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ORIGINAL RESEARCH

Dose Escalation with Simultaneous Integrated Boost (SIB) Using Volumetric Modulated Arc Therapy (VMAT) in Rectal Cancer

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Abstract

Purpose Assess feasibility—rate of PCR, short-term toxicity after neoadjuvant concurrent chemoradiation (NACRT) delivered via simultaneous integrated boost (SIB) using volumetric modulated arc therapy (VMAT) technique for locally advanced rectal cancer.

Methods Retrospective evaluation of patients with locally advanced rectal cancer treated with VMAT-SIB technique preoperatively at an academic tertiary care center in Riyadh, Saudi Arabia between February 2013 and March 2017.

Results One hundred patients with depth of invasion staged as T3/T4 or T2 in 93 and seven patients, respectively. Lymph node metastasis was staged as N1/N2 or N0 in 87 and 13 patients, respectively. Circumferential radial margin (CRM) was involved radiologically prior to treatment in 50 patients. A dose of 55 or 50 Gy was given to 71 and 29 patients, respectively. All treatments were completed without interruption. Grade 3/4 toxicity was not observed. Low anterior resection and abdominoperineal resection were performed with negative proximal, distal, and radial margins in 72 and 28 patients, respectively. There were no immediate significant postoperative complications. Histologically, no residual tumor (grade 0) was noted in 20 patients (pCR). Regression grade 1, 2, and 3 were noted in 31, 34, and 15 patients. Average number of lymph nodes retrieved in the surgical specimen was 12 (range 6–22). Lymph nodes were negative for cancer in 80 patients.

Conclusion Dose escalation with SIB-VMAT as NACRT for rectal cancer is feasible. Moreover, it can increase the rate of pathological complete response with a favorable toxicity profile. Clinical benefit of this approach needs to be validated in a larger cohort of patients with longer follow-up.

Keywords Rectal · Cancer · Volumetric modulated arc therapy (VMAT) · Radiation · Therapy · Surgery · Chemotherapy · Complete · Pathology · Response · Dose · Toxicity · Patients · Simultaneous integrated boost (SIB)

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Introduction

Colorectal cancer is the fourth in the common diagnosed cancer and the second leading cause of cancer death in USA [1]. In Saudi Arabia, colorectal cancer has been the most commonly diagnosed cancer among men and the third commonest among women since 2002 [2].Combined modality treatment including surgery (total mesorectal excision), pelvic radiotherapy (RT) concomitant with chemotherapy with or without adjuvant chemotherapy is recommended for patients with stage II and III rectal cancer [3, 4].The primary aim of using RT in these patients is to reduce the incidence of local recurrence with preoperative RT being preferred over postoperative RT in term of better local control, toxicity pattern and tumor downstaging that helps to obtain sterile circumferential

margin, and thus facilitating complete surgical excision [5]; however, the overall 5-year survival was similar for both RT strategies [3, 5]. Chemotherapy is usually given concomitantly with radiation therapy as a neoadjuvant treatment in advanced rectal cancer cases as addition of chemotherapy has reduce incidence of local recurrence in comparison to those receiving radiation alone, however no difference in overall survival noted [6]. Tumor response to neoadjuvant chemoradiation (NACT) is a predictive factor for clinical outcomes [7, 8]. Around 15% of patients experience a complete pathological response (pCR) with the standard radiation dose (45–50.4 Gy) are those who achieved pCR have a better 5-year recurrence free survival than those with intermediate or poor responses [7–10]. A dose–response relationship exists in favor of higher radiation doses (> 55 Gy) [10]; however, there is no consensus regarding optimal dose [11–13], with another limiting factor for increasing radiation dose is the tolerance of surrounding normal structures like the small intestine and the bladder [14–16].

Altered RT strategies have been used to enhance tumor cell eradication without increased normal tissue toxicity [17–21]. One of these strategy is a simultaneous integrated boost (SIB) in which different doses per fraction are delivered to different target regions [22], while using intensity-modulated radiation therapy (IMRT) improves dose distribution for SIB strategies [21, 23, 24].

This retrospective study aims to assess the feasibility of SIB-VMAT in the treatment of locally advanced rectal cancer: its impact on the rate of complete pathological response and its short-term toxicity.

Materials and Methods

A total of 100 patients at King Faisal Specialist Hospital and Research Center-Riyadh (KFSHRC-R) with locally advanced rectal adenocarcinoma treated between February 2013 and March 2017 with NACRT using a SIB-VMAT technique and capecitabine were included in this retrospective evaluation. Patient and tumor characteristics were retrieved from the electronic health record. All patients had a pretreatment staging work-up in the form of routine labs, CT chest, abdomen, and pelvis; MRI pelvis; and endorectal ultrasound.

NACRT was delivered via SIB-VMAT at a total dose of 50–55 Gy/25 fractions. All patients were instructed to have a full bladder, and oral contrast was given at the time of CT simulation. CT images had a 2-mm slice thickness. The images were transferred to the treatment planning system. The CT images were rigidly co-registered with the MRI images. Co-registration was validated through a visual inspection of anatomical structures with primary emphasis on the mesorectum and secondary emphasis on bone structures. If necessary, registration was corrected manually. From the image registration, MRI delineated gross target volumes (GTVp) were automatically transferred to the CT planning basis, while considering all the data including digital rectal examination, endorectal ultrasonography, and colonoscopy.(GTVn) is any abnormal or suspicious lymph node more than 1 cm in diameter. (CTVp50/55) includes the whole mesorectum with a margin of 2 cm above and below the (GTVp). (CTVn50/55) is a 1-cm margin around the (GTVn). (PTV50/55) includes both the (CTVp50/55) and (CTVn50/55) with a 5-mm margin. (CTV45) includes the rectal tumor with the whole mesorectum in addition to the lymph nodes groups at risk like internal iliac, presacral, and perirectal lymph nodes. External iliac lymph nodes were included only if there was an extension to genitourinary structures. (PTV45) includes the (CTV45) with a 5-mm margin in all directions except anterior margin of 7 mm.

Inverse planning of IMRT for the conventional two volumes were generated with IMRT planning system. A Varian® Synergy linear accelerator with an 82 multi leaf collimator (MLC) was used in the planning. The MLC leaf width was 1 cm at the isocenter. Beam modulation was achieved through a segmented MLC sliding window delivery. The nominal photon energy was 10 MV.

Dose–volume constraints (DVH restriction points) were introduced for the organs at risk (OARs). For the bladder, the constraints dictated that no more than 50% of the volume should receive more than 50 Gy, constraints for the intestine dictated that no more than 20 cc of the volume should receive more than 45 Gy, no more than 150 cc should receive more than 35 Gy, and none at all should receive more than 50 Gy. The goal For PTVs was to achieve that more than 99% of the PTV volume should receive more than 97% of the prescribed dose. All the patients had a daily cone beam CT for accurate set-up verification.

All the patients received concomitant chemotherapy in the form of capecitabine orally at a dose of 825 mg/m2/12 h daily with RT. It was given 5 days per week for 5 weeks.

Results

Patients' characteristics are reported in Table 1. Radiation characteristics, type of surgery, pathological findings, and toxicity are reported in Table 2. There were no significant postoperative complications.

All treatments completed were without a break. Grade 3/4 toxicity was not reported. The most important acute toxicities are shown in Table 2.

The response to treatment was assessed according to AJCC cancer staging manual, 7th edition and the CAP guidelines as modified by Rayan, et al. Histopathology 2005; 47:141–146. Tumor response is reported in Table 2.

Table 1 Patients characteristics

Sex	Male	56 pts.
	Female	44 pts.
Age at diagnosis in years	Average 59.7 years (range 28–102)	
Stage	T2	7 pts.
	T3/T4	93 pts.
	N0	13 pts.
	N1/N2	87 pts.
Distance of lesion from anus in CM	Average 6.47 (range 0–13)	
CRM	Positive in 50 pts.	
	Negative in 50 pts.	
Tumor size in CM	2–11	Average 5.37 (range 2–11)
HB level at presentation in G/L	Category 1 (9 pts.)	
	Category 2 (33 pts.)	
	Category 3 (58 pts.)	

General linear model and chi-square test were used to test the relations between response (primary tumor or nodal) after NACRT and independent variables as shown in Table 3. Smaller tumor length below 4.78 cm and pretreatment negative CRM was significantly associated with pathological complete response at p value .006 and .01, respectively. Positive lymph nodes had a lower chance of being identified in the surgical specimen if the CRM was negative at p value .01 or if the pretreatment lymph node stage was N0 at p value .04. The patients were divided based on their hemoglobin level to three categories: Hb below 10 g/L, 10–12 g/L, and more than 12 g/L then a lower Hb is associated with a higher chance of positive lymph nodes in the surgical specimen at p value .02.

Table 2 Results and toxicity

Dose in Gy	50 Gy in 29 pts.	
	55 Gy in 71 pts.	
Time between end of radiation and surgery in weeks	average 10 (range 6–12)	
Type of surgery	LAR	72 pts.
	APR	28 pts.
Primary tumor response	0	20 pts.
	1	31 pts.
	2	34 pts.
	3	15 pts.
Residual primary tumor size in CM	Average 1.5 (range 0.5–4)	
Nodal response	N0	80 pts.
	N+	20 pts.
No of lymph nodes examined	Average 12 (range 6-22)	
Toxicity	Dysuria	50 pts.
	Anal pain	38 pts.
	Fatigue	30 pts.
	Diarrhea	20 pts.

Discussion

SIB-VMAT has been associated with a significant reduction in toxicity because it spared critical structures outside the target volumes. This is due to a higher level of dose conformity, planned tumor-dose escalation, and irradiation of critical structures within tolerance levels. [25].

The SIB-VMAT technique advantages comes from ability to increase dose per fraction to the high-risk boost volume, while at the same time keeping doses to the elective target volume at a lower level [26]; for example, in this

Table 3 Correlation between primary tumor and nodal response with multiple factors

Response	Correlated factors	p value
Primary tumor response	Sex	0.98
	Age	0.96
	Tumor size	0.006
	Distance from AV	0.44
	CRM	0.01
	Pretreatment (N stage)	0.1
	Initial HB at presentation	0.62
	Time of surgery	0.29
	Type of surgery	0.86
Lymph node response	Sex	0.54
	Age	0.14
	Tumor size	0.08
	Distance from AV	0.2
	CRM	0.01
	Pretreatment (N stage)	0.04
	Initial HB at presentation	0.02
	Time of surgery	0.28
	Type of surgery	0.65

trial, we were able to deliver two fraction sizes, a fraction size (FS) of 2.2 Gy to the boost volume and a FS of 1.8 Gy to the elective target volume, with resultant of total radiation dose of 45 Gy to elective target volume and 55 Gy to boost volume in 25 fractions instead of the traditional dose 50.4–54 Gy in 28–30 fractions resulting in increasing both the total prescribed dose (PD) and biologic dose in addition to a reduction in the overall treatment time (OTT); 5 weeks in comparison to 5.5–6 weeks. Another possible advantage of SIB-VMAT technique in comparison to the sequential IMRT is that the dose distributions are even more conformal with SIB-VMAT resulting in a better coverage of boost volume and more sparing of non-target tissues [27–29]. As noticed before in a trial conducted by Mohan et al., when the most part of the dose has already been delivered, it may be very difficult to achieve a high level of dose conformality with the remaining boost dose [20].

One way to assess the effectiveness of NACRT is to detect the pathological complete response (pCR) rate. The percentage of patients achieving a pCR using concurrent fluoropyrimidine and pelvic radiation therapy is around 12 to 15% [30].

Many studies had shown association between achieving pCR and long-term survival, as those who achieved PCR have better DFS than those who did not [31, 32].

A previous study from this institution reported on preoperative concurrent chemoradiation therapy with the use of radiation therapy 50.4 Gy in 28 fractions in two phases concomitant with flouropyrimidine-based chemotherapy. The rate of pCR is 7.6% compared to 20% in the current study. The main difference between the two groups is the technique of pelvic radiation: IMRT–SIB technique in this study with a total dose of 50–55 Gy in 25 fractions compared to 3DCRTin the previous study in 28 fractions [33].

The SIB-VMAT protocol in this study resulted in a CR rate of 20% with 31% of patients achieving near complete response with a residual microscopic foci of the disease despite the advanced stage of the patients enrolled in this study; 93% of the patients had T3/T4 depth of invasion with an average tumor size of 5.37 cm^3 and positive CRM in 50% of the patients.

A better outcome to radiation is achieved with usually a higher dose: 14 out of 20 patients with pCR received 55 Gy and 23 out 31 patients with near CR received 55 Gy.

Majority of patients achieved pathological sterilization of the resected lymph node; 80 patients in this study despite the advanced pretreatment N stage in 87% of patients (a higher dose of radiation was associated with a better chance of negative lymph nodes in the resected surgical specimen. Out of 63 patients with positive lymph nodes initially and received 55 Gy 49 patients had negative lymph nodes, while 19 of 24 patients achieved negative lymph nodes among those who received 50 Gy.

SIB-VMAT in this study did not cause grade 3 or 4 toxicity and all patients completed the 5 weeks of NACRT while using capecitabine without interruption or dose modification. In contrast to phase III of the ACCORD trial where the treatment arm received 5 weeks of 45 Gy in 25 fractions with concurrent capecitabine 800 mg/m2 twice daily, 5 days per week. Full-dose RT was given in 100% of patients and discontinuation of chemotherapy was observed in 2.8% of patients with dose modification of the chemotherapy regimen performed in 50% of the patients. The overall rate of grade 3 to 4 toxicity was 10.9%; this increase in grade 3 to 4 toxicity was mainly related to diarrhea [34].

The difference in toxicity pattern and severity despite higher dose of radiation therapy with concurrent chemotherapy despite the general thoughts that acceleration of radiotherapy may interfere the delivery of adequate doses of concomitant chemotherapy, and/or worsen the acute toxicity profile of treatment [35], is due to sparing of intestine and bladder by IMRT compared to 3D conformal RT (CRT) [36]. It has been proposed that intestine volumes irradiated to doses higher than 50 and 45 Gy should be smaller than 0 and 20 cc, respectively [37].

Conclusion

Dose escalation with SIB using VMAT as NACRT for rectal cancer is feasible. It may increase the rate of pathological complete response with a favorable toxicity profile; the clinical benefit of this approach needs to be validated in a larger cohort of patients with longer follow-up.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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