Radiation Therapy for Malignancies in the Setting of HIV Disease

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The first 15 years of the AIDS pandemic can be summarized simply by the oxymoron "constant change." The syndrome unfailingly has presented new challenges and demanded nearly continual refinement of our patterns of management. In the future, progressively more effective antiretroviral therapy paradoxically may permit infected patients to live longer and fall victim to more HIV-related and HIV-independent malignancies. Swift's review of the role of radiation therapy in the setting of HIV infection therefore provides a useful "snapshot" of current standards and a necessary warning of likely changes to come. Several points warrant emphasis.

Need for Individualized Care
AIDS is an extraordinarily complex problem. Affected patients typically suffer from several of the myriad medical problems that constitute the syndrome. Consequently, we completely agree with Swift that it is critical to individualize care to each patient's needs and abilities. The decision to provide definitive vs palliative care must take into consideration not only the specifics of the malignancy to be treated but also the host's status, viral load, and the timeline of the patient's disease. For example, the current CD4 count, rapidity of CD4 decline, direction and rate of change of the viral load, and presence or absence of opportunistic infections should all influence treatment objectives and expectations. Perhaps newer measures of immune function, such as the antibody-binding capacity of CD4 cells,[1] are ready to be incorporated into clinical pathways.

Benefit-Risk Ratio of Treatment Critical
The benefit-risk ratio of any treatment, including radiation therapy, for a specific patient is a second critical point. Swift highlights how little unequivocal information exists about the possible immunosuppressive effects of radiation therapy on the ease of HIV replication. We intentionally use irradiation prior to transplantation, in part, for its "immunosuppressive effects," but we do not know whether the effects on HIV replication should be viewed as a similar model. And if the model is similar, precisely how do treatment-related factors, such as the size of the treatment portal(s) and the use of chemotherapy, influence immunosuppression?

Until we clarify these issues, the bottom line must be that if curative treatment of an existing malignancy is possible, it must not be compromised by fear of possible immunosuppression. In fact, the effects of HIV infection are so complex that there are tantalizing suggestions that whole-body radiation therapy may be beneficial.[2,3]

How Has Treatment of Kaposi's Sarcoma Changed?
Kaposi's sarcoma (KS) was the first HIV-associated malignancy to be identified and, in the past, was seen in 40% of all patients who had AIDS. Over time, its frequency has decreased to only 15%,[4] but no single strategy of care has proven uniformly successful. Systemic therapy (immunomodulators and/or cytotoxic chemotherapy) generally offers the prospect of temporary regression of disease and its attendant palliation. In accordance with the observations that KS occurs less commonly in women and that pregnant mice appear to be resistant hosts for KS, the use of human chorionic gonadotropin as a treatment for KS is being explored currently.[5] Yet, some patients continue to require localized therapy for localized areas of symptomatic KS. In this setting, radiation therapy often represents the optimal choice for palliation of pain, bleeding, or
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edema. Total dose and the time course over which it is delivered must be influenced not only by the extent and location of disease but also by the patient’s overall condition and anticipated length of survival.

Our personal recommendations have evolved since the 1980s and differ somewhat from those of Swift. In agreement with the results of a randomized prospective trial conducted by Stelzer and Griffin,[6] we believe that there is a dose-response relationship for KS. Consequently, for patients who are in relatively good general condition, sufficient dose should be administered to prevent the treated lesion from becoming a problem again.

At times, a conventionally fractionated dose of approximately 4,000 cGy (as suggested by Stelzer and Griffin's results) is necessary. More commonly, we have used the more rapid dose-fractionation scheme of 3,000 cGy in 10 fractions over 2 weeks (which is probably functionally equivalent); this treatment regimen has resulted in substantial benefit without substantial toxicity.[7] In contrast, when a briefer duration of palliation will suffice, (eg, for treatment of extensive lesions in patients who have far-advanced AIDS), we decrease the intensity and duration of treatment to 800 cGy in one fraction.

Patients who have oral and/or oropharyngeal lesions represent an important exception to these generalities. The frequent occurrence of severe mucositis following low-dose irradiation of oral-oropharyngeal KS[8] has convinced us to reserve radiation for treatment of symptomatic lesions that have already proven unresponsive to other therapies.

How Has Treatment of Non-Hodgkin's Lymphoma Changed?

Unlike KS, non-Hodgkin's lymphoma (NHL) has increased in frequency and, in the majority of HIV-infected patients, presents as widespread extranodal disease. Numerous chemotherapy regimens have been used, and impressive response rates obtained. However, even for the approximately 50% of patients who attain a "complete response," relapse is common.

We share Swift's disappointment that little has been written about the role of consolidative radiation therapy following systemic treatment, and agree that radiation therapy should be "considered as a consolidative boost in those patients with areas of bulky disease who, after initial chemotherapy, demonstrate a partial or slow response to chemotherapy." In light of the recent improvements in antiretroviral therapy, it may be time to conduct a prospective randomized trial of radiation therapy in the definitive management of these patients, in a manner akin to the non-HIV setting, ie, in those who can tolerate this approach.

Swift only briefly addresses the use of radiation therapy in the palliation of NHL. In our practice, we frequently have been asked to provide palliative therapy for patients with lymphomatous meningitis. To date, this has been a frustrating endeavor. Virtually all of these patients have had far-advanced AIDS, and treatment options have been limited. Because of concerns about bone marrow suppression in these already very compromised patients, we generally have treated only a cranial radiation field and "relied" on intrathecal chemotherapy to clear the cerebrospinal fluid of malignant cells. Patients with grossly evident spinal meningeal disease generally have been treated only to a localized portal.

Unfortunately, it is not uncommon for previously undetectable spinal meningeal involvement to progress rapidly, leading to neurologic dysfunction and the need to irradiate segments of the spinal cord in a patchwork fashion. For this situation, too, a prospective trial of the value of elective (perhaps low-dose craniospinal) irradiation appears to be justified.

A distinction must be made between HIV-associated systemic NHL with meningeal central nervous system (CNS) involvement and primary CNS lymphoma because of the difference in risk of involvement of the spinal cord. Our experience is similar to Swift's, with median survival durations of 2 to 3 months despite treatment. In this situation, our treatment approach also has changed as our experience with HIV-associated primary CNS lymphoma has increased.[9] Initially, all patients with primary CNS lesions that were radiographically indistinguishable from toxoplasmosis were treated with antibiotic therapy for 2 to 3 weeks, and if clinical or radiographic response was not evident, empiric radiation therapy to the brain was recommended. By that time, many of these patients were very ill, and, perhaps as a consequence, our survival rates were consistently poor.

As our knowledge of coexistent CNS infections expanded, we, like Swift, started to recommend biopsy for definitive diagnosis in the hope of detecting the disease at an earlier point in its evolution when it might be more responsive to treatment. We currently advocate immediate biopsy in patients who have negative "toxo-titers" and in those who do not show a rapid response to antitoxoplasmosis medications (85% of infected patients will respond within 1 week and 90% within 2 weeks). Although we have not found a better regimen for patients who have poor performance status and multiple
coexistent medical problems and therefore use the same one employed by Swift (ie, 3,000 cGy in 10 fractions), we consider it to be woefully inadequate. As it has become increasingly apparent that performance status correlates with outcome,[10] the development of better regimens may need to await new diagnostic imaging modalities (perhaps radiolabeled monoclonal antibodies)[11] that can noninvasively detect disease even earlier in its development.

**How Has Treatment of Other Malignancies Changed?**

Cervical and anal cancers are relative latecomers to the list of AIDS-related neoplasms, and thus, less is known about their optimal management. We view Swift's recommendations as good starting points rather than proven strategies. Like Swift, our impression is that we have observed increased toxicity in these patients from the combination of chemotherapy and radiotherapy and have had to interrupt treatment more frequently than otherwise. However, as long as the extent of disease and the patient's general status permits definitive treatment as the goal, we have adopted a philosophy of treatment identical to that used for patients who are not infected by HIV and have been able to complete treatment in most.

**What Does the Future Hold?**

With history as our guide, we expect that AIDS will continue to change in the future. So, too, must our therapeutic approaches. Swift's review should provide the reader with an up-to-date perspective for 1997. Hopefully, the next few years will chronicle sufficiently momentous changes--earlier diagnosis of HIV-associated malignancies, improvement in treatment resulting in better quality of life, and lengthened survival--that Swift's article and our commentary will require radical change.

**References:**


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