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Simultaneous Integrated Boost by Volumetric Modulated Arc Therapy (VMAT) with Concurrent Mitomycin and Capecitabine in Anal Canal Carcinoma

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Abstract

Background: Combined treatment with radiotherapy and chemotherapy is the standard approach in non-metastatic anal carcinoma. Intensity-modulated radiotherapy and volumetric modulated arc therapy are currently the most accepted radiation techniques. We intend to report the clinical outcomes of patients that have been treated with volumetric modulated arc therapy concomitant with mitomycin C and capecitabine.

Methods: This was a retrospective analysis of 11 patients diagnosed with anal carcinoma who received volumetric modulated arc therapy and a simultaneous integrated boost with concurrent chemotherapy. The chemotherapy protocol consisted of intravenous infusions of mitomycin C (12 mg/m^2) on days 1 and 29, and oral capecitabine (825 mg/m^2) twice daily with radiotherapy treatment.

Results: Most patients had stage IIIB (45.4%) disease. The majority of patients (63.7%) received a dose of 59.4Gy per 33 fractions to the primary tumor and enlarged lymph nodes (median dose: 59.4 Gy; range: 54 Gy-61 Gy). The overall treatment period ranged between 34-56 days. All patients received the planned chemotherapy protocol of two cycles with the exception of one patient who received one cycle due hematologic toxicity and intolerance. Grade 3 skin toxicity occurred in three (27.3%) patients followed by grade 3 gastrointestinal toxicities in 18.2% of patients. Grade 2 anemia (18.2%), neutropenia (27.3%), and thrombocytopenia (27.3%) were observed in eight patients. Complete response was achieved in 90.9% of patients. Patients had an overall one-year survival of 89% and overall 3-year survival of 71% (95% CI: 20.75%-38.49%). After the median follow up period of 12 months, patients had a progression-free survival of 75% (95% CI: 21.29%-38.6%) and 2-year colostomy free survival of 68% (95% CI: 17.2%-32.1%).

Conclusion: Volumetric modulated arc therapy is a safe and effective modality of intensity modulated radiotherapy when combined with chemotherapy (mitomycin C and capecitabine) in anal cancer patients.

Keywords: Anal Cancer, Volumetric, Modulated Arc Therapy, Mitomycin C, Capecitabine

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Introduction

Carcinoma of the anal canal is relatively rare, accounting for 2.4% of lower gastrointestinal tract (GI) cancers,[1] and about 0.5% of recently diagnosed new cases in the United States.[2] The most common histologic variety is squamous cell carcinoma in 85% of cases, followed by adenocarcinoma (10%).[3] Less than 3% of patients are diagnosed with other rare subtypes such as melanoma, neuroendocrine tumor, sarcoma, carcinoid, and lymphoma.[4]

There have been several changes in the definitive treatment of squamous cell carcinoma of the anal canal. The current, standard treatment is combined chemoradiation with the chemotherapy drugs mitomycin C (MMC) and 5-fluorouracil (5-FU).[5] Improvements in complete response (CR), locoregional control (LC), sphincter preservation, and progression-free survival (PFS) are the achievements of combined treatment.[6]

Oral fluoropyrimidine-based chemotherapy (capecitabine) replaced 5-FU in a multicenter phase 2 trial. This trial evaluated capecitabine/MMC according to the UK ACT II trial (50.4 Gy in 28 fractions of 1.8 Gy) with MMC (12 mg/m^2) on day 1 and daily capecitabine (825 mg/m^2 every 12 h) with radiotherapy. There were 77% of patients who had a clinical CR and 4 (16%) cases achieved a partial response with acceptable tolerance and toxicities.[7]

The older technique of non-conformal radiotherapy is associated with high rates of grades 3/4 skin and GI toxicities as reported by the Radiation Therapy Oncology Group (RTOG) 98-11 trial that combined the use of external-beam radiotherapy (EBRT) and concurrent 5-FU/MMC.[8] A comparison of treatment planning between 3-dimensional conformal therapy (3D-CRT) and intensity modulated radiotherapy (IMRT) as evaluated by several dosimetry studies has confirmed the superiority of IMRT in sparing and reducing toxicity to normal and critical tissues.[9,10]

Several trials evaluated IMRT with combined chemotherapy. The results confirmed the feasibility and effectiveness of this approach as treatment for anal cancer.[11,12] The combination of

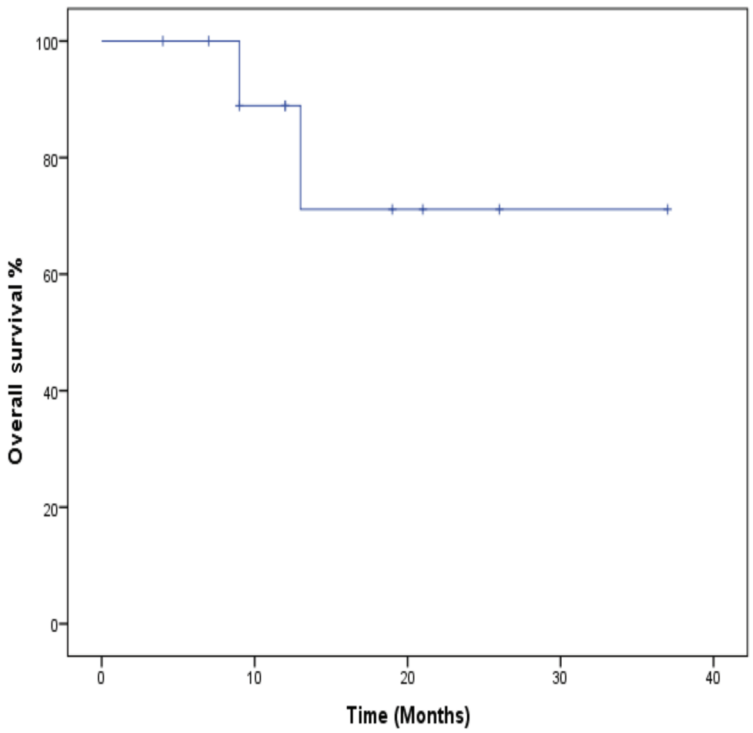

Figure 1. Overall survival.

evolving rotational therapy technique with intensity modulation of radiotherapy dose in volumetric modulated arc therapy (VMAT) has been recently used as a radiotherapy technique for anal cancer treatment. It is technically feasible, with more sparing of risk organs.[13]

In the current study, we aimed to review the clinical outcomes of a consecutive series of patients with anal cancer who received VMAT with simultaneous integrated boost (VMAT-SIB) and concurrent chemotherapy (MMC and capecitabine).

Patients and Methods

Patient population

The study included 11 patients with histologically confirmed squamous cell carcinoma of the anal carcinoma. Patients were treated with concurrent chemotherapy and VMAT radiotherapy between September 2014 and August 2016 at King Abdullah Medical City Oncology Center in Jeddah, Saudi Arabia. The Institutional Review Board at King Abdullah Medical City approved this study.

Patients included in this retrospective analysis had stages T1–T4, N0–N3, and M0 disease according to the cancer staging classification of the American Joint Committee on Cancer Staging (2002).

We obtained patients' data from the electronic and recorded medical files in our center. The data reviewed included general characteristics of the patients – age, sex, and performance status. Tumor staging included primary tumor size (T), nodal staging (N), tumor-node-metastasis (TNM) stage and grade. We recorded the following baseline evaluations: complete clinical history, medical examination that included an objective assessment with digital rectal examination, complete blood report, and radiological staging by total body computed tomography (CT) scan and pelvic MRI.

CT simulation, volume definition, and treatment planning

Patients underwent a CT simulation while in the supine position with both an indexed shaped knee rest and ankle support (CIVCO Medical Solutions, Kalona, IA, USA). The 3-mm slice thickness axial images were acquired from the top of the L1 vertebral body to the mid-femoral shafts. The isocenter was determined in the pelvic region and marked on the patient's skin under laser guidance for daily setup.

The gross tumor volume (GTV) that included the gross tumor and enlarged lymph nodes (LN) was defined based on the MRI and CT results after a non-rigid co-registration with planning CT with Eclipse software (Varian Medical Systems, Inc.,

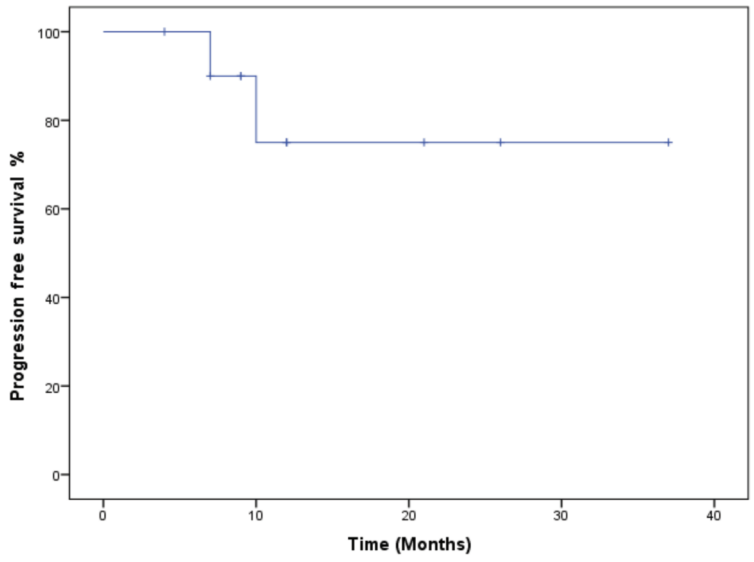

Figure 2. Progression-free survival.

Palo Alto, CA, USA). Clinical target volume (CTV) was obtained after the addition of 2 cm to the primary GTV and 1 cm to the nodal GTV, and then optimized to avoid any non-involved bones and soft tissues. The CTV intermediate risk included the mesorectal region and the inguinal LN, while external and internal iliac, obturator, and presacral LN were included in the advanced stages. Nodal areas were contoured with a 1 cm isotropic margins around the regional vessels and then modified to exclude bones and muscles. For the planning target volume (PTV), 1 cm isotropic margin was added to the CTV in order to account for organ motion and setup error.[14] Optimization of VMAT was performed with version 16.0.03 from Eclipse, (Helios, Varian Medical Systems, Inc., Palo Alto, CA, USA). A maximum dose rate (DR) of 600 MU/min was used. The VMAT was obtained by two coplanar arcs of 360° that shared the same isocenter, which were optimized independently and simultaneously. These two arcs were delivered with opposite rotations (clockwise and counter-clockwise) in order to minimize off-treatment between the two beams. Variable collimator rotation for each arc was set to a value different from zero in order to avoid any tongue and groove effect.

Prescribed doses for the target volumes were related to the clinical stage at presentation; patients with cT2N0 disease were prescribed 50.4 Gy/28 fractions to the gross tumor PTV and 42 Gy/28 fractions to the elective nodal PTV. Patients with stage cT3–T4/N0–N3 received 59.4 Gy/33 fractions to 61.2 Gy/34 fractions to the macroscopic anal PTV, while clinical nodes received 50.4 Gy/30 fractions if ≤3 cm or 54 Gy/30 fractions if >3 cm, and elective nodal PTV was prescribed at 45 Gy/30 fractions. The objectives for target volumes for PTV were as follows: V95 should be at least 95%, V107 ≤10%, and ≤2% should receive <95% of the prescribed dose. A simultaneous integrated boost (SIB) approach was employed for all patients. Radiotherapy delivery was performed under daily cone-beam CT image guidance and kilovoltage images at the first 3 days of treatment followed by weekly imaging thereafter.

The recording data of the cumulative dose volume histograms (DVHs) used for quantitative analysis of the treatment parameters included PTV (D mean, V95 and V107). Dose constraints for organs at risk (OAR) were V45 (195 cc) for the bowel bag; V50 (5%), V40 (35%), and V35 (50%) for the bladder; V40 (5%) and V20 (50%) for the external genitalia; V45 (5%) for the femoral heads, and V50 (5%) and V20 (50%) for the iliac bone.[14,15]

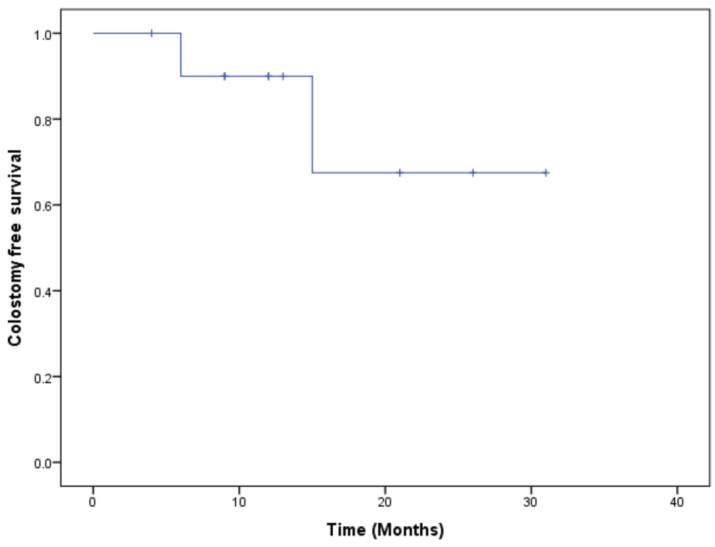

Figure 3. Colostomy-free survival.

Chemotherapy

The chemotherapy regimen was the standard protocol used in our center. In this regimen, patients received IV infusions of MMC (12 mg/m^2) on days 1 and 29, and oral capecitabine (825 mg/m^2) twice per day with each day of radiotherapy. The need for dose modification or reduction due to treatment toxicities in the treated cases was also reported.

Follow-up

Patients underwent weekly assessments of acute radiation toxicities during the radiation treatments. Toxicities were graded according to the Common Toxicity Criteria for Adverse Events (CTCAE) scale version 4.0. We evaluated any genitourinary (GU), GI, hematologic, dermatologic, and osseous events by considering the grades of toxicity, breaking time from radiotherapy, and total time of radiotherapy. Follow-up digital rectal examination and anoscopy were performed at 4, 8, 12, and 26 weeks. Patients underwent MRI at 12 weeks and an anal canal biopsy under general examination was performed at 26 weeks. If no residual disease was found at pathology, patients were classified having a CR. Salvage abdominoperineal resection was offered for pathology determined persistent, locally progressive, or recurrent disease according to imaging and pathology assessments. Conservative salvage treatment was considered when appropriate. Cases with CR were under regular follow-up to detect chronic toxicities and any regional or distal relapse defined as the clinical or radiological appearance of new disease at the site of the primary disease or the reappearance of a new lesion in a distal region. We analyzed the collected outcome and determined progression free survival (PFS), overall survival (OS), and colostomy-free survival (CFS).

Statistical analysis

SPSS software package version 21.0 was used for statistical analysis. Continuous variables were expressed as means and ranges. Categorical variables were expressed as numbers and percentages. The Kaplan-Meier method was used for survival analysis. OS began at the time of diagnosis until the end of the study, lost to follow up, or death for any reason. We calculated PFS from a CR until progression or death. CFS took into account definitive colostomy or any death.

Table 1. Patient and tumor characteristics.

Variables	N (%)
Age (years)	
Mean	61.4
Range	(39-75)
Sex	
Male	8 (73)
Female	3 (27)
ECOG status	
ECOG 0	4 (36.4)
ECOG 1-2	7 (63.6)
T stage	
T1	0 (0)
T2	1 (9.1)
T3	7 (63.6)
T4	3 (27.3)
N stage	
N0	3 (27.3)
N1	3 (27.3)
N2	2 (18.1)
N3	3 (27.3)
TNM stage	
I	0
II	3 (27.3)
IIIA	3 (27.3)
IIIB	5 (45.6)
Grade	
G1	4 (36.4)
G2	4 (36.4)
G3	3 (27.3)
Tumor site	
Anal canal	9 (90.9)
Anal margin	2 (9.1)
Prophylactic colostomy	
Yes	0 (0)
No	11 (100)

ECOG: Eastern Cooperative Oncology Group; TNM: Tumor-node-metastasis

Results

In this retrospective analysis, we reviewed a cohort of 11 patients with non-metastatic anal carcinoma who received treatment from September 2014 to December 2016. All patients had pathologically proven squamous cell carcinoma of the anal cancer. Table 1 lists the

characteristics of the studied patients. Patients had a mean age of 61.4 years (range: 39-75 years). Females comprised 27% of patients with a male to female ratio of 2.6:1. The anal canal primary was seen in 90.9% of patients. The most common presenting tumor stage was T3 stage in seven (63.6%) patients, 9.1% of patients had stage T2 and 27.3% were stage T4. A total of 8 patients had positive nodes, with 3 (27.3%) patients each with N1 and N3 stages, and N2 stage in 18.1% of patients. Most patients had stage IIIB (45.4%) disease at their initial presentation. No patient had human immunodeficiency virus infection.

Table 2 lists the radiotherapy treatment details. Patients received radiotherapy by VMAT-SIB with a median dose of 59.4 Gy (range: 54 Gy-61 Gy). A total of 63.7% of patients received a dose of 59.4 Gy in 33 fractions to the primary tumor PTV and grossly enlarged lymph nodes. All patient received 45 Gy/25 fractions by SIB-VMAT/IMRT to the tumor PTV, LN PTV, and high-risk LNs. The overall treatment period ranged between 34-56 days with a mean of 45 days. Only two patients had treatment interruption for three days. The mean time between diagnosis and onset of radiotherapy was 60 days.

All patients were prescribed two cycles of chemotherapy (MMC and capecitabine); however, one patient received only one cycle due to intolerance and hematological toxicity. One patient had a dose reduction of 20% in the first and second cycles due to poor performance status Easteran Cooperative Oncology Group (ECOG 2), while two patients received a 20% reduced dose in the second cycle (Table 2).

Grade 3 skin toxicity occurred in three (27.3%) patients and was the most common grade 3 non-hematological toxicity followed by grade 3 GI in 18.2% of patients. Grade 2 skin toxicities occurred in 45.5% of patients, whereas 45.5% had grade 2 GI, and 27.3% of patients had grade 2 GU toxicities. Only two (18.2%) patients reported grade 3 diarrhea that required hospital admission and hydration. However, there was no reported grade 3 GU toxicity. In terms of hematological toxicity, eight patients had grade 2 anemia (18.2%), neutropenia (27.3%), and thrombocytopenia (27.3%) as listed in table 3.

Table 2. Treatment characteristics.

Variables	N (%)
Range of radiation dose	54 -61.2 Gy
Total radiation dose	
54 Gy	3 (27.2)
59.4 Gy	7 (63.7)
61.2 Gy	1 (9.1)
Radiation technique	
VMAT-SIB	11 (100)
Radiation therapy phases	
Phase 1: 45 Gy/25 fractions	9 Gy
Phase 2: (Boost)	
14.4 Gy	3 (27.2)
16.2 Gy	7 (63.7)
11 (100)	1 (9.1)
Total radiation therapy duration (days)	
Mean	45
Range	34-56
Radiation therapy breaks ≥3 days	
Yes	2 (18.2)
No	9 (81.8)
Chemotherapy regimen	
MMC+ capecitabine	11 (100)
Chemotherapy cycles	
1	1 (9.1)
2	10 (90.9)
Number of patients that had reduced cycles	
1st cycle	1 (9.1)
2nd cycle	2 (18.2)
Response	
Complete response	6 (54.5)
Partial response	3 (27.3)
Progressive disease	2 (18.2)

VMAT-SIB: Volumetric modulated arc therapy with simultaneous integrated boost; MMC: Mitomycin

The follow-up period ranged between 6 and 37 months with a median of 12 months. Complete response was achieved in 10 (90.9%) patients, while one patient had partial response followed by treatment failure at the 10th month. Another patient had metastatic disease in the liver and lung at the 7th month. The patient with treatment failure was salvaged with radical surgery (abdominoper-

Table 3. Acute toxicities.

Acute toxicity	Grade N (%)			
	0	1	2	3
Non-hematological toxicities				
• Skin	1 (9.1)	2 (18.1)	5 (45.5)	3 (27.3)
• GI	1 (9.1)	3 (27.3)	5 (45.5)	2 (18.1)
• GU	3 (27.3)	5 (45.5)	3 (27.3)	0
• Pain	0	4 (36.4)	6 (54.5)	1 (9.1)
Hematological toxicities				
• Anemia	6 (54.5)	3 (27.3)	2 (18.2)	0
• Neutropenia	2 (18.2)	5 (45.5)	3 (27.3)	1 (9.1)
• Thrombocytopenia	4 (36.4)	4 (36.4)	3 (27.3)	0

GI: Gastrointestinal; GU: Genitourinary

ineal resection), while palliative chemotherapy was offered to the patient with metastatic disease. Two patients died, one due to cancer related metastatic disease and the second because of non-cancer associated medical morbidities. The one-year OS was 89% and the 3-year OS was 71% (95% CI: 20.75%-38.49%; Figure 1). The one- and 3-year PFS were both 75% (95% CI: 21.29%-38.6%; Figure 2). The 2-year CFS was 68% (95% CI: 17.2%-32.1%; Figure 3). No multivariate analysis was performed due to the small number of patients.

Discussion

Combined chemotherapy and radiotherapy is the standard management for non-metastatic anal cell carcinoma due to the advantages of maintaining sphincter function and a positive impressive impact on local control and survival (DFS or OS).[16] Radiotherapy techniques have evolved dramatically from conventional traditional method that used a two-dimensional (2D) technique to 3D-CRT, then to IMRT.

Severe toxicities from combined chemoradiation with 2D radiotherapy that used a 3 of 4 field box technique were attributed to the considerable size of the CTV that extended from the lumbosacral joint superiorly to the anal verge (inferiorly). In order to cover this target volume, many critical organs were included, which led to more acute toxicities and increased treatment breaks that potentially affected the treatment outcome.[17]

Intensity-modulated radiotherapy provides robust conformality and modulation, abrupt dose fall-off, and reliable consistency. Therefore, IMRT may potentially reduce the dose to critical structures, which would result in increased overall treatment tolerability.[15,18] There are numerous treatment approaches with IMRT; recently, the most acceptable approach is VMAT. Volumetric modulated arc therapy is a subtype of IMRT that combines intensity beam modulation with rotational therapy techniques obtained from the application of continuous modulation of a multileaf collimator (MLC), DR variations, and gantry rotational speed dynamics. Volumetric modulated arc therapy is technically feasible for treatment of anal cancer because of its ability to spare organs at risk.[13] This technique combines the advantages of conventional 3D-CRT with rapid delivery and a low number of monitor units, in addition to the advantages of IMRT that include conformal dose distribution and reduced dose to OAR.[5,19]

Retrospective studies that compared IMRT versus 3D-CRT reported more dose conformality and less dose to surrounding normal tissues (small bowel, bladder, external genitalia, and femoral heads) with IMRT, which led to increased treatment compliance, reductions in toxicities, acute and chronic morbidities, treatment breaks and interruptions.[4,11,20-23] The superiority of IMRT has been reported with significantly higher OS,

PFS, and LC.[9] Application of IMRT plans with SIB allows for reduction of treatment planning time, which has a positive effect on tumor control and limits tumor repair and repopulation.[5-11]

Tozzi et al. conducted a retrospective comparison between VMAT and 3D-CRT. They reported an equal effect between the two treatment arms with a 5-year disease specific survival (DSS) of 85.7% for VMAT versus 81.2% for 3D-CRT. Volumetric modulated arc therapy had an LC of 78.1% compared to 82.1% for 3D-CRT. However, there were reduced numbers of acute toxicities in the VMAT arm, from 89% to 68% for grades 2-3 GI toxicities, 39% to 33% for GU toxicities, and 82% to 75% for skin toxicities. A reduction in late toxicities was also reported.[24]

In this cohort study, all patients received SIB-VMAT radiotherapy at a dose of 45 Gy/25 fractions to the tumor PTV, LNs PTV, and high-risk LNs. A total of 63.7% of patients received a dose of 59.4 Gy/33 fractions to the primary tumor PTV and grossly enlarged LNs. A radiotherapy treatment break of 3 days was experienced in 18% of our cases, which was slightly more than reported by Franco et al. (10%) in a study that used combined treatment with VMAT.[25] In contrast, this finding was lower than the 35% reported break times by Kachnic et al. and 41.5% reported by Salama et al. in patients treated with IMRT and chemotherapy.[11,26]

The overall radiation treatment time in our report was 45 days (range: 34-56 days). Patients in a study by Franco et al. used MRI with SIB. Their overall radiation treatment time was 44 days (range: 37- 59 days), which was comparable to our findings.[27] Prolonged radiotherapy delivery time has been proven to negatively impact treatment outcome. Graf et al.[28] reported that patients with an overall treatment time of greater than 41 days had a 5-year LC of 58% versus 79% when the overall treatment time was less than 41 days (P=0.04).

In the current study, skin toxicity was the most common adverse effect. There were 46% of patients who experienced grade 2 toxic reactions and 27% of patients had grade 3 skin toxicities. A study that used VMAT reported grade 2 skin toxicity in 67% of patients and grade 3 in 18%. There were 62% of patients with grade 2 GI toxicities and 5% had grade 3 GU. A total of 16% of patients had grade 2 GU toxicities and 2% had grade 3.[25] In this study, there were 45% of patients with grade 2 GI and 27% with grade 2 GU toxicities. Grade 3 GI were recorded in two (27%) patients and there was no grade 3 GU toxicity reported.

In terms of hematological toxicities, we observed that 18% of patients had grade 2 acute toxicities for anemia, 27% had neutropenia and thrombocytopenia, and 9% of patients had grade 3 neutropenia. In comparison to Franco et al, grade 2 toxicities were reported in 28% for anemia, 18% for neutropenia, and 8% for thrombocytopenia. Grade 3 toxicities were see in 28% for anemia, 18% for neutropenia, and 11% for thrombocytopenia. There were grade 4 toxicities of anemia (8%), neutropenia (13%), and thrombocytopenia (2%).[25] In the aforementioned study, patients received the MMC plus 5-FU chemotherapy regimen.

In our patients, 10/11 patients (91%) had CR. The 3-years OS was 71% and DFS was 75%. Tozzi et al. reported 2-years DSS of 85.7% and LC of 86.3%,[24] whereas Franco et al. reported a 3-year OS of 67.7%, DFS of 55.8%, and LC of 74.1%, which was lower than our report. However, the authors in the previous study focused on locally advanced (T3, T4) or node positive cases.[27] In another study by the same author, no selection of cases was performed as with our series. The results were 85.2% for 3-year OS and 75.1% for DFS. In the aforementioned study, one-year OS and DFS were 100% for each,[25] which was higher than the current study. This could be attributed to the presence of a case with early development of metastatic disease after completion of radiotherapy. This case might not have been correctly staged as metastatic disease at the initial assessment.

The most commonly used regimen in squamous cell carcinoma of the anal canal is concurrent 5-FU and MMC with radiotherapy.

This treatment regimen has a 5-year survival rate of approximately 89%.[6]

A few retrospective studies have assessed capecitabine versus 5-FU; no prospective comparative studies have been performed to detect the efficacy of capecitabine versus 5-FU in stages I to III anal canal squamous cell carcinoma. Several studies reported the safety and efficacy of capecitabine with MMC.[7,29-31]

A meta-analysis review of the use of capecitabine in localized anal canal carcinoma showed an overall CR rate of 91% (87%–95%), which was evaluated at different times (1 to 6 months).[32] There was no difference detected in survival and response in a comparison of capecitabine with 5-FU. Meulendijks et al. recorded comparable results in term of 3-year CR, 3-year LC, and 3-year OS in patients who received 5-FU vs. capecitabine (89.1% vs. 89.7%, 76% vs. 79% and 78% vs. 86%), respectively.[29]

In addition there were less toxicities reported with capecitabine compared to 5-FU with more tolerance and statistically significant reduction in treatment breaks due to hematological toxicities.[30-32] In the current study, patients received two daily doses of capecitabine (825 mg/m^2) with radiotherapy plus MMC (12 mg/m^2) on days 1 and 19. This was the most accepted and practical regimen in our institution to overcome the need for 5-FU infusions. One patient experienced a dose reduction due to poor performance. Another patient received only one cycle. These data were acceptable and comparable to the percentage of dose reductions mentioned in studies that used the same regimens for anal carcinoma. Thind et al. reported that approximately 20% of patients experienced dose reductions of capecitabine due to toxicities.[31]

We noticed a contrast to other studies in terms of gender distribution. The current study had a male to female ratio of 2.6:1; males comprised 73% of cases. Reports of most of series found high incidences of anal carcinoma in female patients.[9,24,25,27,29,31]

Limitations of our study included the small number of cases, which did not allow us to perform multivariable analysis. In general, the incidence of anal cancer is low in Islamic countries and attributed to the low prevalence of HIV and HPV in these countries, in addition to Islamic prohibition of extramarital and abnormal sexual relations.[33-35] Anal canal cancer is a rare cancer in Saudi Arabia. In 2010, 27 cases were diagnosed in Saudi Arabia, 18 males and nine females, which represented 0.3% of all cancer cases diagnosed in the Saudi population.[36]

Conclusion

The use of VMAT-SIB combined with MMC and capecitabine chemotherapy is safe and effective, even in the absence of comparative results. More studies are needed to compare between different regimens. A longer follow-up is mandatory to determine the best treatment to avoid long-term side effects.

Acknowledgments

We are grateful to all our colleagues for their help and advice.

Compliance with Ethical Standards

All procedures in this study were conducted in accordance with the ethical standards of our institution and the Declaration of Helsinki, 1964.

Conflict of Interest

None declared.

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