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Neoadjuvant radiation for clinical T4 colon cancer: A potential improvement to overall survival☆,☆☆

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ABSTRACT

Background: Resection of T4 colon cancer remains challenging compared to lower T stages. Data on the effect of neoadjuvant radiation to improve resectability and survival are lacking. The purpose of this study is to describe the use and outcomes of neoadjuvant radiation therapy in clinical T4 colon cancer.
Methods: Adults with clinical evidence of T4 locally advanced colon cancer were included from the National Cancer Database (2004–2014). Bivariate and multivariable analyses were used to examine the association between neoadjuvant radiation therapy and R_0 resection rate, multivisceral resection, and overall survival.
Results: Fifteen thousand two hundred and seven patients with clinical T4 disease who underwent resection were identified over the study period. One hundred ninety-five (1.3%) underwent neoadjuvant radiation therapy. Factors associated with the use of neoadjuvant radiation therapy included younger age, male sex, private insurance, lower Charlson Comorbidity Index score, and treatment at an academic research program. Neoadjuvant radiation therapy was associated with superior R_0 resection rates (87.2% neoadjuvant radiation therapy vs 79.8% no neoadjuvant radiation therapy; $P = .009$). Five-year overall survival was increased in the neoadjuvant radiation therapy group (62.0% neoadjuvant radiation therapy vs 45.7% no neoadjuvant radiation therapy; $P < .001$). The benefit of neoadjuvant radiation therapy persisted in a Cox proportional hazards multivariable model containing a number of confounding variables, including comorbidity and postoperative chemotherapy (odds ratio 1.37; 95% confidence interval 1.05–1.77; $P = .01$). In a subgroup analysis of T4b patients, there was an even greater size effect in adjusted overall survival (odds ratio 1.71; 95% confidence interval 1.07–2.72; $P = .02$).
Conclusion: Although radiation is rarely used in locally advanced colon cancer, this National Cancer Database analysis suggests that the use of neoadjuvant radiation for clinical T4 disease may be associated with superior R_0 resection rates and improved overall survival. Patients with clinical T4b disease may benefit the most from treatment. Neoadjuvant radiation therapy should be considered on a case-by-case basis in locally advanced colon cancer.

Introduction

Colon cancer with local invasion (American Joint Committee on Cancer stage T4) has been long identified as a difficult disease process for the treating clinician. The 2 main drivers of overall survival for patients with T4 disease include lymph node positivity (N0–N2b) and extent of local invasion (T4a versus T4b). Five-year overall survival is poor and ranges from 60.6% for T4aN0 to 17.5% for T4aN2b compared to 45.7% for T4bN0 to 12.9% for T4bN2b cancers.[1] Margin-negative surgical resection followed potentially by adjuvant chemotherapy is the only curative treatment for this

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population. Multivisceral resection is often needed to obtain clear margins, with high rates of postoperative morbidity (11%–44%) and mortality (2%–7.5%).[2-5]

Neoadjuvant radiation therapy (NRT) has been proposed to improve both R_0 resection rate and survival in this patient population,[6-8] but current studies suffer from small size, selection bias, and lack of a comparison group. Neoadjuvant radiation has a number of potential benefits. First, tumor shrinkage and decreased tumor cell shedding may promote margin-negative resection and local control. Second, radiation therapy morbidity may be less in the neoadjuvant time period compared to the postoperative period, with minimization of radiation to healthy tissue. Finally, adequate blood supply and tissue perfusion in the neoadjuvant setting could make tissues more vulnerable to radiation in comparison to the scarring and decreased blood flow in postoperative tissues.

To address the limited data on the use of radiation therapy in colon cancer, this study analyzed the National Cancer Database (NCDB) for use of NRT in patients with stage T4 locally advanced colon cancer. We hypothesized that NRT would improve R_0 resection rates, decrease multivisceral resection rates, and potentially increase overall survival.

Methods

Data source

The NCDB was developed by both the American Cancer Society and the American College of Surgeons' Commission on Cancer. It abstracts data from more than 1,500 cancer centers in the United States and Puerto Rico and captures approximately 70% of all novel cases of cancer. Trained abstracters are used to collect the data, and quality assessments are carried out using a combination of electronic and site-specific methods.[9,10] This study used data from the deidentified NCDB participant use file. This study was reviewed and deemed exempt by the Vanderbilt University Institutional Review Board (Protocol #161707).

Defining patient cohort

Patients were selected using the International Classification of Diseases for Oncology third edition (ICD-O-3) histology and topography codes. All patients in the NCDB with adenocarcinoma of the colon (ICD-O-3 topography codes C180 and C182–199 and morphology codes 8140–8144, 8210–8211, 8220–8221, 8260–8263, 8480–8481,8490, and 8550) diagnosed during the modern era of chemotherapy (2004–2014) were included. Patients who had clinical staging recorded as T4 were included in the analysis. The exact method of preoperative staging is not available in the NCDB, but the American Joint Committee on Cancer definition for T4 includes both penetration to the surface of the peritoneum (T4a) and invasion or adherence to other organs or structures (T4b).[11] A subgroup analysis was performed on those patients with T4b disease. Exclusion criteria included patients with metastatic disease at presentation, patients not undergoing resection, patients undergoing surgery for palliation, patients with no data on radiation administration, patients with no data on clinical staging, patients receiving intraoperative radiation therapy, and surgery performed outside the reporting facility. Patients were categorized based on whether they received preoperative radiation therapy. Dose and time course of radiation were also recorded when available.

Outcomes

We analyzed a number of data points, including demographics, perioperative outcomes, and 5-year overall survival. The NCDB captures only overall survival and does not contain information on recurrence or disease-free survival. Patient comorbidities were analyzed using the Charlson/Deyo score.[12] The NCDB alters the Charlson score in 2 ways. First, as all patients in the database have some form of neoplasia, it does not count the primary cancer diagnosis condition. It then categorizes the Charlson score as 0 (no comorbidities), 1 (total Charlson score = 1), or 2 (total Charlson score > 2). We assessed hospital volume by categorizing the number of cT4 resections performed by tercile (low, medium, and high). Postoperative radiation therapy was also recorded and defined by initiation of radiation therapy within 90 days of surgery. This was done in an attempt to distinguish postoperative radiation therapy from radiation therapy administered for recurrence.

The primary outcome was R_0 resection as defined by negative margins on final pathology. Secondary outcomes included multivisceral resection, readmission, 30- and 90-day mortality, and overall survival. To examine the rate of preoperative radiation use by year, we conducted a time analysis.

Statistical analysis

Throughout the study, we report continuous and categorical variables as means with standard deviation and proportions. Continuous variables with skewed distributions are reported as the median alongside the interquartile range. Unadjusted comparison of continuous and categorical variables was performed with the either the Student's *t* test or the Wilcoxon rank sum test depending on distribution and Fisher exact test, respectively. In the analysis of survival, the log-rank test was used. An adjusted analysis of overall survival was performed using a multivariable Cox proportional hazards model. All variables were considered using a backward Wald stepwise procedure with a P value of .20 to enter and .05 to eliminate variables. Trend in NRT use by year was compared by the Cochran-Armitage test for trend. All analyses were conducted using SAS statistical software (version 9.3; SAS Institutes Inc, Cary, NC). All tests were 2-sided with an alpha level of 0.05.

Results

Patient characteristics and cohort comparison

A total of 15,207 patients with nonmetastatic clinical T4 colon cancer was identified (Table 1). The median age was 69 (interquartile range 58–79), and 8,136 (53.5%) were women. One hundred ninety-five patients (1.3%) underwent NRT. Most patients in the NRT group underwent 4500 cGy of radiation in 25 fractions over 5 weeks (range: 3900–5040 cGy). Factors associated with the use of NRT included younger age, male sex, private insurance, lower Charlson Comorbidity score, and treatment at an academic research program.

Pathologic and surgical outcomes

Patients in the NRT group had a greater median time to surgery (NRT 137 days vs no NRT 3 days; $P < .0001$). In the analysis of the primary outcome, R_0 resection, NRT had a significantly higher rate of R_0 resection (NRT 87.2% vs no NRT 79.8%; $P = .009$) (Table 2). Increased multivisceral resection rates were observed in the NRT group (NRT 45.6% vs no NRT 21.5%; $P < .001$). The NRT group had significantly higher rates of negative nodal disease on pathology.

Postoperative adjuvant therapy

There was no significant difference in rate of postoperative radiation administration (NRT 4.6% vs no NRT 4.2%; $P < .072$). NRT was associated with reduced adjuvant chemotherapy use (NRT 30.8% vs no NRT 47.4%; $P < .001$).

Table 1
Demographics of cohort.

	All (n = 15,207)	*NRT (n = 195)*	*No NRT (n = 15,207)*
Age, median, y (IQR)	69 (58–79)	58 (51–67)	69 (58–80)
Female sex	8136 (53.5%)	84 (43.1%)	8052 (53.6%)
Race			
White	12,806 (84.2%)	163 (83.6%)	12,643 (84.25)
Black	1731 (11.4%)	26 (13.3%)	1705 (11.4%)
Asian	410 (2.7%)	4 (2.0%)	406 (2.7%)
Other	260 (1.7%)	2 (1.0%)	258 (1.7%)
Insurance type			
Private	4681 (30.8%)	103 (52.8%)	4578 (30.5%)
Medicare	8337 (54.8%)	57 (29.2%)	8280 (55.2%)
Medicaid	973 (6.4%)	22 (11.3%)	951 (6.3%)
Other	390 (2.5%)	4 (2.0%)	386 (2.6%)
Uninsured	817 (5.4%)	9 (4.6%)	817 (5.4%)
Median household income by ZIP Code			
<$38,000	2771 (18.5%)	39 (20.2%)	2732 (18.5%)
$38,000–$47,999	3567 (23.8%)	46 (23.8%)	3521 (23.8%)
$48,000–62,999	4011 (26.7%)	53 (27.5%)	3958 (26.7%)
>$63,000	4645 (30.9%)	55 (28.5%)	4590 (31.0%)
Low education (>21% of adults not graduating from high school)	2657 (17.5%)	34 (17.4%)	2623 (17.5%)
Urban-rural continuum			
Metro	12,419 (81.7%)	144 (73.8%)	12,275 (81.7%)
Urban	2024 (13.3%)	44 (22.5%)	1980 (13.2%)
Rural	764 (5.0%)	7 (3.6%)	757 (5.0%)
Travel >20 miles	3197 (21.0%)	84 (43.1%)	3113 (20.7%)
Charlson score			
0	10,803 (71.0%)	173 (88.7%)	10,630 (70.8%)
1	3245 (21.3%)	17 (8.7%)	3228 (21.5%)
>1	1159 (7.6%)	5 (2.5%)	1154 (7.7%)
Region			
Northeast	3269 (22.2%)	25 (13.8%)	3244 (22.3%)
Midwest	4887 (33.2%)	78 (43.1%)	4809 (33.1%)
South	4196 (28.5%)	52 (28.7%)	4144 (28.5%)
West	2376 (16.1%)	26 (14.4%)	2350 (15.1%)
Facility			
Community cancer program	2257 (14.8%)	12 (6.1%)	2245 (15.0%)
Comprehensive community cancer Program	8874 (58.4%)	85 (43.6%	8789 (58.5%)
Academic/research program	4076 (26.8%)	98 (50.3%)	3978 (26.5%)
Volume			
Low	1462 (9.6%)	18 (9.2%)	1444 (9.6%)
Middle	3311 (21.8%)	46 (23.6%)	3265 (21.8%)
High	10,434 (68.6%)	131 (67.2%)	10,303 (68.6%)
Clinical T stage			
T4, not otherwise specified	7019 (46.1%)	86 (44.1%)	6933 (46.2%)
T4a	4433 (29.1%)	19 (9.7%)	4414 (29.4%)
T4b	3755 (27.7%)	90 (46.1%)	3665 (24.4%)

IQR, interquartile range.

Table 2
Pathologic, perioperative, and survival outcome of cohort.

	All (n = 15,207)	*NRT (n = 195)*	*No NRT (n = 15,207)*	*P value*
R_0 resection	12,149 (79.9%)	170 (87.2%)	11,979 (79.8%)	.01
Size, median, cm (IQR)	6.0 (4.0–8.0)	6.6 (4.0–9.2)	6.0 (4.0–8.0)	.04
Time to surgery, median, d (IQR)	3 (0–17)	137 (113–185)	3 (0–16)	<.0001
Multivisceral resection	3314 (21.8%)	89 (45.6%)	3225 (21.5%)	<.0001
Number of LNs, median (IQR)	18 (13–24)	15 (11–21)	18 (13–24)	<.0001
pN stage				<.0001
0	7030 (46.2%)	142 (72.5%)	6888 (45.9%)	
1	4587 (30.2%)	45 (23.1%)	4542 (30.3%)	
2	3590 (23.6%)	8 (4.1%)	3582 (23.9%)	
Length of stay, d median (IQR)	7 (5–10)	7 (5–10)	7 (5–10)	.61
30-day readmission	928 (6.1%)	6 (3.1%)	922 (6.1%)	.09
Adjuvant chemotherapy	7176 (47.2%)	60 (30.8%)	7116 (47.4%)	<.0001
Adjuvant radiotherapy	645 (4.2%)	9 (4.6%)	636 (4.2%)	.72
30-day mortality	684 (4.5%)	3 (1.5%)	681 (4.5%)	.04
90-day mortality	1192 (7.8%)	5 (2.6%)	1187 (7.9%)	.003
5-year overall survival	45.9%	62.0%	45.7%	<.0001

IQR, interquartile range; *LN*, lymph node.

Table 3
Multivariable Cox proportional hazards model for overall survival.

Overall survival	*Bivariate*		*Multivariable*	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Neoadjuvant radiation	1.71 (1.32–2.23)	<.0001	1.37 (1.05–1.77)	.01
Age >65	0.42 (0.40–0.44)	<.0001	0.49 (0.46–0.52)	<.0001
Female	0.91 (0.87–0.96)	.0003	NS	
Race				
White	REF		REF	
Black	0.90 (0.84–0.98)	.01	1.04 (0.96–1.12)	.32
Other	0.73 (0.64–0.83)	<.0001	0.79 (0.69–0.90)	.0005
Charlson Score >1	0.69 (0.65–0.72)	<.0001	0.81 (0.77–0.85)	<.0001
Volume				
Low	REF		NS	
Middle	0.96 (0.88–1.06)	.42	NS	
High	0.93 (0.85–1.01)	.06	NS	
Multivisceral resection	1.13 (1.06–1.20)	<.0001	NS	
R_0 resection	1.54 (1.46–1.64)	<.0001	1.57 (1.49–1.66)	<.0001
Stage				
I	REF		REF	
II	0.89 (0.74–1.08)	.24	0.83 (0.69–1.01)	.06
III	0.71 (0.58–0.85)	.0003	0.62 (0.52–0.75)	<.0001
Adjuvant chemotherapy	2.01 (1.91–2.11)	<.0001	2.04 (1.93–2.15)	<.0001
Adjuvant radiotherapy	1.33 (1.18–1.51)	<.0001	NS	

HR, hazard ratio; *NS*, not significant; *REF*, reference category.

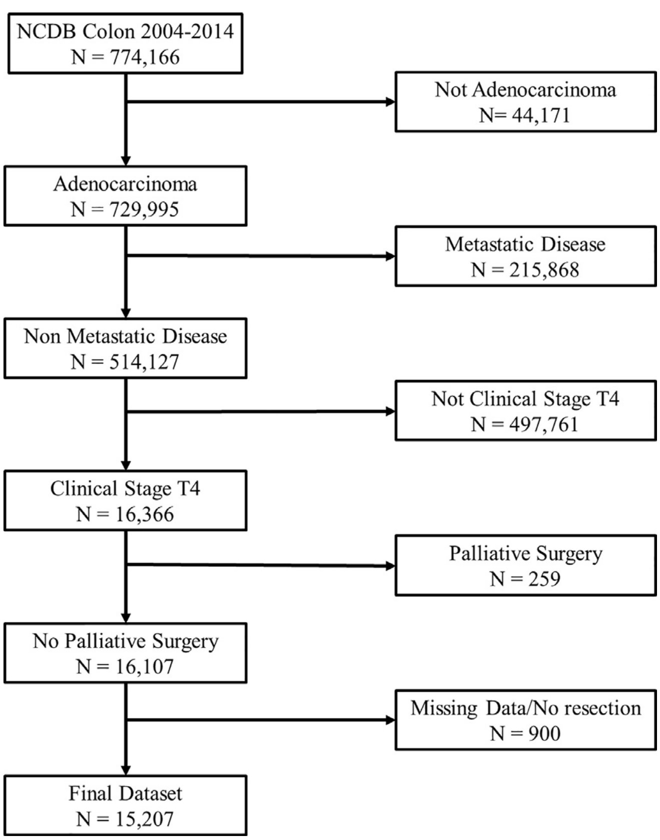

Fig. 1. Flowchart of inclusion and exclusion criteria.

Survival

Over a mean follow-up of 36.1 months, the 5-year overall survival for the cohort was 45.9%. NRT was associated with improved 5-year overall survival (NRT 62.0% vs no NRT 45.7%; P < .001) (Fig. 2). This relationship persisted in a multivariate Cox proportional hazards analysis that included age, stage, and Charlson Comorbidity (hazard ratio 1.37; 95% CI 1.05–1.77; P = .01) (Table 3).

Time Analysis

There was not a significant trend in use of NRT over the study period (Cochrane-Armitage test of trend P = .55) (Fig. 3).

Subgroup analysis: T4b patients

Out of the entire cohort, 3,755 (27.7%) patients were classified as T4b. This group was more likely to undergo NRT (T4, NOS: 1.2% vs T4a: 0.4% vs T4b: 2.4%; P < .001). The 5-year overall survival for the cohort was 46.9%. The administration of NRT was associated with improved 5-year overall survival (NRT 54.2% vs no NRT 46.6%; P = –.002) (Fig. 4). This association persisted in a Cox proportional hazards analysis that included age, stage, and Charlson Comorbidity (hazard ratio 1.71; 95% CI 1.07–2.72; P = .01).

Discussion

This study analyzed the use and outcomes of neoadjuvant radiation therapy for patients with T4 colon cancer across the United States. Important findings included superior R_0 resection rates and an improvement in overall survival with NRT despite increased rates of multivisceral resection with NRT. This is in the setting of a low national rate of NRT for locally advanced colon cancer.

Superior efficacy of neoadjuvant therapy has been demonstrated in rectal cancer.[13-18] For rectal cancer, conventional theory holds that distant recurrence is a far greater determinant in overall survival than local recurrence. So, although preoperative NRT improves locoregional control, no studies using total mesorectal excision resection have shown an improvement in overall survival. Given the data that we present, we find that the NRT group had a higher rate of R_0 resection, which was in turn associated with overall survival. This could be the mechanism by which NRT is associated with improved overall survival. The use of therapies prior to surgery for colon cancer have been poorly explored and have mainly examined chemotherapy. Neoadjuvant chemotherapy in T3 or greater colon cancers was studied by the FOxTROT collaborative group. They found treatment to be safe and feasible. Long-term oncologic results are currently being assessed by a phase III trial.[19] A phase II Danish trial had comparable findings.[20]

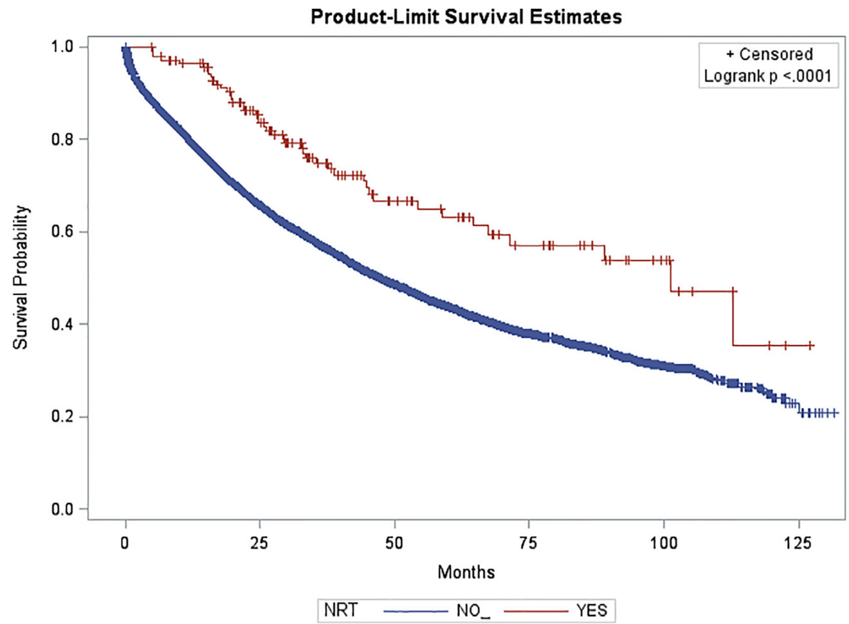

Fig. 2. Kaplan-Meier curve comparing overall survival by neoadjuvant radiation therapy for the entire cohort.

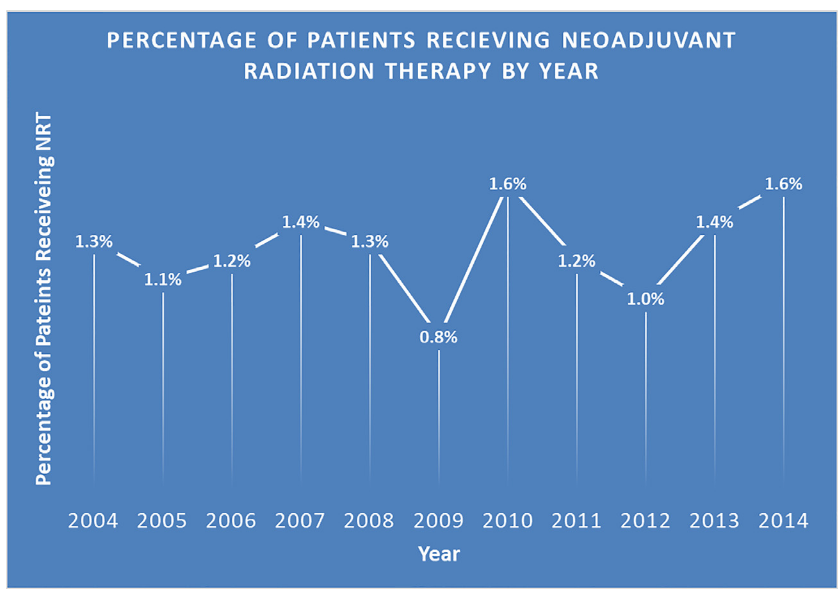

Fig. 3. Percentage of patients receiving neoadjuvant radiation therapy by year.

Limited studies have analyzed radiation therapy as neoadjuvant treatment for colon cancer. A small randomized controlled study examined patients with locally advanced colon cancers receiving adjuvant radiotherapy. They observed no difference in overall survival between patients receiving combination chemotherapy and radiation to those treated with only chemotherapy. But the group undergoing radiotherapy had greater morbidity.[7] Sluggish accrual resulted in termination before reaching the planned enrollment. Neoadjuvant radiation therapy in colon cancer has also been examined in 2 small case series. Compared to this analysis, they had no control group and shorter follow-up. Cukier et al[6] retrospectively analyzed 33 patients at a single institution and found a 3% complete pathologic response rate as well as a 100% R_0 rate. With a median follow-up of 36 months, patients undergoing NRT and resection had 3-year overall survival (OS) and disease-free survival rates of 85.9% and 73.7%, respectively.[6] The second study examined patients with locally advanced sigmoid colon undergoing NRT and resection with median follow-up of 42 months (range, 17–57 months). They observed a 38.1% pathologic complete response rate and a 95.2% R_0 resection rate. Multivisceral resection was performed in 7 patients (33.3%), and 2 patients (9.5%) suffered grade 2 postoperative morbidity. There was no mortality. The predicted 3-year OS was 95.2%.[8] Most recently, our group reported on our experience of 23 patients with locally advanced colon cancer treated with NRT; NRT was associated with increased downstaging and improved unadjusted OS when compared to patients who proceeded directly to surgery.[21]

Notable findings from this current study include an increased rate of R_0 resection in the group undergoing NRT. Radiation therapy has the potential to shrink tumors and allow for improved R_0 resection in rectal cancer.[22] As such, the same benefits may be seen in colon cancer. In the analysis of overall survival, R_0 had a strong association with increased overall survival that persisted when adjusting for important covariates. The association between

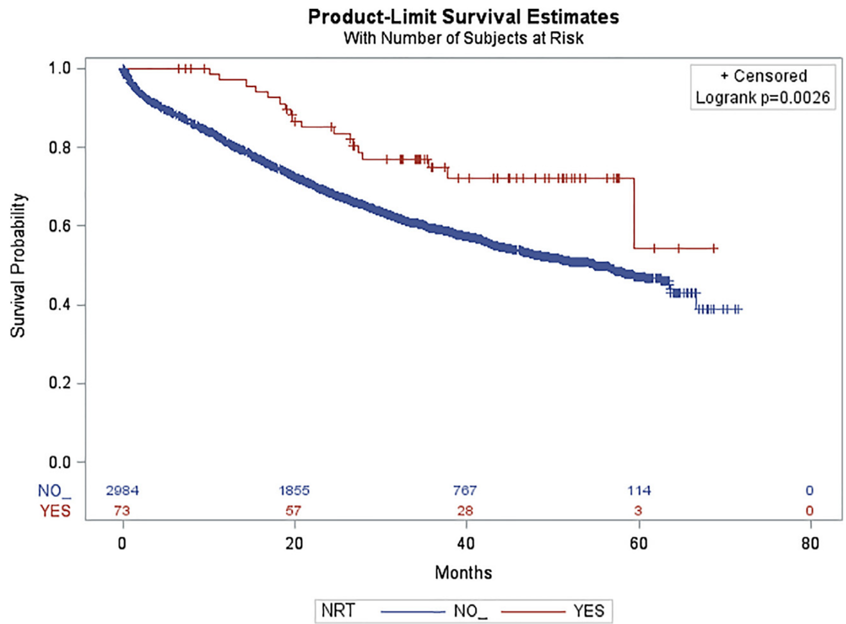

Fig. 4. Kaplan-Meier curve comparing overall survival by neoadjuvant radiation therapy for a subset of T4b patients.

NRT and improved overall survival is likely multifactorial. We did observe significant decreases in the 30- and 90-day mortality rates for patients in the NRT group. However, visual inspection of the Kaplan-Meier curve suggests that survival continued to diverge, even after 90 days. Most patients in the NRT group were pathologic stage 2, while most in the non-NRT group were stage 3. We believe there are a couple of factors at play. First, there is the potential of NRT to treat nodal metastasis, and this results in downstaging for the cohort of patients undergoing NRT. Second, we attempted to control for this by including stage (based on operative pathology) in our Cox proportional hazards model. It would likely bias the non-NRT group toward decreased overall survival, but by including it in our adjusted model, this should mitigate that bias.

Our subgroup analysis of only patients with clinical T4 diseases revealed similar findings of improved adjusted overall survival with an even greater effect size. This suggests that patients with T4b disease may receive an even greater benefit from NRT. This conclusion should be tempered by the fact that almost half of the original cohort were classified as simply T4. For that reason, we initially chose to analyze the cohort as a whole rather than compare T4a and T4b.

Limitations to this study center on weaknesses in the NCDB and selection bias. Details on radiation dosing, fields, and side effects are important data that need to be clarified in future studies. In addition, a key outcome for NRT is local recurrence, which is unfortunately not collected by the database. Data on preoperative staging, tumor location, or organs involved in either tumor extension or multivisceral resection are also not available. An assumption of this study was that clinical staging was conducted with radiology. Finally, as in any study involving a large database, the conclusions were only as strong as the accuracy of the data entry. The data collection process for the NCDB goes to great lengths to standardize and audit data recording.[10] As there was no randomization or even criteria for consideration of NRT, significant selection bias may exist. NRT administration was performed on an ad hoc basis and could bias many of the results, especially overall survival. We attempted to control for this bias using a multivariable Cox proportional hazards analysis, but there were many variables that we were unable to include in the model. The small incidence of patients undergoing NRT is an additional limitation and also contributes to selection bias. The strength of this study lies in the large overall sample size, which permits both an analysis of national use of NRT as well as risk adjustment for factors such as age, stage, hospital types, and clinic-pathologic features. The inclusion of all locally advanced colon adenocarcinoma in the NCDB also allows for analysis of national trends.

In summary, this analysis suggests that the use of neoadjuvant radiation for clinical T4 colon cancer may be associated with superior R_0 resection rates and improved overall survival. However, the growing evidence to support administration of neoadjuvant radiation must be tempered with the understanding that NCDB studies merely show associations with outcomes, in contrast to prospective phase III trials. As such, in the absence of randomized data, we hope that this analysis may promote multidisciplinary discussion of radiation as a potential neoadjuvant option for patients with T4 disease, most notably when an R_0 resection is in question.

In conclusion, neoadjuvant radiation therapy for clinical T4 colon cancer is associated with superior R_0 resection rates and improved overall survival in this NCDB analysis. Patients with T4b disease may receive an even greater benefit from NRT. The use of NRT for patients with clinical T4 colon cancer should be assessed on a case-by-case basis in a multidisciplinary setting. Future prospective trials are warranted to help define the risks and benefits of NRT in this patient population.

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