A Prospective Study on Short Course Radiation Followed by Preoperative Chemotherapy and Delayed Surgery in Carcinoma Rectum – A Single Institution Experience from Department of Radiation Oncology, Government Medical College Kottayam

Preeya Vasanthakumary[1], Anish Kuttappan Soman[2], Rema Padanayil Lekshmikutty[3], Gargy Anjolian David[4]

[1, 2, 3, 4] Department of Radiation Oncology, Government Medical College, Kottayam, Kerala, India.

ABSTRACT

BACKGROUND

The standard treatment for locally advanced rectal tumours (LARC)-cT3 lesions with threatened margins, cT4 lesions and node positive lesions is concurrent chemoradiation followed by surgery or short course radiation followed by immediate or delayed surgery. Surgery is total mesorectal excision with either low anterior resection or abdominoperineal resection depending on the location of the tumour. Radiation reduces local recurrence and improves the overall survival. Chemotherapy is given to increase tumour regression and decrease perioperative metastases. Short fractionation schedule of 5 Gy per fraction for 5 days permits sparing of radiotherapy resources, and saves patients of the morbidity of a protracted course of radiation of 28 days, with similar oncologic outcome. Further, the waiting period for surgery improves tumour down staging and pathological complete response rate.

METHODS

Patients with cT3 or cT4, fixed, node positive LARC received pelvic radiation 5 × 5 Gy and preoperative chemotherapy with FOLFOX regime followed by surgery.

RESULTS

Of the enrolled 27 patients, the median age of the patient was 57 years (range 40 - 80 years). Acute haematological toxicity was 22 % and G.I. toxicity was 11 %. Primary endpoint namely pathological complete response (ypCR) was noticed in 22 %. R0 resection rates (secondary end point) was 63 %, down staging rate was 66.7 % and sphincter preservation rate was 37.1 %. Surgery was not done in 25.9 %, of whom two were not willing for surgery, one patient became metastatic and rest five were deemed inoperable. Acute wound infection was recorded in two patients (10.2 %) and delayed wound healing (5.2 %) was seen in one patient.

CONCLUSIONS

Short-course radiotherapy (RT) induces tumour down staging and sphincter preservation with acceptable toxicities, when surgery is performed after chemotherapy at an interval of 6 – 8 weeks for cT3 lesions with threatened margins, cT4 rectal cancer and N0-2 tumours.

KEYWORDS

Rectal Cancer, Preoperative Chemoradiation, Surgery

Corresponding Author:
Dr. Preeya Vasanthakumary,
Advaitham, Vattackatt,
Kaviyoor P.O., Tiruvalla,
Pathanamthitta District,
Kerala, India.
E-mail: preeya.anilkumar7@gmail.com

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BACKGROUND

The standard treatment regime for locally advanced carcinoma (Ca) rectum is long course chemoradiation or short course radiation with immediate or delayed surgery.[1,2,3] Mesorectal fascia (MRF) involvement, reliably and accurately assessed by high resolution magnetic resonance imaging (MRI), is a predictor of probability of local recurrence and survival.[4,5] MRF involvement necessitates a preoperative treatment strategy which aims at R0 resection postoperatively. R0 resection being an element for local cure, preoperative therapy with radiation or chemoradiation (CRT) are required.[1-3,6] Short course radiation with delayed surgery is a valid option. The practice of short course radiation in the United Kingdom, Scandinavia and the Netherlands are considered after several randomised trials.[7-10] Short course radiation is preferred in these countries as radiation is completed in 5 days. Thus the treatment become more acceptable and budget friendly than long course concurrent chemoradiation.[7] Recent trend is to increase the interval between radiation and surgery. The possible attributable reason is to attain a considerable downsizing and thereby increase both pathological complete response (pCR) and clinical complete response (cCR) rates. ypT0N0 or pCR means absence of tumour cells in the pathological specimen and cCR is clinical complete response, when no tumour is detectable by clinical examination or radiological evaluation after the treatment.[4,5] Surgery practiced was total mesorectal excision (TME) with anterior resection or abdominoperineal resection.[4,6]

In short course radiation with delayed surgery, the delay for surgery is more than 4 weeks, preferably between 8 to 12 weeks. This delay induced tumour down staging and increased the rate of pathological complete response almost similar to that attained with long course radiation with concurrent chemotherapy.[8-13] During the delay period, to achieve a high pathological complete response, FOLFOX based chemotherapy 3 cycles every 2 weeks was administered.[11,12] Thus the purpose of giving chemotherapy was to increase tumour regression and decrease peri operative metastases.[10,11,13-15]

In our study, primary objective was to assess downsizing

1. clinically and radiologically, and
2. pathologically - pathological complete response.

The secondary objective was to assess the surgical outcomes in terms of

1. sphincter preservation rate.
2. complete resection rate.
3. toxicity profile.
   a. acute toxicities-gastrointestinal, haematological and skin toxicities.
   b. postoperative complications-delayed wound healing, wound infection.

Thus, in our study of neoadjuvant short course radiation followed by delayed surgery chemotherapy is administered in the waiting period for surgery.

METHODS

The study was a prospective observational study conducted in patients with carcinoma rectum, attending Radiation Oncology Department of Government Medical College, Kottayam, from July 2017 for one year after institutional review board clearance. The study participants fulfilling the following inclusion criteria were recruited for the study: age above 18 yrs., Eastern Cooperative Oncology Group (ECOG) performance status 0 - 2, clinically stage II / III carcinoma rectum which was resectable or expectation of being resectable after pre-operative chemoradiation, adenocarcinoma confirmed histologically by endoscopic biopsy, superior extent of the tumour located within 15 cm from anal verge, normal renal and liver function test. The criteria for exclusion include: prior pelvic radiation therapy for any reason, history of any form of treatment received for this disease, except for those who have undergone a diverting colostomy, synchronous colon cancer, systemic disease (cardiovascular, renal, hepatic, etc) precluding the patient from receiving chemotherapy.

Treatment

Recruited and eligible LARC patients attending our department, were subjected to an interrogative history of present disease with digital and proctoscopic evaluation of rectum. Complete blood count, blood biochemistry, serum carcinoembryonic antigen and chest X-ray, were done at baseline. Radiological evaluation with MRI / CECT, contrast-enhanced computed tomography of abdomen and pelvis, and colonoscopy with biopsy was done for assessing the clinical stage, extent of tumour and histological type.

All eligible patients received pelvic short course radiation of 25 Gray in 5 fractions with a fraction size of 5 Gray, completed in a week. This was followed 2 weeks later by chemotherapy with FOLFOX regime every 2 weekly for 3 - 4 cycles. FOLFOX4 regime was given intravenously with oxaliplatin at a dose of 85 mg / m^2 on day one as two hour infusion, 5–Fluorouracil 400 mg / m^2 as bolus and 600 mg / m^2 as continuous infusion over 22 hours on days one and two, calcium leucovorin 200 mg / m^2 as two hour infusion on day one and two administered before 5-fluorouracil and the cycle is repeated every two weeks.

2 weeks after completion of third cycle, patients were reassessed with MRI. Feasibility of surgical resection was assessed by the operating surgeon, clinically and radiologically. They were then taken up for low anterior resection or abdominoperineal resection with total mesorectal excision, depending on the location of the tumour. After surgery, patients returned with the detailed histopathological report. They received adjuvant chemotherapy as per the department protocol.

Short-Course Radiation – Simulation and Treatment Planning

All patients with Ca rectum were simulated for planning computed tomography (CT) scan in supine position immobilised with knee and footrest and comfortably filled

bladder. The target volumes and RT short-course technique were, as described previously (13). Primary tumour and any significant lymph nodes with mesorectal infiltration was considered as the gross tumour volume (GTV). GTV primary (GTV P) with 2 cm margin cranio-caudal and laterally encompassing the entire mesorectum at the level of the GTV formed the clinical target volume (CTV) 1. Significant lateral node involvement (GTV N) was covered with 1 cm margin all around (CTV 2). CTV1 was added to CTV 2 to form final CTV. In a view to minimise radiation to the small bowel, elective nodal irradiation was not performed. CTV with 1 cm margin formed the PTV. A 4-field box or 3 fields, 3-D conformal radiotherapy technique with (1 anterior, 1 posterior and 2 lateral beams (right and left) encompassed the contoured PTV. The PTV was covered within the 95 % isodose line of the prescribed dose.

Patient Characteristics	5 Gy X 5 F----------→ Chemotherapy ----------→ Surgery (n = 27)	
Gender		
Male	13	48.2 %
Female	14	51.8 %
Age in Years	57 years	
Type of tumour		
T2	1	3.7 %
T3	15	55.6 %
T4	11	40.7 %
Node positive	25	92.6 %
Node negative	2	7.4 %
WHO Performance Score		
0	0	
1	27	100 %
2	0	
3	0	
Distance between Tumour and anal Verge		
0 - 5	22	81.5 %
> 5 - 10	4	14.8 %
> 10 - 15	1	3.7 %
Histology		
Grade 1 adenocarcinoma	19	70.4 %
Grade 2 adenocarcinoma	6	22.2 %
Adenocarcinoma with signet ring cell	2	7.4 %

Table 1. Characteristics of Participants

Clinical Evaluation, Radiological Reassessment and Treatment Toxicity

Clinical evaluation was done clinically, prior to surgery by per rectal examination with the gloved digit and with proctoscope. Estimation of tumour size (length, thickness), extent of tumour, distance from anal verge, fixity, and cicumferentiality of growth were clinically correlated with MRI findings. As described previously by Shin et al. Complete response (CR) was as a complete resolution of gross tumour on clinical or radiological evaluation (RECIST criteria). Partial response (PR) is 50 % decrease in the size of the original lesion and progressive disease (PD) is defined as a more than 25 % increase in initial lesion or the newly detected lesions. No change in size of lesion are considered as stable disease (SD).[13]

Patients were monitored during treatment for toxicities. The Common Toxicity Criteria for Adverse Events, version v, of the National Cancer Institute (NCI CTCAE) was used for evaluating acute toxicity. Toxicities assessed and appropriate supportive care was provided.[16]

Surgical resection was performed after short course radiation and chemotherapy 4 - 6 weeks later after revaluation for operability, both clinically and radiologically. Total mesorectal excision with anterior resection or abdominoperineal resection was performed depending on the location of the tumour. R0 resection at TME was the intention, as proposed by Kim NK. R0 resection is absence of tumour cells in postoperative surgical margin. When residual tumour cells were seen within 1 mm from the surgical margin, it is categorised as R1 resection.[17,18] Margins were inked for this purpose. Positive or involved margins can be identified peroperatively in operating room by a frozen section and a re-excision with wide and safe margin can be ensured.

Mandard's classification was utilised for assessing primary pathological tumour response.[17] When no tumour cells are identified in the operated specimen pathologically; it is pathological complete response (pCR or ypT0N0). Fibrosis with scattered tumour cells was defined as 'Good pathologic response' / Mandard 1 or 11. Down-staging was evaluated by comparing final postoperative T stage (pathological) to T stage at diagnosis. Postoperative complications were also evaluated. Adjuvant chemotherapy was continued as per our department protocol.

Statistical Analysis

Primary objectives of this study was response, both clinical and pathological, to neoadjuvant short course radiation followed by chemotherapy and surgery. Secondary endpoints were sphincter preservation rate, treatment-related toxicity and R0 resection rate. For all analyses, SPSS software was used.

RESULTS

Results of Groups after Preoperative Treatment and Surgery

Treatment response was evaluated clinically and radiologically after completion of short course radiation and consolidation chemotherapy. Out of 27 patients studied, 21 (77.8 %) patients showed a downsizing of the tumour, 5 patients (18.5 %) were inoperable, and 1 patient (3.7 %) had metastatic progression. Out of 21, 2 patients (7.4 %) were not willing for surgery, 1 patient had poor response and the other patient had a clinical and radiological complete response and hence, opted for 'wait and watch policy.'

After upfront chemotherapy and short-course RT, haematologic and gastro-intestinal toxicities developed in 6 (22 %) and 3 (11 %) patients, respectively. Toxicities were graded according to CTCAE.v5.[16] Haematological toxicities were grade 2 anaemia and grade 3 febrile neutropenia. Gastrointestinal toxicities were graded as grade 1 abdominal pain and grade 1 - 2 diarrhoea. Diarrhoea resolved spontaneously after treatment completion.

Oncological Outcomes

Out of 19 operated patients, 10 (37 %) underwent low anterior resection and 9 (33.3 %) had abdominal perineal resection (APR). 17 (89.5 %) patients had a R0 resection and 2 (10.52 %) had a R1 resection. Postoperative

complications were wound infection in 2 (10.5 %) and delayed wound healing in 1 (5.2 %). Sphincter preservation rate was 37.03 % (10 patients); pathological complete response (ypT0N0) was observed in 6 patients (22 %). All patients were alive at a median follow up of 16 months.

Oncological Outcomes and Complications	(5 Gy X 5) + Chemotherapy n = 27
Loco Regional, Metastatic Status	
Downsizing	21 (77.8 %)
Inoperable	5 (18.5 %)
Distant metastases	1 (3.7 %)
Not Willing for Surgery (Downsizing Present) n = 21	77.8 %
1. Complete radiological response	1 (3.7 %)
2. Poor response, but operable	1 (3.7 %)
Toxicities during Treatment	
Haematological toxicities	6 (22 %)
Gastrointestinal toxicities	3 (11 %)
Deaths	Nil

Table 2. Oncological Outcome after 5GyX 5F Followed by Consolidation Chemotherapy; Treatment-Related Toxicities

Surgery and Pathology	n = 27
Surgery Not Carried Out	8
1. Not willing	2
2. Inoperable	5
3. Metastatic	1
R2 resection	0
R1 resection	2
R0 resection	17
Type of Surgery	
Anterior resection	10
APR	9
no tumour resection	8
Postoperative Complications	
Wound infection	2 (10.5 %)
Delayed wound healing	1 (5.2 %)
Quality of Sphincters	
Preserved sphincter, not operated	8 (29.6 %)
Preserved sphincter, operated	10 (37.03 %)
Sphincter not preserved, operated	9 (33.3 %)
ypT Category	
T0 (complete response)	6 (22.2 %)
T1	1 (3.7 %)
T2	7 (25.9 %)
T3	3 (11.11 %)
T4a (involvement of peritoneum)	0
T4b (involvement of adjacent organs)	2 (7.4 %)
ypN Category	11 (40.7 %)
N0	5 (18.5 %)
N1	0
N2	3 (11.1 %)
Inadequate sampling	

Table 3. Surgical Outcome after Short Course RT and Consolidation Chemotherapy

Initial Pre-op Stage	Downsizing (n=27)	Frequency	Percentage
	Present	**n=18**	
Stage 11 (T3, T4N0)	1. Complete radiological response	1	
Stage 111 (T3, 4N2) (n=23)	2. pCR	6	
	Stage 1		
111B 13	3.ypT1N0	1	66.7%
	4.ypT2N0	2	
	Stage 2		
	5.ypT3N0	2	
	Stage 3		
	6.ypT2N1	5	
	7.ypT3N1	1	
111C 10	**Absent**	**n=9**	
	1. Metastatic	1	33.3%
	2. Progression	6	
	3. R1 resection	2	

Table 4. Oncological Outcome after Treatment Completion

Follow Up

Follow-up visits after treatment completion were recommended at 2, 6, and 12 months for local assessment and for both, acute and long term treatment-related toxicities. Imaging studies were performed after 6 and 12 months of treatment completion.

DISCUSSION

Preoperative long course chemoradiation is the standard treatment for locally advanced rectal cancers.[1] Systemic combination chemotherapy which aims at systemic micro metastasis is thereby delayed, as stated previously in Dutch M1[10] trial. Long course chemo radiation could not be combined with systemic combination chemotherapy concurrently or sequentially due to acute and additive treatment related morbidities. In the studies by Radu et al and others [8,11,14] it was derived that short course radiation followed by combination systemic chemotherapy and delayed surgery could improve local control rates for LARC patients.

Long course chemo radiation when followed sequentially with systemic combination chemotherapy show an increased rate of acute treatment related toxicities and poor adherence to the protracted treatment.[2,12] But, the sequential combination systemic therapy in short course has not shown to summate the toxicities of the treatment schedule thus allowing a more feasible drug delivery. Cochrane database of systematic reviews [3] emphasized that there is no statistical difference in survival outcomes between the two schedules. Short course radiation for 5 days, in contrary, to the protracted long course of 28 days is more cost effective and patient friendly. So, we suggest short-course RT with systemic combination therapy and delayed surgery, a valid alternative treatment option to long course chemo radiation for locally advanced carcinoma rectum with its acceptable toxicity profile and similar outcome.

Local recurrence rate and patient survival was influenced by MRF status [4,5] as determined by MRI scanning. Therefore, for patients with threatened or involved mesorectal fascia, the treatment strategy that induces macroscopic tumour downsizing and sterilisation of surgical margins are preferred. This further contributes to R0 resection and pathological complete response, the forerunners of survival. Down-staging effect was emphasized following short-course RT and delayed surgery in 2 retrospective studies, of Uppsala University[3] and Hartsfield et al.[9] This was the basis of considering down staging and R0 resection as secondary objectives of our study. R0 resection and down staging was 63 % and 66.7 % respectively, and pCR 22 %. Of the 19 operated patients, 17 (89 %) had R0 resections and 6 (31.6 %), had pathological complete response which is similar, as described previously.[13] Besides, as concluded recently in international multicentre RAPIDO trial (ASCO2019), this treatment schedule can be considered as a new standard of care in LARC, with a lower rate of disease related treatment failure and the high pCR rate contributing to organ preservation.[19]

Characters and Result	Polish 11 Trial	RAPIDO Trial	Stellar Trial	Present Study
Study Design	RCT SCRT-→FOLFOX X3---→TME	RCT SCRT-----→CAPOX X6-→TME	Phase 111 RCT, Prospective SCRTarm--→CAPOX X4--→TME	Prospective observational study SCT-→FOLFOX X 3→TME
SCT-+CT-→TME duration	6 Weeks	18 Weeks	12 weeks	7 -8 Weeks
No. of Patients	261	468	238	27
Duration of study	2008-2014	June 2011 and June 2016	From August 30, 2015 to February 7, 2017	July 2017-July 2018
Inclusion Criteria	cT4 or fixed cT3 rectal cancer	stage T4a or T4b and node stage N2 disease, extramural vascular invasion (EMVI), and involved MRFor enlarged lateral lymph nodes	distal or middle third, T3-T4 and/or N+rectal adenocarcinoma	Stage 11(T3, T4 N0, M0) and Stage 111 (T1-4, Node positive) of distal and middle 1/3rd with threatened or involved MRF fascia
A/C Toxicities				
1. Grade-3-4	23%	18%	20%	11.1%
2. Toxic deaths	1%			Nil
pCR	16%	27.7%	18.6%	22%
R0 resection	77%		94.9%	63% (n=27) 89.5%(in operated-19)
Sphincter preservation				37.1%
Local failure	22%	8.7%		22 % (Post NACT alone) Nil (Treatment completed)
Distant mets.	30%	20%		3.7%
Post-Op Complications				
1. Wound infection	29%		30.5%	10.5 %
2. Delayed wound healing				5.2 %

Table 5. Study Characteristics and Results

Limitations

Firstly, the patient number in this study was small. Second, with short median follow-up of 16 months, evaluation of long-term outcomes was impossible. Third, benefit of adding combination chemotherapy with oxaliplatin in the waiting period for surgery was demonstrated only in a few trials.[10,11,13] Fourth, studies with similar protocol for preoperative short course radiation were the two arm studies, polish trial by Bujko et al, and STELLAR trial.[12,14] In these trials, final long-term outcome required further waiting. Fifth, all the above-mentioned results were from centre's outside India. A large randomised multicentre trial in India covering our population would be more suited for exact comparison of our results, considering the few prevalent Indian studies as quasi-experimental.[15]

CONCLUSIONS

Our short term results of R0 resection, pCR, sphincter preservation, downsizing, low acute toxicities and low postoperative complications are favourable and comparable with the above mentioned trials. Short-course radiation and delayed surgery is economical and patient friendly. Therefore, in centres with long waiting lists for radiotherapy, short course radiotherapy with consolidation chemotherapy would be a valid option for preoperative management of LARC, especially for those with comorbidities and advanced age. Saving and channelling of radiotherapy resources, especially in countries which are resource-limited would thus be enabled.

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