Extended Intervals after Neoadjuvant Therapy in Locally Advanced Rectal Cancer: The Key to Improved Tumor Response and Potential Organ Preservation

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BACKGROUND: Many rectal cancer patients experience tumor downstaging and some are found to achieve a pathologic complete response (pCR) after neoadjuvant chemoradiotherapy (nCRT). Previous data suggest that there is an association between the time interval from nCRT completion to surgery and tumor response rates, including pCR. However, these studies have been primarily from single institutions with small sample sizes. The aim of this study was to examine the relationship between a longer interval after nCRT and pCR in a nationally representative cohort of rectal cancer patients.

STUDY DESIGN: Clinical stage II to III rectal cancer patients undergoing nCRT with a documented surgical resection were selected from the 2006 to 2011 National Cancer Data Base. Multivariable logistic regression analysis was used to assess the association between the nCRT–surgery interval time (<6 weeks, 6 to 8 weeks, >8 weeks) and the odds of pCR. The relationship between nCRT–surgery interval, surgical morbidity, and tumor downstaging was also examined.

RESULTS: Overall, 17,255 patients met the inclusion criteria. An nCRT–surgery interval time >8 weeks was associated with higher odds of pCR (odds ratio [OR] 1.12, 95% CI 1.01 to 1.25) and tumor downstaging (OR 1.11, 95% CI 1.02 to 1.25). The longer time delay was also associated with lower odds of 30-day readmission (OR 0.82, 95% CI 0.70 to 0.92).

CONCLUSIONS: An nCRT–surgery interval time >8 weeks results in increased odds of pCR, with no evidence of associated increased surgical complications compared with an interval of 6 to 8 weeks. These data support implementation of a lengthened interval after nCRT to optimize the chances of pCR and perhaps add to the possibility of ultimate organ preservation (nonoperative management). (J Am Coll Surg 2015;221:430–440. © 2015 by the American College of Surgeons)

Colorectal cancer is the third most frequently diagnosed malignancy in the US, with approximately 40,000 new cases of rectal cancer annually.[1] Multimodal therapy, which consists of chemoradiation followed by surgery in the form of a total mesorectal excision, has become the standard of care for locally advanced rectal cancer (stage II and stage

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Abbreviations and Acronyms
NCDB = National Cancer Data Base
nCRT = neoadjuvant chemoradiotherapy
OR = odds ratio
pCR = pathologic complete response

III disease). Neoadjuvant chemoradiotherapy (nCRT) has been shown to significantly reduce the local recurrence rate and has been associated with an increase in the overall survival rate.[2] Despite this, a large percentage of patients in the US still undergo a total proctectomy (abdominoperineal resection) with permanent end colostomy. In contrast, few patients undergo rectal-preserving treatments, such as local excision, or achieve complete tumor disappearance and thereby avoid any surgery whatsoever.[3,4]

The traditional North American paradigm for delivery of neoadjuvant therapy in rectal cancer consists of 45 to 50.4 Gray (Gy) delivered in 25 to 28 fractions, with sensitizing continuous fluorouracil infusion or capecitabine administered throughout the radiation course. Patients then undergo surgical resection approximately 6 to 8 weeks after finishing nCRT.[5,6] This recommendation is based primarily on the Lyon R90-01 trial, which found improved clinical tumor response and pathologic downstaging in patients undergoing surgery 6 to 8 weeks after radiation therapy compared with those with a 2-week interval.[7] As a result of neoadjuvant therapy, many patients experience significant tumor downstaging, and some are found to have a pathologic complete response (pCR) on histologic examination of the resected specimen.[8,9] There is a growing body of data that suggests that pCR is significantly associated with a reduction in both local and systemic recurrence and superior overall survival compared with that in patients with partial or no response.[10] Although pCR may potentially be a marker for favorable tumor biology, it is still imperative in clinical practice to attempt to maximize our chances of attaining pCR. This is especially true if a nonoperative or observational approach is to be considered.

So there is great clinical interest in identifying factors that may increase tumor regression and enhance the pCR rate. This has prompted some researchers to examine the relationship between the length of time between nCRT completion and surgery (nCRT–surgery interval) and subsequent tumor response. These studies suggested a potential association between a longer nCRT–surgery interval and an increased rate of pCR.[11] However, this work has been primarily from single institutions with small sample sizes (between 33 and 397 patients). Consequently, these studies lack sufficient power to adjust for the confounding impact of different radiotherapy dosages and variations in time to surgery after neoadjuvant therapy. The aim of this study was to examine the relationship between an increased nCRT–surgery interval compared with the current standard of care and pCR in a large, nationally representative cohort of rectal cancer patients who underwent neoadjuvant therapy before definitive surgical resection.

METHODS

Study population

Data for this study were retrieved retrospectively from the National Cancer Data Base (NCDB). This hospital-based cancer registry is sponsored by a joint program between the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The database collects information on all types of cancer from more than 1,500 hospitals with Commission-accredited cancer programs in the United States and Puerto Rico. Available information includes patient demographics, treatment regiments, tumor histology, and oncologic staging, as well as other patient characteristics.[12] Participating NCDB institutions report information based in the Facility Oncology Data Standards manual.[13]

A total of 321,768 rectal cancer cases were identified in the NCDB Participant User File report. The analysis was limited to cases of adenocarcinoma, mucinous adenocarcinoma, and signet ring cell carcinoma diagnosed between 2006 and 2011. The sample was further restricted to patients with clinical stage II and III rectal cancer who underwent chemoradiotherapy before surgery and who had a documented surgical resection. Patients with incomplete information about time from diagnosis to surgery and radiation as well as pathologic T and N status were excluded, for a total sample size of 17,255. Figure 1 shows this inclusion process.

Measurement of neoadjuvant chemoradiotherapy–surgery interval time

The database does not contain an explicit variable for nCRT–surgery interval time, but does contain information on number of days between the date of initial diagnosis and the date of the most definitive surgical procedure (A), number of days between the date of diagnosis and the date of radiation therapy initiation at any facility (B), and number of days of radiation therapy treatment (C). The nCRT–surgery interval time was calculated using the following formula: nCRT–surgery interval time = A − B − C. A priori, the nCRT–surgery interval time was categorized as <6 weeks, 6 to 8 weeks, and >8 weeks, based on current clinical practice of a 6- to

Figure 1. Inclusion diagram.

8-week interval. Patients with a short interval of <6 weeks were categorized separately in order to avoid artificially biasing the estimate for patients with an interval of >8 weeks. In a sensitivity analysis, patients in the <6 week group were excluded from the sample and the main analysis was repeated. Because these results were consistent with those from the first analysis, we present the results of the analysis that includes this group because they represented 25% of the cohort.

Measurement of pathologic complete response

The primary endpoint was pCR (ypT0N0). The NCDB does not contain an explicit variable for pCR, but contains individual variables for pathologically determined tumor size and/or extension[14] and pathologically determined absence, presence, or extent of regional lymph node metastasis (pN). Patients with pT0 and pN0 were defined as having a pCR and all others were defined as not having a pCR.

Main analyses

Chi-square tests and ANOVA, as appropriate to the data, were used to compare covariate distributions between the 2 outcomes groups and the 3 nCRT–surgery interval time groups. A priori, patient, hospital, and treatment characteristics that achieved a p value < 0.20 in bivariate analyses were included in multivariable analyses. These characteristics included age, sex, race, insurance status, education, income, metro/urban residence, facility location, facility type, facility volume, clinical stage, histology type, radiation dose, treatment regimen, and tumor size. Logistic regression models were used to assess the association between nCRT–surgery interval time and the odds of having pCR. Interaction terms were added to the multivariable logistic model (nCRT–surgery interval time*dose and nCRT–surgery interval time*treatment regimen) to assess for heterogeneity of the effect of the nCRT–surgery interval time for different levels of radiation dosage and treatment regimen. The p values for both of the interaction terms were not statistically significant and therefore were left out of the final model. All multivariable models used the propensity score method in order to adjust for selection effects of the observational dataset. The propensity score is the probability of being in an interval group given the covariates in the model. It was estimated using a multivariable multinomial logistic regression model and included as a covariate in all models.

In an attempt to identify a more specific nCRT–surgery interval time associated with the highest odds of pCR, a separate analysis was conducted in which patients

Table 1. Patient, Hospital and Pathologic Characteristics Between Neoadjuvant Chemoradiotherapy-Surgery Interval Time Groups

Characteristic	Interval 6 to 8 wk (n = 6,629)	Interval <6 wk (n = 3,786)	Interval >8 wk (n = 6,500)	p Value
Age, y, mean ± SD	59.5 ± 12.2	59.1 ± 12.3	60.3 ± 12.4	<0.001
Sex, n (%)				0.482
Male	4,129 (62.3)	2,362 (62.4)	3,991 (61.4)	
Female	2,500 (37.7)	1,424 (37.6)	2,509 (38.6)	
Race/ethnicity, n (%)				<0.001
White	5,818 (88.4)	3,323 (88.3)	5,540 (85.9)	
Black	463 (7.0)	286 (7.6)	591 (9.2)	
Native American	31 (0.5)	19 (0.5)	26 (0.4)	
Asian/Pacific Islander	224 (3.4)	112 (3.0)	261 (4.0)	
Other	45 (0.7)	23 (0.6)	34 (0.5)	
Primary payer, n (%)				<0.001
Private	3,590 (54.7)	2,060 (54.9)	3,152 (49.1)	
Not insured	302 (4.6)	161 (4.3)	376 (5.9)	
Medicaid	394 (6.0)	208 (5.5)	499 (7.8)	
Medicare	2,201 (33.5)	1,277 (34.0)	2,307 (36.0)	
Veterans Affairs/military	81 (1.2)	44 (1.2)	81 (1.3)	
Average income, n (%)				<0.001
<$30,000	755 (12.0)	489 (13.6)	776 (12.7)	
$30,000–$35,000	1,216 (19.3)	738 (20.5)	1,100 (18.0)	
$35.000–$46,000	1,777 (28.2)	1,062 (29.5)	1,746 (28.6)	
>$46,000	2,548 (40.5)	1,311 (36.4)	2,482 (40.7)	
Average education (not finishing high school), n (%)				<0.001
≥29%	938 (14.9)	623 (17.3)	1,016 (16.6)	
20%–28.9%	1,473 (23.4)	910 (25.3)	1,365 (22.4)	
14%–19.9%	1,638 (26.0)	869 (24.1)	1,547 (25.3)	
<14%	2,246 (35.7)	1,198 (33.3)	2,176 (35.6)	
Population density, n (%)				<0.001
Metro/adjacent	6,178 (93.2)	3,488 (92.1)	6,150 (94.6)	
Rural	451 (6.8)	298 (7.9)	350 (5.4)	
Comorbidity, n (%)				0.100
0	5,308 (80.1)	3,002 (79.3)	5,156 (79.3)	
1	1,102 (16.6)	629 (16.6)	1,073 (16.5)	
≥2	219 (3.3)	155 (4.1)	271 (4.2)	
Hospital type, n (%)				<0.001
Academic	2,540 (38.3)	1,104 (29.2)	2,698 (41.5)	
Community	533 (8.0)	431 (11.4)	491 (7.5)	
Comprehensive	3,519 (53.1)	2,228 (58.9)	3,282 (50.5)	
Other	37 (0.6)	23 (0.6)	29 (0.4)	
Hospital location, n (%)				<0.001
Northeast	440 (6.6)	252 (6.7)	375 (5.8)	
Atlantic	979 (14.8)	420 (11.1)	1,084 (16.7)	
Southeast	1,379 (20.8)	897 (23.7)	1,334 (20.5)	
Great Lakes	1,367 (20.6)	738 (19.5)	1,358 (20.9)	
South	402 (6.1)	272 (7.2)	304 (4.7)	
Midwest	772 (11.6)	415 (11.0)	629 (9.7)	
West	384 (5.8)	290 (7.7)	378 (5.8)	

(Continued)

Table 1. Continued

Characteristic	Interval 6 to 8 wk (n = 6,629)	Interval <6 wk (n = 3,786)	Interval >8 wk (n = 6,500)	p Value
Mountain	231 (3.5)	182 (4.8)	198 (3.0)	
Pacific	675 (10.2)	320 (8.4)	840 (12.9)	
Rectal cancer cases/y, n (%)				<0.001
0–10	779 (11.7)	639 (16.9)	782 (12.0)	
11–30	2,922 (44.1)	1,885 (49.8)	2,722 (41.9)	
>30	2,928 (44.2)	1,262 (33.3)	2,996 (46.1)	
Clinical stage, n (%)				0.010
II	3,156 (47.6)	1,915 (50.6)	3,122 (48.0)	
III	3,473 (52.4)	1,871 (49.4)	3,378 (52.0)	
Histology, n (%)				0.179
Adenocarcinoma	6,151 (92.8)	3,477 (91.8)	6,050 (93.1)	
Mucinous	430 (6.5)	281 (7.4)	401 (6.2)	
Signet ring cell	48 (0.7)	28 (0.7)	49 (0.7)	
Radiation dose, n (%)				<0.001
≥45 Gy	6,395 (96.5)	3,570 (94.3)	6,128 (94.3)	
<45 Gy	234 (3.5)	216 (5.7)	372 (5.7)	
Chemo regimen, n (%)				<0.001
RT + 1 agent	3,482 (56.6)	1,817 (53.7)	3,529 (60.1)	
RT + 2 agents	2,664 (43.4)	1,568 (46.3)	2,339 (39.9)	
Tumor size, mm, n (%)				0.03
0–25	2,915 (43.4)	1,735 (44.2)	2,840 (43.0)	
25–40	1,736 (25.9)	980 (24.9)	1,592 (24.1)	
40–50	860 (12.8)	482 (12.3)	934 (14.1)	
>50	1,203 (17.9)	733 (18.7)	1,245 (18.8)	
Year of diagnosis, n (%)				<0.001
2006	757 (11.4)	553 (14.6)	538 (8.3)	
2007	890 (13.4)	613 (16.2)	719 (11.1)	
2008	1,103 (16.6)	736 (19.4)	880 (13.5)	
2009	1,166 (17.6)	628 (16.6)	1,151 (17.7)	
2010	1,357 (20.5)	632 (16.7)	1,542 (23.7)	
2011	1,356 (20.5)	624 (16.5)	1,670 (25.7)	

RT, radiotherapy.

were categorized into weekly interval groups (<6 weeks, 6 to 8 weeks, 8 to 9 weeks, 9 to 10 weeks, etc). A separate multivariable logistic regression model was used to assess the relationship between this new interval variable and odds of pCR.

Secondary analyses

A series of analyses were conducted to determine if there was an association between nCRT–surgery interval time and several secondary outcomes. Multivariable logistic regression models were used to estimate the effect of nCRT–surgery interval time on 30-day mortality, 30-day unplanned readmission, and tumor downstaging (pT< cT or pN < cN vs no downstaging). An ordinal logistic regression model was used to assess the association between tumor regression grade (pCR, moderate response, minimal response, poor response) and nCRT–surgery interval time. All analyses were performed using SAS software, version 9.3 (SAS Institute Inc). The study was considered exempt by the University of Rochester institutional review board because it did not involve human subjects, according to federal regulations (IRB #00051935).

RESULTS

Of the 17,255 patients with stage II or III rectal cancer, 6,629 (38%) included in this study had an nCRT–surgery interval time greater than 8 weeks. Table 1 presents bivariate associations between covariates and the 3 nCRT–surgery interval time exposure groups. The mean nCRT–surgery interval time was 56.8 days. The proportion of pCR was 13.2% for those with an

Table 2. Bivariate Analysis of Patient and Hospital Characteristics by Overall Pathologic Complete Response Status

Characteristic	pCR (n = 1,983)	No pCR (n = 15,272)	p Value
Age, y, mean ± SD	60.2 ± 12.5	59.8 ± 12.4	0.11
Sex, n (%)			0.005
Male	1,169 (11.0)	9,505 (89.0)	
Female	814 (12.4)	5,767 (87.6)	
Race/ethnicity, n (%)			0.047
White	1,747 (11.7)	13,231 (88.3)	
Black	131 (9.6)	1,230 (90.4)	
Native American	11 (13.7)	69 (86.3)	
Asian/Pacific Islander	78 (12.8)	532 (87.2)	
Other	6 (5.9)	96 (94.1)	
Primary payer, n (%)			<0.001
Private	1,056 (11.8)	7,863 (88.2)	
Not insured	60 (7.0)	792 (93.0)	
Medicaid	91 (8.2)	1,023 (91.8)	
Medicare	726 (12.2)	5,243 (87.8)	
Other government	30 (14.2)	182 (85.8)	
Average income, n (%)			0.073
<$30,000	214 (10.4)	1,853 (89.6)	
$30,000–$35,000	348 (11.1)	2,793 (88.9)	
$35,000–$46,000	527 (11.3)	4,133 (88.7)	
>$46,000	791 (12.3)	5,665 (87.7)	
Average education (not finishing high school), n (%)			0.005
≥29%	259 (9.9)	2,363 (90.1)	
20%–28.9%	434 (11.3)	3,395 (88.7)	
14%–19.9%	469 (11.3)	3,676 (88.7)	
<14%	717 (12.5)	5,010 (87.5)	
Population density, n (%)			0.223
Metro/adjacent	1,865 (11.6)	14,253 (88.4)	
Rural	118 (10.4)	1,019 (89.6)	
Comorbidity, n (%)			0.819
0	1,565 (11.4)	12,144 (88.6)	
1	338 (11.8)	2,537 (88.2)	
≥2	80 (11.9)	591 (88.1)	
Hospital type, n (%)			<0.001
Academic	814 (12.6)	5,648 (87.4)	
Community	118 (7.9)	1,374 (92.1)	
Comprehensive	1,043 (11.3)	8,169 (88.7)	
Other	8 (91.0)	81 (9.0)	
Hospital location, n (%)			<0.001
Northeast	119 (10.9)	976 (89.1)	
Atlantic	311 (12.3)	2,211 (87.7)	
Southeast	374 (10.2)	3,288 (89.8)	
Great Lakes	431 (12.3)	3,074 (87.7)	
South	106 (10.6)	897 (89.4)	
Midwest	258 (13.7)	1,631 (86.3)	
West	100 (9.3)	977 (90.7)	
Mountain	55 (8.9)	565 (8.9)	
Pacific	229 (12.2)	1,653 (12.2)	

pCR, pathologic complete response.

nCRT–surgery interval time of >8 weeks, 11.7% for those with an nCRT–surgery interval time of 6 to 8 weeks, and 8.7% for those with an nCRT–surgery interval time of <6 weeks ($p < 0.001$).

Tables 2 and 3 show bivariate associations between pCR and patient characteristics and tumor/treatment characteristics, respectively. The proportion of patients experiencing pCR was then assessed by week after completion of neoadjuvant therapy and plotted against the cumulative proportion of pCR by week, as seen in Figure 2. The cumulative pCR rate appeared to peak between 10 and 11 weeks (Fig. 2).

Table 4 presents results from the multivariable logistic regression analyses. An nCRT–surgery interval time > 8 weeks was associated with 12% higher odds of pCR as compared with an interval time of 6 to 8 weeks (odds ratio [OR] 1.12, 95% CI 1.01 to 1.25). An interval time of < 6 weeks was associated with lower odds of pCR (OR 0.77, 95% CI 0.66 to 0.89). Patients with no insurance (OR 0.60, 95% CI 0.44 to 0.80) and Medicare (OR 0.67, 95% CI 0.52 to 0.85) had a lower odds of pCR. It is interesting to note that the odds of pCR increased over time. Furthermore, increasing tumor size was associated with higher odds of pCR. In addition, high volume hospitals had a higher odds of pCR (OR 1.42, 95% CI 1.12 to 1.80). In the comparison of weekly interval groups, results indicated that the optimal time window was 10 to 11 weeks, as compared to 6 to 8 weeks (OR 1.27, 95% CI 1.01 to 1.60).

Longer nCRT–surgery interval time was not associated with odds of 30-day mortality (OR 1.13, 95% CI 0.76 to 1.69) or tumor regression grade (OR 1.02, 95% CI 0.95 to 1.18), but was associated with higher odds of tumor downstaging (OR 1.11, 95% CI 1.02 to 1.25) and lower odds of unplanned 30-day readmission (OR 0.82, 95% CI 0.70 to 0.92).

DISCUSSION

It is well established that neoadjuvant therapy should be deployed in appropriate patients with locally advanced rectal cancer. In the midst of significant practice variation

Table 3. Bivariate Analysis of Tumor/Treatment Characteristics by Overall Pathologic Complete Response Status

Characteristic	pCR (n = 1,983), n (%)	No pCR (n = 15,272), n (%)	p Value
nCRT to surgery interval, wk			<0.001
6–8	775 (11.7)	5,854 (88.3)	
<6	329 (8.7)	3,457 (91.3)	
>8	855 (13.2)	5,645 (86.8)	
Annual rectal cancer cases, mean			<0.0001
0–10	188 (8.5)	2,012 (91.5)	
11–30	817 (10.8)	6,712 (89.2)	
>30	954 (13.3)	6,232 (86.7)	
Clinical stage			0.001
II	1,037 (12.3)	7,364 (87.7)	
III	946 (10.7)	7,908 (89.3)	
Histology			<0.001
Adenocarcinoma	1,955 (12.2)	14,040 (87.8)	
Mucinous	16 (1.4)	1,114 (98.6)	
Signet ring cell	12 (9.2)	118 (90.8)	
Radiation dose, Gy			0.005
≥45	1,904 (11.6)	14,433 (88.4)	
<45	79 (8.6)	839 (91.4)	
Chemo regimen			<0.0001
RT + 1 agent	1,129 (12.8)	7,699 (87.2)	
RT + 2 agents	672 (10.2)	5,899 (89.8)	
Tumor size, mm			<0.0001
0–25	962 (12.8)	6,528 (87.2)	
25–40	494 (11.5)	3,814 (88.5)	
40–50	246 (10.8)	2,030 (89.2)	
>50	281 (8.8)	2,900 (91.2)	
Year of diagnosis			<0.0001
2006	174 (9.2)	1,709 (90.8)	
2007	234 (10.3)	2,028 (89.7)	
2008	276 (9.9)	2,506 (90.1)	
2009	357 (11.9)	2,654 (88.1)	
2010	429 (11.9)	3,165 (88.1)	
2011	513 (13.8)	3,210 (86.2)	

nCRT, neoadjuvant chemoradiotherapy; pCR, pathologic complete response; RT, radiotherapy.

in the timing between neoadjuvant radiotherapy and surgery, the 1999 Lyon R90-01 trial compared a 2-week vs a 6-week radiotherapy–surgery interval. This trial demonstrated improved clinical tumor response (72% vs 53%) and more frequent histologic tumor regression (26% vs 10%), effectively establishing 6 weeks as the standard RT–surgery interval.[7] However, recent literature has suggested a link between longer nCRT–surgery duration and increased proportion of patients experiencing pCR, but subsequent conclusions regarding the optimal length of time between nCRT completion and surgery have varied.[11] Kalady and colleagues[15] found that an interval ≥ 8 weeks between neoadjuvant treatment completion and surgical resection was associated with a higher rate of pCR. Additionally, this was correlated with decreased local recurrence and better overall survival.[15] Sloothaak and coworkers[16] showed that surgical resection 15 to 16 weeks after the start of neoadjuvant radiation (approximately 10 weeks after completion) was independently associated with a higher rate of pCR (18%). In contrast, although some studies have reported an increase in pCR with a longer nCRT–surgery interval, others have reported no effect of an increased interval on pCR.[17]

In this study, several patient factors were associated with differences in pCR. Patients with Medicaid and no insurance coverage were noted to have a lower rate of pCR than patients with private insurance. This finding may indicate that patients with private health insurance receive more optimal care with fewer treatment interruptions, but this apparent disparity merits further inquiry because, for example, it may simply represent a surrogate marker for superior health performance status.[18,19] Although our analysis controlled for comorbidity index and clinical stage, one should not be too quick to draw direct conclusions from this finding given the observational nature of the data. Also, an increased odds of pCR was observed over time. However, this may be driven largely by a more recent willingness of providers to recommend a longer nCRT–surgery interval; 46% of patients had an nCRT–surgery interval of >8 weeks in 2011 compared with just 29% of patients in 2006.

Perhaps not surprisingly, increased hospital volume of rectal cancer resections was associated with an independent increase in pCR. This association was similar in strength to that of an nCRT–surgery interval >8 weeks. To our knowledge, this is the first time such an effect has been described in relation to pCR. This result suggests that there may be a comprehensive effect from an institution in which various members of the treatment team such as surgery, medical and radiation oncology, nursing, and other providers are familiar with the work-up and treatment of this disease process. This finding may further support the implementation of a national accreditation program for the perioperative management of patients with rectal cancer.

This study examined the relationship between a longer interval from neoadjuvant radiation to surgical resection and pCR in patients with clinical stage II and III rectal cancer. The overall proportion of patients with pCR was 11.5%, which is on the lower end of the range of

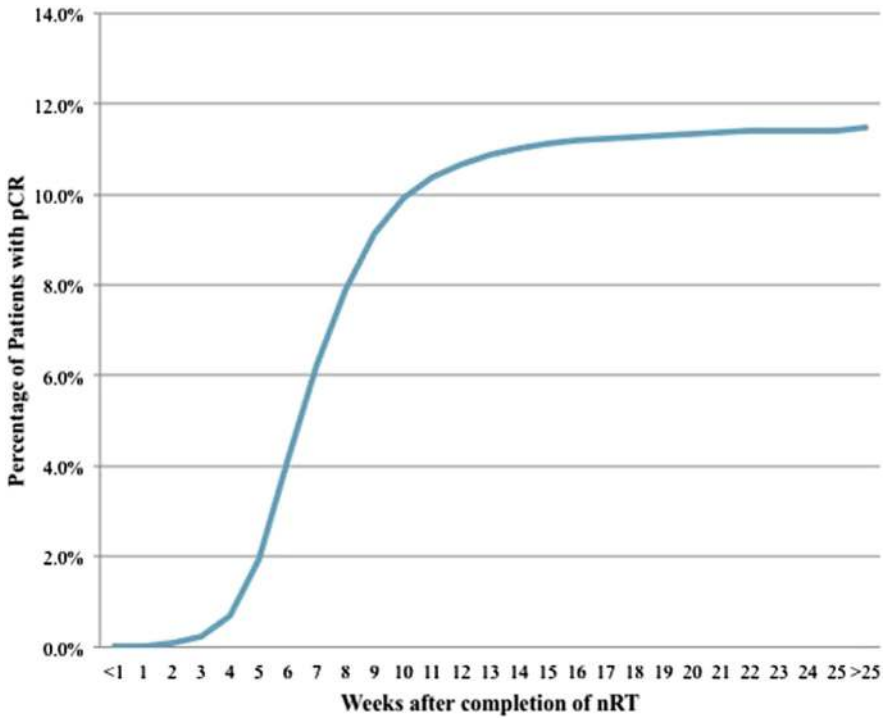

Figure 2. Cumulative proportion of pathologic complete response (pCr) by interval week. nRT, neoadjuvant radiotherapy.

the 8.4% to 22.0% previously reported.[11] It is not surprising to find lower unadjusted rates of pCR in this cohort because it is composed of patients with tumors or various histologic subtypes that have undergone neoadjuvant therapy regimens that may be incomplete. This wide range of reported rates is likely reflective of heterogeneous patient populations receiving different treatment regimens including varying times between neoadjuvant therapy and surgical resection.

This study shows that patients with an nCRT—surgery interval >8 weeks had a small but real increase in the odds of pCR compared with those with an interval between 6 and 8 weeks. To further explore this association, the effect of the nCRT—surgery interval by week was examined. When examining the cumulative proportion of pCR by week, a consistent increase in pCR between 4 and 11 weeks was seen, followed by a leveling off around 10 to 11 weeks. This finding was in accordance with the work of Kalady and associates.[15] In addition, patients who had an nCRT—surgery time of 6 to 8 weeks were compared with each subsequent week in order to determine if there was an optimal waiting period. These results showed that patients who had an nCRT—surgery interval of 10 to 11 weeks had 27% greater odds of pCR than those with an interval of 6 to 8 weeks, which was consistent with the unadjusted results.

However, one must recognize that the histologic response of a tumor to neoadjuvant radiation is not all or nothing, but rather, it exists along a continuum from no response to pCR, although it is typically measured as a categorical measure. This study also found an increased number of patients with tumor downstaging in the longer interval group. This finding is potentially important for both short-term and long-term oncologic outcomes. Obviously, tumor downstaging increases the chances of an R0 resection. In addition, tumor response, as measured by tumor regression grade and downstaging, has also been shown to increase overall and recurrence-free survival in locally advanced rectal cancer.[20-24] However, despite the results of these previous studies, one should acknowledge the imprecision of clinical T and N staging and as a result, tumor downstaging should not be weighted as strongly as our other outcomes.

It is important to acknowledge the limitations of this study. First, we have limited data about the exact treatment regimen of individual patients, such as specific chemotherapy agents, dose reductions, treatment breaks, or incomplete regimens. Additionally, we have limited information about surgical complications and no long-term mortality information. Also, other factors, such as intolerance to neoadjuvant therapy or resulting treatment toxicity, could result in truncated treatment and

Table 4. Binary Logistic Regression, Factors Associated with Pathologic Complete Response

Characteristic	Adjusted OR (95% CI)	p Value
nCRT to surgery interval, wk		
6–8	Reference	
<6	0.79 (0.68–0.91)	0.0009
>8	1.12 (1.02–1.28)	0.04
Rectal cancer resections annually, n		
1–10	Reference	
11–30	1.20 (0.95–1.51)	0.12
≥30	1.42 (1.12–1.80)	0.004
Treatment regimen		
RT, 1 chemo agent	Reference	
RT, ≥2 chemo agents	0.76 (0.68–0.85)	<0.0001
Radiation dose, Gy		
<45	Reference	
≥45	1.28 (0.99–1.65)	0.06
Histology		
Adenocarcinoma	Reference	
Mucinous	0.13 (0.08–0.22)	<0.001
Signet ring cell	0.78 (0.42–1.47)	0.45
Clinical stage		
II	Reference	
III	0.87 (0.78–0.96)	0.008
Tumor size, mm		
0–25	Reference	
25–40	1.14 (1.01–1.28)	0.04
40–50	1.18 (1.02–1.38)	0.03
>50	1.43 (1.24–1.66)	<0.0001
Female sex	1.22 (1.10–1.36)	0.0002
Primary payer		
Private	Reference	
Not insured	0.60 (0.44–0.80)	0.005
Medicaid	0.67 (0.52–0.85)	0.001
Medicare	1.03 (0.89–1.19)	0.74
Other government	1.22 (0.78–1.92)	0.38
Year of diagnosis		
2006	Reference	
2007	1.11 (0.88–1.39)	0.40
2008	1.05 (0.84–1.31)	0.66
2009	1.28 (1.04–1.59)	0.02
2010	1.31 (1.07–1.62)	0.01
2011	1.56 (1.28–1.92)	<0.001

Model also controlled for age, race, average income and education by ZIP code, hospital type, and hospital location.
nCRT, neoadjuvant chemoradiotherapy; OR, odds ratio; RT, radiotherapy.

potentially decreased pCR. Furthermore, we have no data on whether patients underwent reassessment at 6 to 8 weeks after completion of neoadjuvant therapy, which may have influenced the decision to increase the treatment interval. The higher proportion of patients with pCR in the >8 week group may be, at least in part, because of this. Because we do not know the reason for surgeon decision-making regarding longer intervals, some selection bias may be affecting the results.

It is now the practice of some surgeons to extend the interval to surgery if the patient exhibits endoscopic and/or radiologic evidence of a tumor response. Some centers are using PET/CT as an additional tool for interval assessment of tumor response.[25] Such a policy of interval assessment may allow for the identification of patients who have demonstrated a mucosal response to neoadjuvant therapy based on endoscopy supplemented by radiologic reassessment. Clearly, such patients are manifesting a good response to neoadjuvant therapy and could be allocated to a treatment path that involves a longer time period after neoadjuvant therapy to maximize tumor response. Ultimately, some of these patients may meet the criteria for a complete clinical response that at least allows the opportunity to consider an organ preservation strategy (so-called watch and wait strategy).[26] Conversely, patients who do not manifest any significant endoscopic or radiologic response on interval assessment at 6 to 8 weeks after completion of neoadjuvant therapy are not going to benefit from a longer duration post completion and should be scheduled for surgical resection. Such a policy recognizes the heterogeneity in treatment response among patients after neoadjuvant therapy, allowing responders to maximize the benefit from treatment while routing patients who have not responded to resection, as they will not benefit from a longer time interval.

When interpreting the encouraging data from this study, one must acknowledge that only a randomized trial can definitively answer whether a longer interval post neoadjuvant therapy results in improved tumor response and ultimately, complete response. In addition, such a study will allow for a more thorough assessment of the safety of patients with extended intervals. A few trials pursuing this aim are currently accruing patients.[27-30] However, it appears that clinical practice already appears to be shifting toward a longer duration to surgery, especially in high volume centers. This is of particular interest when considering the emerging role of nonoperative observational strategies currently being offered to select patients with complete clinical response and the randomized trial currently investigating the role of this strategy.[31] However, the issue of local recurrence is intimately tied to an observational strategy. Habr-Gama and coworkers[32] recently reported that local recurrence can occur in up to 31% of patients with initial complete clinical response, but salvage therapy is possible in ≥90% of recurrences. The patients in that study ultimately had 94% disease control and 78% organ preservation.[32]

It is certainly important to note that increasing the nCRT–surgery interval will lead to a delay in systemic adjuvant therapy, which could have implications for systemic disease recurrence and overall survival. To this end, randomized trials are exploring the role of systemic chemotherapy in the neoadjuvant period.[33,34] This is particularly important because a large proportion of rectal cancer patients die of metastatic disease, so optimizing systemic therapy is key. Furthermore, the addition of systemic therapy or novel agents to the neoadjuvant period could increase pCR. In addition, follow-up from these trials will be useful in determining whether patients with a longer nCRT–surgery interval experienced a higher incidence of distant recurrence.

Notwithstanding these limitations, our study does have a number of strengths. It is by far the largest study to date to address the relationship of nCRT–surgery interval and subsequent pCR. It is important to note that this database represents the majority of patients diagnosed and treated for rectal cancer in the US. Also, the robust level of oncologic and treatment information in this database overcomes some weaknesses of many administrative billing datasets.

CONCLUSIONS

In summary, with the largest and most direct examination of this topic to date, we have observed that an nCRT–surgery interval >8 weeks is independently associated with an increased proportion of rectal cancer patients experiencing both pCR and tumor downstaging after neoadjuvant radiation. Our data suggest an optimal interval of 10 to 11 weeks, with no observed impact on patient safety. This study also demonstrates that the association between longer intervals and increased pCR persists in a "real-world," population-based sample of rectal cancer patients, not only in highly specialized centers with carefully defined patient cohorts. These data provide strong support for consideration of extending the duration to surgery after completion of neoadjuvant therapy. Unquestionably, the issue of nonoperative approach for patients with apparent complete clinical response remains controversial. It will clearly be some years before sufficient data are available to answer some of these questions with confidence. Having said that, this study strongly suggests that interval assessment of tumor response after neoadjuvant therapy to decide on an extended interval after neoadjuvant therapy should become the standard of care, allowing rational choices to be made between radical resection and potentially nonoperative management.

Author Contributions

Study conception and design: Probst, Becerra, Monson, Fleming
Acquisition of data: Probst, Monson, Fleming
Analysis and interpretation of data: Probst, Becerra, Aquina, Tejani, Wexner, Garcia-Aguilar, Remzi, Dietz, Monson, Fleming
Drafting of manuscript: Probst, Becerra
Critical revision: Probst, Becerra, Aquina, Tejani, Wexner, Garcia-Aguilar, Remzi, Dietz, Monson, Fleming

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11–30.
2. Fleming FJ, Pahlman L, Monson JR. Neoadjuvant therapy in rectal cancer. Dis Colon Rectum 2011;54:901–912.
3. Ricciardi R, Roberts PL, Read TE, et al. Who performs proctectomy for rectal cancer in the United States? Dis Colon Rectum 2011;54:1210–1215.
4. Stitzenberg KB, Sanoff HK, Penn DC, et al. Practice patterns and long-term survival for early-stage rectal cancer. J Clin Oncol 2013;31:4276–4282.
5. Benson AB 3rd, Bekaii-Saab T, Chan E, et al. Rectal cancer. J Natl Compr Canc Netw 2012;10:1528–1564.
6. Monson JR, Weiser MR, Buie WD, et al. Practice parameters for the management of rectal cancer (revised). Dis Colon Rectum 2013;56:535–550.
7. Francois Y, Nemoz CJ, Baulieux J, et al. Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. J Clin Oncol 1999;17:2396.
8. Bosset JF, Calais G, Mineur L, et al. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results–EORTC 22921. J Clin Oncol 2005;23:5620–5627.
9. Gerard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol 2006;24:4620–4625.
10. Martin ST, Heneghan HM, Winter DC. Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. Br J Surg 2012;99:918–928.
11. Foster JD, Jones EL, Falk S, et al. Timing of surgery after long-course neoadjuvant chemoradiotherapy for rectal cancer: a systematic review of the literature. Dis Colon Rectum 2013;56:921–930.
12. Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. Ann Surg Oncol 2008;15:683–690.
13. American College of Surgeons. Facility Oncology Registry Data Standards. Available at: https://www.facs.org/quality-programs/cancer/ncdb/registrymanuals/cocmanuals/fordsmanual. Accessed January 7, 2014.
14. Abbas MA, Chang GJ, Read TE, et al. Optimizing rectal cancer management: analysis of current evidence. Dis Colon Rectum 2014;57:252–259.

15. Kalady MF, de Campos-Lobato LF, Stocchi L, et al. Predictive factors of pathologic complete response after neoadjuvant chemoradiation for rectal cancer. Ann Surg 2009;250:582–589.
16. Sloothaak DA, Geijsen DE, van Leersum NJ, et al. Optimal time interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. Br J Surg 2013;100:933–939.
17. Dolinsky CM, Mahmoud NN, Mick R, et al. Effect of time interval between surgery and preoperative chemoradiotherapy with 5-fluorouracil or 5-fluorouracil and oxaliplatin on outcomes in rectal cancer. J Surg Oncol 2007;96:207–212.
18. Kim MJ, Park JS, Park SI, et al. Accuracy in differentiation of mucinous and nonmucinous rectal carcinoma on MR imaging. J Computer-Assisted Tomog 2003;27:48–55.
19. Yu SK, Chand M, Tait DM, Brown G. Magnetic resonance imaging defined mucinous rectal carcinoma is an independent imaging biomarker for poor prognosis and poor response to preoperative chemoradiotherapy. Eur J Cancer 2014;50:920–927.
20. de Campos-Lobato LF, Stocchi L, da Luz Moreira A, et al. Downstaging without complete pathologic response after neoadjuvant treatment improves cancer outcomes for cIII but not cII rectal cancers. Ann Surg Oncol 2010;17:1758–1766.
21. Diaz-Gonzalez JA, Calvo FA, Cortes J, et al. Prognostic factors for disease-free survival in patients with T3-4 or N+ rectal cancer treated with preoperative chemoradiation therapy, surgery, and intraoperative irradiation. Int J Radiat Oncol Biol 2006;64:1122–1128.
22. Theodoropoulos G, Wise WE, Padmanabhan A, et al. T-level downstaging and complete pathologic response after preoperative chemoradiation for advanced rectal cancer result in decreased recurrence and improved disease-free survival. Dis Colon Rectum 2002;45:895–903.
23. Valentini V, Coco C, Picciocchi A, et al. Does downstaging predict improved outcome after preoperative chemoradiation for extraperitoneal locally advanced rectal cancer? A long-term analysis of 165 patients. Int J Radiat Oncol Biol Phys 2002;53:664–674.
24. Wheeler JM, Dodds E, Warren BF, et al. Preoperative chemoradiotherapy and total mesorectal excision surgery for locally advanced rectal cancer: correlation with rectal cancer regression grade. Dis Colon Rectum 2004;47:2025–2031.
25. Perez RO, Habr-Gama A, Sao Juliao GP, et al. Optimal timing for assessment of tumor response to neoadjuvant chemoradiation in patients with rectal cancer: do all patients benefit from waiting longer than 6 weeks? Int J Radiat Oncol Biol Phys 2012;84:1159–1165.
26. Maas M, Beets-Tan RG, Lambregts DM, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol 2011;29:4633–4640.
27. The Stockholm III Trial on Different Preoperative Radiotherapy Regimens in Rectal Cancer. Available at: http://clinicaltrials.gov/show/NCT00904813. Accessed July 13, 2014.
28. Cancer Research United Kingdom. Treatment for rectal cancer. Available at: http://www.cancerresearchuk.org/cancer-help/trials/a-trial-looking-best-time-surgery-after-treatment-rectal-cancer. Accessed July 13, 2014.
29. STARRCAT Trial: Surgical timing after radiotherapy for rectal cancer. Available at: http://www.controlled-trials.com/ISRCTN88843062. Accessed July 13, 2014.
30. Lefevre JH, Rousseau A, Svrcek M, et al. A multicentric randomized controlled trial on the impact of lengthening the interval between neoadjuvant radiochemotherapy and surgery on complete pathological response in rectal cancer (GRECCAR-6 trial): rationale and design. BMC Cancer 2013;13:417.
31. Garcia-Aguilar J, Memorial Sloan-Kettering Cancer Center. Trial evaluating 3-year disease free survival in patients with locally advanced rectal cancer treated with chemoradiation plus induction or consolidation chemotherapy and total mesorectal excision or non-operative management. In: Clinical Trials.gov. Bethesda (MD): National Library of Medicine (US); 2000. Available at: http://www.cancer.gov/clinicaltrials/search/view?cdrid=755893&version=HealthProfessional. NLM Identifier: NCT02008656. Accessed April 27, 2015.
32. Habr-Gama A, Gama-Rodrigues J, Sao Juliao GP, et al. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. Int J Radiat Oncol Biol Phys 2014;88:822–828.
33. Schrag D. Alliance for Clinical Trials in Oncology. Chemotherapy alone or chemotherapy plus radiation therapy in treating patients with locally advanced rectal cancer undergoing surgery. In: Clinical Trials.gov. Bethesda (MD): National Library of Medicine (US);2000. Available at: http://www.cancer.gov/clinicaltrials/search/view?cdrid=715321&version=HealthProfessional. NLM Identifier: NCT01515787. Accessed April 27, 2015.
34. Schrag D, Weiser MR, Goodman KA, et al. Neoadjuvant chemotherapy without routine use of radiation therapy for patients with locally advanced rectal cancer: a pilot trial. J Clin Oncol 2014;32:513–518.