

PRIMARY RADIATION THERAPY FOR HEAD-AND-NECK CANCER IN THE SETTING OF HUMAN IMMUNODEFICIENCY VIRUS

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Purpose: To analyze outcomes after radiation therapy for head-and-neck cancer among a cohort of patients with human immunodeficiency virus (HIV).

Methods and Materials: The medical records of 12 patients with serologic evidence of HIV who subsequently underwent radiation therapy to a median dose of 68 Gy (range, 64–72 Gy) for newly diagnosed squamous cell carcinoma of the head and neck were reviewed. Six patients (50%) received concurrent chemotherapy. Intensity-modulated radiotherapy was used in 6 cases (50%). All patients had a Karnofsky performance status of 80 or 90. Nine patients (75%) were receiving antiretroviral therapies at the time of treatment, and the median CD4 count was 460 (range, 266–800). Toxicity was graded according to the Radiation Therapy Oncology Group / European Organization for the Treatment of Cancer toxicity criteria.

Results: The 3-year estimates of overall survival and local-regional control were 78% and 92%, respectively. Acute Grade 3+ toxicity occurred in 7 patients (58%), the most common being confluent mucositis (5 patients) and moist skin desquamation (4 patients). Two patients experienced greater than 10% weight loss, and none experienced more than 15% weight loss from baseline. Five patients (42%) experienced treatment breaks in excess of 10 cumulative days, although none required hospitalization. There were no treatment-related fatalities.

Conclusions: Radiation therapy for head-and-neck cancer seems to be relatively well tolerated among appropriately selected patients with HIV. The observed rates of toxicity were comparable to historical controls without HIV. © 2011 Elsevier Inc.

Human immunodeficiency virus, Radiotherapy, Head-and-neck cancer, Toxicity, Immunosuppression.

INTRODUCTION

Patients infected by the human immunodeficiency virus (HIV) are at significantly higher risk of developing a variety of cancers during their lifetime compared with the general population (1–3). However, recently published studies have demonstrated that since the advent of highly active antiretroviral therapy (HAART) therapy in the mid-1990s, there has been a dramatic decrease in the incidence of AIDS-defining cancer (*e.g.*, Kaposi's sarcoma, lymphoma of the central nervous system, cervical cancer), which has been paralleled by an increase in the number of patients developing non-AIDS-defining cancer (4–6). For instance, epidemiologic data are now suggesting a significantly increased incidence of head-and-neck cancer among HIV-positive patients compared with the general population (7–9). Despite these trends, information is limited as to how to optimize treatment of

head-and-neck cancer in the immunocompromised population. One current standard treatment option for head-and-neck cancer is radiation therapy; however, there has been little investigation into the effect of this therapy on HIV-infected patients. In the past, some authors have reported that this regimen is poorly tolerated, particularly for those treated by radiation therapy for anal cancer, and have recommended that modifications such as lower radiation doses and/or smaller field sizes be considered in response to the increased toxicity (10, 11). Others have suggested that CD4 count and/or the use of antiretroviral therapy may or may not be of importance in predicting toxicity (12). The purpose of this study was to analyze outcomes after radiation therapy for head-and-neck cancer among a cohort of patients with HIV and to gain a better understanding of the risks of this therapy with respect to acute and late toxicities.

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METHODS AND MATERIALS

Patients

This study was approved by the institutional review board at the University of California, Davis, School of Medicine. The medical records of 12 patients with serologic evidence of HIV who subsequently underwent definitive radiation therapy at the Department of Radiation Oncology at the University of California, Davis, Cancer Center for newly diagnosed, biopsy-proven squamous cell carcinoma of the head and neck were reviewed. Details of those patients are presented in Table 1. The median CD4 count was 460 (range, 222–800) for the entire study population and was 610 (range, 450–800) for those treated by chemoradiation therapy. Nine patients (75%) were receiving HAART at the time of treatment, the most common regimen consisting of efavirenz, zidovudine, and lamivudine, in combination. All patients had a Karnofsky performance status of 80 or 90 at the start of treatment.

Radiation therapy details

Radiation therapy was delivered using 6-MV photons with techniques available at the time of treatment. In general, the target volumes included the primary tumor site and all areas of gross disease to encompass microscopic spread and lymphatic drainage with margin. Median radiation dose was 68 Gy (range, 64–72 Gy) delivered in 2-Gy fractions. Six patients (50%) were treated using intensity-modulated radiotherapy with inclusion of the low neck in an extended field. The remaining 6 patients (50%) were treated with conventional techniques using opposed lateral fields matched to a low anterior neck field. The median elapsed time during radiation therapy was 53 days (range, 47–79 days). All patients were treated with continuous-course, once-daily radiation therapy delivered 5 days per week. Six patients (50%) received concurrent chemotherapy (4 cisplatin, 2 taxotere) with radiation therapy. A gastrostomy tube (G-tube) was placed for enteral feeding in 6 patients (50%), all of whom were treated with concurrent chemoradiation before the initiation of treatment. All 12 patients were seen and evaluated by a dentist before the first day of radiation therapy.

Endpoints and statistical analysis

All patients were seen at weekly intervals during treatment, at which time toxicity was assessed. Acute and late normal tissue effects were graded according to the Radiation Therapy Oncology Group / European Organization for the Treatment of Cancer radiation toxicity criteria (13). Acute toxicity was defined as that occurring from the commencement of radiation therapy through day 90; thereafter, toxicity was scored as a late effect. Local control was judged to have been attained if there was no evidence of tumor at the primary site based on clinical and radiographic findings at follow-up. Regional failure was recorded separately if there was evidence of a cervical or supraclavicular mass distinct from the primary site. Patients who had persistent disease, either clinically or radiographically, after treatment were referred for salvage neck dissection. Patient follow-up was reported to the date last seen in clinic or to the date of expiration. Median follow-up was 33 months (range, 9–76 months) for the entire patient population, with all events measured from the last day of radiation therapy. Actuarial estimates of overall survival and local-regional control were calculated using the Kaplan-Meier method.

RESULTS

Nine patients (75%) were currently alive at last follow-up. As illustrated in Fig. 1, the 3-year estimate of overall survival

Table 1. Clinical and disease characteristics

Characteristic	Total patients (%)
Primary site	
Tonsil	4 (33)
Larynx/hypopharynx	3 (25)
Nasopharynx	2 (17)
Base of tongue	2 (17)
Unknown primary	1 (8)
AJCC stage (2002)	
I	2 (17)
II	2 (17)
III	2 (17)
IV	6 (50)
T stage	
T0	1 (8)
T1	3 (25)
T2	3 (25)
T3	2 (17)
T4	3 (23)
N stage	
N0	6 (50)
N1	2 (17)
N2	4 (33)
Karnofsky performance status	
90–100	8 (67)
80	4 (33)

Abbreviation: AJCC = American Joint Committee on Cancer.

was 78%. Causes of death were as follows: 1 local-regional cancer progression, 1 distant metastasis to the lungs, and 1 intercurrent disease. Eleven of the 12 patients treated (92%) had a complete clinical response to treatment. The remaining patient underwent salvage neck dissection for palpable disease after concurrent chemoradiation and was found to have a 1-cm focus of malignancy in a single Level II lymph node. The 3-year estimate of local-regional control was 92%.

Acute Grade 3+ toxicity occurred in 7 patients (58%), including 1 patient who was not receiving HAART at the time of treatment. The most common Grade 3+ acute side effects were confluent mucositis (5 patients) and moist skin desquamation (4 patients), with 2 patients developing more than one Grade 3+ toxicity. An additional patient developed severe

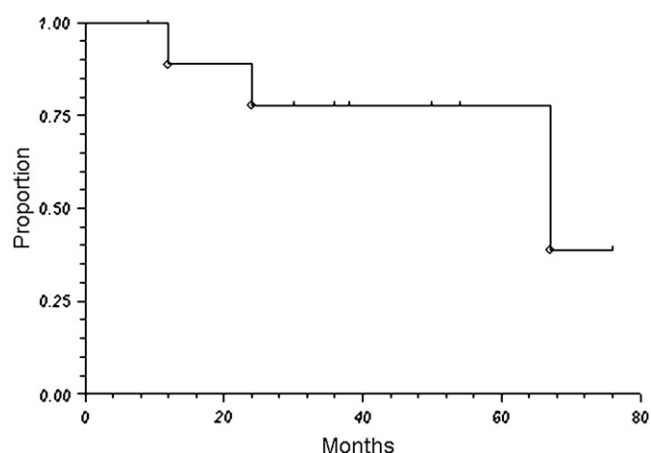


Fig. 1. Overall survival among patients with human immunodeficiency virus treated by primary radiation therapy.

arytenoid edema resulting in whispered speech midway through his course of treatment. This side effect was self-limited and resolved gradually over 3 months after completion of radiation therapy. Three patients (25%) developed oral thrush during radiation therapy, which was managed conservatively with oral nystatin. No other opportunistic infections were reported among the study population. No cases of neutropenic fever were observed.

All 11 patients completed the planned course of radiation therapy, although 5 patients (45%) experienced treatment breaks in excess of 10 cumulative days. None of the patients required hospitalization during treatment. There were no treatment-related fatalities or life-threatening events during the course of radiation therapy. The median weight loss observed over the entirety of treatment was 14 pounds (range, 0–37 pounds), which represented a 7% (range, 0–13%) reduction from baseline. Only 2 patients experienced weight loss in excess of 10% from baseline, and none experienced weight loss in excess of 15%. Figure 2 illustrates weight loss over the course of treatment for the study population.

Mild reductions in the CD4 count from the first to the last week of radiation therapy were observed, which were more prominent among those receiving concurrent chemoradiation. The median CD4 count at the completion of treatment was 355 (range, 85–673) for the entire study population. Although the median CD4 count decreased during treatment from 610 to 205 in the subset of patients treated by chemoradiation, none of the patients required hematopoietic growth factors or blood transfusions, and all experienced a gradual increase in CD4 levels after completion of radiation therapy.

With respect to late toxicity, 2 patients developed esophageal stricture, which presented as worsening dysphagia with a median onset at 4 months of completion of radiation therapy. Both of these patients were successfully treated with dilatation. None of the patients were G-tube dependent at last follow-up. There were no reported cases of neurologic complications or osteoradionecrosis.

DISCUSSION

For immunocompetent patients with reasonable performance status, radiation therapy is an established treatment option in the definitive management of head-and-neck cancer. It is uncertain, however, how this treatment affects the quality of life of patients with HIV, and the reported data on this issue are extremely limited. Although this series is a nonrandomized comparison of a single institutional experience, the results demonstrate that radiation therapy can safely and effectively be administered to patients with HIV without an excessive rate of acute or late side effects. These data are important because they alleviate concerns that toxicity may be intensified in this immunocompromised population, given the generally large areas of mucous membranes and salivary glands that are subjected to irradiation.

Few studies have examined toxicity during head-and-neck cancer irradiation among patients with HIV. The bulk of the literature reporting on outcomes among those undergoing

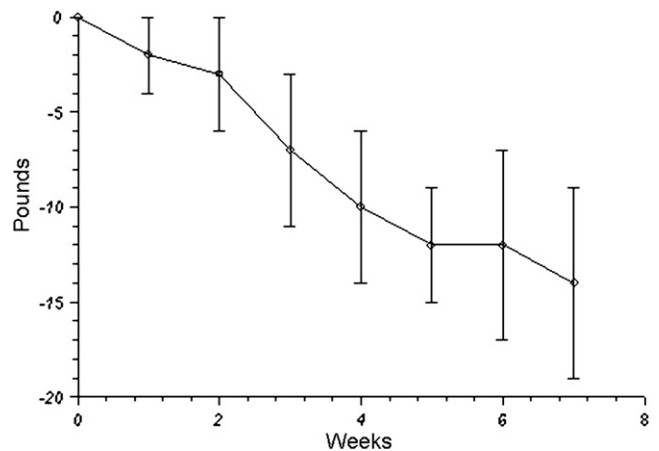


Fig. 2. Mean weight loss in pounds (with standard deviations) among patients with human immunodeficiency virus during the course of radiation therapy.

irradiation in the setting of HIV has focused on anal cancer, a disease in which organ preservation with concurrent chemoradiotherapy represents the standard of care (14–16). Kim *et al.* reported that HIV-positive patients with newly diagnosed anal carcinoma experienced more side effects and had a higher incidence of severe toxicity when treated with this approach than those without HIV infection (14). Similarly, Hoffman *et al.* found that HIV-positive patients with a CD4 count of less than 200 cells per microliter treated with organ preservation therapy for anal cancer had a significantly increased likelihood of experiencing skin, hematologic, and gastrointestinal toxicity compared with those without HIV (12). Notably, the authors identified a CD4 count of less than 200 cells per microliter as predisposing to hospitalization. Most recently, Edelman and Johnstone demonstrated that HIV-positive patients experienced a significantly increased incidence of acute Grade 3 hematologic and skin toxicity compared with HIV-negative patients (15). However, no significant difference in late toxicity was appreciated, and the CD4 count in immunodeficient patients did not seem to correlate with acute or late toxicity.

Although acute Grade 3+ toxicity was reported by 7 patients in the present series, this rate did not seem to be excessive or significantly worse than in historical control individuals without a known history of HIV treated at our institution. This could be related to the fact that 75% of the patients analyzed were receiving HAART therapy at the time of treatment or the fact that the observed median CD4 count was relatively high. It is also notable that all patients in our study underwent dental prophylaxis and G-tube placement before the initiation of therapy, both of which may have played a role in maintaining quality of life in a patient population long believed to be susceptible to enhanced toxicity.

A somewhat surprising finding was that a considerable proportion of patients missed scheduled treatment days despite the relatively well-tolerated nature of therapy. This is particularly relevant because prolonged treatment delays have been associated with adverse outcomes with respect

to local-regional control and overall survival (16). A review of medical records revealed that treatment interruptions were, however, often due to nonmedical reasons and psychosocial problems. This is consistent with our previous findings that patients with anxiety and depression, both of which are fairly common in the HIV population, are more likely to experience treatment breaks (17, 18). Given our data, in conjunction with those from others demonstrating that psychosocial impediments can pose significant barriers to treatment in the HIV-positive population, it may be reasonable to offer referral to appropriate counseling services for this particular subset of patients with head-and-neck cancer in the future (19, 20).

The results of the present study are reassuring, given the concerns that have been expressed about the effects of treatment among HIV-positive patients undergoing radiation therapy for head-and-neck cancer. For instance, it has been proposed that HIV-positive patients have an overall depletion of bone marrow reserves and therefore may be at increased risk of opportunistic infection during chemoradiotherapy, compared with those who are immunocompetent (21). Others have suggested that HIV patients may have exaggerated tissue reactions to radiation therapy. This is supported by data showing that fibroblasts obtained from HIV-positive patients demonstrate an increased sensitivity to radiation in comparison with those from HIV-negative control individuals (22).

Although our study demonstrates that chemoradiotherapy is well tolerated among HIV-positive patients with head-and-neck cancer, it is limited by the number of patients in

the analysis and by selection bias. Clearly, treatment decisions need to be made on a case-by-case basis. In particular, those who undergo definitive radiation therapy are more likely to be compliant with recommended HAART therapy as well. Thus, we urge caution in the extrapolation of our results to those who are not receiving HAART therapy. Additionally, the median CD4 count of the patients in our analysis was 460 cells per microliter, and no patients had a CD4 count below 200, the level where cellular immunity is believed to be lost. Similar to the analysis by Blazy *et al.*, our study also was limited to patients who were generally in good health, with excellent performance status, who had no prior opportunistic infections (23). Future studies could explore the potential consequences of treating patients who are in worse condition or who may have a CD4 count below 200 cells per microliter.

Despite these limitations, it was clear that HIV-positive patients tolerated primary radiation therapy for head-and-neck cancer without an excessive toxicity rate or incidence of exaggerated tissue reactions. Given the scarcity of data addressing this issue, our data provide important assurances that appropriately selected patients with HIV should be offered aggressive treatment for newly diagnosed head-and-neck cancer. This is particularly important because it is unlikely that a prospective trial will ever be performed in this patient population. Gastrostomy tube placement and dental prophylaxis are recommended to minimize treatment complications.

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