# 25-Year Follow-up of HIV-positive Patients with Benign Lymphoepithelial Cysts of the Parotid Glands: A Retrospective Review

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**Abstract.** *Aim: To report long-term outcomes for HIV-positive patients who underwent radiation therapy (RT) for benign lymphoepithelial cysts (BLEC) of the parotid glands. Patients and Methods: In this single institution retrospective study of HIV-associated BLEC of the parotids, the medical records of 37 HIV-positive patients who were treated with RT between 1987-2012 were reviewed. Patients were stratified into two groups; group A consisted of 15 patients (40.5%) who received a total dose of ≤18Gy, with a median dose 10 Gy (range 8-18Gy), and group B consisted of 22 patients (59.5%) who received a total dose of 24 Gy. In addition to dosing information, additional patient data were collected, including demographics, HAART compliance, follow-up, and re-treatment status. Results: The median age at the time of treatment was 41 (range=7-70) years. With a median follow-up of 35 (range=12-75) months for the entire cohort, the complete response (CR) and partial response (PR) rates were 35% and 8%, respectively. All but one of 15 patients in Group A (lower total dose) eventually experienced local failure with the re-emergence of parotid hypertrophy. Among the patients in group B (higher total dose of 24 Gy), 55%, 13%, and 32% experienced CR, PR, and LF, respectively. Median times to failure in groups A and B were 7 and 20 months, respectively (p<0.0001). Similarly, logistic regression test revealed the higher dose to be associated with better response rate (i.e. CR or PR) (p<0.0001), which was also statistically significant (p=0.03) after adjusting for confounding variables (age, race, gender, HAART use, and fractionation). Conclusion: A total dose of 24 Gy continues to be recommended for durable cosmetic control of BLEC of the parotid glands that is associated with HIV-seropositivity.*

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*Key Words:* Radiation therapy (RT), benign lymphoepitheilial cysts (BLEC), parotid gland hyperplasia, HIV positive, highly active antiretroviral therapy (HAART).

Approximately 1.2 million people in the United States are living with human immunodeficiency virus (HIV). In 2011, an estimated 49,300 people were diagnosed with HIV infection (1). Head and neck pathology, including opportunistic infections such as oral candidiasis, occurs in more than 50% of HIV-positive patients (2). These lesions – both malignant and benign – may lead to discomfort, dysfunction, and cosmetic disfigurement (3). The most common salivary gland presentation in HIV individuals is gland swelling (4). Enlargement of the parotid gland in HIV-infected patients is usually secondary to development of benign lymphoepithelial cysts (BLEC) within the gland, and has been reported to occur in up to 6% and 10% of HIV-positive adults and children, respectively, at some point during their disease (14). BLEC is typically characterized by bilateral parotid swelling (less commonly with unilateral) and cluster of differentiation 8 (CD8) lymphocytosis with possible cervical lymphadenopathy (5-8). BLEC has been reported to occur not only in the salivary glands and their lymph nodes, but also within the floor of mouth, tonsil, thyroid gland, intrathoracic region, and pancreas (9-13). The treatment options for BLEC of the parotid gland include close observation, aspiration, highly active anti-retroviral therapy (HAART), sclerotherapy, radiation therapy (RT), and surgery. In this study, we report our 25-year experience utilizing RT as primary treatment for BLEC of the parotids.

Table I. *Patients' demographics and outcomes.*

| Groups | Complete response | Partial response | Treatment failure | All patients (%) |
|---|---|---|---|---|
| Number of Patients | 13 | 4 | 20 | 37 |
| Median age at RT | 41 (35-65) | 37 (7-47) | 42 (26-70) | 41 (7-70) |
| Male /Female | 7 /6 | 3 / 1 | 12/8 | 22 /15 |
| Race | | | | |
| AA | 6 | 2 | 12 | 20 |
| H | 6 | 1 | 8 | 15 |
| C | 1 | 1 | | 2 |
| HAART | 9/13 (69%) | 4/4 (100%) | 8/20 (40%) | 21/37 (57%) |
| Median fup months | 44 (12-75) | 21 (14-39) | 35 (12-68) | 35 (12-75) |
| RT dose 24 Gy | 12/13 (92%) | 3/4 (75%) | 7/20 (35%) | 22/37 (59%) |
| CT sim and 3DRT | 12/13 (92%) | 3/4 (75%) | 7/20 (35%) | 22/37 (59%) |
| Daily fraction size | | | | |
| 2 Gy | 1/13 (8%) | 0 | 13/20 (65%) | 14/37 (38%) |
| 1.5 Gy | 12/13 (92%) | 4/4 (100%) | 7/20 (35%) | 23/37 (62%) |
| Photons (4-6MV or $^{60}$Co) | 12/13 | 4/4 | 20/20 | 23/37 |
| Electrons | 1/13 | 0 | 0 | 1/37 |

H, Hispanic; AA, African American; C, Caucasian; FUP, follow-up.

## Patients and Methods

*Patient eligibility.* Using an institutional database, we identified 37 HIV-positive patients who were treated with RT for BLEC in our department from January 1987-2012. All patients underwent initial complete history, physical examination, and histological confirmation of the diagnosis.

*Radiation treatment.* Informed consent was obtained after the benign nature of the disease and the risks of RT were discussed in great detail with the patients. Patients were referred for dental evaluation prior to starting treatment, with any necessary extractions completed prior to commencing RT. The treatment of patients in this study spans more than two decades, and therefore some variation exists in the RT techniques that were employed. The majority of patients (67.6%) were treated in the 1990's; eight patients (21.6%) were treated in the late 1980s (1987-1989), and four patients (10.8%) were treated in 2000 onwards due to lower referral volume. The majority of patients (26/37, 70.3%) were treated with 6MV photons. Seven and three patients underwent clinical simulation and treatment *via* 4MV photons and $^{60}$Co, respectively. One patient underwent en face electron treatment (9 MeV). Our RT techniques were previously reported in great detail by Goldstein and Beitler *et al.* (15-18). All patients were treated to the bilateral parotids. Based on the total delivered dose, patients were stratified into two groups: Group A consisted of 15 patients (40.5%) who received a total dose of ≤18Gy, with a median dose 10 (8-18) Gy; Group B comprised of 22 patients (59.5%) who received a total dose of 24 Gy; among these patients, 21 received RT in 1.5 Gy fractions (with one patient undergoing 2 Gy × 12 fractions). Fractionation among group A patients was primarily 2 Gy (12/15), with a smaller number (3/15) receiving 1.5 Gy.

*Medical treatment.* Our review spans years during which major advances in HIV treatment occurred, most notably the emergence of HAART as standard-of-care for newly-diagnosed HIV/AIDS. Only nine out of the 37 patients (24.3%) were treated in the era before HAART was widely available (late 1996/1997). The remaining patients were treated following HAART. The majority of patients (21/37, 57%) were on HAART under the care of an infectious disease physician either at the time of the initial consultation, or more often, while on follow-up. As the patient population at our institution, and certainly the population represented in this study, consists largely of underserved and underinsured individuals, HAART compliance/adherence was an issue.

*Follow-up and response evaluation.* Patients generally had follow-up appointments at one month, six months, and one year from the date of treatment completion, and annually thereafter. The response to treatment, which was primarily a cosmetic metric, was evaluated by the patient and treating physician. Each patient completed a subjective evaluation of the cosmetic response communicated to the physician. Physicians also reported a response to treatment following clinical examinations. The primary rationale of this approach was to document an objective evaluation of response as well as the cosmetic satisfaction of the patient. Three possible treatment outcomes were assigned including: complete response (CR), partial response (PR), and treatment failure (TF). CR was defined as complete cosmetic satisfaction greater than or equal to a 75% reduction in parotid size. The BLEC need not completely disappear for a CR. PR was defined as a moderate level of cosmetic satisfaction on the part of the patient with a less than 75% reduction in the parotid size. Finally, treatment failure consisted of a persistent or enlarged BLEC accompanying complete cosmetic dissatisfaction. Toxicity was scaled based upon Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Radiation Toxicity Grading (19).

*Study schema.* For all patients, the following data were tabulated and analyzed, when available: age, race, gender, age at HIV diagnosis, age at RT, HIV-seropositive duration, HAART status, pre-

Table II. *Group A vs. B.*

| Variables Group | A | B | All |
|---|---|---|---|
| Number of Patients | 15 (41%) | 22 (59%) | 37 (100%) |
| Median RT dose, Gy | 10 Gy (range 8-18) | 24 Gy | 24 (8-24) |
| Daily fractionation size | 2 Gy | 1.5 Gy | 1.5-2 Gy |
| Median Fup | 35 (12-68) | 31 (12-75) | 35 (12-75) |
| Median age at RT, years | 39 (26-70) | 41 (7-65) | 41 (7-70) |
| Male /Female | 8/7 | 14/8 | 22 /15 |
| Race | | | |
| AA | 10 | 10 | 20 |
| H | 5 | 10 | 15 |
| C | 0 | 2 | 2 |
| RT outcomes | | | |
| CR | 1 (7%) | 12 (54.5%) | 13 (35%) |
| PR | 0 | 3 (13.6%) | 3 (8%) |
| TF | 14 (93%) | 7 (32%) | 21 (57%) |
| Median time-to-RT failure, months | 7 | 20 | 7 |

RT, Radiation therapy; H, Hispanic; AA, African American; C, Caucasian; FUP, follow up; CR, complete response; PR, partial response; TF, treatment failure.

and post-treatment parotid size, RT technique and dosing, toxicity, and long-term outcomes.

*Statistical methods*. Statistical analyses were performed using STATA 11th edition (Stata Corp LP, College Station, Texas, USA). Chi-square tests, univariate, and multivariate logistic regression analyses determined the degree of correlation between RT outcomes and all aforementioned variables.

## Results

Tables I and II show the demographics and outcomes, respectively, of our study. The median age at RT treatment was 41 (7-70) years. The median age (range) at diagnosis of HIV was 38 (7-53) years, while the median duration between HIV-seropositivity and treatment was 11 (6-35) years. Twenty-two patients were male (59.5%), 20 patients (54.1%) were African American, 15 patients (40.5%) were Hispanic, and two were Caucasian. None of the patients in our study had their diagnosis or management changed by fine-needle aspiration (FNA). The majority of the patients in Group A (9/15, 60%) were treated to a total of 10 Gy in 2-Gy fractions. Two patients were scheduled to receive this regimen, but missed their final fraction, and therefore received a total dose of 8-Gy in four fractions. Two patients received a total dose of 18 Gy in 1.5 Gy by 12 fractions, and the remaining two patients received total doses of 16 and 15 Gy in 2 and 1.5 Gy fractions, respectively. The median RT duration was 22 (15-60) days with a median follow-up of 35 (range 12-75 months). For the entire cohort, the overall response was 43.2% with CR of 35.1% and PR of 8.1% (Table II shows responses of group A *vs*. B).

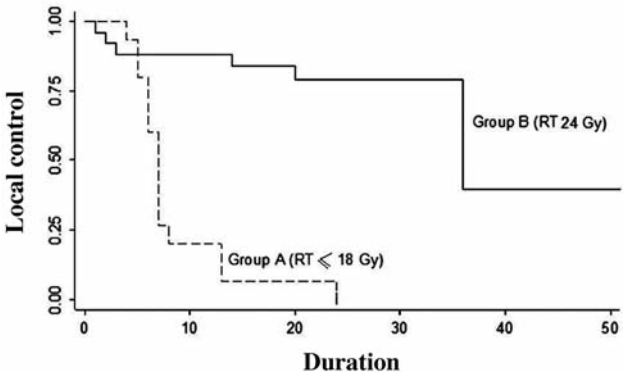


Figure 1. *Kaplan-Meier estimates for local control in group A (≤18 Gy) and group B (24Gy) patients.*

*CR group*. Thirteen out of the 37 patients (43.2%) achieved CR. The median age at RT for this group was 41years (35-65). One of the fifteen patients (6.7%) in group A (lower total dose) achieved CR, while 12 out of 22 (54.5%) in group B (higher dose) patients achieved CR. All but one patient who achieved a CR were treated with 6 MV photons (one with *en face* electrons), and the majority of patients in this group (9/13 or 69%) have records of HAART initiation. The median duration of RT in the CR group was 22 (15-34) days.

*PR group*. Three patients (8.1%), all from group B, experienced a PR. All underwent treatment with 6 MV photons. Their median age was 35 (7-39) years, and all were treated with HAART during treatment or follow-up. The median duration of RT for the partial responders was 24 (21-32) days.

*TF group*. Twenty out of the 37 patients (54.1%) experienced TF while in follow-up. The majority of these patients (13/20, 65%) were from the lower-dose group (group A). Half of these patients were treated with 6MV photons; seven (35%) with 4MV photons, and three (15%) were treated with $^{60}$Co. This cohort's median age was 41.5 (26-70) years, and only eight of the patients (40%) have records of HAART initiation. The median duration of RT in the TF group was 59 (54-63) days. Nine patients who experienced TF underwent re-irradiation without any meaningful cosmetic improvement. There were no re-treatments among complete or partial responders.

A chi-square test showed no statistically significant relationship between race, age, and the duration of time that the BLEC was present prior to treatment with outcome ($p$=0.52, $p$=0.86 $p$=0.56, respectively). In contrast, chi-square test showed a statistically significant correlation of HAART and total RT dose with cosmetic control ($p$=0.001 and $p$<0.0001 respectively). Logistic regression analysis

further examined the relationship between total dose and outcomes. The results showed that 24 Gy was associated with a decrease in local failure ($p<0.0001$). Similarly, multiple regression analyses were conducted to adjust for all confounders (including age, race, gender, HAART, fraction size, and BLEC duration) and showed a statistically significant relationship between total dose and outcome ($p=0.042$). Kaplan-Meier curves showed that group B (higher dose) achieved better cosmetic control, which was consistently higher than that of group A (lower total dose) as shown in Figure 1. Moreover, among Group B patients, a longer follow-up duration correlated positively with improved outcomes when compared to the same relationship among group A patients, $p<0.0001$.

*Toxicity*. All acute toxicities were RTOG grades 1 and 2. Oral mucositis of grades 1 and 2 occurred in 40% and 10% of our patients, respectively. Grade 1 and 2 xerostomia were recorded in 30% and 10%, respectively. Grade 1 dermatitis (skin erythema) was present in 40% of our patients, and grade 1 altered taste was present in 20%. Only two patients (6.7%) from group B, who were treated with 6 MV photons, experienced long-term Grade 1 xerostomia. In addition, a statistically significant relationship was found between patient outcomes and the total duration of the RT ($p<0.0001$). The longer the RT duration, the higher the likelihood of treatment failure, with an inflection point at approximately 22 days. Due perhaps to the small number of patients in our analysis (n=37), our results showed no statistically significant relationship between RT outcome and the remaining variables, including race, gender, age, and fraction size (1.5 *vs*. 2 Gy).

## Discussion

BLEC not only advertises one's HIV status, it can also be disfiguring and is often associated with significant patient distress (26). BLEC involves multicystic, benign lymphoepithelial lesions of one, or more commonly, both parotid glands. The exact pathogenesis of BLEC is unclear, but many believe it results from viral replication and subsequent proliferation of glandular epithelium that becomes trapped within parotid lymph nodes. Subsequent ductal obstruction and dilation may cause for eventual true cyst formation and parotid enlargement (5, 20-22).

The classical clinical presentation of BLEC is bilateral [unilateral in 20% (4, 22)] parotid enlargement that may consist of multiple cysts in one gland (up to 90%). The cysts are typically painless, soft, and enlarge slowly.

In addition to clinical examination, the diagnostic evaluation involves ultrasound, CT, and/or magnetic resonance imaging (MRI) showing multiple thin-walled cysts (4). The treatment options for BLEC include close observation, repeat aspirations, initiation of HAART among the treatment-naive, sclerotherapy, radiotherapy, and surgery (4). Due to the slowly-progressive nature of the lesions, observation is an option, but any acute enlargement warrants for immediate investigation. FNA has been shown to be an effective diagnostic and therapeutic tool and for monitoring for the development of EBV-associated B-cell lymphoma, for which these patients are at an increased risk (23).

Currently, the standard-of-care for HIV is HAART, which alone has been found to reduce and eliminate BLEC in many patients (30). Some patients may seek aspiration, as it is typically a quick outpatient procedure. The main disadvantage, however, is that most aspirated lesions recur swiftly and continue to enlarge (4, 24-26).

Sclerotherapy with doxycycline or bleomycin has been used for the treatment of BLEC. Studies have shown an average reduction in cyst size by 42%-100% with no serious complications (*i.e*. facial nerve injury or infection). The main disadvantage, however, is that most lesions will recur within a few months and enlarge (26-29).

Given the bilateral and progressive nature of the disease, surgery is rarely recommended as the first-line treatment. There is some risk [2.3-6% in one study (26)] of facial nerve injury and a high likelihood of need for multiple surgical procedures following a superficial parotidectomy (4).

Our previous report (35) showed that low-dose external-beam RT can successfully reduce or even eliminate BLEC lesions and parotid gland size (35), and was therefore recommended (15-18). Our initial report showed that response rates following administration of 8-10 Gy were encouraging (15), however, longer follow-up revealed a median control duration of only 9.5 months (16). At that time, the efficacy of a higher total dose was explored. In a unique report by Beitler *et al*. (24) HIV-positive patients with BLEC were treated with 1.5 Gy daily fractions to 24 Gy. Results showed excellent local control after a median follow-up of 24 months (18). Comparing these updated results with earlier series showed a significant improvement in cosmetic control (log rank test, $p<0.02$) for the higher total dose (27). Beitler *et al*. concluded that 24 Gy delivered in 1.5 Gy fractions is a safe and well-tolerated regimen that appeared to be effective in 70% of patients.

In the context of this established management of BLEC, we recommend the following treatment algorithm: HIV confirmation, complete blood count, CD4 counts, viral load, tissue biopsy *via* FNA (to eliminate other possible etiology, including lymphoma), and baseline CT scan to determine the pre-treatment parotid and cyst dimensions. The initiation of HAART, unless counter-indicated, should precede RT. Those whose parotid disease is refractory or resistant to HAART should be offered RT. We further recommend the use of CT-based 3D planning or intensity-modulated RT in order to limit the RT dose to adjacent structures, with the parotids constrained to a mean dose below 26 Gy (31).

Patient compliance and adherence to HAART are important issues that warrant further investigation, as combination therapy is important not only in BLEC, but also in disease management in general. Our patient population consisted of underserved minorities, and we have patient compliance with RT to be related to socioeconomic status and patient resources. Therefore, the treatment modality recommended, as well as the regimen in the case of RT, should be reviewed with these issues in mind. In this cohort, treatment interruptions were due primarily to psychosocial and logistical issues (such as transportation), rather than medical factors. It is our belief that HIV-positive patients with BLEC should be referred to counseling and social work for additional support that could increase compliance.

When treating patients with RT, including the treatment of BLEC, there is a small but potential risk of inducing a secondary malignancy (termed RIS). We were unable to locate any such documented case involving BLEC treatment. Survival duration has drastically improved with the use of HAART; however, all patients should be informed of this potential risk. Historically, most radiation oncologists would concur that a radiation dose of approximately 30 Gy is required for the development of RIS (33-34). However, recent reports have shown that RIS can occur in the context of benign diseases and the use of radiation prophylaxis with total doses as low as 7 Gy (35-38). With the current advances in HAART and HIV/AIDS medical management, the number of patients experiencing parotid enlargement secondary to BLEC is expected to grow due to prolonged life expectancy (39, 40). In conclusion, with the low incidence of side-effects and excellent outcome, our group as well as Beth Israel Medical center investigators (41) highly encourage use at the current total RT dose of 24 Gy given at a daily fraction of 2.0 or 1.5 Gy in 12 or16 fractions, respectively.

The strengths of our analysis include long-term follow-up and the use of an independent statistician not involved in data abstraction. The weaknesses of our study include differing RT techniques, small number of patients, and non-randomized retrospective analysis with its inherent dependence upon the accuracy of pre-existing documentation. Furthermore, as the patient population at our institution, and certainly the population represented in this study, consists largely of underserved and underinsured individuals, HAART compliance/adherence was an issue.

## Conclusion

External-beam radiotherapy to a total dose of 24 Gy continues to be the gold standard RT treatment in the management of BLEC among HIV-positive patients.

## Funding

None.

## Conflicts of Interest

None.

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