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Distance to the anal verge is associated with pathologic complete response to neoadjuvant therapy in locally advanced rectal cancer

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Abstract

Background and Objectives—Achieving a pathologic complete response (pCR) after neoadjuvant therapy has been associated with better prognosis in rectal cancer patients. The objective of this study was to investigate the relationship between distance to the anal verge (DTAV) and pCR.

Methods—Review of a prospectively maintained database of patients with locally advanced rectal cancer who received neoadjuvant treatment was completed. Univariate and multivariate analysis assessed the association between DTAV and pCR after neoadjuvant therapy.

Results—Of 827 included patients, 20% had a pCR. We found that pCR rates were 11% for tumors <4 cm, 24% for tumors 4–6 cm, 30% for tumors at 6–8 cm, 17% for tumors 8–10 cm and 14% for tumors >10 cm from the anal verge ($P = 0.002$). Multivariate analysis also showed a strong association between DTAV and pCR ($P = 0.008$). The bimodal distribution of pCR resulted in a lower odds ratio of pCR for tumors <4 cm and >8 cm from the anal verge.

Conclusions—Patients with low tumors (<4 cm) and higher tumors (>8 cm), were less likely to have a pCR. Further investigation is warranted to determine if these observations are related to tumor biology or possibly differences in radiation technique.

Keywords

Rectal Cancer; pathologic complete response; distance to anal verge; neoadjuvant therapy

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Introduction

The standard of care for patients with locally advanced rectal cancers (AJCC Stage II, Stage III) includes preoperative chemoradiation followed by total mesorectal excision and postoperative chemotherapy. A proportion of patients undergoing preoperative chemoradiation will have a complete pathologic response (pCR) in which no viable tumor cells are noted in the resected specimen. A pCR is associated with favorable oncologic outcome. For example, in the pooled analysis including 3105 patients, Maas et al.(1) found that the overall rate of pCR was 15.6% (range 8 -18%), and patients with pCR were more likely to have a 5 year disease free survival (83.3%) compared with patients without a pCR (65.6%). These patients were less likely to have disease recurrence (HR 0.54, 95%CI 0.40 – 0.73), and less likely to die (HR 0.65, 95%CI 0.47 – 0.89). In an analysis of outcome in locally advanced rectal cancer patients treated with combined modality therapy, Quah et al. (2) found that post treatment pathologic stage, but not pretreatment stage, was the most important predictor of outcome, and patients with ypT0N0 (pCR) had greatly reduced recurrence and significantly prolonged survival.

Predicting complete pathologic response has become increasingly important, as investigators have shown that nonoperative management, or “watch and wait”, is a reasonable approach in select patients (3, 4). In this setting, patients with complete clinical response are observed and only undergo total mesorectal excision if the tumor regrows. Selecting those patients with a high likelihood of a cPR remains the challenge and identifying predictors of response is increasingly important.

The objective of this study was to determine if distance to the anal verge of the tumor (DTAV) was associated with complete pathologic response.

Materials and Methods

A prospectively maintained clinical database at Memorial Sloan Kettering Cancer Center was queried for patients treated from 1998-2011 with locally advanced rectal cancer, AJCC Stage II and Stage III by endorectal ultrasound or magnetic resonance imaging, who received neoadjuvant therapy. All patients were treated with a combination of radiation therapy and 5FU based chemotherapy in the neoadjuvant setting, followed by total mesorectal excision. Patients were excluded if they did not undergo mesorectal excision.

The primary outcome for this study was pathologic complete response (pCR) which was defined as ypT0N0 on final pathology. The primary exposure was distance of the tumor from the anal verge (DTAV). DTAV intervals were selected *a priori* at 2 cm intervals, starting at 4 cm from the anal verge. We felt that this interval would give us the precision to appreciate changes in the pCR based on height, while still being reproducible on exam.

The standard practice during most of the study period was to obtain endorectal ultrasound (with more recent patients undergoing rectal MRI). Tumor height was assessed in clinic using rigid proctoscopy with insufflation. A standard protocol for method of tumor height did not exist, but the participating surgeons had similar practices and techniques. DTAV was

recorded by the operating surgeon prior to commencement of neoadjuvant treatment using proctoscopy.

Pre-treatment characteristics were determined including clinical tumor (cT) stage, clinical nodal (cN) stage, distance from anal verge (DTAV) and tumor grade. Post resection tumor characteristics included pathologic tumor stage (ypT), pathologic nodal stage (ypN), percent tumor response to neoadjuvant treatment, lymphovascular invasion, perineural involvement, number of resected lymph nodes and number of positive lymph nodes. Time from the end of neoadjuvant therapy to surgery date was also recorded. Institutional ethics approval was granted for this study.

Statistical Analysis

Statistical analysis was completed using STATA 12 (Statacorp, College Station TX). Univariate analysis was completed to assess the association between complete pathologic response and other variables. Statistical test of association was done using a χ^2 test. Multivariate logistic regression was completed, adjusting for important confounders. Likelihood ratio was used to test for statistical significance.

Additional Analyses

We assessed the relationship between complete pathologic response and DTAV, adjusting for time from completion of neoadjuvant therapy, in those with known time interval.

We also undertook a sensitivity analysis by including patient with a complete clinical response after neoadjuvant therapy who were managed non-operatively. Patients at MSKCC who fulfill specific imaging (via MRI) and endoscopy criteria after neoadjuvant treatment for rectal cancer are eligible for non-operative management. We included non-operative managed patients if they fulfilled the same preoperative inclusion criteria as our primary cohort. We compared pretreatment tumor characteristics using a χ^2 test. Multivariate analysis on the association between complete response (in this case complete clinical OR complete pathologic response) and DTAV was assessed, adjusting for other important factors in the same manner as in our primary analysis.

Results

Of the 963 patients identified with Stage II or Stage III rectal cancer, who received neoadjuvant treatment, 827 patients (86%) were available for analysis. Patients were excluded for missing variables including unknown distance of the tumor from the anal verge or unknown preoperative tumor or nodal staging. Patient characteristics can be found in Table 1. Of the included patients, all received partial or complete neoadjuvant treatment with radiation and 5-FU based chemotherapy.

Pre-treatment tumor characteristics can also be found in Table 1. The majority of patients had moderately differentiated tumors (88.6%) and were classified as T3 lesions (87.9%). Three quarters of patients were node positive on staging imaging.

Postoperative tumor characteristics can be found in Table 2. Twenty percent of patients had a complete pathologic response as defined by ypT0N0 on final pathology. Over 70% of patients were node negative on final pathology. Of the 617 patients who were node positive on preoperative imaging, 466 (75.5%) were node negative on the final pathology. Compared to clinical T stage (cT), 17 patients were upstaged on pathologic T staging (2.1%), whereas 355 had the same T stage (43%) and 455 patients had downstaging of their T stage (55%). Forty-five of 210 clinically node negative patients (21.4%) had positive nodes on final pathology. Four hundred sixty-six of 617 clinically node positive patients (75.5%) were negative for nodal metastasis on final pathology.

Unfortunately, we had incomplete data on time from the end of neoadjuvant therapy to the operative day. Of the 827 patients, this data was clearly identified in 338 patients (40.6%). Of these patients, the median time to operation was 47 days (IQR 41 - 51).

Univariate Analysis

The univariate analysis, assessing the association between complete pathologic response and DTAV, as well as other factors can be found in Table 3. There was a strong association between DTAV and pathologic complete response ($P = 0.002$). Low tumors (<4 cm from the anal verge) were less likely to have a complete pathologic response. The proportion of patients with a complete pathologic response was highest in groups in which tumor was measured 4 – 6 cm and 6 – 8 cm from the anal verge. Both low tumors and higher tumors had a lower proportion of complete pathologic response.

Analysis of downstaging by DTAV was completed. We found that the distribution of patients who had the tumor stage downstaged following neoadjuvant treatment was similar to those with a pathologic complete response, as seen in Table 4.

Analysis of secondary outcomes including complete pathologic nodal (N) response (ypN0) and complete pathologic tumor (T) response (ypT0) was undertaken (Table 4). The proportion of patients with a complete pathologic T response (ypT0) was associated with DTAV ($P = 0.001$), while complete pathologic N response (ypN0) was not ($P = 0.71$).

Multivariate Analysis

The results of the multivariate analysis can be found in Table 3. After adjusting for clinical tumor and nodal stage, grade and year of surgery, DTAV was found to be strongly associated with complete pathologic response ($P = 0.008$). Similar to the univariate analysis, tumors that were < 4 cm had the lowest odds of a pCR. Tumors at 8 – 10 cm and > 10 cm also had lower odds of a pCR, compared to tumors between 4 – 6 cm and 6 – 8 cm.

Similar results were found on the multivariate analysis assessing complete pathologic T response (ypT0). There was a strong association between DTAV and complete pathologic T response ($P = 0.004$). Tumors at < 4 cm had the lowest odds of having a complete pathologic T response. There was no association found between DTAV and complete pathologic N response (ypN0) in the multivariate model. (Table 5)

Interval between neoadjuvant therapy and surgical resection

Subgroup analysis of those with known time from completion of neoadjuvant treatment and surgery was completed. Within this subgroup (N = 338), the complete pathologic response was similar to the group with unknown interval between neoadjuvant treatment and surgery (18.3% vs. 21.1%, $P = 0.38$). There was no association between the tumor height and time from the end of neoadjuvant treatment and surgery ($P = 0.90$). When the multivariate analysis was completed, including time between neoadjuvant therapy and surgery, the association between DTAV and complete pathologic response was maintained ($P = 0.027$). (Table 6)

Inclusion of patients managed non-operatively

A total of 35 patients were managed non-operatively over the study period, who fulfilled our pre treatment inclusion criteria. A comparison of the patients with a complete pathologic response and those with a complete clinical response managed non-operatively (NOM) can be found in Table 6. The NOM patients had tumors closer to the anal verge than the complete pathologic response patients ($P = 0.026$). Other pretreatment tumor characteristics were similar (grade, clinical tumor stage, clinical nodal stage and overall clinical stage).

Multivariate analysis, adjusting for the same factors as our primary analysis (grade, tumor and nodal stage and year of treatment), found a similar association between tumor height and complete response (Table 7).

Discussion

Our study has shown a bimodal association between distance to the anal verge and pathologic complete response with low tumors (< 4cm) and higher tumors (8 – 10 cm and > 10 cm) less likely to have a complete pathologic response. This association was maintained after adjusting for preoperative characteristics (cT, cN, grade, year of surgery).

Complete pathologic response indicates a very good prognosis compared with those without a complete pathologic response. A meta-analysis, which included 12 studies and 1913 patients, found that those with a complete pathologic response had lower local recurrence (OR 0.45, 95%CI 0.22 – 0.90) a lower distant recurrence (OR 0.15, 95%CI 0.07 – 0.31) and better overall survival (OR 3.6, 95% CI 1.87 – 7.22). (5)

Multiple previous publications have attempted to determine the association between preoperative factors and complete pathologic response. Assessed factors include CEA (6, 7, 8, 9), tumor size (7), nodal status (7), tumor grade (10), tumor circumference (9), molecular markers (11). Distance from the anal verge was assessed in several studies (6, 7, 8, 9, 12, 13, 14). Two studies (9, 12) found no association between tumors >5cm from the anal verge (vs. those < 5cm) and complete pathologic response, while one study did show a relationship between height and response (14). Moureau et al. (13) categorized DTAV into low rectum, mid rectum and upper rectum. No association between these heights and complete pathologic response was identified. Three studies (6, 7, 8) used height as a continuous variable and did not find an association with complete pathologic response.

Our study is unique in categorizing distance to the anal verge into multiple groups. Previous studies that used two groups (i.e. >5 cm vs. ≤5 cm) did not account for the bimodal distribution of response. Similar issues with studies using distance as a continuous variable exists. By categorizing distance to the anal verge into several groups, the bimodal distribution of response was better appreciated.

The study does not allow us to clearly identify the reason for the bimodal association of tumor height and response to chemoradiation. It is possible that during treatment planning, in an attempt to spare the sphincters, low lying tumors do not receive the full treatment dose. Similar concerns with small bowel toxicity and higher tumors could affect treatment planning.

The strength of this study is the completeness of preoperative staging, grade and distance to the anal verge. Additionally, there were a large number of patients with a complete pathologic response (N = 165) available for analysis. The patients included in this study were all operated on at a single institution (Memorial Sloan Kettering Cancer Center), with all pathologic assessment performed within this institution. This allowed for a relatively consistent surgical specimen and pathologic analysis.

All patients received long-course radiation with concurrent 5-FU based chemotherapy. However, details regarding chemotherapy dose reduction are limited. During the study period (1998-2011) the standard protocol was to operate 4-8 weeks after completion of chemoradiation, which is consistent with available data on the cohorts; although, missing data prevented analysis of time from preoperative therapy to surgery. Previous studies have found that in those patients who received neoadjuvant treatment for locally advanced rectal cancer (stage II & III), longer intervals between surgery and the end of treatment corresponded to a higher rate of pathologic complete response, and tumor down staging. (15)

An additional consideration are patients who are selected for non-operative management. We attempted to determine how this group would influence our findings through a sensitivity analysis. This analysis found similar findings to our primary analysis, in identifying a bimodal response to neoadjuvant therapy.

Other potentially interesting variables that could not be analyzed include size and volume of tumor.

Conclusions

We have shown the distance to the anal verge is strongly associated with complete pathologic response. There is a bimodal distribution of complete pathologic response. Very low tumors (< 4 cm) and high tumors (8 – 10 cm, > 10 cm) are less likely to have a complete pathologic response.

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Synopsis

The association between distance to the anal verge and pathologic complete response following neoadjuvant treatment in rectal cancer was explored through a retrospective review. We found that low tumors (<4cm from the anal verge) and high tumors (>8 cm from the anal verge) were associated with lower rates of complete pathologic response.

Table 1

Patient and pretreatment characteristics

Number of Patients (N = 827)		
Age Group		
< 50 years	227	27.40%
50 - 60 years	215	26.00%
60 -70 years	213	25.80%
70 - 80 years	145	17.50%
> 80 years	27	3.30%
Gender		
Male	484	58.50%
Female	343	41.50%
Year		
1998-2002	204	24.70%
2003-2005	258	31.20%
2006-2008	121	14.60%
2009-2011	244	29.50%
Type of Resection		
Low Anterior Resection	677	81.90%
Abdominoperineal resection	150	18.10%
Distance to the Anal Verge		
<4 cm	146	17.70%
4 - 6 cm	218	26.40%
6 - 8 cm	247	29.90%
8 - 10 cm	157	19.00%
>10 cm	59	7.10%
Grade		
Well Differentiated	18	2.20%
Moderately Differentiated	733	88.60%
Poorly Differentiated	70	8.50%
Unknown	6	0.70%
Clinical Tumor Stage		
cT1	7	0.80%
cT2	63	7.60%
cT3	727	87.90%
cT4	30	3.60%

Number of Patients (N = 827)		
Clinical N Stage		
cN0	210	25.40%
cN+	617	74.60%

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Table 2

Post resection tumor characteristics

Number of Patients (N = 827)		
Pathologic Tumor Stage		
ypT0	174	21.0%
ypT1	46	5.6%
ypT2	251	30.4%
ypT3	332	40.1%
ypT4	24	2.9%
Pathologic Node Stage		
ypN0	631	76.3%
ypN1	152	18.4%
ypN2	44	5.3%
Pathologic Stage		
Stage 0	165	20.0%
Stage I	246	29.7%
Stage II	220	26.6%
Stage III	196	23.7%
Tumor Response		
<50%	160	19.3%
50 - 75%	181	21.9%
75 - 90%	189	22.9%
> 90%	259	31.3%
Unknown	38	4.6%

Table 3

Univariate and Multivariate analysis of the association between distance to the anal verge and pathologic complete response (pCR)

Univariate Analysis	Proportion with pCR (n/N)		
< 4 cm	16/146	11.0%	
4 - 6 cm	52/218	23.9%	
6 - 8 cm	63/247	25.5%	P = 0.002
8 - 10 cm	26/157	16.6%	
> 10 cm	8/59	13.6%	
Multivariate Analysis *	Odds Ratio	95%CI	P Value
< 4 cm	1	ref	
4 - 6 cm	2.54	1.36 - 4.75	
6 - 8 cm	2.55	1.37 - 4.74	P = 0.008
8 - 10 cm	1.74	0.87 - 3.48	
> 10 cm	1.29	0.51 - 3.28	

* Adjusted for Clinical Tumor Stage, Clinical Nodal Stage, Grade and Year of Surgery

Table 4

Proportion of patients, by tumor height, who had downstaging of the tumor stage (i.e. from T3 to T2, T2 to T1, etc). DTAV Distance to the anal verge

DTAV	Proportion with T Downstage (n/N)		
< 4 cm	35/87	40.2%	P < 0.001
4 - 6 cm	82/134	61.2%	
6 - 8 cm	95/158	60.1%	
8 - 10 cm	43/101	42.6%	
> 10 cm	11/33	33.3%	

Univariate and Multivariate analysis of the association between distance to the anal verge and a) Complete pathologic tumor response (ypT0) and b) Complete Pathologic Nodal Response (ypN0).

Table 5

Univariate Analysis		Proportion with ypT0 (n/N)		Proportion with ypN0 (n/N) *	
< 4 cm	18/146	12.3%	73/95	76.8%	
4 - 6 cm	52/218	23.9%	130/166	78.3%	
6 - 8 cm	70/247	28.3%	145/192	75.5%	P = 0.71
8 - 10 cm	26/157	16.6%	86/118	72.9%	
> 10 cm	8/59	13.6%	32/46	69.6%	
Multivariate Analysis		Odds Ratio	95%CI	P Value	P Value
		Complete Tumor Response (ypT0) **		Complete Nodal response (ypN0) ***	
< 4 cm	1	ref		1	ref
4 - 6 cm	2.27	1.24 - 4.18		1.03	0.56 - 1.92
6 - 8 cm	2.67	1.47 - 4.85	P = 0.004	0.88	0.48 - 1.60
8 - 10 cm	1.55	0.79 - 3.05		0.81	0.43 - 1.55
> 10 cm	1.18	0.47 - 2.96		0.58	0.26 - 1.31

* Patients with positive nodes on preoperative staging

** Adjusted for clinical T stage, clinical N stage, grade, year of surgery

*** Included only node positive patients on preoperative imaging, adjusted for clinical T stage, year of surgery

Table 6

Comparison of characteristics between patients with a pathologic complete response (pCR) and those treated with a complete clinical response non-operatively (NOM)

	pCR	NOM	
Distance to the Anal Verge			
<4 cm	16/165, 9.7%	5/35, 14.3%	P = 0.026
4 - 6 cm	52/165, 31.5%	19/35, 54.3%	
6 - 8 cm	63/165, 38.2%	4/35, 11.4%	
8 - 10 cm	26/165, 15.7%	5/35, 14.3%	
>10 cm	8/165, 4.9%	2/35, 5.7%	
Grade			
Well Differentiated	4/165, 2.4%	1/35, 2.9%	P = 0.997
Moderately Differentiated	148/165, 89.7%	31/35, 88.6%	
Poorly Differentiated	9/165, 5.5%	2/35, 5.7%	
Unknown	4/165, 2.4%	1/35, 2.9%	
Clinical Tumor Stage			
cT1	1/165, 0.6%	1/35, 2.9%	0.179
cT2	33/165, 20.0%	3/35, 8.6%	
cT3	127/165, 77.0%	31/35, 88.6%	
cT4	4/165, 2.4%	0/35, 0.0%	
Clinical N Stage			
cN0	36/165, 21.8%	8/35, 22.9%	P = 0.893
cN+	129/165, 78.2%	27/35, 77.1%	
Clinical Stage			
Stage II	36/165, 21.8%	9/35, 25.7%	0.616
Stage III	129/165, 78.2%	26/35, 74.3%	

Table 7

Sensitivity analysis; Multivariate analysis of the association between Distance from the Anal Verge and (a) complete pathologic response or (b) complete clinical or pathologic response (OR Odds Ratio, NOM Non operative management, ref Reference)

DTAV	Study Cohort (N = 827) ^a	Known treatment interval (N = 338) ^a	Study Cohort and NOM (N = 862) ^b
	OR (95% CI)	OR (95% CI)	OR (95% CI)
< 4 cm	1 (ref) [*]	1 (ref) ^{**}	1 (ref) ^{***}
4 - 6 cm	2.53 (1.36 - 4.75)	2.31 (0.81 - 6.55)	2.55 (1.46 - 4.44)
6 - 8 cm	2.55 (1.37 - 4.74)	2.25 (0.81 - 6.28)	1.99 (1.13 - 3.49)
8 - 10 cm	1.74 (0.87 - 3.48)	0.64 (0.19 - 2.20)	1.53 (0.82 - 2.85)
> 10 cm	1.29 (0.51 - 3.28)	0.75 (0.16 - 3.55)	1.18 (0.51 - 2.74)

^{*} Test for overall effect P = 0.008

^{**} Test for overall effect P = 0.027

^{***} Test for overall effect P = 0.0054