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ORIGINAL ARTICLE

Analysis of delay in adjuvant chemotherapy in locally advanced rectal cancer

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Abstract

Background Adjuvant chemotherapy (AC) after neoadjuvant chemoradiation and surgical resection has been the standard of care for locally advanced rectal cancer. However, there are no evidence-based guidelines regarding the optimal timing of AC for rectal cancer. The objective of this study was to evaluate the effect of AC timing on overall survival for rectal cancer.

Methods The National Cancer Database (NCDB) from 2004 to 2016 was queried for primary clinical stage II or III rectal cancer patients who had undergone neoadjuvant chemoradiation followed by surgery and AC. Patients were grouped based on AC initiation: early ≤ 4 weeks, intermediate 4–8 weeks, and delayed ≥ 8 weeks. The primary outcome was overall survival.

Results We identified 8722 patients, of which 905 (10.4%) received early AC, 4621 (53.0%) intermediate AC, and 3196 (36.6%) delayed AC. Pathological lymph-node metastasis (ypN +) was positive in 73% of early AC, 74% intermediate AC, and 63% delayed AC ($p < 0.05$). The 5-year survival probability was 71.1% (95% CI 68–74%) for early AC, 73.2% (95% CI 72–75%) intermediate AC, and 65.8% (95% CI 64–68%) delayed AC ($p < 0.001$). Using Cox proportional hazard modeling, patients undergoing delayed AC had an associated decreased survival compared to patients receiving early AC (HR 1.18; 95% CI 1.028–1.353, $p = 0.018$) or intermediate AC (HR 1.28; 95% CI 1.179–1.395, $p < 0.01$).

Conclusions Delay in AC administration may be associated with decreased 5-year survival. Compared to early or intermediate AC, patients in the delayed AC group were observed to have increased risk of death, despite having lower proportions with ypN + disease. Patients with higher socioeconomic and education status were more likely to receive early chemotherapy.

Keywords Locally advanced rectal cancer · Adjuvant chemotherapy

Introduction

An estimated 43,340 rectal cancer cases are diagnosed annually with 53,520 colorectal cancer deaths each year [1]. The National Comprehensive Cancer Network (NCCN) guidelines [2] recommend two options in the treatment of locally advanced rectal cancer: (1) neoadjuvant chemoradiation followed by total mesorectal excision [3–5], or (2) total neoadjuvant therapy, where chemotherapy is given prior to chemoradiation and surgical resection [6, 7]. Despite new data with regard to total neoadjuvant treatment, adjuvant chemotherapy (AC) after chemoradiation and surgery continues to be common in the treatment algorithm for locally advanced (stage II or stage III) rectal cancer [2, 8–11].

However, there are no official guidelines regarding the optimal timing of AC for locally advanced rectal cancer following chemoradiation and surgical resection [2]. General consensus in the surgical and oncology community has led to the practice of beginning AC within 8 weeks following surgery, or as soon as the patient is medically able to undergo AC [12–15]. Whether earlier initiation of AC leads to improved survival is not well known, as there are no large prospective randomized controlled trials evaluating only rectal cancer [16, 17]. All current evidence involves systematic

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reviews of studies containing both colon and rectal cancer patients, which may distort the survival outcomes of rectal cancer patients [13, 14].

Given this lack of data for rectal cancer, the purpose of this study was to examine the effect of AC timing on overall survival in locally advanced rectal cancer in the United States. We hypothesized that earlier administration of AC, following neoadjuvant chemoradiation and definitive surgical resection, may lead to improved survival for non-metastatic locally advanced rectal cancer.

Materials and methods

The National Cancer Database (NCDB) is a national, facility-based, clinical oncology outcomes database established in 1989 as a result of a joint sponsorship by the American College of Surgeons and the American Cancer Society [18]. This database contains hospital registry data collected from more than, 1500 Commission on Cancer accredited facilities, and represents 70% of all newly diagnosed malignancies in the United States each year [18]. Approval for the use of the NCDB was obtained from the Commission on Cancer of the American College of Surgeons and from the institutional review board.

A retrospective review of the NCDB database from 2004 to 2016 was performed to identify patients with a solitary primary clinical stage II or III rectal cancer who had undergone neoadjuvant chemoradiation followed by surgical resection and AC. The years 2004–2016 were chosen for the study as the NCDB began collecting site specific factors in 2004, with data available in participant user files up to 2016. These patients were identified using an International Classification of Disease for Oncology, Third Edition (ICD-O-3) topography code of C19.9 and C20.9. Histological subtypes of rectal cancer based on ICD-O-3 histology coding were included as follows: 8140, 8210, 8260, 8261, 8262, 8263, 8440, 8481, 8560, and 8070. The type of surgical resection performed was queried using Facility Oncology Registry Data Standards (FORDS) codes 30–90.

Once these patients were selected based on inclusion criteria, patients were classified into three groups, which were based on initial timing of AC from the surgical resection date: (1) early AC (≤ 4 weeks), (2) intermediate AC (4–8 weeks), or (3) delayed AC (≥ 8 weeks). Intervals of 4 weeks were chosen based on data available from colon cancer treatment regarding the timing of AC [19]. Patients with stage I or stage IV rectal cancer, more than one primary malignancy, or those with missing timing observations for AC were excluded from the analysis. Comparisons were performed using patients undergoing early AC and patients undergoing intermediate AC separately to a reference group of patients receiving delayed AC after neoadjuvant chemoradiation and surgery.

Demographics collected included age, sex, proximity/distance from patient's residence to hospital, race, insurance type, education level, income, Charlson/Deyo score, and facility type. Education level was defined as percentage of adults who did not graduate from high school in the NCDB dataset. The Charlson/Deyo score was used as a surrogate for co-morbidity status in the NCDB dataset. Clinical outcome variables collected included surgical approach, readmission within 30 days, length of hospital stay (LOS), 30-day mortality, 90-day mortality, vital status, months between diagnosis and last contact/death of the patient, pathological TNM classification, clinical TNM classification, number of lymph nodes examined, and surgical margin status. Pathological lymph-node metastasis was determined by patients in each group with N1 or N2 nodal status. Survival time was calculated in months from date of diagnosis to date of death or the date of last contact provided by the NCDB database.

Descriptive statistics were performed for all variables. A Tukey's studentized *t* test was used to compare continuous variables and Chi-square testing was used to compare categorical variables. Categorical data were reported as percentages, and continuous data were reported as medians with interquartile range or means with standard deviation. The Kaplan–Meier estimate of survival function was used to evaluate the overall survival probability over time. For this estimate, patients in each group that did not have complete or sufficient follow-up data were excluded from the survival analysis. The total number of patients included in the survival analysis was listed below the survival plot, starting at 0 months, with predicted numbers of surviving patients shown in intervals of 25 months. The Cox proportional hazards model was used to compare hazard ratios (HR) for mortality based on AC timing from surgery, adjusted for the predictor variables (age, sex, race, insurance, education, facility type, Charlson/Deyo score, surgical approach, margins, and positive nodes). Two-tailed *p* values were calculated and reported for all primary comparisons. Statistical significance was noted when $p < 0.05$. All data acquisition and statistical analysis was carried out using the Statistical Analysis System (SAS) software, version 9.4 (SAS Institute, Inc., Cary, NC USA).

Results

Patient demographics

A total of 8722 patients with single primary clinical stage II or III rectal cancer who had undergone neoadjuvant chemoradiation followed by surgical resection and AC were evaluated in the NCDB study period from 2004 to 2016. Nine

hundred and five patients (10.4%) underwent early AC, 4621 patients (53.0%) underwent intermediate AC, and 3196 patients (36.6%) underwent delayed AC. In the delayed AC group, 2000 patients (22.9%) started AC between 8 and 12 weeks after surgery, while 1196 patients (13.7%) underwent AC at 12 weeks or later after surgery. Patients with stage 0, stage I, or stage IV rectal cancer (236,494 patients), more than one primary malignancy (39,772 patients), or those with missing or incomplete observations for AC timing (64,135 patients) were excluded from the analysis.

Demographic data are shown in Table 1. Patients receiving delayed AC were older with a median age of 61 years, compared to patients undergoing early AC (58 years) or patients undergoing intermediate AC (58 years) ($p < 0.001$). The early AC group had significantly higher percentages of Caucasian race (87.2 vs. 82.3%, $p = 0.006$), private insurance (54.7 vs. 45%, $p < 0.001$), income > $63,000 (33.3 vs. 27.6%, $p = 0.006$), and level of education (17.4 vs. 21.0%, $p = 0.0014$), compared to delayed AC. Early AC had a significantly lower Charlson/Deyo score index (0.24 vs. 0.31, $p < 0.05$) compared to delayed AC. There was a trend toward increased treatment at a comprehensive care center in the early AC group (45.6 vs. 43.0%, $p = 0.06$) compared to the delayed AC group.

The intermediate AC group had significantly higher percentages of Caucasian race (86.9 vs. 82.3%, $p < 0.001$), private insurance (57.2 vs. 45%, $p < 0.001$), income > $63,000 (33.4 vs. 27.6%, $p = 0.006$), and education level (16.0 vs. 21.0%, $p = 0.0014$), compared to delayed AC. The intermediate AC group had a lower Charlson/Deyo score (0.27 vs. 0.31, $p < 0.05$) in comparison to delayed AC. Patients in the intermediate AC group were more likely to be treated

Table 1 Patient demographic data by timing of adjuvant chemotherapy (AC)

Characteristic	≥8 weeks* ($n = 3196$)	≤4 weeks ($n = 905$)	*p* Value	4–8 weeks ($n = 4621$)	*p* Value
Age, years, median (IQR)	61 (52, 69)	58 (50, 66)	< 0.001	58 (50, 67)	< 0.001
Male sex, *n* (%)	1865 (58.4)	517 (57.1)	0.51	2630 (56.9)	0.205
Proximity to hospital, miles, mean + SD	22.9 ± 69.4	30 ± 165.8	0.20	23.7 ± 75.7	0.66
Race, *n* (%)			0.006		< 0.001
Caucasian	2630 (82.3)	789 (87.2)		4014 (86.9)	
Black	352 (11)	69 (7.6)		343 (7.4)	
Asian	130 (4.1)	29 (3.2)		172 (3.7)	
Other	84 (2.6)	18 (2)		92 (2)	
Insurance, *n* (%)			< 0.001		< 0.001
Private	1439 (45.0)	495 (54.7)		2644 (57.2)	
Government	1480 (46.3)	320 (35.4)		1705 (36.9)	
Not insured	223 (7)	36 (4)		201 (4.4)	
Unknown	54 (1.7)	54 (6)		71 (1.5)	
Education level**, *n* (%)			0.0014		< 0.001
≥29%	649 (21)	152 (17.4)		718 (16)	
20–28.9%	810 (26.2)	197 (22.5)		1075 (24)	
14–19.9%	711 (23)	215 (24.6)		1081 (24.1)	
< 14%	923 (29.8)	310 (35.5)		1606 (35.9)	
Income, *n* (%)			0.006		< 0.001
< $38,000	630 (19.8)	158 (17.6)		785 (17.1)	
$38,000-$47,999	837 (26.4)	208 (23.1)		1102 (24)	
$48,000-$62,999	832 (26.2)	234 (26)		1172 (25.5)	
> $63,000	878 (27.6)	299 (33.3)		1537 (33.4)	
Facility type, *n* (%)			0.06		< 0.001
Academic/research	1015 (33.1)	241(28.3)		1242 (28.5)	
Comprehensive center	1318 (43)	389 (45.6)		2064 (47.3)	
Community cancer center	384 (12.5)	116 (13.6)		531 (12.2)	
Integrated network program	347 (11.3)	107 (12.5)		525 (12)	
Charlson/deyo score, MEAN (SD)	0.31 (0.63)	0.24 (0.53)	< 0.05	0.27 (0.58)	< 0.05

IQR interquartile range, *SD* standard deviation

* = reference group

** = education level provides percentage of adults who did not graduate from high school

at a comprehensive care center (47.3 vs. 43.0%, $p < 0.001$) compared to delayed AC group. Both early AC (30 vs. 22.9 miles, $p = 0.20$) and intermediate AC groups (23.7 vs. 22.9 miles, $p = 0.66$) had similar proximity to the hospital in comparison to delayed AC.

Patient clinical characteristics and outcomes

Clinical characteristics and outcomes are shown in Table 2. Early AC had a higher rate of reported minimally invasive surgery (17.4 vs. 15.8%, $p = 0.009$) and lower readmission rate (2.1 vs. 6.8%, $p < 0.001$) in comparison to delayed AC. Intermediate AC had a higher rate of reported minimal invasive surgery (20.1 vs. 15.8%, $p = 0.009$), a lower readmission rate (3.6 vs. 6.8%, $p < 0.001$), and a shorter median LOS (5 vs. 6 days, $p < 0.001$) compared to delayed AC.

Staging based on TNM classification for each group is provided in Table 2. After surgical resection, the highest percentage of pathological tumor size in each chemotherapy group was T3 (early AC: 51.2%, intermediate AC: 54.9%, delayed AC: 55.0%). Pathological lymph-node metastasis was significantly higher in patients undergoing early AC (73 vs. 63%, $p < 0.001$) and significantly higher in patients undergoing intermediate AC (74 vs. 63%, $p < 0.001$) compared to patients undergoing delayed AC. Both early and intermediate AC had a lower positive surgical margins rate after surgical resection (early AC: 9.5 vs. 11.2%, $p < 0.001$; intermediate AC: 9.3 vs. 11.2%, $p < 0.001$), in comparison to delayed AC.

Overall survival and survival probabilities

Kaplan–Meier estimates of survival based on timing of AC are shown in Fig. 1. The 5-year survival probability based on Kaplan–Meier estimates are shown in Table 3. The 5-year survival probability was higher in patients receiving early AC at 71.1% (95% CI 68–74%) or in intermediate AC at 73.2% (95% CI 72–75%), compared to delayed AC at 65.8% (95% CI 64–68%) ($p < 0.001$). A Cox proportional hazards model to compare hazard ratios for mortality based on timing of AC was performed in Table 4. Patients who underwent delayed AC had an associated decreased overall survival compared to patients receiving early AC (HR 1.18; 95% CI 1.028–1.353, $p = 0.018$) and intermediate AC (OR 1.28; 95% CI 1.179–1.395, $p < 0.01$).

Discussion

Significant variability in the application of AC exists, as no study has been performed that directly examines chemotherapy timing exclusively for rectal cancer [13, 20, 21]. Our data demonstrate a potential association of early AC initiation < 8 weeks with improved 5-year overall survival for rectal cancer compared to delayed AC ≥ 8 weeks. Our study illustrates the wide range in AC timing, from anywhere from less than 4 weeks to greater than 12 weeks. Finally, we demonstrated that patients with higher socioeconomic status, education background, and Caucasian race comprised a larger proportion of patients who received earlier AC.

In our study, timely initiation of AC was associated with a improved 5-year overall survival probability for locally advanced rectal cancer (early AC: 71.1%, intermediate AC: 73.2%, delayed AC 65.8%). To our knowledge, this study represents the largest retrospective analysis evaluating the association of AC timing and survival in exclusively locally advanced rectal cancer. All of the current evidence involves systematic reviews of retrospective studies consisting of both colon and rectal cancer patients; although similar, colon cancer likely contaminates the true survival outcomes of rectal cancer patients [13, 14]. However, the review of available colorectal cancer data is consistent with our findings. In a meta-analysis reviewing more than 15,000 patients with both colon and rectal cancer, Biagi et al. found that delays in starting chemotherapy resulted in decreased survival [2, 13]. Another meta-analysis by Des Guetz et al. recommended AC should be started within 8 weeks after surgery and led to decreased survival when delayed [2, 14].

Although we identified a potential association of AC initiation with improved survival, it is difficult to account for other confounding factors, such as patient co-morbidities and circumferential resection margin positivity, that also affect survival after rectal cancer treatment. In our study, delayed AC had higher positive surgical margin at 11.2% compared to the early AC (9.5%) and intermediate groups (9.3%), which certainly is a contributing factor in the long-term survival from locally advanced rectal cancer [22, 23]. In addition, patients in our early AC cohort were healthier with less clinical co-morbidities reflected by a lower Charlson/Deyo Score, which potentially contributes to an improved 5-year survival [24]. It is widely known that surgical complications, such as anastomotic leakage, result in worse survival in colorectal cancer treatment [25, 26]. However, it has been argued that the decrease in survival seen with anastomotic leak is secondary to the delays in AC. Unfortunately, the NCDB dataset did not provide data on anastomotic leakage complications, precluding us from analyzing a major risk factor influencing rectal cancer survival.

Our data also demonstrate that despite patients receiving delayed AC having a lower proportion of positive lymph-node status (early AC: 73%, intermediate AC: 74%, delayed AC: 63%), their associated risk of death was nevertheless higher compared to patients that underwent earlier AC. It is possible that timely administration of AC < 8 weeks was associated with improved overall survival due to inherent tumor physiology. Chemotherapy is favorable in cancer

Table 2 Patient clinical characteristics/outcomes by timing of adjuvant chemotherapy (AC)

Characteristic	≥8 weeks* ($n=3196$)	≤4 weeks ($n=905$)	p Value	4–8 weeks ($n=4621$)	p Value
Surgical approach, *n* (%)			0.009		< 0.001
Open	911 (28.5)	208 (23)		1246 (27)	
Laparoscopic	376 (11.8)	122 (13.5)		717 (15.5)	
Robotic	127 (4)	35 (3.9)		212 (4.6)	
Unknown	1782 (55.8)	540 (59.7)		2446 (52.9)	
Readmission in 30 days, *n* (%)	217 (6.8)	19 (2.1)	< 0.001	165 (3.6)	< 0.001
Hospital LOS, days, median (IQR)	6 (4, 9)	5 (3, 7)	0.10	5 (4, 7)	< 0.001
Months between diagnosis and last contact/death, mean + SD	55.5 ± 36.5	60.1 ± 39.1	0.002	58.4 ± 37.3	< 0.001
Pathological T, *n* (%)			0.037		0.055
T0	27 (0.9)	6 (0.7)		41 (0.9)	
Tis	1 (< 0.1)	1 (< 0.1)		1 (< 0.1)	
T1	84 (2.7)	25 (2.8)		127 (2.8)	
T2	234 (7.4)	75 (8.4)		417 (9.2)	
T3	1732 (55)	457 (51.2)		2502 (54.9)	
T4	409 (12.9)	98 (11)		506 (1.1)	
TX	736 (21)	230 (25.8)		964 (21.2)	
Pathological N, *n* (%)			< 0.001		< 0.001
N0	922 (29.3)	179 (20.1)		932 (20.5)	
N1	930 (29.6)	286 (32.1)		1574 (34.6)	
N2	633 (20.1)	191 (21.4)		1086 (23.9)	
NX	661 (21)	235 (26.4)		962 (21.1)	
Clinical T, *n* (%)			0.34		0.046
T0	2 (0.06)	0 (0)		5 (0.06)	
Tis	2 (0.06)	0 (0)		1 (0.02)	
T1	117 (3.7)	40 (4.5)		195 (4.2)	
T2	272 (8.5)	89 (9.9)		449 (9.7)	
T3	2193 (68.6)	607 (67.8)		3208 (69.4)	
T4	416 (13)	104 (11.6)		513 (11.1)	
TX	162 (5.1)	56 (6.3)		210 (4.6)	
Clinical N, *n* (%)			< 0.001		< 0.001
N0	1456 (46)	335 (37.6)		1892 (41.3)	
N1	1111 (35.1)	350 (39.2)		1719 (37.5)	
N2	440 (13.9)	148 (16.6)		772 (16.8)	
NX	162 (5.1)	59 (6.6)		203 (4.4)	
Clinical M, *n* (%)			0.75		0.39
M0	3089 (99.5)	872 (99.4)		4490 (99.6)	
M1	15 (0.5)	5 (0.6)		16 (0.4)	
Nodes examined, *n* (%)			0.004		0.96
0	60 (1.9)	35 (3.9)		88 (1.9)	
1–6	124 (3.9)	37 (4.1)		171 (3.7)	
6–12	439 (13.7)	129 (14.3)		627 (13.6)	
12–90	2543 (79.6)	693 (76.6)		3702 (80.1)	
Unknown	30 (0.9)	11 (1.2)		33 (0.7)	
Margins, *n* (%)			< 0.001		0.0035
Positive	358 (11.2)	86 (9.5)		431 (9.3)	
Negative	2762 (86.4)	749 (82.8)		4108 (88.9)	
Unknown	76 (2.4)	70 (7.7)		82 (1.8)	

IQR interquartile range, *SD* standard deviation, *LOS* length of stay

* = reference group

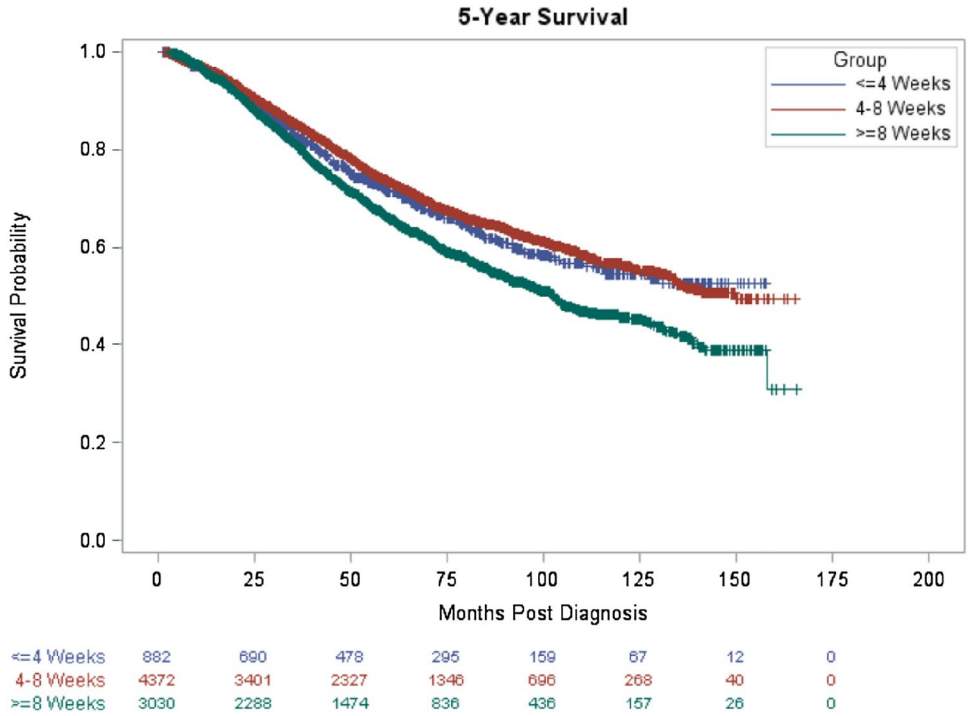

Fig.1 Kaplan–Meier estimates of survival by timing of adjuvant chemotherapy

Table 3 Kaplan–Meier estimates of 5-year overall survival (probability) by timing of adjuvant chemotherapy (AC)

Timing of adjuvant chemotherapy	Survival probability (95% confidence interval)
≤4 weeks	0.711 (0.68–0.74)
4–8 weeks	0.732 (0.72–0.75)
≥8 weeks	0.658 (0.64–0.68)

Table 4 Cox proportional hazard model* for risk of mortality based on timing of adjuvant chemotherapy (AC) compared to delayed chemotherapy

Timing of adjuvant chemotherapy	Hazard ratio	95% confidence interval	*p* value
≤4 weeks	1.18	1.028–1.353	0.0184
4–8 weeks	1.28	1.179–1.359	<0.01

*Controlled for age, sex, race, insurance, education, facility type, Charlson/Deyo score, surgical approach, margins, and positive nodes

treatment as AC eradicates residual micrometastatic tumor cells left behind from surgery [27]. Although surgery is necessary for gross tumor removal, the trauma of surgery can contribute to the release of cancer cells into systemic circulation [28, 29]. Surgery is also thought to remove angiogenesis inhibitors and increase inflammatory oncogenic growth factors, both of which enable increased residual micrometastatic tumor progression to distant locations [13, 28, 30]. As shown in a study on tumor evolution, 65% of distant metastases were clonally different from the nodal metastasis [31], suggesting that distant metastasis plays an important role in overall survival.

Substantial inconsistency exists in the timing and need for chemotherapy after surgery in locally advanced rectal cancer [2]. Scientific literature is contentious on whether AC is even effective in locally advanced rectal cancer, as long-term results from EORTC 22921 randomized study demonstrated AC did not affect overall survival in rectal cancer [32]. In fact, clinicians in some European countries have questioned the need for AC and have employed more individualized approaches for rectal cancer treatment [33]. Our results reflect this time variability, as we found that 10.4% of patients underwent early AC at ≤4 weeks, 53% underwent intermediate AC between 4 and 8 weeks, while 36.6% underwent delayed AC at ≥8 weeks. Although guidelines suggest that AC should begin as soon as the patient is medically able, multiple studies looking at colorectal patients have found that patients are undergoing deferral of AC. In a retrospective study using SEER/Medicare database, Cheung et al. found that 26% of patients received AC after 2 months [15]. In another retrospective study, dos Santos et al. found that nearly 56% of patients underwent AC after 8 weeks [34]. Some of the contributing factors that led to AC starting after 8 weeks were a patient's demographics and clinical condition after surgery, including age, socioeconomics, and post-operative surgical complications [15, 35]. While we did not have information on surgical complication rates, we observed that patients undergoing minimally invasive

surgery with shorter hospital stays were also likely to obtain earlier AC. A significant proportion of patients in our study (36.6%) experienced AC at 8 weeks or later [13, 14]. These patients who received chemotherapy after 8 weeks may have experienced post-operative complications that delayed chemotherapy; however, according to Wasserman et al., the majority of patients do not have a clinical reason to justify delays in AC [36].

Racial and socioeconomic disparities are well known to exist in the treatment of cancer patients of any etiology [38–40]. In particular, colorectal cancer adheres to this variation in clinical outcomes with respect to a patient's race and socioeconomic status, with patients of black race background and lower socioeconomic status having a higher cancer-related mortality rate [39, 40]. Our data demonstrated that patients in both the early and intermediate AC groups had significantly higher proportions of Caucasian patients as well as patients with higher incomes, education status, and access to private insurance. The improved survival and mortality in these groups are possible, because patients with higher socioeconomic background have more access to healthcare [38–40]. In particular, patients in the earlier and intermediate administration of AC groups had higher rates of private insurance and were more commonly insured in general, which has been demonstrated as a contributing factor in the receipt of AC for patients with colon cancer [41]. In addition, we found that patients in the intermediate AC group had more patients undergoing treatment at a comprehensive cancer center, compared to patients in the delayed AC group. With comprehensive cancer centers being associated with improved outcomes, this reflects the racial and socioeconomic status of these patient groups, with more access to healthcare available to those of higher socioeconomic background [38, 42].

This study should be considered with certain limitations in mind. Due to the retrospective design of our study, inherent biases exist within the database, including selection bias and reporting bias. Like all large national database studies that rely on accurate documentation, coding errors may have potentially altered the precision of the data. A limited amount of demographic and clinical characteristics was available in the NCDB database, which did not allow for complete comparisons between the study groups and limited adjustments for the Cox proportional hazard modeling. Disease recurrence was not captured within the NCDB database, which did not allow for evaluation of disease-free survival. The NCDB database also does not capture the adherence or completion of neoadjuvant and adjuvant therapies; therefore, it is unknown if patients completed the full course of documented therapy. This likely resulted in a selection bias, as patients that experienced post-operative complications, and therefore, received delayed AC may have been inherently at higher risk of morbidity and mortality.

Conclusions

The delay in the administration of AC in locally advanced rectal cancer was potentially associated with a decreased 5-year overall survival compared to patients who received earlier AC, although limitations exist. We also observed that patients in the delayed AC group had an increased risk of death, despite a lower proportion with ypN + disease. Therefore, timely administration of AC < 8 weeks may be helpful in the treatment of locally advanced rectal cancer.

Author contributions Farzaneh and Jafari had full access to all of the data in the study and take full responsibility for the integrity of the data and accuracy of the data analysis. Concept and design: Farzaneh, Pigazzi, and Jafari. Acquisition, analysis, or interpretation of data: Farzaneh, Pigazzi, and Jafari. Drafting of the manuscript: Farzaneh. Critical revision of the manuscript: all authors. Statistical analysis: Farzaneh and Dehkordi-Vakil. Administrative, technical, or material support: Farzaneh, Duong, and Jafari. Supervision: Pigazzi and Jafari.

Declarations

Conflict of interest This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors report no conflicts of interest, financial, or otherwise.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study, formal consent is not required.

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