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ORIGINAL RESEARCH

Predictive Significance of Mucinous Histology on Pathologic Complete Response Rate Following Capecitabine-Based Neoadjuvant Chemoradiation in Rectal Cancer: a Comparative Study

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Abstract

Introduction Currently, neoadjuvant fluoropyrimidine-based chemoradiation followed by surgery is considered the standard of care for locally advanced rectal cancer. The current study aimed to investigate the predictive significance of mucinous histology on the pathologic complete response rate following neoadjuvant chemoradiation in locally advanced rectal cancer and to propose potential new treatment protocol for this specific histology.

Material and Method This retrospective study was conducted on 403 patients with locally advanced (clinically T3–4 and/or N1–2) rectal adenocarcinoma who had been treated at three tertiary academic hospitals between 2010 and 2015. Among those 403 patients, 46 (11%) had mucinous rectal cancer (MRC) and 358 (89%) had non-mucinous rectal cancer (NMRC). All patients underwent neoadjuvant chemoradiation with capecitabine followed by low anterior or abdominoperineal resection.

Results There were 268 men and 135 women with a median age of 55 years (range, 26–82 years). Patients with MRC were younger ($p = 0.002$) and presented with a larger tumor size ($p < 0.001$) and a more advanced tumor stage ($p = 0.033$) compared to the ones with MNRC. In the univariate analysis, female gender ($p = 0.009$), distal tumor location ($p = 0.035$), higher tumor stage ($p = 0.049$), node positivity ($p = 0.001$), MRC histology ($p = 0.017$), and high pretreatment CEA level ($p = 0.013$) were observed to be predictive of a poor pathologic complete response. However, in the multivariate analysis, tumor stage was the single most predictive factor of response to neoadjuvant chemoradiation.

Conclusion Mucinous adenocarcinoma is a significant predictive factor for poor pathologic complete response to neoadjuvant capecitabine-based chemoradiation in patients with locally advanced rectal cancer. New treatment modality based on biomarkers may be considered in future prospective studies because of MRC poor prognosis. Immunotherapy combined with chemotherapy and/or radiotherapy may be an attractive option because of the tumor microsatellite instability-high status.

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Keywords Rectal cancer · Mucinous adenocarcinoma · Neoadjuvant chemoradiation · Surgery · Pathologic complete response

Introduction

Currently, neoadjuvant chemoradiation followed by total mesorectal resection (TMR) is considered the standard of care for locally advanced rectal cancer [1, 2]. Following treatment, tumor downstaging has been correlated with improved survival [3–5]. However, there may be a subgroup of patients who may not achieve pathologic complete response (PCR) or partial response (PPR) after treatment. Thus, identifying potential predictors of tumor response to the combined modality such as histopathology, immunohistochemistry, and diffusion-

weighted magnetic resonance imaging (MRI) has been assessed in many prospective and retrospective studies [6–8]. Among the poor prognostic factors identified in the literature, mucinous rectal cancer (MRC) has been reported as a subgroup characterized by an increased rate of locoregional recurrences. Traditionally, MRC has been defined by excessive extracellular mucin comprising more than 50% of the tumor volume [9]. Poor response following neoadjuvant chemoradiation may be postulated secondary to MRC resistance to chemotherapy and/or radiotherapy [10, 11]. However, there is no consensus regarding the predictive significance of histology on tumor response following neoadjuvant treatment. Thus, despite the reported poor response to treatment, patients with MRC continued to receive the same treatment similar to the non-mucinous rectal cancer (NMRC) [12]. The current study aimed to investigate if mucinous histology may be a factor in predicting PCR following neoadjuvant chemoradiation. We also review the literature on MRC to propose new treatment modality that may be effective to improve treatment response and complete resection rates.

Material and Method

This retrospective study was conducted at the radiation oncology departments of three tertiary academic Iranian hospitals following approval by their respective institutional review boards (IRB) in accordance with Helsinki's code of ethics guidelines. All patients had locally advanced adenocarcinoma of the rectum defines as clinically stage T3–4 and/or N1–2 disease. The patients were treated from 2010 to 2015.

Pretreatment Evaluation

Tumor staging was performed according to the seventh edition of the American Joint Committee on Cancer TNM (AJCC) staging system [13]. All patients underwent CT scan of the chest, abdomen, and pelvis along with pelvic MRI and/or endoscopic ultrasound prior to treatment for clinical staging. A comprehensive history and physical examination, including digital rectal examination, colonoscopy, complete blood cell count (CBC), liver and renal function studies, and carcinoembryonic antigen (CEA), was also performed.

External Beam Chemoradiation

Radiotherapy was performed with the two-dimensional (2D) ($n = 188$) or three-dimensional (3D) ($n = 185$) technique using megavoltage (10–15 MV) linear accelerator. All patients were treated in the prone position with a full bladder to reduce small bowel toxicity. A three-field (one posterior-anterior and two lateral fields) or four-field (one anteroposterior, one posteroanterior, and lateral fields) combination was employed in both techniques to further minimize bowel toxicity. Localizing laser and thermoplastic sheets were used for setup accuracy. The median total dose was 45 Gy (range 45–50.4 Gy) in 1.8 Gy/fraction daily dose, 5 days a week. Concurrent chemotherapy consisted of oral capecitabine 825 mg/m^2 twice daily during the entire pelvic radiotherapy period including weekend breaks. All the patients were subsequently referred for surgery, taking placed at a median interval of 6 (range 4–8) weeks after the last radiation therapy session. Two weeks after the completion of surgery, six cycles of chemotherapy consisting of capecitabine 1000 mg/m^2 twice daily for 14 days every 3 weeks and oxaliplatin 130 mg/m^2 intravenously on day 1 (CAPEOX regimen) were given.

Surgical Technique

All patients underwent either a low anterior resection (LAR) or an abdominal peritoneal resection (APR) for curative resection by a colorectal surgeon. Low anterior resection was selected following those criteria: adequate distance of the tumor from the anal verge to allow sphincter preservation, good anal sphincter function, excellent response to neoadjuvant chemotherapy, and patient preference. A temporary diverting loop ileostomy or colostomy was performed following LAR. However, for those with tumor invasion of the anal canal, inadequate distal margins from the anal verge, or poor anal sphincter function, APR and permanent colostomy were selected. Following surgery, the pathologic response was assessed. Patients with complete disappearance of the tumor and pelvic lymph nodes were defined to have a pathologic complete response (pCR). The presence of mucin material without epithelial tumor cell was also defined as complete response. This definition was only found in a patient. The pCR rate among patients who had MRC and NMRC was recorded.

Statistics

Statistical analyses were conducted with IBM SPSS Statistics software, version 22. As appropriate, the chi-square (X^2), Fisher's exact, and Mann–Whitney tests compared the pathological response rates and categorical clinic pathologic characteristics of the study arm and the historical control arm. Additionally, the Student t test compared continuous variables, such as age, tumor size, and radiation dose. For the variable groups, the hazard ratio (HR) for death was calculated with a 95% confidence interval (CI). All statistical tests were two-sided and p values less than 0.05 were considered significant.

Results

There were 403 patients in this retrospective study. Two hundred sixty-eight were males and 135 females. The median age was 55 (range, 16–88) years. Two hundred and sixty-six of the patients (66%) had clinical stage II and 137 (34%) had clinical stage III disease. The median tumor size was 5 cm (range, 3–13 cm). The median distance of the tumor from the anal verge was 5 cm (range, 0–15 cm). Table 1 illustrates the characteristics of patients with MRC ($n = 46$) and NMRC ($n = 347$). Patients with MRC had a younger age ($p = 0.004$), larger tumor ($p \leq 0.001$), and advanced tumor stage ($p = 0.03$) at diagnosis.

All patients completed the chemoradiation as scheduled with no difference in grade 3–4 toxicity between the two groups. After surgery, there was a higher rate of positive margin ($p = 0.049$), larger residual tumor size ($p = 0.002$), higher pathologic tumor stage ($p = 0.041$), and higher nodal stage ($p \leq 0.002$) among MRC patients.

In the univariate analysis, female gender ($p = 0.009$), distal rectal location ($p = 0.035$), higher clinical tumor stage ($p = 0.049$), higher clinical node stage ($p = 0.001$), MRC ($p = 0.017$), and a higher pretreatment level of CEA ($p = 0.013$) were predictive for a poor pathologic complete response rate (Table 2). However, in the multiple logistic regression model, only the clinical tumor stage was an independent predictive factor for pathologic complete response [HR = 13.6, CI = 1.044–173.717; $p = 0.046$].

Discussion

To our knowledge, even though it is retrospective, the current study is one of the largest reports on the effect of neoadjuvant chemoradiation on MRC. There was an 11% incidence of mucinous histology in the study's cohort. In agreement with other studies, MRC patients were significantly younger and predominantly males [14, 15]. Despite a younger age, MRC frequently presented with locally advanced disease at diagnosis and poorer response to treatment which emphasizes its aggressive biology [16–19]. As an illustration, less than 10% of patients with MRC achieved a negative pathological margin, likely reflecting a lower rate of downstaging despite the same protocol for chemoradiation leading to a higher recurrence rate [11, 10, 17, 18, 20–23] Multiparametric magnetic resonance imaging (MRI) has been proposed as a tool to predict margin status following chemoradiation [24]. However, it is unlikely that MRI can modify the disease course unless a drastic change of the treatment protocol for MRC is implemented based on the cancer molecular biology. Traditional clinical predictive factors for PCR in rectal cancer such as extended interval between treatment completion and surgical resection, pretreatment CEA level, and tumor distance from the anal verge did not apply for MRC [25–30]. For example, a meta-analysis of eight prospective studies on rectal cancer by McCawley et al. [30] demonstrated that mucinous histology was a reliable biomarker for poor response to neoadjuvant chemoradiation. Our study corroborated this finding. Thus, we are in the process to investigate whether MRC treatment should be personalized instead of the current one-glove-fit-all approach to all rectal cancer.

Fluoropyrimidine-based chemotherapy with 5-FU or capecitabine has been the standard regimen for rectal cancer. However, it has been reported that MRC may be resistant to 5-FU as a poor response and lower survival has been reported among patients with mucinous histology in patients with locally advanced or metastatic colorectal cancer [31]. Indeed, mucinous histology has been corroborated as a reliable biomarker for poor response following neoadjuvant 5-FU-based chemotherapy and radiotherapy for locally advanced rectal cancer [32]. Molecular biology studies suggest that fluoropyrimidine-based chemotherapy resistance may be linked to the tumor microsatellite instability (MSI) status.

Colorectal mucinous histology has been reported to have a high rate of MSI (MSI-high) compared to non-mucinous histology [33]. Among biomarkers, MSI-high colorectal cancer was reported as a predictor of 5-FU chemoresistance. The resistance mechanism of MSI-high cell lines to antimetabolites was linked to its mutation of the mismatch repair (MMR) mechanism genes which caused a lack of apoptosis when exposed to those agents [34]. In support of this hypothesis, colorectal cancer patients with MMR-deficient tumors did not benefit from adjuvant 5-FU chemotherapy in contrast to MMR competent tumors [35]. Thus, MSI-high colon cancer patients had no improvement in survival if treated with fluoropyrimidine-based regimen [36].

If MRC patients derived little benefit from standard 5-FU-based chemoradiation, how could clinicians develop new treatment protocol for this specific histology to improve pathological response rates and possibly to enhance complete resection rates and locoregional control? Could MSI-high patients benefit from a different systemic therapy?

Pathological specimen from MSI-high tumors frequently presented with a high rate of tumor-infiltration lymphocytes (TILs), suggesting that those tumors triggered an immune response within the host [37, 38]. Those tumors were also linked to a high rate of mutations and increased expression of genes encoding checkpoint receptors including PD1 in TILs, PDL1, and CTLA-4 [39, 40]. Thus, immunotherapy in selected patients with high expression of those genes may be effective in inducing tumor response. Indeed, preliminary study of immunotherapy with pembrolizumab, a PD-1 inhibitor, for patients with MSI-high colon cancer which developed recurrences following conventional chemotherapy has been promising [41]. A high response rate and prolonged progression-free survival were observed. Neoadjuvant immunotherapy and

Table 1 Distribution of the patients' and the tumor clinical characteristics in 403 rectal cancer patients treated with neoadjuvant chemoradiation

Variable	No	Neoadjuvant chemoradiation		*P* value
		Mucinous type	Non-mucinous type	
Patients	403	46	357	
Age				0.002
Mean ± SD	403	49.6 ± 14.8	56.5 ± 14.3	
Sex				0.143
Male	268	35	233	
Female	135	11	124	
Clinical tumor size				< 0.001
Mean ± SD	369	6.8 ± 2.6	5.5 ± 1.8	
Distance from anal verge				0.573
Mean ± SD	283	4.7 ± 2.9	5.1 ± 3.6	
Clinical tumor stage				0.033
T2	33	0	33	
T3	322	37	285	
T4	48	9	39	
Clinical node stage				0.136
Negative node	259	25	234	
Positive node	144	21	123	
Tumor grade				0.897
Grade I	277	32	145	
Grades II–III	126	14	112	
Pretreatment CEA level				0.100
Mean ± SD	300	5.8 ± 9.6	9.6 ± 28.8	
Dose of external RT (Gy)				0.342
Mean ± SD	403	47.3 ± 2.6	47.6 ± 2.6	
Type of rectal surgery				0.35
LAR	258	23	235	
APR	144	23	122	
Surgical margin status				0.049
Free	390	42	348	
Involved	13	4	9	
Pathologic tumor size				0.002
Mean ± SD	403	4.0 ± 2.4	2.9 ± 2.1	
Pathologic tumor stage				0.041
T0–T2	161	12	149	
T3–4	242	34	208	
Pathologic node stage				0.002
Negative node	317	28	289	
Positive node	86	18	68	
Lymphatic-vascular invasion				0.661
No	291	32	259	
Yes	112	14	98	
Perineural invasion				0.335
No	315	39	276	
Yes	88	7	81	

SD, standard deviation; *Gy*, gray; *LAR*, low anterior resection; *APR*, abdominoperineal resection

Table 2 Univariate analysis of potential predictive factors for pathologic complete response after the neoadjuvant treatment

Variable	No	Pathologic complete response		*P* value
		Yes	No	
Patients	403	77	326	
Age				0.725
Mean ± SD	403	55.2 ± 15.6	55.9 ± 14.3	
Sex				0.009
Male	268	61	207	
Female	135	16	119	
Clinical tumor size				0.082
Mean ± SD	369	5.2 ± 1.7	5.7 ± 2.0	
Distance from anal verge				0.035
Mean ± SD	283	6.2 ± 4.4	4.8 ± 3.2	
Clinical tumor stage				0.049
T2	33	6	27	
T3	322	68	254	
T4	48	3	45	
Clinical node stage				0.001
Negative node	259	62	197	
Positive node	144	15	129	
Tumor grade				0.057
Grade I	277	60	217	
Grades II–III	126	17	109	
Histologic type				0.017
Mucinous	77	3	74	
Non-mucinous	326	43	283	
Pretreatment CEA level				0.013
Mean ± SD	300	5.2 ± 7.6	10.4 ± 28.5	
Dose of external RT (Gy)				0.322
Mean ± SD	403	47.9 ± 2.6	47.5 ± 2.6	

SD, standard deviation; *Gy*, gray; *LAR*, low anterior resection; *APR*, abdominoperineal resection

radiotherapy may be effective in increasing pathological complete response rates and complete resection rates for MRC because of the abscopal effect of radiotherapy. Radiation dose escalation has been proven to be safe and effective to improve pCR rates and local control in patients with locally advanced rectal cancer [42, 43]. Increasing radiation dose to the tumor may also enhance its radio-vaccination effect through increased production of the circulating tumor antigens and is currently being investigated in trials combining radiotherapy and immunotherapy for solid tumors [44]. On the other hand, immunotherapy may also be combined with chemotherapy in the neoadjuvant setting for MRC as it has been reported to improve survival in colon cancer compared to chemotherapy alone [45]. Prospective trials combining immunotherapy with chemotherapy and/or radiotherapy to improve downstaging and resection rates for MRC should be conducted to test this hypothesis.

The limitations of this study include its retrospective nature and the use of conventional radiotherapy for the treatment of MRC instead of newer modality such as intensity-modulated radiotherapy. Nevertheless, our study highlights the need for an alternative protocol treatment as fluoropyrimidine-based chemotherapy and radiotherapy are ineffective in downstaging locally advanced MRC for a curative surgical resection.

Conclusion

Mucinous adenocarcinoma is a significant predictive factor for poor pathological response to capecitabine-based neoadjuvant chemoradiation in patients with locally advanced rectal cancer. New treatment protocol is required for MRC. Immunotherapy may be an attractive option for MRC because of its MSI-high status. Prospective studies combining immunotherapy and/or chemotherapy and radiotherapy should be considered in the future to improve the pCR and to potentially increase the complete resection rates for locally advanced MRC.

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Compliance with Ethical Standards

This retrospective study was conducted at the radiation oncology departments of three tertiary academic Iranian hospitals following approval by their respective institutional review boards (IRB) in accordance with Helsinki's code of ethics guidelines.

Conflict of Interest The authors declare that they have no conflict of interest.

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