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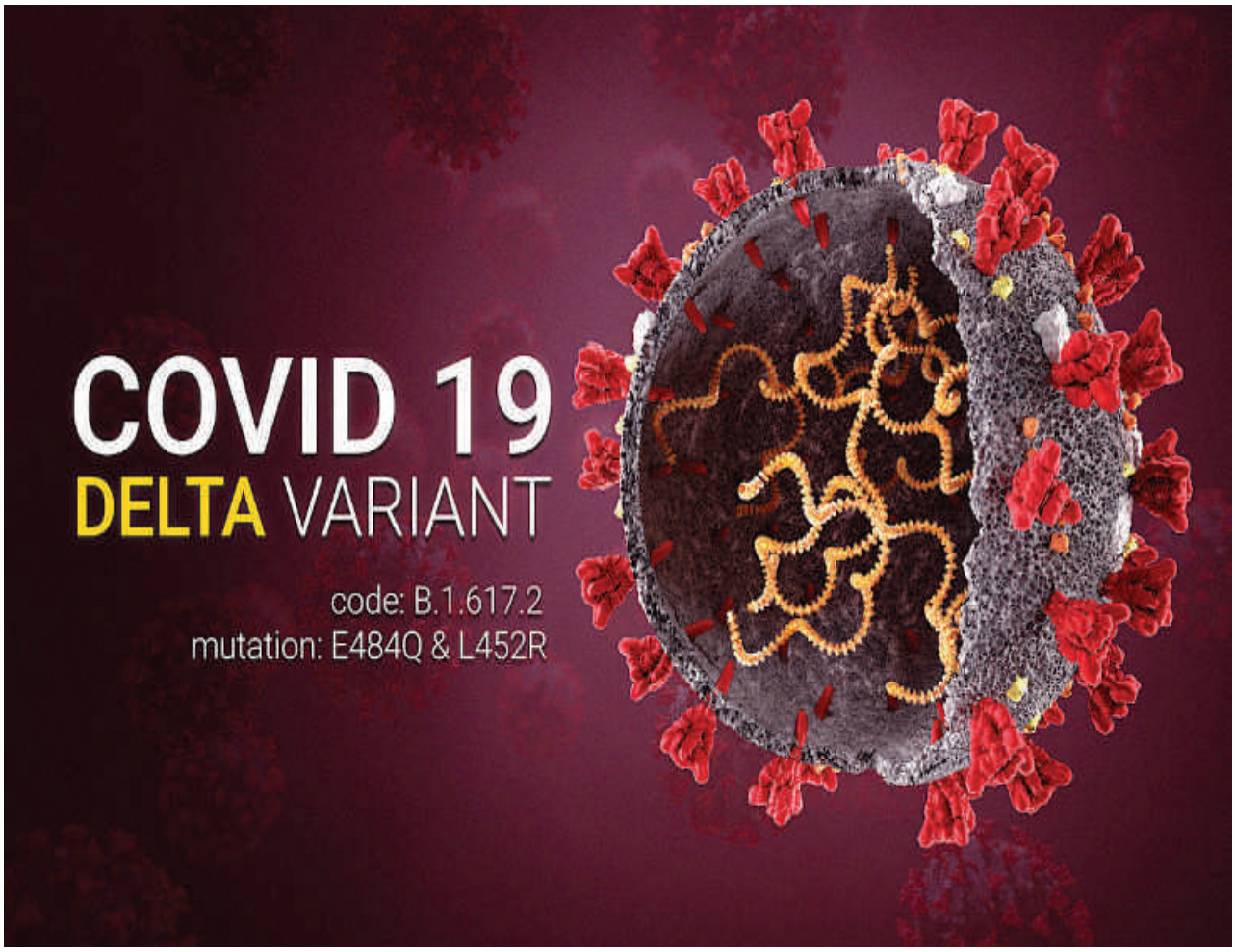

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Original Article

Evaluation Of Pathological Response And Its Predictors In Carcinoma Rectum Following Neoadjuvant Chemoradiation

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Abstract

Background: Neoadjuvant chemoradiation followed by surgery is the standard of care in locally advanced rectal tumors. Better pathologic response after chemoradiation is associated with better outcomes. Pathologic response may depend on various, patient and tumor related factors. The aim of our study was to assess the pathological response using a modified Ryan scoring system and to study various factors which influence the response.

Materials and Methods: This is a retrospective study carried out at a tertiary cancer centre in India. Patient details and histopathology reports of rectal cancer patients who took neoadjuvant chemoradiation from January 2016 to December 2018 were analyzed. Demographic details, pathological response assessed by modified Ryans tumor regression grade (TRG) score and various factors which influence the pathological response were studied. Those with TRG score 0 (complete response) and1(near complete response) were grouped together as good responders and those with score 3 (partial response) and 4 (poor or no response) as poor responders. Univariate and multivariate analyses were performed using logistic regression to determine factors which influence pathologic response.

Results: There were a total of 83 patients. Males and females were equally distributed. 43.4%(n=36) of patients had lower rectal tumors,32.5%(n=27) had mid rectal tumors and 24.1%(n=20) had upper rectal tumors. 46% of patients were good responders which includes complete responders ,17% (n=14) and those with a near complete response,29% (n=24). 54% of patients were poor responders ,which includes those with incomplete response,36% (n=34) and with no or poor response,18% (n=15). Among the upper rectal tumors, only 20% had good response and among the mid and lower rectal tumors 54% had good response.(p value 0.02) .63% of males were good responders in comparison to 37% among females (p value 0.05).

Discussion: Response to neoadjuvant chemoradiation with capecitabine in locally advanced rectal tumors in our institute is similar to the literature data with a complete response in 16.9%, near complete response in 28.9% partial response in 36.1% and no response in 18.1% of patients, according to modified Ryan score. It was found that upper rectal tumors had a poorer response when compared to mid and lower tumors and females had a poorer response compared to males.

Conclusion: Even though neoadjuvant chemoradiation remains the standard of care in locally advanced rectal carcinomas, its benefit in upper rectal tumors needs to be validated in larger studies.

Keywords: Rectal cancer, Neoadjuvant chemoradiation, Modified Ryan TRG score, Pathological response

Introduction

Colorectal cancer is a major health problem worldwide. It is the fourth most common cancer in the world . Almost 60% of cases are encountered in developed countries. In India, the annual incidence rates (AARs) for rectal cancer is around 6 per 100000 for males and 3 per 100000 for females [(1)]

Treatment of rectal cancer depends on the stage of disease at presentation and locally advanced rectal cancers (T3,T4 or node positive disease) need multimodality treatment.[(2,3)]

Preoperative chemoradiation has been shown to cause tumor regression, and is the standard of care in locally advanced rectal cancers. Tumor downstaging has been associated with an increased probability of tumor resectability,[(4,5)] a higher rate of sphincter–saving procedures,[(6,7)] and increased local control and patient survival.[(8,9,10,11)]

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As pathological complete response (pCR) indicate better clinical outcomes, it would be very useful if we can find out patient and tumor related factors which would predict a pCR. It is also beneficial for clinicians in determining prognosis and could assist with treatment decisions.

The factors that predict response to therapy in rectal cancer have not been well–characterized. Several small retrospective studies have looked at factors associated with tumor response to neoadjuvant chemoradiation including higher radiation doses,[12] different chemotherapy agents,[13] interval to surgery,[14,15] and molecular markers such as P53 gene mutation[16,17] and endogenous P21 expression[18] but there are no reliable methods to predict pCR after neoadjuvant chemoradiation in carcinoma rectum.[19]

The aim of our study is to assess the pathological response following neoadjuvant chemoradiation and surgery using modified Ryan score in patients with locally advanced carcinoma rectum and to find the predictors of pathological response.

Materials and Methods

This is a single institution retrospective carried out at Malabar Cancer Centre, Thalassery, a rural tertiary cancer Centre in Kerala, India. All cases of locally advanced carcinoma rectum (composite stages II and III) who took neoadjuvant chemoradiation from January 2016 to December 2018 were included in the study. Patients with dual malignancies and with multiple missing data points were excluded.

Preoperatively patients were evaluated with clinical examination, flexible endoscopy, CT scan of chest and abdomen and MRI of pelvis. Depending on the distance from the anal verge, tumors were classified as lower rectal (up to 5 cms), mid rectal (5–10 cms), and upper rectal tumors (10–15cms).

Planning CT scan was taken with proper immobilization and rectal and intravenous contrast. Planning was done in either Eclipse 13.7 or Monaco 5. All patients were treated with 3D conformal radiation therapy in Varian clinic ix or Elekta Versa HD machine up to a dose of 50.4 Gy in 28 fractions. GTV (gross tumor volume) and mean dose to CTV (clinical target volume) was retrieved from either of the planning systems. Cardiology fitness was obtained before starting capecitabine at a dose of 825 mg/m^2 for 5 days a week. Patients were reviewed weekly once or when indicated, while on radiation therapy. Patients were taken up for surgery 6–8 weeks after chemoradiation.

Post–operative specimens were examined by onco–pathologists and response to chemoradiation was reported using modified Ryan TRG score. Score 0(complete response),1(near complete response) were grouped together as good responders and score 3(partial response),4(poor or no response) as poor responders.

Patient medical records and the colorectal cancer clinical database were reviewed to collect the following information: gender, age, tumor differentiation, pre–treatment tumor distance from the anal verge, clinical TNM stage, radiotherapy treatment volumes and dose, chemotherapy dose and time interval between completion of chemoradiation treatment and surgery.

Statistical analysis

Nonparametric data are presented with median and range and others as mean. The association between variables was evaluated for significance, using chi–square test for categorical variables and Wilcoxon rank sum test for continuous variables.

Univariate and multivariate analyses were performed using logistic regression to determine factors associated with a pathologic complete response. A p value < 0.05 was considered statistically significant

Results

There were a total of 83 patients who underwent neo–adjuvant chemoradiation followed by surgery during our study period. Patients were grouped into two cohorts namely good responders and poor responders. Demographics, tumor characteristics, and treatment variables for the total population and each cohort are provided in (Table 1).

46% of patients were good responders which includes complete responders ,17% (n=14) and those with a near complete response,29% (n=24).

54% of patients were poor responders ,which includes those with incomplete response,36% (n=34) and with no or poor response,18% (n=15) .

Site of the tumour was significantly different between two groups. Among the upper rectal tumors, only 20% were good responders and among the mid and lower rectal tumors 54% were good responders.(p value 0.02). Sex of the patient was also significantly different among two groups.63% of males were good responders in comparison to 37% among females (p value 0.05).

Clinical T stage, N stage and composite stage of the disease were not significantly different between two cohorts. Hence we tried to find out whether there is any difference in response with respect to GTV (Gross tumor volume) or mean dose to CTV (clinical target volume), but we could not find any statistically significant difference among the two groups for these variables also.

VARIABLE	TOTAL CASES	GOOD RESPONDERS (RYAN SCORE 0,1)	POOR RESPONDERS (RYAN SCORE 2,3)	P VALUE
Gender Male Female	 42 (50.6%) 41 (49.4%)	 24 (63.2%) 14 (36.8%)	 18 (40%) 27 (60%)	 0.05
Age in years Median age(range)	 61 (33–75)	 61 (33–75)	 60 (35–75)	0.73
ECOG PS PS 1 PS 2	 80 (96.4%) 3 (3.6%)	 37 (97.4%) 1 (2.6%)	 43 (95.6%) 2 (4.4%)	 0.66
Site of tumor Upper rectum Mid rectum Lower rectum	 20 (24%) 27 (36%) 36 (40%)	 4 (20%) 13 (48%) 21 (58%)	 16 (80%) 14 (52%) 15 (42%)	 0.02
Differentiation Well Moderate poor	 55 (66%) 20 (24%) 8 (10%)	 26 (47%) 6 (30%) 6 (75%)	 29 (53%) 14 (70%) 2 (25%)	 0.09
Clinical TNM stage Stage II Stage III	 4 (5%) 79 (95%)	 1 (25%) 37 (47%)	 3 (75%) 42 (53%)	 0.39
Clinical T stage T2 T3 T4	 4 (5%) 69 (83%) 10 (12%)	 1 (25%) 35 (51%) 2 (20%)	 3 (75%) 34 (49%) 8 (80%)	 0.10
Clinical N stage N0 N1 N2	 8 (10%) 33 (40%) 42 (50%)	 3 (38%) 17 (51%) 18 (43%)	 5 (42%) 16 (49%) 24 (57%)	 0.80
GTV volume Mean	88.75 cc	72 cc	102.9cc	0.46
Mean dose to high risk CTV	5103.2 cGy	5106.4 cGy	5100.6 cGy	0.86
Median delay for surgery in days	59 (32–176)	60 (35–90)	57 (32–176)	0.51

Table 1: Patient Demographics and Tumor Characteristics

Definition of Variables for Univariate and Multivariate Analyses.

For univariate and multivariate analysis, variables were analysed as discrete binary variables. Age greater than 60 was chosen as it was the median age in our study. When considering the site of the tumor, upper rectum is considered as a variable, as the benefit of neoadjuvant chemoradiation in upper rectal tumors is still questioned. Well differentiated tumors are expected to have a better outcome than others and hence considered as a variable. The average of mean dose received by the high risk CTV is 5100 cGy and hence this was considered as the cut–off point when considering the mean dose.

To find a cut off value for analysis of the GTV volume, a receiver operator characteristic (ROC) curve was drawn and the most accurate point used to determine the volume was 67 cc. An ROC curve was also drawn to find a cut off value for the time delay for surgery after neoadjuvant chemoradiation and it was found to be 8 weeks.

Logistic regression analysis was not done for T stage and N stage as majority of tumors were T3 and node positive.

Univariate Predictors

Results of univariate analysis are shown in (Table 2). Site of the tumor and sex of the patient are the variables significantly associated with pathological response. Upper rectal tumors had a poorer response compared to mid and lower rectal tumors (p value–0.012) (odds ratio–0.40). And males had a better response compared to females.(p value–0.037)(odds ratio–2.6)

Multivariate Predictors

Results of multivariate analysis are shown in (Table 3). Again, site of tumor was significantly associated with pathological response. 54% (n=34) of mid and lower rectal tumors were good responders, but only 20% (n=4) of upper rectal tumors had a better pathological response with Ryans score 0 or 1. (p value–0.03) (odds ratio–0.267). Males had a better response compared to females in multivariate analysis also (p value–0.004) (odds ratio–5.13).

Discussion

This study was carried out to find out various factors which could influence the pathological response after neoadjuvant chemoradiation in locally advanced carcinoma of rectum. In our study 46% of patients were good responders which includes complete pathological response (17%) and near complete response (29%). In both univariate and multivariate analysis, site of the tumor and sex of the patient were the only independent predictors of pathological response. Site of tumor being in the upper rectum is a negative predictor of good pathologic response and male sex was a positive predictor of good pathologic response. All other variables namely age of the patient, ECOG performance status, differentiation of the tumor, GTV volume, and mean delay in surgery had no significant association with pathological response.

A study by Das et al which included 562 patients of which 108 (19%) had a pathologic complete response.[20] Tumor distance less than 5 cm from the anal verge and circumferential extent more than 60% were significant negative predictors of response to chemoradiation, but only circumferential extent was significantly associated with lack of a pathologic complete response. In our study, mid and lower rectum were significant positive predictors of response, but we could not collect the data on circumferential extent of the tumor retrospectively. Instead we calculated the gross tumor volume which

Variable	Definition	Good responders	Poor responders	P value	Odds ratio
Age	<61 yrs >/= 61	18 (44%) 20 (48%)	23 (56%) 22 (52%)	.734	1.162 (.489–2.757)
Gender	Male female	24 (63.2%) 14 (36.8%)	18 (40%) 27 (60%)	.037	2.571 (1.057–.255)
Distance from anal verge	Upper rectum Mid and lower rectum	4 (20%) 34(54%)	16 (80%) 29 (46%)	.012	.405 (.166 –.986)
Differentiation	Well Moderate/poor	26 (47.3%) 12 (43%)	29 (52.7%) 16 (57%)	.703	1.195 (.478 –2.99)
GTV Volume	</=67 cc >67 cc	20 (50%) 18 (42%)	20 (50%) 25 (58%)	.458	.720 (.303–1.713)
Median Delay for surgery in days	</= 8 weeks >8 weeks	15 (42%) 23 (49%)	21 (58%) 24 (51%)	.510	1.342 (.559–3.219)

Table 2: Univariate Analysis with Pathologic Response as Dependent Variable

Variable	Definition	Good responders	Poor responders	P value	Odds ratio
Age	<61 yrs >/= 61	18 (44%) 20 (48%)	23 (56%) 22 (52%)	0.74	1.186 (.42– 3.28)
Gender	Male Female	24 (63.2%) 14 (36.8%)	18 (40%) 27 (60%)	0.004	5.126 (1.6–15.8)
Distance from anal verge	Upper rectum Mid and lower rectum	4 (20%) 34(54%)	16 (80%) 29 (46%)	0.03	.267 (.084– .849)
Differentiation	Well Moderate/poor	26 (47.3%) 12 (43%)	29 (52.7%) 16 (57%)	0.57	1.38 (.445–4.3)
GTV Volume	</=67 cc >67 cc	20 (50%) 18 (42%)	20 (50%) 25 (58%)	0.39	.644 (.236–1.76)
Median Delay for surgery in days	</= 8 weeks >8 weeks	15 (42%) 23 (49%)	21 (58%) 24 (51%)	.743	1.186 (.428–3.28)

Table 3: Multivariate analysis with Pathologic Response as Dependent Variable

was contoured. But we could not find any significant association between GTV volume and tumor response.

Another study by Garcia–Aguilar et al[21] evaluated the predictors of pCR in 168 patients with locally advanced rectal cancer, but they were not able to identify any clinical factors associated with pCR.

There are three major trials evaluating local recurrence in rectal cancer with neoadjuvant and adjuvant therapy that include data based on tumor location .The first trial, the Swedish Rectal Cancer Trial[22] published in 1997, was a landmark article demonstrating significant improvements in local control and overall survival for patients undergoing neoadjuvant short–course RT. The study population composed of stage I to III patients 27% of whom had upper rectal lesions (>11 cm from anal verge). The authors found that neoadjuvant treatment with short–course RT had a significant effect on decreasing rates of local recurrence for mid and low rectal tumors (P< .001, P = .003), however, the effect on upper rectal tumors was not significant (P = .3) on long–term follow–up.[23]

Another study, the German CAO/ARO/AIO trial, is limited to patients with T3/4 tumors who were staged with ERUS and CT scans, 15% of whom had upper rectal lesions (>10 cm from anal verge). There was no subset analysis in this study, but there was no difference in local recurrence outcomes between upper and lower rectal tumors.[24]

The Dutch TME trial,[25] also found a significant correlation between local recurrence rates and tumor location within the rectum. Of the 1805 patients included in the trial, 30% had upper rectal tumors (10.1 to 15 cm from anal verge), 40% were mid–rectal (5.1 to 10 cm), and 30% were lower rectal (< 5 cm) tumors as determined by flexible endoscopy. The patient population was also included all stages of disease, the majority of whom were stage I–III. The data at 2–year follow–up shows that both mid–rectal tumors and lower rectal tumors had a significantly higher risk of developing local recurrence compared to upper rectal tumors (hazard ratio [HR] 2.13, 95% CI 1.13–4.01, P= .02; HR 2.78, 95% CI 1.22–6.31, P = .02). However, on univariate subgroup analysis, patients with upper rectal tumors who were administered neoadjuvant RT were found to have no improvement in local recurrence rates (P=.17) compared to the surgery–alone cohort at 2–year follow–up; these results were confirmed at 5–year follow–up (P = .122) [26]. Findings of our study should be read along with the findings of this study which shows that there is no benefit with neoadjuvant chemoradiation for upper rectal tumors.

There are various studies which have studied the difference in incidence and prognosis of colorectal cancers by sex. One meta –analysis[27] has shown a better disease free survival and overall survival for female patients when compared to males but we could not find any study, which specifically studied the effect of sex on pathologic response after neoadjuvant chemoradiation. We can infer that there is some dependence on sex in final outcome of colorectal patients which may be attributed to the difference in anatomy and local hemodynamic of the tumor. In our study males had a significantly better response to chemoradiation.

We understand that our study has its own limitations. Mainly it is a retrospective study and it is single institutional. Despite its drawbacks, all our patients were treated with a standard and uniform protocol. All the data are available for further studies and in future we plan to do survival analysis for these patients.

Conclusion

In conclusion, distance of the rectal tumor from the anal verge significantly affects the pathological response after neoadjuvant chemo radiation. Even though neoadjuvant chemoradiation remains the standard of care in locally advanced rectal carcinomas, its benefit in upper rectal tumors needs to be validated in larger studies.

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Conflict of Interest

There are no conflicts of interest

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