

Cervical Cancer Treatment in HIV-Positive Patients: A Survey of Treatment Practices in India

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PURPOSE Chemoradiation remains a challenge in women living with HIV (WLWH) and cervical cancer primarily because of concerns regarding immune status. With limited literature available to help guide the management of these patients, clinical practices among oncologists are variable across India. Hence, we conducted a survey among radiation oncologists in India to assess the patterns of current practices of treating cervical cancer with chemoradiation in WLWH.

MATERIALS AND METHODS A questionnaire consisting of 12 questions related to the treatment of cervical cancer in WLWH was distributed to radiation oncologists at two national conferences in India.

RESULTS The questionnaire was distributed to 105 radiation oncologists, and 90 (85.7%) responses were received. 95.5% of respondents reported that patients with advanced cervical cancer constituted the majority of their practice. Chemoradiation was reported as the most common modality of planned treatment. Ninety-four percentage of respondents reported that they referred patients to an antiretroviral therapy clinic before starting definitive treatment. The majority of respondents (68%) do not plan for concurrent chemotherapy if CD4 counts were < 200 cells/mm³. As many as 50% of respondents reported that they would only start antiretroviral therapy when CD4 counts drop. Poor social support (37.6%), concurrent infections during treatment (28.2%), acute toxicities (21.2%), and poor nutrition (13%) were cited as the most common reasons for treatment interruption in cervical cancer patients with HIV.

CONCLUSION This survey highlights the prevalent inconsistencies in treatment protocols employed by radiation oncologists in India for the management of locally advanced cervical cancer in WLWH. It also reflects the need for social and nutritional support to help improve compliance and thereby improve outcomes in these patients.

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INTRODUCTION

Cervical cancer is the second most common form of cancer among women in developing countries and the leading cause of cancer-related mortality.¹ According to GLOBOCAN 2018 estimates, the incidence of cervical cancer in India in 2018 was 96,922 and the prevalence was 2,25,689.² Cervical cancer incidence has been reported to be six times higher in HIV-positive women than in HIV-negative women.³ In the developing countries, women living with HIV (WLWH) and cervical cancer typically present at a younger age and have advanced-stage cervical cancer at the time of presentation.⁴⁻⁶

Concurrent chemoradiation is the standard of care for cervical cancer in patients with stage IB2-IVA disease, on the basis of the International Federation of Gynaecology and Obstetrics staging system.⁷ Multiple randomized controlled trials (RCTs) and a Cochrane

database review of 19 RCTs have shown improved survival in patients with locally advanced cervical cancer (LACC) treated with concurrent chemoradiation with acceptable toxicities.⁸ Also, a recent phase III RCT demonstrated superiority of chemoradiation treatment specifically in stage IIIB disease.⁹ In WLWH and cervical cancer, implementation of a full course of chemoradiation treatment remains a challenge primarily because of concerns about immune status. HIV infection may cause the destruction of CD4 lymphocytes, which in turn suppresses immunity and leads to the occurrence of opportunistic infections.¹⁰

With the advent of antiretroviral therapy (ART), there has been considerable improvement in the immune status of WLWH.¹¹ Several case studies have suggested that chemoradiation in these patients is tolerable, whereas other studies suggest that chemoradiation may be associated with increased

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

To understand the pattern of current practices among radiation oncologists in treating cervical cancer in women living with HIV. This is the only survey assessing the attitude and knowledge among radiation oncologists for the treatment of these patients.

Knowledge Generated

In this survey, although a majority of respondents preferred to plan for chemoradiation in women living with HIV with good performance status presenting with locally advanced cervical cancer, few respondents still preferred planning radiotherapy alone. Two third of the respondents reported omitting concurrent chemotherapy if the CD4 cell counts were < 200 cells/mm³, whereas one third preferred to modify radiotherapy schedule as well. Surprisingly, half of the respondents believed in starting antiretroviral therapy only after CD4 counts drop.

Relevance

The findings of the survey will help in drawing attention to this patient population and facilitate learning among oncologists regarding optimal management in these patients.

toxicities, especially hematologic and GI toxicities, in HIV-positive women.^{6,12-14} Many ART agents are also known to have interactions with chemotherapeutic agents, since both are metabolized by a similar cytochrome p450 enzyme pathway.¹² Additionally, these patients may have poor compliance to treatment owing to poor nutritional status and a lack of social support.¹⁵

There is a paucity of data regarding the outcomes, compliance, and toxicity associated with the treatment of cervical cancer in WLWH, especially in India. With scarce evidence available for the management of these patients, clinical practices and treatment strategies used by radiation oncologists in India remain variable across the country and possibly worldwide. Therefore, we conducted a survey of radiation oncologists from across India with the aim of assessing current practices used to treat cervical cancer in WLWH. Taking into consideration the fact that WLWH with cervical cancer in developing countries commonly present with locally advanced stage where the primary modality of therapy is radiation, our survey was aimed at radiation oncologists in India.

MATERIALS AND METHODS

We developed a questionnaire to assess the practice of using radiation to treat cervical cancer in WLWH. The questionnaire consisted of 12 questions pertaining to the treatment of cervical cancer in WLWH and was distributed to radiation oncologists attending the annual conferences of the Association of Radiation Oncologists of India and the Indian Brachytherapy Society held in 2018, where large attendance by radiation oncologists was expected. The survey was approved by the institutional ethics committee. We collected information about each respondent's specialty and experience in treating cervical cancer, especially in WLWH. The survey was focused on the treatment practices of these radiation oncologists for WLWH with cervical cancer. The survey included questions regarding

baseline CD4 counts and HIV viral load before the treatment of WLWH with cervical cancer. The responders were asked about the timing of referral to an ART clinic. We also collected information regarding the treatment compliance of patients and the reasons for dropouts. The questionnaire is included in the Data Supplement. Data were entered and analyzed using software package SPSS version 23. Descriptive statistics were used to analyze the quantitative data from the survey.

RESULTS

Demographics

Of the 105 radiation oncologists who were given our survey, 90 (85.7%) provided their responses to our questions. Demographic information for the respondents is listed in [Table 1](#).

Of the 90 respondents, 69 (76.6%) reported that they treat more than 50 patients with cervical cancer annually and 33 (36.7%) reported that they were treating at least 10 WLWH with cervical cancer. Approximately 10% of the radiation oncologists who treat more than 100 patients with cervical cancer annually reported that they treat < 5 WLWH with cervical cancer annually. Eighty-six (95.5%) respondents reported that patients with advanced cancer constituted the majority of their practice.

Treatment Strategies

The treatment plans reported by the respondents are shown in [Table 2](#). The most common modality of treatment plan was reported to be chemoradiation (92.2%), followed by radiation alone (6.7%). Eighty-five (94.4%) radiation oncologists reported that they always refer patients to the ART clinic before starting the definitive treatment. Seventy-five (83.3%) radiation oncologists believed that CD4 lymphocyte count and HIV viral load should always be checked before commencing cancer-directed therapy. The majority of respondents (68%) did not plan for concurrent

TABLE 1. Demographic Information for Respondents

Characteristic	Percentage
No. of patients with cervical cancer seen in clinic annually	
> 100	43.3
51-100	33.3
25-50	13.4
< 25	10
No. of HIV-positive patients with cervical cancer seen in clinic annually	
> 25	13.3
11-25	23.3
5-10	25.6
< 5	37.8
Most common FIGO stage of HIV-positive patients with cervical cancer seen in clinic	
I-IIA	4.4
IIB-IIIB	92.2
IV	3.3

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

chemotherapy if the CD4 count is < 200 cells/mm³, whereas 33% reported that they would alter the radiotherapy schedule for the same. Forty-five respondents

TABLE 2. Treatment Plans for HIV-Positive Patients With Cervical Cancer by the Responding Radiation Oncologists

Characteristic	No. (%)
Treatment of choice in HIV-positive patients with LACC with good performance status	
Concurrent chemoradiation	83 (92.2)
Radical radiotherapy alone	6 (6.7)
Surgery with or without adjuvant radiotherapy	1 (1.1)
Palliative radiotherapy	0 (0)
Is the radiotherapy schedule altered when CD4 counts are < 200 cells/mm ³ ?	
Yes	19 (21.1)
No	60 (66.7)
Sometimes	11 (12.2)
Is chemotherapy planned when CD4 counts are < 200 cells/mm ³ ?	
Yes	29 (32.2)
No	61 (67.8)
When do HIV-positive patients with cervical cancer receive ART at their institution?	
CD4 counts < 500 cells/mm ³	11 (12.2)
CD4 counts < 350 cells/mm ³	18 (20)
CD4 counts < 200 cells/mm ³	16 (17.8)
All patients with HIV infection with any CD4 count	39 (43.3)
Missing data	6 (6.7)

Abbreviations: ART, antiretroviral therapy; LACC, locally advanced cervical cancer.

(50%) believed that ART should be initiated only when CD4 counts drop.

Treatment Compliance

Twenty-four (26.7%) respondents reported that up to three fourths of their cervical cancer patients with HIV do not complete the planned treatment. Poor social support (37.6%), concurrent infections during treatment (28.2%), acute toxicities (21.1%), and poor nutrition (12.9%) were cited as the most common reasons for treatment interruption in these patients (Fig 1).

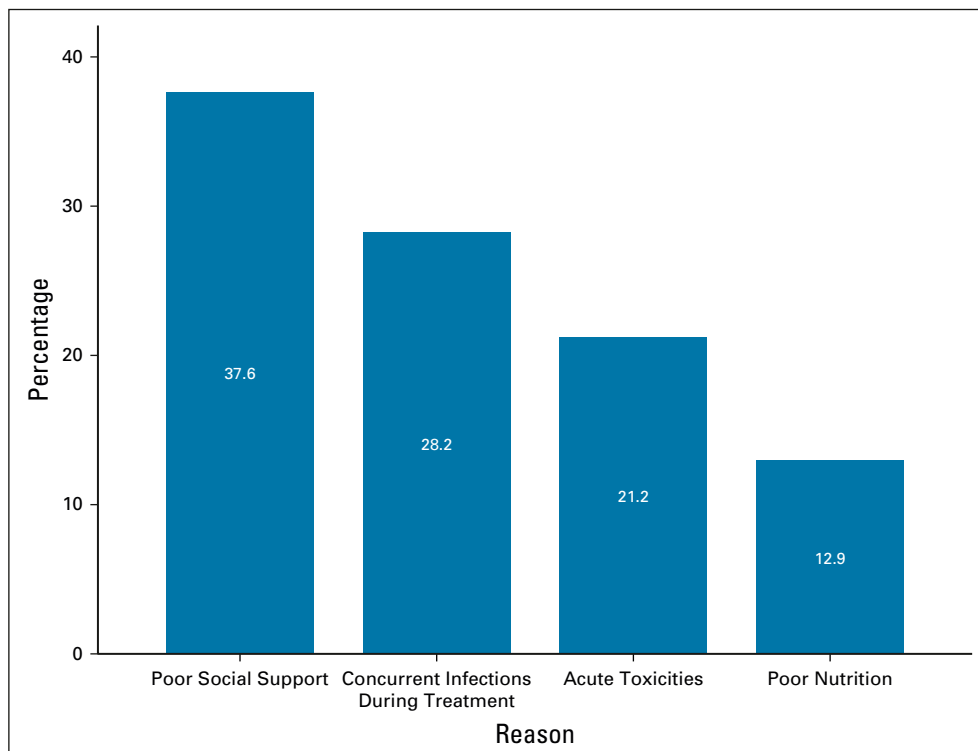
DISCUSSION

There is limited literature regarding the optimal management of cervical cancer in WLWH. Although chemoradiation remains the standard of care for patients with LACC, there is a lack of robust evidence regarding the optimal management of WLWH with LACC considering the fact that this patient population has been historically excluded from the majority of large-scale clinical trials. Therefore, our survey was conducted to assess the treatment strategies used by radiation oncologists across the country in WLWH with LACC.

In the current survey, 86 (95.5%) respondents indicated that the majority of WLWH with cervical cancer had locally advanced-stage disease. This is consistent with other studies from low- and middle-income countries where these patients usually present with advanced disease because of a lack of access to screening and a decreased chance for early diagnosis.⁵ It is worth noting that a large majority of respondents preferred to use chemoradiation to treat for WLWH with LACC with good performance status reflecting their unbiased attitude in treating these patients for optimal outcome. It has been reported in recent studies that women with well-managed HIV infection on ART show equivalent survival and toxicity profile as HIV-uninfected patients when treated with radiation with concurrent cisplatin.^{6,16} A recent study by Grover et al¹⁷ also observed that the initiation of curative chemoradiation in patients with cervical cancer was not predicted by HIV status. Hence, the management of cervical cancer in HIV-positive patients may not differ dramatically from HIV-negative patients if they are immunocompetent, which can be achieved by current HIV/AIDS treatment strategies. However, 7% of respondents still preferred to plan for radiation alone in their patients. This reflects the pressing need for continuing medical education, addressing this topic to facilitate learning and improve knowledge among oncologists for better patient care.

The CD4 cell count was cited as an important parameter for deciding on both radiotherapy schedule and concurrent chemotherapy. The risk for opportunistic infections increases as CD4 cell counts drop to < 200 cells/mm³.⁴ Sixty-one respondents reported omitting concurrent chemotherapy if the CD4 cell counts were < 200 cells/mm³. Surprisingly, one third of respondents preferred to modify

FIG 1. Reasons for treatment interruption.



the radiotherapy schedule as well in patients with lower CD4 cell counts, probably because of concerns about treatment compliance. Furthermore, previous studies have shown that patients on ART are more likely to tolerate chemoradiation.^{14,16} Hence, the management of these patients essentially involves coordination among oncologists and HIV physicians.

In our survey, 17% of respondents did not routinely check CD4 cell counts or HIV viral loads before initiating cervical cancer-directed therapy. This suggests that one of five respondents was not well-informed regarding management algorithms or clinically acceptable workflow for simultaneous management of HIV and cervical cancer in their patient population. For inexplicable reasons, 6% of respondents do not routinely refer patients to ART clinics before starting treatment. It is particularly concerning that as many as 50% of respondents believed that ART should be started only after CD4 counts drop, even when current guidelines recommend the initiation of ART regardless of CD4 cell counts in patients with HIV.¹⁸ This clearly highlights the gaps in knowledge among oncologists in India regarding HIV management in patients with cervical cancer and an urgent unmet need for more uniform guidelines.

According to reports by Simonds et al from South Africa and by Grover et al from Botswana, treatment completion was an independent factor used to predict disease control.^{5,6} In the current survey, we found that compliance to radiotherapy was reported to be low because of multiple factors, including poor social support, toxicities, concurrent infections, and nutrition. More than one third of the

respondents cited poor social support as the major hurdle for treatment completion. Unfortunately, both social stigma and discrimination remain associated with HIV in India, hampering patient access to optimal treatment. Taken together, these findings show that good psychosocial support is of paramount importance for these patients during their treatment.

It is believed that WLWH treated with chemoradiation for cervical cancer are at higher risk for grade 3 or 4 hematologic and GI toxicities, as reported by Shrivastava et al.¹³ Twenty-one percentage of respondents also cited acute toxicities as the reason for poor compliance to treatment. However, it has also been suggested that toxicities may not differ much if patients are well-managed for HIV in the modern post-ART era, as reported in a recent study.¹⁶ Concurrent infections during treatment have also been mentioned as one of the reasons for treatment incompleteness. Neutropenia leading to sepsis in these groups of patients could possibly lead to treatment interruption in these groups of patients. This highlights the need of a multidisciplinary team consisting of oncologists, physician, and medical social worker for optimal management of these patients.

The current survey suffers from limitations inherent to all cross-sectional studies. Additionally, the results of this survey only represent the opinions and practices of radiation oncologists who attended the national conferences and hence reflect the current concepts and practices across India, primarily among academically inclined radiation oncologists. However, to our knowledge, this is the

first survey focused on treatment practices used by radiation oncologists for cervical cancer in WLWH in the low- and middle-income countries setting. The distribution of the handouts during the conferences among motivated oncologists ensured such a high response rate. The survey provides a useful snapshot into their knowledge and attitudes of treating these patients. Despite the above limitations, we believe that the findings of our study will help draw attention to this vulnerable patient population and will facilitate the development of recommendations and educational

opportunities focused on managing the treatment of cervical cancer patients with HIV in India.

In conclusion, this survey provides much-needed insights into inconsistencies in the treatment protocols employed by radiation oncologists in India for the management of LACC in WLWH. It also shows the need for social and nutritional support to improve compliance, to improve outcomes for these patients. Thus, further studies are needed to develop uniform guidelines for the management of HIV-infected patients with cervical cancer.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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