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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 postoperative 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 6 cm from the anal verge are more likely to achieve a pCR.

Methods: Using data from our prospectively maintained tumor registry, a query was completed to identify all patients with locally advanced rectal adenocarcinoma who underwent treatment at Fox Chase Cancer Center from 2002 to 2015. Demographics, pretreatment, posttreatment, 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 to neoadjuvant treatment. Tumor location ranged from 0 to 13 cm from the anal verge. Longitudinal tumor length was recorded in 111 patients, facilitating the calculation of mean tumor distance from the anal verge. This ranged from 0 to 15.5 cm. 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.

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

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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 postoperative chemotherapy.[2,3] Of those patients who undergo neoadjuvant therapy and subsequent surgical resection, it is estimated that approximately 15%-30% achieve a pathologic complete 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 postoperative 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 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 4-6 cm and 6-8 cm from the anal verge are more likely to achieve pCR (odds ratio [OR]: 2.54, 95% confidence interval [CI] = 1.36-4.75 and OR: 2.55, 95% CI = 1.37-4.74, respectively),[15] and one prior investigation reported a statistically significant correlation between pCR and tumors more than 5 cm 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 6 cm from the anal verge are more likely to achieve a pCR.

Materials and 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 to 2015. Waiver of individual informed consent was granted for this retrospective investigation. Only those patients with American Joint Committee on Cancer stage II or III disease who underwent pretreatment endoscopic evaluation at Fox Chase, followed by neoadjuvant chemoradiation and subsequent surgical resection, were included (Fig. 1). Standard practice at Fox Chase involved definitive surgical extirpation 8-10 weeks after the completion of external-beam radiation. Throughout the study period, all patients underwent an open, laparoscopic, or robotic total mesorectal excision. Demographic, pretreatment, posttreatment, and final pathologic TNM staging data were collected as well as treatment intervals in days, recurrence status, and vital status. Specific pretreatment 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 (Fig. 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 variables into two levels based on an estimated rectal midpoint of 6 cm (0-6 cm *versus* >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,