Predicting Factors of Complete Pathological Response in Locally Advanced Rectal Cancer

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Abstract

Background:
Current treatment of choice for locally advanced rectal cancer is neoadjuvant chemoradiotherapy (neo-CRT) followed by surgical resection and adjuvant chemotherapy. Some patients may experience complete pathological response (cPR) after the neoadjuvant treatment. However, the predicting factors are still debated.

Methods:
In this registry-based retrospective cohort study, 258 patients with locally advanced rectal cancer were included. Patients were categorized into two groups with or without cPR. Logistic regression analysis was recruited to investigate the odds ratio for all independent variables, and those with significant results were included in multivariate regression analysis.

Results:
Achievement of cPR was 21.3%. The odds ratio of cPR was significantly lower when the tumor distance from the anal verge was > 10 centimeters (OR = 0.24, $P = 0.040$). Also, the odds of cPR with N1 involvement in comparison with N0 involvement decreased for 0.41 ($P = 0.043$). It was also true for patients with N2 involvement in comparison with N0 involvement (OR = 0.31, $P = 0.031$). Higher odds ratio of cPR was observed in patients who underwent surgery in > 12 weeks after neo-CRT (OR = 2.9, $P = 0.022$). Furthermore, the odds of cPR decreased for 0.9 with increasing in carcinoembryonic antigen (CEA) level ($P = 0.044$).

Conclusion:
Patients with rectal cancer in clinical stage II or lower, without the involvement of the lymphatic system at diagnosis, and with tumors located in the lower parts of the rectum, with lower levels of CEA, and longer duration between neo-CRT and surgery were more likely to achieve cPR after neo-CRT. With the current knowledge, the "wait and watch policy" is still debated and needs to be defined more precisely by upcoming studies.

Keywords:
Rectal cancer, Complete pathologic response, Neoadjuvant chemoradiotherapy, Wait and watch policy, Iran

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Introduction

Rectal cancer is one of the most prevalent cancers worldwide, affecting many people yearly and causing high rates of morbidity and mortality among them.[1,2] Though recent advances in chemotherapy, radiotherapy,

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and surgery have decreased the morbidity and mortality rates.[2]

The current standard of care in locally advanced rectal cancer (stages II and III) is neoadjuvant chemoradiotherapy (neo-CRT), followed by surgery and adjuvant chemotherapy.[3-6] The utility of new neo-CRT methods not only has improved the surgical outcomes but also has helped in saving patients' organs in a greater proportion of patients.[7] However, response to treatment is different among those undergoing neo-CRT. Some patients experience disease advancement, some may experience partial response, and in some, complete pathological response (cPR) may be seen.[4,7-10]

Complete pathological response is defined as the absence of any viable cancerous cells in the microscopic pathological study of the excised specimen after neo-CRT. Based on previous studies, cPR have been achieved in 10% to 35% of patients after neo-CRT with an increasing rate in recent years.[1,3-5,7,8,11-19]

Considering the previous experiences, cPR has been associated with improved survival and prognosis and less probability of local and systemic recurrence.[1,4,5,7-9,12,14,19-27] Moreover, the achievement of cPR has led to a new approach in the treatment of rectal cancer entitled "wait and watch policy", which basically equals not performing the routine surgery and instead to do a close follow-up of patients and in case of recurrence, to provide salvage treatment. In addition, some studies have proposed to change the standard surgical technique from total mesorectal excision to less aggressive techniques that lead to less morbidity in patients.[3,4,6,9-14,17,23,25,27-32]

Despite these theories, predicting each patient's response to neo-CRT is not easy.[3,9,10,14,23,33,34] In recent years, many studies have tried to find the predicting factors of cPR following neo-CRT in rectal cancer.[5,9,11,13-19,21,23,28,29,35-42] Even so, there is still no agreement on any of the proposed factors regarding predictors of cPR and "wait and watch policy" in the treatment of rectal cancer.[3,12,15,17,19,20,28,31,33,38,43-45] Therefore, considering its importance, it is still a hot topic of research in rectal cancer treatment. Accordingly, we aimed to study this important issue among Iranian patients suffering from rectal cancer to investigate the predicting factors of cPR following neo-CRT and the feasibility of the wait and watch policy.

Materials and Methods

In this registry-based retrospective cohort study, we included patients suffering from rectal cancer who underwent curative intents surgery (operable cases in clinical stage II-III) in four teaching and non-teaching hospitals across Tehran province, Iran, from 2013 to 2015 and received capecitabine-based neo-CRT in these centers or any other canters.

Since 2014 a clinical registry program has been established for colorectal cancer in a collaborative network by the partnership of some of the high-volume cancer centers in Tehran, Iran, called QRN-CRC to evaluate and compare the quality of care indicators and outcomes in a continuing robust process. The structure, contents, and standards of the clinical registry and QRN-CRC were reported in detail elsewhere.[46]

By providing an electronic data entry platform, provided based on a standard dataset to collect clinical data related to patients with colorectal cancer, met the inclusion criteria, all essential variables such as staging (clinical, pathological), surgery and other neoadjuvant and adjuvant treatment, as well as pathological and specific factors were collected. A few trained registrars in a supervised teamwork abstracted and actively followed up all the included cases and entered them in the database.

Criteria and definitions

Patients with topographic code of C.20 and morphologies including all kinds of adenocarcinoma, not otherwise specified were accepted (squamous, neuroendocrine, and melanomas were excluded). The rectosigmoid cases were excluded based on clinical jurisdiction. cPR was defined as not finding any viable cancerous cells in the excised specimen during the surgery and included all T0N0 or TinsN0 cases reported in pathology reports. Based on the definition, patients were divided into two groups of those with or without achieving cPR. Finally, 258 patients were included in this study.

Statistical analysis

In this study, at first, each of the variables was examined with chi-square and t-test to investigate if there is a significant relationship between them and achievement of cPR. Age and serum carcinoembryonic

antigen (CEA) levels were considered numerical, and others were considered categorical variables. Logistic regression analysis was recruited to investigate the odds ratio for all independent variables, and finally, those with significant results were included in the multivariate regression analysis in a stepwise manner to investigate the effect of the most influential variable associated with cPR. In all parts of the study, *P* values < 0.05 and a confidence interval of 95% were considered the significance level.

Results

Achievement of cPR was seen in 21.3% (55 of 258) following neo-CRT. The mean ages of those with and without cPR were 54.4±1.7 and 55.7±09 years, respectively ($P=0.51$). Among those with cPR, 67.2% were male, while in the other group, 68.3% of patients were male ($P=0.43$).

The mean tumor distance from the anal verge among all patients was 6.5±0.2 centimeters. The mean distance in patients with and without achievement of cPR were 5.5±0.4 and 6.7±0.3 centimeters, respectively ($P=0.07$).

There was a close to significance – and still not statistically significant – difference between serum CEA level at diagnosis and cPR. The mean serum CEA level of all patients, with and without cPR were 8.4±0.1, 7.7±04, and 8.6±0.2 ng/L, respectively ($P=0.057$).

Considering the depth of tumor (T staging) in patients with achievement of cPR, most of them (72.7%) were T3, followed by 12.7% with T2, and 3.6% with T4. The data were not available in the files of 10.9% of patients. There was no significant difference between these patients and those without achievement of cPR ($P=0.10$). However, lymph node involvement (N staging) was significantly related to the achievement of cPR, as with the increasing number of involved lymph nodes, the achievement of cPR was decreased ($P=0.002$). Finally, the clinical staging of disease among our patients was significantly related to the achievement of cPR ($P=0.006$).

Among the studied patients, 92.8% received long-course neo-CRT (25-30 sessions and a total 5000 Gy), and the other 7.8% received short-course neo-CRT (5-8 sessions and a total 2500 Gy). This variable was not significantly related to the achievement of cPR ($P=0.88$).

Patients were divided into three groups regarding the gap between completion of neo-CRT and surgery. The groups were defined as the gap of fewer than 8 weeks, 8 to 12 weeks, and more than 12 weeks. Based on the performed analysis, those patients who underwent surgery after 12 weeks of completion of neo-CRT had a higher chance of achievement of pCR ($P=0.005$). Though, other groups showed no significant relationship.

The details of the above-mentioned information are shown in Table 1.

Moreover, based on these findings, multivariate regression analysis was performed with the following variables of age, sex, tumor distance from the anal verge, serum CEA level, short- or long-course neo-CRT, and gap between neo-CRT and surgery.

Based on the analysis, the odds ratio of cPR was significantly lower when the tumor distance from the anal verge was more than 10 cm (OR=0.24, 95% CI=0.06, 0.9) ($P=0.040$). Also, the odds of achievement of cPR in patients with N1 involvement in comparison with those with N0 involvement decreases for 0.41 ($P=0.043$). It is also true for patients with N2 involvement in comparison with those of N0 involvement (OR=0.31, $P=0.031$). We also observed higher odds of cPR in patients who underwent surgery more than 12 weeks after neoadjuvant chemoradiation therapy (OR=2.9, 95% CI, 1.17, 7.52) ($P=0.022$).

Furthermore, considering the serum CEA level, the odds of achievement of cPR decreased for 0.9 with increasing in CEA level, and it was statistically significant ($P=0.044$). The details of multivariate regression analysis are shown in Table 2.

Discussion

Rectal cancer is one of the most prevalent cancers worldwide, suffering many people and causing significant morbidity and mortality.[1,2] The current gold standard of treatment for locally advanced rectal cancer (stages II and III) is neo-CRT, followed by surgery and adjuvant chemotherapy.[1-6] However, with advances in chemoradiotherapy techniques, a new subject has evolved, and that is the varied response of patients to neo-CRT that could change the decision of radical

Table 1. Patients' characteristics with and without complete pathological response following neoadjuvant chemoradiotherapy

Characteristic	cPR	No cPR	*P* value
Total (%)	55 (21.3%)	203 (79.7%)	
Age (mean±SE)	54.41±1.71	55.71±0.92	0.51
Gender (%)			
Male	37 (67.2)	125 (68.3%)	0.43
Female	18 (32.7%)	58 (31.6%)	
Distance from the anal verge (cm, %)			
≤5	25 (45.4%)	84 (41.3%)	
5-10	16 (29.0%)	63 (31.0%)	0.156
>10	3 (5.4%)	31 (15.2%)	
Unknown	11 (20.0%)	25 (12.3%)	
CEA (ng/L, mean±SE)	7.72±0.49	8.65±0.21	0.057
Clinical T (%)			
T2	7 (12.7%)	13 (5.9%)	
T3	40 (72.7%)	131 (64.5%)	0.103
T4	2 (3.6%)	15 (7.3%)	
NA	6 (10.9%)	44 (21.6%)	
Clinical N (%)			
N0	20 (36.3%)	29 (14.2%)	
N1	20 (36.3%)	85 (41.8%)	0.002
N2	8 (14.5%)	45 (22.1%)	
NA	7 (12.7%)	44 (21.6%)	
Clinical stage (%)			
I	3 (5.4%)	5 (2.4%)	
II	17 (30.9%)	26 (12.8%)	0.006
III	28 (50.9%)	128 (63%)	
NA	7 (12.7%)	44 (21.6%)	
Long vs. short course of neo-CRT (%)			
Long	51 (92.7%)	187 (92.1%)	0.881
Short	4 (7.2%)	16 (7.8%)	
Time interval – neo-CRT to surgery (wk)			
Interval≤8	9 (16.3%)	53 (26.1%)	
8<Interval≤12	12 (21.8%)	61 (30%)	0.002
Interval>12	28 (50.9%)	49 (24.1%)	
NA	6 (10.9%)	40 (19.7%)	
Calendar time			
2013	13 (23.6%)	32 (15.8%)	
2014	8 (14.5%)	62 (30.6%)	0.045
2015	34 (61.8%)	108 (53.4%)	

Abbreviations: NA, Not assessed; neo-CRT, neoadjuvant chemoradiotherapy; cPR, complete pathologic response; SE, standard error.

Table 2. Investigation of potentially effective factors on achievement of complete pathologic response following neoadjuvant chemoradiotherapy – Multivariate regression analysis

Predicting factors	Odds ratio	95% CI	*P* value
Age group			
Under 50	Reference		
50-70	0.94	0.43, 2.04	0.877
Over 70	0.58	0.16, 2.03	0.403
Female sex	0.72	0.30 – 1.71	0.459
Distance from the anal verge (cm)			
≤5	Reference		
5-10	0.70	0.31, 1.57	0.391
>10	0.24	0.06, 0.95	0.043
Unknown	1.64	0.57, 4.68	0.349
Clinical T			
T3 vs T2	0.43	0.12, 1.45	0.174
T4 vs T2	0.30	0.04, 2.05	0.222
Unknown	0.20	0.04, 0.94	0.04
Clinical N			
N1 vs. N0	0.41	0.17, 0.97	0.043
N2 vs. N0	0.31	0.11, 0.90	0.031
Unknown	0.27	0.07, 0.91	0.035
CEA	0.90	0.81 – 0.99	0.044
Long vs. short course of neo-CRT	0.34	0.11, 1.09	0.071
Time interval – neo-CRT to surgery (wk)			
8-12 vs.<8	1.40	0.50, 3.91	0.514
>12 vs.<8	2.96	1.17, 7.52	0.022
Unknown	0.37	0.06, 2.33	0.293
Calendar time			
2013	Reference		
2014	0.35	0.11, 1.11	0.072
2015	0.84	0.32, 2.18	0.722

Abbreviations: neo-CRT, neoadjuvant chemoradiotherapy; CEA, carcinoembryonic antigen.

surgery to a more limited one, endoscopic treatment, or even no surgical treatment and following the so-called "wait and watch policy".[4,7-10]

A group of patients may experience the advancement of their disease, while others may experience partial or even cPR. cPR means that the following surgery, and based on the microscopic study of the excised specimen, no viable cancerous cells could be found. Based on the previous studies, 10% to 35% of patients

could achieve cPR following neo-CRT, with an increasing rate during recent years.[1,3-5,7-8,11-19, 47-50] We found 21% of our patients achieved cPR following neo-CRT, which is acceptable when considering past experiences.

Previous studies have found that cPR was associated with increased survival and better prognosis, and less probability of local and systemic recurrence.[1,4-5,7-9,12,14,19-27] Moreover, the achievement of cPR has led to a new approach to the treatment of rectal cancer, called the "wait and watch policy" simplified as not to perform the routine surgery in these patients and instead to follow them closely, and in case of recurrence, to provide salvage treatment. Furthermore, some of the previous studies have suggested changing the standard surgical technique of total mesorectal excision to less invasive techniques, which may lead to retrieval of patients' organs and less morbidity and mortality. Also, with the increasing gap between neo-CRT and surgery, it could be possible to benefit from the maximum effect of neo-CRT.[3-4,6,9-14,17,23,25,27-31]

However, predicting each patient's response to neo-CRT is not easy.[3,9-10,14,23,33] Currently, the gold standard to evaluate the patient's response is the pathological study of the excised specimen during surgery.[7,9,12,14,23,34] During the past years, many studies have tried to investigate the predicting factors of response to such treatment. The factors are size, grading and differentiation of tumor, tumor distance from the anal verge, serum CEA and fibrinogen level, blood cell counts, gap between neo-CRT and surgery, and many other proposed factors.[5,9,11,13-19,21,23,28-29,35-41] Also, some factors including involvement of lymph nodes at the beginning of disease, unfavorable tissue presentations like lymphovascular and perineural invasion, and high-grade tumors have been proposed to be associated with lymphatic system involvement even despite the achievement of cPR.[42] Even so, there is still no agreement on any of the above-mentioned factors regarding predictor factors of cPR and wait and watch policy in the treatment of rectal cancer.[3,12,15,17,19-20,28,31,33,38,43,44]

In the current study, based on the univariate regression analysis, some of the variables were found to be effective in the achievement of cPR following neo-CRT. These included closer located tumors to the anal verge, absence of lymph node involvement at diagnosis, lower clinical stage at diagnosis, and longer gap beyond 12 weeks between neo-CRT and surgery. Although serum CEA level was not significantly related to the achievement of cPR, it was very close to becoming significant. This could become significantly related if the sample size was larger. In fact, the lack of precise and correct data in the files of patients made us exclude some of the patients from our study, which led to the current sample size.

Following that, a multivariate regression analysis was performed to eliminate the effect of confounding factors. Based on it, tumor distance from the anal verge and absence of lymph node involvement at diagnosis were found to be the effective and predicting factors of achieving cPR following neo-CRT. Serum CEA level and the gap between neo-CRT and surgery, were statistically significant with the achievement of cPR.

Previous studies have found tumors located closer to the anal verge and the absence of lymph node involvement as predicting factors of achievement of cPR too. Amongst, a recent study from the Netherlands proposed that tumors in lower parts of the rectum and those without lymphatic involvement were associated with higher rates of achieving cPR.[12]

In another retrospective cohort study in 2015, serum CEA level at diagnosis, closeness to the anal verge, and statins consumption were correlated with achievement of cPR.[11] Moreover, Peng and colleagues found that absence of lymph node involvement, lower T stage, lower CEA level after neo-CRT, and longer gap than 7 weeks between neo-CRT and surgery were associated with higher rates of cPR achievement.[5]

Considering our results indicating that the absence of lymph node involvement is associated with the achievement of cPR, it could be concluded that patients with clinical stages over stage II of rectal cancer are less likely to achieve cPR following neo-CRT. It is consistent with the finding of some previous studies that have shown that desired tumor specifics, including lower N and T staging, are associated with the achievement of cPR.[5,18]

In the current study serum CEA level was significantly correlated with achievement of cPR. Previous studies have also found serum CEA levels– before and after neo-CRT– are associated with the

achievement of cPR.[5,11,14,17,19,34]

On the other hand, many of the previous studies have shown the association of achieving cPR with the gap between neo-CRT and surgery. Although there is still no agreement about the exact duration, it seems as longer as the duration would be, the chance of achieving cPR after neo-CRT would increase.[1,2,5,7,9,21,35,36,39] The gap between neo-CRT and surgery was significantly associated with the achievement of cPR in our study too, especially longer gaps of more than 12 weeks.

Considering the findings of previous investigations, many other variables, including and not limited to tumor size and grading, medical history of patients, and post neo-CRT serum CEA level, could be considered as predicting factors for achieving cPR. Although we tried to collect such data, the incompleteness of patients' files prevented us from including other variables in this study.

This study, like other studies, has its limitations. The first and the most important issue is its retrospective nature, which prevented us from collecting precise and complete data about some of the patients. Some of the files were incomplete or consisted of misleading data. We tried to overcome such a problem by studying different available files of patients, including inpatient and outpatient files, to complete and correct the gathered data. When impossible, patients with incomplete data were eliminated. This, itself, led to a not large enough sample size and the inability to include other potential variables, which is the other limitation of our study. Some other variables that were proposed by previous studies were not possible to be collected as such data were not registered in the files. We tried to eliminate the confounding factors to decrease the bias of our results, though it was not possible to do so completely because of mainly the retrospective manner of our study.

Nevertheless, and despite the mentioned limitations, this is one of the first studies in Iran and even in the Middle East that directly approaches to investigate the "wait and watch policy" and predicting factors of achieving cPR after neo-CRT in patients with rectal cancer.

Conclusion

It is logical to propose that patients with rectal cancer in clinical stage II or lower, without the involvement of the lymphatic system at diagnosis, and with tumors located in the lower parts of the rectum, with lower levels of serum CEA levels and longer duration between neo-CRT and surgery are more likely to achieve cPR after neo-CRT. However, prospective studies with a larger sample size and more variables are needed to achieve more precise results. With the current knowledge, although very interesting, the "wait and watch policy" is still debating and needs to be defined more precisely by upcoming studies.

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Conflict of Interest

The authors declare no conflict of interest related to this work.

Ethical Approval

This study was approved by the Research Ethics Committee of Tehran University of Medical Sciences IR.TUMS.IKHC.REC.1398.023.

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