Radiotherapy in patients with HIV: current issues and review of the literature

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Abstract

Although the introduction of highly active antiretroviral therapy has radically improved the life expectancy of HIV patients, HIV status has been considered a major limit to oncological treatment in cancer patients due to worse prognosis and greater expected toxicity than in immunocompetent patients. The use of radiation with or without chemotherapy and/or new drugs represents the current standard of care in several oncological scenarios. The introduction of new drugs, including immunotherapy and molecular target therapy, as well as the recent, significant improvement in radiotherapy technology including Intensity Modulated Radiotherapy, Image Guided Radiotherapy and stereotactic ablative radiotherapy are optimising the feasibility of such anticancer treatments. These potential innovations open a new scenario for HIV cancer patients.

The aim of this review is to discuss the role of radiotherapy, with or without associated drugs, in HIV cancer patients focusing on the efficacy and tolerability of this approach based on available evidence. Moreover, the biological bases of interaction between HIV and radiotherapy, preclinical studies and immunomodulation by radiation in the HIV setting were the object of our evaluation and discussion.

Introduction

According to recent estimates made by the Global Burden of Disease Study, in 2015 more than 38.8 million people worldwide were affected by HIV/AIDS[1]. Several approaches have been implemented to control HIV infection, including educational programmes on sexual health, specific programmes aimed at key populations, and more widespread access to antiretroviral therapy for treatment and prevention[1]. Indeed, the decrease in incidence, along with the drop in HIV-related deaths is closely related to the introduction of highly active antiretroviral therapy (HAART) in 1996[2]. On the contrary, an increased incidence of cancer has been reported. Specifically, in the pre-HAART era, the incidence of cancer in HIV patients was 31% compared to 58% after the introduction of these antiretroviral drugs[3].

Although death rates in people living with HIV remain much lower in high-income countries than in other areas of the world, some countries with limited resources have shown encouraging rates of HAART coverage and viral suppression[1]. Hence, access to adequate care and (radio)therapy to treat cancer in HIV infected people should be expanded on a global level.

Historically, HIV has been considered a limitation in cancer treatment because of worse prognosis and higher toxicity compared to non-HIV patients.

Nevertheless, several historical studies were carried out prior to the diffusion of HAART.

Additionally, the introduction of new drugs (immunotherapy and target therapies) and an improvement in radiotherapy technology, including Intensity Modulated Radiotherapy and Image Guided Radiotherapy, are optimising the effectiveness and tolerability of cancer treatment[4]. Despite these developments, the role of radiotherapy alone or in combination with drugs remains to be defined in HIV cancer patients.

The aim of this review is to discuss the role of radiotherapy, with or without associated drugs, in HIV cancer patients focusing on the efficacy and tolerability of this approach based on available evidence. Moreover, the biological bases of interaction between HIV and radiotherapy, preclinical studies and immunomodulation by radiation in the HIV setting were the object of our evaluation and discussion.

Search strategy and selection criteria

Literature search

A detailed literature search strategy was developed *a priori.*

Key words and subject terms used in the search included: ("hiv"[MeSH Terms] OR "hiv"[All Fields]) AND ("radiotherapy"[MeSH Terms] OR "radiotherapy"[All Fields] OR ("cancer"[All Fields] AND "radiotherapy"[All Fields]) OR "cancer radiotherapy"[All Fields])

Study selection

We searched Medline, Google Scholar, PubMed, and the ProQuest Dissertation, and Theses databases for reports published in English between June 1946, and January 2017. Our detailed search algorithm is shown in the text. We identified additional references by carrying out a manual search of the References of all the included articles. Two independent reviewers (NGL and SS) identified potential studies and exported them to an electronic reference management software program (Ref Works version 2.0). NGL and SS determined eligibility by first reviewing the title and abstract and then the full paper. Disagreements were resolved by consensus; if consensus was not achieved, then a third author (FA) provided an assessment of eligibility. Since the data for eligibility were dichotomous (yes vs no), we established inter-rater agreement at both the title and abstract review stage, and then after reviewing the full by calculating Cohen's κ coefficient (http://facultyvassaredu/lowry/kappa.html). A study was included when it reported on cancer-related radiotherapy and included patients with HIV. A study was excluded when no detailed information (e.g. outcome of radiotherapy, clinical manifestations related to the underlying HIV) was reported. Haematological diseases, Kaposi disease and brain tumours were excluded. Review articles were excluded from the analysis. With regard to data

extraction, all the papers were analysed for the following information: study design (retrospective, prospective, case-control, cross-sectional and case series); number of patients, sex, and age (mean, range); type of radiotherapy; dose prescription, type of anti-retroviral therapy; type of underlying solid cancer; outcome in terms of toxicity profile; CD4 count and viral load. **Figure 1.**

Anti-retroviral HIV therapy, immune system response and cancer

HAART has revolutionised the survival of HIV patients by guaranteeing CD4 count normalisation and reducing viral load. Despite these therapeutic improvements, HAART is considered a lifelong treatment because it is unable to eliminate HIV, even in patients with a negative viral load[5].

Moreover, it has been demonstrated that prolonged use of HAART can cause viral resistance, especially in advanced stages of infection, thus triggering cancer in some patients[6]. In fact, several DNA and RNA viruses have been associated with human cancers. Three distinct mechanisms have been described to explain the oncogenic role of these viruses: a) viruses can directly induce transformation of infected cells. Host cell growth and survival can be deregulated by integration or after establishing a stable episome following virus infection. Alternatively, recognition of viral genes by host cells can initiate DNA damage response which many viruses require for replication; b) viral infection can lead to cancer by inducing chronic inflammation, thus encouraging carcinogenic transformation[7]; c) HIV represents a unique situation, as it is not itself oncogenic, but it does inhibit the patient's immune system, disrupting immunosurveillance and allowing hyper-mutated malignant cells to emerge. A meta-analysis showed that HIV-related depression confers an elevated risk of malignancy similar to what is observed among solid organ transplant recipients[8]. Moreover, a possible association of various non-AIDS-defining malignancies and HIV related to a mechanism whereby suppressed cell-mediated immunity, impaired immune surveillance, angiogenesis, and reduced apoptosis provide a prolific environment for aggressive tumorigenesis has been proposed[9]. Additionally, HIV induced an irreversible alteration in the innate and adaptive immune system, infecting CD4 T cells, which were progressively destroyed while CD8 T-cells were chronically activated[10]. Various HIV proteins (gp120, Tat and Nef) are apparently able to induce an apoptotic process in uninfected CD4 T-cells, conversely an alternative thesis proposed that CD4 T-cells may be killed by natural killer cells[11]. Consequently, new immunological strategies are needed to improve the efficacy of HAART. Therefore, the use of oncological drugs is being evaluated for use in HIV patients in an attempt to deplete infected cells. In particular, immunotherapies are under investigation in order to combine an immune response against HIV and cancer antigens. In fact, inhibitor signals through immune checkpoints on CD4 and CD8 T-cells allow tumour cells to avoid immunosurveillance. A comparable process is used by HIV, which increases the expression of the immune checkpoint, in particular PD-1, thereby promoting disease progression[12] and immune escape[13] - **Figure 2**. A recent publication

reported that immune checkpoint expression is associated with persistence in HIV activity. Prescribing Ipilimumab (human immunoglobulin G1 inhibitor antibody to CTLA-4) in a patient with metastatic melanoma allowed to increase the CD4 T-cell count[14]. To date, two ongoing phase 1 clinical trials (NCT02408861, NCT02595866) are evaluating the use of immunotherapies in HIV cancer patients.

Radiotherapy in HIV cancer patients

Biological bases of interaction between HIV and radiotherapy

For HIV patients affected by cancer, radiotherapy represents an important local treatment option. Considerable evidence has shown that the risk of treatment-related side effects is higher in HIV patients compared to immunocompetent patients[15].

These clinical observations are likely related to the direct and/or indirect effects of HIV infection that probably enhance the effect of ionising radiation.

In HIV patients, the levels of glutathione and other related endogenous thiols, as well as the levels of superoxide dismutase and catalase have been reduced[16]. Reductions both in the levels of glutathione and related endogenous thiols, as well as in the levels of superoxide dismutase and catalase have been reported in HIV patients[16]. These decreases in the endogenous antioxidant systems enhance the oxidative stress, resulting in an increase in the production of reactive oxygen species[17].

Any stimulation of polymorphonuclear cells, monocytes/macrophages, or T-cells, as is the case with HIV, increases the production of reactive oxygen species[17]. Increased oxidative stress plays an important role in cell death, including apoptosis or necrosis of epithelial cells, melanocytes, endothelial cells, and stromal cells through various mechanisms including both direct and indirect DNA damage[17].

Thus, the state of chronic immune activation and the various drugs that are used in HIV patients leads to a constant state of oxidative stress, which is further emphasised by the up-regulation of tumour necrosis factor alpha (TNF) by HIV itself[18]. Moreover reactive oxygen species, HIV and TNF activate the transcription of nuclear factor-kb (NF-kb), which further increases TNF and reactive oxygen species levels.

Several nutrients, including vitamins, flavonoids, minerals, and amino acids play an important role as scavengers of reactive oxygen species which maintain the redox potential within the cells and thus protect them from electrophiles and

reactive oxygen species[17]. Alterations in the bowel mucosa of HIV patients affect the absorption of these nutrients, thus contributing to the depletion of the scavenger system[17].

All these direct or indirect mechanisms trigger an increase in the production of reactive oxygen species, which themselves are mediators of the damaging effect of radiation, and also leading to a depletion of radio-protective thiols[19].

Pre-clinical studies HIV and radiotherapy

In vivo and *in vitro* studies have shown some evidence of increased sensitivity to radiation in HIV patients with cancer[15, 20-27].

Formenti et al. showed that in Kaposi's sarcoma, fibroblasts derived from the skin biopsies of HIV patients were more radiosensitive as compared to non–HIV patients[15]. However, the mechanism of the increased radiosensitivity of AIDS cancer patients is still not well defined.

In addition, several preclinical studies highlighted that the Tat-expressing Jurkat cells and HIV-infected Jurkat cells have greater toxicity to the metabolites of clindamycin and sulfonamides, and consequently a deficiency of intracellular glutathione concentrations, which has been hypothesised as an explanation for radio-sensitivity[20.]

Sun et al. reported the effects of the HIV-1 Tat protein on cellular response to ionising radiation of two Tat-expressing cell lines (TT2 and TE671-Tat) derived from human rhabdomyosarcoma cells[21]. The authors concluded that the HIV-1 Tat protein sensitises rhabdomyosarcoma cells to radiation by dysregulating cell cycle checkpoints and reducing cellular capacity to repair radiation-induced damage. These results imply that radiotherapy for any type of cancer could be more effective in HIV patients than in non-HIV infected ones[21].

Moreover, other preclinical reports have suggested that HIV protease inhibitors, considered as components of antiretroviral therapy, play an important role in the radio-sensitisation of normal tissue and tumour cells[22-23].

HIV protease inhibitors may inhibit the phosphatidylinositol 3-kinase/Akt (PI3K) pathway, which is considered an important survival mechanism in some tumour cells. In these cells, PI3K is overexpressed resulting in radiation resistance[28]. The effect of HIV protease inhibitors on the PI3K pathway has been observed both *in vivo* and *in vitro*[24]. Gupta et al, in fact, tested two of the most common HIV protease inhibitors (Amprenavir and Nelfinavir) *in vivo* as adjuvant antitumour agents[24]. The authors concluded that the combination of drug and radiation exerted greater synergistic effects as compared to either modality alone. Another study conducted by Pajonk et al. concluded that one

HIV protease inhibitor, Saquinavir, is a radiation sensitiser inhibiting proteasome activity in mammalian cells[27]. Furthermore, in the HAART era, HIV protease inhibitors may also act as radiation/chemotherapy sensitisers by triggering other molecular processes such as proteasome inhibition, endoplasmic reticulum stress, unfolded protein response and autophagy[29].

Several studies have shown that HIV protease inhibitors induce cell apoptosis via activation of endoplasmic reticulum stress[30]. Liu et al. evaluated the role of endoplasmic reticulum stress in HIV and HIV protease inhibitors by inducing a radiosensitivity effect in head and neck squamous cancer cells. Their results demonstrated that the HIV protease inhibitor drugs, Lopinavir and Ritonavir, dose-dependently sensitised head and neck squamous carcinoma cells to irradiation, and inhibited cell growth. Lopinavir and Ritonavir induced activation of endoplasmic reticulum stress, which was correlated to the down-regulation of cyclin D1 expression and cell arrest in the G0/G1 phase. HIV protease inhibitors caused unfolded protein response activation in head and neck squamous carcinoma cells. One of the three main branches of unfolded protein response identified to date includes PERK (double-stranded RNA-activated protein kinase-like ER kinase) in addition to IRE1 and ATF6. PERK activation allows phosphorylation of eIF2α which then further leads to ATF4 expression. The resulting PERK/eIF2α/ATF-4 activation represses global protein translation, reduces cyclin D1 protein levels and induces cell cycle arrest. ATF-4 also produces CHOP expression, which inhibits cell growth[26]. The results of this study suggest that the activation of endoplasmic reticulum stress response is one of the principle mechanisms underlying HIV protease inhibitor-induced radiosensitivity[26].

In conclusion, considering the safety of these drugs, these agents are defined as excellent candidates for testing as radiation sensitisers in clinical trials even for non-HIV infected subjects[24].

CD4 counts in HIV cancer patients undergoing oncological treatment

CD4 T-cells are directly involved in the adaptive immune response[31], in fact CD4 T-cells help the activation and proliferation of CD8 T-cells[32], the generation of CD8 T-cell memory[33] and the activation of macrophages and eosinophils[31].

Anecdotal experience suggests that patients with a pre-treatment CD4 count <200 cell/mm^3 (i.e., AIDS patients) have an increased probability of developing toxicity when treated with chemotherapy and radiotherapy. Conversely, HIV patients with a CD4 count >200 cell/mm^3, good performance status and who were treated with HAART showed tolerability and outcomes comparable to non-HIV subjects. **Table 1** reports the studies that focused on this issue.

One of the first reports was published by Holland et al.[34]. AIDS patients should be considered for palliative treatment based on worse results and a significantly higher probability of side effects. Similar results were obtained by Hoffmann et al., who observed that the toxicity profile was significantly worse in subjects with severe immunodeficiency[35]. Other clinical studies confirmed these conclusions in terms of clinical outcomes and tolerability[36-39].

HAART influenced clinical outcomes and patients appear to have died of HIV and not of cancer progression[38]. Alfawali et al. discussed some interesting data about the impact of concurrent chemotherapy and radiotherapy and CD4 count during follow-up in HIV anal cancer patients. In fact, a median CD4 count of 305 cell/mm^3 was measured at diagnosis while during follow-up patients showed a progressive CD4 reduction. The authors concluded that being immunosuppressed might be associated with a greater probability of AIDS-related death[40]. Wexler et al. described that patients with a median CD4 count value <350 cells/ mm^3 and a median viral load value >700 copies/ml have an increased risk of hospitalisation and haematological toxicity (p=0.03). This study also reported a decrease in CD4 count after chemotherapy and radiotherapy in all patients but one, and the decrease persisted for at least eight months after radiotherapy. A comparison of CD4 levels before and after radiotherapy revealed that only 28% of patients presented a >10% drop in CD4. The authors concluded that a low CD4 count or higher viral load at disease presentation was associated with increased haematological toxicity and negative impact on the tolerability of treatment. Moreover, pelvic bone marrow irradiation, tumour site and dose prescription can influence the delay in CD4 recovery[41-42]. A reduction in the CD4 count during follow-up was confirmed in other studies, however this condition has no impact on clinical outcomes[37,43]. More recently, an innovative oncological approach that included chemotherapy, radiotherapy and cetuximab in HIV anal cancer patients was published. An analysis of the CD4 count confirmed a significantly decreased level between baseline and the end of treatment. Nevertheless, during follow-up some recovery was achieved after the end of treatment without any impact on HIV viral load[44]. Other studies which focused on prostate cancer, cervical carcinoma, head and neck, and lung cancer analysed the correlation of CD4 levels and clinical outcomes.

Most of the publications confirmed that CD4 counts did not impact on oncological efficacy when chemotherapy and radiotherapy were used[45-51], while only one paper, which focused on lung cancer, demonstrated a worse survival rate correlated to CD4 count[52].

In conclusion, data regarding the correlation between CD4 count and treatment toxicity remain insufficient and the role of the CD4 count continues to be controversial and needs additional investigation.

Clinical studies on radiotherapy in HIV patients

Anal cancer

Anal cancer is 80- to 120-fold more common in HIV/AIDS patients than in the general population and the incidence is still increasing[22]. Randomised trials established that the combination of radiotherapy and chemotherapy with 5-fluorouracile and Mitomycin C is the standard treatment for anal canal cancer because it can cure many patients and guarantying a preservation of anal sphincter function[53].

Over twenty clinical reports [22-23,34-36,39,41,43,54-69] have been published and non homogeneous results have been reported in terms of outcomes and toxicity, as shown in **Table 2**.

Studies published before the introduction of HAART reported that HIV/AIDS anal cancer patients were defined as poor responders to conventional chemo-radiotherapy. In fact, HIV patients were more prone to a greater number of treatment discontinuation, hospitalisation and a reduction in radiotherapy and chemotherapy dose prescriptions [34,54]. After 1996, controversial results were reported. In fact, various studies showed that concurrent chemotherapy and radiotherapy were associated with a higher probability of developing acute and late cutaneous, gastrointestinal and myelosuppressive toxicities as compared to non-HIV patients[22-23, 35, 38-41,43,55,57,59,61,63-64]. These toxicities correlated with a negative impact in overall survival and cancer-free survival[58, 66, 68], in particular in patients with a CD4 count < 200 cell/mm [35,38].

Currently, the best oncological approach for HIV/AIDS patients is still controversial and multidisciplinary discussion is reasonable.

Considering some new drugs in combination with radiotherapy, a single trial evaluated the use of cetuximab (an anti-epithelial growth factor receptor antibody). Good results in terms of loco-regional control were observed with a locoregional recurrence probability of 20%. Nevertheless, grade 4 toxicity was reported in 26% of HIV patients[44].

To date, toxicity still remains a relevant issue in the management of anal cancer in HIV patients because low tolerability to radiotherapy is considered to be predictive of cancer progression[61]. Currently, intensity modulated radiotherapy is under investigation in anal cancer in order to establish its impact in terms of quality of life and tolerability in immunocompetent anal cancer patients[70].

In summary, the results of previously published series confirmed that prescribing concurrent chemo-radiotherapy with curative intent should be taken into consideration in HIV anal cancer patients. Furthermore, despite the potentially higher risk of toxicity, treatment de-intensification is not recommended[54-56].

Gynaecological cancer and lung cancer in HIV patients

Cervical cancer

Cervical cancer is a common malignancy in HIV-infected women, and is considered one of the AIDS-defining cancers[71]. The higher incidence of cervical cancer can be explained by the fact that genital human papillomavirus infection is more common in HIV patients (63% vs. 30%)[71]. Concomitant radiotherapy and chemotherapy is the gold standard for locally advanced cervical carcinoma.

There are no published randomised clinical trials comparing outcomes of HIV and non-HIV patients; the only available data are from low quality, observational, retrospective studies performed in developing countries where access to chemotherapy and radio/brachytherapy is limited - **Table 3**[72-76]. In these studies information regarding treatment compliance and treatment modalities (i.e., radiotherapy dose or brachytherapy use) is lacking. Most of these reports showed a detrimental effect in terms of survival in HIV patients[72-74].

A possible explanation for the worse outcome in HIV patients is that HIV infection is associated with microsatellite instability and loss of heterozygosity, which is a factor that enhances the aggressiveness of virus-related cancers[77]. Another possible explanation is that HIV infection is associated with anaemia; it is well known that lack of oxygenation affects tumour radiosensitivity and is an adverse prognostic factor, especially in cervical cancer[78].

Several studies confirm the impact of new radiation technologies, including Intensity Modulated Radiotherapy and Image Guided Radiotherapy, on reducing pelvic toxicity when compared to the available historical data on conformal techniques[79]. Thus, these preliminary findings could be promising even when applied to the setting of cervical cancer HIV patients.

In conclusion, although literature data suggest that HIV patients with cervical cancer have a poor prognosis, international guidelines recommend treating these patients with curative intent, like their HIV-seronegative counterparts. Moreover, starting HAART prior to commencing radio(chemo) therapy is important since HAART enhances anticancer treatment efficacy and tolerability.

Lung cancer and HIV

Radiotherapy in combination with chemotherapy is the treatment of choice for locally advanced lung cancer. There are no published prospective clinical trials specifically assessing the efficacy and toxicity of radiotherapy and chemotherapy regimens in HIV patients; the only available data come from case-control series and case reports - **Table 3**[49,52,80]. Toxicity deriving from radiation treatment seems to be higher in HIV patients affected by lung cancer, with the

Grade 3-4 oesophageal toxicity rate being as high as 31% and an 80% incidence of radiation-induced oesophagitis possibly due to increased mucosal vulnerability and concurrent opportunistic oesophageal infections[81]. These data must be considered with caution because they rely on studies in which old radiation techniques were used; modern Intensity Modulated Radiotherapy can effectively reduce toxicity by minimising the dose to organs at risk such as the oesophagus and the lungs[82-84]. Using highly conformal radiation techniques in these particularly fragile patients is thereby crucial, also considering that pulmonary function can be compromised by opportunistic pulmonary infections with subsequent fibrosis[52]. A study compared the oncological outcomes of 64 lung cancer HIV patients treated before and after beginning of treatment with HAART and found that median overall survival was 3.8 months for the pre-HAART population vs. 7 months for the post-HAART patients (p=0.01), and that the cancer-related mortality rate at 1-year was 85% vs. 67%. In this study, the majorities of patients had locally advanced disease (79-91%) and were therefore treated with chemotherapy with or without radiotherapy, but chemotherapy was more frequent among post-HAART patients (79.4% vs. 48%). These data confirm that specific antineoplastic treatments and HAART have a synergistic effect and can be feasibly and safely administered together[85].

In conclusion, in the absence of definitive data, lung cancer in HIV patients should be treated the same way as in the general population, with particular attention to the management of side effects; Intensity Modulated Radiotherapy should be used to minimise treatment-related toxicity.

Head-Neck and HIV

Radiotherapy alone or in combination with drugs is the mainstay of the conservative approach in most head and neck cancers. Presently, there is little information on head and neck cancer in HIV patients, as shown in **Table 4**[86-88].

Patients with a diagnosis of head and neck cancer and HIV show limited tumour response and extensive skin or mucosal toxicities due to their immune-compromised status.

In a retrospective analysis, 8 HIV patients with head and neck carcinoma, squamous cell carcinoma, Kaposi Sarcoma, lymphoma received radiotherapy alone. All patients had received antiretroviral therapy and antifungal medication during radiotherapy. An analysis of clinical outcomes showed that all patients had partial (non KS patients) or complete response (all KS patients) to radiotherapy. The authors concluded that HIV is not a contraindication for radiotherapy and that selected HIV-infected patients with non-KS malignant neoplasms could benefit from radical radiotherapy[88].

Mourad et al. published the largest retrospective single-centre investigation of definitive radiotherapy with or without chemotherapy in head and neck HIV patients. The authors concluded that definitive radiotherapy with or without chemotherapy in HIV patients seems to be less effective as compared to the observed outcomes of non-HIV patients[87].

In conclusion, despite the limited literature, head and neck cancer in HIV patients should be treated according to international guidelines. In immunocompetent patients, the use of modern radiotherapy, like Intensity Modulated Radiotherapy, represents the standard of care in order to spare critical organs and subsequently reduce acute and late side effects[89]. This technological approach should be administered to HIV head and neck cancer patients as well.

Breast cancer and HIV

Breast cancer is the most common female oncological disease. Nevertheless, the incidence of breast cancer in HIV patients is no higher than in the general population, though only few studies have been published- **Table 4**[90-91].

Voutsadakis et al. discussed the specific pathophysiological mechanism in HIV patients with breast cancers and reported data concerning HIV women treated with surgery, radiotherapy and/or systemic therapy. The HIV population is mainly made up of young women and this could partially explain the more aggressive biology of breast cancer in this setting of patients. Oestrogen levels in premenopausal women with HIV have been found to be lower compared to non-HIV patients. In fact, women with HIV often have an early, significant loss of fat, which is an essential tissue in the production of oestrogen. Lower oestrogen levels may place breast cancer cells at a survival disadvantage and decrease their malignant latent capability. Nevertheless, HIV breast cancer patients have a poor prognosis consistently with their younger age[92] although other reports did not confirm this hypothesis[90].

Moreover, it remains unclear whether the presence of the virus in tumour cells may play a role in breast cancer pathogenesis or if the virus only plays a role when immunosurveillance is labile[93].

In conclusion, breast cancer HIV patients should be treated according to the guidelines for immunocompetent patients. To date, conformal radiation therapy (tangential fields) is considered the standard radiation technical approach. Additionally, the routine use of Intensity Modulated Radiotherapy or rotation techniques (i.e., Volumetric Modulated Arc Therapy) is usually recommended in selected patients, including those with unfavorable clinical conditions (i.e., pectus excavatum and bilateral breast cancer) for whom a decrease in heart, lung and contralateral breast dose is necessary.

Prostate Cancer and HIV

The incidence of prostate cancer among HIV-infected men is unknown and there is a lack of data on this topic. Patients with AIDS and prostate cancer often have rapid disease progression due to their severely depressed immune system, and poor response to androgen deprivation therapy related to their hypogonadism baseline status. The etiopathogenesis of hypogonadism is not completely understood, but it would appear that multifactorial elements may be involved (HIV status, malnutrition, HAART and infections)[94].

Preliminary results of radiotherapy for prostate cancer in HIV patients were published by Ng et al. Fourteen patients were treated with brachytherapy, external beam radiotherapy or a combination of these treatments, and in 4 cases elective nodal irradiation was carried out. During follow-up, PSA values for the majority of patients were under biochemical control. There were no unusual urinary or rectal toxicities and treatment complications were congruent with non-HIV patients. Moreover, radiotherapy did not appear to have a long term negative effect on the immune system: the average CD4 count remained stable and the viral load increased in only 2 of 14 patients[95]. Kahn et al published a matched cohort analysis of definitive radiotherapy for prostate cancer in HIV patients. They reported the biochemical outcome and toxicity of patients treated with radiotherapy (Intensity Modulated radiotherapy or conformal radiotherapy) to the prostate with or without whole-pelvis irradiation and compared the results to a matched control population including non-HIV or unknown HIV status subjects. Acute and late genitourinary and gastrointestinal toxicities were lower in HIV patients than in non-HIV and similar biochemical control probability was observed. Interestingly, pre- and post-radiotherapy viral loads were found to be predictive of biochemical failure. HIV patients developed an average decline in CD4 count of 193 cell/mm^3 although CD4 values were not predictive of biochemical failure[96] - **Table 4.**

In conclusion, HIV prostate cancer patients would appear to be eligible for all therapeutic treatment options. As previously described, when pelvic irradiation is provided a CD4 count reduction is observed. Intensity Modulated radiotherapy treatment is an innovative technique to increase treatment tolerability and to reduce bone marrow irradiation[97].

Clinical solutions and future direction

The use of radiation with or without chemotherapy and/or new drugs is considered the standard of care in several oncological scenarios. Nowadays, we may assume that CD4 T-cell levels could have an impact in terms of tolerability

and in some cases on clinical outcomes in HIV patients, especially in subjects treated in the pre-HAART era. HAART has undoubtedly revolutionised survival in HIV patients, guaranteeing normalisation of CD4 count and reducing the viral load, even though viral resistance associated with the use of HAART still remains an open question. Therefore, this issue needs to be taken into account in the cancer treatment strategy. In the last few decades massive technological improvements in radiotherapy and the introduction of new drugs based on genomic and mutational cancer profiles (i.e., immunotherapy and target therapies) have improved cancer-specific survival and treatment tolerability.

To date, the most common cancer diagnosis in HIV patients remains anal cancer, often involving large treatment volumes of tumours and healthy tissues. As described in the literature, the exposure of high volumes of bone marrow reserve to radiation is associated with a reduction of, and persistently low CD4 values after the end of radiotherapy and a pelvic bone marrow sparing should be strongly suggested. Therefore, the introduction of intensity modulated radiotherapy and stereotactic ablative radiotherapy has allowed radiation oncologists to prescribe higher conformal doses to targets and to minimise involvement of nearby healthy tissues – **Figure 3**. Intensity Modulated Radiotherapy is considered an advancement of 3-dimensional conformal radiotherapy, allowing for a decrease in the exposure of normal tissue, in particular in anal, cervical or prostate cancer, where pelvic irradiation is frequently prescribed to HIV and non-HIV patients. Similarly, Intensity Modulated Radiotherapy in the treatment of head and neck cancer has clearly demonstrated the possibility to strongly reduce the dose to functional organs including salivary glands, mucosa and swallowing structures, thereby allowing treatment to be completed without discontinuation due to side effects which could be crucial in fragile subjects including HIV patients.

Stereotactic ablative radiotherapy is an innovative radiotherapy approach that allows to deliver a very high conformal dose to the cancer, with rapid dose fall off on healthy surrounding tissue – **Figure 4**. In fact, immunocompetent patients who are not eligible for surgery due to comorbidities would benefit from stereotactic ablative radiotherapy in non-small cell lung cancer, thus representing a new standard curative option. Several experiences demonstrated that stereotactic ablative radiotherapy can guarantee excellent results [98] and it is currently under investigation for use in operable early stage non-small cell lung cancer, with promising preliminary results[99]. Specifically, stereotactic ablative radiotherapy may provide a non-invasive and very appealing alternative curative approach for HIV patients in whom comorbidities (i.e., concurrent pulmonary infection) can affect the feasibility of surgical resection.

Moreover, recent literature has started to consider radiotherapy as being immunostimulating and immunosuppressive. Both radiation-induced direct cellular death and pro-inflammatory cytokines are responsible for dendritic cell activation, and for the promotion of T-cell (CD8 and CD4) activation[100]. T-cells are essential in order to obtain tumour regression after irradiation with an ablative dose (15-20 Gy); in fact an *in vivo* study demonstrated that nude mice

lacking a concentration of T-cells and B cells or with a wild-type host without CD8 T-cells did not respond to radiation to the tumour cells [101]. Moreover, chemotherapy (e.g. paclitaxel and dacarbazine) can suppress T-cell activity thus decreasing immune radiation-induced tumour suppression. On the other hand, cyclophosphamide promotes T_{17}−helper differentiation thereby improving radiation-induced tumour suppression[102]. Hence, these studies underline the potential interaction between radio and/or chemotherapy and immune system modulation in cancer. Additionally, several experiences have started to demonstrate that the presence of tumour infiltrating T-cells is correlated with a better clinical outcome in several cancer histologies [103].

One of the most intriguing clinical approaches is the combination of radiotherapy and immune-checkpoint inhibitors in oncological patients, **Figure 2**. In fact, it has been demonstrated that patients with an adequate immune system and pre-existing tumour-specific T cells had better outcomes with the use of immune-checkpoint therapies[104]. Moreover, it seems that the use of localised radiotherapy can promote both tumour-specific T cells and response to immune-therapies[105].

Additionally, initial *in vivo* studies reported that the combination of immune therapies and radiotherapy induced immune infiltration in the cancer microenvironment and promotes the abscopal effect[106].

To our knowledge, only one study evaluated the use of stereotactic intracranial radiotherapy and ipilimumab in a metastatic melanoma HIV cancer patient[107]. Hence, integration of immunotherapy, radiotherapy and HIV open up a new research field in order to establish the impact of these therapies on improving cancer survival and controlling HIV infection.

Conclusions

In most HIV cancer patients, radiotherapy alone or in combination with chemotherapy seems to be feasible and to provide comparable clinical outcomes to immunocompetent cancer patients, even if an increased toxicity profile has been reported in several HIV cancer series. The recent introduction of immunotherapy represents an emerging tool to improve survival in the oncological setting and to enhance the efficacy of HAART. . Moreover, the most up-to-date technological treatments (Intensity Modulated Radiotherapy and stereotactic ablative radiotherapy) allow clinicians to reduce irradiation to healthy tissue. Recently, radiotherapy itself has also been involved as a potential promoting factor for immune system activation (immuno-modulation and abscopal effect). While modern technologies are emerging as the new standard in most anatomic districts due to the proven advantage in terms of reduced side effects, prospective clinical studies are warranted to confirm the association of new drugs and the recent intriguing hypotheses on immunomodulation.

Contributors

FA, NGL, SS, ZB searched the literature, assisted with the organisation of the manuscript, interpreted and collected data, and wrote and edited the Review. DB, UR and DR assisted with the organisation of the manuscript, interpreted and collected data, and wrote and edited the Review. AF, RM, AF, FR and SF interpreted and collected data, helped to design the figures and panel, and wrote and edited the Review.

Declaration of interests

We declare no competing interests.

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Figure 1. Search strategy flowchart for the inclusion and exclusion of studies

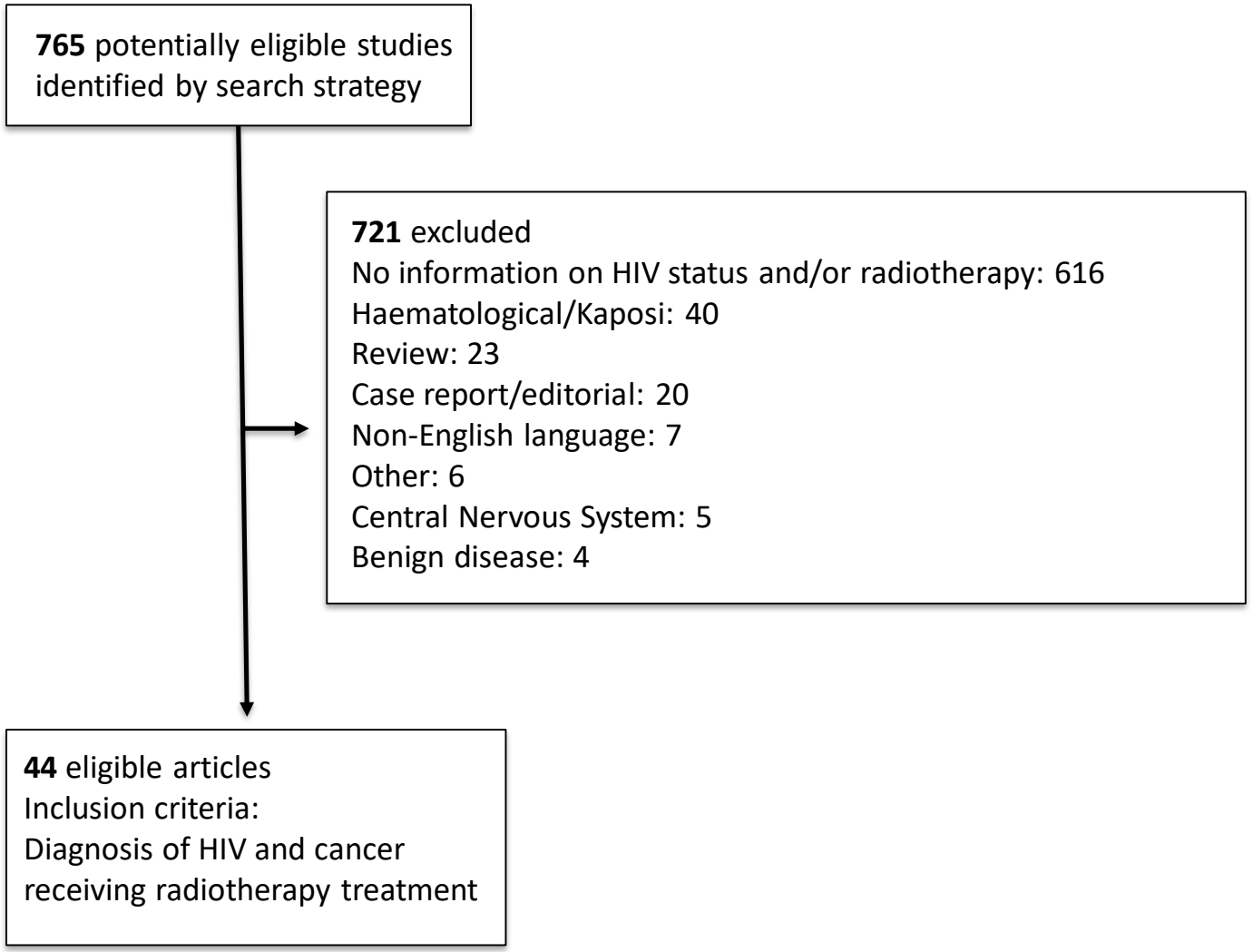


Figure 2. HIV effect on CD4 T-cell and HAART & immunotherapy effect to HIV and cancer cell

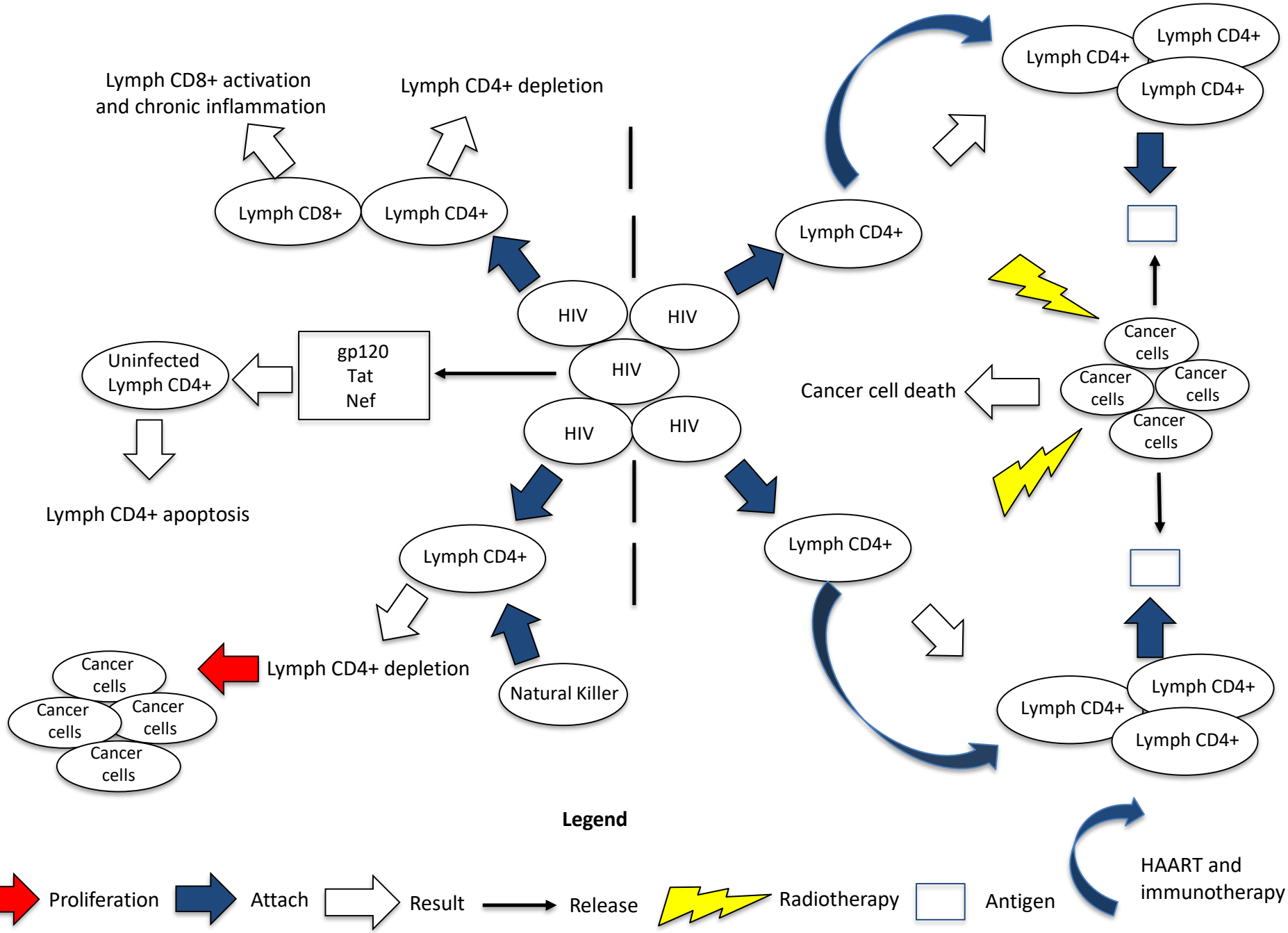
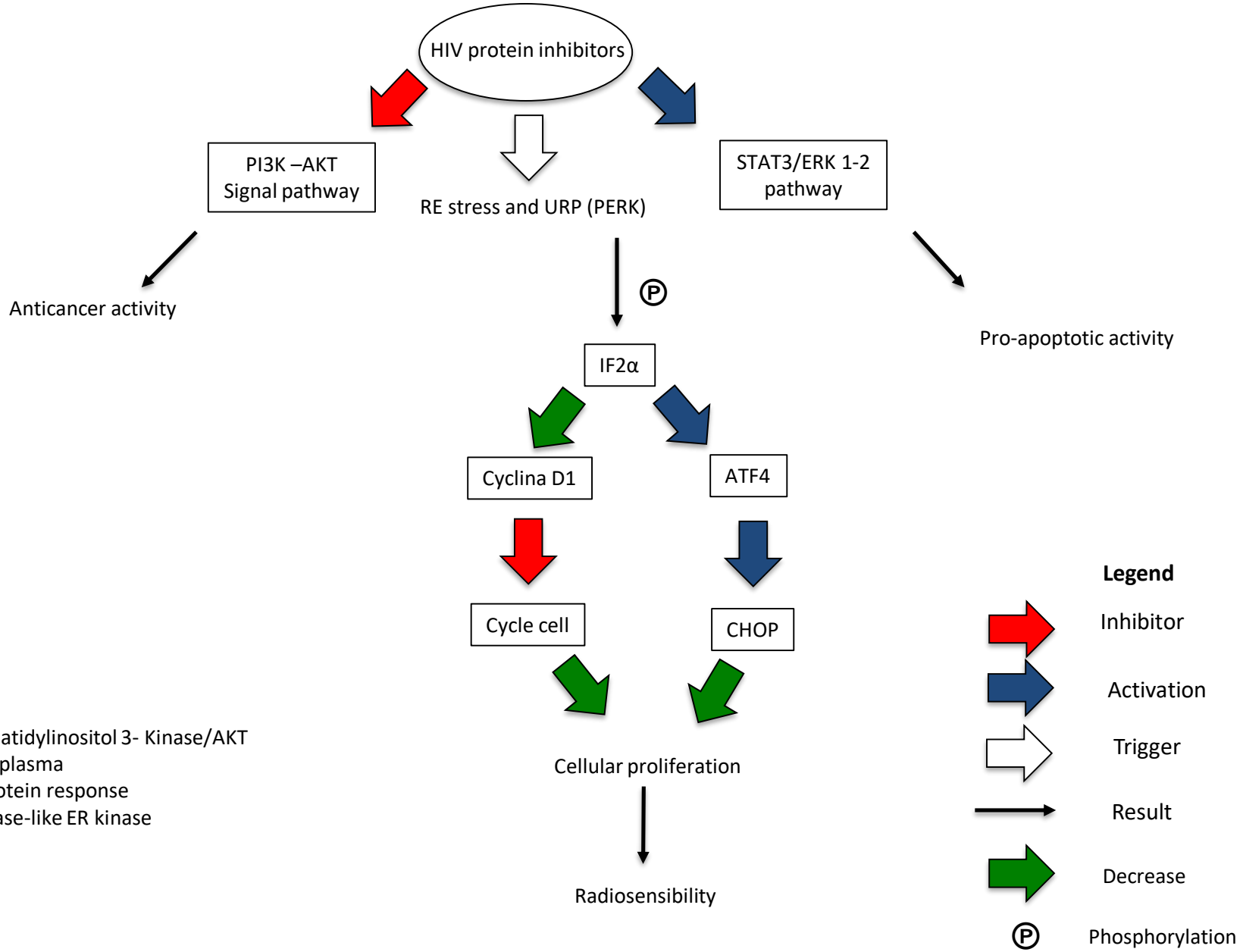


Figure 3. Anticancer and radiosensitivity activities of HIV protein inhibitors in cancer cell



PI3 – AKT: phosphatidylinositol 3- Kinase/AKT
RE: reticular endoplasma
URP: Unfolded protein response
PERK: protein kinase-like ER kinase

Figure 2. HIV effect on CD4 T-cell and HAART & immunotherapy effect on HIV and cancer cell

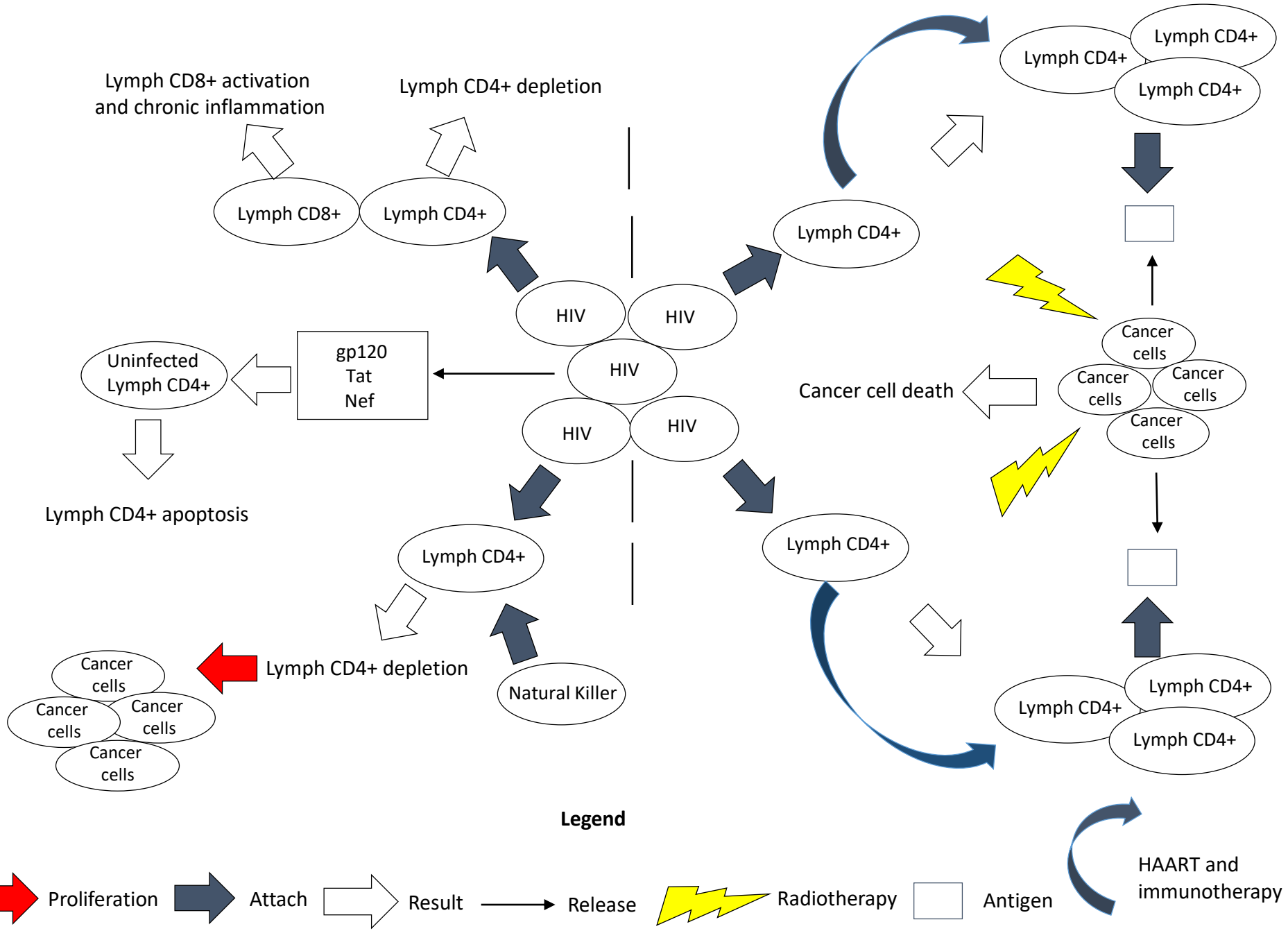
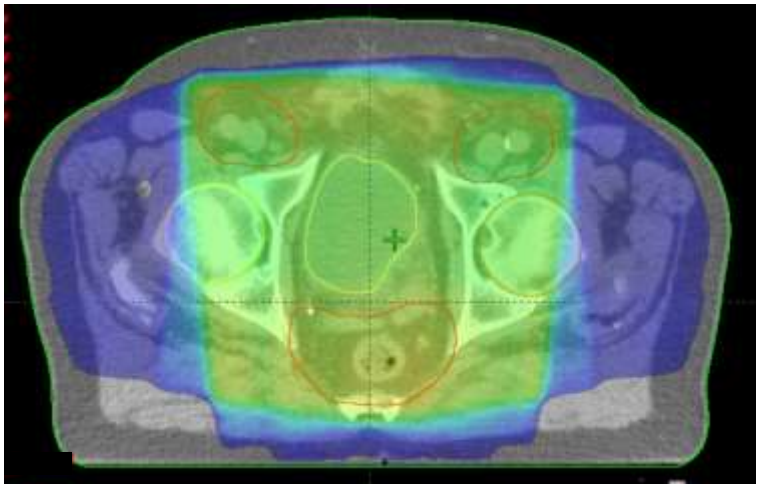
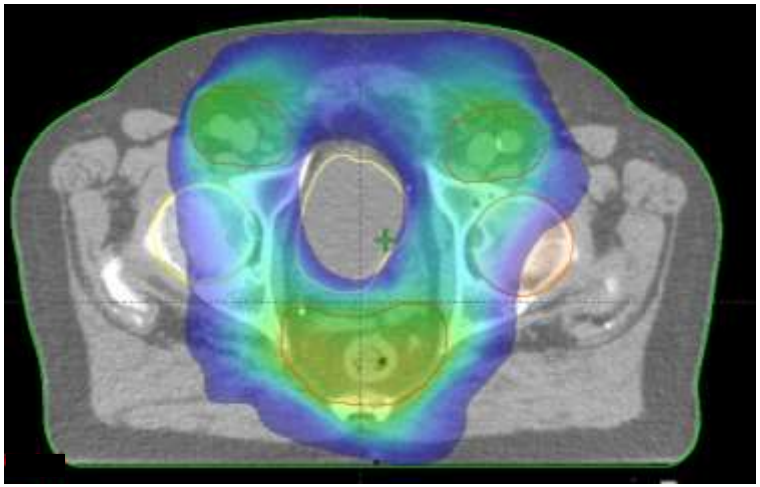


Figure 3: Comparative planning and dose distribuction in patient with HIV+ anal cancer



a Conformal radiation treatment (3D-CRT)



b Volumetric Modulated Arc Therapy (VMAT – IMRT)

Figure 4: HIV+ patient with early stage non-small cell lung cancer (white arrow) treated with stereotactic ablative radiotherapy (Volumetric Modulated Arc Therapy). Dose prescription of 54Gy in 3 fractions. The colour wash indicates the high dose distribution focused on tumor lesion.

Table 1. CD4 count variation, CD4 toxicity and clinical impact of oncological treatment in HIV cancer patients.

Authors	Year	Study	Histology	HIV (pts)	Retro-viral therapy	CD4 count	Toxicity CD4/RT	Pre-RT CD4/prognosis	Conclusion on outcomes
Holland et al.[34]	1994	RP	Anal cancer	7	NA	<200 c: 4 pts ≥300 c: 3 pts	NA	Yes	Detrimental in pts CD4 low levels
Kao et al.[50]	1999	RP	H&N	8	NA	NA	No	No	Not detrimental
Hoffman et al.[35]	1999	RP	Anal cancer	17	NA	< 200 c: 8 pts ≥ 200 c:9 pts	NA	Yes	Not detrimental
Tirelli et al.[49]	2000	RP	Lung cancer	36	HAART	150mc	NA	No	Not detrimental
Place et al.[38]	2001	RP	Anal cancer	23	HAART & No-HAART	SCCIS: 222 mc SCC: 200 mc	NA	Yes	Detrimental
Spano et al.[52]	2004	RP	Lung cancer	22	HAART	< 200 c: 2 pts 200-500 c:15 pts ≥500 c: 5 pts	NA	Yes	Detrimental
Blazy et al.[39]	2005	RP	Anal cancer	9	HAART	< 200 c: 4 pts 200-500 c:4 pts >500 c: 1 pts	NA	NA	Not detrimental
Wexler et al.[41]	2008	RP	Anal cancer	32	HAART	350 mc	Yes	Yes	Detrimental
Seo et al.[61]	2008	PR	Anal cancer	17	HAART	190 Mc	NA	No	Not detrimental
Oehler-Janne et al.[22]	2008	RP	Anal cancer	40	HAART	321 mc	NA	No	Not detrimental
Ng et al.[45]	2008	RP	Prostate	14	HAART	523 Mc	NA	No	Not detrimental
Abramowitz et al.[62]	2009	RP	Anal cancer	44	HAART	NA	NA	No	Not detrimental
Fraunholz et al.[43]	2010	RP	Anal cancer	21	HAART	347.5 mc	Yes	NA	Not detrimental
Hauerstock et al.[63]	2010	RP	Anal cancer	34	HAART	<350 c: 19 pts ≥350 c: 11 pts Unknown: 4 pts	NA	No	Not detrimental
Kahn et al.[47]	2011	match pair analysis	Prostate	13	HAART	<300 c: 4 pts ≥300 c: 8 pts	Yes	No	Not detrimental
Alfa-Wali et al.[40]	2012	PR	Anal cancer	60	HAART & No-HAART	All pts: 305 mc All CRT: 289 mc CRT No-HAART: 209 mc CRT HAART: 332 mc	Yes	No	Detrimental
Martellotta et al.[36]	2012	RP	Anal cancer	65	HAART (96.8%) No-HAART	< 200 c: 24 pts 200-400 c:14 pts >400 c: 21 pts	NA	No	Not detrimental

					(3.2%)	Unknown: 6 pts			
Sankatsing et al.[42]	2013	PR	Mixed	90	cART	RT: 400 c No-RT: 471 c	Yes	NA	NA
Fraunholz et al.[37]	2014	RP	Anal cancer	36	HAART	367 mc	Yes	NA	Not detrimental
White et al.[65]	2014	RP	Anal cancer	53	HAART	455 mc	NA	No	Inconclusive*
Grew et al.[66]	2015	RP	Anal cancer	39	HAART	381 mc	NA	No	Not detrimental
Simonds et al.[48]	2015	RP	Cervix	36	HAART	341 mc	NA	No	Not detrimental
Sparano et al.[44]	2016	PR	Anal cancer	45	HAART	401 mc	Yes	No	Not detrimental

RP: retrospective; PR: prospective; pts: patients; RT: radiotherapy; CRT: chemo-radiotherapy; c: count; mc: median count; Mc: mean count; HAART: highly active antiretroviral therapy, cART: combination antiretroviral therapy; NA: not available; SCC: squamous cell cancer; SCCI: squamous cell cancer in situ; H&N: Head and Neck.

*OS: p=0.06 (C.I. 0.32-0.97)

Table 2. Relationships between HIV status and oncological outcomes in anal patients

Authors	Year	Study	Histology	HIV (pts)	Indications	Follow-Up	Toxicity acute	Toxicity late	Outcomes	HIV and outcomes
Chadha et al.[54]	1994	RP	Anal cancer	9	Concurrent CT/RT (40 Gy + boost 10 Gy)	9 mo	Yes	Yes	NA	Detrimental in pts CD4 low levels
Holland et al.[34]	1994	RP	Anal cancer	7	Concurrent CT/RT, CT, RT (50.4 Gy)	NA	Yes*	Yes*	NA	Detrimental in pts CD4 low levels
Peddata et al.[55]	1997	RP	Anal cancer	8	Concurrent CT/RT (30 Gy - 3DCRT)	41 mo	Yes	NA	NA	Inconclusive
Hoffman et al.[35]	1999	RP	Anal cancer	17	Concurrent CT/RT (51.8 Gy 3DCRT)	17 mo	Yes <200 CD4	NA	mDFS 13.5 mo	Detrimental AIDS
Cleator et al.[56]	2000	RP	Anal cancer	12	Concurrent CT/RT (38-51+boost 10-18 Gy 3DCRT)	4.8 yrs	No	NA	OS@5 yrs:60%	Not detrimental
Kim et al.[57]	2001	RP	Anal cancer	13	Concurrent CT/RT (50-54 Gy 3DCRT)	25.4 mo	Yes	Yes	mOS 3.1 yrs	Detrimental HIV in OS
Place et al.[38]	2001	RP	Anal cancer	23	Concurrent CT/RT (30-60 Gy)	5 yrs	Yes	NA	NA	Detrimental in pts CD4 low levels and No-HAART
Stadler et al.[58]	2004	RP	Anal cancer	14	Concurrent CT/RT (54 Gy 3D-CRT)	NA	NA	NA	OS@5 yrs:40%	Detrimental (HIV+ treated with in HAART on OS)
Blazy et al.[40]	2005	RP	Anal cancer	9	Concurrent CT/RT (60 Gy)	36 mo	Yes	No	NA	Not detrimental
Edelman et al.[59]	2006	RP	Anal cancer	17	Concurrent CT/RT (50.4-59.4 Gy)	25.6 mo	Yes	Yes	OS@18 mo:67%	Not detrimental
Oehler-Janne et al.[23]	2006	RP	Anal cancer	10	CT-RT, CT (53.6 Gy + boost 14 Gy brachy)	44 mo	Yes	Yes	OS@5 yrs:70%	Detrimental
Wexler et al.[41]	2008	RP	Anal cancer	32	Concurrent CT/RT (54 Gy 3DCRT)	35 mo	Yes	No	OS@5 yrs: 65%	N/D to HIV-
Oehler-Janne et al.[22]	2008	RP	Anal cancer	40	Concurrent CT/RT (52-60 Gy) ± brachy	36 mo	Yes	No	OS@5 yrs:61%	Detrimental
Chiao et al.[60]	2008	RP	Anal cancer	175	CT, RT	32 mo	NA	NA	OS@2 yrs: 77%	N/D to HIV-
Seo et al.[61]	2008	PR	Anal cancer	17	Concurrent CT/RT	3.1 yrs	Yes	NA	OS@3 yrs: 91.7%	N/D to HIV-

					(56.3-58.8 Gy 3D-CRT)					
Abramowitz et al.[62]	2009	RP	Anal cancer	44	RT (45 Gy 3D-CRT + brachytherapy or boost to 60-65 Gy)	27 mo	N/D	N/D	OS@3 yrs: 85%	N/D to HIV-
Hauerstock et al.[63]	2010	RP	Anal cancer	34	Concurrent CT/RT (54 Gy 3D-CRT-IMRT)	25.2 mo	Yes	NA	OS@3 yrs:69%	Not detrimental
Fraunholz et al.[43]	2010	RP	Anal cancer	21	Concurrent CT/RT (54 Gy + boost 5.4- 10.8 Gy 3D-CRT)	53 mo	Yes	Yes	OS@5 yrs:67%	Not detrimental
Hammad et al.[64]	2011	RP	Anal cancer	13	Concurrent CT/RT (45-63 Gy)	NA	Yes	NA	mOS: 33.5 mo	N/D to HIV-
Munoz-Bongrand et al.[68]	2011	RP	Anal cancer	20	Concurrent CT/RT (60-70 Gy 3D-CRT)	32.5 mo	NA	NA	OS@5 yrs: 39%	Detrimental HIV in OS and LC
Martellotta et al.[36]	2012	RP	Anal cancer	65	Concurrent CT/RT (53.9%)	NA	N/D	N/D	mOS (mo) HIV+ 106	N/D to HIV-
Alfa-Wali et al.[40]	2012	PR	Anal cancer	60	Concurrent CT/RT (50.4-60 Gy)	6.5 yrs	Yes Grade 3:30%	NA	OS@5yrs: 64%	N/D to HIV-
White et al.[65]	2014	RP	Anal cancer	53	Concurrent CT/RT (54 Gy 3D-CRT-IMRT)	34 mo	N/D	N/D	OS@3 yrs:72%	N/D to HIV-
Fraunholz et al.[37]	2014	RP	Anal cancer	36	Concurrent CT/RT (54 Gy 3D-CRT)	66 mo	N/D	NA	OS@5 yrs:74%	N/D to HIV-
Grew et al.[66]	2015	RP	Anal cancer	39	Concurrent CT/RT (54 Gy 3DCRT-IMRT)	15 mo	N/D	NA	OS@3yrs: 76%	Detrimental HIV in OS and CFS
Wieghard et al.[67]	2016	RP	Anal cancer	14	Concurrent CT/RT (45-54 Gy IMRT)	29.2 mo	N/D	N/D	mOS (mo) HIV+ 68.8 HIV- 110.9	N/D to HIV-
Sparano et al.[44]	2016	PR	Anal cancer	45	Concurrent CT/RT and Cetuximab (45-54 Gy 3D-CRT-IMRT)	56 mo	Yes	NA	OS@3yrs: 79%	Not detrimental
Martin et al.[69]	2017	RP	Anal cancer	42	Concurrent CT/RT (50.4 Gy 3D-CRT-IMRT)	51 mo	N/D	N/D	OS@5yrs HIV+70.7% HIV – 78.4%	N/D to HIV-

RP: retrospective; PR: prospective; pts: patients; N/A: not available; N/D: no differences between HIV and no-HIV; c: count; mc: median count; mOS: median overall survival; OS: overall survival; mo: months; yrs: years, IMRT: intensity modulated radiotherapy, 3D-CRT: conformal radiotherapy; brachy: brachytherapy; CFS: colonstomy free-survival; mDFS: median disease free survival.

*Unclear grade toxicity

Table 3. Relationships between HIV status and oncological outcomes in gynaecological and lung cancer patients.

Authors	Year	Study	Histology	HIV (pts)	Indications	Follow-Up	Toxicity acute	Toxicity late	Outcomes	HIV and outcomes
Shrivastava et al.[72]	2005	RP	Cervical carcinoma	42	RT (EBRT, ICT)	12 mo	Yes	Yes	NA	Detrimental in HIV
Gichangi et al.[73]	2006	PR	Cervical carcinoma	41	RT (EBRT)	NA	Yes	NA	NA	Detrimental in HIV
Kigula-Mugambe et al.[74]	2006	RP	Cervical carcinoma	7	RT (EBRT, ICT)	NA	NA	NA	OS@4 yrs: 0%	Detrimental in HIV
Simonds et al.[75]	2012	RP	Cervical carcinoma	59	CT, RT (3D-CRT + HDR)	NA	Yes	NA	NA	NA
Simonds et al.[76]	2015	RP	Cervical carcinoma	36	CT, RT (EBRT)	NA	Yes	NA	NA	NA
Tirelli et al.[49]	2000	RP	Lung cancer	36	S, CT, RT	NA	Yes	NA	mOS: 5 mo	Detrimental in HIV
Spano et al.[52]	2004	RP	Lung cancer	22	S, CT, RT	NA	No	No	mOS: 7 mo	Not detrimental
Suneja et al.[80]	2013	RP	Lung cancer	337	S, CT, RT	NA	NA	NA	Lower in HIV	Inconclusive

RP: retrospective study; PR: prospective study; pts: patients; S: surgery; CT: chemotherapy, RT: radiotherapy, EBRT: external beam radiotherapy, 3D-CRT: conformal radiotherapy, HDR: High dose rate; ICT: intracavital therapy; NA: not available; mOS: median survival; mo: months

Table 4. Relationships between HIV status and oncological outcomes in prostate, head and neck and breast cancer patients.

Authors	Year	Study	Histology	HIV (pts)	Indications	Follow-Up	Toxicity acute	Toxicity late	Outcomes	HIV and outcomes
Kao et al.[50]	1999	RP	H&N	8	RT (3D-CRT)	NA	No	No	NA	Notdetrimental
Levinson et al.[9]	2005	RP	Prostate	5	RT (brachytherapy and 3D-CRT)	NA	NA	NA	NA	NA
Oluwole et al.[90]	2005	RP	Breast	5	RT (1 patient)	NA	NA	NA	NA	NA
Ng et al.[45]	2008	RP	Prostate	14	RT (palladium-103 +/- external beam – IMRT)	26 mo	No	NA	NA	NA
Sanfilippo et al.[86]	2010	RP	H&N	13	RT, CT (66.4 Gy)	22 mo	No	No	NA	Not detrimental
Kahn et al.[47]	2011	Match pair analysis	Prostate	13	RT (3D-CRT – IMRT)	39 mo	No	No	OS N/D	N/D to HIV-
Mourad et al.[87]	2013	RP	H&N	71	S, CT, RT (70 Gy)	47 mo	Yes	Yes	OS@4 yrs: 55%	Detrimental in HIV
Phakathi et al.[91]	2016	PR	Breast	14	S, CT,RT	NA	NA	NA	NA	N/D to HIV-

H&N: head and neck; RP: retrospective; PR: prospective; pts: patients; S: surgery; CT: chemotherapy; RT: radiotherapy NA: not available; N/D: no differences; OS: overall survival, mo: months; yrs: years, IMRT: intensity modulated radiotherapy, 3D-CRT: conformal radiotherapy.