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Predictors of Pathologic Complete Response Following Neoadjuvant Chemoradiotherapy for Rectal Cancer

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Abstract

Background—Some patients with rectal cancer who receive neoadjuvant chemoradiotherapy (nCRT) achieve a pathologic complete response (pCR) and may be eligible for less radical surgery or non-operative management. The aim of this study was to identify variables that predict pCR after nCRT for rectal cancer and to examine the impact of pCR on postoperative complications.

Methods—A retrospective review was performed of the NCDB from 2006 to 2011. Patients with rectal cancer who received nCRT followed by radical resection were included in this study. Multivariable analysis of the association between clinicopathologic characteristics and pCR was performed, and propensity-adjusted analysis was used to identify differences in postoperative morbidity between pCR and non-pCR patients.

Results—A total of 23,747 patients were included in the study. Factors associated with pCR included lower tumor grade, lower clinical T and N stage, higher radiation dose, and delaying surgery by more than 6–8 weeks after the end of radiation, while lack of health insurance was linked with a lower likelihood of pCR. Complete response was not associated with an increased risk of major postoperative complications.

Conclusions—Several clinical, pathologic, and treatment variables can help to predict which patients are most likely to have pCR after nCRT for rectal cancer. Awareness of these variables can be valuable in counseling patients regarding prognosis and treatment options.

Neoadjuvant therapy is the current standard of care for locally advanced rectal cancer. In the US, this therapy typically takes the form of concurrent long-course chemoradiation (nCRT). Some patients with rectal cancer who receive nCRT achieve a pathologic complete response (pCR) that is associated with an improved long-term prognosis compared with patients who have residual tumor in the final specimen.^{1,2} Standard surgery for rectal cancer can result in significant morbidity with negative long-term impact on bowel, urinary and sexual function,

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and the need for a temporary or permanent ostomy. Over the past decade, there has been increasing interest in ‘watchful waiting’ as an alternative to radical resection.^{3–5} In this approach, patients who demonstrate a complete clinical response (cCR) following neoadjuvant therapy do not undergo surgery but instead are monitored closely and offered salvage surgery in the event of relapse.⁶ Emerging data suggest that certain low-risk tumors may be appropriate candidates for this strategy.^{7–11} However, it is well established that cCR does not equate to pCR as residual tumor may be identified in up to 75 % of resected specimens where the gross tumor has clinically disappeared.^{12,13} Furthermore, even among patients with complete pathologic resolution of the primary tumor, residual nodal disease is present in up to 15 % of cases^{14,15} and is an independent predictor of poor outcomes.¹⁶ Consequently, it is of clinical interest to identify factors that can predict pCR, both to optimize the likelihood of achieving pCR and to select patients who may potentially avoid surgery after completion of nCRT.

The aim of this study was to identify clinicopathologic and treatment-related variables that predict pCR after nCRT for rectal cancer and to examine the impact of pCR on postoperative complications.

METHODS

After approval from the Institutional Review Board, the American College of Surgeons’ (ACS) National Cancer Database (NCDB) was queried to identify patients from 2006 to 2011 with non-metastatic rectal adenocarcinoma who received nCRT followed by radical surgery. Documentation of several cancer-specific variables (e.g. circumferential resection margin) in the NCDB began at various time points between 2004 and 2010; thus, the study period was chosen to provide the largest sample of rectal cancer patients with the most complete information available in the database at the time the study was conducted. Patients were queried from the rectal cancer Participant User Files (PUF) of the NCDB. For adenocarcinoma, the following International Classification of Diseases (ICD)-O-3 codes were used: 8140–8148, 8200, 8260–8263, and 8480–8496.

Data were collected regarding patient, disease, and treatment variables. Patient variables included age, sex, race, geographic setting, insurance coverage, and comorbidities. Disease variables included year of diagnosis, grade, size, clinical TNM stage, pathologic TNM stage, number of nodes examined, preoperative carcinoembryonic antigen (CEA), presence of tumor deposits, lymphovascular invasion (LVI), perineural invasion (PNI), tumor regression grade, and margin status. Treatment variables included treating facility type, surgical procedure, surgical approach, radiation modality, radiation dose, and interval from end of radiation to surgery.

The main outcome was predictors of pCR, defined as the absence of tumor in the final pathologic specimen (ypT0/x, N0/x). The notation ‘x’ in pathology reports indicates that tumor cannot be assessed in the specimen; among patients with biopsy-proven tumor who then undergo neoadjuvant treatment, it signifies the absence of tumor in the final specimen (and thus a complete response). Additional outcomes were the associations between postoperative complications with pCR. Postoperative length of stay (LOS), 30-day mortality

and unplanned readmission were used as surrogate indicators for postoperative complications as this variable is not documented in the NCDB.

Patient, disease, and treatment characteristics were reported using the mean, median and range for continuous variables, and frequencies and relative frequencies for categorical variables. The association between response status and patient characteristics were evaluated using the Mann–Whitney *U* test and Fisher's exact test for continuous and categorical variables, respectively. Factors that may be independently associated with response status were identified using a multivariable logistic regression model and the backwards selection method (alpha exit = 0.05).

The association between LOS and response status was examined using a two-sided independent sample *t* test, where a log-transformation was used to meet assumptions. Analysis of covariance (ANCOVA) was then used to compare LOS between response groups while adjusting, via propensity score, for the significant factors identified in the multivariable model.

The association between response status and both 30-day mortality and unplanned readmission was examined using Fisher's exact test. A stratified logistic regression model, stratified by propensity score, was used to evaluate these associations while adjusting for the factors identified in the multivariable model. Odds ratios and corresponding 95 % confidence intervals were obtained from model estimates.

All analyses were conducted using SAS v9.4 (SAS Institute Inc., Cary, NC, USA) at a significance level of 0.05.

RESULTS

A total of 23,747 patients, with a median age of 60 years, met the inclusion criteria. Characteristics of the study cohort are summarized in Table 1. The vast majority of patients were White, had few or no comorbidities, and had government or private health insurance. Tumors were predominantly moderately differentiated and approximately one-third were larger than 5 cm. Pre-therapy clinical stage was T3–4 in 85 % of patients and node positive in 46.7 % of patients. On final pathology, these proportions decreased to 44.3 and 27.6 %, respectively, indicating downstaging in a substantial proportion of the patient cohort. Most patients were treated with external beam therapy at a dose of 4500–5040 cGy, and sphincter preservation was possible in two-thirds of the patients. The interval from the end of radiation to surgery was 6 weeks or longer in 77.2 % of patients.

Factors Associated with Pathologic Complete Response (pCR)

The proportion of patients with pCR was 23.3 %. On multivariable analysis, larger pre-therapy tumor size, lower grade, lower clinical T and N stage, higher radiation dose, and delaying surgery by more than 6–8 weeks after the end of radiation were independently associated with pCR, while lack of health insurance was associated with a lower likelihood of pCR. Patients treated earlier in the study cohort were more likely to have pCR. A pCR

was associated with a significant decrement in the number of nodes examined in the pathologic specimen compared with specimens with residual tumor (Table 2).

Postoperative Morbidity

In the propensity-adjusted analysis, the mean LOS was 0.23 days shorter in the pCR group ($p = 0.045$). Overall 30-day mortality was 0.7 %, and the unplanned readmission rate was 7.1 %. No difference in 30-day mortality or unplanned readmissions was observed between the two groups (Table 3).

DISCUSSION

Predictors of pCR

Rates of pCR after neoadjuvant treatment for rectal cancer are highly variable in the literature, ranging from 0 to 30 % or higher, depending on the population in question.^{17–36} In our national sample, 23.3 % of non-metastatic rectal cancer patients treated with nCRT and radical surgery between 2006 and 2011 achieved a pCR, without significant differences being identified between facility locations on multivariable analysis. This represents an impressive fraction of treated cases and suggests appropriate application of standard techniques across cancer treatment centers nationwide.

We identified several clinicopathologic and treatment-related factors that were independently associated with pCR. Lower tumor grade, lower clinical T and N stage, higher radiation dose, and delaying surgery by more than 6–8 weeks after the end of radiation were associated with higher odds of pCR, whereas lack of health insurance was linked with a lower likelihood of pCR. Numerous retrospective cohort studies have previously examined this question and have identified a variety of disease-related variables as potential predictors of pCR. These include low pre-therapy CEA,^{17,21,26, 28,37,38} low CEA after nCRT,^{29, 35} small pre-^{31,38} and post-treatment tumor size,²² pre-treatment tumor ‘movability’,²² low N category,³¹ low tumor grade,³⁶ shorter distance from the anal verge,^{18,36} smaller circumferential tumor extent,^{18,28} and low neutrophil to lymphocyte ratio.³⁸ Identification and awareness of these factors may help to predict which patients are more likely to achieve pCR with neoadjuvant treatment, and may be used to counsel patients more accurately regarding their prognosis and treatment options. It is interesting that several of these factors are also those that make a rectal tumor more suitable for transanal excision;³⁹ thus, patients with tumors that exhibit most or all of these features may potentially be identified as safe candidates for less radical surgery following neoadjuvant therapy.⁹

Studies have also found a number of treatment-related variables that are associated with a higher likelihood of complete response, including the interval from the end of radiation to surgery,^{19,20,23,27,32,40–42} type of concurrent chemotherapy used,⁴³ and radiation dose.^{44–46} In particular, the interval from the end of radiation to surgery has been of special interest and has been directly addressed by multiple studies as well as a meta-analysis.⁴¹ Although the exact ideal interval to optimize pCR has not been identified, the overall conclusion from these studies is that pCR rates improve with delaying surgery by more than 6–8 weeks after the end of nCRT. A recently published study using NCDB data provided the largest dataset

focusing on the question of the interval from the end of nCRT to surgery, and concurred with the published literature that an interval of more than 8 weeks is associated with increased rates of complete response.⁴² Our results, which are derived from the same dataset, are consistent with those findings but, furthermore, offer additional variables that can help identify those patients most likely to respond.

There is an established relationship between radiation dose and achieving pCR,^{44–46} which was reflected in our own findings, that a higher radiation dose was associated with an increased likelihood of pCR. Current National Comprehensive Cancer Network (NCCN) guidelines for resectable tumors recommend a standard dose of 4500 cGy, with consideration for a tumor bed boost of 540 cGy.⁴⁷ In our study, more than 80 % of patients were treated with a dose within this range. The use of progressively higher doses naturally raises concerns regarding treatment toxicity; however, a recent meta-analysis of 14 studies including 487 patients with locally advanced rectal cancer, all treated with doses of 6000 cGy, demonstrated acceptable early toxicity, with a pCR rate of 20.4 % and a pooled estimate of 10.3 % for grade 3 or higher toxicity.³⁴ The application of intensity-modulated radiation therapy (IMRT), while not yet standard treatment, may help to reduce this toxicity further without compromising response rates.^{25,33,48–50} Similar to previous studies, we did not identify a lower likelihood of pCR in patients who received IMRT relative to standard external beam therapy.

A new finding of this study was that lack of health insurance independently predicted a lower likelihood of pCR. Lack of insurance is known to be associated with poorer outcomes for several cancer types, including rectal cancer,^{51–54} which may be related to disparities in access to comprehensive, guideline-based cancer services. However, it is important to remember that all patients in this study cohort received nCRT and radical surgery, regardless of insurance status, suggesting that other, unmeasured factors associated with a lack of insurance likely affect patient outcomes and response to treatment, beyond the issue of access. This reinforces the need to address gaps in the care and overall health of this vulnerable patient population.

Two unexpected findings resulted from our multivariable analysis. First, the likelihood of achieving pCR decreased over the course of the study period. One explanation for this finding is that a proportion of patients with a cCR may have been treated with transanal excision or non-operative management during the study period. Excluding these patients (who are more likely to have pCR on the final specimen) from the study population would result in skewing of the sample to include fewer patients with pCR over time. Other possible contributing factors include the administration of short-course radiotherapy or chemotherapy without radiotherapy as alternative neoadjuvant strategies for rectal cancer patients. However, among all patients treated with neoadjuvant therapy during the study period, only 2.1 % received an abbreviated radiation dose (<3000 cGy) and only 3.9 % received chemotherapy without radiotherapy, with no significant increase in either strategy over time. Thus, these factors are unlikely to explain the reduction in pCR in later years.

Skewing of the patient sample due to selection bias likely also explains the other surprising result of our analysis, namely that larger tumor size correlated with a higher likelihood of

pCR, a finding that directly contradicts those of previous studies.^{22,31,38} We hypothesized that proportionately more of the smaller tumors were selected for transanal excision after nCRT and were excluded from the analysis if they had pCR, whereas those with residual disease went on to have definitive radical resection and were thus included in our patient cohort. This would make it seem as though smaller size correlates negatively with pCR.

Postoperative Morbidity

There has been some controversy regarding the association between pCR and postoperative morbidity after nCRT. Horisberger et al.⁵⁵ compared rectal cancer patients receiving nCRT with a concurrent capecitabine and irinotecan regimen by type of pathologic response (major vs. minor responders/non-responders) and found an association between major response to nCRT and anastomotic leak rate. Stelzmueller et al.⁵⁶ found that tumor downstaging in the final specimen was associated with an increased risk of major postoperative complications. In addition, Maggiori et al.⁵⁷ found the reverse to be true in a group of patients undergoing laparoscopic total mesorectal excision, with fewer major complications, less infection-related morbidity, lower clinical anastomotic leak rates, and shorter LOS in patients with pCR. On the other hand, Duldulao et al.⁵⁸ and Berkel et al.⁵⁹ found no significant difference in postoperative complications between patients with pCR compared with non-pCR patients.

Using LOS, 30-day mortality, and unplanned readmissions as surrogates for major postoperative complications, we found no significant differences between patients with pCR and those with residual tumor. Our propensity-adjusted analysis demonstrated a slightly longer LOS among patients with residual tumor relative to those with pCR, but it is questionable whether this is of clinical relevance.

Strengths and Limitations of the Study

This study represents the largest published dataset to date examining predictors of pCR after nCRT in rectal cancer. The NCDB accounts for 70 % of all newly diagnosed cases treated in the US during the study period. These data are derived from Commission on Cancer (COC)-accredited facilities which are subject to national standards for maintenance of quality of cancer care. As such, they provide a robust reinforcement to the existing literature and a fairly accurate representation of national outcomes. It is possible that rectal cancer cases not represented in the NCDB (and therefore excluded from this study) may not meet national standards with respect to management of this disease, and may differ in the way they were treated. However, these cases are expected to comprise predominantly patients who did not receive neoadjuvant treatment before surgery, since receiving neoadjuvant treatment is itself a quality measure for care of locally advanced rectal cancer. As our study focused on patients who completed neoadjuvant treatment, our findings are likely valid for addressing the study question.

Limitations of this study include missing or unmeasured variables that may potentially be related to pCR, including information on specific chemotherapy regimens. As noted earlier, the exclusion of patients treated with transanal excision or non-operative management is a source of potential bias. On the other hand, including such patients in the analysis would be problematic given the lack of nodal staging information for that subset of patients.

CONCLUSIONS

Nearly one-quarter of rectal cancer patients undergoing surgical resection achieved a pCR following treatment with nCRT. pCR was not associated with an increased risk of major postoperative complications. Factors associated with pCR included lower tumor grade, lower clinical T and N stage, higher radiation dose, and delaying surgery by more than 6–8 weeks after the end of radiation, while lack of health insurance was linked with a lower likelihood of pCR. Awareness of these variables can be valuable in counseling patients regarding prognosis and treatment options.

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TABLE 1

Characteristics of the study cohort

Variable	All (%)	pCR (%)	Residual tumor (%)	<i>p</i> value ^a
Number of patients	23,747	5512 (23.3)	18,235 (76.8)	–
Demographic factors				
Age (years)				
Mean/median/range	60.0/60.0/18.0–90.0	60.5/60.00/19.0–90.0	59.8/60.0/18.0–90.0	<0.001
Sex				
Male	62.2	24.3	75.7	0.031
Female	37.8	25.5	74.5	
Race				
White	87.4	24.7	75.3	0.101
Black	7.9	23.5	76.5	
Other	4.7	26.8	73.2	
Insurance				
Private	52.4	25.2	74.8	0.090
Government	42.8	24.5	75.5	
None	4.8	21.9	78.1	
Setting				
Metropolitan	78.6	24.7	75.3	0.312
Urban	18.6	25.4	74.6	
Rural	2.8	23.4	76.6	
Comorbidities ^b				
0	79.8	24.9	75.1	0.305
1	16.3	23.7	76.3	
2+	3.8	25.5	74.5	
Disease factors				
Year				
2006	12.9	31.9	68.1	<0.001
2007	15.0	30.4	69.6	
2008	17.0	27.3	72.7	
2009	17.9	25.2	74.8	
2010	18.6	18.2	81.8	
2011	18.6	18.8	81.2	
Grade				
Well differentiated	8.6	23.3	76.7	<0.001
Moderately differentiated	76.8	22.8	77.2	
Poorly differentiated	13.4	19.6	80.4	
Undifferentiated	1.2	14.4	85.6	
Pre-therapy tumor size (cm)				
No tumor	0.1	100.0	0	<0.001
<1	4.7	9.4	90.6	

Variable	All (%)	pCR (%)	Residual tumor (%)	<i>p</i> value ^a
1–2	10.9	11.8	88.3	
2–3	16.2	18.0	82.0	
3–4	18.5	24.5	75.5	
4–5	16.9	24.7	75.3	
5+	32.5	22.8	77.2	
Clinical TNM stage				
0	0.1	18.8	81.3	<0.001
1	9.1	23.7	76.3	
2	44.5	25.9	74.1	
3	46.3	24.0	76.0	
Clinical T category				
1	3.8	28.3	71.7	<0.001
2	10.6	26.4	73.6	
3	78.7	24.9	75.1	
4	6.8	17.9	82.1	
Clinical N category				
0	53.2	25.6	74.4	<0.001
1	41.4	25.0	75.0	
2	5.3	17.9	82.1	
Pathologic T category				
0/X	24.5	100	0	–
1	6.3	0	100	
2	24.8	0	100	
3	40.8	0	100	
4	3.5	0	100	
Pathologic N category				
0/X	72.4	32.1	67.9	<0.001
1	19.3	6.7	93.3	
2	8.3	2.7	97.3	
Number of nodes examined				
Mean/median/range	13.5/13.0/ 0.0–90.0	12.5/12.0/ 0.0–90	0 13.8/13.0/ 0.0–90.0	<0.001
CEA				
Negative	57.2	26.7	73.3	<0.001
Positive	42.8	18.5	81.5	
Tumor deposits				
Absent	93.7	18.0	82.0	<0.001
Present	6.3	3.6	96.4	
Tumor regression grade				
0	32.6	70.3	29.7	<0.001
1	37.1	4.9	95.1	
2	21.0	2.2	97.8	
3	9.3	2.0	98.0	

Variable	All (%)	pCR (%)	Residual tumor (%)	p value ^a
LVI				
Negative	85.7	13.0	87.0	<0.001
Positive	14.3	2.5	97.5	
PNI				
Negative	89.8	17.3	82.7	<0.001
Positive	10.2	1.9	98.1	
Margin status				
Negative	94.5	74.4	25.6	<0.001
Positive	5.5	11.5	88.5	
Treatment factors				
Facility type				
CCP	9.3	23.4	76.6	0.008
CCCP	54.4	25.5	74.5	
Academic	36.4	24.0	76.0	
Surgery				
Partial proctectomy	58.5	25.5	74.5	<0.001
Total proctectomy	28.1	23.5	76.5	
Pull through	8.3	25.8	74.2	
Total proctocolectomy	2.4	24.7	75.3	
Pelvic exenteration	2.7	18.8	81.2	
Surgical approach				
MIS	28.8	20.8	79.2	0.036
Open/converted to open	71.2	17.6	82.4	
Radiation modality				
External beam	73.5	25.0	75.0	0.681
Conformal/3D	14.8	24.1	75.9	
IMRT	11.1	24.2	75.8	
Other	0.5	22.8	77.2	
Radiation dose (cGy)				
<4500	3.4	19.9	80.1	0.024
4500–5040	81.2	25.2	74.8	
5041–5400	10.6	25.7	74.3	
>5400	4.8	26.4	73.6	
Interval from end of radiation to surgery (weeks)				
<6	22.8	22.1	77.9	0.088
6–8	36.7	24.3	75.7	
8–10	23.0	23.7	76.3	
10–12	8.7	23.6	76.4	
12+	8.7	23.3	76.7	

pCR pathologic complete response, CEA carcinoembryonic antigen, LVI lymphovascular invasion, PNI perineural invasion, 3D three-dimensional, IMRT intensity-modulated radiation therapy, NCDB National Cancer Database

^aUnivariable model

^bComorbidities are documented in the NCDB as the Charlson–Deyo comorbidity score

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TABLE 2

Factors associated with pCR (multivariable model)

Variable	Adjusted OR for pCR (95 % CI)	p value
Insurance		
Private	1.0	0.001
Government	0.98 (0.89–1.08)	
None	0.64 (0.50–0.81)	
Year of diagnosis		
2006	1.0	<0.001
2007	0.95 (0.81–1.11)	
2008	0.68 (0.58–0.80)	
2009	0.67 (0.57–0.78)	
2010	0.35 (0.30–0.42)	
2011	0.38 (0.32–0.45)	
Grade		
Well differentiated	1.0	0.002
Moderately differentiated	1.01 (0.86–1.19)	
Poorly differentiated	0.78 (0.63–0.96)	
Undifferentiated	0.73 (0.46–1.17)	
Pre-therapy tumor size (cm)		
<1	1.0	<0.001
1–2	1.22 (0.87–1.71)	
2–3	2.16 (1.59–2.95)	
3–4	3.16 (2.33–4.29)	
4–5	3.13 (2.30–4.25)	
>5	3.07 (2.27–4.14)	
Clinical T category		
T1	1.0	0.002
T2	0.84 (0.63–1.12)	
T3	0.80 (0.62–1.04)	
T4	0.57 (0.42–0.78)	
Clinical N category		
N0	1.0	0.014
N1	0.97 (0.88–1.07)	
N2	0.71 (0.56–0.89)	
Radiation dose (cGy)		
<4500	1.0	0.015
4500–5040	1.40 (1.06–1.85)	
5041–5400	1.57 (1.16–2.13)	
>5400	1.63 (1.16–2.28)	
Interval to surgery (weeks)		
<6	1.0	0.012

Variable	Adjusted OR for pCR (95 % CI)	p value
6–8	1.15 (1.02–1.30)	
8–10	1.27 (1.11–1.45)	
10–12	1.18 (0.98–1.42)	
>12	1.25 (1.03–1.51)	
Nodes examined		
Per additional node	0.99 (0.98–0.99)	<0.001

pCR pathologic complete response, *OR* odds ratio, *CI* confidence interval

TABLE 3

Postoperative course by response status (propensity-adjusted analysis)

	pCR [mean (SE)]	Residual tumor [mean (SE)]	Mean difference (SE)	<i>p</i> value
LOS, days	7.26 (0.14)	7.49 (0.07)	−0.23 (0.15)	0.045

	pCR (%)	Residual tumor (%)	Adjusted OR (95 % CI)	pCR versus residual tumor
30-day mortality	0.7	0.7	0.61 (0.33–1.14)	0.119
Unplanned readmissions	6.6	7.3	0.90 (0.75–1.08)	0.271

pCR pathologic complete response, *SE* standard error, *LOS* length of stay, *OR* odds ratio, *CI* confidence interval