Published in final edited form as:

J Surg Res. 2018 April ; 224: 215–221. doi:10.1016/j.jss.2017.11.072.

Pathologic response following treatment for locally advanced rectal cancer: Does location matter?

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Abstract

BACKGROUND: Despite advances in the treatment of rectal adenocarcinoma, the management of locally advanced disease remains a challenge. The standard of care for patients with Stages II and III rectal cancer includes neoadjuvant chemoradiation followed by total mesorectal excision and post-operative chemotherapy. Much effort has been dedicated to the identification of predictive factors associated with pathologic complete response (pCR). The aim of our study was to examine our institutional experience and determine whether any association exists between anatomic tumor location and the rate of pCR. We hypothesized that lesions more than 6cm from the anal verge are more likely to achieve a pCR.

METHODS: Using data from our prospectively maintained tumor registry, a query was completed for all patients with locally advanced rectal adenocarcinoma who underwent treatment at Fox Chase Cancer Center from 2002–2015. Demographics, pre-treatment, post-treatment, and final pathologic TNM staging data were collected as well as treatment intervals in days, recurrence status, overall survival, and disease-free survival. Patients with incomplete endoscopic data, staging information, survival, or recurrence status were excluded. The primary outcome measured was the degree of pathologic response. Logistic regression was used to adjust for covariates.

RESULTS: Of the 135 patients eligible in the study cohort, 39% were female and 61% were male. Regarding initial clinical stage, 43% were Stage II and 57% were Stage III. A total of 29% had a pCR, 43% had partial pathologic response, and 28% had no response from neoadjuvant treatment. Tumor location ranged from 0–13cm from the anal verge. Longitudinal tumor length

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Poster presentation completed at the 2017 Annual Scientific Meeting of the American Society of Colon & Rectal Surgeons (June 10th–14th), Seattle, WA.

All authors made substantial contributions to each phase of our study's development and manuscript drafting. Specifically, Drs. Ward, Sigurdson, and Farma helped develop the study's conception and design. Data acquisition was largely performed by Dr. Ward, Mr. Esposito, Dr. Wernick, and Mr. Manstein. Ms. Ruth, Dr. Ward, and Dr. Sorenson assisted in the analysis and interpretation of data. All authors were involved in the drafting or critical revision of the manuscript and gave individual approval of this submitted version.

was recorded in 111 patients, facilitating the calculation of mean tumor distance from the anal verge. This ranged from zero to 15.5cm. Univariate and multivariable analyses were completed using pCR as a primary outcome. No statistically significant difference was noted based on tumor location, regardless of measurement approach.

CONCLUSION: Anatomic location of cancer of the rectum does not affect pCR following neoadjuvant therapy and subsequent surgical resection.

Keywords

rectal adenocarcinoma; complete pathologic response; neoadjuvant therapy; rectal tumor location; rectal cancer

INTRODUCTION

Despite advances in the multidisciplinary treatment of rectal adenocarcinoma, the management of locally advanced disease remains a challenge.[1] It is well established that the current standard of care for patients with Stages II and III rectal cancer includes neoadjuvant chemoradiation followed by total mesorectal excision and post-operative chemotherapy.[2, 3] Of those patients who undergo neoadjuvant therapy and subsequent surgical resection, it is estimated that approximately 15% to 30% achieve a complete pathologic response (pCR) with no tumor cells identified within the surgical specimen.[2, 4] These findings have contributed to a number of single-institution series demonstrating successful patient outcomes for a “Wait and See” approach which eliminates surgery following evidence of pCR with neoadjuvant treatment alone.[4] Most patients attain more modest results which include tumor downstaging and clinical improvement as a consequence of preoperative and perioperative oncologic therapy.[5]

Unfortunately, despite the relatively uniform administration of preoperative therapy, a substantial subset of patients achieves minimal to no response at the time of post-operative pathologic analysis.[5] Although individual tumor biology is assumed to be largely responsible, the ability to predict the pathologic response to neoadjuvant chemoradiation remains elusive.[6] Substantial research has been dedicated to the identification of predictive factors associated with the degree of pathologic response.[2] If it were possible to accurately predict an individual patient’s complete response to neoadjuvant treatment (i.e., pCR), organ preservation and the avoidance of an unnecessary extirpative procedure would be feasible. Similarly, if the reliable prediction of a tumor’s resistance to preoperative chemoradiation was possible, a given patient could avoid the local and systemic toxicity associated with such treatment while proceeding directly to surgery.[7]

While attempting to identify predictive factors of pathologic response in rectal cancer, only a small number of studies have examined anatomic tumor location within the rectum as a possible contributor to a lesion’s responsiveness to neoadjuvant treatment.[8–15] Previously, there had been limited evidence that tumor location affects pathologic response. However, recent data suggest that mid-rectal tumors positioned 4–6cm and 6–8cm from the anal verge are more likely to achieve pCR (OR 2.54 [95%CI 1.36–4.75] and 2.55 [95%CI 1.37–4.74], respectively) [15] and one prior investigation reported a statistically significant correlation

between pCR and tumors greater than 5cm from the anal verge (OR 3.82 [95%CI 1.6–8.7]). [14] The aim of our study was to examine our institutional experience and determine whether any association exists between anatomic tumor location and the rate of pCR. In light of the limited evidence suggesting decreased pCR with low rectal tumors,[14, 15] we hypothesized that lesions more than 6cm from the anal verge are more likely to achieve a pCR.

MATERIALS & METHODS

Following approval by our center's institutional review board, the prospectively maintained Fox Chase Cancer Center tumor registry was queried for all patients with locally advanced rectal adenocarcinoma who underwent treatment at our institution from 2002–2015. Waiver of individual informed consent was granted for this retrospective investigation. Only those patients with AJCC Stage II or III disease who underwent pretreatment endoscopic evaluation at Fox Chase, followed by neoadjuvant chemoradiation and subsequent surgical resection were included (Figure 1). Standard practice at Fox Chase involved definitive surgical extirpation 8–10 weeks following the completion of external beam radiation. Throughout the study period, all patients underwent an open, laparoscopic, or robotic total mesorectal excision. Demographic, pre-treatment, post-treatment, and final pathologic TNM staging data were collected as well as treatment intervals in days, recurrence status, and vital status. Specific pre-treatment endoscopic measurements were obtained using standard colonoscopy and endorectal ultrasound. Measurements included distance of the distal-most tumor edge from the anal verge (DTAV), overall tumor length (OTL), and mean tumor distance from the anal verge (MTAV). MTAV, a more descriptive assessment of tumor location within the rectum, was calculated by adding half the OTL to DTAV (Figure 2). Patients with incomplete endoscopic data, staging information, survival, or recurrence status were excluded. The primary outcome was the degree of pathologic response.

STATISTICAL ANALYSIS

We explored the association between the tumor location variables (DTAV or MTAV) and pCR by initially categorizing the location variable into two levels based on an estimated rectal midpoint of 6cm (0–6cm vs >6 cm). We also considered cutpoints of approximately 3 cm intervals, as used in a recent study examining DTAV.[15] Differences in pCR by tumor location variables were determined using Chi-square and Cochran-Armitage trend tests. Differences in pCR by tumor location, patient demographic, tumor, and treatment characteristics were determined using Chi-square tests and Cochran-Armitage trend tests for categorical variables. Multivariable logistic regression models with pCR as the outcome variable were constructed to examine tumor location variables with adjustment for covariates (gender, age at diagnosis, and clinical T-stage). We used the Bonferroni correction as appropriate to adjust for multiple comparisons using DTAV and MTAV. All statistical tests were two-sided and family-wise Type I error values .05 were considered significant. Analyses were done using SAS statistical software version 9.4 (Cary, NC).

RESULTS

Of the 135 patients eligible in the study cohort, 52 (39%) were female and 83 (61%) were male, with mean age at diagnosis of 59.4 years (range 22–92 years). With regard to neoadjuvant therapy, 115 (85%) patients received 5-FU or capecitabine single-agent treatment, 6 (4.4%) received multi-agent treatment, and agent-specific information was unknown in 13 (9.6%) patients. Similarly, 54 (40%) received concomitant three-dimensional conformal radiotherapy via 3 or 4-field technique, 50 (37%) had intensity-modulated radiation therapy, and radiotherapy type was unknown in 31 (23%) patients. Among the 118 (87%) patients with available radiation dosage information, median dose administered was 50.4 Gray (Gy), with a range of 16.8–55.0 Gy. A total of 108 (80%) of patients completed their assigned neoadjuvant chemoradiation regimen, 9 (6.7%) did not complete both chemotherapy and radiation, and completion data was unavailable for 18 (13%) patients. Regarding initial clinical stage, 58 patients (43%) were AJCC Stage II and 77 patients (57%) were Stage III. A total of 39 patients (29%) had a pCR, 58 (43%) had partial pathologic response, and 38 (28%) had no response from neoadjuvant treatment (Table 1).

DTAV ranged from zero to 13.0cm from the anal verge. Assuming a conventional rectal midpoint of 6.0cm, 82 patients (61%) had a DTAV less than or equal to 6.0cm while 53 patients (39%) had a DTAV greater than 6.0cm. Using pCR as a primary outcome, response did not differ between tumors with a DTAV below or above 6cm (pCR: 28.3% for 6.1–13cm vs 29.3% for 0–6cm, OR 0.95 [95%CI=0.44–2.05], $p=0.90$) (Table 2). With covariate adjustment for age, gender and clinical T-stage, the associations between DTAV and pCR were unchanged ($p=0.64$). In sensitivity analyses, DTAV was considered as both categorical and continuous. With DTAV split at the median value of 5cm, for high vs low, pCR was 25.8% for >5cm vs 31.9% for 0–5cm (OR 0.74 [95%CI=0.35–1.57], $p=0.43$). DTAV was also grouped into 3.0cm anatomic segments (0 to 2.9cm, 3.0 to 5.9cm, 6.0 to 8.9cm, 9.0 and greater) and no statistical significance was observed (trend test $p=0.95$) between anatomic tumor grouping and pCR. With DTAV as a linear variable (cm) in a logistic model, the OR was 1.00 (95%CI=0.91–1.11), $p=0.97$. A comparison of tumor location based on DTAV and presence or absence of pCR is demonstrated in Figure 3.

OTL was recorded in 111 patients, facilitating the calculation of MTAV for this group. MTAV ranged from zero to 15.5cm. A total of 46 patients (41%) had an MTAV distance less than or equal to 6.0cm while 65 (59%) had an MTAV greater than 6.0cm. Univariate analysis was completed with pCR as a primary outcome and no statistical significance was observed between anatomic tumor group and pCR (pCR: 23.1% for 6.1–16cm vs 32.6% for 0–6cm, OR 0.62 [95%CI=0.27–1.44], $p=0.27$) (Table 2). With covariate adjustment for age, gender and clinical T-stage, the associations between MTAV and pCR were unchanged ($p=0.25$). Additionally, univariate analysis was completed for DTAV (0–6cm vs 6.1–13cm) and again for MTAV (0–6cm vs 6.1–16cm) using any degree of pathologic downstaging as the primary outcome. No statistical significance was observed between DTAV groups and pathologic downstaging ($p=0.72$) or MTAV groups and pathologic downstaging ($p=0.97$). A comparison of tumor location based on MTAV and presence or absence of pCR is demonstrated in Figure 4.

DISCUSSION

The results of our investigation suggest that no association exists between anatomic tumor location and the rate of pCR. Regardless of the type of measurement approach or anatomic division along the length of the rectum, no statistical significance could be discerned between tumor position and pathologic response. Regarding percentage of pCR achieved, our data falls within the normal range as published by other groups.[2, 4] As graphically demonstrated in Figures 3 and 4, the distribution of tumors along the longitudinal length of the rectum was relatively uniform, regardless of measurement technique. Although previous investigations have largely used DTAV to describe tumor location,[15] we also opted to examine MTAV and considered it to be more descriptive of a tumor's position since DTAV is not reflective of the OTL or location of the bulk of a given tumor. Ultimately, there was no difference when compared with both pCR and any pathologic downstaging.

Our findings are in contrast to the recent work of Patel et al, which demonstrated a bimodal association between DTAV and pCR. In their retrospective study of 827 similarly selected patients (i.e., Stages II-III rectal adenocarcinoma with pre-treatment endoscopic evaluation and follow-on neoadjuvant chemoradiation) at a major regional referral center, patients with rectal tumors less than 4cm from the anal verge and greater than 8cm from the anal verge were less likely to achieve a pCR.[15] These results were comparable to the recently published investigation of Restivo et al, during which a retrospective review of 260 rectal adenocarcinoma patients treated via neoadjuvant therapy and surgical resection at an Italian colorectal referral center revealed a statistically significant correlation between pCR and tumors with DTAV greater than 5cm.[14] Although no association between pCR and DTAV was observed in a similar investigation by Das et al, his group did demonstrate a statistically significant association between pathologic downstaging and DTAV greater than 5cm in their retrospective review of 562 patients with locally advanced disease.[11] Taken together, these data suggest that adenocarcinoma of the low rectum, or tumors with DTAV less than 6cm, portend a worse pathologic response than those lesions of the upper rectum.[11, 14, 15]

Interestingly, although of limited number, the majority of previously published data comparing pathologic response with DTAV has not shown a statistically significant association with either pCR or tumor downstaging.[8–10, 12, 13] These data are suggestive of an association between pathologic response and tumor location, as two groups showed pathologic response in tumors greater than 5cm from the anal verge [11, 14] while the other demonstrated a bimodal distribution of pCR tumors.[15] Although all illustrate worse pathologic response among low rectal lesions, these data and the behavior of mid and upper rectal tumors are difficult to interpret. It is well-established that rectal cancers within 6cm of the anal verge have a worse prognosis. This is likely a consequence of the difficulty of margin-negative surgical extirpation of cancers close to the anal sphincter complex in the narrow pelvis.[16] However, as these findings have no association with a tumor's inherent biologic susceptibility or resistance to neoadjuvant chemoradiation, prognostic confounding may explain this trend in these positive studies.

Our study is unique in its use of both DTAV and MTAV as the primary variables measured. Although all previous investigations used pCR as a primary outcome, only one identified

DTAV as the primary variable measured.[15] Similarly, aside from Patel et al, none of these groups focused their analyses on anatomic segments and tumor location along the longitudinal length of the rectum. Ours is the only study, regardless of the presence or absence of a statistically significant association between pathologic response and tumor location, which measured tumor location using both DTAV and MTAV.[8–14] Although DTAV may be considered more relevant from an operative standpoint, we opted to include MTAV as a more descriptive measurement of a tumor's true location within the rectum since OTL is considered.

Despite our findings, our study does have several limitations. As a retrospective observational study, our approach inherently lends itself to selection and information biases which are difficult to control for. Also, when compared to the previously published investigations of the same type, our sample size is modest and possibly underpowered. Completed at a regional NCI-designated cancer center, our single institutional study may not be representative of all other hospitals, both community and university-based, throughout the United States. Our investigative design is also subject to facility-specific variability in clinical practice patterns which could clearly be controlled for by a multi-institutional approach.

CONCLUSION

Anatomic location of tumor within the rectum does not affect complete pathologic response following neoadjuvant therapy and subsequent surgical resection for rectal adenocarcinoma. The anatomic distribution of rectal tumors is relatively uniform and is not predictive of tumor response to treatment. Other contributing factors should be sought in the continued search for tumor characteristics which may be preoperatively identified as having significant impact on pathologic responsiveness to neoadjuvant chemoradiation. The capacity to identify the subset of rectal cancer patients that are more likely to develop pCR, combined with an aggressive surveillance program within this group, may eliminate the need for operative extirpation and the accompanying morbidity and mortality that may ensue.

Acknowledgments

Disclosure Information/Funding Support: Nothing to disclose. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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Figure 1:

Flow diagram of patients selected for analysis. FCCC: Fox Chase Cancer Center; AJCC: American Joint Committee on Cancer; DTAV: tumor distance from the anal verge; MTAV: mean tumor distance from the anal verge

Figure 2:
Pelvic magnetic resonance image (with contrast), T1-weighted sagittal view, of a male study patient's mid-rectal tumor depicting measurements of interest. DTAV: tumor distance from the anal verge; MTAV: mean tumor distance from the anal verge; OTL: overall tumor length

Figure 3:

Histogram comparing rectal tumor distance from the anal verge and the presence or absence of complete pathologic response. DTAV: tumor distance from the anal verge

Figure 4:

Histogram comparing mean rectal tumor distance from the anal verge and the presence or absence of complete pathologic response. MTAV: mean tumor distance from the anal verge

Table 1:**Patient Demographics and Staging**

	N	%
Gender		
Female	52	38.5
Male	83	61.5
Race		
White	117	86.7
Black	11	8.1
Other	7	5.2
Age at Diagnosis		
Mean	59.4	
22–49	29	21.5
50–59	42	31.1
60–69	34	25.2
70–79	17	12.6
80–92	13	9.6
Clinical Stage		
IIA	57	42.2
IIB	0	0.0
IIC	1	0.7
IIIA	7	5.2
IIIB	66	48.9
IIIC	4	3.0
Pathologic Stage		
0	39	28.9
I	37	27.4
IIA	27	20.0
IIB	1	0.7
IIC	0	0.0
IIIA	6	4.4
IIIB	15	11.1
IIIC	6	4.4
IV	3	2.2
Pathologic Response		
Complete	39	28.9
Improvement	58	43.0
No Improvement	38	28.1

Table 2:**Tumor Location and Pathologic Complete Response**

	N	pCR	Pathologic Complete Response (pCR)		P-value	Adjusted OR (95%CI) [#]	P-value
			% pCR	OR (95%CI)			
Tumor Distance from Anal Verge (DTAV)							
0–6 cm	82	24	29.3	Ref	0.90	Ref	0.64
6<–13 cm	53	15	28.3	0.95 (0.44–2.05)		0.82 (0.36–1.87)	
Mean Distance from Anal Verge (MTAV)[*]							
0–6 cm	46	15	32.6	Ref	0.27	Ref	0.25
6<–16 cm	65	15	23.1	0.62 (0.27–1.44)		0.60 (0.25–1.43)	

^{*} Excludes 24 patients without MTAV measured.

[#] Adjusted model includes age at diagnosis (<70 vs. 70), gender, clinical stage (II vs. III).

Ref: reference group