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RESEARCH ARTICLE

IS NEOADJUVANT CHEMORADIATION A GOLD STANDARD FOR CARCINOMA RECTUM? A COMPREHENSIVE ANALYSIS OF OUTCOMES AND PROGNOSTIC FACTORS FROM A TERTIARY CARE CENTRE FROM INDIA

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ABSTRACT

Introduction: The management of rectal cancer has changed over the years with an emphasis on neoadjuvant chemoradiation (NACRT) followed by surgery. Multiple western studies had shown better local control and sphincter preservation with preoperative chemoradiation in carcinoma rectum. However, data from India is lacking. Thus, we conducted the retrospective study in our institution to show the impact of neoadjuvant chemoradiation on sphincter preservation in carcinoma rectum.

Aims: Down staging, local control and sphincter preservation in carcinoma rectum.

Materials and Methods: The retrospective study was conducted in our institution which enrolled 126 patients with histologically confirmed diagnosis of carcinoma rectum (stage I-III) treated with neoadjuvant chemoradiation followed by surgery from Jan2009-Dec2013. Total dose of 45Gy in 25 fractions over 5weeks was delivered using 3D-CRT technique. All patients received 5-FU/LV(5-Fluorouracil/Leucovorin) weekly with 5-FU 325mg/m^2 and LV 30mg/m^2 on D1 of every week. 4-8weeks after completion of NACRT, patients were assessed for disease response, sphinchter preservation possibility and resectability of tumour. Pathologic assessment of response was seen in the resected tumours. Impact of different prognostic factors on clinical outcome was analysed.

Results: Median age of presentation was 48 years (range 18-77 years). Out of 126 patients, 86 were males and 40 were females. Most of the patients presented with bleeding per rectum (94.4%). Mean duration of symptoms was 9 months. Most of the patients presented with T3 disease (50.8%) followed by T2 (43.6%) and T4 (5.6%). Out of 126 patients, 83(65.9%) had N1 disease and 10(7.9%) had N2 disease. Lymph nodes were not involved in 33(26.2%). Most of our patients presented with stage III disease (73.8%). Mean distance of tumor was 4.2cm from anal verge. All the patients had histologically proven adenocarcinoma with signet ring cell and mucinous variety seen in 9.5% and 7.1% respectively. Most of the patients had moderately differentiated adenocarcinoma (43.7%). Well differentiated and poorly differentiated variety were seen in 6 and 5 patients respectively. With NACRT 82(65.07%) patients out of 126 were down staged and were amenable for surgery. Among 126 patients, 63(50.0%) underwent LAR(low anterior resection) and thus 50% of the patients had sphincter preserved and 53(42.1%) underwent APR(abdomino-perineal resection). Pathological complete response was seen in 14(11.9%) patients. Local control was seen in 60% of the patients. Patients with Hb>12gm//dl and tumours more than 3 cm from anal verge showed better sphincter preservation (p=0.018,p=0.011 respectively). Though grade of the tumour did not have impact on sphincter preservation however survival was improved in low grade tumours. Type of histology, lymph node positivity, pre op CEA did not have any significant impact on outcome.

Conclusion: This study represents the largest Indian experience with standard neoadjuvant chemoradiation followed by surgery in rectal cancer. Down staging of tumor, improved local control and increased sphincter preservation was seen in our study. Pretreatment Hemoglobin status, distance from anal verge and grade of the tumour came out to be the important prognostic factors.

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INTRODUCTION

Rectal cancer comprises approximately 25% of all primary colorectal cancers and follows a different natural history as compared to carcinoma colon. (Hawkes *et al*., 2011) Surgery is the mainstay of treatment but inspite of curative resections a significant proportion of patients develop local recurrence (20%-50%). (Pilipshen *et al*., 1984; Rich *et al*., 1983) To further improve the outcome of these patients multiple adjuvant and neoadjuvant approaches have been extensively explored. Several landmark trials demonstrated that radiotherapy (RT) decreases local recurrence rates by 50%–60% as compared to surgery alone. (Folkesson *et al*., 2005; Sebag-Montefiore *et al*., 2009; Kapiteijn *et al*., 2001) Systematic reviews/meta-analyses

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have examined the role of radiotherapy (RT) in resectable rectal cancer, (Colorectal Cancer Collaborative, 2001; Camma *et al*., 2000). These meta-analyses concluded that the data favored preoperative RT, rather than postoperative RT and that a biologically equivalent dose of >30 Gy is more effective in reducing local relapse. While initially adjuvant treatment was standard of care, high toxicity and poor compliance lead to trials looking at neoadjuvant treatment. German CAO/ARO/ AIO Rectal Cancer Trial changed the standard of care for patients with cT3 and/or node-positive rectal cancer to preoperative chemoradiation in 2004. (Sauer *et al*., 2004) They had shown better local control and sphincter preservation with preoperative chemoradiation in carcinoma rectum. However, data from India is lacking. Keeping this background in mind a retrospective study was conducted in our institution to show the impact of neoadjuvant chemoradiation on sphincter preservation in carcinoma rectum.

MATERIALS AND METHODS

The retrospective study was conducted in our institution which enrolled one hundred twenty-six patients with histologically confirmed diagnosis of carcinoma rectum(stage I-III) treated with neoadjuvant chemoradiation (NACRT) followed by surgery from Jan, 2009-Dec, 2013. A complete history was recorded and physical examination including local examination of disease. Baseline investigations like complete blood count, blood biochemistry, proctosigmoidoscopy and CEA was done. All patients underwent routine abdominal and pelvic computed tomography (CT) scans and chest x-rays. Preoperative staging was done with CT scans. Radiation therapy was delivered by photon radiation generated by a 6-MV or 15-MV linear accelerator. Total dose of 45Gy in 25 fractions over 5 weeks was delivered using 3D-CRT technique. All patients received 5-FU/LV weekly with 5-FU 325mg/m^2 and LV 30mg/m^2 on D1 of every week. 4-8weeks after completion of NACRT patients were reviewed in surgery department for the assessment of disease response, sphinchter preservation possibility and resectability of tumour. Surgical procedures included abdominoperineal resection (APR), low anterior resection (LAR), APR plus total mesorectal excision (TME), LAR plus TME, ultra-LAR plus TME and total proctolectomy. Pathologic assessment of response was seen in the resected tumours.

RESULTS

Patient characteristics: The age of the patients ranged from 18 years to 77 years with median age of 48 yrs. Out of 126 patients, 86 were males and 40 were females with male to female ratio of 2.15:1. History of smoking was present in 50(39.7%) patients. Most of the patients presented with bleeding per rectum (94.4%). Other presenting symptoms were altered bowel habits, discharge per rectum, abdominal pain, perianal pain, anorexia and weight loss. Most of the patients presented with more than one symptom with mean duration of symptoms of 9 months. Most of the patients presented with T3 disease (50.8%) followed by T2(43.6%) and T4(5.6%). Out of 126 patients, 83(65.9%) had N1 disease and 10(7.9%) had N2 disease. Lymph nodes were not involved in 33(26.2%). Most of our patients presented with stage III disease (73.8%). Mean distance of tumor was 4.2cm from anal verge. (Table 1)

Pathological characteristics: All the patients had histologically proven adenocarcinoma with signet ring cell and mucinous variety seen in 9.5% and 7.1% respectively. Most of the patients had moderately differentiated adenocarcinoma (43.7%). Well differentiated and poorly differentiated variety were seen in 6 and 5 patients respectively. (Table 2)

Treatment characteristics: External beam radiotherapy was delivered by photon radiation generated by a 6-MV or 15-MV linear accelerator. All patients were planned with 3D conformal radiotherapy and external radiation dose of 45Gy/25#/5weeks was delivered to whole pelvis by 4 field technique. Injection 5-FU 325mg/m^2 along with Injection LV 30mg/m^2 were administered concurrently with external beam radiation on D1 of every week for 5 weeks.

Table 1. Patient characteristics

Patient characteristics	No(%)
Median age (years)	48
Gender:	
Male	86(68.2)
Female	40(31.8)
T stage:	
T2	55(43.6)
T3	64(50.8)
T4	7(5.6)
N stage:	
N0	33(26.2)
N1	83(65.9)
N2	10(7.9)
Stage:	
I	9(7.1)
IIA	20(15.9)
IIB	3(2.3)
IIIA	44(34.9)
IIIB	46(36.5)
IIIC	3(2.3)
Smoker	50(39.7)
Non smoker	76(60.3)
Distance of tumor from anal verge(cm):	
<1	16(12.7)
1-3	28(22.2)
>3	82(65.1)

Table 2. Pathological characteristics

Pathological subtypes	No(%)
Signet ring cell	12(9.5)
Non signet ring cell types	114(90.5)
Grade	
WD	6(4.7)
MD	55(43.6)
PD	5(3.9)
Undefined	60(47.6)

Table 3. Response

Clinical response	No (%)
CR	20(15.8)
PR	62(49.2)
PD	9(7.1)
SD	35(27.8)
Pathologic response	No (%)
pCR	14(11.9)
pPR	48(41.0)
pSD+PD	55(47.1)

Table 4. Surgical procedures

Surgical procedures	No (%)
APR	50(39.6)
APR+ TME	3(2.3)
LAR	56(44.4)
LAR+TME	6(4.7)
ULAR + TME	1(0.8)
Total proctocolectomy	1(0.8)
Not fit for surgery	9(7.1)

Table 5. Toxicity

Toxicity	Grade 1 No(%)	Grade 2 No(%)	Grade 3No(%)	Grade 4 No(%)
Acute				
Diarrhea	65(51.6)	43(34.1)	14(11.1)	4(3.2)
Hematologic effects	77(61.1)	39(30.9)	7(5.6)	3(2.4)
Dermatologic effects	73(57.9)	39(30.9)	10(7.9)	4(3.2)
Late (grade 3 or 4)				
Gastrointestinal effects	-	-	15(11.9)	0(0)
Bladder problems	-	-	6(4.7)	4(3.1)

Clinical Response: After 4-8 weeks of completion of chemoradiation patients were assessed clinically and radiologically (CECT-chest, abdomen and pelvis) by a team of surgeons and radiation oncologists. Clinical complete response was seen in 20(15.8%) patients and clinical partial response was seen in 62(49.2%). (Table 3) However down staging was not possible in 35% patients and 9 patients were not taken up for surgery due to progressive disease. Among 126 patients, 63(50.0%) underwent LAR and 53(42.1%) underwent APR. Total proctocolectomy was done in one patient. (Table 4)

Post-op histopathological characteristics: Pathological complete response (pCR) was seen in 14(11%) patients and pathological partial response (pPR) was seen in 48(41%) patients. Median number of lymph node dissected was 3 and median number of lymph node positive was zero. 13 patients had positive resection limit and 3 out of those had circumfrential resection margin positive. (Table 3)

Toxicity: Most of the patients had grade 1 or 2 acute toxicities. Grade3/4 diarrhoea and haematological toxicity was seen in 18(14.3%) and 10(8.0%) patients respectively. Grade 3/4 dermatological effects were observed in 14(11.1%). Grade 3 late gastrointestinal effects including chronic diarrhea and small-bowel obstruction occurred in 15(11.9%) patients. Bladder problems occurred in 10(7.8%) patients. (Table 5)

Prognostic factors: Patients with Hb>12gm//dl and tumours more than 3 cm from anal verge showed better sphincter preservation (p=0.018, p=0.011 respectively). Though grade of the tumour did not have impact on sphincter preservation however survival was improved in low grade tumours. Type of histology, lymph node positivity, pre op CEA did not have any significant impact on outcome.

DISCUSSION

Considerable debate was going on throughout the last decade regarding optimal approach to adjuvant therapy in rectal cancer. Although both pre- and postoperative adjuvant therapy can be effective, there has been a significant recent trend toward greater use of neoadjuvant treatment. Tumor down staging, improved resectability, and potential for expanded sphincter preservation options in the distal rectum also encourage the use of a neoadjuvant approach in the management of this disease. Recent studies from Europe have demonstrated that appropriate neoadjuvant preoperative radiation results in improvement of both local control and survival, and these results have had a significant impact on the current management of this disease. (Kapiteijn *et al*., 2001; Frykholm *et al*., 1993) However Indian data is lacking and this has prompted us to conduct this retrospective analysis showing impact of neoadjuvant chemoradiation on local control, sphincter preservation and survival in ca rectum in our set up in a developing country. Our median follow up period was 16 months. The median age of presentation in this study was 48 years which was lesser than the median age reported in other studies in western literature. Onaitis *et al*. (2001) showed median age of 59 years in their study whereas in German Rectal cancer study (Sauer *et al*., 2004) it was further higher and was of 62 years. Male to female ratio was 2.15 in our study as compared to 1.95 and 2.40 in FFCD 9203 (Gerard *et al*., 2006) and German rectal cancer study respectively. Most of the patients presented with bleeding per rectum (94.4%) in our study. Most of the patients (50.8%) presented with T3 disease which was quite comparable with other studies (Sauer *et al*., 2004; Gerard *et al*., 2006; Gerard *et al*., 2012). Also most of the patients were node positive (N1or N2) similar to previous studies. Overall stage wise most of the patients in our study were stage III. Mean distance from anal verge was 4.2cm in our study. 65.1% of the patients had tumor distance >3cm from anal verge. Most of the patients had moderately differentiated adenocarcinoma (43.7%) in our study with 43.1% in FFCD 9203 and 51.2% in ACCORD 12 study (Gerard *et al*., 2006; Gerard *et al*., 2012). Total dose of 45Gy/25#/5weeks was delivered along with 5-FU 325mg/m^2 bolus along with Injection LV 30mg/m^2 concurrently on D1 of every week for 5 weeks similar to preoperative radiotherapy with 45Gy in 25 fractions during 5 weeks with concurrent chemotherapy with fluorouracil 350 mg/m2/d during 5 days, together with leucovorin, was administered during the first and fifth week in FFCD 9203 study. In German rectal cancer study, preoperative treatment consisted of 5040 cGy delivered in fractions of 180 cGy per day, five days per week, and fluorouracil, given in a 120-hour continuous intravenous infusion at a dose of 1000 mg per square meter per day during the first and fifth weeks of radiotherapy. Dose of 5-FU was kept slightly on lower side keeping in view of the overall poor general condition of our Indian population.

A number of randomized trials have evaluated the effectiveness of addition of chemotherapy to radiation administered either preoperatively following clinical evaluation and staging or post-operatively following pathological staging of pT3-4 and or N1-2 disease. Putative benefits of the addition of chemotherapy concurrent with pre or post-operative RT include local radiotherapy sensitization and eradication of micrometastasis. Pre-operative chemoradiation has the potential to increase rates of pathological complete response and sphincter preservation. In the index study pathological complete response (ypCR) was seen in 11.9% patients. Gerard *et al* and Sauer *et al* in their study showed ypCR rate of 12.1% and 8%in their preoperative chemoradiation arm respectively. Slightly higher ypCR rates were seen in ACCORD 12 study with rates of 19.6% and 13.9% in study arm and control arm respectively. Recent Cochrane review in stage 2 and 3 resectable disease found that addition of chemotherapy to preoperative radiation enhances pCR and improves local control but has no effect on disease free survival or overall survival. However our surgical resection was not satisfactory and median number of lymph node dissected was only three. Resection margin was positive in 11% of the cases and one-fourth of them showed positive circumfrential resection margin (CRM). FFCD 9203 study had around 7% positive CRM whereas ACCORD 12 study showed slightly higher rates (7-12%) of positive CRM. Downstaging in the index study was seen in 65% of the patients and 50% of the patients had their sphincter preserved which is quite comparable to FFCD 9203 study. Somewhat higher rates of sphichter preservation (67-71%) were seen in ACCORD 12

study but comparatively lower rates in German rectal cancer study. With respect to the type of chemotherapy administered concurrently with RT the equivalence of bolus 5-FU/LV and infusional 5-FU in concurrent chemoradiation is supported by the results of a phase 3 trial in which similar outcomes with respect to overall survival and relapse free survival were observed when an infusion of 5-FU or bolus 5-FU were administered concurrently with post-operative radiation. (Smalley *et al*., 2006) On the other results from earlier trial from the North Central Cancer Treatment group showed that post-operative administration of infusional 5-FU during pelvic irradiation was associated with longer overall survival. (O'Connell *et al.*, 1994) Recent studies have shown that capecitabine is equivalent to perioperative chemoradiation. In this index study we have used bolus 5-FU and LV which have shown reasonably good response when compared to western studies reported in literature. Though different trials have added oxaliplatin to the adjuvant therapy, however, addition of oxaliplatin to neoadjuvant chemoradiation is not recommended at this point of time and we have also followed the same principle. One of the reason for better tumor response and preservation of sphincter with pre-operative chemoradiation is irradiating tissue that is surgery naive and thus better oxygenated, may result in increased sensitivity to radiotherapy. This is also reflected in our study in indirect manner when it is found that patients with haemoglobin>12gm% showed superior local control and sphincter preservation as compared to those with haemoglobin<12gm%. Grade of the tumour also came out to be another prognostic factor in the index study. Though grade of the tumour did not have impact on sphincter preservation however survival was improved in low grade tumours. Tumours more than 3 cm from anal verge showed better sphincter preservation, however, distance from anal verge has not been mentioned as prognostic factor in any of the neoadjuvant chemoradiation trials reported in western literature. As the follow-up is short (median follow up period-10months) in our study there is nodata regarding important clinical end points, such as disease free survival, overall survival and late toxicity are available. Most of the patients had grade 1 or 2 acute toxicities. Grade3/4 diarrhoea and haematological toxicity was seen in 18(14.3%) and 10(8.0%) patients respectively in our study though slightly higher but comparable to 12% and 6% grade ¾ diarrhea and haematological toxicity respectively in German rectal cancer study. This slight difference might to be due to poor tolerability in our patients. FFCD 9203 study also had similar overall grade ¾ toxicity of 14.9%.

Conclusion

This study represents the largest Indian experience with standard neoadjuvant chemoradiation followed by surgery in rectal cancer. Down staging of tumor, improved local control and increased sphincter preservation was seen in our study. Pretreatment Hemoglobin status, distance from anal verge and grade of the tumour came out to be the important prognostic factors. This study is not without flaws because of its retrospective nature and short follow up period. More prospective trials are required in Indian setting to see the impact of neoadjuvant chemoradiation in patients with poor performance and tolerability.

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