A Phase II Study of Radiation Dose Escalation using Simultaneous Integrated Boost Technique during Neoadjuvant Radiation Therapy for Locally Advanced Rectal Cancer

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ABSTRACT

Introduction: Patients who achieve pCR after neoadjuvant radiochemotherapy in locally advanced rectal cancer are known to have improved survival. Radiation dose escalation has been associated with improved pathological response. We have explored the potential of radiation dose escalation in neoadjuvant treatment of locally advanced rectal cancer patients. The impact of dose escalation on surgical complication rates as well as acute toxicity was also studied.

Material and methods: 22 prospectively enrolled eligible LARC patients received dose escalation (total dose to GTV 5880 cGy in 28 fractions). Four were excluded from analysis. 17 underwent surgery and were eligible for primary end point analysis of pathological response assessment while 1 was deemed inoperable. This prospective cohort was compared with 30 patients of LARC who had received a dose of 5040 cGy in 28 fractions at our institute. Independent student t test was used for testing of mean difference between two groups whereas paired t – test was used for paired observation. P-value < 0.05 is considered statistically significant.

Results: 24% patients achieved pCR in dose escalation arm. In control arm, 19% patients achieved pCR(p =0.532). 59% patients achieved a major response in dose escalation arm compared to 56% in control arm. This difference was not statistically significant. Grade 3 Skin toxicity was significantly increased in dose escalation arm (11% vs 0%; p= 0.025). Grade 3 or higher GI and GU toxicities were not increased. There was no significant difference in surgical complication rates in two arms.

Conclusion: In this single institution phase II study, escalation of radiation dose with a boost to GTV to 5880 cGy led to improvement in pathological response, although statistical significance could not be reached. Long term follow-up is needed to document chronic radiation related toxicity and impact on survival in this cohort.

Keywords: Radiation Dose Escalation, Simultaneous Integrated Boost Technique, Neoadjuvant Radiation Therapy, Locally Advanced Rectal Cancer

INTRODUCTION

Neoadjuvant radiotherapy with concurrent chemotherapy is an essential component in treatment of locally advanced rectal cancer.[1] The advantages of NARTCT are improved local control, decreased long term toxicity, better patient compliance, probability of sphincter sparing surgery and consequent better quality of life.[2,3] But perhaps the most promising advantage of NARTCT is its potential to fully eradicate the gross disease or achievement of pCR- defined as no residual cancer on histological examination of the surgical specimen. Various studies have reported that after NARTCT complete pathological response (pCR) - is between 15% to 27%.[4] Patients who achieve pCR after NARTCT have better long-term outcomes including local recurrence, overall and disease-free survival.[4-7]

Because pCR has been established as a surrogate for improved survival outcomes, researchers have explored the various ways in which treatment response can be improved. There are many potential ways in which pathological response rates can be improved. Broadly these approaches can be divided in two categories. (i) intensification of neoadjuvant treatment and (ii) increasing the interval between NARTCT and surgery to allow more time for radiation to act. Using induction chemotherapy before neoadjuvant radiochemotherapy, giving 1 or 2 cycles of chemotherapy in the waiting period between NARTCT and surgery, escalation of radiation dose and using multiple chemotherapy agents are some of the ways of treatment intensification.

Multiple studies have explored the role of higher than conventional RT dose in achieving better pathological response. RTOG conducted a randomised phase II study of 106 LARC patients in which treatment intensification using radiation or chemotherapy was tested. In radiation dose intensification arm, patients received pelvic hyper fractionated radiation 55.2 to 60 Gy at 1.2 Gy bid with concurrent Fluorouracil while in another arm, chemotherapy intensification was done using concurrent Fluorouracil plus irinotecan with pelvic radiation therapy 50.4 to 54 Gy at 1.8 Gy per day. The pCR rate was same (28%) in both arms. Although there was no difference in pCR rate in two arms, radiation dose escalation did achieve a higher than conventional pCR rate in this study.[8] In a randomized phase III trial by Jakobsen et al, 248 patients were randomized to

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receive 50.4 Gy in 28 fractions to the tumor and pelvic lymph nodes or the same treatment supplemented with an endorectal boost given as high-dose-rate brachytherapy (10 Gy in 2 fractions). Major response rate was improved significantly for T3 tumors (tumor regression grade, 1+2), 29% for standard arm and 44% for dose escalation arm, respectively (p = .04). Similar to the study by Gunther et al, dose escalation did not increase toxicity or surgical complication rates.[9] The association of radiation dose escalation with improved pathological response has also been demonstrated in meta- analysis. Burbach et al. confirmed that high doses of radiation are associated with a high pCR rate (pooled rate: 20.4– 95% CI 16.8–24.5%) in a meta-analysis on 18 trials of preoperative RT delivery doses more than or equal to 60 Gy for locally advanced rectal cancers.[10] The advent of highly conformal radiation techniques has made it possible to increase radiation dose without compromising on organ sparing. This study aims to utilise these techniques for dose escalation and exploring its relationship with pathological response rates.

MATERIAL AND METHODS

Study Design: It was a two-arm, non-randomized study conducted between April 2019 to August 2020 at a teaching hospital in North India. The study was approved by Institutional Ethical Committee and written informed consent was taken from all the patients.

Inclusion and exclusion criteria

Patients aged 18 years or more with histopathologically proven adenocarcinoma rectum stage T3-4N0M0 or any T with N1-2M0 (AJCC 8th stage group II and III) who were referred to division of radiation oncology for neoadjuvant radiation therapy were included. Patients with recurrent tumor, with a history of bowel surgery , radiation therapy or chemotherapy prior to current diagnosis or with inflammatory bowel disease were excluded. Other exclusion criteria were long segment disease (>10 cm), any condition in which chemotherapy is contraindicated, histology other than adenocarcinoma, or evidence of distant metastases on presentation.

Procedures: All eligible candidates were staged according to American Joint Committee on Cancer's staging of carcinoma rectum (AJCC 8th edition). On first visit, detailed history was documented and complete physical examination was done. Baseline blood counts, metabolic profile, viral markers and serum CEA levels were done. GI surgery review was done for future resection planning. Medical oncology review was done for planning of concurrent chemotherapy. Afterwards, patients were subjected to a standardised mould room procedure. Supine position with arms over head was used. Strict bladder protocol was followed for all patients. Patients were asked to pass urine and then drink 2 glasses (200 ml) of water. Planning CT scan was done after 30 minutes of drinking water. Same protocol was followed on each day before treatment. Radio-opaque marker was used to identify the anal verge. For planning CT, 3mm slices were taken from inferior edge of the L2 through mid-thigh. CT data sets of the patients was transferred to the contouring workstation (Monaco Focal sim Version -5.11.02). Whenever available, baseline CT/MR was fused with planning CT scan. Contouring was done on MONACO treatment planning system version 5.11.02 (Monte Carlo based) or TOMO treatment planning system (TOMO-H version 2.1.2). Briefly, contouring protocol was as follows:

GTV PRIMARY was contoured as the visible disease on planning CT scan, with inputs from MRI, PET scan and endoscopy finding.

All visible gross nodes were included in GTV NODE.

CTV-P was contoured including the GTV, internal iliac, presacral, pararectal and external iliac nodes in all cases. These were included on expanding the GTV by 3 cm to generate CTV. Bone was edited out of CTV.

CTV NODE: Vessels were marked starting from level of bifurcation of common iliac vessels. Elective nodal volume was constructed by taking a margin of 7 mm along the common iliac, internal iliac, presacral and obturator vessels for corresponding nodal regions, and 10 mm margin anterolaterally along external iliac vessels. External iliac vessels were marked up to the appearance of femoral head.

PTV 45 was a 5 mm expansion on CTV PRIMARY and CTV NODE while PTV 50.4 was a 5 mm expansion on CTV PRIMARY + 10 mm expansion on GTV NODE.

PTV_{boost} was contoured as GTV PRIMARY + 3 mm isotropic margin.

Urinary bladder- PTV, bowel, femoral heads, pelvic bones and genitalia were contoured as OARs.

Dose Prescription: 45 Gy in 25 fractions was prescribed to PTV 45, which was followed by a boost of 5.4 Gy in 3 fractions to PTV 50.4. PTV_{boost} volume (GTV PRIMARY with a 3 mm margin) was treated with 210 cGy per fraction for 28 fractions to a total dose of 5880 cGy using a simultaneous integrated boost technique. 195 cc and 5 cc of bowel was kept below 30 Gy and 45 Gy respectively. Maximum dose to bladder was constrained to less than 50.4 Gy. 98 % of the PTV was prescribed to receive at least 95 % of the prescribed dose. Accepted dose variation within the PTV was between 95% and 107% of the prescribed dose.

Radiation treatment delivery and monitoring of acute toxicity: RT was delivered 5 days a week using 6 MV photons by VMAT/IGRT technique on INFINITY or SYNERGY S linear accelerators (Elekta inc) or TOMOTHERAPY H (ACCURAY). All patients received concurrent chemotherapy. The two chemotherapy regimen used were Oral Capecitabine 825 mg/m^2 twice daily only on the days of radiation or 5-FU 400 mg/m^2 intravenous bolus injection with Injection Leucovorin 20 mg/m^2 intravenous bolus for 4 days during week 1 and 5 of radiation. Skin and Bowel/Bladder Toxicity was monitored and graded according to common toxicity criteria for adverse events (CTCAE) version 5.0. at the end of week 2, week 4, week 6 and week 8 of commencement of radiation treatment. After completion of treatment the patients were followed

up after 6 to 8 weeks. Patients were referred to GI Surgeon after 6-8 weeks of radiation therapy completion. Following parameters were noted for assessment of perioperative complications: Duration of surgery, length of hospital stay and after how many days nasogastric tube and urinary catheter was removed.

Post-Surgery (histopathological examination) Documentation of histopathological examination of excised specimen including gross tumor size, number of nodes resected and involved, presence of lympho vascular invasion, perineural invasion or extra nodal extension Pathological T and N stage and Tumor Regression Grade as per modified Ryan scheme (FIGURE A). Modified Ryan scheme was chosen as regression grading system as it is preferred by AJCC as well as College of American pathologists (CAP).[11,12]

STATISTICAL ANALYSIS

A detailed analysis was undertaken on response to treatment. Independent student t test was used for testing of mean difference between two groups whereas paired t – test was used for paired observation. Odds ratio calculation was used to predict the probability of an unfavourable pathologic outcome. Cross tables were generated and Pearson's chi square test was used for testing of associations. P-value < 0.05 was considered statistically significant. All analysis was done using Statistical Package for Social Sciences program software, version 24.0 (SPSS, Chicago, IL). The demographic, tumor related, imaging, dosimetric, surgical and pathological data thus collected was compared with retrospective data of patients of locally advanced rectal cancer who were treated in our institution from 1st march 2015 to 28th February 2019.

RESULTS

Between April 2019 and August 2020, 28 patients were prospectively enrolled in dose escalation arm (arm A), which was compared with retrospective cohort of 35 patients who received standard radiation dose (arm B). Figure E depicts patient enrolment for both arms. The sample size of 31 patients for prospective dose escalation arm could not be met due to decreased footfall of patients in ongoing COVID pandemic. In arm A, 17 patients were eligible for pathological response assessment. For secondary end point analysis of toxicity and intraoperative complications ,18 and 17 patients were respectively eligible. In arm B, 27 patients underwent surgery and were eligible for primary end point analysis. For secondary end point analysis of acute toxicity assessment, 30 patients were eligible and for analysis of intraoperative complications 27 patients were eligible. (FIGURE B)

Patient, tumor and treatment characteristics (Table 1)
Median age of patients in arm A was 53.5 years and in arm B, it was 52 years. Majority of patients were males (83% in arm A and 73 % in arm B). In both the arms, patients presented most commonly with T3 tumors (94% in arm A versus 86% in arm B). T4 disease was present equally (6% in arm A vs 7% in arm B). Percentage wise incidence of low rectal tumors (defined as tumors having caudal edge within 4 cm from anal verge) in arms A and B were 44% and 53 % respectively. In arm A, the mean dose received by *PTV50.4* was 5424 cGy and 98% of volume of *PTV50.4* received 5045 cGy, both of which were comparable to respective doses received by patients in arm B (D98 = 4976 cGy and Dmean = 5141 cGy). All patients in arm A received a simultaneous boost dose of 840 cGy to GTV (labelled as PTV_{boost}). The mean dose received by PTV_{boost} was 6026.33 cGy and dose received by 98% of PTV_{boost} was 5884 cGy. All patients received oral Capecitabine as concurrent chemotherapy in arm A. In arm B, 27% patients received intravenous chemotherapy (iv 5 FU/leucovorin) and 73% patients received oral capecitabine. In arm A patients completed their scheduled radiation in mean duration of 39 days while in arm B the duration was 40 days. LAR was performed in 53% patients in arm A and 41 % in arm B. APR was performed in 47% patients in arm A and 59 % patients in arm B.

Pathological response assessment (Table 2)
Overall, there was no statistically significant difference in pathological response in the two arms. Dose escalation led to more proportion of patients achieving complete pathological response pCR (TRG 0) (24% in arm A vs 19% in arm B) although this difference did not achieve statistical significance (p value= 0.532). The percentage of patients who achieved near complete response (TRG grade 1) was comparable in two arms (35% in arm A and 37% in arm B) . In terms of tumor regression grade, there was no poor responder (TRG 3) in arm A, while in arm B 3 patients (11%) patients showed poor response. 59% of patients had a favourable response (TRG 0 and 1) in arm A, compared to 56% in arm B although this difference was not statistically significant (p value= 0.831).

Toxicity analysis (Table 3)
Overall, skin toxicity was mild. There was a statistically significant increase in skin toxicity in arm A compared to arm B at the end of eighth week with 33% patients in arm A reporting grade 2 skin toxicity compared to 10% in arm B and 11% patients reporting grade 3 skin toxicity compared to none in arm B (p value = 0.025). This did not interrupt the treatment as grade 3 toxicity peaked after completion of whole course of radiotherapy. Diarrhea, proctitis and pain during defaecation were the common gastro intestinal toxicities. Diarrhea was the dominant gastrointestinal side effect, appearing in more than one-half of the patients in both arms. Majority of patients in both arms had grade 1 diarrhoea. On first follow up, significantly greater number of patients had grade 1 diarrhea in arm B (28% in arm A vs 57% in arm B; p value= 0.052). No patient experienced grade 3 gastrointestinal toxicity. Patients experienced less Genito-urinary toxicity compared to skin and gastrointestinal toxicity. Most common GU toxicities were dysuria, increase in urinary frequency and urgency. No patient experienced grade 3 or higher genitourinary toxicity. At the end of sixth week, significantly greater number of patients in arm A had grade 1 or 2 GU toxicity (73% in arm A versus 30 % in arm B; p value = 0.017).

Surgical complications (Table 4)

There was no statistically significant difference in intraoperative and immediate post-operative complications in the two arms. The mean duration of surgery in arm A was 182 minutes while in arm B it was 177 minutes. The difference was not, however, statistically significant. (p value = 0.703). Patients in both arms had a mean stay in hospital of 9 days. Nasogastric tube was removed and oral feeding started after 2 days of surgery in both the arms. Urinary catheter was removed after a mean of 2.29 days after surgery

Description	Tumor regression grade
No viable cancer cells (complete response)	0
Single cells or rare small group of cancer cells (near complete response)	1
Residual cancer with evident tumor regression, but more than single cells or rare small group of cancer cells (partial response)	2
Extensive residual cancer with no evident tumor regression (poor or no response)	3

Figure-A: Modified ryan scheme for tumor regression grade

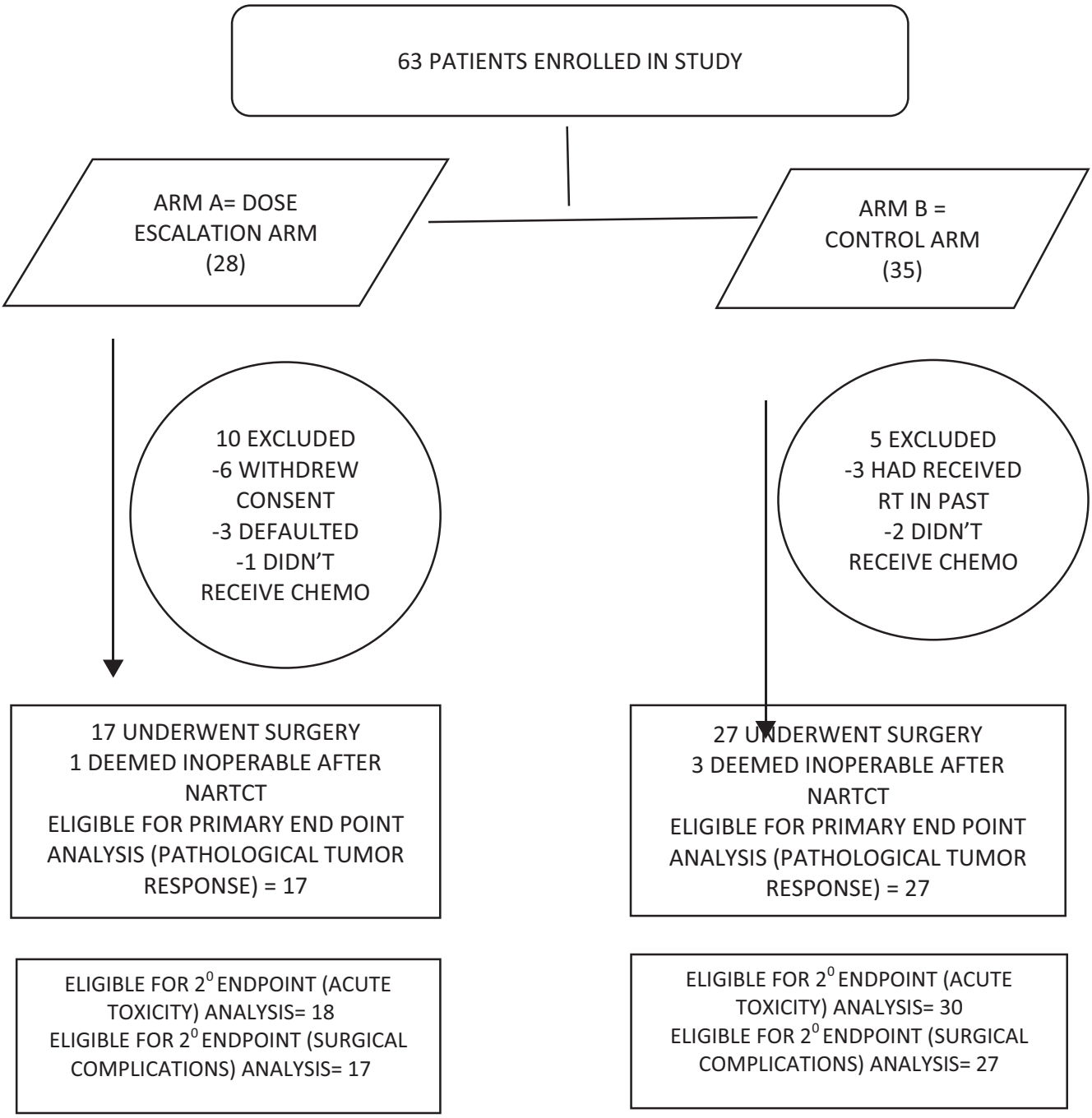

Figure-B: Consort diagram

Characterstics	Subgroup	Dose escalation ARM (18)	Control ARM (30)
Age (years)	Median and range	53.5 (42.75-61.25)	52 (41.25-61)
Gender	Males	15 (83%)	22 (73%)
	Females	3 (17%)	8 (27%)
T stage	T2	0	2 (7%)
	T3	17 (94%)	26 (86%)
	T4a	0	2 (7%)
	T4b	1 (6%)	0
N stage	N0	0	4 (13%)
	N1a	2 (11%)	5 (17%)
	N1b	5 (28%)	15 (50%)
	N2a	11(61%)	4 (13%)
	N2b	0	2 (7%)
Stage group	IIA	0	4 (13%)
	IIIA	0	2 (7%)
	IIIB	17 (94%)	23 (77%)
	IIIC	1 (6%)	1 (3%)
Distance from anal verge (cm)	< 4	8 (44%)	16 (53%)
	4-8.0	8 (44%)	9 (30%)
	> 8	2 (11%)	5 (17%)
Grade	Well differentiated	3 (17%)	1 (3%)
	Moderately differentiated	14 (78%)	26 (87%)
	Poorly differentiated	1 (6%)	3 (10%)
Concurrent chemo	Capecitabine	18 (100%)	22 (73%)
	FU/LV	0	8 (27%)
Total dose of radiation	cGy	5880	5040
Overall treatment time (days)	Mean	39	40
Type of surgery	APR	8 (47%)	16 (59%)
	LAR	9 (53%)	11 (41%)

Table-1: patient, tumor and treatment characterstics

Tumour regression grade	Dose escalation ARM (17)		Control ARM (27)		p-value
	N	Percentage	N	Percentage	
0	4	24%	5	19%	0.532
1	6	35%	10	37%	
2	7	41%	9	33%	
3	0	0%	3	11%	

Table-2: Pathological response assessment

Type	Grade	Dose escalation ARM (18)	Control ARM (30)	P value
Skin	1	10 (56%)	24 (80%)	0.025
	2	6 (33%)	3 (10%)	
	3	2 (11%)	0 (0%)	
GI	1	5 (28%)	17 (57%)	0.052
	2	0 (0%)	3 (10%)	
	3	0 (0%)	0 (0%)	
GU	1	12(67%)	8 (27%)	0.017
	2	1 (6%)	1 (3%)	
	3	0 (0%)	0 (0%)	

*GI - gastrointestinal , GU - genitourinary

Table-3: Toxicity analysis

Parameter	Dose escalation ARM (17)	Control ARM (27)	p-value
Duration of surgery (min)	182.06	177.78	0.703
Length of hospital stay (days)	9.00	9.00	1.000
Nasogastric tube removal on POD	1.88	2.15	0.391
Urinary catheter removal on POD	2.29	2.61	0.298

*POD - post operative day

Table-4: Surgical complications

in arm A, and after a mean of 2.61 days in arm B, but this difference was not statistically significant (p value = 0.298).

DISCUSSION

Our results suggest that escalation of radiation dose to 5880 cGy in patients of locally advanced rectal cancer using a simultaneous boost IGRT technique is feasible and led to a higher proportion of patients achieving improved pathological response. While this does not increase grade 3 or higher acute GI and GU toxicities or surgical complications, increased grade 3 skin toxicity can be a concern. In our study, radiation dose escalation to 5880 cGy led to more proportion of patients achieving a pathologically complete response. Specifically, dose escalation led to 5% improvement in pCR rates over standard arm. We have employed technique of external beam simultaneous integrated boost of 210 cGy per fraction to GTV primary. This amounts to a biologically equivalent dose (BED) of 71.15 Gy. Although not statistically significant, dose escalation led to 3% more patients achieving a major response (TRG 0 and 1) (59% vs 56%; p = 0.831). The pCR rate in dose escalation arm was 24% and in control arm it was 19%. These results are in line with published data on radiation dose escalation in locally advanced rectal cancer in neoadjuvant setting. In the multicentric randomized phase III INTERACT trial[13,] 534 patients of locally advanced rectal cancer were randomized to either radiation dose intensification up to 55 Gy to GTV or by adding oxaliplatin (chemotherapy intensification). Radiation dose intensification was by integrated concomitant radiation boost of 10 Gy delivered as 1 Gy per fraction on a twice weekly basis for a total of 10 fractions over 5 weeks. The BED in concomitant boost arm was 67.7 Gy. The Major pathological response rate (TRG 1 to 2) was significantly higher in the radiation boost group (62% vs 52%; p = 0.039) although both the arms had similar pCR rates. (24.4 % and 23.8 %; p= not significant). In India, Reena engineer et al[14] randomized 90 patients to receive either concurrent radiochemotherapy up to a total dose of 45 Gy in 25 fractions with Capecitabine or 45 Gy EBRT to pelvis alone (without chemotherapy) followed by 20 Gy boost to primary tumor site. Although RT boost arm patients didn't receive chemotherapy, still pCR rate was higher (11%) with dose escalation compared to CRT (7%) demonstrating the potential for radiation dose escalation in achieving better pathological outcomes. The pCR rate of 24% with RT dose escalation seems to be promising as we compare our findings with the recently published RAPIDO trial with much bigger cohort.[15] In the standard arm, patients received 50 Gy or 50.4 Gy long course RT with concurrent chemotherapy followed by TME surgery while in experimental arm, after 5X5 Gy Short course RT, patients received chemotherapy before undergoing surgery. Chemotherapy intensification led to doubling of pCR rates in experimental arm (28% in experimental arm vs 14 % in standard arm; p<0.0001). Our pCR rate of 24% with only RT dose escalation is nearer to the 28% pCR achieved with chemotherapy intensification and much higher than 14 % achieved in standard arm. However, it must be kept in mind that RAPIDO cohort had very advanced tumors. We have explored the potential of dose escalation in rectal cancer using highly conformal modern radiotherapy techniques including VMAT IGRT. We are able to achieve a pCR rate of 24% with dose escalation. We had anticipated a higher pCR rate in dose escalation arm. One possible reason in failing to achieve a higher pCR rate is the narrow margins given to GTV (3mm isotropic margin) for boost treatment. Given the daily variation in position of rectum with respect to bladder filling as well as food intake, perhaps a more liberal margin would have further decreased the possibility of marginal tumor miss. 11% patients who received escalated dose of radiation had grade 3 skin toxicity. None of the patients experienced grade 3 gastrointestinal or genitourinary toxicity, suggesting that the escalated radiation treatment in neoadjuvant setting was well tolerated. In the metanalysis by Burbach et al.[10] Pooled acute grade 3 or more toxicity was 10.3% (95% CI 5.4–18.6%). In the endorectal brachytherapy boost trial by Jakobsen et al[9], there was no significant increase in toxicity in dose escalated arm. Diarrhea was, as in our study, most common gastrointestinal side effect, appearing in more than one half of patients. In the study by Sun Myint[16] dose escalation did not lead to an increase in grade 3-4 toxicity from radiotherapy and no delay in wound healing or anastomotic leakage. Significantly, none of the patients in dose escalation arm in our study required treatment interruption or dose modification due to acute toxicity. The overall tolerable toxicity profile might be attributable to the implementation of strict bladder protocol during simulation and treatment delivery, tight dose constraints to organs at risk and daily image guidance using on board imaging. We analysed surgical complications based on four end points. These are – duration of surgery, length of hospital stay after surgery, time since surgery (in days) when urinary catheter was removed, and time since surgery (in days) when nasogastric tube was removed. All these four are established factors to predict for surgical efficiency and intra- and immediate post-operative complications. In our study, we found no statistically significant difference between the two arms in terms of mean duration of surgery (182 minutes in arm A versus 177 minutes in arm B; p= 0.703). Radiation dose escalation did not lead to an increase in total operative time. Likewise, length of post-operative hospital stay is a commonly used indicator of surgical efficiency. In our study, the mean length of hospital stay was in agreement with literature reported data. There was no statistically significant difference between the two arms in terms of mean length of hospital stay (9 days in each arm). Urinary drainage using trans-urethral catheterisation after colorectal surgery has been routinely employed for prevention of urinary retention and also for monitoring of urinary output. The study by Kin et al[17] found that urinary retention in post-operative period was associated with longer operative time, an indicator of intraoperative complications. Optimal utilization of urinary catheterization is of paramount importance in improving the outcomes of rectal surgery. ERAS Society guidelines recommend routine transurethral catheterisation for 1–3

days after colorectal surgery.[18] In our study, we found no statistically significant difference in the two arms in terms of time of removal of urinary catheter since surgery (2.3 days after surgery in arm A versus 2.6 days after surgery in arm B; p= 0.298), indicating that radiation dose escalation did not adversely affect the intraoperative and immediate post-operative urinary complications. Prophylactic Nasogastric tube placement is routinely employed for patients undergoing colorectal surgery to help hasten return of normal bowel function, increasing patient comfort by decreasing abdominal distension, decreasing risk of aspiration of gastric contents, and to protect anastomotic leakage. In our study, nasogastric tube was removed at a mean of 2 days after surgery in both the arms. This indicates that dose escalation did not lead to increased surgical complications which might have warranted delayed NG tube removal.

In conclusion, through this single institution phase II study, we are able to demonstrate an improvement in pathological response using a radiation dose escalation method. Dose escalation led to an increase in grade 3 acute skin toxicity, without any significant increase in acute major gastrointestinal and genitourinary toxicity. Intra- operative and immediate post-operative complications did not increase in patients who received increased dose of radiation. Long term follow-up is needed to document chronic radiation related toxicity as well as effect on overall and disease-free survival in this cohort. The strengths of this study include using image guidance based conformal radiation techniques for boost, maintenance of strict bladder protocol, using homogenous chemotherapy regimen, good follow up of patients, and longitudinal tracing of toxicity. More randomised studies will help define the role of dose escalation in conformal RT era in rectal cancer.

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