Original Article

Factors influencing response to neoadjuvant chemoradiation and outcomes in rectal cancer patients: tertiary Indian cancer hospital experience

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Background: In the treatment of rectal cancers several randomized trials have demonstrated benefits of neoadjuvant chemoradiotherapy (NACRT) in downstaging as well as survival among these patients. We investigated the patient and tumor related variables dictating the outcomes in these patients.

Methods: Biopsy proven treatment naive 182 rectal cancer patients underwent NACRT from June 2006 to December 2010. The entire patients received long course conventionally fractionated external beam radiotherapy with concurrent oral Capecitabine. At 6 weeks from completion of NACRT clinico-radiological assessment was carried out for surgical feasibility. All patients were given postoperative adjuvant chemotherapy either single agent or multi drug regimen depending upon biopsy report.

Results: Among 182 patients, 131 (72%) underwent surgery and initial T stage and signet ring cell morphology were major determinant of operability. Among the 131 operated patients at median follow up of 36 months, 94 (72%) are alive and disease free. With a median follow up of 42 months the 5-year disease free survival (DFS) and overall survival (OS) was 60% and 77%. The majority of the failures were distal but with more advanced disease at presentation both local and distal failures were similar. While assessing survival by multivariate analysis patients having positive nodes post-surgery had a significantly poorer DFS (P=0.001), while signet ring cell morphology and pre-treatment carcino-embryonic antigen (CEA) levels strongly influenced OS (P=0.03).

Conclusions: The outcome of our patients were similar to World Literature and signet ring cell morphology, pre-treatment CEA level, and pathological nodal staging all were influential in determining survival. Besides this, the study also highlights the fact that tumours with signet ring cell morphology appearing in younger population with poor survival needs prospective evaluation for more intense CRT regimen and aggressive surgical resections.

Keywords: Signet ring carcinoma; neoadjuvant chemoradiotherapy (NACRT); carcino-embryonic antigen level (CEA level); operability

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Introduction

Colorectal cancer accounts for third most commonly diagnosed cancer in the world. In India, rectal cancer accounts for 6th most common digestive tract cancer as per cancer group projection from 2010 to 2020 (1).

Several randomized trials have demonstrated that neoadjuvant chemoradiotherapy (NACRT), as compared with postoperative CRT, downstaged tumours and improved local control, frequently permitting sphincter preservation in patients with low rectal tumours. Preoperative CRT was also associated with reduced toxicity (2-4). Though downstaging is achieved in majority of the tumours receiving long course NACRT the extent of downstaging and survival may vary from patient to patient. Many factors have been reported in literature that predicts response to (NACRT) of which advanced stage at presentation is the most important (5). Other factors such as mucinous and signet ring pathology also influence the outcomes and the data is scant. Therefore we studied the factors that can indicate the tumour response to preoperative CRT as well as the factors that influence disease free survival (DFS) and overall survival (OS) in our set of patients. In this study we present the results of a prospectively maintained data of rectal cancer patients who underwent NACRT and surgery at our centre.

Materials and methods

Patient selection

This study included 182 patients who underwent NACRT for biopsy proven rectal cancers at our institute between June 2006 and December 2010. The eligibility criteria included patient's age more than 18 years, Karnofsky Performance Status (KPS) >70, resectable or unresectable rectal cancer who underwent chemoradiation as pre-operative treatment with different intent along with oral concurrent chemotherapy. The patients with distant metastasis at presentation, or who underwent short course of radiotherapy and those who did not receive concurrent chemotherapy or received altered fractionated RT were excluded from the study.

For initial staging evaluation all the patients underwent contrast enhanced computed tomography (CECT) abdomen and pelvis and chest X-ray. Additional MRI pelvis was done only in six patients. Multiplanar reformats were used to report T staging and involvement of mesorectal fascia (MRF) which was reported in most of the cases. The tumors were labelled as T3 if there was perirectal fat stranding and T4 if there was definite invasion of the surrounding organ. A thorough clinical examination including a careful per-rectal examination both by an onco-surgeon as well as radiation oncologist was performed. Distance from anal margin was assessed by digital rectal examination in majority of the patients. In addition colonoscopic evaluation and biopsy, serum carcino-embryonic antigen (CEA) estimation was also done.

Treatment protocol

Radiotherapy was given to a dose of 45-50.4 Gy in conventional fractionation (180-200 cGy per fraction, one fraction per day and five fractions per week) with treatment ranging between 5-5.5 weeks. All the patients received oral capecitabine concurrently to a dose of 850 mg/m^2 in twice daily. Post chemoradiation at 6 weeks, patients were assessed by per-rectal examination and pelvic imaging and surgery was planned if deemed resectable. All the eligible patients underwent complete total mesorectal excision with either low anterior resection or abdominoperineal resection (APR) with permanent colostomy. The post-operative specimen was analysed in detail for tumour size, nodal stage, pathological response, margin status including circumferential resection margin, tumour regression grade (TRG) score using Mendard's scoring were assessed. Every attempt was made by the pathologist to retrieve maximum nodes possible. All patients were planned for adjuvant chemotherapy. If all the nodes were negative in the resected specimen they were planned for 6 cycles of adjuvant chemotherapy of capecitabine alone, and for node positive disease 6 cycles of CAPOX (capecitabine 1,000 mg/m^2 and injection oxaliplatin) was advised. Patient who had unresectable tumour post CRT were given further chemotherapy (preferably CAPOX) and were continued to assess for operability every 3 months or till disease progression and were taken up for surgery if deemed operable.

Follow up

All patients were reviewed weekly during CRT for treatment compliance, toxicities and need for symptomatic management. The toxicities were recorded as per common terminology criteria for adverse events (CTCAE) version 3 criteria. Weekly blood counts were done to monitor haematological parameters. Post-surgery the further follow up were scheduled 3 monthly for the first 2 years and

Table 1 Patient and disease characteristics on presentation (n=182)

Characteristics	N	%
Age		
Median (years)	42 [18-77]	
<40 years	78	43
≥40 years	104	57
Sex		
Male	127	70
Female	55	30
Distance from anal verge		
0-5 cm	139	76
>5-10 cm	39	22
≥10 cm	4	2
Luminal obstruction requiring pre radiotherapy colostomy	51	28
CEA		
<5 ng/mL	113	62
≥5 ng/mL	69	38
Histopathological type		
WD/MD adenocarcinoma	110	60
PD adenocarcinoma	24	13
Mucinous cell cancer	18	10
Signet cell cancer	30	17
T stage		
T2	3	2
T3	151	83
T4	28	15
N stage		
N0	19	10
N1	25	14
N2	138	76
CRM (CT scan imaging)		
CRM free	91	50
CRM involved	52	27
CRM threatened	20	11
Not reported	19	10

CEA, carcino-embryonic antigen; MD, moderately differentiated.

then 6 monthly for 5 years. Complete blood count liver function tests and renal function tests with CEA were done at each follow up. Colono videoscope examinations were performed at 1-year postoperatively and then once every 3 years. Recurrence was diagnosed pathologically by surgical resection, biopsy or cytology and/or radiological findings showing an increase in tumour size over time.

Statistical analysis

DFS was calculated from the date of registration to the date of disease recurrence and OS till the date of last follow up. DFS and OS were calculated using Kaplan-Meir actuarial method. The analysis used standard log rank test with an intention to treat basis. Univariate and multivariate analysis were performed to find out factors affecting both DFS and OS. The patients who underwent surgical resection after chemo-radiation the factors influencing DFS and OS in both univariate and multivariate analysis were observed. All the statistical analysis was performed using SPSS version 18.

Results

Total 182 patients underwent NACRT. The patient and disease pre-treatment characteristics are being summarized in *Table 1*. The median age was 42 years and there were more males than females (70% *vs.* 30%) and 38% of the patients had MRF threatened or involved at presentation.

Following the institutional protocol 178 patients completed NACRT, of these 131 (72%) of the patients underwent surgical resection. Twenty nine patients continued to have unresectable disease post chemo radiation were given palliative chemotherapy. Nine (5%) patients refused surgery due to fear of colostomy and 11 (6%) patients were found to have distant metastasis on imaging at 6 weeks so were given palliative chemotherapy. Two patients died of myocardial infarction post CRT. Capecitabine based adjuvant chemotherapy was received by 112 (85%) of the patients.

The major factors affecting tumour downsizing and subsequent R0 surgical resection were advanced T stage and signet ring cell pathology (*Table 2*).

Acute toxicity

During the chemo-radiation protocol most of the patients tolerated treatment well. The main acute side effects are being summarized in *Table 3*. The toxicity grading was done as per the CTCAE version 3. In gastrointestinal toxicity majority had grade 1 anorexia or diarrhoea. The skin toxicity was limited to perianal skin and groins. In haematological toxicity a large number had grade 1 anaemia which improved with regular haematinics.

Table 2 Factors affecting surgical resection (n=131)

Factors	N	Surgical resection (n)	%	P
Age				0.587
<40 years	74	55	74	
≥40 years	97	76	78	
CEA				0.701
<5 ng/mL	107	83	77	
≥5 ng/mL	64	48	75	
Histology				0.042
WD/MD adenocarcinoma	103	86	83	
PD adenocarcinoma	22	16	73	
Mucinous cell cancer	18	12	67	
Signet cell cancer	28	17	60	
T stage				0.03
T2	3	3		
T3	151	113		
T4	28	15		
N stage				0.613
N0	19	13	78	
N1	25	20	80	
N2	38	98	76	

CEA, carcino-embryonic antigen; MD, moderately differentiated.

Table 3 Acute toxicities of the treatment

Location	N (%)
Gastrointestinal	
Grade 0	50 (27.5)
Grade 1	107 (58.8)
Grade 2	23 (12.6)
Grade 3	8 (4.0)
Genitourinary	
Grade 0	138 (75.8)
Grade 1	39 (21.4)
Grade 2	4 (2.2)
Grade 3	1 (0.5)
Skin	
Grade 0	39 (21.4)
Grade 1	76 (41.8)
Grade 2	59 (32.4)
Grade 3	8 (4.4)
Hematological	
Grade 0	105 (57.7)
Grade 1	71 (39.0)
Grade 2	6 (3.3)
Grade 3	0

The surgical complications were few and mostly due to wound infection in 10 patients, anastomotic leak in 2 patients and urinary leak from perineal wound in 1 patient respectively. The wound healing rate was mostly within time and only 10 (17.2%) patients had delayed wound healing.

Survival

The median follow up for all the patients was 43 [4-88] and 47 [8-88] months for the patients who underwent resection. Two patients died of acute myocardial infarction post CRT. The analysis of tumour control and survival has been restricted to the 131 patients who underwent R0 or R1 resection. Of the 131 patients, 91 (72%) are alive and disease free. At 5 years the DFS and OS was 60% and 77% (*Figures 1*,*2*). For the patients who did not undergo surgery their median survival was 13 [3-78] months since the disease progressed locally and distally and most of them died by 2 years.

Factors affecting local and distant failures

Of the 131 operated patients 9 (7%) failed locally and 4 (3%) failed locally and distally, while the majority 26 (20%) failed distally. The majority of distant failures were in lung (30%), liver (23%) and paraaortic nodes (20%). The details of patterns of failure and the factors influencing is being represented in (*Table 4*). Of the 16 patients whose circumferential resection margin was positive, 10 (62%) failed. Four locally and 3 distant metastasis and 2 failed both local and distant.

Of the 28 (20.3%) patients achieving complete pathological (pCR) response, only 1 failed locally while 3 patients had distant metastasis.

Factors affecting DFS and OS

Using Kaplan-Meier actuarial method both univariate and multivariate analyses were performed in terms of DFS and

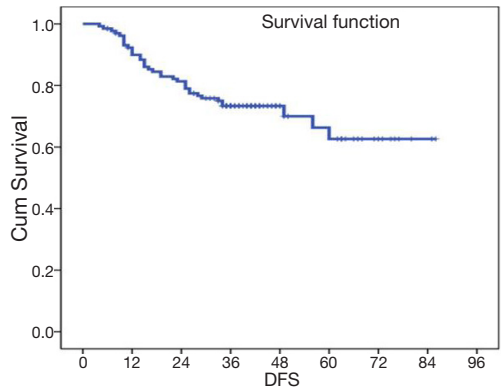

Figure 1 DFS for all patients. DFS, disease free survival.

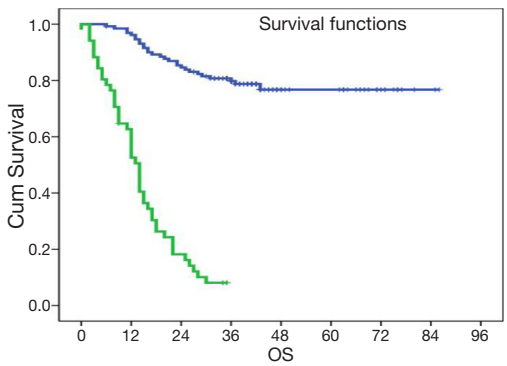

Figure 2 OS for operated *vs.* non operated patients. OS, overall survival.

OS (*Tables 4,5*).

In univariate analysis DFS was inferior in pre RT CEA levels of ≥5 ng/mL, signet ring cell pathology, R1 resection, and lack of tumour downstaging represented by pathological T & N stage and higher TRG scores. On multivariate analysis the factors independently affecting inferior DFS were only the pathological node positivity.

OS was inferior in patients with young age of patients, pre RT CEA levels of ≥5 ng/mL, higher pathological T, N stage and TRG scores. In multivariate analysis the factors independently affecting OS were only signet ring cell pathology and a trend towards worse survival for the patients presenting with pre RT CEA levels of ≥5 ng/mL.

Multivariate analysis for DFS and OS being represented in *Tables 5,6*.

Table 4 Pattern of failures in patients with surgical resection

Variables	N	Locoregional	Local + distant	Distant
CEA				
<5 ng/mL	83	8	2	10
≥5 ng/mL	48	1	2	14
Histology				
WD/MD adenocarcinoma	86	5	1	15
PD adenocarcinoma	16	0	0	4
Mucinous cell cancer	12	0	1	1
Signet cell cancer	17	4	2	4
ypT stage				
ypT0	31	0	1	3
ypT1	23	2	0	5
ypT2	32	0	0	5
ypT3	33	3	1	9
ypT4	12	4	2	2
ypN stage				
ypN0	80	2	2	7
ypN1	31	4	0	10
ypN2	20	3	2	7
PCR	28	0	1	3
TRG score				
1/5	28	0	1	2
2/5	28	2	0	5
3/5	31	0	0	7
4/5	22	4	0	5
5/5	16	3	2	2
CRM				
Negative	115	6	2	20
Positive	16	3	2	4

CEA, carcino-embryonic antigen; MD, moderately differentiated; TRG, tumour regression score.

Discussion

The response to NACRT can vary in locally advanced rectal cancers and thus affect survival. Therefore it is very important to predict these factors before starting NACRT so as to deliver the appropriate treatments. In the present study the factors predicting poor OS were locally advanced tumours with signet ring cell pathology and baseline high CEA levels.

The most common histopathological type of rectal cancer being adenocarcinoma and in accordance to world data our study also had 2/3rd patients with the same. Rectal

Table 5 Univariate analysis and multivariate analysis for factors affecting DFS

Variables (n=131)	N	5-yr DFS (%)	Univariate	Multivariate		
			P value	P value	Exp (B)	95% CI
Age group			0.004	0.137	1.767	0.835-3.743
≤40 years	55	61				
>40 years	76	82				
CEA range			0.04	0.15	2.274	0.970-5.331
<5	83	79				
≥5	48	62				
Histopathology			0.018			
WD/MD adenocarcinoma	86	69				
PD adenocarcinoma	16	72				
Mucinous cell cancer	12	83				
Signet cell cancer	17	41				
Non signet cell cancer	152	71	0.002	0.169	1.937	0.756-4.962
Signet cell cancer	30	41				
PCR	28	89	0.155			
other than pCR	103	69				
CRM			0.04	0.566	0.791	0.355-1.331
Negative	115	76				
Positive	16	35				
ypT stage			0.0001	0.780	0.927	0.546-1.575
ypT0	31	87				
ypT1	23	68				
ypT2	32	84				
ypT3	33	66				
ypT4	12	20				
ypN stage			0.001	0.005	1.733	1.080-2.781
ypN0	80	85				
ypN1	31	64				
ypN2	20	56				
TRG score			0.006	0.213	0.522	0.140-1.949
1/5	28	93				
2/5	28	78				
3/5	31	75				
4/5	22	62				
5/5	16	55				

DFS, disease free survival; CEA, carcino-embryonic antigen; MD, moderately differentiated.

cancers with signet ring cell morphology is reported as rare in most of the literature, the incidence ranging from 1-13% in most of the studies (6-8). In our study the signet ring cell carcinomas were seen in 17% patients and majority (19 patients) were in younger age group of <40 years. The three main concerns regarding signet ring cell carcinomas being younger age at presentation, locally advanced and unresectable to begin with and hence poor survival. Chang *et al.* in Stanford University studied these early onset sporadic rectal cancers and found that signet ring

Table 6 Univariate and multivariate analysis of factors affecting OS

Variables (n=131)	N	5-yr OS	Univariate	Multivariate		
			P value	P value	Exp (B)	95% CI
Fixity on DRE			0.01	0.16	1.972	0.865-4.496
Mobile	93	83				
Fixed	38	63				
Age group			0.015	0.304	1.558	0.669-3.633
≤40 years	55	67				
>40 years	76	87				
CEA range			0.05	0.045	2.599	1.097-6.610
<5	83	89				
≥5	48	70				
Histopathology			0.001			
WD/MD adenocarcinoma	86	82				
PD adenocarcinoma	16	72				
Mucinous cell cancer	12	83				
Signet cell cancer	17	41				
Non signet cell cancer	152	83	0.001	0.010	2.821	1.046-7.612
Signet cell cancer	30	37				
PCR	28	89	0.220			
Other than pCR	103	73				
CRM			0.247			
Negative	115	78				
Positive	16	67				
ypT stage			0.001	0.581	1.191	0.640-2.218
ypT0	31	90				
ypT1	23	80				
ypT2	32	84				
ypT3	33	77				
ypT4	12	18				
ypN stage			0.001	0.139	1.506	0.875-2.589
ypN0	80	89				
ypN1	31	65				
ypN2	20	43				
TRG score			0.03	0.828	1.060	0.625-1.799
1/5	28	93				
2/5	28	84				
3/5	31	80				
4/5	22	67				
5/5	16	50				

OS, overall survival; DRE, basis of clinical; CEA, carcino-embryonic antigen; MD, moderately differentiated; TRG, tumour regression score.

cell differentiation was the major factor leading to poor outcomes in these patients (8).

Patients having signet cell pathology only 17 (56%) underwent downstaging and subsequent surgical resection. Among the operated patients again 11 (65%) of them failed both locally and distally leading to a significantly poorer OS when compared to moderately differentiated (MD) adenocarcinoma. In multivariate analysis signet ring cell carcinoma stood out to be an independent poor prognostic factor for an inferior OS but not for DFS. This indicates that after recurrence the salvage therapy is more effective for prolonging survival in patients with non-signet ring cell tumours compared to the signet cell ones, therefore there is a need for more aggressive salvage strategies for signet ring cell cancers.

A report from National Cancer Database on 244,794 colorectal cases from America reported that signet ring cell histology was independently associated with higher risk of death (HR 1.42, 95% CI, 1.33-1.51) (9). The Korean National registry also reported their SEER database of signet ring cell carcinoma and found to have higher grade and worse DFS (10). In accordance to our series similar data were available regarding higher disease burden and primarily unresectable stage of rectal signet cell carcinoma (11). This was similar to a German series of 34 patients with 65% being primarily unresectable (12).

Another, rather contradictory study among Indian population stated signet ring cell carcinomas to be associated with better pCR rates and better survival (13). This prompts us to study prospectively with a larger population about actual behaviour of signet ring cell carcinomas and whether their histology per se or their late presentation is actually responsible for the worse outcome.

Several studies have proved the importance of serum CEA level as tumour marker for rectal cancers and its significant impact upon resectability, DFS and OS suggesting it could predict occult distant metastasis as well as predict CRT response and serves as an important marker in patient outcomes (14,15). It inhibits cell death by causing a loss of anchorage to the extracellular matrix. Tumour cells containing a high density of CEA are resistant to radiation (16). In the present study, pre-treatment CEA level of ≥5 ng/mL was associated with worse DFS and OS and was an independent factor predicting OS on multivariate analysis. Similarly in a study from Korea, the 5-year DFS rate was significantly higher in the CEA <5 ng/mL group than in the CEA ≥5 ng/mL group (73.2% *vs.* 60.9%, P=0.002) (17).

Pathological T and N stage are known to be important factors influencing DFS and OS (18). Pathological nodal staging was an independent prognostic marker in most of the studies analyzing the postoperative predictive factors for survival (4,19). In the present study patients with positive nodes in the pathological specimen had significantly higher rates of distant failures leading to poorer DFS which was also a significant factor in multivariate analysis.

Tumour regression is categorized on the basis of a semi quantitative assessment comparing the amount of viable tumour with the amount of fibrosis TRG and is a good indicator of tumour response (20). This was reflected in our patients where the lower TRG score was associated with better survival in the univariate analysis but was not a significant factor on the multivariate analysis.

Due to resource constraint most of the patients were staged on the basis of clinical (DRE) and CT scan imaging. Though preoperative staging with MRI is considered the standard of care there are studies in the literature which suggest that CECT can be used for initial staging in the resource constrained environment (21,22). Rectal cancer mostly present in younger age group in India, a factor which is neither hereditary nor diet related (1) (*Table 1*). In our study about 43% of the patients were below 40 years and the negative effect of age upon disease free and OS has recently been highlighted in few studies where the younger patients had statistically significant difference in survival and fared poorly (7,23). Similarly in our study patients with age less than 40 years had 5 years DFS and OS (61% and 68% *vs.* 68% and 88%) respectively and compared to the other group results were statistically significant (P=0.001 and 0.009). But in multivariate analysis this was not significant. This was in contrast to another study were advanced age was associated with worse OS (24).

Overall the survival outcomes of our patients are comparable with the data in the literature. Besides this the study highlights the fact that locally advanced tumors having CRM threatened margins with high CEA levels and signet ring cell morphology are independent good predictive markers for poorer survival pre NACTRT. Therefore more aggressive neoadjuvant treatment strategies both in terms of locoregional and systemic should be employed to treat these aggressive tumours.

Patients with positive nodes in the surgical specimens have a high chance of failures more so distally. Though most of the patients in this study received adjuvant chemotherapy still almost half of the node positive patients failed distally. Therefore pN stage serves as a good marker post neoadjuvant treatment, indicating a need for more

aggressive adjuvant chemotherapy regimens to tackle distant metastasis (25,26).

Conclusions

The outcome of our patients were similar to World Literature and signet ring cell morphology, initial stage, pre-treatment CEA level, and pathological nodal staging all were influential in determining survival. Besides this the study also highlights the fact that locally advanced tumours with signet cell histology are aggressive and fare poorly in terms of achieving R0 resection and poorer survival compared to the other histologies, therefore more intensive chemo radiation strategies like neoadjuvant chemotherapy followed by chemo radiation and aggressive surgical resections can be attempted. The possibility of radiotherapy dose escalation and addition of newer biological agents in conjunction would be the future direction.

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