THE COMPLETE CLINICAL RESPONSE IN RECTAL CARCINOMA AFTER CHEMO RADIATION

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ABSTRACT

Objective: To determine the complete clinical response in rectal carcinoma after neoadjuvant chemo radiation.
Study Design: Cross-sectional study.
Place and Duration of Study: This study was conducted in Clinical Oncology department, Jinnah Postgraduate Medical Centre Karachi, from Jan 2016 to Jan 2017.
Material and Methods: Seventy Two Patients meeting the inclusion criteria were enrolled in study after complete staging workup. Neoadjuvant concurrent chemoradiotherapy was planned, consisting of oral capecitabine 825mg/m^2 BID five days a week along with 50.4 Gy Radiotherapy with linac machine. Radiation was delivered over a period of 5 weeks at a rate of 1.8 Gy/day. Patients received Radiotherapy in Atomic Energy Medical Centre (AEMC) and in Sindh Institute Urology & Transplant (SIUT), Radiation department. Chemotherapy was given in clinical oncology department of JPMC. Sixty one patients completed planned treatment and were available for post concomitant chemo radiotherapy response assessment with Pelvic CT/MRI after 6-8 weeks of completion of concomitant chemo radiotherapy. Response assessment was done according to Response Evaluation Criteria in solid tumor (RECIST) criteria version 1.1 and then Patients were referred for surgical evaluation.
Result: A total of 61 cases of locally advanced adenocarcinoma rectal cancer patients were included in the study. Mean age of the patients was 41 years with ± 17.06 years SD. Complete clinical response was identified in 4 (6.6%) while 31 (50.8%) were identified as partial response, progressive disease was 13 (21.3%) and 13 (21.3%) were with stable disease. All confounding variables were found statistically significant with *p*-value found less than 0.05.
Conclusion: Neo-adjuvant chemoradiotherapy for locally advanced rectal cancer is associated with high rates of tumor response in terms of downs tagging (complete & partial) and is relatively safe with acceptable morbidity, which favors its use in future.

Keywords: Advanced adenocarcinoma rectal cancer, Chemo-radiation, Complete clinical response (cCR), Neo-adjuvant chemoradiotherapy, Pelvic CT/MRI.

INTRODUCTION

Rectal cancer is notorious and lethal disease and it ranks 3rd among men is United States of America and 2nd in women regarding cancer related deaths[1]. Disease is common, worldwide burden is 1.4 million new case and 694000 deaths in 2012. In 2017, in United States of America 39910 new cases are expected to report[2]. Rectal cancer is 30% more common in males and older age is more affected. Disease is more common in developed countries and less frequently found in Africa and Asia[3]. According to Surveillance Epidemiology and End Results programme (SEER) data 2013, healthy population risk of developing rectal cancer is about 4.4% throughout their lives[4].

Treatment of locally advanced non metastatic rectal cancer has evolved in last 2 decades. Initially surgery alone is main stay of treatment for locally advanced rectal cancer but it shows dispiriting results in terms of local recurrence with positive histopathological margins in surgical specimens. Now multidisciplinary team approach is well known these days that involves close co-ordination between surgeon, oncologist, radiologist, pathologist and radiation oncologist. The precise meaning of locally advanced rectal cancer is needed to be addressed, it usually means a tumor which is unresectable surgically and it includes TNM stage II and III tumors[5].

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Now neo-adjuvant concurrent chemoradiotherapy followed by surgery is standard of care as compare to post op Concomitant Chemo radiotherapy (CCRT), as it potentially down stage the tumor, prevents the local relapse 7.1% versus 10%, prolongs the median time to local recurrence, improves histopathological results and decrease toxicity profiles[6]. The main objective of neo-adjuvant CCRT is actually down staging of tumor with complete clinical response seen up to 4.5%[7] it can be outstanding up to 26.8% with improve local control[8,9]. Now current strategies are moving towards wait and see policy for organ preservation[10]. The adverse effects of CCRT including mucositis, diarrhea, more seriously neutropenia and possibility of progression of disease.

The purpose of this study is to assess the complete clinical response of rectal cancer to the neo-adjuvant chemoradiotherapy in our population and to compare the trends with international population.

METERIAL AND METHODS

A cross-sectional study was conducted in Clinical Oncology department, Jinnah Post-graduate Medical Centre, Karachi from Jan, 2016 to Jan 2017. All the patients were provided with written informed consent as no confidential information was recorded, additionally the study does not pose any potential risk to the health of the enrolled participants after approval from institutional Ethic review committee. Histopathological confirmed locally advanced non metastatic rectal adenocarcinoma. ECOG performance status (0-2). Good renal and liver function tests. The patients who had not received any prior treatment (surgery, chemotherapy, radiotherapy). Metastatic cancer. ECOG performance status 3-4. Second primary in rectum. The patients who denied radiotherapy.

The pre-treatment work-up was based on thorough history and physical examination including digital rectal examination and diagnosis was established on tissue biopsy via colonoscopy, proctosigmoidoscopy. Metastatic workup included chest X-ray PA view, Abdominopelvic computed tomography or magnetic resonance imaging (CT/MRI). TNM staging system was used to stage the tumor according to clinical and radiological findings. Complete blood counts, blood chemistry including liver and renal function test, serum electrolytes, Carcino Embroyonic Antigen (CEA) levels, viral markers screening and ECG was done.

Neoadjuvant concurrent chemoradiotherapy was planned, consisting of oral capecitabine 825mg/m^2 BID five days a week along with 50.4 Gy Radiotherapy with linac machine. Radiation was delivered over a period of 5 weeks at a rate of 1.8 Gy/day. Patients received Radio therapy in Atomic Energy Medical Center and in Sindh Institute of Urology & Trasplant radiation department. Chemotherapy was given in clinical oncology department of Jinnah Post-graduate Medical Centre. Sixty one patients completed planned treatment and were available for post Concomitant Chemo radiotherapy (CCRT) response assessment with Pelvic CT/MRI after 6-8 weeks of completion of Concomitant Chemo radiotherapy (CCRT). Response assessment was done according to Response evaluation criteria in solid tumor (RECIST) criteria version 1.1. And then Patients were referred for surgical evaluation.

During whole course of treatment patients were followed every weekly for any subjective complaints along with clinical examination. Complete blood count (CBC), and Serum creatinine were repeated weekly while Liver function tests and hepatitis profile were done before treatment only and were repeated if deemed necessary on clinical examination. After completion of Concomitant Chemo radiotherapy (CCRT) patients were given rest for 6-8 weeks and advised to come in Outdoor Patient Department (OPD) if they develop any complaint.

For calculation of sample size prevalence of rectal cancer was taken 4.1% reported for local population[11].

The sample size is calculated with the help of WHO sample size calculator. with the help of

the following formula for sample size, value of prevalence was taken 4.1% with 95% confidence interval and 5% bound of error;

$$ss=\frac{1.96^2 * (0.041) * (1-0.041)}{0.05^2}, \quad ss=\frac{Z^2 * (p) * (1-p)}{d^2}$$

Where:

Z = Z value (e.g. 1.96 for 95% confidence level)

p = percentage picking a choice [prevalence], expressed as decimal

d = confidence interval, expressed as decimal sample size was calculated 59. However sample size was inflated to seventy-two patients meeting the inclusion criteria were enrolled in study after complete staging workup. Sample was collected by non probability consecutive technique.

SPSS version 21 was used for data analysis. Frequency and percentages of the following variables were described: Age, sex, presenting complaints, tumor location histological grade, pre-chemo radiation clinical stage, T and N status, post CCRT clinical response. Continuous variable i.e. age of the patient has been summarized with mean and standard deviation, median and range. The outcome complete clinical response was the unit of analysis and each unit (progressive, complete, partial and stable) was analyzed with 95% confidence interval. One way ANOVA were used to assess the mean difference

Table-I: Patient characteristics of rectal carcinoma.

Variables		Count	Table Total n%
Gender	Female	17	27.9%
	Male	44	72.1%
Diagnosis	Moderate diff	27	44.3%
	Poorly diff.	25	41.0%
	Well diff.	9	14.8%
Tumor Location	Low Lying	32	52.5%
	Middle Third	16	26.2%
	Upper Third	13	21.3%
Staging Modality	CT Scan	44	72.1%
	MRI	17	27.9%
T stage	T1	1	1.6%
	T2	8	13.1%
	T3	36	59.0%
	T4	16	26.2%
N Stage	N0	6	9.8%
	N1	32	52.5%
	N2	23	37.7%
TNM Staging	IIA	11	18.0%
	IIIA	10	16.4%
	IIIB	27	44.3%
	IIIC	13	21.3%
Age Groups	≤30 Years	23	37.7%
	31-50 Years	17	27.9%
	51-70 Years	21	34.4%
	>70 Years	0	0.0%
Presenting Complain	Abdominal Pain	3	4.91%
	Bleeding PR	44	72.1%
	Weight Loss	5	8.1%
	Pain at defection	6	9.8%
	Pain bleeding	3	4.91%

of age and CEA levels with response of treatment in terms of (complete, partial, stable, progressive response). To check the association of all confounding variables with response assessment parameters (complete, partial, stable, progressive response) Fisher test were used. A *p*-value of ≤0.05 was treated as significant.

Table-II: Correlation of study variables and treatment outcome.

Study Variable		Clinical response				*p*-value
		Complete Response (n=4)	Partial Response n=(31)	Progressive n=(13)	Stable Disease n=(13)	
Gender	Female	2 (3.3%)	13 (21.3%)	2 (3.3%)	0 (0%)	0.018*
	Male	2 (3.3%)	18 (29.5%)	11 (18%)	13 (21.3%)	
Tumor Location	Low Lying	3 (4.9%)	16 (26.2%)	10 (16.4%)	3 (4.9%)	0.019*
	Middle Third	1 (1.6%)	7 (11.5%)	0 (0%)	8 (13.1%)	
	Upper Third	0 (0%)	8 (13.1%)	3 (4.9%)	2 (3.3%)	
Staging modality	CT Scan	4 (6.6%)	22 (36.1%)	12 (19.7%)	6 (9.8%)	0.036*
	MRI	0 (0%)	9 (14.8%)	1 (1.6%)	7 (11.5%)	
T stage	T1	0 (0%)	0 (0%)	1 (1.6%)	0 (0%)	0.609
	T2	1 (1.6%)	4 (6.6%)	1 (1.6%)	2 (3.3%)	
	T3	3 (4.9%)	20 (32.8%)	7 (11.5%)	6 (9.8%)	
	T4	0 (0%)	7 (11.5%)	4 (6.6%)	5 (8.2%)	
N Stage	N0	2 (3.3%)	0 (0%)	2 (3.3%)	2 (3.3%)	0.026*
	N1	2 (3.3%)	20 (32.8%)	5 (8.2%)	5 (8.2%)	
	N2	0 (0%)	11 (18%)	6 (9.8%)	6 (9.8%)	
TNM Staging	IIA	2 (3.3%)	3 (4.9%)	4 (6.6%)	2 (3.3%)	0.012*
	IIIA	0 (0%)	8 (13.1%)	1 (1.6%)	1 (1.6%)	
	IIIB	2 (3.3%)	18 (29.5%)	3 (4.9%)	4(6.6%)	
	IIIC	0 (0%)	2 (3.3%)	5 (8.2%)	6 (9.8%)	
Age Groups	<30 Years	0 (0%)	12 (19.7%)	8 (13.1%)	3 (4.9%)	0.007*
	31-50 Years	2 (3.3%)	4 (6.6%)	3 (4.9%)	8 (13.1%)	
	51-70 Years	2 (3.3%)	15 (24.6%)	2 (3.3%)	2 (3.3%)	
	>70 Years	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Presenting Complain	Abdominal Pain	0 (0%)	0 (0%)	1 (1.63%)	2 (3.27%)	0.010*
	Bleeding PR	3 (4.9%)	28 (45.9%)	7 (11.5%)	6 (9.8%)	
	Weight Loss	1 (1.63%)	0(0%)	2 (3.27%)	2 (3.27%)	
	Pain at defection	0 (0%)	2 (3.27%)	1 (1.63%)	3 (4.9%)	
	Bleeding Pain	0 (0%)	1 (1.6%)	2 (3.27%)	0 (0%)	
Diagnosis	Moderate Differentiated	1 (1.6%)	17 (27.9%)	2 (3.3%)	7 (11.5%)	0.044*
	Poorly differentiated	1 (1.6%)	10 (16.4%)	10 (16.4%)	4 (6.6%)	
	Well differentiated	2 (3.3%)	4 (6.6%)	1 (1.6%)	2 (3.3%)	

RESULTS

A total of 61 cases of locally advanced adenocarcinoma rectal cancer patients were included in the study. Mean age of the patients was 41 years with ± 17.06 years SD. Mean adjuvant were recorded 3.61 with ± 4.35 with a range (1-24). Most of the patients were male 44 (72.1%) its mean male have more predominant as compare to female patients. Age stratification was done, most of the patient's age group is 30 years which included 23 (37.7%) patients. Regarding histologic diagnosis of the tumors, 27 (44.3%) were moderately differentiated while 25 (41%) were poorly differentiated only 9 (14.8%)

patients found well differentiated. Clinical "T" staging was recorded in 61 patients, 8 (13.1%) of all cases were in the T2 category, while 36 (59%) were present in the T3 category. Only 1 (1.6%) cases showed T1 stage while 16 (26.2%) of the tumors showed T4 staging. Most of them done CT-Scan. Clinical "N" staging was recorded, out of which 6 (9.8%) cases were in the N0 category, 32 (52.5%) in the N1 category, 23 (37.7%) in the N2 category. Bleeding PR presenting complaint was observed most in the patients (table-I).

Table-III: Relation between age and CEA level with responses.

Parameters	Treatment outcome	Values	*p*-value
Age	Complete Response	49.5 ± 13.4	0.04
	Partial Response	44.2 ± 14.08	
	Progressive	32.1 ± 13.05	
	Stable Disease	39 ± 13.8	
CEA level	Complete Response	2.77 ± 0.51	0.004
	Partial Response	4.39 ± 2.9	
	Progressive	6.93 ± 1.7	
	Stable Disease	3.97 ± 2.17	

Complete clinical response was identified in 4 (6.6%) while 31 (50.8%) were identified as partial response, progressive disease was 13 (21.3%) and 13 (21.3%) were with stable disease. Fisher test was applied with outcome variable clinical response (table-II). All confounding variables were found statistically significant with *p*-value found less than 0.05. Seventy two patients were enrolled initially. Sixty one patients had post chemoradiotherapy assessment and they had completed their treatment without any modification. Two patients were referred to other radiation centers. Two patients quit treatment. Two patients were lost to follow up. In 1 patient chemoradiotherapy was hold due to illness. Four patients died without taking any treatment (table-II).

Table-III shows significant deffernce relation between age and CEA level with responses after taking treatment. After applying post-hoc test there is no significance difference between pair wise responses with age $p>0.05$. And only progressive response is significantly different from partial response and stable disease among CEA-level $p=0.015$ and $p=0.017$ respectively.

DISCUSSION

Clinical trials have established neoadjuvant CCRT as preferred treatment approach in stage II/III rectal cancer as compare to adjuvant Concomitant Chemo radiotherapy (CCRT). Neo-adjuvant treatment modality has several advantages over adjuvant CCRT which includes tumor down staging reduction in transmural thickness good compliance, less toxicity, decreased rate of local relapse and increased rate of complete local pathological response[8-10,12]. Tumor is more susceptible to radiotherapy (RTP) preoperatively as local blood supply is intact and tumor oxygenation is good leading toward improved local control associated with reduced toxicity. Local relapse is 6% and 13% in neoadjuvant chemoradiotherapy vs adjuvant chemoradiotherapy[9]. Middle and lower rectal cancer benefit more from neoadjuvant chemoradiotherapy as compared to upper third of rectal cancer[13]. In this

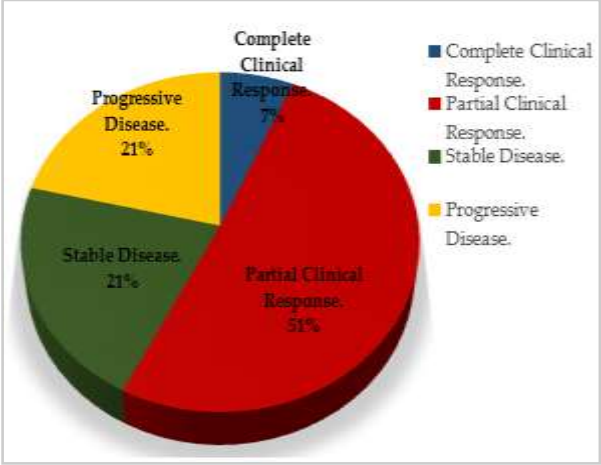

Figure: Post chemoradiation clinical response in rectal carcinoma patients.

study, post chemo radiation complete clinical response was found in 6.6%, partial response was found in 50.8%, stable disease was found in 21.3% and progressive disease was found in 21.3% which were very much comparable to the international studies[14] (figure). Similarly, a study conducted in India Sirohi *et al* determines complete clinical response (CR) in 5 (4.5%), partial response in 98 (89%) and stable disease in 7 (6.4%) patients[7]. Another study Azhar *et al* showed 56.7% partial response and no complete clinical response was found[14]. Complete clinical response found in other studies were 11%[15] and 19%[16] it can be as high as in Habr gamma 27%[8]. Literature review showed only limited data available to access theclinical response of neoadjuvant chemoradio-therapy. Phase III trials were found but most of the trials addressed the complete pathological response but only 38 trials were found presented the data on determination of complete clinical response/partial clinical response[16]. Only 5 studies were found having T2 /T3 tumors treated with neoadjuvant chemoradiotherapy and didn't proceed to surgery[17].

The lower response rates found in our study can be explained on the basis of higher percentages of T3 and T4 59% and 26% respectively, higher nodal status N2 in 37% as compared to other studies having more percentage of T2 and very few with T3 and no T4 tumors with mostly N0 nodal status[16]. Most of our patients were with poorly differentiated histology 41% and with younger age groups (table-I).

As a matter of fact data from international studies suggest the leading role of trimodality treatment preferably neoadjuvant chemoradiotherapy followed by surgery or wait and see policy for organ preservation. Neoadjuvant chemo radio-therapy proved its promising role in tumor down staging, improved local control, decreased toxicity profile and improved pathological outcomes[5-6]. The results of our study also favored its use in terms of tumor down staging, although complete clinical response were seen in very small number of patients but this is first study in Pakistan to find complete clinical response in this geographical area, and we reported a reasonable percentage of patients with stable and progressive disease 21.3%. We have to find out those prognostic and predictive markers which are responsible for low complete clinical response. Studies are also needed to see overall survival and progression free survival (PFS) in those patients who opted for wait and watch policy instead of surgery.

CONCLUSION

Neo-adjuvant chemoradiotherapy for locally advanced rectal cancers is associated with high rates of tumor response in terms of down-stagging (complete & partial) and is relatively safe with acceptable morbidity. Delaying radical surgery and adopting a 'wait and See' policy might be wiseable approach for selected cT1 or cT2 tumors who achieve a cCR.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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