Adjuvant chemotherapy after neoadjuvant chemoradiation and proctectomy improves survival irrespective of pathologic response in rectal adenocarcinoma: a population-based cohort study

Samer A. Naffouje1 · Yuen-Joyce Liu2 · Sivesh K. Kamarajah3,4 · George I. Salti2,5 · Fadi Dahdaleh5

Accepted: 24 August 2022 / Published online: 1 September 2022 © The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2022

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 A total of 19,867 patients met inclusion/exclusion criteria. Mean age was 58.6 ± 12.0 years, and 12,396 (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 = 3801) and incomplete (pIR, N = 16,066) subgroups, and pIR further subcategorized into ypN0 (N = 10,191) and ypN+ (N = 5875) 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.

Keywords Neoadjuvant chemoradiation · Outcomes · Rectal cancer · Adjuvant chemotherapy

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.

* Fadi Dahdaleh
Fadi.Dahdaleh@EEHealth.org
1 Department of Surgical Oncology, H. Lee Moffitt Cancer Center, Tampa, FL, USA
2 Department of General Surgery, University of Illinois Hospital and Health Sciences System, Chicago, IL, USA
3 Department of Upper Gastrointestinal Surgery, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Trust, Birmingham, UK
4 Institute of Cancer and Genomics Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK
5 Department of Surgical Oncology, Edward-Elmhurst Health, 120 Spalding Drive, Ste 205, Naperville, IL 60540, USA
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 was 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 III 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 USA. 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 was 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 4500 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 and 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 method 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 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 3801 cases (19.1%). A total of 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.

Propensity score matching

As described above, the included cohort was stratified into pCR (N = 3801) and pIR (N = 16,066) groups, with the pIR group further subcategorized into ypNO (N = 10,191) and ypN+ (N = 5875) subgroups. Within the pCR group, 2505 patients did not receive AC whereas 1296 did. Baseline characteristics among these two subgroups were conducted and, notably, patients who received AC were significantly younger (57.1 ± 11.5 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 1292 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).

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, 6202 patients did not receive AC whereas 3989 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 2970 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. 2).

Finally, in patients with pIR and ypN+, 2993 did not receive AC whereas 2882 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). A total of 2629 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. 2).

Discussion

Neoadjuvant CRT and TME are 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. Given existing limitations in prospective studies examining AC’s role in this setting, those findings collectively suggest that AC should not be omitted after neoadjuvant CRT based on final pathologic staging.

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
Fig. 1  Flow diagram demonstrating the steps of patient selection
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 [12–15]. 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

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

| N     | 19867  |
|-------|--------|
| Age (years) | Mean ± SD 58.6 ± 12.0 |
|         | Median 59 |
| Sex     | Male 12396 (62.4%) |
|         | Female 7471 (37.6%) |
| Race    | White 16267 (81.9%) |
|         | Black 1439 (7.2%) |
|         | Other 2161 (10.9%) |
| Charlson score | 0 15854 (79.8%) |
|         | 1 3099 (15.6%) |
|         | 2 625 (3.1%) |
|         | 3+ 289 (1.5%) |
| Grade   | Well differentiated 1412 (7.1%) |
|         | Moderately differentiated 13657 (68.7%) |
|         | Poorly differentiated 1857 (9.3%) |
|         | Not reported 2941 (14.8%) |
| Clinical T stage | T1 116 (0.6%) |
|         | T2 958 (4.8%) |
|         | T3 17249 (86.8%) |
|         | T4 1544 (7.8%) |
| Clinical N stage | Negative 9205 (46.3%) |
|         | Positive 10662 (53.7%) |
| Clinical stage | Stage II 9205 (46.3%) |
|         | Stage III 10662 (53.7%) |
| Radiation-surgery interval | 5–8 weeks 11991 (60.4%) |
|         | 9–12 weeks 7876 (39.6%) |
| Surgery | LAR 13801 (69.5%) |
|         | APR 4938 (24.9%) |
|         | Proctocolectomy 541 (2.7%) |
|         | Exenteration 587 (3.0%) |
| Approach | Open 12964 (65.3%) |
|         | Minimally-invasive 6903 (34.7%) |
| Retrieved lymph nodes | Mean ± SD 18.7 ± 7.6 |
|         | Median 16 |
| Pathologic T stage | T0 4525 (22.8%) |
|         | T1 1221 (6.1%) |
|         | T2 5045 (25.4%) |
|         | T3 8528 (42.9%) |
|         | T4 548 (2.8%) |
| Pathologic N stage | N0 13992 (70.4%) |
|         | N1 4088 (20.6%) |
|         | N2 1787 (9.0%) |
| Response | Complete response 3801 (19.1%) |
|         | Partial response 10122 (50.9%) |
|         | No response 5944 (29.9%) |
| Adjuvant systemic therapy | No 11700 (58.9%) |
|         | Yes 8167 (41.1%) |
| Follow up (months) | Mean ± SD 62.4 ± 35.6 |
|         | Median 55.1 |
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.

| Table 2 | Comparison of the unmatched and matched datasets of the patient subgroup who achieved pathologic complete response (N = 3801) by the receipt of adjuvant systemic therapy |
|---------|----------------------------------------------------------------------------------|
|         | Unmatched dataset                                                                 | Matched dataset 1:1                                                                 |
|         | No AC | AC | p   | No AC | AC | p   |
| N       | 2505  | 1296 | <0.001*  | 1292 | 1292 | 0.713 |
| Age (years) | 60.8 ± 12.5 | 57.1 ± 11.2 | 0.141   | 57.3 ± 12.0  | 57.1 ± 11.1 | 0.936   |
| Sex     |       |     |     |       |     |     |
| Male    | 1567  | 779 | 62.6% | 517   | 39.9% | 0.115 |
| Female  | 938   | 517 | 37.4% | 395   | 39.9% | 0.952 |
| Race    |       |     |     |       |     |     |
| White   | 2077  | 1071 | 82.9% | 514   | 42.8% | 0.039*  |
| Black   | 184   | 78  | 7.3%  | 37    | 6.1%  | 0.851   |
| Other   | 244   | 147 | 11.3% | 124   | 26.9% | 0.723   |
| Charlson Score | 0.039* |       |     | 0.843 |     |     |
| 0       | 1976  | 1073 | 78.9% | 514   | 50.8% |       |
| 1       | 413   | 176 | 16.5% | 34    | 8.6%  |       |
| 2       | 84    | 35  | 4.4%  | 10    | 2.4%  |       |
| 3+      | 32    | 12  | 4.4%  | 10    | 2.4%  |       |
| Grade   |       |     |     |       |     |     |
| Well diff | 162  | 91  | 6.5%  | 46    | 2.9%  |       |
| Moderately diff | 1572 | 827 | 62.8% | 827   | 52.6% |       |
| Poorly diff | 184  | 88  | 7.3%  | 12    | 7.3%  |       |
| Not reported | 587  | 290 | 23.4% | 290   | 18.2% |       |
| Clinical stage | <0.001* |       |     | 0.843 |     |     |
| Stage II | 1349 | 565 | 43.6% | 565   | 43.6% |       |
| Stage III | 1156 | 731 | 65.6% | 731   | 65.6% |       |
| Rad-surg interval | 0.703 |       |     | 0.524 |     |     |
| 5–8 weeks | 1449 | 758 | 58.5% | 758   | 58.5% |       |
| 9–12 weeks | 1056 | 538 | 41.5% | 538   | 41.5% |       |
| Surgery  |       |     |     |       |     |     |
| LAR     | 1775  | 915 | 70.9% | 915   | 70.9% |       |
| APR     | 608   | 313 | 24.3% | 313   | 24.3% |       |
| Proctocolectomy | 68   | 41  | 2.7%  | 41    | 2.7%  |       |
| Exenteration | 54   | 27  | 2.2%  | 27    | 2.2%  |       |
| Approach |      |     |     |       |     |     |
| Open    | 1652  | 787 | 65.9% | 787   | 60.7% | 0.001*  |
| MIS     | 853   | 509 | 34.1% | 509   | 39.3% | 0.888   |
| 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 | 0.906 |

APR abdominoperineal resection, AC adjuvant systemic therapy, Diff differentiated, LAR low abdominal resection, MIS minimally invasive surgery

*Statistically significant
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.

While an intent-to-treat analysis would have been particularly useful, this was not possible as NCDB does not detail proposed treatment plans at time of diagnosis and further does not include information on why AC was not pursued or offered. In an effort to counteract this effect, strict inclusion and exclusion criteria were used to select patients based on upfront clinical staging alone. Moreover, only patients undergoing “optimal” surgery were included in an effort to lessen likelihood of AC utilization as a means to compensate for insufficient surgery. 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

| 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 |
|---------|-------------------------------------------------------------------------------------------------|
|         | Unmatched dataset | Matched dataset 1:1 |
|         | No AC | AC | p | No AC | AC | p |
| N       | 6202  | 3989 |       | 3970  | 3970 | 0.697 |
| Age (years) | 60.6 ± 12.1 | 56.8 ± 10.9 | <0.001* | 57.1 ± 11.5 | 57.0 ± 10.8 |
| Sex | 0.974 | 0.981 |
| Male | 3920 (63.2%) | 2520 (63.2%) | 2508 (63.2%) | 2507 (63.1%) |
| Female | 2282 (36.8%) | 1469 (36.8%) | 1462 (36.8%) | 1463 (36.9%) |
| Race | 0.283 | 0.804 |
| White | 5072 (81.8%) | 3287 (82.4%) | 3255 (82.0%) | 3269 (82.3%) |
| Black | 473 (7.6%) | 271 (6.8%) | 286 (7.2%) | 271 (6.8%) |
| Other | 657 (10.6%) | 431 (10.8%) | 429 (10.8%) | 430 (10.8%) |
| Charlson score | 0.825 | 0.825 |
| 0 | 4756 (76.7%) | 3250 (81.5%) | 3217 (81.0%) | 3232 (81.4%) |
| 1 | 1086 (17.5%) | 579 (14.5%) | 599 (15.1%) | 578 (14.6%) |
| 2 | 241 (3.9%) | 102 (2.6%) | 93 (2.3%) | 102 (2.6%) |
| 3+ | 119 (1.9%) | 58 (1.5%) | 61 (1.5%) | 58 (1.5%) |
| Grade | 0.491 | 0.972 |
| Well diff | 497 (8.0%) | 291 (7.3%) | 288 (7.3%) | 291 (7.3%) |
| Moderately diff | 4374 (70.5%) | 2839 (71.2%) | 2847 (71.7%) | 2828 (71.2%) |
| Poorly diff | 481 (7.8%) | 325 (8.1%) | 316 (8.0%) | 321 (8.1%) |
| Not reported | 850 (13.7%) | 534 (13.4%) | 519 (13.1%) | 530 (13.4%) |
| Rad-surg interval | 0.005* | 0.550 |
| 5–8 weeks | 3614 (58.3%) | 2435 (61.0%) | 2393 (60.3%) | 2419 (60.9%) |
| 9–12 weeks | 2588 (41.7%) | 1554 (39.0%) | 1577 (39.7%) | 1551 (39.1%) |
| Surgery | 0.612 | 0.990 |
| LAR | 4311 (69.5%) | 159 (2.6%) | 201 (3.2%) | 201 (2.6%) |
| APR | 1531 (24.7%) | 117 (2.6%) | 117 (2.9%) | 117 (2.9%) |
| Proctocolectomy | 159 (2.6%) | 108 (2.7%) | 103 (2.6%) | 107 (2.7%) |
| Exenteration | 201 (3.2%) | 117 (2.9%) | 117 (2.9%) | 117 (2.9%) |
| Approach | <0.001* | 0.835 |
| Open | 4035 (65.1%) | 2454 (61.5%) | 2455 (61.8%) | 2446 (61.6%) |
| MIS | 2167 (34.9%) | 1535 (38.5%) | 1515 (38.2%) | 1524 (38.4%) |
| Retrieved nodes | 18.4 ± 7.5 | 18.7 ± 7.3 | 18.6 ± 7.8 | 18.7 ± 7.2 |
| T downstaging | 0.028* | 0.513 |
| Achieved | 4562 (73.0%) | 3086 (77.4%) | 3059 (77.1%) | 3067 (77.3%) |
| Not achieved | 1640 (26.4%) | 903 (22.6%) | 911 (22.9%) | 903 (22.7%) |
| Path T stage | 0.600 | 0.829 |
| T0 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| T1 | 616 (10.0%) | 386 (9.7%) | 371 (9.3%) | 383 (9.6%) |
| T2 | 2306 (37.2%) | 1529 (38.3%) | 1513 (38.1%) | 1523 (38.4%) |
| T3 | 3086 (49.8%) | 1943 (48.7%) | 1965 (49.5%) | 1933 (48.7%) |
| T4 | 192 (3.1%) | 131 (3.3%) | 121 (3.0%) | 131 (3.3%) |
| Median follow-up | 56.1 | 54.9 | 0.011* | 55.0 | 55.0 | 0.875 |

APR abdominopelvic resection, AC adjuvant systemic therapy, Diff differentiated, LAR low abdominal resection, MIS minimally invasive surgery

*Statistically significant
Fig. 2  A Kaplan–Meier survival analysis of the matched patients with pathologic complete response to neoadjuvant chemoradiation by the status of adjuvant systemic therapy. B Kaplan–Meier survival analysis of the matched patients with pathologic incomplete response and ypN0 by the status of adjuvant systemic therapy. C Kaplan–Meier survival analysis of the matched patients with pathologic incomplete response and ypN+ by the status of adjuvant systemic therapy.
Patients with pathologic incomplete response to neoadjuvant chemoradiation and ypNO:

- AC: NR (mean 141.6 ± 1.5 months)
- No AC: NR (mean 129.9 ± 1.2 months)

\[ p < 0.001 \]

| Months | Cumulative survival |
|--------|--------------------|
| 0      | 1.00               |
| 12     | 0.98               |
| 24     | 0.95               |
| 36     | 0.92               |
| 48     | 0.89               |
| 60     | 0.86               |
| 72     | 0.83               |
| 84     | 0.80               |
| 96     | 0.77               |
| 108    | 0.74               |
| 120    | 0.71               |
| 132    | 0.67               |
| 144    | 0.66               |
| 156    | 0.60               |
| 168    | 0.56               |

| N entering | N withdrawing | N exposed to risk | N of events | Cumulative survival |
|------------|---------------|-------------------|-------------|---------------------|
| 3,970      | 55            | 3,942             | 12          | 1.00                |
| 3,903      | 260           | 3,773             | 79          | 0.98                |
| 3,564      | 553           | 3,287             | 82          | 0.95                |
| 2,929      | 554           | 2,652             | 75          | 0.92                |
| 2,300      | 492           | 2,054             | 69          | 0.89                |
| 1,739      | 409           | 1,534             | 62          | 0.86                |
| 1,268      | 280           | 1,123             | 33          | 0.83                |
| 945        | 240           | 825               | 36          | 0.80                |
| 669        | 183           | 577               | 19          | 0.77                |
| 467        | 153           | 390               | 17          | 0.74                |
| 297        | 123           | 235               | 7           | 0.71                |
| 167        | 86            | 124               | 7           | 0.67                |
| 74         | 52            | 48                | 1           | 0.66                |
| 21         | 19            | 12                | 1           | 0.60                |

| N entering | N withdrawing | N exposed to risk | N of events | Cumulative survival |
|------------|---------------|-------------------|-------------|---------------------|
| 3,970      | 63            | 3,938             | 43          | 0.99                |
| 3,864      | 258           | 3,735             | 108         | 0.96                |
| 3,498      | 480           | 3,258             | 139         | 0.92                |
| 2,879      | 480           | 2,639             | 128         | 0.87                |
| 2,271      | 432           | 2,055             | 97          | 0.83                |
| 1,742      | 363           | 1,560             | 72          | 0.80                |
| 1,307      | 275           | 1,169             | 48          | 0.76                |
| 984        | 215           | 876               | 34          | 0.73                |
| 735        | 174           | 648               | 19          | 0.71                |
| 542        | 151           | 466               | 18          | 0.68                |
| 373        | 147           | 299               | 8           | 0.67                |
| 218        | 111           | 162               | 8           | 0.63                |
| 99         | 67            | 65                | 8           | 0.56                |
| 24         | 12            |                    | 0           |                    |

Fig. 2  (continued)
Patients with pathologic incomplete response to neoadjuvant chemoradiation and ypN+:

AC  155.9 ± 5.4 months  p<0.001
No AC  126.5 ± 7.6 months

| Months | AC | No AC |
|--------|----|-------|
| 0      | 2,629 | 2,543 |
| 12     | 2,575 | 2,249 |
| 24     | 2,346 | 1,829 |
| 36     | 1,912 | 1,448 |
| 48     | 1,507 | 1,110 |
| 60     | 1,121 | 846  |
| 72     | 852  | 646  |
| 96     | 628  | 461  |
| 120    | 461  | 307  |
| 144    | 199  | 109  |
| 168    | 109  | 56   |

| Months | AC | No AC |
|--------|----|-------|
| 0      | 2,615 | 2,481 |
| 12     | 2,511 | 2,129 |
| 24     | 2,201 | 1,715 |
| 36     | 1,765 | 1,344 |
| 48     | 1,370 | 1,018 |
| 60     | 1,019 | 763  |
| 72     | 767  | 561  |
| 96     | 561  | 398  |
| 120    | 257  | 157  |
| 144    | 83   | 83   |
| 168    | 36   | 8    |

Cumulative survival

AC: 0.99 0.95 0.89 0.83 0.76 0.71 0.66 0.62 0.58 0.56 0.53 0.53 0.50 0.50
No AC: 0.98 0.91 0.84 0.76 0.69 0.63 0.60 0.57 0.54 0.52 0.49 0.48 0.46 0.44

Fig. 2 (continued)
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.

**Table 4** Comparison of the unmatched and matched datasets of the patient subgroup who achieved pathologic incomplete response with ypN+ (N = 5875) by the receipt of adjuvant systemic therapy

|                           | Unmatched dataset | Matched dataset 1:1 |
|---------------------------|-------------------|---------------------|
|                           | No AC | AC | p   | No AC | AC | p   |
| N                         | 2993  | 2882 |    | 2629  | 2629 |    |
| Age (years)               | 58.3 ± 12.7 | 55.9 ± 11.5 | <0.001* | 56.9 ± 12.3 | 56.5 ± 11.5 | 0.180 |
| Sex                       |        |    | 0.220 |        |    | 0.295 |
| Male                      | 1862 (62.2%) | 1748 (60.7%) |    | 1633 (62.1%) | 1596 (60.7%) |    |
| Female                    | 1131 (37.8%) | 1134 (39.3%) |    | 996 (37.9%) | 1033 (39.3%) |    |
| Race                      |        |    | 0.306 |        |    | 0.843 |
| White                     | 2411 (80.6%) | 2349 (81.5%) |    | 2131 (81.1%) | 2142 (81.5%) |    |
| Black                     | 236 (7.9%) | 197 (6.8%) |    | 198 (7.5%) | 187 (7.1%) |    |
| Other                     | 346 (11.6%) | 336 (11.7%) |    | 300 (1.4%) | 300 (1.1%) |    |
| Charlson score            |        |    | 0.087 |        |    | 0.824 |
| 0                         | 2407 (80.4%) | 2392 (83.0%) |    | 2392 (83.0%) | 2386 (83.0%) |    |
| 1                         | 459 (15.3%) | 386 (13.4%) |    | 388 (14.8%) | 365 (13.9%) |    |
| 2                         | 90 (3.0%) | 73 (2.5%) |    | 71 (2.7%) | 69 (2.6%) |    |
| 3+                        | 37 (1.2%) | 31 (1.1%) |    | 30 (1.1%) | 29 (1.1%) |    |
| Grade                     |        |    | 0.222 |        |    | 0.836 |
| Well diff                 | 197 (6.6%) | 174 (6.0%) |    | 166 (6.3%) | 166 (6.3%) |    |
| Moderately diff           | 2024 (67.6%) | 2021 (70.1%) |    | 1805 (68.7%) | 1832 (69.7%) |    |
| Poorly diff               | 409 (13.7%) | 370 (12.8%) |    | 349 (13.3%) | 340 (12.9%) |    |
| Not reported              | 363 (12.1%) | 317 (11.0%) |    | 309 (11.8%) | 291 (11.1%) |    |
| Rad-surg interval         |        |    | 0.146 |        |    | 0.647 |
| 5–8 weeks                 | 1876 (62.7%) | 1859 (64.5%) |    | 1662 (63.2%) | 1678 (63.8%) |    |
| 9–12 weeks                | 1117 (37.3%) | 1023 (35.5%) |    | 967 (36.8%) | 951 (36.2%) |    |
| Surgery                   |        |    | 0.114 |        |    | 0.897 |
| LAR                       | 2027 (67.7%) | 2028 (70.4%) |    | 1822 (69.3%) | 1829 (69.6%) |    |
| APR                       | 784 (26.2%) | 683 (23.7%) |    | 640 (24.3%) | 642 (24.4%) |    |
| Proctocolectomy           | 81 (2.7%) | 84 (2.9%) |    | 75 (2.9%) | 76 (2.9%) |    |
| Exenteration              | 101 (3.4%) | 87 (3.0%) |    | 92 (3.5%) | 82 (3.1%) |    |
| Approach                  |        |    | 0.002* |        |    | 0.407 |
| Open                      | 2110 (70.5%) | 1926 (66.8%) |    | 1806 (68.7%) | 1778 (67.6%) |    |
| MIS                       | 883 (29.5%) | 956 (33.2%) |    | 823 (31.3%) | 851 (32.4%) |    |
| 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             |        |    | 0.379 |        |    | 0.417 |
| Achieved                  | 1277 (42.7%) | 1197 (41.5%) |    | 1074 (40.9%) | 1103 (42.0%) |    |
| Not achieved              | 1716 (57.3%) | 1685 (58.5%) |    | 1555 (59.1%) | 1526 (58.0%) |    |
| Path T stage              |        |    | 0.003* |        |    | 0.996 |
| T0                        | 417 (13.9%) | 307 (10.7%) |    | 304 (11.6%) | 302 (11.5%) |    |
| T1                        | 115 (3.8%) | 102 (3.5%) |    | 92 (3.5%) | 94 (3.6%) |    |
| T2                        | 591 (19.7%) | 619 (21.5%) |    | 543 (20.7%) | 554 (21.1%) |    |
| T3                        | 1755 (58.6%) | 1744 (60.5%) |    | 1582 (60.2%) | 1573 (59.8%) |    |
| T4                        | 115 (3.8%) | 110 (3.8%) |    | 108 (4.1%) | 106 (4.0%) |    |
| Median follow-up          | 52.8 | 53.3 | 0.411 | 53.0 | 53.1 | 0.908 |

*APR abdominoperineal resection, AC adjuvant systemic therapy, Diff differentiated, LAR low abdominal resection, MIS minimally invasive surgery

*Statistically significant

**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.
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.

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

Declarations

Consent for publication All authors have read and approved the manuscript.

Conflict of interest The authors declare no competing interests.

References

1. Kapiteijn E, Marijnissen CA, Nast-Kolb D, Neoptolemos JP, Desmedt C, Kemeny N, et al. (2007) Preoperative chemotherapy with FOLFOX4 combined with or without involved-field radiotherapy as compared with neoadjuvant chemoradiotherapy for rectal cancer: 6-year results of a phase III trial. Lancet 370(9592):1136–43
2. Sauer R, Liersch T, Merkel S, et al. (2012) Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 30(16):1926–33
3. Petersen SH, Harling H, Kirkeby LT, Wille-Jørgensen P, Mocellin S, et al. (2012) Postoperative adjuvant chemotherapy in rectal cancer operated for cure. Cochrane Database Syst Rev (3):CD004078.
4. Network CC (2022) NCCN Guidelines: rectal cancer
5. Glyn-Jones R, Wyrwicz L, Tjulandin SA, et al. (2017) Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment, and follow-up. Ann Oncol 28(suppl_4):iv22–40
6. Bosset JF, Collette L, Calais G, et al. (2006) Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 355(11):1114–123
7. Ciommo L, Marzano S, Boffi L, et al. (1996) Adjuvant postoperative radiotherapy in rectal cancer: 148 cases treated at Florence University with 8 years median follow-up. Radiother Oncol 40(2):127–33
8. Biagi JJ, Raphael MJ, Mackillop WI, Kong W, King WD, Booth CM (2011) Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. JAMA 305(22):2335–2342
9. Bilimoria KY, Stewart AK, Winchester DP, Ko CY (2008) The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. Ann Surg Oncol 15(3):683–690
10. Breugem AJ, van Gijn W, Muller EW, et al. (2015) Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomized phase III trial. Ann Oncol 26(4):696–701
11. Ghagan JV, Whealan MD, Phelan MJ, et al. (2020) Improved survival with adjuvant chemotherapy in locally advanced rectal cancer patients treated with preoperative chemoradiation regardless of pathologic response. Surg Oncol 32:35–40
12. Polanco PM, Mokdad AA, Zhu H, Choti MA, Huerta S (2018) Association of adjuvant chemotherapy with overall survival in patients with rectal cancer and pathologic complete response following neoadjuvant chemotheraphy and resection. JAMA Oncol 4(7):938–943
13. Turner MC, Keenan JE, Rushing CN, et al. (2019) Adjuvant chemotherapy improves survival following resection of locally advanced rectal cancer with pathologic complete response. J Gastrointest Surg 23(8):1614–1622
14. Janjan NA, Crane C, Feig BW, et al. (2001) Improved overall survival among responders to preoperative chemoradiation for locally advanced rectal cancer. Am J Clin Oncol 24(2):107–112
15. Dossa F, Acuna SA, Rickles AS, et al. (2018) Association between adjuvant chemotherapy and overall survival in patients with rectal cancer and pathological complete response after neoadjuvant chemoradiation. JAMA Oncol 4(7):930–937
16. Garcia-Albeniz X, Gallego R, Hofheinz RD, et al. (2014) Adjuvant therapy sparing in rectal cancer achieving complete response after chemoradiation. World J Gastroenterol 20(42):15820–15829
17. Lim YJ, Kim Y, Kong M (2019) Adjuvant chemotherapy in rectal cancer patients who achieved a pathological complete response after preoperative chemoradiation: a systematic review and meta-analysis. Sci Rep 9(1):10008
18. Valentin-V, van Stiphout RG, Lammering G, et al. (2011) Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials. J Clin Oncol 29(23):3163–3172

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.