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Abstract

Purpose: Total Neoadjuvant Therapy (TNT) is increasingly used in Stage II and III rectal cancer. The PRODIGE 23 and RAPIDO trials showed upfront chemoradiation improves disease-free survival, pathologic complete response, local control, and reduces metastasis, underscoring importance of treatment completion. Failure to complete TNT may lead to worse outcomes. This study aims to identify factors associated with failure to complete TNT, specifically concurrent chemoradiation.

Methods: A retrospective NCDB analysis (2018–2020) included Stage II–III rectal adenocarcinoma patients undergoing TNT and resection. TNT was defined as multiagent chemotherapy and radiation prior to resection, with radiation >90 days after diagnosis. We analyzed patients following the PRODIGE 23 model. Demographics (age, sex, race/ethnicity, comorbidities, insurance, income, rurality) were included.. Fisher's Exact tests assessed bivariate associations. Logistic regression modeled radiation discontinuation: Cox proportional hazards models assessed survival.

Results: Of 3,267 patients, 58 (1.78%) did not complete radiation. Ages were 18–49 (26.7%), 50–64 (47.4%), ≥65 (25.9%); 62.6% were male. Insurance included private (57.9%) and Medicare (24.5%). Academic facilities treated 39.2%. Males (OR=0.52) and patients at academic centers were more likely to complete radiation ($p=0.0133$, $p<0.0001$). Patients at community (OR=6.12), comprehensive (OR=3.09), and integrated (OR=4.3) centers were more likely to

discontinue. Ages 50–64 were significantly more likely to complete therapy than 18–49 or ≥65 ($p=0.0069$). Private insurance also correlated with higher completion ($p<0.05$).

Conclusion: Completion of neoadjuvant radiation correlates with pCR in TNT. Patients <50 or ≥65, females, and those treated outside academic centers were at higher risk for discontinuation.

Keywords: Total Neoadjuvant Therapy, Rectal Cancer, Chemoradiation, Risk Factors

Introduction

Colorectal cancer remains the third leading cause of cancer related death in the United States. For rectal cancer specifically, the American Cancer Society estimates an incidence rate of 11.2 new cases per 100,000 people per year and a colorectum mortality rate of 13.9 per 100,000 people per year [1]. The German Rectal Trial established pre-operative chemoradiation followed by total mesorectal excision and adjuvant chemotherapy as the US standard-of-care for patients with locally advanced rectal cancer [2]. Since then, the treatment for rectal cancer has evolved with efforts focused on increasing distant disease control with total neoadjuvant therapy (TNT) [3]. The PRODIGE 23 trial, a phase 3 randomized clinical trial for locally advanced rectal cancer (LARC), demonstrated that total neoadjuvant therapy (TNT) with mFOLFIRINOX induction chemotherapy followed by preoperative chemoradiotherapy significantly improved disease-free survival (DFS) and overall survival (OS) compared to the standard of care (preoperative chemoradiotherapy, surgery, and adjuvant chemotherapy). Seven-year follow-up data confirmed these benefits. Improved DFS and metastasis-free survival (MFS) were also observed in the TNT group, suggesting it should be considered a best option of care for LARC patients. The RAPIDO trial compared two treatment strategies for locally advanced rectal cancer: a standard of care (long-course chemoradiotherapy, surgery, and optional adjuvant chemotherapy) and an experimental "Total Neoadjuvant Therapy" (TNT) approach involving short-course radiotherapy followed by upfront chemotherapy with capecitabine and oxaliplatin, and then surgery. The trial concluded that the experimental TNT approach, while associated with an increase in serious adverse events (at an acceptable rate for clinical practice), reduced disease-related treatment failure at 3 years (primarily due to fewer distant metastases) and doubled the rate of pathological complete response (pCR) compared to the standard of care [4,5].

TNT has become an increasingly common approach where 6-9 cycles of systemic therapy are delivered in addition to radiation therapy prior to surgery to address micrometastases early and to improve treatment compliance rates [4-6]. These studies have also shown that patients who complete a TNT regimen exhibit improved disease-free survival and pathologic complete response rates when compared to patients who did not receive both radiation and full chemotherapy prior to resection, leading to widespread adoption of TNT in the treatment for patients with stage II and III rectal cancer [7,8].

As the interruption of TNT regimens may lead to less optimal outcomes, the aim of our study is to identify demographic risk factors associated with failure to complete TNT, specifically the radiation portion of the treatment regimen using the National Cancer Database [9]. In our study, we define TNT as administration of systemic multiagent chemotherapy followed by chemoradiation and then surgical resection as defined in the PRODIGE trial.

Methods

Data

Database Description

The NCDB is a joint project of the American Cancer Society and the Commission on Cancer (CoC) of the American College of Surgeons. The NCDB, established in 1989, is a nationwide, facility-based, comprehensive clinical oncology data set that pulls from over 1,500 Commission on Cancer (CoC) and American Cancer Society accredited facilities across the United States, capturing approximately 70% of all newly diagnosed cancer cases annually [9]. The database includes information on patient demographics, tumor characteristics, and treatment details. The dataset ensures no duplication of patient information, and all data is deidentified [10].

Our study analyzed a three-year (2018-2020) retrospective cohort of rectal cancer data in the NCDB.

Patient Selection and Stratification

The NCDB was queried for adult patients (≥ 18 years) presenting with pathologically proven stage II or stage III AJCC rectal cancer who underwent TNT and subsequent resection. Cases with stage I or stage IV cancer, unknown cancer stage, missing demographic data, and non-adenocarcinoma histology were excluded. Stage I cancers were excluded due to limited evidence that TNT is superior to standard treatment, such as surgical resection with adjuvant therapy, for localized disease. Additionally, there are limited trials to support TNT in the management of metastatic disease, thus Stage IV cancers were excluded [11]. Cases with an age less than 18 years, or missing demographic data were not considered. Total neoadjuvant therapy was defined as cases with documented multiagent chemotherapy and radiation given prior to resection. We included patients who received systemic chemotherapy first, followed by chemoradiation and subsequent surgery. These were patients who were treated with the PRODIGE 23 trial paradigm. Patients who did not undergo TNT were excluded.

Data Points (Variables Analyzed)

We extracted the demographic factors of studied subjects age, sex, race and ethnicity, comorbidities, insurance status, area income, and rurality. To define TNT in the database, we included only patients who completed multiagent chemotherapy and subsequent chemoradiation followed by surgical resection. Patients who began radiation >90 days after diagnosis were included to ensure only those who completed systemic chemotherapy were considered [12]. The

primary outcome was the discontinuation of radiation. Secondary outcome measures included mortality and length of stay.

Statistical Methods

Categorical variables were summarized using frequency and percentage. Continuous variables were reported as mean ± standard deviation (SD) for normally distributed data and as median for non-normally distributed data. Bivariate associations were assessed using Fisher's Exact tests for categorical variables and the independent Student's t-test for continuous parametric data to compare the two patient groups at a univariate level.

Discontinuation of radiation was modeled using multivariate logistic regression. Overall patient survival was analyzed using Cox proportional hazards models.

Statistical analyses were performed using the Statistical Package for Social Sciences software (SPSS, version 24; SPSS, Inc). An alpha level of 5% was used, with statistical significance set at p-value <0.05.

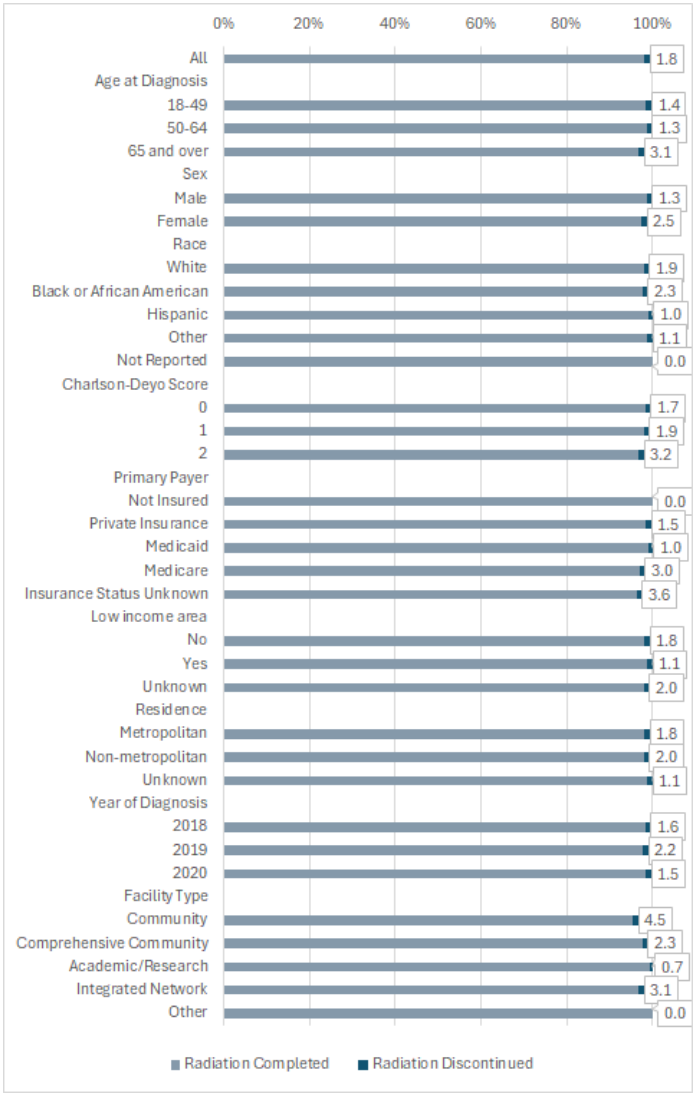
Results

Over the three-year study period, 3,267 patients met the inclusion criteria for TNT treatment, 58 of which did not complete radiation therapy (1.78% of dataset). Of the total patients included, 26.7% were between ages 18-49, 47.4% were ages 50-64, and 25.9% were ages 65 and older. Males made up 62.6% of patients included. Of patients, 57.9% had private insurance, 24.5% received Medicare, and 39.2% were treated at an academic research facility (Table 1). Male patients and patients treated at an academic research facility were significantly more likely than women to complete their radiation therapy ($p = 0.0133$ and $p = <.0001$,

respectively). Additionally, patients ages 50-64 were significantly more likely to complete their radiation therapy compared to patients ages 18-49 or patients 65 years or older ($p = 0.0069$).

Patients with private insurance were significantly more likely to complete their radiation course ($p < 0.05$). Patients receiving Medicare comprised 41.4% of patients who did not complete their radiation treatment ($p<0.02$). The rates of discontinuing radiation are displayed in Figure 1.

Fig. 1 Rate of discontinuing radiation in cases of clinical stage II/III rectal cancer with total neoadjuvant therapy, NCDB 2018-2020.



Multivariable analysis showed that receiving treatment at an academic facility remained significant for predicting completion of radiation therapy. Patients at every other type of facility, which is defined as community (OR 6.12), comprehensive community (OR 3.09), and integrated network (OR 4.3) facilities were more likely to discontinue radiation treatment (Table 2). Additionally, men were less likely to discontinue radiation treatment (OR = 0.52).

The adjusted hazards ratios and 95% confidence intervals from Cox proportional hazards models of overall patient survival were determined for the dataset (Table 3). This analysis revealed consistent findings of increased risk for not completing radiation amongst patients who did not receive treatment at an academic facility. There was no significantly increased risk of death in patients who discontinued radiation (p=0.79).

Discussion

In this large-scale analysis of a nationwide cancer registry, we found that patients who are older, female, and who did not receive treatment at an academic facility were at increased risk for not completing the prescribed radiation course of their TNT regimen (Figure 1).

Although local control is excellent with trimodality therapy per the German Rectal Cancer Trial, distant recurrence rates remain high, ranging from 25-30% [3]. A shift towards delivering systemic therapy in the upfront, neoadjuvant setting has shown to be efficacious in addressing micrometastatic disease earlier and improving poor compliance seen with adjuvant therapy in recent randomized clinical trials [4,5]. Despite the RAPIDO trial enrolling a cohort of patients at higher risk of distant relapse, defined as patients with least one high risk factor (T4a-b, N2 disease, extramural venous invasion, involved mesorectal fascia, or lateral lymph nodes), TNT with either 6 cycles of CAPOX or 9 cycles of FOLFOX showed improvement in distant

disease control. Additionally, the PRODIGE 23 trial, which utilized 6 cycles of modified FOLFIRINOX in the neoadjuvant setting also showed improvements in distant control rates [4]. Although the STELLAR, PRODIGE 23 and RAPIDO trials testing the efficacy of TNT have all showed improvement in pathologic complete response rates, RAPIDO and STELLAR used the 5-fraction short course radiation treatment regimen. PRODIGE 23 used a 5-6 weeklong course regimen. However, given the recent 5-year RAPIDO update showing worse local control with short-course radiation therapy when compared to long-course, the use of long-course radiation therapy has become increasingly preferred, especially in patients with high risk factors such as those included in the RAPIDO study [13]. Overall, the use of TNT in these studies has shown improved pathologic complete response rates, disease free survival, and distant control. Although compliance has been improved with delivering neoadjuvant therapy compared to in the adjuvant setting, there are certain cohorts of patients that continue to be at risk of not completing therapy.

In our study, not receiving treatment at an academic facility remained a significant predictor of not completing radiation therapy on multivariate analysis. Patients who received treatment at an academic facility had better outcomes given the previously mentioned high rates of completed radiation when compared to the other facility types. There are various factors that could potentially contribute to this finding. For instance, patients willing to travel to an Academic Comprehensive Cancer Program (ACAD) may inherently be more motivated to complete their care plan as prescribed. The NCDB defines ACAD facilities as those that participate in postgraduate medical education in at least four program areas with more than 500 newly diagnosed cancer cases each year [14]. For reference, community cancer programs (CCP) accession 100-500 newly diagnosed cancer cases each year; comprehensive community cancer programs (CCCP) accession 500 or more newly diagnosed cancer cases each year; and integrated

network cancer programs (INCP) belong to an organization that owns a group of facilities offering cancer care [14].

Patients receiving Medicare benefits comprised approximately 25% of the patients included in the dataset but disproportionately made up over 40% of the patients who failed to complete the prescribed radiation course ($p<0.02$).

Although there were significant findings, overall, failure to complete radiation treatment as prescribed in a TNT regimen was a rare event (Table 4 and Figure 1). The adjusted hazards ratios and 95% confidence intervals from Cox proportional hazards models of overall patient survival were determined for the dataset (Table 3). There was a small signal for increased risk of death for those who discontinued radiation, but this finding was not significant. This is likely due to the small number of patients in this group and the effect of other risk factors in the model.

As with most retrospective database studies, this study has several inherent limitations. The NCDB, lacks surgical, chemotherapy, and radiation details. And as with any retrospective database, there are missing or incomplete data for many patients.

The analysis of overall survival was limited to the variables coded in the NCDB. Causes of death and the patterns of tumor recurrences were not captured. Furthermore, the NCDB does not define the treatment facility type in patients less than 40 years old, which could have potentially affected our findings given that 26.7% of patients in this dataset were ages 18-49. Additionally, we excluded patients who received radiation therapy less than 90 days from diagnosis. These patients represent a significant portion of patients treated in the US since the publication of results from the OPRA trial and CAO/ARO/AIO-12 trials, which found better response rates with chemoradiation first, which prompts a key question for continued research. Our study was limited to include patients who began radiation >90 days after diagnosis to ensure

only those who completed systemic chemotherapy were considered. This study therefore included just patients who had systemic chemotherapy first followed by chemoradiation. Furthermore, although we identified factors that were associated with failure to complete radiation, the overall rates of failure to complete radiation treatment as prescribed in a TNT regimen was a rare event (Table 4 and Figure 1), limiting the power of this study. However, given the rarity of this event, these results from a large nationwide cancer study should be leveraged to identify patients who are at risk for incomplete treatment. Unfortunately, the reason for discontinuation of radiation treatment is not well documented in the NCDB and further prospective studies on risk factors identified in this study will be necessary to draw conclusions regarding these patients. Despite these limitations, the analysis and outcomes of our study are robust enough to draw meaningful conclusions to address this important question of risk associated with discontinuation of radiation therapy of TNT regimen.

Conclusion

Patients who are older, female, and did not receive treatment at an academic facility were at an increased risk for not completing the prescribed radiation course of their TNT regimen. Identification of at-risk patients can allow for early interventions to mitigate barriers to completion of TNT.

Table 1. Summary of total neoadjuvant therapy in clinical stage II/III rectal cancer, NCDB 2018-2020.

	All	Radiation Complete	Radiation Discontinued	p-value
All, n (%)	3,267 (100.0)	3,209 (100.0)	58 (100.0)	
Age, n (%)				0.0069
18-49	871 (26.7)	859 (26.8)	12 (20.7)	
50-64	1,549 (47.4)	1,529 (47.6)	20 (34.5)	
65 and older	847 (25.9)	821 (25.6)	26 (44.8)	
Sex, n (%)				0.0133
Male	2,046 (62.6)	2,019 (62.9)	27 (46.6)	
Female	1,221 (37.4)	1,190 (37.1)	31 (53.4)	
Race, n (%)				0.7493
White	2,530 (77.4)	2,482 (77.3)	48 (82.8)	
Black or African American	220 (6.7)	215 (6.7)	5 (8.6)	
Hispanic	295 (9.0)	292 (9.1)	3 (5.2)	
Other	174 (5.3)	172 (5.4)	2 (3.4)	
Not Reported	48 (1.5)	48 (1.5)		
Charlson-Deyo Score, n (%)				0.2569
0	2,598 (79.5)	2,555 (79.6)	43 (74.1)	
1	483 (14.8)	474 (14.8)	9 (15.5)	
2 or more	186 (5.7)	180 (5.6)	6 (10.3)	

Insurance Status, n (%)				0.0220
Not Insured	124 (3.8)	124 (3.9)		
Private Insurance	1,890 (57.9)	1,861 (58.0)	29 (50.0)	
Medicaid	413 (12.6)	409 (12.7)	4 (6.9)	
Medicare	812 (24.9)	788 (24.6)	24 (41.4)	
Unknown	28 (0.9)	27 (0.8)	1 (1.7)	
Low Income Area, n (%)				0.6004
No	2,367 (72.5)	2,324 (72.4)	43 (74.1)	
Yes	358 (11.0)	354 (11.0)	4 (6.9)	
Unknown	542 (16.6)	531 (16.5)	11 (19.0)	
Residence, n (%)				0.8671
Metropolitan	2,684 (82.2)	2,637 (82.2)	47 (81.0)	
Non-metropolitan	490 (15.0)	480 (15.0)	10 (17.2)	
Unknown	93 (2.8)	92 (2.9)	1 (1.7)	
Facility Type				<.0001
Community	110 (3.4)	105 (3.3)	5 (8.6)	
Comprehensive Community	854 (26.1)	834 (26.0)	20 (34.5)	
Academic/Research	1,266 (38.8)	1,257 (39.2)	9 (15.5)	
Integrated Network	773 (23.7)	749 (23.3)	24 (41.4)	
Other	264 (8.1)	264 (8.2)		

Table 2. Adjusted odds ratios and 95% confidence intervals from logistic regression models of discontinuing radiation in cases of clinical stage II/III rectal cancer with total neoadjuvant therapy, NCDB 2018-2020.

	OR (95% CI)
Age (reference= 18-49)	
50-64	0.65 (0.31,1.36)
65 and over	1.44 (0.55,3.82)
Sex (reference= Female)	
Male	0.52 (0.31,0.88)
Race (reference= White)	
Black or African American	1.53 (0.58,4.05)
Hispanic	0.89 (0.27,2.95)
Not Reported	.
Other	0.84 (0.20,3.56)
Comorbidity Index (reference=0)	
1	1.04 (0.50,2.16)
2 or more	1.67 (0.68,4.09)
Insurance (reference= Private)	
Insurance Status Unknown	2.25 (0.29,17.71)
Medicaid	0.60 (0.21,1.74)
Medicare	0.97 (0.41,2.29)

Not Insured	.
Low Income (reference= No)	
Yes	0.59 (0.20,1.71)
Unknown	1.09 (0.55,2.15)
Residence (reference= Metropolitan)	
Non-metropolitan	1.14 (0.55,2.36)
Unknown	0.79 (0.11,5.93)
Facility Type (reference= Academic/Research)	
Community	6.12 (1.97,19.03)
Comprehensive Community	3.09 (1.39,6.88)
Integrated Network	4.30 (1.97,9.36)
Other	.

Table 3 Adjusted hazard ratios and 95% confidence intervals from Cox proportional hazard models of overall patient survival in cases of clinical stage II/III rectal cancer with total neoadjuvant therapy, NCDB 2018-2020.

	HR (95% CI)	p-value
Age (reference= 18-49)		
50-64	1.07 (0.62,1.85)	0.808 0
65 and over	1.33 (0.63,2.82)	0.453 6
Sex (reference= Female)		
Male	1.03 (0.70,1.50)	0.901 4
Race (reference= White)		
Black or African American	1.32 (0.67,2.60)	0.424 8
Hispanic	0.53 (0.21,1.33)	0.175 9
Not Reported	1.07 (0.46,2.49)	0.872 1
Other	0.59 (0.08,4.27)	0.599 5

Comorbidity Index (reference=0)		
	1.09	0.746
1	(0.64,1.85)	8
	2.25	0.006
2 or more	(1.26,4.04)	3
Insurance (reference= Private)		
	0.87	0.818
Insurance Status Unknown	(0.27,2.84)	1
	1.27	0.425
Medicaid	(0.71,2.28)	9
	1.29	0.429
Medicare	(0.69,2.40)	6
	1.25	0.827
Not Insured	(0.17,9.15)	1
Low Income (reference= No)		
	1.31	0.339
Yes	(0.76,2.26)	5
	1.17	0.534
Unknown	(0.71,1.95)	9
Residence (reference= Metropolitan)		
	1.56	0.068
Non-metropolitan	(0.97,2.51)	6

	1.35	0.566
Unknown	(0.49,3.74)	1
Facility Type (reference= Academic/Research)		
	2.72	0.024
Community	(1.14,6.51)	3
	1.63	0.045
Comprehensive Community	(1.01,2.63)	8
	1.54	0.081
Integrated Network	(0.95,2.51)	3
	1.40	0.457
Other	(0.58,3.36)	6
Discontinued Radiation (reference= No)		
	1.21	0.792
Yes	(0.30,4.95)	6

Table 4 Reason for discontinuing radiation in cases of clinical stage II/III rectal cancer with total neoadjuvant therapy, NCDB 2018-2020.

	n (%)
	3,267
All	(100.0)
Radiation Treatment Discontinued Early	
Radiation Rx completed as prescribed	3,209 (98.2)
Radiation Rx discontinued early-toxicity	28 (0.9)
Radiation Rx discontinued early contraindicated due to other patient risk factors	5 (0.2)
Radiation Rx discontinued early-patient decision	21 (0.6)
Radiation Rx discontinued early-reason not documented	4 (0.1)

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