**	**< 0.001**
High anterior resection	37/269 (13.8%)	0/145 (0.0%)	
Low anterior resection	167/269 (62.1%)	78/145 (53.8%)	
Very low anterior resection	12/269 (4.5%)	22/145 (15.2%)	
Intersphincteric resection	8/269 (3.0%)	1/145 (0.7%)	
Abdominoperineal resection	20/269 (7.4%)	23/145 (15.9%)	
Pelvic exenteration	9/269 (3.3%)	14/145 (9.7%)	
Other procedure	16/269 (5.9%)	7/145 (4.8%)	
Unknown	1/270 (0.4%)	0/145 (0.0%)	
Residual tumor classification	**Available n = 198**	**Available n = 122**	**1.000**
R0	190/198 (96.0%)	117/122 (95.9%)	
R1/R2	8/198 (4.0%)	5/122 (4.1%)	
RX/unknown/missing	72/270 (26.7%)	23/145 (15.9%)	
Postoperative pathological stage	**Available n = 262**	**Available n = 135**	**< 0.001**
Stage 0	1/262 (0.4%)	11/135 (8.1%)	
Stage I	26/262 (9.9%)	22/135 (16.3%)	
Stage II	77/262 (29.4%)	55/135 (40.7%)	

Values are n/N (%). Denominators are patients with available data; unknown proportions use the full treatment groups. P values compare overall distributions using unadjusted chi-square or Fisher's exact tests, excluding unknown values. Pathological stage denotes pStage after upfront surgery and ypStage after preoperative CRT. CRT, chemoradiotherapy; R0, no residual tumor; R1, microscopic residual tumor; R2, macroscopic residual tumor; RX, residual tumor status cannot be assessed.

Characteristic	Upfront surgery (n = 270)	Preoperative CRT (n = 145)	P value
Surgical approach	**Available n = 270**	**Available n = 143**	**0.369**
Stage III	151/262 (57.6%)	43/135 (31.9%)	
Stage IV	7/262 (2.7%)	4/135 (3.0%)	
Unknown	8/270 (3.0%)	10/145 (6.9%)	
Postoperative treatment	**N = 270**	**N = 145**	**0.047**
None	93/270 (34.4%)	33/145 (22.8%)	
Chemotherapy alone	160/270 (59.3%)	101/145 (69.7%)	
Chemoradiotherapy	16/270 (5.9%)	9/145 (6.2%)	
Radiotherapy alone	1/270 (0.4%)	2/145 (1.4%)	

Values are n/N (%). Denominators are patients with available data; unknown proportions use the full treatment groups. P values compare overall distributions using unadjusted chi-square or Fisher's exact tests, excluding unknown values. Pathological stage denotes pStage after upfront surgery and ypStage after preoperative CRT. CRT, chemoradiotherapy; R0, no residual tumor; R1, microscopic residual tumor; R2, macroscopic residual tumor; RX, residual tumor status cannot be assessed.

Survival outcomes and recurrence patterns

Median follow-up was 4.17 years (95% CI 3.59–4.56). DFS was analyzed in 410 patients (266 upfront surgery and 144 preoperative CRT), with 74 and 51 events, respectively. OS was analyzed in 411 patients (268 and 143, respectively), with 21 and 16 deaths.

ATT-weighted 5-year DFS was 66.4% after upfront surgery and 58.6% after preoperative CRT; the facility-stratified HR was 1.55 (95% CI 0.95–2.52; P = 0.081). Corresponding 5-year OS estimates were 89.8% and 84.9%, with an HR of 1.36 (95% CI 0.61–3.01; P = 0.454) (Fig. 2 and Table 4). Treatment-by-log-time interactions were not significant for DFS or OS (P = 0.127 and P = 0.157, respectively).

Table 4
Primary survival outcomes and recurrence patterns.

Outcome	Upfront surgery	Preoperative CRT	Effect estimate (CRT vs upfront)	P value
Disease-free survival				
Analysis sample, n/events	266 / 74	144 / 51		
5-year disease-free survival	66.4%	58.6%	HR 1.55 (95% CI 0.95–2.52)	0.081
Overall survival				
Analysis sample, n/deaths	268 / 21	143 / 16		
5-year overall survival	89.8%	84.9%	HR 1.36 (95% CI 0.61–3.01)	0.454
Recurrence patterns in the DFS cohort, n/N (%)				
Any recurrence	73/265 (27.5%)	47/144 (32.6%)		0.307
Recurrence status unknown	1/266 (0.4%)	0/144 (0.0%)		
Any locoregional recurrence	9/265 (3.4%)	8/144 (5.6%)		0.309
Any distant or other recurrence	68/265 (25.7%)	40/144 (27.8%)		0.641
Locoregional only	5/265 (1.9%)	7/144 (4.9%)		
Distant or other only	64/265 (24.2%)	39/144 (27.1%)		
Both locoregional and distant/other recurrence	4/265 (1.5%)	1/144 (0.7%)		

Five-year survival estimates are from ATT-weighted Kaplan–Meier curves. HRs compare preoperative CRT with upfront surgery using facility-stratified, ATT-weighted Cox models with robust variance and all available follow-up. Sample and event counts are unweighted. Recurrence proportions use patients with known recurrence status in the DFS cohort (265 upfront surgery; 144 preoperative CRT); P values are from two-sided Fisher's exact tests. ATT, average treatment effect among the treated; CI, confidence interval; CRT, chemoradiotherapy; DFS, disease-free survival; HR, hazard ratio.

Among 409 patients with known recurrence status, recurrence was recorded in 73/265 patients (27.5%) after upfront surgery and 47/144 (32.6%) after preoperative CRT (P = 0.307). Locoregional recurrence was recorded in nine (3.4%) and eight (5.6%) patients, respectively (P = 0.309). Distant or other recurrence occurred in 68 (25.7%) and 40 (27.8%) patients, respectively (P = 0.641) (Table 4).

Discussion

In this multicenter cohort of 415 young Asian patients with clinical stage II–III rectal cancer, preoperative CRT was not significantly associated with improved postoperative DFS or OS after adjustment for preoperative patient characteristics, including clinical stage, using ATT weighting, nor was it associated with the incidence of locoregional or other recurrences. These findings do not support a clear oncological advantage of preoperative CRT among this population of young patients with rectal cancer in East and Southeast Asia.

To our knowledge, this is the first multinational study in Asia to compare postoperative survival after these treatment strategies specifically in early-onset clinical stage II–III rectal cancer. In contrast to previous population-based registries which rarely capture treatment-level detail, the ESEA CRC-01 registry provided standardized, patient-level clinical, pathological, and treatment data across 11 centers in eight countries and regions in East and Southeast Asia, supporting comparisons that are otherwise difficult to perform in this population. In addition, facility-stratified, ATT-weighted analysis further addressed both patient-level confounding and between-institution variation in treatment practice. R0 resection was achieved in approximately 96% of evaluable patients in both groups, suggesting that surgical quality was comparable between groups and that the observed outcome differences are unlikely to be explained by differential surgical completeness.

Nonetheless, these findings require cautious interpretation. Although weighting balanced clinical T and N categories, pretreatment MRI findings such as mesorectal fascia involvement and extramural vascular invasion were unavailable. If these adverse features were more common among CRT recipients, residual confounding could shift the estimated HR against CRT. The lower proportion of postoperative pathological stage III disease after CRT may reflect treatment response, although this cross-sectional comparison, based on a higher baseline clinical stage III proportion in the CRT group, cannot directly quantify downstaging within individual patients. Procedure differences may reflect tumor location and local extent rather than an effect of CRT on surgical requirements. In addition, the greater use of postoperative chemotherapy alone after CRT and variation in preoperative regimens also make it difficult to attribute the survival findings to CRT alone. Moreover, locoregional recurrence proportions did not differ significantly between groups, but this unadjusted comparison was based on only 17 events, and differences in surgical procedure between groups further limit assessment of the true impact of CRT on local control.

There are also several other limitations. This surgical registry excludes patients who did not reach resection. Excluding patients with progression or serious toxicity before surgery could favor CRT, whereas excluding good responders managed nonoperatively could bias results against it. Institutional treatment preferences and incomplete within-facility overlap also limit causal inference. Moreover, postoperative surveillance was not confirmed to be uniform, potentially affecting recurrence detection and DFS estimates. Furthermore, only 37 deaths occurred over a median follow-up of 4.17 years, limiting assessment of long-term OS differences. These results do not establish equivalence and apply to resected patients with baseline characteristics similar to those of the CRT group.

In conclusion, preoperative CRT was not significantly associated with improved postoperative survival in this cohort of young Asian patients who underwent resection. Future studies should follow patients from treatment initiation and record pretreatment local-risk features, treatment completion, recurrence, and functional outcomes.

Declarations

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Competing interests: The authors declare no competing interests.

Ethics approval: The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of the National Cancer Center, Japan (approval no. 2024-280). Approval or an applicable waiver was obtained at the other participating institutions in accordance with local requirements.

Data availability

Deidentified participant data may be made available to qualified investigators upon reasonable request and approval by the ESEA CRC Research Collaborative Group.

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Figures

Figure 1. Study flow diagram

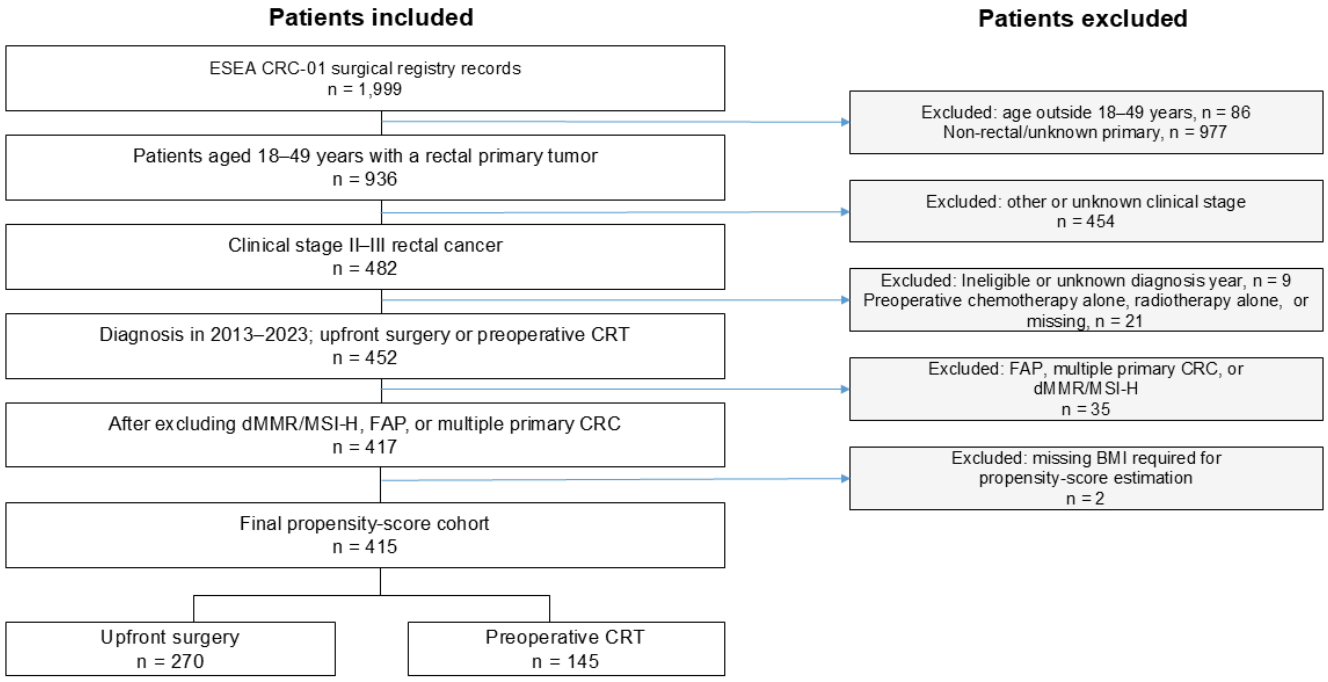


Figure 1

Study flow diagram

Patient selection from the ESEA CRC-01 surgical registry. The final propensity-score cohort comprised 415 patients: 270 who underwent upfront surgery and 145 who received preoperative chemoradiotherapy followed by surgery. BMI, body mass index; CRC, colorectal cancer; CRT, chemoradiotherapy; dMMR, deficient mismatch repair; FAP, familial adenomatous polyposis; MSI-H, high microsatellite instability

Figure 2. ATT-weighted survival curves

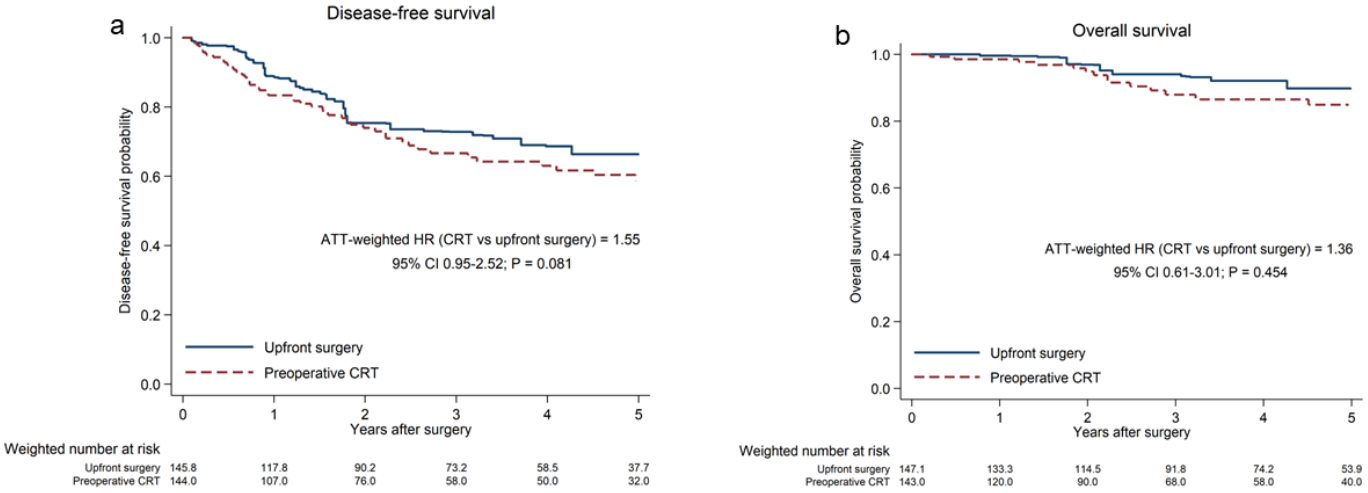


Figure 2

ATT-weighted postoperative survival according to preoperative treatment

(a) Disease-free survival and (b) overall survival. Solid lines indicate upfront surgery; dashed lines indicate preoperative chemoradiotherapy. Curves were estimated using ATT-weighted Kaplan–Meier methods. Hazard ratios compare preoperative chemoradiotherapy with upfront surgery and were estimated using facility-stratified, ATT-weighted Cox models with robust variance estimation. Numbers at risk are sums of ATT weights. ATT, average treatment effect among the treated; CI, confidence interval; CRT, chemoradiotherapy; HR, hazard ratio