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ORIGINAL RESEARCH

Prospective study of neoadjuvant chemoradiotherapy using intensity-modulated radiotherapy and 5 fluorouracil for locally advanced rectal cancer – toxicities and response assessment

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Aims and objectives: The past 2 decades witnessed the strengthening of evidence favoring the role of neoadjuvant chemoradiation (CHRT) in the treatment of locally advanced rectal cancer. The study aims to evaluate the response and acute toxicities to neoadjuvant CHRT using intensity-modulated radiotherapy (IMRT) in the treatment of rectal cancer. Predictive factors to achieve pathological complete response (pCR) were analyzed, as a secondary endpoint.

Materials and methods: All consecutive patients who underwent IMRT as part of neoadjuvant CHRT in the treatment of rectal cancer between August 2014 and December 2016 at a tertiary cancer care center were accrued for the study. The cohort underwent CHRT with IMRT technique at a dose of 50.4 Gy in 28 fractions concurrent with continuous infusion of 5 fluorouracil during the first and the last 4 days of CHRT. Surgery was performed 6 weeks later and the pathological response to CHRT was noted.

Results: Forty-three subjects were accrued for the study. Radiation dermatitis and diarrhea were the only observed grade ≥3 acute toxicities. Sphincter preservation rate (SPR) was 43.3%. pCR was observed in 32.6%. Univariate and multivariate logistic regression showed that carcinoembryonic antigen was the only independent predictive factor to achieve pCR.

Conclusion: IMRT as part of neoadjuvant CHRT in the treatment of locally advanced rectal cancer is well tolerated and gives comparable results with respect to earlier studies in terms of pathological response and SPR. Further randomized controlled studies are needed to firmly state that IMRT is superior to 3-dimensional conformal radiotherapy.

Keywords: IMRT, rectal cancer, chemoradiation, neoadjuvant, response

Introduction

The past decade has seen preoperative concurrent chemoradiation (CHRT) followed by surgery 6 weeks later as the dominating trend in the management of carcinoma of the rectum.[1] Despite the fact that there are benefits of preoperative radiotherapy, the toxicities associated with the conventional broad fields or improper radiation techniques at some places were of significant concern for the oncologists.[2]

The past 2 decades have also seen the emergence of intensity-modulated radiotherapy (IMRT) along with gradual replacement of conventional techniques. IMRT hails with advantages of lower doses delivered to the organs at risk (OARs)

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as it makes the dose cloud or isodose lines conform to the shape of the volume of interest. The reduced dose to OARs like small bowel and urinary bladder translates into decreased toxicities, both acute and late, as seen in studies involving pelvic malignancies such as cervical, endometrial, and prostate cancers.[3–5] However, this is derived largely from prospective and retrospective data rather than planned randomized studies comparing IMRT vs conventional techniques.

Materials and methods

After the ethical board approval (Institutional Review Board, Rajiv Gandhi Cancer Hospital and Research Centre, Delhi, India) of the prospective observational study, all patients undergoing CHRT for locally advanced rectal cancers were evaluated for response and toxicity profile. All consecutive patients attending the radiation department of a tertiary care cancer hospital opting for IMRT technique between August 2014 and December 2016 were accrued for this study. Written informed consent was obtained from all the patients who participated in this study. The cohort underwent whole abdomen MRI with contrast and serum carcinoembryonic antigen (CEA) levels prior to the treatment.

Patients were immobilized with the help of orfit-ray™ (Orfit Industries, Wijnegem, Belgium) thermoplastic cast and CT simulation was performed with SOMATOM sensation open™ (Global Siemens Healthcare, Erlanger, Germany) in supine position. Contrast-enhanced CT scans were performed with 3 mm slice thickness along with bladder protocol (the patient is asked to void and then drink 700 mL water and the scan is performed on having the sensation to pass urine). Contouring was done using Varian Eclipse™ Version 10 (Varian Medical Systems, Palo Alto, CA, USA) according to the Radiation Therapy Oncology Group (RTOG) guidelines.[6] Conventional fractionation IMRT was used (total dose of 50.4 Gy with daily fractions of 1.8 Gy, 5 days a week) along with concurrent chemotherapy with 5 fluorouracil (5FU) 1000 mg/m^2 in continuous infusion during the first and last 4 days of radiation. Patients were assessed weekly for acute toxicities such as skin reactions, vomiting, cystitis, diarrhea, and hematological toxicities. RTOG scoring scale was used to grade acute toxicities.[7]

At 6 weeks post-CHRT, contrast MRI-based response evaluation was done using RECIST 1.1 criteria.[8] Surgery – either low anterior resection (LAR) or abdominoperineal resection – was performed, and pathological response to neoadjuvant CHRT was graded according to the College of American Pathologist guidelines.[9] The primary endpoint was to evaluate down-staging and pathological response to CHRT. The secondary endpoint was to find out factors predictive for pathological complete response (pCR) to CHRT.

Statistical analysis

The descriptive statistics for quantitative variables are presented using mean (with SD), while categorical variables are presented in frequencies along with respective percentages. To compare categorical variables, Chi-square test or Fisher's exact test was used according to the nature of data. Univariate and multivariate logistic regression were used to identify the associated independent predictive factors to achieve pCR. A p-value <0.05 was considered statistically significant. All p-values reported are two-tailed. Statistical Package for the Social Sciences version 20.0 (IBM Corporation, Armonk, NY, USA) was used to carry out all statistical computations.

Results

Forty-three patients were treated with CHRT followed by surgery after 6 weeks. The pretreatment clinical characteristics have been tabulated in Table 1. The mean dose received by 95% of planning target volume was 50.17 ± 0.39 Gy. Mean volume of small bowel that received dose >45 Gy (SBV45 Gy) was 78.79 ± 48.38 cc, while mean volume of urinary bladder receiving >50 Gy was 24.73 ± 7.93%. Diarrhea and radiation dermatitis were the only observed grade ≥3 acute toxicities (Table 2). The relationship between diarrhea and SBV45 Gy has been depicted in Table 3. It was noted that

Table 1 Pretreatment clinical characteristics

Characteristics	
Age (mean ± SD, years)	45.28 ± 14.29
Sex, male:female	2.3:1
Tumor grade	
Well	23.3%
Moderately	67.4%
Poorly	9.3%
Comorbidities present	32.6%
Carcinoembryonic antigen (CEA) level (mean ± SD)	7.1 ± 6.1 ng/mL
Craniocaudal length of tumor in MRI (mean ± SD)	5.2 ± 1.9 cm
Full circumferential tumor involvement in MRI	55.8%
Mean length from anal verge to tumor in MRI (mean ± SD)	4.8 ± 2.2 cm
Tumor stage	
II	46.5%
III	53.5%
Hemoglobin level (mean ± SD)	11.65 ± 1.61 gm/dL
Interval to surgery	45 ± 3 days

acute diarrheal toxicity of grades ≥3 was experienced when the SBV45 Gy exceeded 120 cc.

All patients underwent concurrent chemotherapy with continuous 5FU infusion. Chemotherapy dose reduction was done in 11.6% of patients during the second cycle in view of toxicities. Radiological response assessment with MRI at 6 weeks showed complete response [CR] in only one patient. Of the 30 lower rectal tumors (<5 cm from anal verge), 13 patients underwent LAR, and hence, sphincter preservation rate (SPR) was 43.3%. Pathological response assessment showed complete pathological response in 32.60%, moderate response in 30.20%, minimal response in 23.3%, and poor response in 14%. The details of down-staging (both "T" and "N" stages) have been tabulated in Tables 4 and 5. Univariate and multivariate logistic regression showed that pretreatment CEA level was the only independent predictive factor of pCR (Table 6). Additionally, a cutoff value of pretreatment CEA of ≤4.80 ng/mL (sensitivity – 71.4%; specificity – 75.9%) was derived using receiver operating characteristic (ROC) curve to predict pCR (Figure 1). Moreover, it was observed that the pretreatment CEA level was significantly associated with the length of the disease and overall clinical stage (Table 7). The outcomes of different CHRT studies using IMRT are summarized in Table 8.

Discussion

Clinical results of IMRT for rectal cancer as a part of CHRT have not been adequately documented worldwide. The studies mentioned in the literature are difficult to compare, as the protocols of both radiotherapy (total dose, boost technique, and dose per fraction) and chemotherapy vary between studies. The results of various studies using IMRT as part of CHRT are summarized in Table 8.

Grade ≥3 skin toxicities varied from 0.03% to 21% among different IMRT studies, compared to 12% in the present study (Table 8). Dermatitis was observed predominantly over the medial thigh and perineum. This occurred more in lesions of the lower rectum where doses were delivered up to or beyond the anal verge.

One of the advantages of IMRT over 3-dimensional conformal radiotherapy (3DCRT) lies in its ability to spare the small bowel. In a study conducted by Yang et al, the cases with grade ≥2 diarrhea were higher in rectal cancer patients who were treated with 3DCRT as part of CHRT in contrast to IMRT (32% vs 11%).[27] Concurrently, RTOG 0822 (which was a Phase II trial using IMRT) did not result in significant difference in gastrointestinal toxicities.[10] Nevertheless, this was a single-arm study, with IMRT as part of CHRT and the outcomes were compared with the results of RTOG 0247.[30]

Table 2 Acute toxicities

	Grade 0 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Skin reactions	0 (0)	14 (32.6)	24 (55.8)	5 (11.6)	0 (0)
Vomiting	31 (72)	10 (23.3)	2 (4.7)	0 (0)	0 (0)
Cystitis	0 (0)	43 (100)	0 (0)	0 (0)	0 (0)
Neutropenia	28 (65.1)	13 (30.2)	2 (4.7)	0 (0)	0 (0)
Anemia	41 (95.3)	2 (4.7)	0 (0)	0 (0)	0 (0)
Thrombocytopenia	43 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	0 (0)	20 (46.5)	19 (44.2)	3 (7)	1 (2.3)

Table 3 The relationship between grades of diarrhea and SBV45 Gy

	Grade 1	Grade 2	Grade 3	Grade 4
SBV45 Gy (mean ± SD)	43.36 ± 18.52 cc	83.16 ± 24.77 cc	139.66 ± 16.84 cc	191.52 ± 1.74 cc

Abbreviation: SBV45, mean volume of small bowel that received dose >45 Gy.

Table 4 Pathological down-staging – T stage

		ypT stage				Total
		ypT0	ypT1	ypT2	ypT3	
cT stage	cT2	4	0	0	1	5
	cT3	9	0	10	14	33
	cT4	1	1	1	2	5
Total		14	1	11	17	43

Table 5 Pathological down-staging – N stage

		ypNstage			Total
		ypN0	ypN1	ypN2	
cN stage	cN0	20	0	0	20
	cN1	11	5	0	16
	cN2	0	2	5	7
Total		31	7	5	43

Table 6 Univariate and multivariate analyses with pCR as a dependent variable

Variables	Groups	Univariate analysis		Multivariate analysis	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	Continuous	0.96 (0.92–1.01)	0.137	1.02 (0.96–1.09)	0.552
Sex	Male	1.99 (0.44–8.6)	0.387	1.37 (0.13–14.73)	0.793
	Female	1		–	–
Comorbidities	Yes	0.45 (0.10–1.96)	0.286	1.62 (0.21–12.40)	0.644
	No			–	–
Tumor grade	I	2.67 (0.62–11.45)	0.187	–	–
	II and III	1		–	–
T stage	T2	1		–	–
	T3	0.09 (0.01–1.09)	0.051	–	–
	T4	0.06 (0.003–1.39)	0.080	–	–
N stage	Negative	0.21 (0.05–0.85)	0.028	3.35 (0.65–17.42)	0.150
	Positive	1		–	–
Length of the disease	Continuous	1.30 (0.87–1.96)	0.200	1.06 (0.67–1.67)	0.806
Distance from the anal verge	Continuous	0.93 (0.69–1.25)	0.617	1.16 (0.78–1.72)	0.473
CRM	Yes	0.46 (0.13–1.68)	0.239	1.58 (0.31–8.12)	0.582
	No	1		–	–
CEA	Continuous	0.70 (0.53–0.93)	0.015	1.38 (1.04–1.90)	0.044

Abbreviations: pCR, pathological complete response; CRM, circumferential resection margin; CEA, carcinoembryonic antigen.

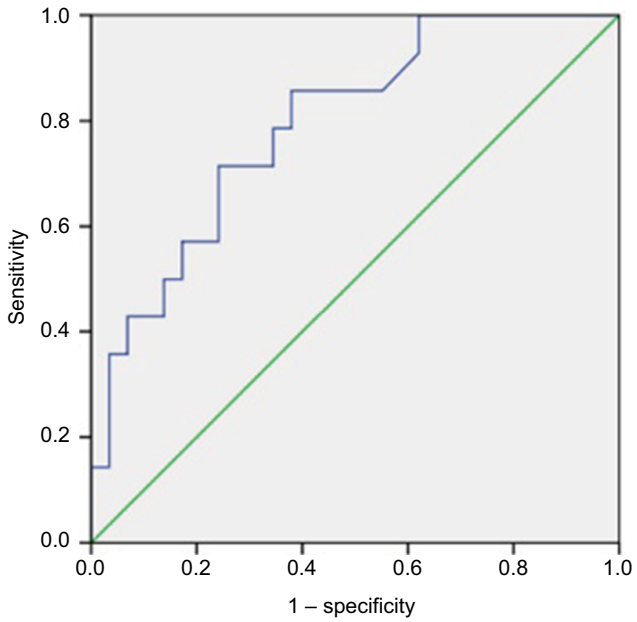


Figure 1 Receiver operating characteristic curve showing the sensitivity and specificity of pretreatment carcinoembryonic antigen levels to achieve pathological complete response.

Grade ≥3 diarrhea was experienced by 9.3% of the patients (4/43) in the present study, while the same has been reported between 1% and 18% among other IMRT studies (Table 8). It was noted that acute diarrheal toxicity grade ≥3 was experienced when the SBV45 Gy exceeded 120 cc. This is lower if compared to the QUANTEC guidelines, suggesting SBV45 Gy as 195 cc. This difference in the values could be a result of the variations in the ethnicity, contouring, planning, beam angles, and diets.

Compared to small bowel, urinary bladder has more tolerance toward radiation. Even though IMRT has more dosimetric avoidance of urinary bladder than 3DCRT, it is unlikely to reflect clinically. All patients in our study had only grade 1 cystitis. Except for one study conducted by Hernando-Requejo et al, showing grade ≥3 genitourinary (GU) toxicities of up to 5%, the remaining IMRT series failed to identify any grade ≥3 GU toxicities.[12,16,18,25,26] Similarly, grade ≥3 hematological toxicities are less in almost all the IMRT studies, ranging between 0%–6%.[14–17,22,24,26,28] Nonetheless, another study which is a Phase I trial using hypofractionated IMRT in rectal cancer showed 13% grade ≥3 anemia. This study was discontinued due to toxicities. Apart from two cases (4.7%) of neutropenia, no other grade ≥2 hematological toxicities were observed in the present study.

Despite toxicity reduction, sphincter preservation is another advantage of CHRT which converts abdominoperineal resection candidates to LAR ones. The German rectal cancer study demonstrated SPR of 39% in those who underwent preoperative CHRT by the conventional technique, while the present study showed 43.3%.[1] Yet another study using IMRT by helical tomotherapy achieved an SPR of 85.2%.[16]

pCR rates range from 0%–50% among various IMRT studies.[12,22,24,25,28] This wide range might be due to varying radiation doses, dose per fraction, chemotherapy regimen

Table 7 Relationship of preoperative CEA level with patient and disease-related characteristics

Characteristic	Category	Preoperative CEA level		*p*-value
		≤5 ng/mL (n = 17)	≥5 ng/mL (n = 26)	
Age	≤50 years	12	16	0.543
	>50 years	5	10	
Sex	Male	12	18	0.925
	Female	5	8	
Tumor grade	WD	5	5	0.656
	MD	11	18	
	PD	1	3	
Comorbidities	Absent	12	17	0.722
	Present	5	9	
Length of the disease	<5 cm	10	6	0.018
	≥5 cm	7	20	
Distance from the anal verge	≤5 cm	10	20	0.206
	>5 cm	7	6	
CRM	No	10	9	0.118
	Yes	7	17	
T stage	T2	2	2	0.763
	T3	14	21	
	T4	1	3	
N stage	Node negative	11	9	0.053
	Node positive	6	17	
Clinical Stage	Stage II	12	8	0.014
	Stage III	5	18	

Abbreviations: CEA, carcinoembryonic antigen; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; CRM, circumferential resection margin.

used, and certain factors of tumor biology are still unexplored and under research. Among these, Cubillo et al, who delivered equivalent 2 Gy per fraction (EQD2) of 60.4 Gy using the simultaneous integrated boost technique along with bevacizumab or cetuximab, achieved a pCR rate of 50%.[13] As depicted in Table 8, only three studies have delivered EQD2 dose of 49.4 Gy (1.8 Gy per fraction to the tumor) without any boost.[21,26,30] Of these, only one study has used 5FU or capecitabine and reported a pCR rate of 19.4%, compared to 32.6% in the present study.[30]

Predictors to achieve pCR have been extensively studied. A meta-analysis demonstrated interval to surgery as the independent variable to achieve the same.[31] Another meta-analysis evaluated the role of pretreatment CEA level and concluded that a normal level of CEA predicted more pCR.[32] The present study nevertheless kept one variable as a constant, as the interval to surgery was at a mean of 45 days with an SD of 3 days. The current study suggests that the independent predictive factor to achieve pCR is the pretreatment CEA level when surgery is performed at a mean interval of 45 days. Further, an ROC curve showed pretreatment CEA of ≤4.80 ng/mL (sensitivity – 71.4%; specificity – 75.9%) as a cutoff value to predict pCR (Figure 1). It was also noted that the rectal cancer patients with high pretreatment CEA levels (>5 ng/mL) demonstrated a significant association with increasing length of the disease and overall clinical stage (Table 7). Similarly, Filiz et al demonstrated a statistically significant correlation between preoperative serum CEA levels and overall clinical stage.[33] However, the authors did not find any relationship with the length of the disease. The data from this study should be interpreted with caution as the number of patients was small.

Conclusion

IMRT as part of neoadjuvant CHRT in the treatment of locally advanced rectal cancer is well tolerated and gives comparable results with earlier studies in terms of pathological response, acute toxicities, and SPR. Pretreatment CEA turned out to be the independent predictor to achieve pCR when surgery was performed at a mean interval of 45 days. Further randomized controlled studies are needed to categorically state that IMRT is superior to 3DCRT.

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Disclosure

The authors report no conflicts of interest in this work.

Table 8 Summary of studies which used IMRT for the treatment of rectal cancer

Reference; year	N	Boost type	Total dose EQD2 (Gy)		Chemotherapy regimen	Grade 3/4 acute toxicities (%)				pCR (%)
			Early	Late		Diarrhea	Skin	Hematological	GU	
Hong et al; 2015[10]	79	Seq			Capox	18	–	–	–	
Engels et al; 2013[11]	108	SIB	57.4	59.6	Nil	1	–	–	–	–
Hernando–Requejo et al; 2014[12]	74	SIB	60.4	63.3	Cap	10	–	–	5	30.6
Cubillo et al; 2012[13]	16	SIB	60.4	63.3	Capox/capiri + bevacizumab/cetuximab	6	–	–	–	50
Zhu et al; 2014[14]	78	SIB	56.1	57.2	Capox	10	18	4	–	23.7
Zhu et al; 2013[15]	32	SIB	56.1	57.2	Capox	16	–	6	–	35.7
Huang et al; 2014[16,a]	36	SIB	50.5	50.6	Cap	11	–	0	0	14.3
Arbea et al; 2011[17]	100	NB	49.3–49.9[b]	51.1–52.3[b]	Capox	9	–	2	–	13
Aristu et al; 2008[18]	20	NB	49.9	52.3	Capox	10	–	–	0	20
Ballonoff et al; 2008[19]	10	SIB	56.1	57.2	Cap	13	–	–	–	38
Freedman et al; 2007[20]	8	SIB	56.1	57.2	Cap	13	–	Anemia 13	–	0
Gasent Blesa et al; 2012[21]	27	Seq	49.4	48.4	Capox	15	–	–	–	26
Li et al; 2011[22]	63	SIB	52.1	53.6	Cap	10	3	Neutropenia 2	–	31
Richetti et al; 2010[23,c]	25	NR	49.4–52.9[d,e]	48.4–51.9[d,e]	Cap	8	–	–	–	
Zhu et al; 2013[24]	42	NB	44.9	45.8	Capox	12	21	2	–	15.7
Parekh et al; 2013[25]	20	SIB	50	50	5FU/Cap	40[f]	35[f]	10[f]	0[f]	21.4
Jabbour et al; 2012[26]	30	Seq	49.4	48.4	5FU/Cap or Capox/capiri or FOLFOX	3	–	Anemia 0 WBC 0	0	
Yang et al; 2013[27]	98	SIB	50[d]	50[d]	5FU/Cap	11[f]	–	–	–	
Samuelian et al; 2011[28]	31	SIB	50	50	5FU/Cap	3	0.03	0.03	–	19
Ng et al; 2016[29]	203	Seq	49.4	48.4	5FU/Cap	1	–	–	0	19.4
Simson et al; current study 2016	43	NB	49.4	48.4	5FU	9	12	0	0	32.6

Notes: [a]Technique used in this study was helical tomotherapy. [b]The study initially utilized 2.5 Gy per fraction and later reduced to 2.37 Gy in view of toxicities. [c]Technique used in this study was volumetric modulated arc therapy. [d]Median dose. [e]Dose and dose per fraction of boost not reported. [f]Reported as grade 2 or higher. The "–" symbols indicate not reported.

Abbreviations: IMRT, intensity-modulated radiotherapy; N, patient number; EQD2, equivalent 2 Gy per fraction; pCR, pathological complete response; GU, genitourinary; Seq, sequential; SIB, simultaneous integrated boost; NB, no boost; NR, not reported; Cap, capecitabine; Capox, capecitabine and oxaliplatin; Capiri, capecitabine and irinotecan; 5FU, 5 fluorouracil; FOLFOX, 5 fluorouracil, leucovorin and oxaliplatin; WBC, white blood count.

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