



Patterns of care and outcomes for adjuvant treatment of pT3N0 rectal cancer using the National Cancer Database

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Background: The standard of care in locally advanced rectal cancer is preoperative chemoradiation followed by surgical resection. However, the optimal treatment paradigm is currently controversial for patients with pathological T3N0 (pT3N0) in the era of total mesorectal excision (TME). Given the paucity of data, we conducted an analysis using the National Cancer Database (NCDB) to identify patterns of care and outcomes.

Methods: We utilized the NCDB to identify 7,836 non-metastatic, pT3N0 rectal cancer patients who did not receive neoadjuvant therapy from 2004–2014. Univariate and multivariable analysis for factors affecting treatment selection were completed using logistic regression. Overall survival (OS) analyses were completed using Cox regression modeling, incorporating propensity scores with inverse probability of treatment weighting (IPTW) and conditional landmark analysis.

Results: There was a significant improvement in OS in patients receiving adjuvant chemotherapy ($P < 0.01$) or radiotherapy (RT) with chemotherapy ($P < 0.01$) *vs.* observation alone. There was no significant difference between RT *vs.* observation ($P = 0.54$) and chemotherapy *vs.* chemotherapy with RT cohorts ($P = 0.15$). Multivariable analysis showed age, gender, race, insurance status, income, Charlson-Deyo Comorbidity Condition (CDCC) score, facility location, grade, surgical margin, RT, and chemotherapy to be statistically significant predictors of OS. After correcting for indication and immortal time biases, chemotherapy, with or without RT, improved OS compared with observation [hazard ratio (HR) 0.48, $P < 0.001$]. This benefit was maintained in the margin negative cohort.

Conclusions: Practice patterns vary in the management of pT3N0 rectal cancer patients. This analysis suggests that the use of adjuvant therapy, particularly adjuvant chemotherapy with or without RT, appears to improve OS.

Keywords: Rectal neoplasms; chemoradiotherapy; chemotherapy; adjuvant; propensity score; cohort studies

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Introduction

Colorectal cancer (CRC) is the 3rd most common cause of cancer in the United States (US), with incidence of 135,430 cases in 2017, of which 39,910 are rectal cancers (1). Furthermore, CRC is the 2nd and 3rd leading cause of death in males and females, respectively. While the overall incidence in CRC in the US is declining, there has been a notable increase in incidence among young adults since the 1980s (2). Currently, the standard of care treatment for locally advanced rectal cancer is neoadjuvant chemoradiation therapy followed by surgery. However, in the era of improved preoperative imaging and total mesorectal excision (TME), the management of clinical and pathological concordant T3N0 remains controversial.

In the US, patients presenting with clinical T3N0 rectal cancer are often treated with neoadjuvant chemoradiation therapy followed by surgery. Indeed, neoadjuvant chemoradiation therapy was shown to be better tolerated, increase local control, allow for tumor downstaging and improve likelihood of sphincter-preserving therapy in the seminal German Rectal Study comparing neoadjuvant to adjuvant chemoradiation therapy in locally advanced rectal cancer (3,4). Furthermore, the Dutch Colorectal Cancer Group (Dutch CKVO 9504) conducted a trial in which short course neoadjuvant radiation therapy was compared with TME alone in patients with resectable rectal cancer, and similarly, an improvement in local control was found without any difference in overall survival (OS) (5-7). However, there is a concern that neoadjuvant therapy may overtreat patients at lower risk of recurrence with unnecessary late toxicity.

Patients with T3N0 rectal cancer have an excellent prognosis with 5-year OS 74–84%, disease free survival (DFS) 63–75%, local recurrence (LR) 5–11%, and distant relapse 13–20% (8). Therefore, there might be a subgroup of patients with T3N0 disease who might not benefit from radiation therapy, especially in the TME era. There have been a number of retrospective series that report rates of LR of 2.7–9% among T3N0 patients undergoing TME (9-12).

However, identifying patients with true T3N0 presents a unique challenge as there are high rates of discordance between clinical and pathologic staging. Indeed, Guillem *et al.* published a retrospective review of 188 endorectal ultrasound/MRI staged T3N0 patients treated with neoadjuvant chemoradiation therapy followed by TME and found, despite combined modality therapy, 22% of patients had nodal positive disease (13). In another

study by Lombardi *et al.* the rate of nodal positivity after neoadjuvant chemoradiation therapy in patients with clinical T3N0 disease was 28% (14). Similarly, in the German Rectal Study, only 25% of pre-operative group had positive nodal disease in comparison to 40% in the post-operative group. However, in the German Rectal Study, 18% of postoperative patients were over-staged and were considered not eligible for any adjuvant therapy following surgical resection.

Nevertheless, for those patients who receive upfront surgery with TME and are found to have pT3N0 disease, the optimal adjuvant treatment regimen remains to be described. There are no prospective randomized controlled studies that address this cohort of patients. Therefore, given the paucity of data available, we conducted this retrospective observational study utilizing the National Cancer Database (NCDB) for rectal cancer treated between 2004 and 2014 to determine patterns of care and outcomes for pT3N0 patients.

Methods

Data source

The NCDB is an oncological database that captures incident cancer data from >1,500 Commission on Cancer (COC)-accredited facilities nationwide. The database includes >70% of newly diagnosed cancer cases and captures a number of variables, including: demographics, tumor staging, course of treatment. Moreover, all patient information in the NCDB is de-identified. Therefore, this study was exempt from institutional review board evaluation.

Statistics

A total of 221,886 patients were identified from the NCDB with an International Classification of Disease for Oncology, 3rd Edition (ICD-O-3) site code of C209, corresponding to rectal cancer (*Figure 1*). We first identified the cohort who underwent surgery for their rectal cancer (N=168,707). Next, we included cases in which no neoadjuvant therapy was administered (N=75,217). Finally, we selected patients with non-metastatic and pT3N0 disease, which comprised the final target population of interest (N=7,836). Using this cohort of patients, we then determined the proportion of patients who received no additional treatment (N=4,114) and any adjuvant therapy (N=3,466), with the remaining

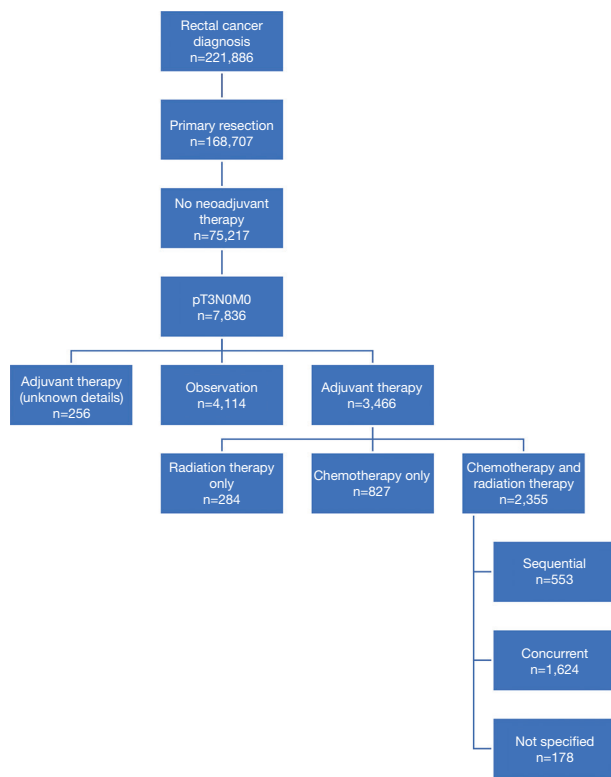


Figure 1 Consolidated Standards of Reporting (CONSORT) diagram depicting the selection criteria used to identify non-metastatic, pT3N0M0 rectal cancer treated with upfront surgery.

with unreported details excluded from further analysis (N=256). Among the adjuvant therapy subgroup, we further stratified based on chemotherapy alone (N=827), radiation alone (N=284) and chemotherapy and RT (N=2,355) (*Figure 2A*). In order to better describe the adjuvant chemotherapy and RT subgroup, we defined concurrent chemoRT (N=1,624) as chemotherapy starting within the median RT treatment time (40 days), with sequential chemotherapy and RT (N=553) or unknown (N=178) for treatment not meeting this definition (*Figure 2B*).

The NCDB contains information on OS only. Therefore, all end points in this study relate to impact on OS. Univariate analysis of patient characteristics and OS was performed using the Kaplan-Meier method, with the log rank method (Mantel-Cox) to assess for significance. Factors included in the analysis are listed in *Table 1*.

Characteristics associated with OS were evaluated in univariate fashion using log-rank testing. Based upon the sample size as a means to reduce under-capturing influential factors, statistically significant or near-significant ($P < 0.10$)

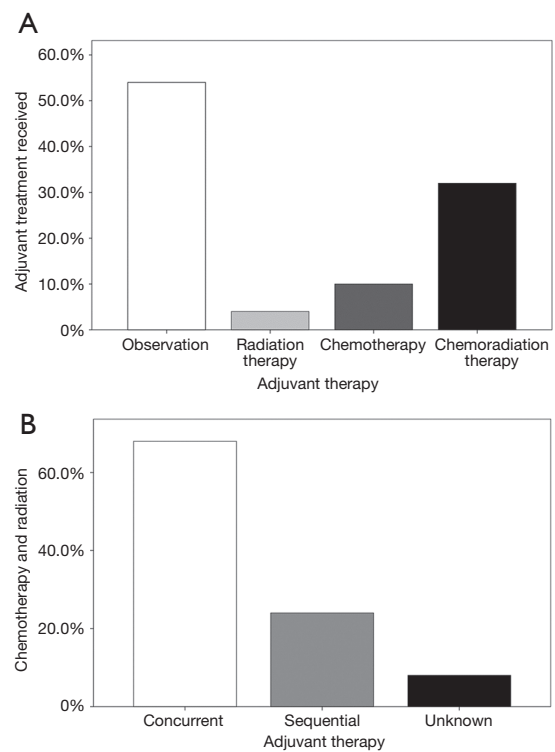


Figure 2 Bar graphs depicting the treatment strategies used in the adjuvant setting for non-metastatic, pT3N0M0 (A) and the specific combination of chemotherapy and radiation therapy (B).

were incorporated in Multivariable Cox proportional hazards regression modeling using backward stepwise methodology. Cases with missing data were excluded from regression analyses. The receipt of adjuvant therapy, compared to observation, introduces an inherent bias by virtue of the fact that patients must live a certain period of time following primary therapy in order to receive adjuvant therapy. Therefore, to mitigate the risk of immortal time bias, a conditional landmark analysis was thereafter conducted using a cutoff of 3 months or more of follow-up.

To better account for selection bias, propensity scores were calculated for various treatment arm utilization (15,16). Scores were validated through measurement of absolute standardized differences between arms (< 0.10) within designated equally distributed quintiles (17-19). Inverse probability of treatment weighting (IPTW) was then used to better estimate the effect of radiation therapy utilization, entering this as a covariate in the final regression model (20). Sensitivity analyses were conducted on the final Cox model within each propensity score quintile, verifying the findings below (21).

Table 1 Baseline characteristics after exclusion of those without known adjuvant therapy details (n=7,580)

Characteristics	Observation (N=4,114)	RT (N=284)	Chemotherapy (N=827)	Chemotherapy/RT (N=2,355)
Age, years (median, IQ range)	75 [64–82]	73 [60–81]	62 [53–72]	63 [54–71]
Gender [n (%)]				
Male	2,397 (58.3)	166 (58.5)	503 (60.8)	1,441 (61.2)
Female	1,717 (41.7)	118 (41.5)	324 (39.2)	914 (38.8)
Race [n (%)]				
Caucasian	3,606 (87.7)	246 (86.6)	703 (85.0)	1,998 (84.8)
African American	330 (8.0)	24 (8.5)	72 (8.7)	245 (10.4)
Other	138 (3.4)	13 (4.6)	43 (5.2)	93 (3.9)
Unknown	40 (1.0)	1 (0.4)	9 (1.1)	19 (0.8)
Ethnicity [n (%)]				
Non-Hispanic	3,622 (88.0)	248 (87.3)	704 (85.1)	2,048 (87.0)
Hispanic	221 (5.4)	20 (7.0)	61 (7.4)	139 (5.9)
Unknown	271 (6.6)	16 (5.6)	62 (7.5)	168 (7.1)
Insurance status [n (%)]				
Uninsured	99 (2.4)	8 (2.8)	36 (4.4)	112 (4.8)
Private	1,080 (26.3)	73 (25.7)	388 (46.9)	1,096 (46.5)
Medicare/Medicaid/Other Govt.	2,877 (69.9)	199 (70.1)	389 (47.0)	1,116 (47.4)
Unknown	58 (1.4)	4 (1.4)	14 (1.7)	31 (1.3)
Median income quartile [n (%)]				
<\$38,000	746 (18.1)	55 (19.4)	133 (16.1)	452 (19.2)
\$38,000–47,999	1,030 (25.0)	72 (25.4)	207 (25.0)	613 (26.0)
\$48,000–62,999	1,098 (26.7)	79 (27.8)	220 (26.6)	624 (26.5)
>\$63,000	1,168 (28.4)	73 (25.7)	258 (31.2)	639 (27.1)
Unknown	72 (1.8)	5 (1.8)	9 (1.1)	27 (1.1)
Educational quartile [n (%)]				
≥21%	727 (17.7)	58 (20.4)	157 (19.0)	469 (19.9)
13–20.9%	1,139 (27.7)	83 (29.2)	215 (26.0)	662 (28.1)
7–12.9%	1,283 (31.2)	89 (31.3)	268 (32.4)	753 (32.0)
<7%	896 (21.8)	49 (17.3)	178 (21.5)	446 (18.9)
Unknown	69 (1.7)	5 (1.8)	9 (1.1)	25 (1.1)
CDCC score [n (%)]				
0	2,759 (67.1)	197 (69.4)	609 (73.6)	1,844 (78.3)
1	954 (23.2)	59 (20.8)	179 (21.6)	423 (18.0)
2+	401 (9.7)	28 (9.9)	39 (4.7)	88 (3.7)

Table 1 (continued)

Table 1 (continued)

Characteristics	Observation (N=4,114)	RT (N=284)	Chemotherapy (N=827)	Chemotherapy/RT (N=2,355)
Distance from facility [n (%)]				
≤10 miles	2,098 (51.0)	161 (56.7)	402 (48.6)	1,266 (53.8)
>10 miles	1,867 (45.4)	110 (38.7)	390 (47.2)	1,005 (42.7)
Unknown	149 (3.6)	13 (4.6)	35 (4.2)	84 (3.6)
Facility type [n (%)]				
Community	447 (10.9)	46 (16.2)	84 (10.2)	341 (14.5)
Comprehensive community	2,047 (49.8)	151 (53.2)	368 (44.5)	1,218 (51.7)
Academic/research	1,225 (29.8)	63 (22.2)	273 (33.0)	565 (24.0)
Integrated network	342 (8.3)	19 (6.7)	66 (8.0)	155 (6.6)
Other	4 (0.1)	1 (0.4)	0 (0.0)	4 (0.2)
Unknown	49 (1.2)	4 (1.4)	36 (4.4)	72 (3.1)
Facility location [n (%)]				
Northeast	786 (19.1)	48 (16.9)	168 (20.3)	418 (17.7)
Mid/South Atlantic	853 (20.7)	56 (19.7)	170 (20.6)	469 (19.9)
East/North/Central	767 (18.6)	59 (20.8)	148 (17.9)	445 (18.9)
Midwest	949 (23.1)	62 (21.8)	187 (22.6)	583 (24.8)
Mountain/Pacific	710 (17.3)	55 (19.4)	118 (14.3)	368 (15.6)
Unknown	49 (1.2)	4 (1.4)	36 (4.4)	72 (3.1)
Facility setting [n (%)]				
Metropolitan	3,260 (79.2)	229 (80.6)	686 (83.0)	1,832 (77.8)
Urban	624 (15.2)	42 (14.8)	109 (13.2)	414 (17.6)
Rural	97 (2.4)	2 (0.7)	11 (1.3)	43 (1.8)
Unknown	133 (3.2)	11 (3.9)	21 (2.5)	66 (2.8)
Year of diagnosis [n (%)]				
2006–2009	2,142 (52.1)	179 (63.0)	426 (51.5)	1,398 (59.4)
2010–2013	1,972 (47.9)	105 (37.0)	401 (48.5)	957 (40.6)
Grade [n (%)]				
Well differentiated	334 (8.1)	30 (10.6)	61 (7.4)	195 (8.3)
Moderately differentiated	3,173 (77.1)	197 (69.4)	618 (74.7)	1,734 (73.6)
Poorly/undifferentiated	499 (12.1)	46 (16.2)	110 (13.3)	303 (12.9)
Unknown	108 (2.6)	11 (3.9)	38 (4.6)	123 (5.2)
LVSI [n (%)]				
Absent	1,516 (36.8)	75 (26.4)	283 (34.2)	680 (28.9)
Present	279 (6.8)	14 (4.9)	67 (8.1)	155 (6.6)
Unknown	2,319 (56.4)	195 (68.7)	477 (57.7)	1,520 (64.5)

Table 1 (continued)

Table 1 (continued)

Characteristics	Observation (N=4,114)	RT (N=284)	Chemotherapy (N=827)	Chemotherapy/RT (N=2,355)
Tumor size [n (%)]				
≤5 cm	2,520 (61.3)	161 (56.7)	537 (64.9)	1,375 (58.4)
>5 cm	1,594 (38.7)	123 (43.3)	290 (35.1)	980 (41.6)
LN dissection [n (%)]				
No	162 (3.9)	48 (16.9)	45 (5.4)	262 (11.1)
Yes	3,952 (96.1)	236 (83.1)	782 (94.6)	2,093 (88.9)
Margin status [n (%)]				
Negative	3,801 (92.4)	214 (75.4)	725 (87.7)	1,917 (81.4)
Positive	230 (5.6)	38 (13.4)	68 (8.2)	227 (9.6)

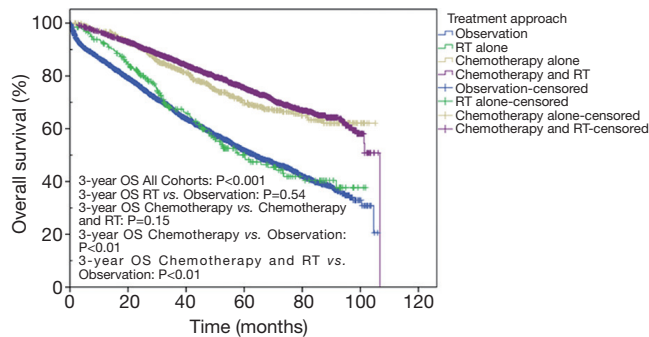


Figure 3 Kaplan Meier overall survival curve for pT3N0 patients treated with observation, RT alone, chemotherapy alone or chemotherapy with RT.

Results

Patient and treatment characteristics

Baseline characteristics of the patients included in this study are shown in *Table 1*. Of the 7,580 patients with nonmetastatic, pT3N0 rectal cancer who did not receive neoadjuvant therapy and had known adjuvant therapy, there was a nearly equal proportion of patients who went on to observation (54.3%) and adjuvant therapy (45.7%). Of those patients receiving adjuvant therapy, 8.2% received RT alone, 23.9% received chemotherapy alone, and 67.9% received chemotherapy and RT (*Figure 2A*). Of note, chemotherapy and RT were delivered concurrently in 69.0% of patients (*Figure 2B*). The median time from diagnosis to initiation of treatment was 84 days (IQ 55–126 days). Among the patients receiving radiation therapy, the median dose was 50.4 Gy (IQ 45–50.4 Gy) and the median elapsed

days for RT was 40 days (IQ 38–45 days).

Treatment outcomes

With a median follow-up of 38.6 months, the mean unadjusted OS was 61.9, 62.5, 81.0 and 83.4 months for observation, RT, chemotherapy and chemotherapy with RT. The 3-year unadjusted OS was 66.7%, 67.4%, 83.3%, and 86.0% for observation, RT alone, chemotherapy alone and chemotherapy with RT, respectively ($P<0.001$) (*Figure 3*). Moreover, there was no difference in 3-year unadjusted OS between observation and RT alone ($P=0.54$) or chemotherapy alone and chemotherapy with RT ($P=0.15$). There was a significant improvement in OS in patients that received adjuvant chemotherapy ($P<0.01$) or RT with chemotherapy ($P<0.01$) when compared to observation alone.

Univariate analysis

The complete list of factors evaluated by univariate analysis are shown in *Table 2*. Demographic variables that had a significant impact on OS include: age, sex, race, insurance status, median income, distance from facility, facility type, and facility location. Patient specific variables that impacted OS include: CDCC score, histologic grade, primary tumor size, lymph node dissection and margin status. Treatment variables that significantly impacted OS include: treatment approach, receipt of RT, receipt of chemotherapy, and timing of chemotherapy in relation to RT. Ethnicity, education level, metropolitan or urban setting, year of diagnosis, and the presence of LVSI were not statistically

Table 2 Factors associated with survival on univariate analysis

Variables	P value	Mean overall survival months (95% CI)
Age	<0.0001	
≤70		84.6 (83.3–86.0)
>70		56.2 (54.6–57.7)
Gender	0.013	
Male		70.6 (69.2–72.1)
Female		72.8 (71.1–74.5)
Race	0.001	
Caucasian		71.2 (70.0–72.4)
African American		69.4 (65.9–72.9)
Other		82.1 (77.1–87.0)
Ethnicity	0.117	
Non-Hispanic		71.5 (70.3–72.7)
Hispanic		73.5 (69.3–77.7)
Insurance status	<0.0001	
Uninsured		79.8 (74.0–85.6)
Private		84.1 (82.5–85.6)
Medicare/Medicaid/other Govt.		63.3 (61.9–64.8)
Median income quartile	<0.0001	
<\$38,000		67.7 (65.1–70.3)
\$38,000–47,999		69.1 (67.0–71.2)
\$48,000–62,999		73.2 (71.2–75.3)
>\$63,000		75.1 (73.1–77.1)
Educational quartile	0.173	
≥21%		69.8 (67.3–72.2)
13–20.9%		71.5 (69.5–73.6)
7–12.9%		72.6 (70.6–74.5)
<7%		72.5 (70.2–74.7)
CDCC score	<0.0001	
0		75.6 (74.3–76.9)
1		66.1 (63.7–68.5)
2+		49.0 (45.4–52.7)
Distance from facility	0.001	
≤10 miles		70.5 (69.0–72.0)
>10 miles		73.7 (72.0–75.3)

Table 2 (continued)

Table 2 (continued)

Variables	P value	Mean overall survival months (95% CI)
Facility type	<0.0001	
Community		66.0 (62.9–69.1)
Comprehensive community		70.0 (68.4–71.6)
Academic/research		73.6 (71.6–75.7)
Integrated network		72.5 (68.7–76.4)
Other		80.3 (64.7–95.9)
Facility location	0.023	
Northeast		67.1 (64.6–69.6)
Mid/South Atlantic		71.4 (69.0–73.8)
East/North/Central		70.3 (67.8–72.8)
Midwest		69.9 (67.8–72.0)
Mountain/Pacific		73.3 (70.8–75.8)
Facility setting	0.105	
Metropolitan		71.6 (70.3–72.8)
Urban		73.4 (70.7–76.0)
Rural		61.0 (54.8–67.2)
Year of diagnosis	0.076	
2006–2009		71.0 (69.7–72.3)
2010–2013		48.1 (47.2–49.2)
Grade	<0.0001	
Well differentiated		71.5 (67.8–75.2)
Moderately differentiated		72.6 (71.3–73.9)
Poorly/undifferentiated		66.1 (63.0–69.2)
LVSI	0.204	
Absent		48.6 (47.5–49.8)
Present		45.8 (43.7–47.9)
Tumor size	0.006	
≤5 cm		72.5 (71.1–73.9)
>5 cm		69.8 (68.1–71.6)
LN dissection	<0.0001	
No		60.3 (56.5–64.2)
Yes		72.4 (71.2–73.6)
Margin status	<0.0001	
Negative		73.4 (72.2–74.6)
Positive		56.4 (52.6–60.2)

Table 2 (continued)

Table 2 (continued)

Variables	P value	Mean overall survival months (95% CI)
Treatment	<0.0001	
Observation		61.9 (60.3–63.5)
Radiation therapy		62.5 (57.4–67.5)
Chemotherapy		81.0 (78.0–84.1)
Chemoradiation therapy		83.4 (81.6–85.2)
Receipt of RT	<0.0001	
No		65.8 (64.4–67.2)
Yes		81.4 (79.7–83.0)
Receipt of chemotherapy	<0.0001	
No		62.1 (60.6–63.6)
Yes		82.9 (81.4–84.5)
Timing of chemotherapy	<0.0001	
Sequential		89.0 (85.8–92.2)
Concurrent		81.3 (79.1–83.5)

CI, confidence interval; CDCC, Charlson/Deyo comorbidity condition; Govt, government; Mid, middle; LVSI, lymphovascular space invasion; LN, lymph node; RT, radiation therapy.

significant.

Multivariable analysis

The results of multivariable cox regression analysis, with a 3-month conditional landmark, are shown in *Table 3*. Demographic variables that impacted OS were: age >70 [HR 2.05 (1.82–2.31), $P<0.0001$], female sex [HR 0.87 (0.79–0.96), being uninsured (reference, $P<0.0001$), higher median income: 3rd quartile [HR 0.78 (0.68–0.90), $P=0.001$] or 4th quartile [HR 0.76 (0.66–0.88) $P<0.0001$], and facility location: NE (reference, $P=0.02$). Mid/South Atlantic [HR 0.84 (0.72–0.98), $P=0.027$] or Mountain/Pacific [HR 0.81 (0.69–0.96) $P=0.013$]. Interestingly, race, distance from facility, facility type and year of diagnosis, did not impact OS in the final model.

Patient specific variables with significant impact on OS include: CDCC score: 1 [HR 1.27 (1.13–1.42) $P<0.0001$] or 2+ [HR 1.84 (1.58–2.14) $P<0.0001$], well-differentiated tumors (reference, $P=0.004$), and positive surgical margins [HR 1.95 (1.67–2.28) $P<0.0001$]. Finally, type of therapy received also impacted OS: chemotherapy alone [HR 0.74

(0.62–0.89) $P=0.001$] or chemotherapy and RT [HR 0.57 (0.50–0.65) $P<0.0001$]. Moreover, tumor size and receipt of lymph node dissection did not impact OS.

In addition, separate multivariable cox regression analyses were performed on the subset of patients that had negative surgical margins ($N=5,069$) and positive surgical margins ($N=415$). In the margin negative subset, RT alone did not impact OS [HR 0.89 (0.70–1.14) $P=0.361$]; however, chemotherapy alone [HR 0.74 (0.61–0.89) $P=0.002$] and chemotherapy with RT [HR 0.59 (0.52–0.68) $P<0.0001$] still had improved OS. Moreover, in the margin positive subset, only chemotherapy with RT [HR 0.44 (0.31–0.63) $P<0.0001$] impacted OS.

Propensity-score adjusted analysis

Propensity scores with IPTW for the receipt of radiation alone or radiation with chemotherapy were generated. A doubly robust cox regression model, adjusted for IPTW, demonstrated that the cohort of patients who received RT (either alone or with chemotherapy) was associated with reduced risk of overall mortality when compared with no RT [HR 0.48 (0.43–0.54) $P<0.0001$]. This benefit was maintained in the margin negative cohort [HR 0.52 (0.46–0.59) $P<0.0001$] and margin positive cohort [HR 0.49 (0.36–0.67) $P<0.0001$]. However, subset analysis revealed no difference in OS when comparing adjuvant chemoradiation therapy with chemotherapy alone [HR 0.91 (0.61–1.4) $P=0.66$]. Similarly, no significant difference in OS was seen among the margin negative cohort [HR 0.86 (0.55–1.3) $P=0.51$] or the margin positive cohort [HR 0.53 (0.16–1.8) $P=0.3$].

Discussion

The management of rectal cancer has evolved significantly over the last 30 years. Currently, the standard of care treatment for patients with clinical Stage II rectal cancer and above, in the US, is neoadjuvant CRT followed by TME based on the German Rectal Study (4). Moreover, the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-03 trial randomized a similar population of patients to neoadjuvant CRT followed by TME or TME followed by adjuvant CRT. Although NSABP R-03 did not complete accrual, at a median follow-up of 8.4 years, there was improved DFS (64.7% vs. 53.4%) and 15% pCR rate, with no recurrence in this subgroup of patients, further supporting a neoadjuvant approach for this cohort of

Table 3 Multivariable Cox regression analysis with a 3-month conditional landmark for inclusion

Variables	P value	Hazard ratio (95% CI)
Age		
≤70	–	–
>70	<0.0001	2.048 (1.816–2.310)
Gender		
Male	–	–
Female	0.005	0.869 (0.788–0.958)
Insurance status		
Uninsured	–	–
Private	0.111	0.753 (0.532–1.068)
Medicare/Medicaid/Other Govt.	0.781	1.050 (0.743–1.484)
Median income quartile		
<\$38,000	–	–
\$38,000–47,999	0.513	0.955 (0.834–1.095)
\$48,000–62,999	0.001	0.783 (0.679–0.902)
>\$63,000	<0.0001	0.760 (0.658–0.879)
CDCC score		
0	–	–
1	<0.0001	1.267 (1.132–1.418)
2+	<0.0001	1.841 (1.582–2.143)

Table 3 (continued)**Table 3** (continued)

Variables	P value	Hazard ratio (95% CI)
Facility location		
Northeast	–	–
Mid/South Atlantic	0.027	0.840 (0.719–0.981)
East/North/Central	0.466	0.945 (0.811–1.101)
Midwest	0.910	0.991 (0.855–1.150)
Mountain/Pacific	0.013	0.814 (0.691–0.958)
Grade		
Well differentiated	–	–
Moderately differentiated	0.326	0.917 (0.771–1.090)
Poorly/undifferentiated	0.176	1.152 (0.938–1.415)
Margin status (Y/N)		
Negative	–	–
Positive	<0.0001	1.951 (1.673–2.275)
Treatment		
Observation	–	–
Radiation therapy	0.445	0.918 (0.736–1.144)
Chemotherapy	0.001	0.744 (0.623–0.888)
Chemoradiation therapy	<0.0001	0.571 (0.504–0.647)

Factors included for multivariable analysis prior to backward stepwise selection: age, gender, race, insurance status, median income quartile, CDCC score, distance from facility, facility type, facility location, year of diagnosis, grade, tumor size, LN dissection, margin status, treatment. CI, confidence interval; CDCC, Charlson/Deyo Comorbidity Condition; Govt, Government; Mid, middle.

patients (22).

The Swedish Rectal Cancer Trial (SRCT) was a large randomized control trial that recruited patients with resectable rectal cancer and randomized them to preoperative short course RT (25 Gy in 5 fractions) followed by surgery or surgery alone (23). This is the only randomized trial in rectal cancer that showed both a statistically significant local control benefit, LRR of 9% *vs.* 26%, and OS benefit, 38% *vs.* 30%, for RT (24). The benefit of RT in terms of local control was demonstrated for Stages I–III. However, it should be noted that this study was performed in the pre-TME era, and the observed benefit of RT has been attributed to suboptimal surgery.

The concept that the rectum is encapsulated within a fibrous sheath that contains perirectal lymphatic tissue

was first formally described in 19th century, and has been referred to as the “Holy Plane” of rectal surgery (25). It was not until Heald published his experience with TME for 115 patients with rectal cancer, achieving a 5-year local control of 97.4%, that the technique started to gain traction (26). Therefore, the Dutch CKVO 9504 trial included a similar cohort of patients as the SRCT and patients were randomized to preoperative short course RT (25 Gy in 5 fractions) followed by TME or TME alone. In this study, there was a local control benefit of RT with 10-year LR of 5% *vs.* 11%. In contrast to the SRCT, there was no difference in OS for the entire cohort. However, subgroup analysis did identify a statistically significant benefit in OS for patients with Stage III disease and negative circumferential margins (50% *vs.* 40%) (7). Nevertheless,

this trial demonstrated that improved surgical technique with TME did not negate the observed LC benefit that was seen in the SCRT.

In the current study, patterns of care for patients with pT3N0 disease were reviewed using the NCDB database. Among the 6,767 patients identified with pT3N0 disease with no preoperative therapy given, the proportion of patients treated with adjuvant therapy was similar to those who underwent observation (47% vs. 53%, respectively). This finding is reflective of current NCCN guidelines that recommend adjuvant CRT or observation for patients with favorable pathologic findings (well-moderately differentiated, invading <2 mm mesorectum, no LVI and involving proximal rectum) (27). Interestingly, while the vast majority of patients that received adjuvant therapy were treated with adjuvant CRT (68.6%), nearly a third were treated with either RT (8.3%) or chemotherapy (23.1%) alone in the adjuvant setting. Therefore, we set out to investigate which adjuvant strategy was associated with the greatest clinical outcome using a large oncological national database.

Patients with pT3N0 rectal cancer had improved OS if they received adjuvant chemotherapy ($P<0.01$) or adjuvant CRT ($P<0.01$) when compared to patients that underwent observation. Moreover, there was no difference in OS for patients treated with adjuvant RT or observation ($P=0.54$) or between patients treated with adjuvant chemotherapy or adjuvant CRT ($P=0.15$). The 3-year unadjusted OS rates were 66.7%, 67.4%, 83.3%, and 86% for patients undergoing observation, adjuvant RT, adjuvant chemotherapy or adjuvant CRT, respectively ($P<0.001$). The benefit of adjuvant chemotherapy (HR 0.74, $P=0.001$) or adjuvant CRT (HR 0.57, $P<0.001$) on OS persisted on multivariable cox regression. Moreover, among patients with negative margins, RT alone offered no benefit over observation (HR 0.89, $P=0.361$); however, chemotherapy (HR 0.74, $P=0.002$) and CRT (HR 0.59, $P<0.0001$) were associated with improved OS. However, for patients with positive margins, only chemotherapy and CRT offered a benefit over observation (HR 0.44, $P<0.0001$). Indication bias was accounted for by propensity scoring with IPTW-adjusted modeling, and chemotherapy, with or without radiation, remained associated with improved OS (HR 0.48, $P<0.001$) and this was seen in the margin negative and positive cohort as well. These results suggest that chemotherapy plays an integral role in the survival benefits seen with adjuvant therapy, likely by a reduction in the risk of distant progression. With increasing supporting data

of short-course radiation therapy (25 Gy in 5 fractions) in the neoadjuvant setting, there should still remain a focus on incorporation of chemotherapy in sequential fashion, as supported by the Polish II study (28).

Despite these compelling findings, there are several limitations of this study. Firstly, the NCDB is comprised of COC-accredited facilities, and the outcomes from these institutions may not be generalizable to all hospital systems. Secondly, despite our attempt to control for confounding variables by performing a propensity score analysis, there may be additional confounders that were not identified. Moreover, tumor location within the rectum and pretherapy prognostic imaging findings are not recorded in the NCDB and cannot be accounted for. Finally, the NCDB does not report other important clinical outcomes, including: LR, regional recurrence or distant metastases. The importance of these clinical outcomes can be appreciated in the context of adjuvant therapy offered. For example, radiation therapy would be expected to impact locoregional recurrence while chemotherapy would be expected to mitigate distant metastasis, which may impact reported OS differentially.

Recently, multiple trials are evaluating the utility of preoperative MRI to identify good prognosis stage I, II and III patients that might be adequately managed with surgery alone. The MERCURY trial identified “good” prognostic features as MRI-anticipated negative CRM and MRI-predicted T2-T3b (<5 mm from muscularis propria) disease regardless of nodal stage. For “good” prognosis T3 tumors, LR was 1.7% with a 5-year OS and DFS of 68% and 81%, respectively (29). Likewise, the Optimierte Chirurgie Und MRT (OCUM) trial used MRI to identify low-risk tumors and defined them as tumors with minimum distance of >1 mm from mesorectal fascia and those tumors in upper third of rectum, regardless of nodal stage. This low-risk group was treated with TME alone and there was a 5-year LR rate of 2.7% with 5-year DFS of 76% (30). Finally, the QuickSilver trial evaluated the safety and feasibility of utilizing specific MRI criteria to identify “good prognosis” rectal tumors prior to resection, with a primary outcome of positive CRM rate. The criteria used in this study include: distance to mesorectal fascia >1 mm, definite T2, T2/early T3 or definite T3 with <5 mm extramural depth of invasion and no or equivocal extramural venous invasion. The authors observed a CRM rate of 4.9%, and concluded that MRI may be able to adequately identify patients with “good prognosis” and this subset may not need chemoRT (31). The importance of pretherapy imaging and the evolving role of MRI in risk stratification cannot be overstated.

Currently, the European Society for Medical Oncology (ESMO) guidelines for rectal cancer stratify patients based on depth of invasion beyond muscularis propria as well as primary tumor location within the rectum. Using these strata, patients with primary tumors located in the middle or high rectum with up to 5 mm depth of invasion are recommended to proceed with TME alone (32).

Conclusions

Our study demonstrates the variety of adjuvant treatment strategies that are currently utilized in the US. Moreover, after adjusting for indication bias with propensity score matching, we found that receipt of adjuvant chemotherapy or CRT improved OS when compared to observation. Although both chemotherapy and CRT have similar effects on OS there was no difference in OS appreciated between adjuvant chemotherapy alone and CRT. Therefore, patients who are found to have pT3N0 disease after TME surgery may benefit from adjuvant chemotherapy alone to maximize outcomes and minimize the morbidity associated with adjuvant CRT. However, there is likely a subgroup of pT3N0 patients that benefit from additional local therapy (e.g., R1-2 resection, close CRM, high grade, LVSI, PNI, and deep perirectal fat invasion), and adjuvant CRT may be justified in this population of patients. NCDB is deficient in recording all risk factors and therefore would not be suitable to define such population. Therefore, in patients with pT3pN0, either adjuvant chemotherapy or chemoradiation is recommended while the latter should be considered in higher risk patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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