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CLINICAL ARTICLE

Aerobic cervical bacteriology and antibiotic sensitivity patterns in patients with advanced cervical cancer before and after radiotherapy at a national referral hospital in Uganda

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ABSTRACT

Objective: To determine prevalent aerobic cervical bacteria and sensitivity to commonly used antibiotics in patients with advanced cervical cancer before and after 4 weeks of external beam radiotherapy (EBRT). *Methods:* Cervical swabs were collected prior to the initial radiation dose and after 4 weeks of radiotherapy at Mulago Hospital. Aerobic culture was performed on blood agar, chocolate agar, and MacConkey agar, and incubated at 35–37 ° for 24–48 hours. Isolates were identified using colonial morphology, Gram staining, and biochemical analysis. Sensitivity testing was performed via Kirby–Bauer disk diffusion and dilution. Differences in the proportions of bacteria isolated before and after radiotherapy were compared. Paired *t* test was used to obtain differences in sensitivity before and after radiotherapy. *Results:* Normal flora increased significantly after EBRT ($P = 0.02$). There was no significant change in overall proportion of positive cultures. Sensitivity to commonly used antibiotics improved ($P = 0.05$) and resistance significantly decreased ($P = 0.005$). Significant differences were seen mainly with ciprofloxacin, ceftriaxone, and gentamicin. *Conclusion:* Four weeks of EBRT did not sterilize the cervix but resulted in an increase in normal flora. Radiotherapy appeared to reduce resistance to commonly used antibiotics. Sensitivity to chloramphenicol was higher than for the more commonly used antibiotics.

1. Introduction

Cervical cancer, which is the most common malignancy among women in Uganda, accounts for 40% of all cancers affecting women [1]. Uganda has one of the highest age-standardized incidence rates for cancer of the cervix (52.7 per 100 000 women) [2].

The majority (80%) of patients diagnosed with cervical cancer in Mulago Hospital, Uganda, have advanced cancer [1]. Often, they have large necrotic/ulcerative lesions associated with infection and a foul-smelling discharge. Immunosuppressive effects of cancer and radiotherapy, as well as anemia from chronic bleeding, combine to increase the risk of pelvic infections and sepsis—common causes of death in these patients [3]. Patients' endogenous cervical flora is often a source of organisms involved in the causation of abnormal discharge, pelvic infection, and sepsis [4]. Therefore, any focus of infection should be recognized and treated before and during antineoplastic therapy.

It was previously thought that radiotherapy had a sterilizing effect on cervical/vaginal flora [5]. This might have been because high doses of radiation are bactericidal in vitro. However, while some studies [6–8] have found significant increases in aerobes/aerobic spore forms, others [9–11] have found no change in frequency and composition of cervical vaginal flora. Anaerobes and fungi in patients with cervical cancer are reportedly sparse and unaffected by radiotherapy [7,8,10,11].

Changes in aerobic flora may imply a changing sensitivity profile and, therefore, affect the choice of antimicrobial treatment for cervical infection and abnormal vaginal discharge. It may also explain the persistence of abnormal discharge and the development of fever in patients undergoing radiotherapy [7].

Patients with foul-smelling vaginal discharge are routinely prescribed empirical broad-spectrum antibiotics targeting cervical flora prior to radiotherapy [12], not taking into consideration current sensitivity patterns—despite growing evidence of resistance to commonly used antibiotics [12,13].

The most commonly used antibiotics among patients with advanced cancer and foul-smelling vaginal discharge in the study setting are ciprofloxacin, ampicillin/cloxacillin, and ceftriaxone with metronidazole to provide aerobic and anaerobic coverage. Less commonly used drugs are amoxicillin and cephalosporins.

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Persistence of vaginal discharge and emergence of febrile symptoms among patients with advanced cancer of the cervix who are undergoing radiotherapy might indicate a change in flora or microbial sensitivity to the routinely used antibiotics started empirically.

The aim of the present study was to describe the pattern of aerobic bacteria and sensitivity to commonly used antibiotics. We also sought to determine the effect of radiotherapy on aerobic bacterial pattern and sensitivity.

2. Materials and methods

A prospective study with a single cohort was conducted on the gynecologic oncology ward of Mulago Hospital—a national referral hospital for Uganda and a teaching hospital for Makerere University—between February 1 and April 30, 2013. Study participants were women with confirmed advanced cervical cancer (stage IIB and above) scheduled for radiotherapy. The study was approved by the College of Health Sciences Research and Ethics Committee, Makerere University, and the Uganda National Council of Science and Technology. Written consent was obtained from each participant. An interviewer-administered questionnaire was used to collect data on patient demographics and clinical features.

Using an aseptic technique, a sterile swab stick was used to obtain a specimen from the cervical lesion. The swabs were then transported in charcoal-free Amies transport medium to the laboratory within 2 hours for analysis by a qualified laboratory technician. No swabs were collected outside routine working hours of the laboratory. The aerobic culture was performed on blood agar, chocolate agar, and MacConkey agar, and incubated at 35–37 ° for 24–48 hours. Isolates were identified via colonial morphology, Gram staining, and biochemical analysis; sensitivity testing was performed via Kirby–Bauer disk diffusion and dilution methods against nitroimidazoles, penicillins, cephalosporins, sulfonamides, aminoglycosides, quinolones/fluoroquinolones, macrolides, and tetracyclines—as specified in the *Manual of Clinical Microbiology* [14]. This procedure was carried out for all participants before they began radiotherapy and after at least 4 weeks of radiotherapy. Ten percent of the swabs were taken to 2 laboratories (medical school laboratory and MBN Diagnostic Laboratory) for quality control purposes.

Stata version 10 (StataCorp, College Station, TX, USA) was used for data analysis. Proportions of positive aerobic cultures were computed before and after radiotherapy. Statistical significance was tested via χ^2 test. Paired *t* test was applied to measure the significance of the differences in sensitivity profiles before and after radiotherapy. Significance (type II error) was set at 0.05.

3. Results

Fifty-three participants with stage IIB–IVA cervical cancer were evaluated. Mean age was 49.4 ± 4.6 years (range, 28–80 years). All patients had symptoms of vaginal discharge with or without associated fever prior to treatment. Ampicillin/cloxacillin and ceftriaxone were the drugs most commonly used empirically to target aerobes before radiotherapy (Table 1). The normal flora increased significantly after 4 weeks of radiotherapy ($P = 0.02$) (Tables 2, 3).

Resistance to the most commonly used broad-spectrum antibiotics (ampicillin, ciprofloxacin, and cephalosporins) was notably high before radiotherapy (11/25 for ciprofloxacin, 17/25 for ampicillin, and 7/25 for ceftriaxone). Several pathogens that were resistant to ciprofloxacin, ampicillin, augmentin, and cephalosporins were sensitive to chloramphenicol—a now uncommonly prescribed antibiotic. After 4 weeks of external beam radiation therapy (EBRT), sensitivity to commonly used antibiotics improved ($P = 0.05$; paired *t* test), while resistance significantly decreased ($P = 0.005$; paired *t* test). Significant differences were seen with ciprofloxacin, ceftriaxone, and gentamicin (Table 4). Subanalysis of cultures by HIV serostatus did not show any significant findings for all flora, normal flora, or pathogens (Table 5).

Table 1
Sociodemographic and clinical characteristics (n = 53).[a]

Characteristic	Value
Marital status	
Single	2 (4)
Married	27 (51)
Cohabiting	4 (8)
Divorced	9 (17)
Separated	4 (8)
Widowed	7 (13)
Clinical stage of disease	
IIB	15 (28)
IIIA	15 (28)
IIIB	19 (36)
IVA	4 (8)
Age, y	49.4 ± 4.6 (28–80)
25–34	4 (8)
35–44	12 (23)
45–54	21 (40)
55–64	9 (17)
65–74	4 (8)
75–84	3 (6)
History of vaginal discharge or fever prior to radiotherapy	
Discharge	53 (100)
Fever	3 (6)
Patients who had received at least 1 antibiotic prior to evaluation	
Ampicillin/cloxacillin	11 (21)
Ceftriaxone	11 (21)
Ciprofloxacin	6 (11)
Metronidazole	23 (44)
Amoxicillin	1 (2)
HIV serostatus	
Positive	10 (19)
Negative	43 (81)

[a] Values are given as number (percentage) or mean ± SD.

4. Discussion

In the present study, the proportion of normal flora increased significantly after 4 weeks of EBRT. This could be attributed to reduction of necrotic tissue on the cervix. Minimization of necrotic tissue followed by tissue repair and repopulation with growing cells improves blood and oxygen supply, as well as immune cell access, and therefore pathogenic bacteria are eliminated.

Studies have shown that radiation modifies immunity in human papillomavirus (HPV)-associated head and neck cancer and that radiation-induced loss of cell surface CD47 enhances immune-mediated clearance of HPV-positive cancer. It also promotes tumor-specific effector CD8 + T cells via dendritic cell activation, and the efficacy of high-dose radiotherapy depends on the presence of CD8 + cells. Infiltration with Langerhans cells in cancer tissues improves local response to radiation treatment partly by T-cell-mediated antitumor activity [15,16].

Table 2
Proportions of isolates before and after radiotherapy (n = 53).

		Positive culture after radiotherapy			*P* value
		Yes	No	Total	
All flora					0.35
Positive culture before radiotherapy	Yes	20	10	30	
	No	18	5	23	
	Total	38	15	53	
Normal flora					0.02
Positive culture before radiotherapy	Yes	7	10	17	
	No	22	14	36	
	Total	29	24	53	
Pathogens					0.4
Positive culture before radiotherapy	Yes	13	5	18	
	No	9	26	35	
	Total	22	31	53	

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