Adjuvant Chemotherapy After Neoadjuvant Chemoradiation and Proctectomy Improves Survival Irrespective of Pathologic Response in Rectal Adenocarcinoma: A Population-Based Cohort Study

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Research Article

Keywords: neoadjuvant chemoradiation, outcomes, rectal cancer, adjuvant chemotherapy

Posted Date: May 13th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1624119/v1

Abstract

Background

This study sought to determine whether adjuvant chemotherapy (AC) compared to no AC (noAC) after neoadjuvant chemoradiation (CRT) and resection for rectal adenocarcinoma prolongs survival. Current guidelines from expert groups are conflicting, and data to support administering AC to patients who received neoadjuvant CRT are lacking.

Methods

19867 patients met inclusion/exclusion criteria. Mean age was 58.6±12.0 years, and 12396 (62.4%) were males. Complete response (CR) was documented in 3801 (19.1%) patients and 8167 (41.1%) received AC. The cohort was stratified into pathological complete (pCR, N=3,801) and incomplete (pIR, N=16,066) subgroups, and pIR further subcategorized into ypN0 (N=10,191) and ypN+ (N=5,875) subgroups. After propensity score matching, AC was associated with improved OS in the pCR subgroups (mean 139.1±1.9 vs. 134.0±2.2 months; p<0.001), in pIR ypN0 subgroup (141.6±1.5 vs. 129.9±1.2 months, p<0.001) and in pIR ypN+ subgroup (155.9±5.4 vs. 126.5±7.6 months; p<0.001).

Results

AC was associated with improved OS in patients who received neoadjuvant CRT followed by proctectomy for clinical stages II and III rectal adenocarcinoma. This effect persisted irrespective of pathological response status.

Conclusions

AC following neoadjuvant CRT and surgery is associated with improved OS in patients with rectal adenocarcinoma. These findings warrant adoption of AC after neoadjuvant CRT and surgery for clinical stage II and III rectal adenocarcinoma.

Introduction

A treatment strategy which incorporates neoadjuvant radiotherapy (RT) or chemoradiotherapy (CRT) and total mesorectal excision (TME) remains standard of care in the management of rectal adenocarcinoma as it optimizes locoregional control and offers a chance at cure. [1,2] While the benefit of adjuvant chemotherapy (AC) has been documented in resected high-risk stage II and stage III colon cancer, [3] the effect of AC following CRT and TME remains less clear.

The National Comprehensive Cancer Network (NCCN) recommends that patients with locally advanced rectal cancer who undergo neoadjuvant CRT or RT should receive AC [4], whereas the European Society for Medical Oncology (ESMO) recommends AC for patients with yp stage III and high-risk yp stage II. [5] The effect of AC after CRT and TME has been examined in several randomized controlled trials, and an overall

survival (OS) benefit over observation has not been detected. For example, in the European Organization for Research and Treatment of Cancer (EORTC) trial, adjuvant fluorouracil plus leucovorin in patients treated with neoadjuvant RT with or without chemotherapy did not significantly improve OS compared to observation alone. [6] Other trials similarly found no advantage to AC in this setting. [7] Despite that, proponents of AC cite flaws in existing trials largely related to poor compliance with AC, as only 43% of subjects in EORTC received AC, for example. Moreover, failure to adhere to study protocols due to treatment delays, dose reductions, and inability to complete intended therapy were common, all of which likely further diminished potential beneficial effects of AC [8].

Therefore, this study aims to evaluate the effect of AC on OS in patients with stage II and II rectal adenocarcinoma treated with neoadjuvant CRT using the National Cancer Database (NCDB), hypothesizing that AC improves OS. A secondary aim is to examine OS in patient subgroups according to tumor and nodal pathological response. To account for potential treatment selection bias, propensity score matching (PSM) was utilized and OS was assessed in individual relevant subgroups of patients.

Methods

NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. [9] Data from Over 1500 CoC-accredited hospitals includes > 70% of all newly diagnosed cancers in the United States. Clinicopathologic data as well as information on demographics, facility type and outcomes are recorded prospectively.

The NCDB participant user file 2004–2018 for rectal cancer was utilized to identify patients over 18 years of age diagnosed with clinical stages II/III rectal adenocarcinoma. International Classification of Diseases for Oncology Third Edition (ICD-O-3) was used to select for adenocarcinoma (ICD-O-3 morphology codes: 8240–8248). Clinical staging was determined based on radiologic imaging according to the American Joint Commission on Cancer (AJCC). Therefore, clinical T and N staging used were available prior to treatment initiation.

Only patients who received long-course neoadjuvant CRT were included. Long-course neoadjuvant CRT was defined as receipt of at least 25 fractions to a total of 4,500 cGy to the rectum or pelvis. Accepted radiation modalities as reported in NCDB included External Beam Radiation Therapy (EBRT), Intensity-Modulated Radiation Therapy (IMRT), and 3-Dimensional Conformal Computed Tomography (3D-CRT). Consistent with contemporary recommendations, only patients who underwent resection between 5–12 weeks met inclusion criteria. Patients who did not receive neoadjuvant CRT, received fewer fractions / lower doses of radiation, had unknown sites of radiation, and those who underwent surgical resection outside the abovementioned timeframe were excluded. Similarly, patients with alternate histologies, metastatic disease (stage IV), and those with clinical stages I and 0 were excluded. Patients with other cancer diagnoses and those with missing data on receipt of neoadjuvant CRT were also excluded.

Included proctectomy procedures were Low Anterior Resection (LAR), Abdominoperineal Resection (APR), proctocolectomy, and pelvic exenteration, as coded in NCDB. Patients with missing information on surgical procedure or approach were excluded. Only patients surviving beyond 90 days were included to adjust for immortal time bias. Other patient-level characteristics were analyzed as defined in NCDB: age, race, Charlson/Deyo comorbidity score (CDCC), year of diagnosis, insurance status (Medicaid/Medicare, private insurance, uninsured), zip code-level, education status, and urban versus rural area of residence. In addition, the following hospital-level characteristics were analyzed: facility type (academic, community, other), and facility location (Midwest, Northeast, South, West). Finally, the following clinicopathologic characteristics were analyzed: clinical T status, clinical N status (cN0, cN1, cN2, cN3, cNx), and tumor grade/differentiation (well/moderate, poor/anaplastic, unknown).

The study's primary aim was to evaluate the specific effect of AC on OS and to further evaluate AC's effect in prespecified subgroups based on pathologic response. To minimize potential confounding factors from suboptimal surgery, only patients with ≥ 12 nodes and negative proximal, distal, and circumferential margins were included.

After application of inclusion/exclusion criteria, patients were stratified according to pathologic response into pathologic complete response (pCR) and pathologic incomplete response (pIR) groups. pCR was defined in NCDB as ypT0ypN0. Next, the pIR cohort was further subcategorized according to pathologic nodal status into ypN0 and ypN+. A propensity score was then calculated for each group based on a multivariable regression model which adjusts for all demographic and clinical variables including age, sex, race, Charlson score, grade, radiation-surgery interval, type and approach of the surgical resection, and median time of follow-up. After building logistic models, patients were matched at a ratio of 1:1 in each group per the status of AC using the nearest neighbor method with a 0.1 caliper width. Conditional logistic regression was applied to compare categorical variables, whereas mixed effect modeling was used to compare continuous variables between patients who received AC vs. those who did not. Finally, Kaplan Meier methods was applied to estimate OS among matched subgroups. IBM SPSS v25 (Armonk, NY) with R 3.3.3 plugin software was used for statistical analysis. Significance was set at $p < 0.05$ throughout.

Results

Clinicopathologic Characteristics

The NCDB participant user file for rectal cancer included 314,844 patients. After application of inclusion/exclusion criteria, 19,867 patients with clinical stage II/III rectal adenocarcinoma who completed long-course neoadjuvant CRT and underwent resection remained (Fig. 1). Mean age for the entire cohort was 58.6 ± 12.0 years, and 12,396 (62.4%) were males. There were 17,249 (86.8%) patients with clinical stage T3, and 10,662 (53.7%) were node-positive (clinical stage III). Of 19,867 patients, 11,991 (60.4%) underwent resection within 5–8 weeks from conclusion of neoadjuvant CRT, and the most commonly performed procedure was LAR (N = 13,801, 69.5%). The median number of retrieved nodes

was 16, and pCR was documented in 3,801 cases (19.1%). 8.167 patients (41.1%) received AC and median follow up time was 55.1 months. Table 1 summarizes the demographic, clinical, and pathologic characteristics of the selected population.

Table 1
Summary of the demographic and clinical characteristics of the selected patient population

N		**19,867**
Age (years)	Mean ± SD	58.6 ± 12.0
	Median	59
Sex	Male	12,396 (62.4%)
	Female	7,471 (37.6%)
Race	White	16,267 (81.9%)
	Black	1,439 (7.2%)
	Other	2,161 (10.9%)
Charlson Score	0	15,854 (79.8%)
	1	3,099 (15.6%)
	2	625 (3.1%)
	3+	289 (1.5%)
Grade	Well differentiated	1,412 (7.1%)
	Moderately differentiated	13,657 (68.7%)
	Poorly differentiated	1,857 (9.3%)
	Not reported	2,941 (14.8%)
Clinical T stage	T1	116 (0.6%)
	T2	958 (4.8%)
	T3	17,249 (86.8%)
	T4	1,544 (7.8%)
Clinical N stage	Negative	9,205 (46.3%)
	Positive	10,662 (53.7%)
Clinical stage	Stage II	9,205 (46.3%)
	Stage III	10,662 (53.7%)
Radiation-surgery interval	5–8 weeks	11,991 (60.4%)
	9–12 weeks	7,876 (39.6%)

N		19,867
Surgery	LAR	13,801 (69.5%)
	APR	4,938 (24.9%)
	Proctocolectomy	541 (2.7%)
	Exenteration	587 (3.0%)
Approach	Open	12,964 (65.3%)
	Minimally-invasive	6,903 (34.7%)
Retrieved lymph nodes	Mean ± SD	18.7 ± 7.6
	Median	16
Pathologic T stage	T0	4,525 (22.8%)
	T1	1,221 (6.1%)
	T2	5,045 (25.4%)
	T3	8,528 (42.9%)
	T4	548 (2.8%)
Pathologic N stage	N0	13,992 (70.4%)
	N1	4,088 (20.6%)
	N2	1,787 (9.0%)
Response	Complete response	3,801 (19.1%)
	Partial response	10,122 (50.9%)
	No response	5,944 (29.9%)
Adjuvant systemic therapy	No	11,700 (58.9%)
	Yes	8,167 (41.1%)
Follow up (months)	Mean ± SD	62.4 ± 35.6
	Median	55.1

Propensity Score Matching

As described above, the included cohort was stratified into pCR (N = 3,801) and pIR (N = 16,066) groups, with the pIR group further subcategorized into ypN0 (N = 10,191) and ypN+ (N = 5,875) subgroups. Within the pCR group, 2,505 patients did not receive AC whereas 1,296 did. Baseline characteristics among these two subgroups was conducted and, notably, patients who received AC were significantly younger (57.1 ± 11.2 vs. 60.8 ± 12.5 years; $p < 0.001$), more likely to have a Charlson score of 0 (82.8% vs. 78.9%; p =

0.039), more commonly had clinical stage III tumors (56.4% vs. 46.1%; $p < 0.001$), and were more likely to undergo minimally-invasive surgical resection (39.3% vs. 34.1%; $p = 0.001$). Propensity score was carried out as described among 1,292 patients from each subgroup, which resulted in well-balanced cohorts. Standardized mean differences were calculated for each variable and ranged between 0.01 and 0.05, indicating good balance (Table 2).

Table 2

Comparison of the unmatched and matched datasets of the patient subgroup who achieved pathologic complete response (N = 3,801) by the receipt of adjuvant systemic therapy. **APR**: Abdominoperineal Resection; **AC**: Adjuvant Systemic Therapy; **Diff.**: Differentiated; **LAR**: Low Abdominal Resection; **MIS**: Minimally Invasive Surgery. * Statistically significant.

	Unmatched dataset			**Matched dataset 1:1**		
	No AC	**AC**	**p**	**No AC**	**AC**	**p**
N	2,505	1,296		1,292	1,292	
Age (years)	60.8 ± 12.5	57.1 ± 11.2	< 0.001*	57.3 ± 12.0	57.1 ± 11.1	0.713
Sex	1,567 (62.6%)	779 (60.1%)	0.141	777 (60.1%)	779 (60.3%)	0.936
Male	938 (37.4%)	517 (39.9%)		515 (39.9%)	513 (39.7%)	
Female						
Race	2,077 (82.9%)	1,071 (82.6%)	0.115	1,073 (83.0%)	1,068 (82.7%)	0.952
White	184 (7.3%)	78 (6.0%)		78 (6.0%)	78 (6.0%)	
Black	244 (9.7%)	147 (11.3%)		141 (10.9%)	146 (11.3%)	
Other						
Charlson Score	1,976 (78.9%)	1,073 (82.8%)	0.039*	1,079 (83.5%)	1,069 (82.7%)	0.851
0	413 (16.5%)	176 (13.6%)		165 (12.8%)	176 (13.6%)	
1	84 (3.4%)	35 (2.7%)		33 (2.6%)	35 (2.7%)	
2	32 (1.3%)	12 (0.9%)		15 (1.2%)	12 (0.9%)	
3+						
Grade	162 (6.5%)	91 (7.0%)	0.723	84 (6.5%)	90 (7.0%)	0.936
Well diff.	1,572 (62.8%)	827 (63.8%)		831 (64.3%)	825 (63.9%)	
Moderately diff.	184 (7.3%)	88 (6.8%)		82 (6.3%)	87 (6.7%)	
Poorly diff.	587 (23.4%)	290 (22.4%)		295 (22.8%)	290 (22.4%)	
Not reported						
Clinical stage	1,349 (53.9%)	565 (43.6%)	< 0.001*	559 (43.3%)	564 (43.7%)	0.843
Stage II	1,156 (46.1%)	731 (56.4%)		733 (56.7%)	728 (56.3%)	
Stage III						

	Unmatched dataset			Matched dataset 1:1		
Rad-surg interval	1,449 (57.8%)	758 (58.5%)	0.703	739 (57.2%)	755 (58.4%)	0.524
5–8 weeks	1,056 (42.2%)	538 (41.5%)		553 (42.8%)	537 (41.6%)	
9–12 weeks						
Surgery	1,775 (70.9%)	915 (70.6%)	0.888	920 (71.2%)	914 (70.7%)	0.972
LAR	608 (24.3%)	313 (24.2%)		303 (23.5%)	312 (24.1%)	
APR	68 (2.7%)	41 (3.2%)		40 (3.1%)	39 (3.0%)	
Proctocolectomy	54 (2.2%)	27 (2.1%)		29 (2.2%)	27 (2.1%)	
Exenteration						
Approach	1,652 (65.9%)	787 (60.7%)	0.001*	784 (60.7%)	785 (60.8%)	0.968
Open	853 (34.1%)	509 (39.3%)		508 (39.3%)	507 (39.2%)	
MIS						
Retrieved nodes	18.2 ± 7.1	18.6 ± 7.7	0.113	18.3 ± 7.1	18.5 ± 7.6	0.471
Median follow up	56.2	56.8	0.828	56.3	56.5	0.906

Association of Adjuvant Chemotherapy with Survival in Matched Subgroups

Survival was then estimated for matched subgroups, and patients who received AC had increased mean OS compared to no AC in the pCR subgroups (139.1 ± 1.9 vs. 134.0 ± 2.2 months, median not reached in both groups; $p < 0.001$). The absolute 5-year OS benefit of AC was 4% (92% vs. 88%; $p < 0.001$).

In the pIR ypN0 group, 6,202 patients did not receive AC whereas 3,989 did. Comparison of baseline characteristics similarly revealed that AC patients were younger (56.8 ± 10.9 vs. 60.6 ± 12.1 years; $p < 0.001$), had higher rates of Charlson score 0 (81.5% vs. 76.7%; $p < 0.001$), underwent surgery within 5–8 weeks (61.0% vs. 58.3%; $p = 0.005$), had minimally-invasive procedures (38.5% vs. 34.9%; $p < 0.001$), and sustained T downstaging (77.4% vs. 73.0%; $p < 0.001$). Propensity-score matching was carried out similarly to yield 2,970 well balanced cohorts (Table 3). Again, AC patients had a longer mean OS compared to those who did not receive AC (141.6 ± 1.5 vs. 129.9 ± 1.2 months, medians not reached in both groups; $p < 0.001$). The absolute incremental 5-year OS advantage associated with AC was 6% (89% vs. 83%; $p < 0.001$, Fig. 3).

Table 3
Comparison of the unmatched and matched datasets of the patient subgroup who achieved pathologic incomplete response with ypN0 (N = 10,191) by the receipt of adjuvant systemic therapy. **APR**: Abdominoperineal Resection; **AC**: Adjuvant Systemic Therapy; **Diff.**: Differentiated; **LAR**: Low Abdominal Resection; **MIS**: Minimally Invasive Surgery. * Statistically significant.

	Unmatched dataset			**Matched dataset 1:1**		
	No AC	**AC**	**p**	**No AC**	**AC**	**p**
N	6,202	3,989		3,970	3,970	
Age (years)	60.6 ± 12.1	56.8 ± 10.9	< 0.001*	57.1 ± 11.5	57.0 ± 10.8	0.697
Sex	3,920 (63.2%)	2,520 (63.2%)	0.974	2,508 (63.2%)	2,507 (63.1%)	0.981
Male	2,282 (36.8%)	1,469 (36.8%)		1,462 (36.8%)	1,463 (36.9%)	
Female						
Race	5,072 (81.8%)	3,287 (82.4%)	0.283	3,255 (82.0%)	3,269 (82.3%)	0.804
White	473 (7.6%)	271 (6.8%)		286 (7.2%)	271 (6.8%)	
Black	657 (10.6%)	431 (10.8%)		429 (10.8%)	430 (10.8%)	
Other						
Charlson Score	4,756 (76.7%)	3,250 (81.5%)	< 0.001*	3,217 (81.0%)	3,232 (81.4%)	0.825
0	1,086 (17.5%)	579 (14.5%)		599 (15.1%)	578 (14.6%)	
1	241 (3.9%)	102 (2.6%)		93 (2.3%)	102 (2.6%)	
2	119 (1.9%)	58 (1.5%)		61 (1.5%)	58 (1.5%)	
3+						
Grade	497 (8.0%)	291 (7.3%)	0.491	288 (7.3%)	291 (7.3%)	0.972
Well diff.	4,374 (70.5%)	2,839 (71.2%)		2,847 (71.7%)	2,828 (71.2%)	
Moderately diff.	481 (7.8%)	325 (8.1%)		316 (8.0%)	321 (8.1%)	
Poorly diff.	850 (13.7%)	534 (13.4%)		519 (13.1%)	530 (13.4%)	
Not reported						
Rad-surg interval	3,614 (58.3%)	2,435 (61.0%)	0.005*	2,393 (60.3%)	2,419 (60.9%)	0.550
5–8 weeks	2,588 (41.7%)	1,554 (39.0%)		1,577 (39.7%)	1,551 (39.1%)	
9–12 weeks						

	Unmatched dataset			Matched dataset 1:1		
Surgery	4,311 (69.5%)	2,745 (68.8%)	0.612	2,742 (69.1%)	2,732 (68.8%)	0.990
LAR	1,531 (24.7%)	1,019 (25.5%)		1,008 (25.4%)	1,014 (25.5%)	
APR	159 (2.6%)	108 (2.7%)		103 (2.6%)	107 (2.7%)	
Proctocolectomy	201 (3.2%)	117 (2.9%)		117 (2.9%)	117 (2.9%)	
Exenteration						
Approach	4,035 (65.1%)	2,454 (61.5%)	< 0.001*	2,455 (61.8%)	2,446 (61.6%)	0.835
Open	2,167 (34.9%)	1,535 (38.5%)		1,515 (38.2%)	1,524 (38.4%)	
MIS						
Retrieved nodes	18.4 ± 7.5	18.7 ± 7.3	0.028*	18.6 ± 7.8	18.7 ± 7.2	0.513
T downstaging	4,562 (73.0%)	3,086 (77.4%)	< 0.001*	3,059 (77.1%)	3,067 (77.3%)	0.831
Achieved	1,640 (26.4%)	903 (22.6%)		911 (22.9%)	903 (22.7%)	
Not achieved						
Path T stage	0 (0.0%)	0 (0.0%)	0.600	0 (0.0%)	0 (0.0%)	0.829
T0	618 (10.0%)	386 (9.7%)		371 (9.3%)	383 (9.6%)	
T1	2,306 (37.2%)	1,529 (38.3%)		1,513 (38.1%)	1,523 (38.4%)	
T2	3,086 (49.8%)	1,943 (48.7%)		1,965 (49.5%)	1,933 (48.7%)	
T3	192 (3.1%)	131 (3.3%)		121 (3.0%)	131 (3.3%)	
T4						
Median follow up	56.1	54.9	0.011*	55.0	55.0	0.875

Finally, in patients with pIR and ypN+, 2,993 did not receive AC whereas 2,882 did. Baseline comparison of clinicopathologic factors revealed that AC patients were younger (55.9 ± 11.5 vs. 58.3 ± 12.7 years; $p < 0.001$) and more commonly underwent minimally-invasive resections more commonly (33.2% vs. 29.5%; $p = 0.002$) but were less likely to be downstaged to ypT0 (10.7% vs. 13.9%; $p = 0.003$). 2,629 patients were matched by AC receipt status, and matched subgroups were well balanced (Table 4). Survival was improved with AC in matched pIR and ypN + patients (median OS in the AC subgroup (155.9 ± 5.4 vs. 126.5 ± 7.6 months; $p < 0.001$). The absolute 5-year OS advantage associated with AC was 7% (76% vs. 69%; $p < 0.001$, Fig. 4).

Table 4
Comparison of the unmatched and matched datasets of the patient subgroup who achieved pathologic incomplete response with ypN+ (N = 5,875) by the receipt of adjuvant systemic therapy. **APR**: Abdominoperineal Resection; **AC**: Adjuvant Systemic Therapy; **Diff.**: Differentiated; **LAR**: Low Abdominal Resection; **MIS**: Minimally Invasive Surgery. * Statistically significant.

	Unmatched dataset			**Matched dataset 1:1**		
	No AC	**AC**	**p**	**No AC**	**AC**	**p**
N	2,993	2,882		2,629	2,629	
Age (years)	58.3 ± 12.7	55.9 ± 11.5	< 0.001*	56.9 ± 12.3	56.5 ± 11.5	0.180
Sex	1,862 (62.2%)	1,748 (60.7%)	0.220	1,633 (62.1%)	1,596 (60.7%)	0.295
Male	1,131 (37.8%)	1,134 (39.3%)		996 (37.9%)	1,033 (39.3%)	
Female						
Race	2,411 (80.6%)	2,349 (81.5%)	0.306	2,131 (81.1%)	2,142 (81.5%)	0.843
White	236 (7.9%)	197 (6.8%)		198 (7.5%)	187 (7.1%)	
Black	346 (11.6%)	336 (11.7%)		300 (1.4%)	300 (11.4%)	
Other						
Charlson Score	2,407 (80.4%)	2,392 (83.0%)	0.087	2,140 (81.4%)	2,166 (82.4%)	0.824
0	459 (15.3%)	386 (13.4%)		388 (14.8%)	365 (13.9%)	
1	90 (3.0%)	73 (2.5%)		71 (2.7%)	69 (2.6%)	
2	37 (1.2%)	31 (1.1%)		30 (1.1%)	29 (1.1%)	
3+						
Grade	197 (6.6%)	174 (6.0%)	0.222	166 (6.3%)	166 (6.3%)	0.836
Well diff.	2,024 (67.6%)	2,021 (70.1%)		1,805 (68.7%)	1,832 (69.7%)	
Moderately diff.	409 (13.7%)	370 (12.8%)		349 (13.3%)	340 (12.9%)	
Poorly diff.	363 (12.1%)	317 (11.0%)		309 (11.8%)	291 (11.1%)	
Not reported						
Rad-surg interval	1,876 (62.7%)	1,859 (64.5%)	0.146	1,662 (63.2%)	1,678 (63.8%)	0.647
5–8 weeks	1,117 (37.3%)	1,023 (35.5%)		967 (36.8%)	951 (36.2%)	
9–12 weeks						

	Unmatched dataset			Matched dataset 1:1		
Surgery	2,027 (67.7%)	2,028 (70.4%)	0.114	1,822 (69.3%)	1,829 (69.6%)	0.897
LAR	784 (26.2%)	683 (23.7%)		640 (24.3%)	642 (24.4%)	
APR	81 (2.7%)	84 (2.9%)		75 (2.9%)	76 (2.9%)	
Proctocolectomy	101 (3.4%)	87 (3.0%)		92 (3.5%)	82 (3.1%)	
Exenteration						
Approach	2,110 (70.5%)	1,926 (66.8%)	0.002*	1,806 (68.7%)	1,778 (67.6%)	0.407
Open	883 (29.5%)	956 (33.2%)		823 (31.3%)	851 (32.4%)	
MIS						
Retrieved nodes	19.1 ± 8.1	19.4 ± 7.8	0.832	19.2 ± 8.3	19.3 ± 7.7	0.587
Positive nodes	3.4 ± 3.5	3.4 ± 3.5	0.146	3.4 ± 3.5	3.4 ± 3.5	0.887
T downstaging	1,277 (42.7%)	1,197 (41.5%)	0.379	1,074 (40.9%)	1,103 (42.0%)	0.417
Achieved	1,716 (57.3%)	1,685 (58.5%)		1,555 (59.1%)	1,526 (58.0%)	
Not achieved						
Path T stage	417 (13.9%)	307 (10.7%)	0.003*	304 (11.6%)	302 (11.5%)	0.996
T0	115 (3.8%)	102 (3.5%)		92 (3.5%)	94 (3.6%)	
T1	591 (19.7%)	619 (21.5%)		543 (20.7%)	554 (21.1%)	
T2	1,755 (58.6%)	1,744 (60.5%)		1,582 (60.2%)	1,573 (59.8%)	
T3	115 (3.8%)	110 (3.8%)		108 (4.1%)	106 (4.0%)	
T4						
Median follow up	52.8	53.3	0.411	53.0	53.1	0.908

Discussion

Neoadjuvant CRT and TME is the standard of care for patients with stage II and III rectal adenocarcinoma. In this study which utilized a national population-based cohort and included 19,867 patients who received neoadjuvant CRT followed by proctectomy for clinical stages II and III rectal adenocarcinoma, AC was associated with improved OS after accounting for potential biases through propensity score matching. Importantly, on individual stratified analyses by pathologic response to preoperative therapy, an OS advantage persisted irrespective of response in both pathologic node positive

and node negative patients. Those findings collectively suggest that AC should be considered after neoadjuvant CRT, whenever possible.

To date, four randomized controlled trials have evaluated the value of AC in patients with rectal adenocarcinoma treated with upfront CRT. In the seminal EORTC trial, patients who received neoadjuvant RT with or without chemotherapy were randomized to observation versus fluorouracil plus leucovorin, and OS was not significantly different (10-year OS 51.8 vs. 48.4%, HR 0.91, 95% CI 0.77–1.09). [6] Notably, a minority of patients ultimately received intended AC in that study with a rate of 43%, indicating poor adherence to study protocol. In another important trial by Cionini et al., OS was similarly comparable among patients that received AC (leucovorin-modulated fluorouracil) and those who did not following neoadjuvant CRT and TME. [7] Compliance to AC again emerged as a notable limitation, as 28% of patients assigned to AC did not receive it. The Dutch colorectal PROCTOR/SCRIPT trials included patients with stage II or III rectal adenocarcinoma who underwent neoadjuvant RT or CRT followed by TME and were then randomly assigned to observation vs. adjuvant fluorouracil/leucovorin (PROCTOR) or to observation vs. adjuvant capecitabine (SCRIPT). [10] A combined analysis of both studies again showed no significant difference in OS at 5 years. [10] In the present study, while compliance with AC was consistent with the aforementioned studies (41.1%), an OS advantage was detected in all analyzed subgroups. This is possibly related to the considerably larger sample size and due to improved overall care in a more contemporary time period.

NCCN guidelines recommend AC for patients with locally advanced rectal adenocarcinoma treated with upfront CRT. [4] Whether AC improves oncologic outcomes in this setting has been addressed previously using NCDB, and increased OS has consistently been observed [11–13]. Most recently, Gahagan et al. analyzed NCDB between 2006 and 2013 and included patients with stage II and III rectal adenocarcinoma treated with neoadjuvant CRT and noted an OS advantage with AC. In this study, OS was similarly improved with AC despite several key methodological differences. First, included patients in this study were treated in a more contemporary period (2004–2018) and underwent a strict selection criteria in an effort to exclude patients receiving suboptimal surgical resection (negative CRM and adequate LN yield). This likely minimized chances of under-staging and further limited the potential detrimental effect of inadequate surgery on OS. Second, independent subgroup analyses were conducted and stratified by pathologic response according to both tumor and nodal status to allow for comparison of additional matched subsets. Finally, patients who did sustain a complete response were also studied and matched independently, further supporting AC's role in this subgroup.

Existing research supports that attaining pCR in patients who have undergone neoadjuvant CRT and TME is associated with improved oncologic outcomes overall. [12,14,15] [12] Even without AC, pCR has been associated with increased 5-year disease-free and OS rates of 96% (95%, CI: 77–99) and 100%, respectively. [16] A systematic review and meta-analysis including pooled data from NCDB reported a trend towards improved OS with AC, but data was limited due to heterogeneity in the included samples. [17] Indeed, whether AC represents overtreatment in this group has therefore been considered. For example, in

an analysis of European RCTs, OS improvement in patients with ypT0N0 disease was minimal when compared to non-responders [18]. In this study, AC conferred a meaningful OS improvement in all subgroups irrespective of tumor or nodal response status, suggesting AC should be considered universally. Specifically, in pIR and ypN + patients, a 5-year OS incremental advantage associated with AC was 7% compared to 4% in the pCR subgroup. While it is not possible to cross compare incremental OS improvements, this data suggests that response is unlikely to considerably affect a decision to pursue AC.

This study has several limitations, most of which are due to its retrospective design and inherent biases associated with large dataset analyses. First, while NCDB employs rigorous quality control measures and high regulatory standards, coding errors and observer bias remain possible. Second, important granular details on type and extent of postoperative chemotherapy are lacking. This certainly may have affected OS and, consequently, study conclusions. However, in an effort to overcome that, this study employed stringent selection criteria aimed at excluding patients who may have received substandard preoperative therapy. Third, selection bias is unavoidable in this retrospective analysis and it is therefore possible that patients selected to receive AC had fewer comorbidities and better overall performance status which may have contributed to improved outcomes. On the other hand, AC was likely recommended more commonly to patients with more adverse pathologic features, which may have introduced counteracting bias against the study's findings. In an effort to mitigate these potential issues, multivariable regression and propensity score matching were utilized to generate well-balanced groups and individual subgroup analyses were then conducted. Last, patterns and timing of relapses are not made available in NCDB, and this of course limits interpretation of the true effect of chemotherapy in these groups of patients.

Conclusion

In this study, AC after neoadjuvant CRT in patients with stage II and III rectal adenocarcinoma who underwent "optimal" surgery was associated with improved OS. Despite a lack of prospective data to support AC in this setting, this study suggests that AC should be administered whenever possible.

Declarations

Author Contribution:

Study conception and design: FD, SN

Acquisition of data: SN

Analysis and interpretation of data: FD, SN, IS

Drafting of manuscript: IS, TP, FD

Critical revision: FD, SN

All authors have read and approved the manuscript.

Disclosure of funding, commercial interests and support:

The authors do not receive funding from any agency and otherwise have no non-financial interests to disclose.

Data availability statement:

The authors confirm that the data supporting the findings of this study are available within the article and the National Cancer Database.

Disclosures

The authors have no financial disclosures or conflicts of interest to report.

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Figures

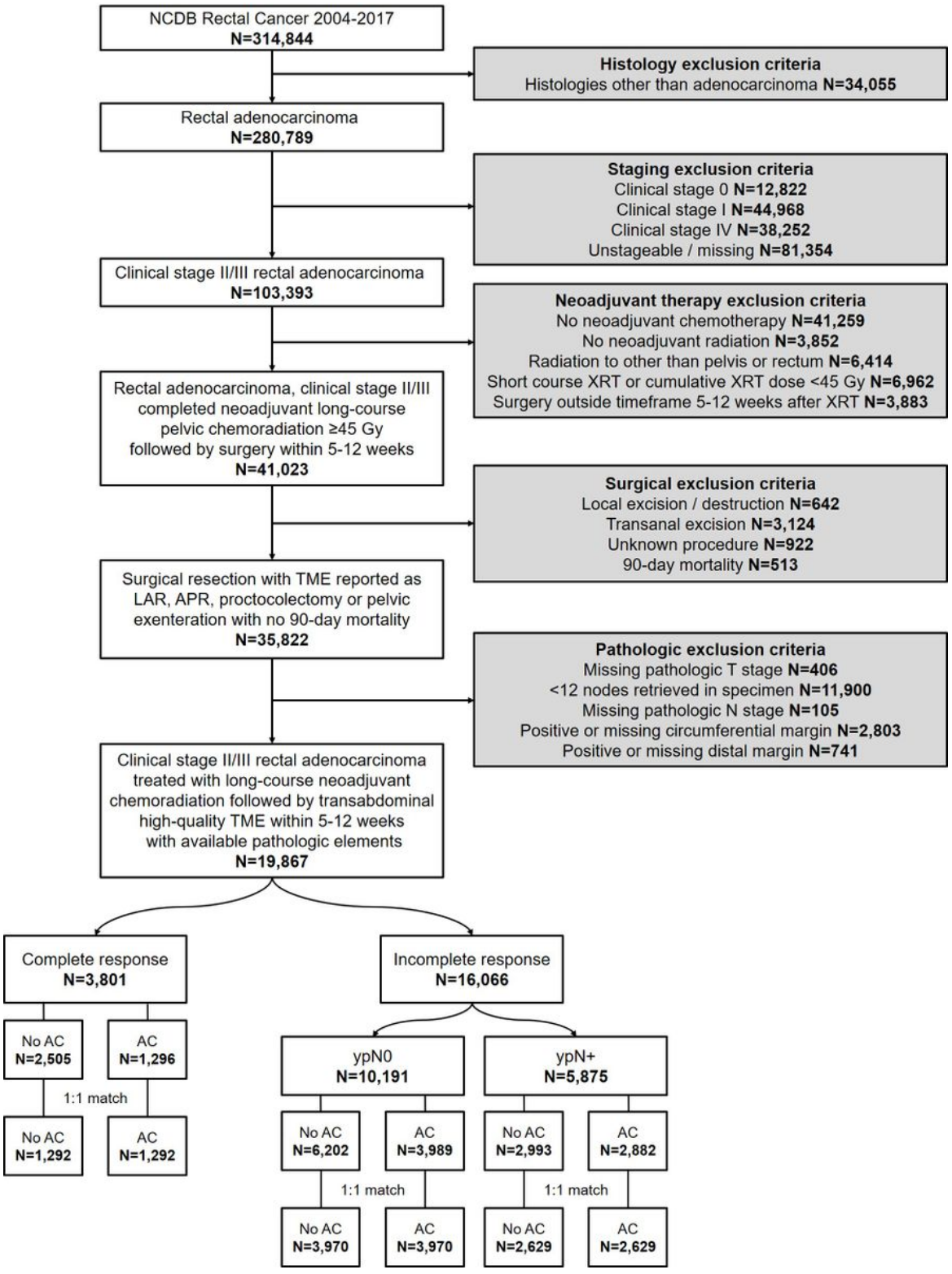

Figure 1

flow diagram demonstrating the steps of patient selection.

Figure 2

2A: Kaplan Meier survival analysis of the matched patients with pathologic complete response by the status of adjuvant systemic therapy.

2B: Kaplan Meier survival analysis of the matched patients with pathologic incomplete response and ypN0 by the status of adjuvant systemic therapy.

2C: Kaplan Meier survival analysis of the matched patients with pathologic incomplete response and ypN+ by the status of adjuvant systemic therapy.