Original Article

Outcomes of patients with anal cancer treated with volumetric-modulated arc therapy or intensity-modulated radiotherapy and concurrent chemotherapy

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ABSTRACT

Aims: To evaluate the results of chemoradiation with intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT) for the treatment of anal canal cancer patients at three institutions that had advanced devices.

Materials and Methods: A retrospective analysis was performed for patients treated with 5-fluorouracil and mitomycin-based chemotherapy and IMRT or VMAT for anal cancer from 2011 to 2013. Complete response (CR) rates, colostomy-free survival (CFS), disease-free survival (DFS), overall survival (OS), and toxicities were investigated. Toxicities were evaluated with the Common Terminology Criteria for Adverse Events, Version 3.0.

Results: Fifteen patients were included in the analysis. The majority of patients had T2 (53.3%) and N0 (40%) disease according to the staging system that was developed by the American Joint Committee on Cancer. CR was observed in 14 patients (93%), and the median follow-up was 26 months (13–42 months). The 3-year CFS, DFS, and OS were 86%, 86%, and 88%, respectively. Acute Grade 3 toxicities were observed as 6% of hematological, 26% of gastrointestinal, and 26% of dermatological.

Conclusion: Early results confirm that IMRT or VMAT for anal cancer treatment reduces acute toxicities while maintaining high control rates.

KEY WORDS: Anal cancer, chemoradiotherapy, intensity-modulated radiation therapy, volumetric-modulated arc therapy

INTRODUCTION

Squamous cell carcinoma of the anal canal was treated with extensive surgery with unsatisfactory outcomes until Nigro *et al*.'s report at 1974.[1] Complete response (CR) was seen at two of three patients who underwent surgery after preoperative radiochemotherapy. Third patient refused surgery and was doing well without recurrence 13 months later. These findings pointed to the improvements of treatment, more curable, and less toxic. Randomized Phase III trials confirmed superiority of definitive radiochemotherapy compared with other treatment schedules.[2,3] After Radiation Therapy Oncology Group (RTOG)/Eastern Cooperative Oncology Group (ECOG) Intergroup Trial, definitive radiotherapy and mitomycin with 5-fluorouracil (5-FU)-based chemotherapy had been the most common treatment approach for anal cancer.[4] The overall survival (OS) rates ranged from 56% to 76% and colostomy-free survival (CFS) was 70% for 5 years.[2-5] Although the majority of anal canal cancer patients were cured with radiochemotherapy, the incidence of acute and late adverse effects of treatment was considerable.

Most prospective randomized trials assessed effectiveness of different chemotherapy schedules with similar radiotherapy techniques which large nonconformal fields or three-dimensional (3-D)

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conformal fields were used. In RTOG 98-11 trial, major acute Grade 3 or higher toxicities were skin reactions (49%), hematologic effects (61%), and gastrointestinal toxicities (37%).[5] Major late Grade 3 or higher toxicities were skin reactions (3%) and gastrointestinal problems (3%). Intensity-modulated radiation therapy (IMRT) was not allowed due to the trial protocol. IMRT provides dosimetric advantages by optimally manipulating the intensities of individual beams within each field. Normal structures that are in proximity can be protected without decrease at the target organ dose. As a result of tightly modulating dose, reduced toxicity rates are reported without compromising outcomes. Anal canal radiotherapy comprises large treatment volume including elective regional nodes and skin in the gluteal fold. IMRT gives opportunity for organ protection such as small bowel, skin, and bladder. A phase II trial RTOG 0529 reported control and toxicity rates of IMRT usage in anal cancer at 2012.[6] The 2-year locoregional control rate was 80%. As expected, early gastrointestinal and skin toxicities were decreased.[7] Hence, IMRT causes reduction of adverse effects, improves quality of life, and also leads to reductions in unplanned treatment breaks which might improve local control. Volumetric-modulated arc therapy (VMAT) is an IMRT technique presented at 2001. VMAT gives the opportunity of radiation delivery by rotating the gantry of a linac through one or more arcs with the radiation continuously on. Eventually, VMAT can generate highly conformal dose distributions in a faster time.

Herein, we present the outcome of 15 anal cancer patients treated with IMRT or VMAT schedule. In addition, we undertook a selective brief literature review on clinical studies for the treatment of patients with anal cancer.

MATERIALS AND METHODS

Patients

This multicenter retrospective study was conducted on anal canal cancer patients treated with definitive Radiotherapy (RT) with or without chemotherapy from November 2011 to November 2013 in three institutions. Inclusion criteria were as follows: Histologically confirmed squamous cell carcinoma and ECOG performance status ≤2. Patients with distant metastasis were excluded. All patients provided informed consent before study entry. A total of 15 patients (11 females, 4 males) were identified. Medical records of the patients fulfilling eligibility criteria were reviewed using a standardized data sheet.

Acute treatment-related toxicities were assessed due to the Common Terminology Criteria for Adverse Events, version 3.0 as well as CR, CFS, disease-free survival (DFS), and OS. All patients were evaluated with physical examination bimonthly after treatment was completed for the first 6 months and every 3 months for the first 2 years and then biannually for years 3 through 5. The CR was defined as no metabolic activity at positron emission tomography-computed tomography (PET-CT) and no radiographic or clinic presence of residual tumor with sigmoidoscopy or proctoscopy during the first 6 months' evaluation. Laboratory work, flexible sigmoidoscopy or proctoscopy, magnetic resonance imaging scan of the abdomen, PET-CT, and other imaging studies were performed by doctors' discretion during follow-ups.

Radiotherapy

Planning-CT in the supine position with intravenous contrast agents were acquired with 2-mm slice thickness. PET-CT co-registration was used for tumor and involved lymph nodes delineation. Gross tumor volume (GTV) was defined as macroscopic disease for primary and lymph nodes. Elective node regions including mesorectum, inguinal, iliac, obturator, and presacral lymph nodes were delineated as clinical target volumes (CTVs). The high-risk CTV (CTV1) was the nodal regions below the bottom of sacroiliac joints. The low-risk CTV (CTV2) included distal common iliacs superior of the same plane. The GTVs were expanded by 2 cm and the CTV1 and CTV2 by 1 cm for the planning target volume 1 (PTV1). The second PTV (PTV2) contained a margin of 2 cm from GTVs and 1 cm from CTV1. The boost PTV (PTVboost) contained 1 cm margin from GTVs. All normal structures were contoured also. IMRT and VMAT plannings were performed with the schedule of two phases at Eclipse treatment planning (Varian Medical Systems, Palo Alto, CA, USA). At first phase, 37.5 Gy to PTV1 and 45 Gy to PTV2 in 25 fractions were prescribed with simultaneous integrated boost technique. Patients boosted with a second phase to the dose due to their T and N stage. Patients with T2 were irradiated to a total dose of 54 Gy in 5 fractions prescribed for PTVboost. In patients with T3–T4 tumors, the boost was increased to a total dose of 59 Gy in 7 fractions. Involved nodes <5 cm received 54 Gy and nodes >5 cm received 59 Gy. For treatment planning, the dose was normalized to the mean dose in PTVs. For intensity optimization, the prescribed dose encompassed at least 95% of the PTV. In addition, no >2% of any PTV received >110% of its prescribed dose, whereas no >1% of any PTV received <93% of the prescribed dose. Irradiation was delivered with 4–7 coplanar beam angles by a 6-MV dynamic MLC system (Varian Medical Systems, Palo Alto, CA, USA) using a sliding window technique or using VMAT.

Chemotherapy

Systemic therapy preferably consisted of concomitant 5-FU at day 1–5 (750 mg/m^2/day) and mitomycin C at day 1 (10 mg/m^2) in weeks 1 and 5 (n = 9). Four patients did not receive any systemic therapy due to age (>75 years).

Statistical analyses

Statistical analyses were performed using Statistical Package for the Social Sciences software (SPSS, ver. 16, SPSS Inc., Chicago, IL, USA). DFS and OS rates were calculated using Kaplan–Meier estimates. The OS rates were calculated from the date of pathological diagnosis to death or the date of the last follow-up visit for patients who were still alive. The DFS rates were estimated from the date of pathological diagnosis to the

time of any documented disease after radiotherapy or to the date of the last follow-up visit for those remaining disease free.

RESULTS

Patient characteristics

Table 1 shows the patient characteristics. The median age of the patients was 58 years (range 41–85 years). Majority of the patients had T2 (n = 8, 53.3%) and N0 (n = 6, 40%) disease. Full-course radiotherapy was completed by all of patients. The median radiation dose prescribed to the target volume was 59 Gy (range, 54–61 Gy). Only one patient had a treatment break >3 days.

Toxicity

Table 2 shows the major treatment-related acute toxicities. The most common Grade 3 toxicities were symptomatic moist desquamation and gastrointestinal toxicity (emesis, nausea, and diarrhea). Grade 3 neutropenia was occurred in one patient and no Grade 4 acute reaction was observed.

Response

CR was reported at 14 patients during the first 3 months after treatment was completed. CRs were proved by biopsy at 90% of the patients. One elderly patient, who treated with radiotherapy only, had partial response and then liver metastasis was observed.

Survival

Median duration of follow-up was 26 months (13–42 months). At the time of the analysis, 14 patients (93%) were alive without disease. One patient recurred locally at the 14th month and had salvage surgery with abdominoperineal resection. The patient with partial response was died as a result of liver metastasis. Overall, two patients (13.3%) who were treated only with radiotherapy developed recurrence during the follow-up period. Three-year CFS and DFS rates were both 86% and OS rate was 88%.

Table 1: Patients and tumour characteristics

Variable	*n* (%)
Age	
Median 58 years (41-85 years)	15 (100)
Gender	
Female	11 (73)
Male	4 (27)
Stage	
II	5 (33.3)
IIIA	5 (33.3)
IIIB	5 (33.3)
Primary Tumour	
T2	8 (53)
T3	4 (27)
T4	3 (20)
Lymph Nodes	
N0	6 (40)
N1	4 (27)
N2	5 (33)
Chemotherapy	
Yes	11 (73)
No	4 (27)
Radiotherapy Dose	
54 Gy	7 (47)
59 Gy	7 (47)
61 Gy	1 (6)
Radiotherapy Tecnique	
Dynamic IMRT	7 (47)
Volumetric Arc	8 (53)

DISCUSSION

It is estimated anal canal cancer will continue to rise 2% annually and majority of patients will be diagnosed with locally advanced disease. Definitive chemoradiotherapy approach gives the opportunity for sphincter preservation since Nigro *et al*.'s study.[1] Later, nonrandomized studies provided support for nonsurgical treatments.[8-10] Trials comparing radiotherapy and chemoradiotherapy demonstrated that chemoradiation significantly improved locoregional control and CFS.[2,3,11] A Phase III trial from EORTC and Randomized Anal Cancer Trial (ACT) I study from The United Kingdom Coordinating Committee on Cancer Research were reported better local control rates with chemoradiotherapy including 5-FU and mitomycin.[2,3] Recently, long-term results from ACT I trial were published showing a clear benefit of chemoradiotherapy on local control and also OS after 13 years of median follow-up time.[12]

Consequently, trials were aimed to show the efficacy of different chemotherapy schedules concurrently with similar radiotherapy techniques and doses.[4,5,13,14] The largest trial including 940 patients was designed to determine more effective chemotherapy schedule and duration in the UK ACT II.[13] Progression-free survival rates of up to 74% at 3 years and CFS rates of up to 75% were reported with no difference between groups. Hence, additional chemotherapy schedule showed no efficacy.

The other contemporary trial RTOG 98-11 has investigated the role of induction chemotherapy.[5] No advantage of induction therapy was observed. Further, long-term results of RTOG 98-11 trial showed that DFS and OS were significantly lower for patients receiving cisplatin compared with mitomycin.[15-17] However, one retrospective analysis suggests that induction chemotherapy may be beneficial for the subset of patients with T4 anal cancer.[18] Better CFS rates were reported. In addition, a trial assessing different chemotherapy schedule, oxaliplatin and capecitabine, reported promising preliminary results. Today, according to the randomized trials, 5-fluorouracil and mitomycin-based radiotherapy was recommended for the primary treatment in anal cancer.

Studies also investigated the effect of higher radiotherapy doses or shortening of overall treatment time. The trial of ACCORD 03 evaluated further escalation of radiotherapy dose, but no benefit was reported with the dose increase.[14] Effects of treatment interruptions on outcomes were observed in a

Table 2: Acute toxicity

Grade 3 toxicity	*n* (%)
Skin	
Radiation dermatitis	4 (27)
Gastrointestinal	
Emesis-Nausea	2 (13.3)
Diarrhoea	2 (13.3)
Neutropenia	1 (6.6)

Phase II trial, RTOG 92-08.[19] Lower locoregional control rates were considered to be the result of planned treatment break in the delivery of chemoradiotherapy. ACT II trial reported better CFS rates and was associated with the absence of treatment interruptions. However, combined treatment schedules came with the cost of significant toxicities and treatment breaks were required in up to 80% of patients.[20] Acute Grade 3 or more hematologic toxicity of 61% and nonhematologic toxicity of 74% rates were observed at ACT II trial. Effectiveness with mitomycin included chemotherapy was reported significantly better, but acute adverse effects were common, irrespective of treatment. Acute skin reactions such as anoproctitis and perineal dermatitis were reported dose dependently, at 30% of patients after doses of 25–30 Gy and at 50%–60% of patients after doses 54–60 Gy.[21] Late side effects were increased frequency and urgency of defecation, chronic perineal dermatitis, dyspareunia, and impotence. Serious late toxicity, anal ulcer or necrosis, has been reported in about 5%–15% of those receiving higher radiation doses.

Innovations in radiotherapy such as IMRT or VMAT techniques may lead to lower toxicity ratios. The early randomized trials included 3-D radiotherapy planning.[13,14] With IMRT/VMAT, dose distribution to PTV is highly conformal and dose at critical organs is minimal. The only prospective Phase II trial RTOG 0529 was assessing toxicities at anal cancer patients treated with IMRT and chemotherapy.[6] Trial showed lower toxicity ratios with IMRT, as well as it has been the guide for anal canal radiotherapy contouring techniques. Clinical outcomes data are not mature yet, but they are of great interest because of the risk of underdosing associated with IMRT.

CONCLUSION

In addition to analyzing CFS, DFS and OS, the toxicity rates of treatment that consist advanced RT techniques such as IMRT or VMAT were identified in this retrospective studies. As noted in our analysis, DFS and OS rates for 3 years were 86% and 88% comparable with that seen in ACT II and RTOG 98-11 trials for groups treated with mitomycin-based concurrent chemotherapy. Radiotherapy with dynamic IMRT and especially VMAT has more advantages, such as shorter planning and treatment time as well as benefitting the patient. Survival ratios were observed similar, but toxicities were lower and only one elderly patient had treatment break >3 days. Indeed, no Grade 4 toxicity was reported. We did not observe late reactions also. Extended follow-up will further assess the durability of these findings. Ultimately, IMRT and VMAT-based chemoradiotherapy leads to mitigation of toxicities with successful treatment results.

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Conflicts of interest

There are no conflicts of interest.

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