Original Article

Efficacy of Neoadjuvant Chemoradiation in Carcinoma Rectum

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ABSTRACT

Aims and objectives: The aim of this paper was to study the impact of neoadjuvant chemoradiation on downstaging of locally advanced rectal carcinoma, sphincter saving procedures and toxicity profile of chemoradiation.

Method: 31 patients were studied who had locally advanced adenocarcinoma of rectum. They were treated preoperatively with 20 frations of 225 cGy (5 days/wk) radiation (total of 45Gy over 28 days). Chemotherapy consisted of 5-FU (500mg/m.sq) only for day 1, 2, & 3. After an interval of of 4-6 wks, all patients were submitted to surgery.The principles of TME was

Results: The median follow up in our study was 1year. At 1 year the overall survival in operated cases was 100% with no disease relapse. 67% of patients underwent low anterior resection,6.5% had proctosigmoidectomy with end colostomy,16.5% had a palliative surgical procedure, 6.5% became non compliant after neoadjuvant and 3.2% expired preoperatively during chemoradiation. At the time of surgery 82.6% of patients had pathological downstaging of tomour and 45.4% had lymphnode downstaging.Consequently 67.7% of patients underwent a sphincter preserving surgical procedure.
The incidence of complication was 29% with grade 2 mucositis and 9.7% with grade 1 mucositis. Myelosuppression was seen in non.

Conclusion: Significant downstaging of disease was seen with this regime of treatment and with improved subsequent sphincterv preserving procedures with acceptable toxicity profile.

Keywords: Rectal carcinoma, neoadjuvant, chemoradiation.

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INTRODUCTION

The incidence of rectal carcinoma in India is estimated in the range of 1.6-5.5 per lakh in men and 1.5-2.0 per lakh in women[1].

In United States Colorectal carcinoma is 4th most common cause of cancer and second most common of cancer related deaths. In contrast this disesase is uncommon in developing countries[2].

The cancer of the rectum is mainly treated by radical surgical resection but due to increase in local failure rates in the pelvis ranging between 20-70%[3] it has led clinicians to increase the use of chemoradiation either preoperatively or postoperatively in order to improve local control and overall survival.

Adjuvant chemoradiation has been a standard practice for treatment of rectal cancer. Unfortunately in our setup good number of patients present when growth is locally advanced and is unresectable. This has led to development of neoadjuvant chemoradiation.

Adjuvant therapy in defined as a chemoradiation given after a definte surgical resection and neoadjuvant theraphy as a chemoradiation prior to definitve surgical procedure, in order to downstage the tomour and then possible definitive surgical procedure.

The aim of our study was to assess the impact of neoadjuvant chemoradiation in locally advanced rectal cancer in terms of downstaging of tomour, possible sphincter saving procedure in low level rectal cancers and toxicity profile.

MATERIALS AND METHODS

This study was a prospective study conducted in a territiory care hospital SKIMS SRINAGAR KASHMIR INDIA from sept.2007 to sept. 2009. 31 patients with histopathological examination documented adenocarcinoma of rectum were included in the study. All the patients had locally advanced disease (T3-T4 and N0-N2). Patients with distant metastasis,synchronous growth, second malignancy, age>60 years and psychiatric illness were excluded from the study.

After clinical and radiological assessment, 83.9% (n=26) had fixed growth (T4), 16.1% (n=5) had tethered growth (T3)

The nodal status of disease was N1 in 45.2%(n=14).N2 in 29%(n=9) and No in 25.8%(n=8).All had Mo as per CT status.

In 48.4% (n=15) distance from anal verge was < 6cm & 51.6% (n=16) had distance > 6cm from anal verge with meandistance 4.12 chemo radiation were given in concurrent setting 5-FV 500mg/m2 as an 1v bolus dose over 3-5 min was given in first three & last three fractions of 28 day radiation protocol. The radiation protocol consisted of 225 c Gv fraction given five days a week from total of 20fraction over 4 week amounting to total cumulative dose of 45-G.Chemoherapy was given half an hour before radiation.

ADJUVANT chemotherapy of 5 FU 400-500mg/m2 6 or 1-5 day was also given 4 weeks for a total of 6 cycles.

Radiotherapy was delivered on a cobalt-60 moleeub. Patients were heated with AP/PA field.Superior border of field was at junction of L5-S1 & inferior border 3cm-belowthe lower limit of primary tumour, or at inferior aspect of obturator foremen.Latest border were 1.5 cm lateral to the widest bony margin of two pelvic side walls.

SURGERY

- Type of surgery was determined by the level of lesion.
- Principal of TME was applied to ensure lateral free margins.
- Adequate free margin in each side of growth was ensured.
- Gut continuity was restored by anastomosing proximal colon with distal remnant using hand-sewn or stappled technique.
- The proximal diversion was provided in the form of ostomy whenever needed.

RESULTS

A total of 31 patients including males & 7 females underwent the study with an average age of 42.9+14.9 years.At diagnosic 51.6% (n=16) had lesion at > 6cm of anal verge & rest i.e 48.4% (n=15) had lesion at <6cm from anal verge with average fraction of 7.3 +_ 2.2cm years. Digital rectal examination (DRE) before neoadjuvant therapy (at presentation) showed fixed growth in 83.9% (n=26) & tethered growth in 16.1% (n=5)patients.Five percent i.e 16.1% (n=5) had stage T3 (tetherad) & rest 83.9% (n=26) had T stage T4 (fixed growth)

Nodal status of diease was N0 in 25.8% (n=8), N1 in 45.2% (n=14) & N2 in 29.0% (n=9). None of thepatients had distant metastesis at presentation.

HPE revealed adeocarcinoma in all patients fifty one % (51%) i.e n=16 had well differentiated odenocarecinoma, 29% (n=9) had moderately differentiatedodenocarcinoma & 19.4% (n=6) had poorly differentiated adenocarcinoma.

After instruction of neo-adjuvant chemradiation the clinical staging based on D&E,revealed no palpable growth in 3.2% (n=1),mobile growth in 6.5% (n=2), tethered growth in 61.3% (n=19) & fixed in 29.0% (n=9)

The T –staging revealed T0, T2, T3 & T4 growth in 3.2%, 6.5%, 61.3% & 29.0% respectively.

Similarly N-staging revealed NO, N1 & N2 stage in 61.3%, 29.0% & 9.7% of patients.

On the basis of resuls complete response was seen in3.2%, partial response in 80.6% & stable disease in 16.1% of patients.

28 patients (90.3%) underwent surgery. One patient died during neadjuvantt-heraphy and two became noncomplite for surgery.

Low Anterio resection was performed in 67.7% (n=21) patients, palliative surgery in 16.1% (n=5) were performed as the growth was unresectable.

Interior operative HPE showed resectable growth in 23-patients with T0, T2, T3 & T4 in 4.3%, 8.9%, 73.9% & 13% respectively.

Resection linen were free of tumour cells,patient characteristics are tabulated in table1 and the various downstaging results have been described in table 2.

All patients presented with bleeding per rectum.

During our treatment no haemato-logical toxicity (erythema, neutron-penia) was observed while one major non haematological toxicities (National Cancer Institute Toxicity Criteria) was diarrhea/vomiting. In our study grade 1 diarrhea occurred in 29% and grade 2 in 9.7% and 5 patients (16.1%) had vomiting respectively.

DISCUSSION

It has been found that mobility of the tomour is the single pre-treatment prognostic value factor, therefore the role of neoadjuvant chemoradiation for downstaging of tomour and thus better respectability[4]. Neoadjuvant chemoradiation is particularly appealing in locally advanced disease due to high local reccurence[5]. In our study 23 patients out of total of 31 underwent curative surgery, 1 patient died preoperatively, two became non compliant and five were treated with palliative surgery. Patient who underwent curative surgeries showed both pathological and radiological downstaging. 82.8% had pathological downstaging with respect totomour size and bowel wall infiltration (Tstage) and 45.4% ha lymph noode downstaging. Clinical downstaging measured by increase in mobility and tomour showed complete response only in one patient, where 80.61% patients showed partial response and 16.1% showed a stable disease. Valentini *et al*[6] treated patients with extraperitoneal disease and preoperative chemoradiation.

This study no complete response in 77.0 % and stable disease in 2.3% of patients which are comparable to our results.Also chen *et al*[7] showed downstaging of 74% patients in his study. Minsky *et al*[8] and Mohiddin *et al*[9] showed pathological complete response(Pcr) of 20% and 90% respectively. In our study Pcr was seen in 4.3% of patients. In 23 patients with resectable growths H.P.E showed To in 1(4.3%), T2 in 2 (8.7%), T3 in 17(73.9%) andT4 in 3(13%). Lymphnode status was N0 in 73.9% and N1 in 26.1%. Resection lines were free of tomour cells in all patients.

After chemoradiation 64.5% patients showed downstaging on the basis of clinical and radiological data with respect to T staging with p value of <0.05% (sig). Similarly 35.5% patients showed downstaging with respect to N staging on clinical and radiological data with p value of 0.00% (sig). In our study 83.9% patients had T4 tomour representing a group of patients with locally advanced disease. This may account for low pathological complete response rate(4.3%) seen in our study campered to 10-30% in other studies by Janjan *et al*[10], Basset *et al*[11]. The patients with T and N downstaging have shown a significantly improved local control,freedom from distant metastasis, disease free survival and over all improved survival- Valentini *et al*[6]. Despite a low Pcr rate our pathological downstaging was 82.6% in T staging and 45.1% in N staging which is clinically meaningful to this group of patients with advanced disease.

Preoperative radioimaging and endorectal ultrasound after neoadjuvant is aguide for surgical management. However in our study and other studies Hiotis *et al* (12ch were not detectable preoperatively.) Many patients with clinical downstaging had persistent foci of disease, whi ch were not detectable preoperatively. Therefore clinical decision should be made only on the basis of palpable disease. One patient in our study had lymphnode status of No on CT, but H.P.E was positive for the disease During our treatment no haematological toxicity (erythema, neutropenia) was observed while one major non haematological toxicities was diarrhea/vomiting.In our study grade 1 diarrhea occurred in 29% and grade 2 in 9.7% and 5 patients (16.1%) had vomiting respectively,

(Our all patients were non vegetarain taking high fatty diet we cannot comment on wether high fatty diet increases the risk of carcinoma rectum or not)

In our study 15 patients had growth <6cms from anal verge. Out of which 57.1% had sphin ter saving procedure, camparable to results seen by Wieser *et al* in a study of 148 patients with sphincteri saving surgeries in 57.1%(13). Similarly colostomy was in 42.9% in our study and 43% in study by Wieser *et al*.

Also 3 year recurrence free survival for stapled anastomosis were 85% (P-0.001). The mean follow up was 1 year in our stud y and was found that all patients were disease free at that moment.

CONCLUSION

Patient who received neo adjuvant chemoradiation for locally advanced rectal carcinoma subsequently undergo sphincter saving procedure with acceptable toxicity profile and thus should be considred for all patients with locally advanced disease without any evidence of distant metastasis and co-morbidity.

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Table 1. Digital Rectal examination and Radiological Staging before Neoadjuvant Therapy (at presentation) in the Studied Subjects

Distance from Anal Verge (cm)	mean ± SD	7.3 ± 2.2 (4,12)	
Clinical Staging (DRE)	Tethered	5	16.1
	Fixed	26	83.9
T stage (CT)	T3	5	16.1
	T4	26	83.9
N stage (CT)	N0	8	25.8
	N1	14	45.2
	N2	9	29.0
M stage (CT)	M0	31	100.0
Adenocarcinoma	Well differentiated	16	51.6
	Moderately differentiated	9	29.0
	Poorly differentiated	6	19.4

(Table 4)Clinical staging of 31 patients was completely fixed (83.9%), tethered (16.1%),N 0 25.8%,N1 45.2% andN2 29% M STAGE (O) 100% at presentation.

Table 2. Demographic characteristics of the Studied Patients

		n	%
Dwelling	Rural	27	87.1
	Urban	4	12.9
Dietary status (Non vegetarian)		31	100.0
Non Obese (Normal)		31	100.0

All patients were non vegetarian taking high fatty diet

Table 3. Study report

Characteristics	N	%
Total Patients	31	100
Male	24	77.4
Female	7	22.6
Distance from anal verge		
< 6cm	15	48.4
>6cm	16	51.6
Surgical technique		
LAR	21	67.7
APR	2	6.5
Palliative	5	16.1
Noncompliance	2	6.5
Death	1	3.2

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Table 4. Radiological & Pathological obserbation

	Radiological				Pathological			
T-stage	**Pre-treatment**		**Post treatment**		**Pre Treatment**		**Post Treatment**	
	n	%	n	%	n	%	n	%
T0	0	0	1	3.2	0	0	1	4.3
T1(freely mobile)	0	0	0	0.0	0	0	0	0
T2(mobile)	0	0	2	6.5	0	0	2	8.7
T3(Tethered)	5	16.1	19	61.3	4	17.4	17	73.9
T4(fixed)	26	83.9	9	29.0	19	82.6	3	13
P-Value			<0.05(sig)				<0.05(sig)	
T- down staging			20	64.5			19	82.6
N-staging								
N0	8	25.8	19	61.3	6	26.1	17	73.9
N1	14	45.2	9	29.0	10	43.5	6	26.1
N2	9	29.0	3	9.7	7	30.4	0	0
P-value			0.00(sig)				<0.05(sig)	
Nodal down staging			11	35.5			11	45.8

Table 5. Toxicity profile after Neoadjuvant therapy in the studied subjects

		N	%
Diarrhoea	Grade 1	9	29.0
	Grade 2	3	9.7
Nausea		4	12.9
Vomiting		5	16.1
Erythema		0	0.0

(Table 5)Toxicity profile showing 29.0% patients had grade 1 diarrhea and 9.7% had grade 2 diarrhea.Erythema was not seen in any patient.