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Original Research Article

VMAT dosimetric study in rectal cancer patients

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The aim of this study was to evaluate the dosimetric results of patients treated by arc-therapy for rectal cancer at Al Kindy Oncology Center in Casablanca, Morocco. Twenty-five patients with locally advanced rectal cancer (T3, T4, N1, N2) treated by arc-therapy at doses of 46 Gy with a boost of 4 Gy sequentially or simultaneously integrated were collected. We analyzed and compared the dosimetric data of the two techniques using the dose volume histograms as well as the indices of conformity and homogeneity. Statistical analysis was performed using the SPSS v23 system (IBM Inc., Chicago, IL). Arc-therapy with simultaneous or sequential integrated boost allowed better coverage of target volumes. In fact, the D2% and D98% were (104.66 ± 0.50) and (96.62 ± 0.78), respectively. The homogeneity index was (0.078 ± 0.018) and the conformity index was (0.99 ± 0.015). For organs at risk, V30%, V40% and V50% were respectively (15.97 ± 12.97), (7.99 ± 9.15) and (2.36 ± 5.89) for the small bowel. When at the average dose, it was 13.38 Gy. The bladder was largely protected with a V40% of (33.01 ± 18.82) and an average dose of (27.89 ± 13.07) Gy. The V40% of the femoral heads was (3.68 ± 8.25). A comparison of the simultaneous integrated boost with the sequential boost showed that the coverage of the PTVs was similar. For organs at risk, the simultaneous integrated boost has very significantly (P <0.05) reduced doses in the small bowel. For the bladder and femoral heads the results of both techniques were similar. This study clearly shows that the Volumetric Modulated Arc Therapy (VMAT) technique provides a better dose distribution for PTV and OARs. The simultaneous integrated boost reduced the irradiated volumes of the small bowel resulting in a reduction in complications and toxicities.

Keywords: DVH, ORAs, rectal cancer, target volumes, toxicity, VMAT.

INTRODUCTION

Cancers of the middle and lower rectum account for more than 70% of malignant tumors of the rectum (International Center for Research on Cancer, 2018). At the time of diagnosis, most cases are already in the middle or advanced stage. Clinical practice often relies on abdominoperineal resection (APA) surgery. However, the low rate of sphincter preservation is detrimental to patients' quality of life as well as their psychological and mental health (Vendrely et al., 2018). Currently, the treatment for cancer of the lower and middle rectum is multidisciplinary. Rectal surgery with total resection of the mesorectum (TME) after neo-adjuvant radiotherapy is widely accepted compared to primary surgery (Kapiteijn et al., 2001). For large rectal tumors with or without lymph nodes metastases (T3, T4, with / or without N1, N2) neo-adjuvant radiotherapy reduces the risk of local tumor recurrence, while maximizing the surgical possibilities for sphincter preservation (Kapiteijn et al., 2001).

Imaging-guided radiotherapy such as volumetric modulated arc-therapy (VMAT), intensity-modulated radiotherapy (IMRT) or tomotherapy has resulted in a better conformation to target volume with better

dosimetric protection of organs at risk (OAR) (Wen et al., 2015; Lin et al., 2017).

The objective of this retrospective study was to report the dosimetric and clinical results of simultaneous integrated boost (SIB) or sequential simulated rectal tumor radiotherapy with rectal tumor associated with induction chemotherapy with Capecitabine in 25 patients treated at the Al Kindy Oncology Center in Casablanca.

MATERIALS AND METHODS

This is a retrospective study of the medical and dosimetric records of 25 patients treated for a tumor of the lower and middle rectum (T3, T4 with or without N1, N2) located between 2 and 12 cm from the anal margin. This study included patients with Karnofsky Performance Status greater than 70 and adenocarcinoma according to histological type. All patients received oral chemotherapy with Capecitabine (825 mg/m^2 twice daily and 5 days per week for 5 weeks) concomitant with radiotherapy. Surgery with total mesorectal excision (TME) was done for all patients after about 6 to 8 weeks of completing radio chemotherapy.

Pretreatment assessment

All the patients were subjected to a complete history by meticulous clinical examination, a total colonoscopy, and a biopsy of the tumor by rectoscopy. Pelvic MRI and CT scan of the chest and abdomen were conducted to determine the TNM classification of the tumor. The biological assessment included a complete blood count, blood electrolytes, carcinoembryonic antigen (CEA), CA19-9 carbohydrate antigen, creatinine, blood urea acid, and liver function tests. Cardiac function was studied using an electrocardiogram and an echocardiogram.

Radiotherapy

Each patient had undergone a computed tomography-based simulation with 3 mm dorsal supine sections with a full bladder and intravenous contrast media. The delineation of target volumes and organs at risk (OAR) was the same for all patients in accordance with ICRU 83 recommendations. Gross tumor volume (GTV) was defined clinically with rectoscopy and MRI. Gross tumor volume (GTV) is defined by data from clinical examination, rectoscopy and MRI. It adds to this volume a ganglionic GTV which includes lymphadenopathies whose small diameter was greater than 1 cm. The anatomo-clinical target volume (CTV) in addition to GTV, included the whole mesorectum and presacral spaces. The perineum was included if the surgeon felt that an AAP was necessary. The CTV also included the perirectal, obturator and internal iliac ganglion areas. External iliac lymph nodes were considered part of the CTV if there was tumor extension to the vagina, uterus, cervix, prostate or bladder. The inguinal ganglia were included only when the tumor invaded the lower third of the vagina or the anal canal. The planning target volume (PTV) included CTV with a margin of 1cm. PTVG corresponded to GTV with a margin of 5 mm ante-posteriorly and a margin of 5 to 10mm vertically and laterally. OARs delineated the bladder in their entirety, the femoral heads and the small bowel. The small bowels with the peritoneal cavity were contoured up to 1.5 cm above the PTV.

The treatment plans were performed on an Eclipse 13.5 treatment planning system (Varian Medical Systems, Palo Alto, CA). For the arc-therapy plans, the planning was done by two coplanar arcs with a photon beam of 6 MV. The first arc was planned from 179° to 181° clockwise and the second arc counterclockwise with a collimation angle of 330° and 30°.

For 17 patients, the PTV prescribed dose was 46 Gy (23 fractions of 2 Gy) followed by a sequential boost of 4 Gy on PTVG. For other patients, PTV and PTVG were treated with a simultaneous integrated boost in 25 sessions simultaneously giving 1.84 Gy per fraction to the PTV and 2Gy to the PTVG.

The primary objective of the constraints was a good coverage of planning target volumes by 95% reference isodose. The dose limits for OARs, including the small bowel, were V30 <40%, V15 <50%, and V50 <5%. For the bladder, the dose limit was V40 <45%; and for the femur, the limit was V40 <5%.

For the dosimetric evaluation, the D98%, D95%, D50%, D5%, D2% and the total volume of PTV and the volume covered by isodose 95% were recorded for PTVs. We also calculated the conformity index and the homogeneity index. For the bladder we collected the D_{max} the V20, V30, V40, V50 and the D_{mean}. For the intestine we collected the V15, V20, V30, V40, V50, D_{max} and D_{mean}. The femoral heads were evaluated on the V30, V40, D_{mean} and D_{max}.

Monitoring and toxicity

During radiotherapy, a weekly consultation was conducted to evaluate the toxicity and acute complications of the treatment. Then, at the end of the radiotherapy, clinical examination and rectoscopy were performed before the surgery. A follow-up consultation was done every three months in the first two years and then every six months thereafter. An MRI was requested at the first consultation then annually.

Statistical analysis

Data analysis was performed using Statistical Package for the Social Sciences (IBM Inc., Chicago, IL, USA).

RESULTS

A total of 25 patients with cancer of the middle and lower rectum were treated in 2017. The average age of the patients was 58.8 years (extreme of 37 to 76 years). The sex

Table 1. VMAT dosimetric parameters results in PTV

Dose(Gy)	Mean	Standard Deviation
D2%	52.33	0.54
D5%	52.05	0.52
D50%	50.85	0.55
D95%	49.09	0.67
D98%	48.32	0.78
IH/IC		
IH	0.08	0.02
IC	0.99	0.02
UM		
UM	772.17	162.38

Table 2. VMAT dosimetric parameters results in OARs

OARs	Dose (Gy)	
Small Bowels	**Mean**	**Standard Deviation**
V15%	41.08	26.84
V20%	33.93	24.28
V30%	15.97	12.97
V40%	7.99	9.16
V50%	2.36	5.89
Dmax	47.47	4.42
Dmean	13.38	7.51
Bladder		
Dmax	50.60	1.88
V20%	64.08	29.55
V30%	47.94	24.25
V40%	33.01	18.82
V50%	3.90	9.71
Dmean	27.89	13.08
Femoral Heads		
Dmean	26.62	13.77
Dmax	37.09	13.12
V30%	17.30	28.98

ratio was one woman for every two men. The lower edge of their tumor was between 2 and 4 cm from the margin of the anus in 7 cases, and between 5 and 10 cm in 18 other cases with a median distance of 4.5 cm.

Clinical stage: There were 5 cases T2 = 20%, 17 cases T3 (68%) and 3 cases T4 (12%). For nodal status 7% of cases were N0, 40% N1 and 53% N2. All patients had adenocarcinoma (ADK). There were 10 patients with a well differentiated ADK, 7 cases had a moderately differentiated ADK and 8 poorly differentiated cases. The median survival was 14.86 months (range 4-19 months).

Target coverage, homogeneity and conformity index

All PTVs received doses ranging from 95 to 107% of the prescribed dose. The D98% also called quasi-mini-absorbed dose was (96.62% ± 0.78) while the D95% was (98.16% ± 0.67). The D2%, called the almost maximal absorbed dose, was (104.66% ± 0.50). The homogeneity index was very close to 0 (0.078 ± 0.018). For the conformity index it was (0.99 ± 0.015). Table 1 presents a summary of the coverage of PTV parameters.

Organs at risk

Dose limits were respected in all organs at risk. For the small bowel the V30%, V40% and V50% were respectively (15.97 ± 12.97), (7.99 9.15) and (2.36 ± 5.89) but at the D_{mean}, it was 13.38 Gy. The bladder was largely protected with a V40% of (33.01 ± 18.82). The mean dose was (27.89 ± 13.07) Gy. Finally, the V40% of the femoral heads was (3.68 ± 8.25). Results for doses received by OARs are summarized in Table 2.

A comparison of the simultaneous integrated boost with the sequential boost showed that the coverage of PTV was similar except for the homogeneity index which was in favor of integrated boost radiotherapy (Table 3). For organs at risk, the simultaneous integrated boost had very significantly ($P < 0.05$) reduced doses in the small intestine. While the results of both techniques were similar in the bladder and femoral heads (Table 4).

Table 3. Comparison of dosimetric coverage in PTV between sequential boost and simultaneous integrated boost (SIB).

	Sequential boost		SIB		
Dose (Gy)	**Mean**	**Standard Deviation**	**Mean**	**Standard Deviation**	**P-Value**
D2%	52.453	0.509	51.905	0.490	0.116
D5%	52.146	0.587	51.730	0.476	0.171
D50%	50.825	0.647	50.920	0.626	0.598
D95%	48.957	0.694	49.535	0.512	0.889
D98%	48.085	0.014	49.130	0.010	0.146
IH/IC					
IH	0.086	0.017	0.054	0.003	0.023
IC	0.989	0.017	0.996	0.003	0.922

Table 4. Comparison of dosimetric coverage in OARs between sequential boost and simultaneous integrated boost (SIB)

OARs	**Sequential boost**		**SIB**		
	Dose(Gy)		**Dose(Gy)**		
Small Bowels	**Mean**	**standard deviation**	**Mean**	**Standard Deviation**	**P- Value**
V15%	62.90	25.69	34.20	13.86	0.010
V20%	54.92	21.89	26.18	12.10	0.005
V30%	34.46	17.78	9.69	6.94	0.031
V40%	16.12	8.87	3.45	4.87	0.034
V50%	3.67	4.58	0.00	0.00	0.188
Dmax	51.68	1.76	44.61	3.57	0.013
Dmoy	23.39	15.61	9.77	5.89	0.023
Bladder					
Dmax	51.44	2.32	50.71	0.52	0.986
V20%	80.07	19.92	44.69	21.95	0.291
V30%	57.13	19.51	30.97	15.06	0.496
V40%	37.87	13.12	19.28	10.65	0.371
V50%	7.76	8.89	0.13	0.25	0.313
Dmoy	32.01	7.60	18.43	7.83	0.323
Femoral Heads					
D50	24.06	7.57	23.33	15.97	0.732
Dmax	44.59	10.28	37.11	8.52	0.383
V30%	25.63	27.53	6.35	4.62	0.232
V40%	6.15	8.30	0.54	0.72	0.334

Toxicity

For the patients studied, no grade IV toxicity was recorded. Grade III proctitis was observed in 5 patients (20%), grade III diarrhea in 7 patients (28%) and grade III cystitis in 2 patients (8%). One patient developed grade III neutropenia which led to discontinuation of concomitant oral chemotherapy while another patient developed grade III dermatitis.

Surgery

Surgery was performed for all patients after 4 and 7 weeks of radiotherapy. It consisted of abdominal perineal amputation without sphincter preservation for 7 patients (28%) and anterior resection for the other patients (72%). The occurrence of distant metastases (28%) associated with locoregional recurrence in 3 patients resulted in death after 7 years.

DISCUSSION

Arc-therapy was initially applied in rectal cancer by Duthoy et al. (2004) in a planned study comparing 3D-CRT treatment and intensity modulated arc therapy (VMAT). They found that VMAT plans could be delivered within 5 to 10 minutes and resulted in a lower dose for the small bowel than 3D-CRT, without creating significant sub-doses in PTV. Richetti et al. (2010) reported the technical and clinical

experience of 25 patients with locally advanced rectal cancer treated with VMAT. They performed a planned comparison with a cohort of matched patients undergoing conformational radiotherapy (Richetti et al., 2010). They concluded that VMAT provided better dose conformity with significant savings of femoral heads and a significant reduction in full and average doses to normal tissues. In a dosimetric comparative study, Wen et al. (2015) delivered a dose of 50 Gy on PTVG in 23 fractions of 2.17 Gy and 46 Gy on PTV in 23 fractions of 2 Gy. They concluded that VMAT allows good conformity (0.37 ± 0.09 vs 0.71 ± 0.06) and homogeneity (1.04 ± 0.01 vs 1.13 ± 0.01) of PTVG and PTV. In another study, Lin et al. (2017) prescribed a dose of 50.4Gy in 28 fractions. They showed that VMAT provides good coverage of PTV with a conformity index of (0.85 ± 0.04) and homogeneity index of (1.06 ± 0.02) . The VMAT with two arcs and 50 Gy in 25 sessions of 2 Gy allowed a good coverage of the PTV with a conformity index of (1.21 ± 0.07) according to Shang et al. (2014).

Kaplan et al. (2019) compared VMAT to IMRT in rectal cancer. They reported a good dose distribution on PTV with D2% = (52.88 ± 0.18) Gy, D98% = (49.97 ± 0.11) Gy, IH = (0.056 ± 0.003) and IC = (0.995 ± 0.003). The results obtained in this study are (104.66 ± 0.50) Gy for D2%, (96.62 ± 0.78) Gy for D98%, (0.99 ± 0.015) for IC and (0.078 ± 0.018) for IH and they are in perfect agreement with those of literature. Therefore, we can conclude that VMAT allows good results in terms of conformity, homogeneity and PTV coverage.

Organs at risk (OAR)

In the majority of published studies, VMAT has achieved the dose constraint objectives. Indeed, Wen et al. (2015) had a good DVH for the small bowel with a D_{mean} of 16.92Gy and D5% of 35.53 Gy. In a study comparing VMAT to 3D radiotherapy, Droge et al. (2015) demonstrated better protection of the small bowel by VMAT (V40 = 28.4% and D_{mean} = (16.24 ± 3.09) Gy). Even in the low-dose region, there was a decrease in small bowel irradiation with VMAT compared to 3D-CRT. This is very important because V15% is strongly associated with the acute toxicity of the small bowel according to the study by Baglan et al. (2002) [11]. In this study, regarding the small bowel we obtained a V40% of (7.99 ± 9.15), a V15% of (41.08 ± 9.15) and a D_{mean} of (13.38 ± 7, 51). Our results are in agreement with those published in other studies (Wen et al., 2015; Lin et al., 2017; Duthoy et al., 2004; Shang et al., 2014). For the bladder, the V40 was 66.5% in Droge et al. (2015) and the D_{mean} was (24.8 ± 31.82) Gy in Kaplan et al. (2019). For doses greater than 30 Gy, VMAT also showed a clear advantage in bladder preservation (Yang et al., 2015). In our series, the bladder V40% and D_{mean} were respectively (33.01 ± 18.82) Gy and (27.89 ± 13.08) Gy. These results are comparable with those of (Kaplan et al., 2019; Droge et al., 2015 and Baglan et al., 2002). With regard to the femoral heads, Kaplan et al. (2019) reported a V30% of (2.4 ± 0.7) Gy and a D_{mean} of (12.37 ± 1.33). In our series, the V30% and D_{mean} btained were respectively (17.30 ± 28.98) Gy and (26.62 ± 13.77). These results are comparable to those published in the literature (Kaplan et al., 2019).

Comparison of sequential boost with integrated boost:

In the series of Yamashita et al. (2017), the VMAT with integrated boost compared to conventional radiotherapy showed an increase in doses at the level of the PVG at a dose of 54 Gy, without increasing the toxicity of organs at risk. It also improved PCR and sphincter preservation. Similar results were found by Lupattelli et al. (2017) and Yang et al. (2019) in retrospective series with doses of 58.75 Gy. In our study, the boost consists of delivering 4 Gy on the PTVG either sequentially or in simultaneous integrated boost that reduced the doses in the small bowels ($P < 0.05$).

Conclusion

For cancers of the lower and middle rectum, the VMAT allows a dose distribution very consistent in terms of target volumes while preserving organs at risk. The simultaneous integrated boost technique gives similar results with better protection of the small bowel. VMAT with integrated simultaneous boost is a new approach that is promising in providing higher doses to target volumes and thus, increase complete histological responses (PCRs) to neoadjuvant treatments and increase the locoregional control of rectal cancer.

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