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***The role of radiotherapy in the  
management of cancer patients  
infected by human  
immunodeficiency virus (HIV)***



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## FOREWORD

Cancer and AIDS are both pandemics: they have an emotional and social impact that goes far beyond the physical disruption they cause. These are usually perceived and addressed as independent disease entities. When these coexist in one patient, however, the appropriate management of the cancer needs to be modified from the standard clinical protocols. New protocols appearing in the radiotherapy literature have been investigative rather than definitive and, with few exceptions, analyse the results of small series of patients.

The IAEA has extensive projects in radiation oncology in developing countries. In Africa, there is concern that AIDS related cancers utilise an increasing amount of scarce resources, that they frequently require equipment for the management of superficial tumours, and that inadequate training is available in the management of these cancers. This report developed from the need to address these concerns.

An Advisory Group Meeting (AGM) on the Relationship between Human Immunodeficiency Virus (HIV) and Cancer Management Protocols for Developing Countries was convened in October 1999. A reading of this report will show that considerable amount of further investigation is required to respond authoritatively to many of the management decisions that need be made. It is also evident that the greatest number of patients requiring optimal management protocols live in sub-Saharan Africa — a region where research resources are at a minimum. The IAEA has made available limited funding for a research project in determining the intermediate term effects of radiation therapy on the immune system in AIDS related cervical cancer.

The expert contributions of all the participants in the AGM leading to this publication are gratefully acknowledged. Special thanks are due to A. Munro, Radiation Oncology, Ninewells Hospital and Medical School, Dundee, United Kingdom, for his assistance in producing the final report and updating the text and references. Thanks are also due to M. Parkin of the International Agency for Research on Cancer, Lyon, France, for his continuing work on determining the extent of cancer in general and AIDS related cancers in particular. The IAEA officer responsible for this publication was V. Levin of the Division of Human Health.

### *EDITORIAL NOTE*

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## 1. THE HIV EPIDEMIC

Cancer and AIDS are both pandemics: they have an emotional and social impact that go far beyond the physical disruption they cause. Each attracts billions of dollars of research funds and both receive justifiable priority over heart disease and mental health topics in news coverage and funding.

In both fields, AIDS and cancer, research is progressing rapidly and, as the accumulation of data on worldwide trends in both spread and treatment takes a few years to compile, there are potential problems with topicality and redundancy. A title proposed in 1996 might lose relevance by the time of implementation in the year 2000. Not only has no authoritative text appeared on the title, but the more general topic “The Role of Radiotherapy in the Human Immunodeficiency Virus (HIV) Infected Patient” (developed or developing countries) has not been addressed. The majority of publications on HIV are concerned with fundamental research (where drug companies are spending their money), drug therapy (where health care systems are spending their money), and epidemiology (the chief remit of UNAIDS). Radiotherapy has a major role to play in the practical management of patients with HIV infection and malignancy and yet there have only been around 200 articles and book chapters on the subject.

The meeting identified issues with major implications for the expenditure on health resources for Member States.

### 1.1. HIV infection in the world

The HIV pandemic was first noted in 1981 when a clustering of atypical *Pneumocystis carinii* pneumonia cases was noted in homosexual males in Los Angeles and New York. This was found to be related to an immune deficiency which had further clinical consequences: other forms of opportunistic infection; Kaposi’s sarcoma and other malignancies. The original combination of clinical features, *Pneumocystis carinii* pneumonia and Kaposi's sarcoma, was used to define the Acquired Immune Deficiency Syndrome (AIDS).

The identification of a viral aetiology for the immunosuppression, together with the characterisation of human immunodeficiency virus (HIV) in 1983 and subsequent serological testing for incidence and prevalence of the virus led to numerous theories of the origin of the disease. The worldwide distribution of the virus was apparent from the outset. The mechanisms of transmission initially identified were unprotected homosexual intercourse, the common use of infected needles by intravenous drug users and blood transfusion, particularly in haemophiliacs. The current pandemic, however, has been propagated predominantly by unprotected heterosexual intercourse with an infected individual. Mother–child transmission is also important in populations with a high prevalence of infection.

The pandemic currently has its highest concentration in sub-Saharan Africa with up to 35% of populations infected. Only four countries (Bahamas, Cambodia, Guyana and Haiti) of 30 countries with a prevalence of HIV seropositivity >3% of the population are from outside this region.

This, however, is recognised as a worldwide problem with increasing numbers of cases within some regions.

## ESTIMATED NUMBER OF PEOPLE LIVING WITH HIV/AIDS, END 1999

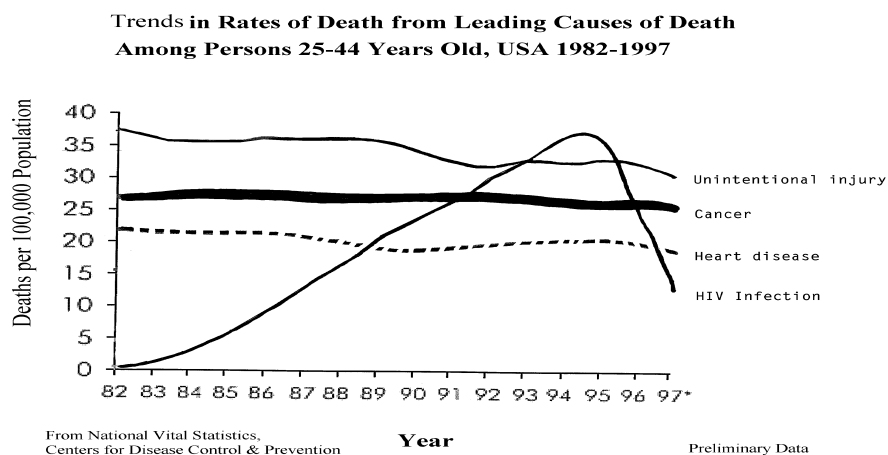
Country	Adults (15–49)	Adult rate (%)
<b>Global total</b>	<b>33 000 000</b>	<b>1.07</b>
<b>Sub-Saharan Africa</b>	<b>23 400 000</b>	<b>8.57</b>
Botswana	280 000	35.80
Swaziland	120 000	25.25
Zimbabwe	1 400 000	25.06
Lesotho	240 000	23.57
Zambia	830 000	19.95
South Africa	4 100 000	19.94
Namibia	150 000	19.54
Malawi	760 000	15.96
Kenya	2 000 000	13.95
Central African Republic	230 000	13.84
Mozambique	1 100 000	13.22
Djibouti	35 000	11.75
Burundi	340 000	11.32
Rwanda	370 000	11.21
Cote d'Ivoire	730 000	10.76
Ethiopia	2 900 000	10.63
Uganda	770 000	8.30
United Rep. of Tanzania	1 200 000	8.09
Cameroon	520 000	7.73
Burkina Faso	330 000	6.44
Congo	82 000	6.43
Togo	120 000	5.98
Haiti	200 000	5.17
Dem. Republic of Congo	1 100 000	5.07
Nigeria	2 600 000	5.06
Gabon	22 000	4.16
Bahamas	6 800	4.13
Cambodia	210 000	4.04
Ghana	330 000	3.60
Guyana	15 000	3.01

POPULATIONS AND HIV POPULATIONS IN 1999 (REF: UNAIDS)

Region	Population	HIV infected persons
Western Europe	400 181 000	520 000
North Africa & Middle East	322 211 000	220 000
Sub-Saharan Africa	593 027 000	24 500 000
South & South East Asia	1 859 821 000	5 600 000
Eastern Europe & Central Asia	373 424 000	420 000
East Asia & Pacific	1 451 707 000	530 000
Australia & New Zealand	21 891 000	15 000
North America	301 591 000	900 000
Caribbean	30 932 000	360 000
Latin America	455 247 000	1 300 000
TOTAL	5 837 110 000	34 300 000

Thus, in 1999 there were 34.3 million people alive with HIV infections. About 5.4 million new infections occurred in 1998. Of these, 620 000 were children.

The resulting rise in deaths has not been universal. The developed countries have, in fact, demonstrated falling death rates because of a number of factors. The trend in the USA is representative of many countries where the AIDS death rate only fleetingly, 1992 to 1995, became the leading cause of death in one specific age group (25 to 44).



*Trends in rates of death from leading causes of death among persons 25–44 years old, USA, 1982–1997.*

Among the leading causes of years of potential life lost before the age of 65 (YPLL65) since the inception of the AIDS pandemic in 1982, AIDS has never reached the level of even heart disease which is a less significant cause of YPLL65 than cancer in the USA.

## **1.2. Infective causes of cancer**

It is estimated that over 15% of all cancers worldwide owe their origin to infection notably by hepatitis B and C, human papilloma virus (HPV), helicobacter pylori and Epstein-Barr virus (EBV). Parasitic infections by schistosomiasis and liver flukes also contribute to cancer aetiology.

HIV is not a directly oncogenes virus — it does not result in genetic modifications affecting cellular replication — however, it facilitates the development of cancers by its effect on the immune system, and, since its removal would prevent occurrence of such cancers, it should be considered as “causative”.

## **1.3. Testing for HIV and AIDS**

The definition of the onset of AIDS (a clinical syndrome) during the evolution of HIV infection is a somewhat arbitrary process. The definitions used are based on the presence of symptoms and signs commonly seen in other diseases endemic in Africa such as tuberculosis, malaria, and trypanosomiasis. This is an obvious cause of diagnostic difficulty: that which is “AIDS” may not actually be so; the converse will also be true.

The initial “incubation period” from seroconversion (HIV positive test) to the development of full-blown AIDS occurs in a median period of about seven years. There is thereafter rapid progression to death with a median survival of about 9 months in Africa (and other developing countries) without the use of anti-retroviral drugs. With full support for treatment of the disease and its symptoms, survival is extended to about 18 months.

In the early phase of AIDS, laboratory testing is the only way of proving the presence of infection. Antigen-detection tests using *Enzyme-Linked Immunoabsorbant Assay* (ELISA) are now, in contrast to initial versions of the test, reasonably (98%) reliable and can be performed on a single fresh specimen of blood, saliva, urine or other bodily fluid.

## **1.4. Cancer associated with HIV**

The reduced immune response resulting from HIV infection increases the probability of developing several cancers. The cancers developed do not necessarily contribute to the final cause of death of the patient because of competing risks of mortality from infection and other causes, including treatment.

The most conspicuous cancers, occurring with over a twenty-fold increase compared with the general population are Kaposi’s sarcoma (epidemic Kaposi’s sarcoma) and non-Hodgkin’s lymphoma (NHL). Large increases in risk (5 to 20 fold) occur with squamous carcinoma of the conjunctiva, Hodgkin’s disease and leiomyosarcoma in children. There is less convincing evidence that the incidence of tumours of the testis, oral cavity, cervix, brain (other than NHL), lung, breast, thyroid and myeloma may also be increased.

## 2. MALIGNANCY IN HIV

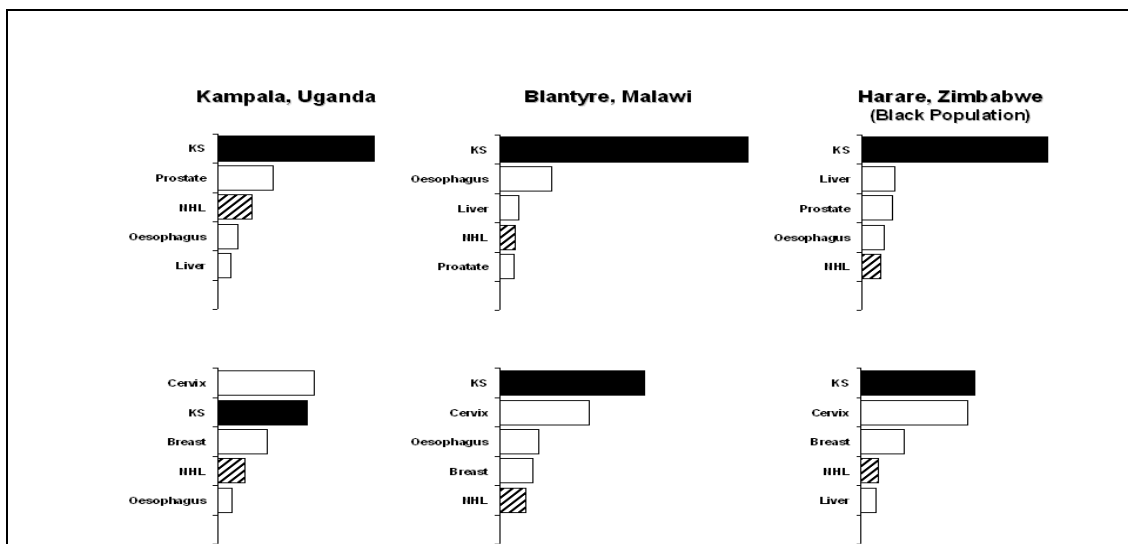
### 2.1. Kaposi's sarcoma

Before the AIDS epidemic, Kaposi's sarcoma was endemic in Central Africa (Rwanda, Burundi, Uganda, Tanzania and Malawi) and was also observed, although with much lower rates in the East Mediterranean region especially southern Europe. It was a rare disease in other countries. Endemic Kaposi's sarcoma is a relatively indolent tumour, mainly confined to the legs in elderly men.

The risk of developing Kaposi's sarcoma is enormously increased in HIV positive subjects in North America and Europe. While morphologically and histologically the same cancer, Epidemic Kaposi's sarcoma is far more aggressive. It is widespread on the skin and more frequently involves mucosal surfaces, lymph nodes and internal organs.

The risks of developing epidemic Kaposi's sarcoma is also noted to be dependent on the mode of transmission of HIV. The risk is much greater in HIV infection acquired through homosexual contacts than in other risk groups. Furthermore, in homosexual transmission, the risk is associated with the number of partners and oro-anal contact suggesting faecal contamination. In heterosexual transmission, the probability of developing epidemic Kaposi's sarcoma is increased if HIV was contracted from a partner from a high-risk country.

In Africa, where HIV infection is almost entirely through heterosexual contact, about 10–15% of AIDS cases will develop epidemic Kaposi's sarcoma. The risk of epidemic Kaposi's sarcoma in HIV infection is much lower in Africa than in Europe/USA — about 20–100 fold. This probably reflects a higher baseline risk of Kaposi's sarcoma in non-HIV infected Africans so that the actual incidence of Kaposi's sarcoma in African countries with a high prevalence of HIV infection in the population is now very high: Kaposi's sarcoma is the most common cancer of men and women in Uganda, Zimbabwe and Malawi.



*The five most common cancers in three East African cities 1996–1997  
(Courtesy of M. Parkin, IARC, Lyon)*

Many of the features of the epidemiology of Kaposi's sarcoma have been explained by the discovery of KSHV/HHV-8 virus and its identification as the cause of Kaposi's sarcoma. This virus is much more common in African populations, and in homosexual males, than in the general population of Europe and North America. Positive serology for HHV-8 in HIV positive subjects reliably predicts which of these subjects will develop epidemic Kaposi's sarcoma.

The risks of developing Kaposi's sarcoma are increased by the presence of KSHV but this effect is greatly enhanced by the presence of HIV.

<b>KSHV serostatus</b>	<b>HIV serostatus</b>	<b>OR</b>
–	–	1.0
+	+	12.
+	+	1700

*An increased risk of developing epidemic Kaposi's sarcoma is related to KSHV and HIV serostatus (Courtesy of F. Sitas, SAIMR, Johannesburg)*

## **2.2. Non-Hodgkin's lymphoma**

About 3% of adult AIDS cases present with non-Hodgkins lymphomas (NHL). After the diagnosis of AIDS more lymphomas develop so that some 5–10% of HIV positive subjects will ultimately develop a lymphoma.

AIDS associated lymphomas are predominantly of B-cell origin (>90%) and are far more frequently extranodal.

A proportion is also associated with the presence of a second virus, the Epstein-Barr virus (EBV), within the tumour.

<b>Site</b>	<b>Occurrence</b>	<b>Type</b>	<b>EBV</b>	<b>Immune suppression</b>
Systematic (mainly extranodal)	75%	B cell	75%	++
		Burkitt	35%	+
Brain	25%	B cell	100%	+++

The risk of NHL in HIV positive subjects in Europe/North America is increased some 50-fold so that in certain populations (e.g. white males in San Francisco) show quite marked increases in NHL incidence. In contrast, the risk of NHL in HIV infected Africans does not seem to be greatly increased (2–10-fold) so that increases in NHL incidence in Africa are very modest.

In North American and European children, NHL is the most cancer observed in HIV infection — about 1.5% of AIDS diagnoses. Burkitt's lymphoma (BL), in particular, is greatly increased in frequency with an estimated relative risk of 200 or so in HIV positive children. Endemic BL has been a common cancer in tropical Africa. It has a quite characteristic clinical

presentation, and almost all cases are EBV positive. The relative risk of BL was not increased in the presence of HIV infection in a recent study in Uganda.

### **2.3. Squamous cell carcinoma of the conjunctiva**

A large variety of ocular tumours occur in both childhood and adulthood but are relatively uncommon. Squamous cell carcinomas of conjunctiva are normally rare although they have long been described in parts of Africa, and it is possible that aetiology is related to solar UV exposure.

A 10-fold increase in conjunctival tumours has been observed from the African data from 1990.

### **2.4. Hodgkin's disease**

The evidence for Hodgkin's disease (HD) association with HIV is based solely on cohort studies on HIV positive subjects and AIDS registers. The indications are that there may be a 5 to 10-fold increase in this disease.

Of the usual four subtypes, mixed cellularity and lymphocyte depleted histologies predominate in HIV positive subjects.

### **2.5. Childhood leiomyosarcoma**

Because of its rarity, the association has been made mainly on case reports and series which suggest an increased frequency in children.

### **2.6. Other cancers**

Many other cancers have been reported in HIV positive subjects, but the evidence for a statistical association, let alone a causative relationship, is very weak.

Cervical cancer has been an AIDS defining malignancy since 1993. The relationship will be discussed in Section 6. After a period of confusion, it does seem clear that the risk of pre-invasive cervical malignant disease (CIN) is increased by HIV infection *independently* of the presence of HPV infection (of course, the two infections transmitted sexually tend to coexist in the same woman). For invasive cervix cancer, the evidence is not consistent, while some prospective studies of AIDS cases (in Italy) suggest an increased risk, others (in the USA) do not.

Anal cancer, while not AIDS defining, will be further discussed in (Section 8).

Hepatocellular cancer is associated with hepatitis B and C virus and is increased in transplant (immuno suppressed) recipients. No increase has been noted in HIV patients similarly immuno-compromised.

Other tumours (testis, oral cavity, brain, lung, breast, thyroid and myeloma) have been implicated but no significant increase has been confirmed. Management principles specific to HIV patients should be applied to patients with these and all other cancers as in Section 3.

### 3. PRINCIPLES OF MANAGEMENT FOR HIV RELATED MALIGNANCY

It is rare in oncology for other medical problems to be more important or life threatening than the patient's malignant disease. However, in managing tumours in HIV positive patients, the malignant disease may not be the dominant clinical issue. The underlying infection was, until the recent introduction of effective anti-retroviral therapy, almost uniformly fatal. It is against this background of an underlying fatal disease that the management of HIV related malignancy must be set. The usual oncological rules of practice do not apply: cure at any cost is not a sensible option. Very often the best decision is simply to treat with the simplest, most effective, palliative regimen available. Any decision to treat radically has to be tempered by the realisation that the patient's life span will be limited, regardless of the success or failure of the treatment for the malignant disease. Nowhere in oncology is an individualised approach to decision-making more important than in HIV oncology. While guidelines need to be established for a given department, protocol-driven treatment is usually inappropriate and the patient should, wherever possible, be fully involved in decisions concerning management of both the HIV infection and of the malignant disease.

#### 3.1. Management

The following management options are available for any patient with HIV related malignancy:

- Active observation for asymptomatic disease
- Local treatment (palliative or radical) for disease that is localised but symptomatic
- Systemic treatment (palliative or radical) for disseminated symptomatic disease.

It should be emphasised that, for a patient with asymptomatic malignancy and HIV infection, active observation is a perfectly reasonable policy. Simply because a cancer is present does not mean that it has to be treated.

Ideally, the assessment and initial management decisions concerning patients with HIV related malignant disease should be carried out in a multidisciplinary clinic with the following disciplines represented:

- HIV/infectious diseases
- Virology
- Oncology (both radiation oncology and medical oncology and relevant surgical oncologists)
- HIV counselling
- HIV nursing
- Cancer nursing.

The degree of respect and autonomy granted to a patient with HIV infection and cancer should be no less than that granted to any other patient with cancer. An HIV positive patient with cancer has the same ethical rights as any other patient. These rights include:

- The right to be treated as a human being
- The right to feel secure about the health program
- The right to privacy
- The right to service
- The right to understand the cost of treatment
- The right to be advised of education or research activities
- The right to counselling on refusal to receive treatment.



During the Second International Consultation on HIV/AIDS and Human Rights, September 1996 held in Geneva, published by the UN in 1998, it was made explicit that the right to the highest attainable standard of physical and mental health, among other things, includes “the prevention, treatment and control of epidemic disease” and creation of conditions which will ensure all people medical service and medical attention in the event of sickness. It emphasises that States have to take special measures to ensure that all groups in society will have equal access to HIV related prevention, care and treatment services.

Quite apart from the unique social and cultural context within which HIV related malignancy occurs, there are specific problems and difficulties related to the coexistence of HIV, immuno-suppression and malignant disease. HIV infected patients have impaired marrow function and impaired cellular immunity and will therefore be more vulnerable to the myelosuppressive and immuno-suppressive effects of anti-cancer treatments. Their nutritional and physical status may be impaired and this will further limit their ability to withstand treatment. Many of the drugs, such as AZT (zidovudine), used to treat the HIV virus are themselves myelosuppressive and this will also limit the ability to deliver cancer treatment according to orthodox schedules. All concomitant treatments such as antibiotic prophylaxis, anti-retroviral therapy, complementary therapies should be identified by the oncologist before starting treatment for the tumour.

<b>Problem</b>	<b>Solution</b>
Any HIV positive patient treated with drugs or radiation for malignant disease requires careful monitoring for toxicity.	Dose should be modified or treatment abandoned if excessive toxicity is noted. This monitoring is an active process and decisions about modifying or withdrawing treatment have to be made rapidly. This implies the necessity for good communication between the oncologist, the patient and the patient's primary care givers.
HIV itself may be more important than the tumour	Individualised approach to therapeutic decision making Multidisciplinary clinic Full involvement of patient in decision making
Interactions with other treatments	Full drug history Awareness of potential problems
HIV related myelosuppression and immuno-suppression	Careful monitoring (clinical, FBC) Prompt access to oncology service and supportive care Prophylactic antibiotics (e.g. cotrimoxazole 480mg b.d. for duration of treatment)
Fear and anxiety	Careful and sensitive communication and psychological support

### **3.2. The problem of definition of AIDS**

The concept that, at some point during the natural history of HIV infection, an individual crosses a critical boundary, from HIV positive to AIDS, is gradually being replaced by an appreciation that HIV infection is a dynamic process and that the transition to AIDS is

simply a somewhat arbitrary milestone along the way. AIDS is, to some extent, simply a convenient clinical means for identifying individuals with HIV who are somewhat more immunosuppressed than others, and who are experiencing some of the complications associated with immunosuppression.

The Centers for Disease Control and Prevention (CDC) DC criteria for defining AIDS have changed several times since the epidemic was first identified in 1982. The latest (1993 Revised Classification System for HIV infection and Expanded Surveillance Case Definition for AIDS among adolescents and adults. MMWR 41(RR-17)) criteria for diagnosing AIDS are, in the presence of a positive test for HIV, any of the following:

1. CD4 + T lymphocyte count less than 200 per mL (or less than 14% of total lymphocytes)
2. Candidiasis of bronchi, trachea, or lungs
3. Candidiasis, oesophageal
4. Cervical cancer, invasive
5. Coccidioidomycosis, disseminated or extrapulmonary
6. Cryptococcosis, extrapulmonary
7. Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)
8. Cytomegalovirus disease (other than liver, spleen, or nodes)
9. Cytomegalovirus retinitis (with loss of vision)
10. Encephalopathy, HIV related
11. Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or oesophagitis
12. Histoplasmosis, disseminated or extrapulmonary
13. Isosporiasis, chronic intestinal (greater than 1 month's duration)
14. Kaposi's sarcoma
15. Lymphoma, Burkitt's (or equivalent term)
16. Lymphoma, immunoblastic (or equivalent term)
17. Lymphoma, primary, of brain
18. Mycobacterium avium complex or *M. kansasii*, disseminated or extrapulmonary
19. Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)
20. Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
21. Pneumocystis carinii pneumonia
22. Pneumonia, recurrent
23. Progressive multifocal leukoencephalopathy
24. Salmonella septicemia, recurrent
25. Toxoplasmosis of brain
26. Wasting syndrome due to HIV

Further explanatory details on the above are found in the above reference.

This definition may work well in the developed world but may be less useful in the developing world where cancer of the cervix and tuberculosis are common. The malignant conditions that are now regarded as AIDS defining diagnoses in HIV positive individuals are:

- Kaposi's sarcoma
- Invasive carcinoma of the cervix
- Non-Hodgkin's lymphoma (NHL)
- Immunoblastic lymphoma
- Burkitt's lymphoma
- Primary cerebral lymphoma.

There is no fundamentally important distinction, in terms of the principles of clinical management of malignant disease in the HIV positive patient, to be drawn between tumours (such as cancer of the cervix) that are AIDS defining, tumours (such as breast cancer) arising by coincidence in HIV positive patients, or tumours (such as squamous carcinoma of the conjunctiva) which arise with increased frequency in HIV infected patients.

Similarly, many diseases such as leishmaniasis, trypanosomiasis and tuberculosis (in a HIV seronegative patient) can result in a erroneous clinical diagnosis of AIDS.

### **3.3. Prognostic factors in HIV related malignancy**

As with any tumour, the prognosis in HIV associated malignancy is related to the extent and bulk of the tumour. This information is classically summarised as FIGO stage for cancer of the cervix, as Ann Arbor or Cotswold stage for lymphomas, and as TNM stage for most other solid tumours. These clinico-anatomic staging systems are not entirely adequate for staging HIV related malignancy.

The underlying viral infection, and resultant immuno-suppression, will have a major effect on prognosis and this has been incorporated into the AIDS clinical trials group (ACTG) staging for Kaposi's sarcoma (refer Section 4).

This staging system incorporates immunological information (CD4+ lymphocyte count) as well as information about systemic symptoms. In clinical practice, there is usually reasonable correlation between CD4+ count and systemic symptoms: the patients with systemic symptoms are those with CD4+ counts less than 200 per mL. Given that, even where available in developing countries, CD4+ counting is relatively expensive (US \$25.00 per test). It is reasonable to identify patients with poor prognosis using clinical criteria. These are patients who, for any given clinico-anatomic stage of their malignancy, are likely to fare less well, and in whom it may be reasonable to treat palliatively without any attempt to cure. The clinical criteria associated with poor prognosis for HIV related malignancy comprise any one of the following:

- Weight loss of >10% over the previous 6 months
- Unexplained fever
- Night sweats
- Unexplained diarrhoea for >2 weeks
- History of opportunistic infection
- Evidence of encephalopathy: dementia, confusion
- Karnovsky status  $\leq 70$ .

These features are not an absolute contraindication to radical treatment but they do indicate that such treatment may be poorly tolerated and is unlikely to be effective. It is advisable to discuss these issues openly with patients wherever possible.

### **3.4. Anti-retroviral therapy**

The introduction of effective anti-retroviral therapy has transformed the management and clinical consequences of HIV infection in the developed world. Mortality from HIV related illness is falling. The acronym 'HAART' epitomises the new optimism: Highly Active Anti-retroviral Therapy. Drugs used include AZT (zidovudine), didanosine, 3TC and protease inhibitors such as saquinavir, ritonavir or indinavir. The use of protease inhibitors, in

particular, appears to be associated with a sharp decline in the incidence of Kaposi's sarcoma. The essential principles of anti-retroviral therapy are similar to those of combination chemotherapy:

- Use multiple drugs synchronously rather than sequentially
- Use drugs with different modes of action
- Use drugs with non-overlapping toxicities

The recommendations for optimal therapy change rapidly as new drugs become available. The Web sites at <http://www.hivatis.org> or <http://www.cdc.gov/hiv/pubs/mmwr.htm> are useful sources of information as are the Morbidity and Mortality Weekly reports produced by the CDC in Atlanta (e.g. MMWR 1998 47(RR-5)). These are available on the worldwide web via <http://www.cdc.gov>. The practical consequence for HIV oncologists of the increasing use of anti-retroviral therapy is that the potential for drug interactions between anti-cancer treatment and the treatment for the underlying HIV infection has increased markedly. Patients are very often taking new drugs, which have been pushed rapidly through pre-clinical testing, and there may be little published information on toxicity or metabolism. Problems identified so far include pancreatitis and peripheral neuropathy. The only protection against unforeseen toxic interactions is careful monitoring and a high index of suspicion when unexpected events occur. Many of the anti-retroviral drugs are myelosuppressive and there may be difficulties in combining chemotherapy or wide-field irradiation with such treatment. The problem is that even a temporary cessation of anti-retroviral therapy can cause resistance to emerge. It is probably best to continue with anti-retroviral therapy during treatment for cancer with the option of suspending the anti-retroviral therapy when the copy number of HIV-RNA falls below 500 per mL or more current modifications as shown on the above Web site. This approach presupposes the ability to measure viral copy number.

Although the development of effective anti-retroviral treatment is encouraging, there are major problems with the worldwide availability of such treatment. Scheduling is very important; delay of even an hour or so in taking medication may result in the emergence of potentially transmissible drug resistance. This is not just a personal tragedy; it can affect whole populations. Compliance with prescribed drugs and complex schedules is essential and may, in some health care systems, be hard to achieve. The major issue is, however, cost. The drug costs alone are US \$12 000 per annum and there are additional costs associated with blood tests, hospital attendance, etc. Few individuals in the developing world are likely to have access to such expensive treatment.

### **3.5. HIV related malignancy: ethical economics and economic ethics**

There is an ethical need to offer optimal therapy to cancer patients who are HIV infected, especially if a clinical benefit is anticipated. Minimal therapy alternatives must be studied not only because of cost considerations, but also because of problems with the increased toxicity of cancer treatment in immuno-compromised patients. Even in societies where health-care is well funded, there are problems with the equitable delivery of care to patients with HIV related malignancy. At St Bartholomew's Hospital, London between 1992 and 1996 fewer than 10% of the patients with Kaposi's sarcoma accounted for 50% of expenditure on treating that condition. A small minority of patients may consume a disproportionate amount of resources. If this pattern were to be repeated in the developing world then major inequalities in the provision of care for patients with HIV related malignancy could arise. When resources are finite then any expensive intervention carries

with it an opportunity cost; the resources consumed are unavailable for other patients; Peter has been robbed to pay Paul.

The experience in the Philippines highlights the potential economic difficulties in managing HIV related malignancy in the developing world. In the Philippines, there have been about 1600 cases of AIDS in adults and children since the beginning of the epidemic. Based on the Department of Health's 1995 statistics, there are 234 AIDS cases, and 113 have died. In 1997, there were about 24 000 HIV infected people alive among the 70 million Filipinos. The projected number will reach 90 000 by the year 2000. The Department of Health has recorded five cases of HIV related cancers: 2 Kaposi's sarcoma; 2 cancers of the cervix; one anal cancer. As with many other developing countries, case finding is a problem. In fact, for the past 8 years, one of the busiest radiotherapy departments in the country has reported only 2 cases.

The government-run hospital that houses most of the AIDS and HIV cases in the country operates at a mere US \$50 000 annually for its HIV/AIDS ward. A patient with HIV requires medications amounting to US \$750 per month whilst the treatment of full-blown disease costs at least US \$7500 monthly. Given these monetary requirements, the budget allotted by the government would only be enough to cover the drug costs for six HIV positive patients. The cost pressure will only increase when these patients develop complications and malignancies.

The cost of a course of radiotherapy ranges from US \$250–1000, depending on the treatment machine used. The monthly minimum salary is about US \$135. This indicates the degree to which the costs of radiotherapy will financially incapacitate the average citizen and his family. Even with a short palliative course, the average Filipino could not afford the treatment. The money may not even be enough to acquire the basic services such as food. If this is the case, how then can basic supportive care for cases where no clinical benefit is anticipated be given? Hence, whether optimal therapy or supportive therapy is required, a "no therapy" regimen may ultimately be selected because of the cost implications.

It is next to impossible to implement a comprehensive programme for managing HIV related malignancies in a third world country such as the Philippines, countries in which it is already impossible to provide basic health care for the majority of citizens. Most of those who have been afflicted with HIV have only been diagnosed with assistance of the different non-governmental organizations that rely heavily on charitable funding.

It is a basic tenet of medical ethics that the physician–patient relationship is contractual in nature. Physicians should work in alliance with their patients and work for the promotion of the rights of their patients such as:

- To receive information from the physicians and to discuss the benefits, risks, and costs of appropriate treatment alternatives
- To make decisions regarding the health care that is recommended by his/her physician and accept or refuse any recommended medical treatment
- To be treated with courtesy, respect, dignity, responsiveness and timely attention
- To have confidentiality respected
- To receive continuing health care
- To have available adequate health care regardless of socio-economic status.

The ethics associated with the treatment of cancer and HIV are no different from the principles announced by Pope John Paul II in an address in 1999 to the participants at a meeting of the International Gynaecological Society held at Vatican City. The pontiff said that cancer patients should get effective and accessible treatment and steps should be taken to relieve their pain. He went on to say that ineffective treatment or treatment which aggravates suffering should be avoided, as should the imposition of unusual and extraordinary therapeutic methods.

Even with the right ethical perspectives, the problems are primarily economic, particularly the costs associated with treatment, and the capacity of the state or government to offer the available and affordable resources to everyone.

## 4. KAPOSÍ'S SARCOMA

### 4.1. Introduction

#### 4.1.1. General introduction

Moriz Kaposi in 1872 first described five patients presenting with 'sarcoma idiopathicum multiple hemorrhagicum' [1]. In 1912 Sternberg termed this disease Kaposi's sarcoma — now referred to as classical Kaposi's sarcoma — an indolent tumour seen typically in men of Mediterranean or east European Jewish origin. Since then various forms of this disease have been observed. In 1914, Hallenberg described the first cases of African or endemic Kaposi's sarcoma. In the 1960s the first reports discussing Kaposi's sarcoma following organ transplantation and immuno-suppressive therapy were published [2]. After 1981, the epidemic form associated with AIDS was described in 1981 by Hymes [3].

#### 4.1.2. Aetiology and pathogenesis

KS is now known to be associated with a  $\gamma$ -2 herpes virus designated HHV-8 (KSHV). The virus has been identified, using PCR-based techniques, in all forms of KS: classical Mediterranean; endemic African; paediatric; epidemic (HIV related). HHV-8 is closely related to the Epstein-Barr virus (EBV) and, like EBV, may be transmitted in saliva. Although the rate of HHV-8 infection in homosexual men is related to the number of sexual partners, there is no evidence to suggest that transmission is exclusively through sexual contact. Recent evidence from Africa on HHV-8 prevalence in children suggests that the infection is acquired through normal social contacts within the family. In the developed world, the seroprevalence of HHV-8 in the general population is between 5 and 10%; for HIV positive homosexual men the figure is 30%. In Africa, the general prevalence is much higher, over 15%, and increases with age: <2% under the age of 5; 15% in those aged between 15 and 40; >27% in those older than 40 [4].

The development and progression of KS is, particularly in the earlier stages, heavily dependent upon cytokines. Autocrine stimulation, whereby cytokines produced in KS lesions can stimulate the development and growth of KS cells, is an important mechanism. HHV-8 has a variety of actions, many of which are important in the pathogenesis of KS. These actions include: production of an analogue of cyclin D which will increase the proportion of actively cycling cells; production of a bcl-2 analogue (vbcl-2) and a protein (vFLIP) both of which will prevent apoptosis; stimulation of angiogenesis mediated by a G protein coupled receptor (GPCR) as well as by the production of angiogenic proteins which are also inhibitory to macrophages (vMIPs).

#### 4.1.3. Epidemiology

Kaposi's sarcoma is the most frequent neoplasm occurring in AIDS patients, particularly in young homosexual men [3, 5, 6]. KS was the first malignancy to be described in AIDS. It was, in fact, the rarity of KS in the USA before the HIV epidemic that, indirectly, contributed to the identification of AIDS itself. When two, previously rare, diseases are found together with increasing frequency in a defined social group then something unexpected is happening. The unexpected event was an epidemic of virally acquired immunosuppression now known to be caused by HIV, the previously rare conditions that occurred together were KS and PCP (*Pneumocystis carinii* pneumonia) and the defined social group was the homosexual male community.

By the end of 1998, nearly 57 000 people in the USA had developed KS as a result of HIV related immunosuppression. The incidence of KS as an AIDS defining illness in the USA has declined since 1993, the year in which the definition of AIDS was changed to allow a low (<200 per  $\mu$ l) CD4 count to be considered an AIDS defining criterion. Part of this decrease is likely to be artefactual: patients with HIV infection are diagnosed as having AIDS earlier in the natural history of the infection before they have had time to develop KS. Some of the decrease is, however, genuine. The Swiss cohort study has shown a significant decrease in the rate of KS in HIV positive individuals since the introduction of HAART (highly active retroviral therapy) in the mid-1990s [7].

In the early days of the HIV epidemic, the majority of patients died from opportunistic infections. With the development of treatment and prophylaxis for PCP, there was a change in the mortality pattern, an increasing proportion of patients dying with malignancy, particularly KS and NHL. With the development of HAART, and subsequent decline in the rate at which HIV positive individuals develop KS, we might anticipate a relative decline in KS as a cause of death but a rise in the proportion of patients dying from NHL.

Currently, in the USA about 1000 HIV positive men and 100 HIV positive women are diagnosed with AIDS each year because they have developed KS. The relative risk of KS in HIV positive individuals is, compared to the US population as a whole, 106 000 for homosexual men and 13 000 for heterosexual men. The rate for women is unknown. Cohort data suggest that the risk of developing KS is 35% at ten years after the acquisition of infection with HIV plus HHV-8.

It is much more difficult to unravel the epidemiology of HIV related KS in the developing world. Under-reporting of HIV related KS, together with higher background rates of KS not related to HIV infection, results in difficulty in obtaining accurate estimates of the prevalence of HIV related KS, particularly in sub-Saharan Africa. It would be misleading to estimate the likely prevalence of KS by calculating from the anticipated number of individuals infected with both HIV and HHV-8 and applying the 35% at 10 years rate mentioned above. The problem here is that not all types of HIV may be as synergistic with HHV-8 as the HIV types encountered in the US AIDS epidemic. The predominant HIV virus in the USA is HIV-1, in Africa HIV-2 is the dominant form.

## **4.2. Clinical features**

### **4.2.1. General features**

The classic lesion of KS is a raised macule which is purplish in colour and which may be surrounded, because of extravasated red cells, by a yellowish halo. Individual lesions are, at first, inconspicuous particularly in those with dark skin, but will increase in both size and number. Lesions may eventually coalesce into plaques and these plaques may ulcerate and bleed. When lesions are elliptical in shape they tend to lie with long axes parallel to Langer's lines. Koebner's phenomenon is also encountered: KS lesions may develop preferentially at sites of previous trauma — scars after previous surgery, for example.

Oedema is almost always a feature of KS and its severity may appear out of all proportion to the visible skin lesions. This is because KS will involve and obstruct dermal and sub-dermal lymphatics as well as spreading directly to lymph nodes. Facial and periorbital oedema, genital oedema and lymphoedema of the legs are the main clinical manifestations of this phenomenon and can be both disfiguring and incapacitating.



Lesion in moist, protected sites, such as the perineum, the glans penis and the axillae, may become exuberant and polypoid. Surface ulceration and bleeding may occur. Secondary infection of KS lesions is common, particularly in the oral cavity, and will exacerbate any associated pain or swelling.

#### **4.2.2. Endemic (African) KS**

In the 1950s, Kaposi's sarcoma was recognised as a relatively common neoplasm endemic in native populations in Equatorial Africa, comprising approximately 9% of all cancers seen in Ugandan males. African KS follows two main clinical patterns: an *indolent* neoplasm identical to the classic disease seen in Europe and North America; an *aggressive* form with exophytic tumours that may invade the subcutaneous and surrounding tissue including the underlying bone. Oedema and ulceration of coalescing skin nodules often develop, particularly in the lower limbs. In Africa, both the indolent and locally aggressive forms of Kaposi's sarcoma occur with a male and female ratio of 1.5 to 1, comparable to that observed with the classic Kaposi's sarcoma tumour. In general, however, patients in Africa are significantly younger than their European counterparts.

#### **4.2.3. Classical (Mediterranean) KS**

This was the form of the disease first described by Kaposi in 1872. The patient is typically an elderly male with gross oedema of both legs and multiple KS lesions, particularly affecting the upper thighs and groin. The course of the disease is indolent; the main problems are related to the disability imposed by the swelling and stiffening of the legs. Visceral involvement is uncommon.

#### **4.2.4. Paediatric (lymphadenopathic) KS**

A third variant, a *lymphadenopathic* form of Kaposi's sarcoma is also seen in Africa, primarily in children. In these cases, the generalized lymphadenopathy is frequently associated with organ involvement. The prognosis of the lymphadenopathic form is very poor, with 100% fatality within three years.

#### **4.2.5. Epidemic (HIV related) KS**

The clinical pattern of KS occurring in the context of HIV infection is characterised by its extreme variability. Some patients have an indolent inconspicuous form of the disease, with only one or two small KS lesions developing over a decade or so. At the other end of the spectrum are patients who present with aggressive disease involving multiple cutaneous sites, with extensive oedema and involvement of major organs, especially the lung and gastrointestinal tract. These patients may die within weeks from uncontrolled KS. The clinical course of patients with HIV related KS can lie anywhere between these two extremes. It is often prudent not to rush to intervene in patients with AIDS and KS. The KS may, clinically, be the least of their current or future problems and an aggressive approach to treating KS might jeopardise both their quality of life and the management of more important clinical issues, such as opportunistic infections or other malignancies.

The psychological burden of HIV related KS should not be underestimated. KS can be regarded as a barometer of underlying immunosuppression: each new lesion reminds patients that their immune system is failing; each glance in the mirror brings an intimation of impending mortality. KS is a highly visible disease: the stigmata are conspicuous and an

individual with KS is unlikely to be able to conceal the diagnosis from family, friends and acquaintances. This can cause patients to feel outcast from their community or social group and further exacerbates their problems.

### 4.3. Diagnosis

The diagnosis of KS in an individual known to be HIV positive is usually straightforward. The characteristic appearance of the lesions and the tempo of the disease are sufficient to establish the diagnosis. Although, in the developed world, biopsy is considered mandatory it is, in the developing world, difficult to justify the expense and inconvenience of obtaining histological proof of the diagnosis. Biopsy can be reserved for those cases where there is genuine clinical doubt.

### 4.4. Staging and assessment

The most useful classification system is that of the AIDS Clinical Trials Group (ACTG) staging system for AIDS related malignancies [8, 9].

#### ACTG STAGING SYSTEM FOR KAPOSI'S SARCOMA

	<b>Good risk (0) all of the following</b>	<b>Poor risk (1) any of the following</b>
Tumour (T)	Confined to skin and/or lymph nodes and/or Minimal oral disease*	Tumour-associated oedema or ulceration Extensive oral Kaposi's sarcoma Gastrointestinal Kaposi's sarcoma Kaposi's sarcoma in other non-nodal viscera
Immune system (I)	CD4 cells $\geq 200$ microL	CD4 cells $\leq 200$ microL
Systemic illness (S)	No history of OI or thrush No "B" symptoms** Performance status $\geq 70$ Karnofsky	History of OI and/or thrush "B" symptoms present Performance status $\leq 70$ Other HIV related illness (e.g. neurological disease, lymphoma)

\*Minimal oral disease is non-nodular Kaposi's sarcoma confined to the palate.

\*\*B symptoms are: unexplained fever, night sweats,  $>10\%$  involuntary weight loss, diarrhoea persisting more than 2 weeks.

The above classification is applicable to:

Classical [Mediterranean] Kaposi's sarcoma  
Endemic [African] Kaposi's sarcoma  
Lymphadenopathic [Paediatric] Kaposi's sarcoma  
Epidemic [AIDS related] Kaposi's sarcoma

With involvement of:

Cutaneous or muco-cutaneous structures  
Lymph nodes  
Viscera

## 4.5. Management

The management of KS must be tailored to the clinical and social circumstances of the individual patient. Watchful waiting is a perfectly legitimate management strategy. Given the heterogeneity of the disease itself, and the heterogeneity of the circumstances in which it is encountered, there is no universal imperative dictating immediate intervention. The normal rules of palliative treatment apply: in particular, the concept that the treatment should not be worse than the disease itself.

### 4.5.1. Local treatment — General considerations

Radiotherapy is the mainstay of local treatment for KS. Orthovoltage is suitable for the treatment of solitary lesions. The judicious application of bolus is required when using megavoltage machines and electrons. Other approaches, including the intralesional administration of drugs such as interferon or vinblastine, have proved to be of only limited applicability.

Small, localised lesions of Kaposi's sarcoma may be treated by local field irradiation and excellent palliation has been obtained with doses as low as 20 Gy. Various dosage schedules have been reported for the treatment of endemic KS, varying from a single dose of 8 Gy to fractionated regimens of 40 to 45 Gy with the clear time-dose-fractionation response shown [10, 11].

Studies specific to HIV related Kaposi's sarcoma began in the 1990s. A study by de Wit [18], using a single fraction of 8 Gy, set out to quantify the responses previously noted at this dose. While the objective response rate was only 34% (CR 6/74, PR 9/74), the subjective response for pain and cosmesis was a high 90%. The response was noted to be of short duration with 23 of 36 evaluable sites having relapsed by 4 months. This single fraction protocol had earlier been supported by Berson [17].

Stelzer [19] randomised skin lesions to one of three regimens: 8 Gy in a single fraction, 20 Gy in 10 fractions and 40 Gy in 20 fractions. Patient characteristics and follow-up differences were minimised by randomisation for each site treated. The results are shown below:

Regimen	Complete response	Median TTF*	40w actuarial failure rate
8 Gy 1f	50%	13w	84%
20 Gy 10f	79%	26w	62%
40 Gy 20f	83%	43w	48%

\*TTF: time to treatment failure.

Complete response rates and duration of control were superior in the 2 higher dose arms than in the single fraction arm. Acute and late toxicity was more pronounced with higher doses but did not exceed RTOG Grade I. The authors, however, advocate that their study be used as only ONE factor in the selection of a treatment regime.

In the study from Créteil, France [20–22] a 92% objective response (CR 66%; PR 26%) was reported for 6,464 skin lesions treated by two split course protocols of 10 Gy in 4

fractions (low dose) or 20 Gy in 8 fractions (high dose) followed by a rest, then 10 Gy in 4 fractions. The high dose regimen delivered a total dose of 30 Gy in 12 fractions over 5 weeks. Similarly, high response rates of 89% but with lower CR (CR 32%; PR 57%) were observed at 20 Gy in 10 fractions over 2 weeks in a study from Germany [23].

In the prospective study of Harrison et al. [24] the authors compared 2 treatment schedules in a site randomised trial on 596 lesions. The treatments used were 16 Gy in 4 fractions over 4 days or 8 Gy as a single fraction. They considered a single fraction of 8 Gy to be an acceptable treatment in terms of both response and skin pigmentation.

<b>Regimen</b>	<b>Complete response</b>	<b>Partial response</b>
8 Gy 1f	53%	13%
16 Gy 4f	49%	15%

In the developing world, with limited and difficult access to radiotherapy equipment, there are compelling arguments for keeping treatment as brief and as uncomplicated as possible. It is better to accept the risk that re-treatment may be necessary than it is to insist that whatever the inconvenience to patients and whatever the resource implications, all patients must be treated with protracted course of radiotherapy. It is perfectly reasonable to use single fractions of radiotherapy whenever this is possible and, wherever possible, fractionated treatments should be completed within a week. The doses and fractionation schemes used should depend upon treatment site and volume and are discussed in more detail below.

#### **4.6. Local treatment — Specific sites**

##### **4.6.1. Skin**

A single fraction of 8 Gy will provide useful palliation for skin lesions. Wide-field treatments can be given to the lower half of the body using parallel opposed fields and a dose of 6 Gy. Upper hemibody treatment can also be used but caution is required because of the risk of damaging the lungs. Parallel opposed fields extending from the umbilicus to the mid-femur and treated using <sup>60</sup>Co or 4 to 6 MV X-rays are useful in the treatment of extensive Kaposi's sarcoma of the "boxer shorts" area, a clinical presentation in which there is often pelvic node involvement with lymphoedema of the lower limbs.

##### **4.6.2. Oral cavity and oropharynx**

Lesions in the mouth and pharynx often result in significant and disabling symptoms: foeter; pain; loosening of the teeth; difficulty swallowing; difficulties with speech; respiratory problems. Treatment is better given sooner than later as lesions at these sites often become secondarily infected and this can complicate management.

This site has consistently [11, 15, 17, 20, 25] been associated with problems of unexpectedly severe mucositis following conventional doses of radiation therapy in HIV positive patients. Cooper and Fried [13] and Watkins et al. [26] drew attention to this specific management problem. Other authors have repeated this experience. Chak et al. [15] in their nine patients progressively reduced doses to the oral cavity using 2 Gy fractions from a total of 18 Gy eventually down to 12 Gy Berson et al. [17] in 45 patients reduced dose per fraction

from 4 Gy initially to 1.8–2.0 Gy and then to 1.5 Gy. They also lowered the total dose to 15 Gy. It is interesting to note that, when lesions were accessible to intraoral cones [20], 6 patients, treatment resulted only in mild reactions.

An attenuated dose of 15.2 Gy, delivered in 1.9 Gy fractions four days per week with one week rest [18] using parallel opposed fields, resulted in mild reactions in 65.7%, moderate reactions in 14.3% and severe reactions in 20% of patients. This is an unacceptable rate of severe side effects for what is, after all, a palliative treatment.

The simplest approach is to treat with single weekly fractions of 3 Gy and give a total of four fractions (12 Gy in 4 fractions over 28 days). This will produce significant relief of symptoms without causing significant mucositis. An alternative, but more resource-intensive, regimen is to give 16 Gy in 10 fractions in two weeks. Treatment is best given using parallel opposed megavoltage techniques but ipsilateral single fields using orthovoltage equipment may provide useful benefit. Good supportive care is essential and this includes: dental assessment; nutritional support; symptomatic management of reactions; good oral hygiene; mouthwashes [26]; analgesia and prophylactic anti-fungal treatment.

#### **4.6.3. Genitals**

The penis and scrotum have been treated with radiotherapy [12, 14, 20, 21, 23] in doses ranging from single fractions of 6 Gy to 20 Gy in 4 or more fractions. No specific problems have been noted regarding treatment responses or reactions at this site.

#### **4.6.4. Eyelids and conjunctiva**

Small lesions of the conjunctiva of the eyelid or eye can be irradiated effectively with orthovoltage therapy using inexpensive internal and external eye shields for lens protection [12, 13, 16, 17, 20, 21, 27]. Doses used vary from 8 Gy in a single fraction to 20 Gy in 10 fractions. Local reactions are, at these doses, acceptable.

#### **4.6.5. Nodes**

These have a prompt high response rate [17] with an 8 Gy single fraction being as effective as fractionated treatment.

#### **4.6.6. Visceral**

Small series of patients with bronchial [14, 17] and gastric [17] obstruction have received radiotherapy. As the involvement of these sites is usually a late manifestation of the disease, rapid relief of symptoms is the objective with duration being irrelevant. Single fractions should be used wherever possible.

#### **4.6.7. Systemic treatment**

Systemic treatment for KS is indicated when there is cutaneous involvement that is beyond local treatment with radiotherapy, either in terms of extent or tempo of disease, or where there is visceral involvement that is either causing symptoms or is about to do so. A variety of drugs and regimens have been used for treating KS. The most recent data from the developed world supports the use of taxanes and liposomal anthracyclines for treating HIV related KS. These drugs are extremely expensive and, particularly in the case of the taxanes,

can produce severe toxicity. They are feasible treatments only if the health care system can afford to purchase the drugs and if the facilities exist for close supervision and monitoring of treated patients. The combination of vincristine (2mg IV bolus) and Bleomycin (30mg IV as a six hour infusion) given every 3 weeks is effective against KS and has the advantage that the drugs are cheap and not excessively myelosuppressive.

#### **4.7. Evaluation of outcome**

Criteria for the assessment of response to treatment of Kaposi's sarcoma in HIV positive patients have been proposed and discussed [6, 19]. There are problems with simply importing conventional oncological response criteria for the assessment of response in patients with HIV related malignancy. The most important question is that of relevance: the malignancy is not always the most important factor in the patient's illness. A pragmatic, rather than a pristine, approach can therefore be justified. It is regrettable that so little attention has been paid to the evaluation of symptomatic benefit in patients treated for HIV related malignancy. The criteria developed for use in the developed world are:

**Complete response:** Absence of detectable lesion persisting for 4 weeks. With persistent pigmentation, a confirmatory biopsy of a representative part of the lesion is required.

**Partial response:** A 50% decrease in number or size without the appearance of new lesions. Size reduction may be the sum of the bi-dimensional product of measurement of lesions or flattening. Flattening alone of 75% of the lesions.

**Stable disease:** not meeting the criteria above.

**Progressive disease:** An increase in size of 25% and/or new lesions and/or a change from macular to plaque-like or nodular appearance.

##### **4.7.1. Outcome and prognosis**

The survival of a patient with HIV related KS is usually dictated by the degree of severity of the underlying immunosuppression and survival cannot therefore be a particularly useful endpoint for evaluating therapy for KS. The main goal of treatment is the relief of symptoms and, using the approaches outlined above, this can be achieved, to some extent at least, for the majority of patients. The duration of response may, however, be short lived. Even with the most aggressive systemic chemotherapy, the median duration of response is only about ten months. Given such results, it is more sensible to accept a high rate of re-treatment than it is to use an aggressive initial approach to treatment.

#### **4.8. Future developments**

The viral origin of KS provides opportunities for both prevention and treatment. Unfortunately, these approaches are of theoretical rather than practical value and any advances will come too late to help the thousands of patients who will develop KS within the next five years. New drugs aimed at inhibiting angiogenesis are likely to be too expensive for routine use. Older drugs, such as thalidomide, which have anti-angiogenic properties may be worth exploring. Their effectiveness will be in the earlier stages of the disease — by the time that a patient has widespread disease, particularly if there is visceral involvement, it is unlikely that treatment strategies based on preventing angiogenesis will have any meaningful clinical benefit.

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## 5. NON-HODGKIN'S LYMPHOMA (NHL)

### 5.1. Introduction

#### 5.1.1. General

Non-Hodgkin's lymphomas were recognised as part of the acquired immunodeficiency syndrome early in the course of the epidemic and, in 1982, were incorporated into the CDC criteria for defining AIDS. These lymphomas are characteristically aggressive and often involve extra-nodal sites.

#### 5.1.2. Aetiology and pathogenesis

Some HIV positive individuals are more susceptible than others to the development of HIV related lymphomas. Reduced susceptibility is related to particular variants of the chemokine receptor gene, CCR5. The immunosuppression associated with HIV is a major mechanism involved in the formation of lymphomas. The two main viruses whose carcinogenic potential is thereby potentiated are the Epstein-Barr virus (EBV) and human herpes virus-8 (HHV-8). There is no evidence that HIV, by itself, can induce the formation of lymphomas but it can, in effect, function as a co-carcinogen. HIV may also affect the interaction between transformed cells and the surface of endothelial cells. This effect, mediated by the HIV Tat gene product, will further enhance the development and establishment of lymphoid malignancy [1].

The lymphomas develop against a background of chronic antigenic stimulation and the vast majority are of B-cell origin. Analysis of surface markers suggests that the transforming event occurs at the post germinal centre phase of lymphocyte development. Once malignant transformation has occurred, the expansion of the abnormal clone is stimulated by cytokines. These may include IL-6, TNF-beta, and IL-10. Some chemokines may be produced by HIV infected macrophages and monocytes, others are produced by the lymphoma cells themselves and can produce autocrine stimulation of the abnormal clone.

The lymphomas associated with HIV infection fall into four main clinico-pathological categories: diffuse large cell lymphoma (DLCL); Burkitt's lymphoma (BL); primary lymphomas of the central nervous system (PCNSL); primary effusion lymphomas (PEL). The diffuse large cell lymphoma can be further subdivided into large non-cleaved cell (LNCCL) and immunoblastic plasmacytoid (IBPL) subtypes. EBV infection occurs in 30% of HIV related Burkitt's, 100% of primary CNS lymphomas, 40% of the non-CNS LNCCL, 90% of the non-CNS IBPL and 90% of the primary effusion lymphomas. HHV-8 infection is found in 100% of the primary effusion lymphomas but does not appear to be associated with any other type of HIV related lymphoma. It is, however, associated with Castleman's disease — a non-malignant lymphoproliferative disorder that occurs with increased frequency in HIV positive individuals. Activation of *c-myc* can be demonstrated in all HIV related Burkitt's, mutations of *bcl-6* are common in all types of HIV related lymphoma.

The degree and duration of HIV related immunosuppression affects the type of lymphoma that develops. Primary CNS lymphomas are associated with profound immunosuppression and usually occur late in the course of HIV infection. The other types of lymphoma may occur much earlier in the course of HIV infection: this has obvious implications for therapeutic decision-making.

### 5.1.3. Epidemiology

In the developed world, NHL was an AIDS defining diagnosis in less than 5% of patients but was the cause of death in over 15% of patients with AIDS [2]. This disproportion draws attention to the fact that NHL often occurs late in the natural history of HIV infection and may, for many patients, be the final episode in their illness. The widespread use of highly active retroviral therapy (HAART) will no doubt change the pattern somewhat. There is already preliminary evidence to suggest that, although deaths from opportunistic infections have decreased, there has been no parallel decrease in the incidence of NHL [3]. This suggests that NHL may, proportionally, become increasingly important in the management of HIV positive patients treated with HAART.

A survey of 51 033 people with AIDS identified 2,156 patients with NHL, a rate of 4.3%. This represented a relative risk, compared with the normal population, of 165. Of these lymphomas, 39% were high grade, 15% were primary CNS lymphomas, 40% were extranodal. Even when the CNS was excluded as an extranodal site, extranodal lymphomas were twenty times more common in patients with AIDS compared to the general population. The relative risk of NHL in HIV infection is particularly great for particular pathological subtypes [4].

Type of lymphoma	Relative risk AIDS c.f. general population
Burkitt's	261
High grade diffuse immunoblastic	652
Intermediate grade	113
Low grade	14

Castleman's disease, although not strictly a neoplasm, is a lymphoproliferative condition found with increased frequency in HIV positive individuals. Classically, it was described as two forms: the hyaline vascular type (90% of cases) and the plasma-cell type (10%). The plasma-cell variant is the form found in association with HIV and all patients with HIV related Castleman's disease have evidence of infection with HHV-8 [5]. The development of Castleman's disease in an HIV infected individual is a useful indicator that the particular individual is at high risk of developing malignancy, particularly KS or PEL.

## 5.2. Clinical features

The clinical features of NHL in HIV infection are as heterogeneous as the tumours themselves. The lymphomas are, at presentation, advanced and aggressive. The vast majority of patients present with B symptoms (fever, weight loss, drenching night sweats) and it may be difficult to disentangle these from wasting syndromes associated with HIV infection itself or from the symptoms produced by an occult opportunistic infection. Lymphadenopathy is common in HIV infection and arises for a variety of reasons. Rapid enlargement of a single group of nodes should, however, suggest the development of lymphoma. The extranodal sites commonly involved by HIV related lymphoma include the CNS, the meninges, the gastrointestinal tract and the skin. The body cavity lymphomas present as a distinct clinical entity.

### **5.2.1. Primary CNS lymphoma (PCNSL)**

The majority, over 75%, of primary CNS lymphomas develop in patients who are already known to have AIDS. These patients are usually severely immunosuppressed; 50% of them have CD4 counts less than 50/dL. The clinical presentation is similar to that for any intra-cerebral space-occupying lesion: headache, changes in affect and level of consciousness, focal neurological signs, visual disturbances. The onset can be extremely rapid and this can make the differential diagnosis from opportunistic infection extremely difficult.

### **5.2.2. Nodal NHL including Burkitt's**

Patients with HIV related NHL usually have widespread nodal disease and B symptoms at presentation. Involvement of the bone marrow, with consequent impaired marrow reserve, is present in nearly 25% of patients at diagnosis. Unusual nodal sites may be involved: occipital, epitrochlear, parotid. Direct involvement of the overlying skin by a rapidly enlarging nodal mass is another feature of HIV related NHL.

### **5.2.3. Gastrointestinal NHL**

These tumours can present anywhere in the GI tract from posterior pharyngeal wall to rectum. Upper GI lymphomas will present with dysphagia, nausea, vomiting and anorexia. The small bowel lymphomas will cause symptoms of malabsorption, weight loss and sub-acute obstruction. Rectal tumours will cause bleeding, discharge, change in bowel habit, pain and tenesmus.

### **5.2.4. Meningeal NHL**

Lymphomas involving the meninges classically present with cranial nerve palsies, backache or spinal root pain. Non-specific presentations, with headache and confusion may, however, also occur.

### **5.2.5. Primary effusion lymphomas**

These unusual lymphomas (syn. body cavity lymphomas) were first described in the context of HIV infection. If they had occurred previously, they appear to have gone unrecognised. Patients present with pleural effusions or ascites, without any evidence of bulk disease. There may be some minor thickening of pleural or peritoneal membranes, but there are no obvious tumour masses. The symptoms are simply those caused by the accumulation of fluid: dyspnoea, chest discomfort, abdominal discomfort, abdominal swelling.

### **5.2.6. Castleman's disease**

In non-HIV infected individuals, Castleman's disease can present as an indolent enlargement of the spleen or a single group of nodes. The plasma-cell variant that is typically associated with HIV infection tends to present as multifocal lymphadenopathy, with splenomegaly. Fever and splenomegaly are the cardinal features of the syndrome. Other features include: enlargement of the liver, peripheral lymphadenopathy, oedema. Cough, dyspnoea, and other respiratory symptoms are common. Hypersplenism may produce anemia, leucopenia and thrombocytopenia.

### **5.3. Diagnosis**

#### **5.3.1. *Nodal lymphomas and extranodal lymphomas with accessible disease***

A biopsy should be performed before any treatment is started. The differential diagnosis of lymphadenopathy in HIV infected individuals is extensive and it would be a therapeutic disaster to treat an occult infection as if it were a malignancy. Aspiration biopsy is inadequate: cytological examination alone can be misleading and only a formal biopsy will provide information on both tissue architecture and cytology.

#### **5.3.2. *Primary CNS lymphomas***

The initial investigations should be a CT scan and/or MRI scan of the brain. Lymphoma typically forms a space-occupying lesion (SOL) which enhances after contrast. There is often considerable oedema and the disease is often multifocal. Target lesions may be found both in CNS lymphoma and in the main differential diagnosis, toxoplasmosis [6]. HIV positive patients with intracerebral space occupying lesions present a diagnostic dilemma. They are often in poor general condition, with advanced immunosuppression. Neurosurgical intervention, even a stereotactically guided biopsy, may be hazardous. Quite apart from any risks associated with anesthesia, there is the added risk of increased cerebral oedema and coning following any biopsy. The position is further complicated by the fact that some CNS complications, such as toxoplasmosis, are potentially treatable, whilst others, such as CNS lymphoma, somewhat less so.

In fit patients, a biopsy of the space occupying lesion should be performed whenever possible. In patients who are less fit, or when there is no easy access to neurosurgery, then other approaches are necessary. One approach, when the tempo of disease is reasonably slow, is to treat the patient as if they had toxoplasmosis and re-assess after two weeks. If the patient deteriorates on such treatment, then assume that they have lymphoma and treat accordingly. If they improve, then accept the diagnosis of toxoplasmosis. If they remain unchanged, then reconsider the question of biopsy.

In patients with an intracranial SOL, whose clinical condition is deteriorating rapidly, and in whom infection has been excluded, then empirical treatment for CNS NHL, without a tissue diagnosis, may be perfectly reasonable.

### **5.4. Staging and assessment**

It is so unusual for a lymphoma to be truly localized in a patient who is HIV positive that an obsessional approach to staging investigations is unnecessary. It is reasonable to assume that all patients have widespread disease, and treat accordingly. Bone marrow examination may be useful, mainly because it gives an indication of haemopoietic capacity. CT scanning of chest and abdomen will provide useful baseline data, but is unlikely to change management.

### **5.5. Management of HIV related NHL**

#### **5.5.1. *Primary CNS lymphomas (PCNSL)***

Even with aggressive therapy, the survival for these patients is poor, dominated as it is by the underlying immunosuppression. For many patients, the development of CNS

lymphoma marks the terminal phase of their HIV infection. Management should be planned accordingly: officious striving, simply for the sake of it, is never good medicine.

Radiotherapy is the mainstay of treatment. There is no evidence that adding chemotherapy to cranial irradiation for patients with PCNSL improves survival or response rates. For fit patients, with good performance status and minimal immunosuppression, a radical course of cranial irradiation (45 Gy in 20 to 25 fractions) might be justified. It should be emphasised that such patients are few and far between.

The vast majority of patients can only be treated palliatively. The regimen chosen will reflect both available resources and the general condition of the patient. For patients in very poor general condition, and who are to be treated at all, regimens should be kept very simple: 6 Gy single fractions repeated weekly to a maximum of 6 fractions. Patients in better general condition may have useful benefit from split course palliative treatment: 18 Gy in 3 fractions in 3 days, then 3-week gap. If there has been improvement clinically and/or radiologically, then the three fractions can be repeated.

The use of steroids is controversial. There is no evidence that steroids, per se, improve the response of the tumour. They will, however, help to control any cerebral oedema related to the presence of the tumour. The additional immunosuppression associated with high dose steroid is a disadvantage and therefore such treatment should be used as sparingly as possible.

#### **5.5.2. Other lymphomas (nodal, non-CNS extra nodal, primary effusion lymphomas)**

These lymphomas should be treated systemically with chemotherapy. Vincristine alone or Vincristine (2 mg) + Bleomycin (30 mg) repeated 3-weekly may provide useful palliation but, for more definitive treatment in patients with good marrow reserves, CHOP at 75% of conventional doses is appropriate:

Cyclophosphamide	600 mg/m <sup>2</sup>	intravenous	q.21
Doxorubicin	50 mg/m <sup>2</sup>	intravenous	q.21
Vincristine	2 mg	intravenous	q.21
Prednisone	75 mg/m <sup>2</sup>	oral	D1-D5

This is repeated at 21-day intervals to a total of 6 courses if blood counts remain adequate. The median survival time of reasonable performance status patients is about 11 months. Bone marrow depression is a contraindication to aggressive chemotherapy. This regimen may result in up to 30% of patients developing febrile neutropenia and prophylactic antibiotics (e.g. co-trimoxazole) should be given for the duration of treatment.

Radiotherapy has a role to play in patients who have failed chemotherapy, especially those with bulky disease, pain, bleeding, skin involvement, incipient obstruction of airways, ureteric obstruction, superior mediastinal syndrome, or leg oedema from pelvic adenopathy. Local radiotherapy can be given using 6 Gy fractions as outlined for CNS lymphomas, except when there is oro-pharyngeal mucosa within the field. In these circumstances, a regimen of 12 Gy in 4 weekly fractions, repeated after a 3 week gap, may be useful: total dose 24 Gy in 8 fractions over 11 weeks.

Symptoms from bulky diseases may be successfully relieved using wide-field or hemibody radiation administered as a single fraction of 6 Gy. This treatment should include medication and hydration to prevent severe nausea or tumour lysis syndrome.

### **5.5.3. Spinal cord compression: extradural or meningeal lymphoma**

This should be treated by radiotherapy. There is no proven benefit from surgery, unless the diagnosis is in doubt and tissue is required for diagnosis. The following fractionation schemes are appropriate: 8 Gy single fraction, 10 Gy in 2 fractions, 20 Gy in 5 fractions.

### **5.5.4. Castleman's disease**

Splenic radiation has a useful role to play in the palliation of the hypersplenism that may be associated with Castleman's disease in patients with HIV infection. Treatment has to be given cautiously, with careful assessment of blood counts before each fraction, but, over time, may produce reduction in transfusion requirements and shrinkage of the spleen. A reasonably safe schedule is to give 1 Gy weekly to a single anterior field that does not attempt to encompass the whole spleen. This treatment can be given effectively using an 8 × 8 cm field on a 250 kv XRT machine.

## **5.6. Outcome and prognosis**

Both response to treatment and survival are heavily influenced by the patient's general condition. In patients with CNS lymphoma, despite attempts at aggressive therapy, the typical median survival is 4 months. Patients who are bed-bound at diagnosis have a median survival of less than 6 weeks.

For patients in good general condition, and who are treated with intensive chemotherapy for non-CNS lymphomas, prolonged remission and survival are possible. The International Prognostic Index (IPI) can be applied to patients with HIV related lymphomas. Only 24% in a recent series belonged to low, or low-intermediate risk groups but the median survival times were more than five years and 17 months respectively. The majority, 75%, were in the high risk or high-intermediate risk groups: median survivals were 6.8 months and 10.9 months respectively [7].

## **5.7. Future developments**

One of the more interesting developments in the management of HIV related NHL has been the recent observation that hydroxyurea has useful activity against EBV-related neoplasms [8]. Hydroxyurea is an orally active agent that has been widely used in oncology for many decades. It has also been reported to have activity against HIV [9]. If the potential of these early results is fulfilled, then we may be able not just to treat, but to prevent a significant proportion of HIV related non-Hodgkin's lymphomas.

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## 6. CARCINOMA OF THE CERVIX

### 6.1. Introduction

#### 6.1.1. *General introduction*

Cancer of the uterine cervix is the fourth most common malignant neoplasm in women in the world after breast, colorectal and endometrial cancer. In Sub-Saharan Africa and many other developing regions, it is the most common cancer in women. The association between HIV infection and cervical neoplasia was recognised in the 1980s and, in 1993, the CDC criteria for defining AIDS were modified to include invasive squamous cancer of the cervix as an AIDS defining condition in an HIV positive woman.

#### 6.1.2. *Aetiology and pathogenesis*

Human papilloma virus (HPV), particularly types 16 and 18, is the most common causative agent. Risk factors include low socio-economic status, first intercourse at early age, sexual promiscuity and large number of pregnancies. It is uncommon in nulliparous women. Many of these risk factors are shared with the acquisition of HIV by heterosexual exposure.

Sustained and/or up-regulated expression of the HPV encoded transforming proteins, E6 and E7 and their interaction with host cell tumour suppressor proteins that regulate normal cell growth and progression through the cell cycle appear to be fundamental in the development of cervical cancer. These pathogenic effects of viral and cellular interactions are potentially more pronounced and complex in HIV infected women. Both intercellular and intracellular interaction between HIV and HPV are possible. HIV specific antigen detected in monocytes, macrophages and endothelial cells within the cervical mucosa and infiltration of HIV infected CD4+ macrophages and lymphocytes into cervical epithelium suggest that HIV infected cells may come into close proximity to HPV infected basal epithelium cells [1].

The impact of concurrent HIV on the rate of progression in CIN is uncertain. Anecdotal reports suggest that the rate of transformation may be increased in certain individuals, but there is little hard evidence to suggest that this invariably applies to all patients.

#### 6.1.3. *Epidemiology*

The risk of squamous intra-epithelial lesions (SIL) in patients attending Sexually Transmitted Disease (STD) clinics and drug addiction clinics is further increased ( $\times 4.5$ ) by the acquisition of HIV infection [2]. The prevalence of HIV infection in 2198 patients recruited from gynaecology outpatient clinics in Cote d'Ivoire was 21.7% [3]. The same authors report that, of 94 women with SIL, 38 (40%) were HIV positive. These data are provocative but there are few hard data to support the contention that HIV infection causes invasive cancer of the cervix: the association may simply reflect the common epidemiological background for the two viral infections, HPV and HIV [4]. Many patients may acquire their HIV infection after they develop their malignant cervical changes [5]. Looking at the problem from the other direction: 38% of a cohort of 1680 HIV positive women had abnormal cervical smears [6], again confirming the association but not necessarily implying a causal relationship.



## 6.2. Clinical features

The cardinal symptom of invasive cervical cancer is post-coital bleeding. Inter-menstrual bleeding, excessive menstrual bleeding or post-menopausal bleeding suggest moderately advanced disease. In the later stages of the disease, foul-smelling chronic discharge, anaemia, lower abdominal pain and backache may occur. Haematuria and rectal bleeding indicate invasion of the bladder and rectum respectively.

## 6.3. Diagnosis

Asymptomatic cervical malignant change can often be diagnosed cytologically by cervical (Pap) smear. Unfortunately, there is some evidence that the false negative rate may be higher in HIV positive, as opposed to HIV negative women [7]. False negative rates of 15 to 20% are reported. This implies that it may be unwise to rely on a “normal” smear to exclude cervical malignancy in an HIV positive woman. Maiman et al. [7] in a study of 248 HIV infected women all of whom had cytology, colposcopy and biopsy concluded that 38% of all CIN in 13% of all the total patients would have been missed if colposcopy and biopsy had not been done. Baseline colposcopy in HIV infected patients is therefore essential.

Since the prevalence of disease is greater in HIV positive patients than in the general population optimal screening strategies should therefore take an important position. Screening high risk populations, although the intention is to detect early intra-epithelial lesions, may detect a significant number of lesions that have already progressed to invasive carcinoma. The definitive diagnosis of cervical neoplasia requires biopsy of the cervix. In some of the pre-invasive lesions diagnosis and therapy can be combined as a cone biopsy.

## 6.4. Staging (FIGO)

FIGO (International Federation of Gynaecologists and Obstetricians) [8] is designed as a clinical staging system with the minimum of special investigations. Analysis of subgroups, for example barrel (>4 cm) cervix within Stage I, or the presence or absence of ureteric involvement within Stage III, may provide additional prognostic information but the basic classification system has nevertheless proved very valuable for clinical use.

The staging may be summarised as follows:

- 0 *Carcinoma in situ*
- I Cervical carcinoma confined to the cervix. Extension to corpus disregarded
  - I.A Pre-clinical invasive carcinoma diagnosed by microscopy only
    - IA.1. Minimal microscopic stromal invasion <3 mm in depth; <7 mm in width
    - IA.2. Tumour with invasive component 5 mm or less in depth taken from the base of the epithelium and 7mm or less in horizontal spread
  - I.B. Tumour larger than IA2. Confined to the cervix
- II. Cervical carcinoma invades beyond uterus but not pelvic wall or the lower third of the vagina
  - II.A Without parametrial invasion. [Up to upper 2/3 of the vagina]
  - II.B. With parametrial invasion

- III. Cervical carcinoma extends to the pelvic wall or involves lower third of vagina or causes hydronephrosis or non functioning kidney
  - III.A. Tumour involves lower third of the vagina with no extension to pelvic walls
  - III.B. Tumour extends to pelvic wall or causes hydronephrosis or non functioning kidney unless known to be due to other cause
- IV.A. Tumour invades mucosa of bladder or rectum or extends beyond true pelvis
- IV.B. Distant metastases

## **6.5. Management**

### **6.5.1. *Diagnosis and management of cervical intra-epithelial neoplasia (CIN)***

Screening programs for cervical neoplasm are expected, given adequate facilities for treatment, to reduce both the incidence and mortality rates. It has been demonstrated [6] that HIV positive women have an increased rate of abnormal cytology including inflammatory changes. Initial accurate diagnosis can therefore be difficult. Therapeutic results for CIN in HIV infected patients are less predictable than those in HIV negative women. Fruchter et al [9] compared a group of 127 HIV positive women who underwent standard treatment for CIN with a group of 193 HIV negative patients. Three years after treatment, 62% of the HIV positive women, but only 18% of the HIV negative women, had developed recurrent CIN. The degree of immunosuppression, assessed as decreased CD4 count, correlated with the development of recurrent disease.

The optimal screening strategy for HIV positive women in the developed world is, after two negative smears six months apart, to screen using annual smears [10]. This is, however, an expensive strategy; each quality adjusted life year saved costs \$14,800.

The management of established CIN is surgical. The precise techniques will depend upon local expertise and resources. Complications, however, are significantly more frequent in HIV positive patients [11].

### **6.5.2. *Diagnosis and management of invasive cervical cancer in HIV negative women***

The standard approaches to the management of invasive cervical cancer in HIV negative women may be summarised as follows:

#### ***Stage IA***

Local surgery is the preferred management. The extent will depend mainly upon the patient's desire to maintain fertility. Limited procedures include: conisation; excision/ destruction of whole transformation zone by diathermy loop or electrocautery; cryocautery; cold-coagulation; laser ablation. (prior colposcopy mandatory). When fertility is not an issue, the treatment of choice is a simple hysterectomy. Radiotherapy is as effective as surgery and, where surgical expertise is not available, is a satisfactory alternative. Brachytherapy alone to a dose of 60 Gy to point A in a single low dose rate application is sufficient to control the cancer.

### ***Stages IB and IIA***

The results of treatment with surgery are comparable to those of radiotherapy and the initial decision should be based on available local expertise. When experts in both techniques are available then surgery, because of better preservation of sexual function and decreased late morbidity, is to be preferred for younger patients.

#### ***Radical (Wertheim) hysterectomy***

Wertheim hysterectomy: After determining that pelvic nodes are not involved by sampling, surgery continues with the removal of the uterus, cervix, parametria, upper third of vagina and a complete pelvic lymphadenectomy. It is usually not necessary to sacrifice ovaries, but this is frequently added in older patients.

#### ***Radical radiotherapy***

Radiotherapy: 45–50 Gy/22–25F/5 weeks with external beam therapy plus intracavitary treatment to the equivalent of 25–30 Gy to point ‘A’ given before or after the end of external beam therapy.

### ***Stages IIB, IIIA and IIIB***

Although these patients have moderately advanced disease, they can still be cured. The usual approach is to treat these patients solely with radiotherapy. However, particularly in France, combined approaches, integrating surgery and radiotherapy, have been employed.

#### ***Radiotherapy***

Radiotherapy: 45–50 Gy in 22–25 fractions over 5 weeks with external beam therapy plus intracavitary treatment to the equivalent of 25–30 Gy to point ‘A’ given before or after the end of external beam therapy.

### ***Stage IV***

Palliative treatment is all that can be offered and there is nothing to be gained from the use of protracted treatment schedules. Single fractions of 8 Gy weekly will often relieve pain and bleeding and can be repeated to a total of three fractions (24 Gy in 3 fractions).

#### ***6.5.3. Invasive cervical cancer in HIV positive women***

Invasive cervical carcinoma in women with low CD4 counts, as opposed to simply HIV positive women, present with more advanced tumours [12]. There is no evidence that invasive cancer follows a more aggressive clinical course, recurrence rates are higher nor that survival is shorter. Treatment strategies for HIV positive women must take this into account and be modified according to both the degree of immunodeficiency and the stage of the cancer.

#### ***Patient with intact immune system: CD4 >200***

There is no evidence that customary management need be changed in patients with patients with essentially intact immune systems. The use of anti-retrovirals and prophylaxis against opportunistic infections should be continued during this period.

### ***Patients with moderate immune impairment: CD4 count 50 to 200***

A standard management approach is advocated but the physician should be alert to early signs of intolerance to radiotherapy and the possibility of developing infection. Care should be exercised in minimising the field sizes. The trimming of corners in the pelvic fields, even if not usually practised, may be advantageous in these patients. The use of anti-retrovirals and prophylactic against opportunistic infections should be continued during this period.

### ***Patients with severe immune impairment: CD4 <50***

These severely immune-compromised patients should receive palliative treatment using weekly fractions e.g. 3 Gy once per week for 4 fractions, then a 3-week gap, then 3 Gy once per week for 4 fractions (24 Gy in 8 fractions in 9 weeks).

## **6.6. Outcome and prognosis**

For patients with early stage disease and profound immunosuppression, the HIV infection, rather than the tumour will dictate prognosis. Conversely, for patients who present with advanced cervical cancer, but with normal CD4 counts, the outlook will be dominated by the progress of the tumour. Most patients will lie somewhere between these two extremes and it is, consequently, not possible to be dogmatic about outcome. An infinite number of permutations are possible. The essential rule is to make decisions based on the management of the patient as a whole, rather than simply looking at the tumour or at the HIV infection. The presence of a positive HIV test should not exclude a woman from having adequate management for her cervix cancer, nor should a diagnosis of cancer of the cervix necessarily compromise the management of a woman's HIV infection.

Survival rates for HIV positive women with cervical cancer have not been specifically reported but it is worth remembering that in HIV negative women the survival rates for Stage IA and IB disease are over 90%. Even women with advanced disease, IIIA and IIB, may have a 5-year survival rate of more than 50%.

## **6.7. Future developments and studies**

There is a need to establish the effect of radical radiotherapy on the immune system of an HIV infected patient with cervical carcinoma. This can be done by monitoring the levels of CD4 cell count before and after therapy and also on 3-month follow-up.

This study would be best carried out in a region where there is high prevalence of both HIV and cervical cancer which at this moment is Sub-Saharan Africa.

There is also a need to look into the use of retinoids and 5-Fluorouracil creams in HIV infected patients. These topical agents have been found to offer high cure rates in the treatment of CIN in HIV negative patients.

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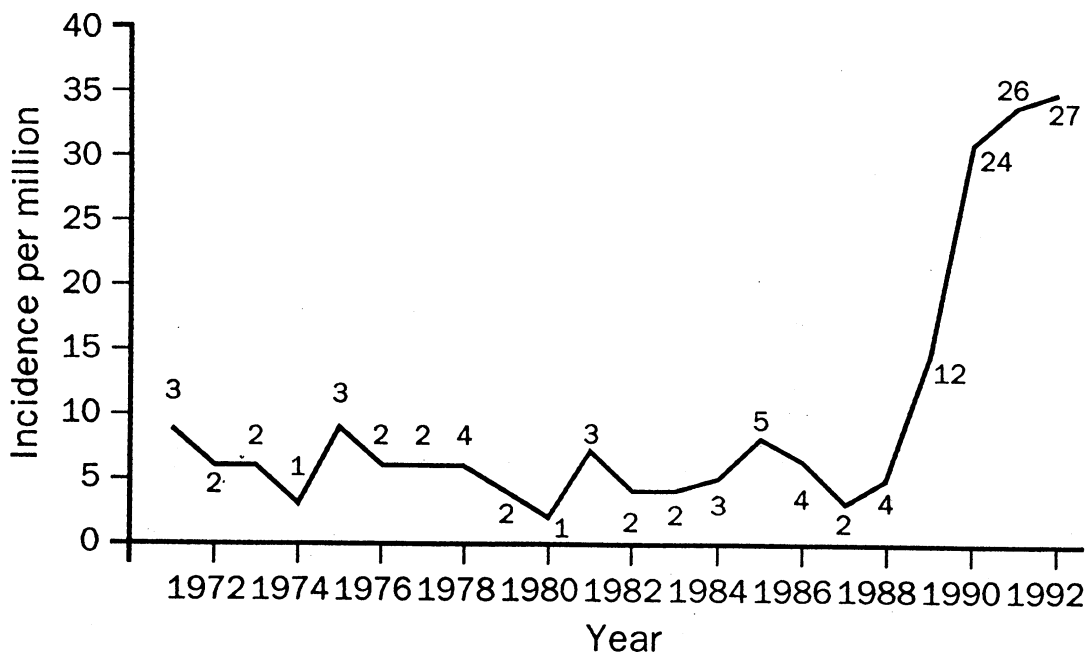
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## 7. OCULAR TUMOURS

### 7.1. Squamous cell carcinoma of the conjunctiva

Conjunctival squamous carcinoma is uncommon even in countries with high sun exposure. However, the incidence of squamous cell carcinoma now manifests epidemic trends in some sub-Saharan countries, notably Uganda and Rwanda [1, 2].

The incidence in Uganda was an average of two tumours per million population from 1970 to 1988. The incidence increased ten fold from 1988 to 1992 and has continued to increase. HIV infection is a significant risk factor for the development of squamous cell carcinoma of the conjunctiva. Most workers have found a relative risk of 13 fold [1–3]. These case control studies were all done in the early 1990s. HIV infection has significantly changed the clinical features of this cancer.



Prior to the advent of HIV, conjunctival squamous cell carcinoma was a relatively rare cancer with a slow locally invasive mode of spread. The tumour in the era of HIV infection has assumed a very aggressive course with the majority of patients presenting with advanced disease in only three months [1]. The tumour was commonly seen in the 40+ years age group, but now has shifted to the younger age groups, commonly being seen in the 20–35 years age group.

In the HIV infected patients, the cancer appears early in the course of the disease stage. Failure to adequately control this tumour will result in terrible local morbidity and eventual death in patients who may be in otherwise good performance status. Since this cancer has been relatively rare in tropical Africa and virtually not seen in the western countries, it is posing a challenge to most ophthalmologists working in the developing countries with meagre resources.

There is hardly any data on the management of this cancer. However, the number of cases in Uganda has significantly increased since 1992 and this has provided an opportunity to increase our knowledge about this cancer. In order to improve the management of this cancer in developing countries and in view of the fact that inadequate treatment leads to recurrences that are very difficult to handle, the following staging of the cancer has been proposed.

Clinical staging of this cancer, not previously done, forms the basis for proper management and recording of results of the management of this cancer.

#### STAGING OF SQUAMOUS CELL CARCINOMA OF THE CONJUNCTIVA

Stage	Extent
I	tumour <6 mm and mobile over the sclera
II(A)	tumour >6 mm or/and fixed onto the sclera (irrespective of size) or/and corneal involvement
II(B)	extra-ocular muscle involvement
III	globe perforation or/and orbital involvement
IV	extra-orbital spread

##### 7.1.1. Treatment guidelines

Stage I: Surgical excision leaving a minimum of 2 mm margins. It is important that tumour excision at this stage is complete.

Excision should be followed by beta plaque applications commenced within twenty four hours of a surgical excision using twice weekly doses of 10 cGy for three weeks (total 60 Gy) to the excision bed. Inadequate excision, leaving residual tumour thickness in excess of the range of beta particles, will commonly lead to recurrence which occurs as a higher stage cancer with a poorer prognosis. Adequate and complete excision of the tumour at stage I can offer a complete cure of the cancer if it is immediately followed by radiotherapy.

Stage II(A): The surgical procedure involves the removal of the tumour with a 3 mm surgical excision margin, lamella sclerectomy, and keratectomy.

The above surgical procedures should be followed by beta plaque applications to the excision bed. In cases where the tumour has involved more than half the scleral thickness, beta plaque applications may not be adequate. Strontium can deliver effective radiation to about a 3 mm depth.

Stage II(B): Extra ocular muscle involvement poses particularly difficult management problems as the tumour grows quite fast due to the increased blood supply from the extra-ocular muscles. As the visual acuity is still normal, enucleation is unacceptable to almost all patients. Complete excision of the tumour may prove to be impossible if the eye is to be saved

because of the posterior extension of the tumour. Radiotherapy by implanting caesium needles may be a possibility to be considered. Surgical revision may be required for late fibrosis.

Stage III: The surgical procedure of enucleation should be followed by radiotherapy to the orbit — a dose of 45 Gy in 20 fractions or its biological equivalent may be effective.

Stage IV: The management is palliative with radiotherapy or chemotherapy.

In stages I and II, it is important to note that careful surgical excision with minimal seeding of tumour tissue followed by radiotherapy can be curative. It is strongly advised that patients should be referred to appropriate centres for proper management if the personnel is not able to handle the case. There is no place for incision biopsies for diagnostic purposes unless the tumour is in stage III or stage IV. In the early stages, I and II, incision biopsies would lead to very rapid spread of the tumour due to seeding.

## **7.2. Ocular lymphomas**

Orbital lymphomas have been reported associated with HIV infection. This has an elevated association with concurrent or subsequent lymphoma. These may be retro-orbital or intraocular.

Retro-orbital lymphoma presents as a proptosis and will mimic other causes of intraorbital masses. They have therefore not posed a big challenge to health workers. Orbital lymphomas that occur sporadically require a surgical excision for diagnostic purposes. An orbitotomy through either the lateral or inferior approach is recommended to excise the tumour. Focal radiotherapy in orbital lymphomas that are localised only to the orbit is recommended. A central beam block is usually employed to shield the anterior compartment. The field could included in whole brain irradiation in the presence of Central Nervous System (CNS) involvement. A dose of 20 Gy in 5 fractions should be effective in controlling the tumour locally.

Intraocular lymphoma is a recognised entity in non-Hodgkins CNS lymphoma and has also been described [4] in AIDS patients. As this may mimic cytomegalovirus retinitis, failure of response to treatment should be an indication for biopsy. A similar radiotherapy technique to retro-orbital lymphoma is used.

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## 8. ANAL CANCER

### 8.1. Introduction

#### 8.1.1. General

The incidence of premalignant and malignant lesions of the anus is increased in HIV positive individuals. Although not an AIDS defining diagnosis, anal cancer occurs sufficiently frequently in HIV positive men and women to warrant specific consideration in the context of HIV infection.

#### 8.1.2. Aetiology and pathogenesis

Malignant and premalignant lesions of the anal canal are strongly associated with infection by the human papilloma virus (HPV). The sub-types that are specifically associated with anogenital malignancies are 16, 18, 31, 33, 35, 45, 51, 52 and 56. The risk of malignant transformation is greatest with types 16 and 18 and, between them, they account for over 60% of cases. The virus infects the basal cells of the stratified epithelium and viral oncogenes E6 and E7 are able to express their oncoproteins. These proteins are produced by infected cells as they migrate through the spinous layer of the epithelium and mature virus is released at the epithelial surface. The oncoproteins produced by HPV have profound effects upon the cell cycle. The E6 protein is able to inactivate the p53 gene product and the E7 protein can inactivate the retinoblastoma gene product. The p53 protein and the retinoblastoma gene product both function as tumour suppressors: HPV infection can therefore inhibit a normal mechanism for protecting against the development and establishment of malignancy [1]. Cell-mediated immune mechanisms are particularly important in protecting against HPV infection. Since it is these very mechanisms that are impaired by HIV infection, it is easy to postulate a series of events leading to an increased risk of pre-invasive and invasive anal malignancy in HIV positive individuals.

The development of invasive anal cancer probably follows a cytological and histological sequence similar to that of cervical cancer. There are atypical cytological changes, confined to the epithelium itself, which progress until the basement membrane is breached and frank invasion is identified. We know much less about the process in the anus than we do about the analogous processes in the cervix simply because proctoscopy with exfoliative cytology and biopsy are rarely performed.

#### 8.1.3. Epidemiology

The incidence of anal cancer in men who have practiced receptive anal intercourse is approximately 4.5 times as high as it is in the general population: 35 per 100 000 compared with 8 per 100 000. The relative risk of anal cancer in people with AIDS is 31.7 (95% confidence interval 11.6 to 69.2) [2]. The incidence of anal cancer amongst HIV positive women is unknown. As with many conditions, what you find depends upon how hard you look. In one series of HIV positive women, the prevalence of abnormal anal cytology was 14% of 109 women [3]. The increased incidence of anal cancer in homosexual men preceded the development of the AIDS epidemic [2] but there is some evidence that the risk of premalignant anal changes may be further increased by HIV infection in this population. A study of HIV positive and HIV negative homosexual men showed that the relative risk for anal intraepithelial neoplasia was 3.7 for HIV positive, as opposed to HIV negative, men [4].

It is easy to postulate the mechanism of transmission of HPV during receptive anal intercourse. It is less straightforward to consider how HPV infection of the anal canal might occur in the absence of anal intercourse. One possibility is that the virus is transferred during other forms of sexual activity, insertion of fingers, objects, etc. into the anus.

## **8.2. Clinical features**

Premalignant changes in the epithelium of the anal canal are asymptomatic. Once invasive malignancy has developed then the following symptoms can occur: pruritus; bleeding; mucus discharge; pain on anal intercourse; pelvic pain; tenesmus; abnormal ano-rectal sensations.

## **8.3. Diagnosis**

The diagnosis of invasive malignancy must always be confirmed by biopsy. Lymphomas can present as ano-rectal tumours in the HIV positive population and esoteric opportunistic infections, such as fungal infections, may mimic anal cancer.

## **8.4. Staging and assessment**

Staging investigations should include history, physical examination including anoscopy/proctoscopy/sigmoidoscopy and examination of the anogenital region for concurrent malignancies (i.e. cervix). Full blood count and liver function tests should also be performed. When available, CT scan or MRI imaging of the abdomen and pelvis should be performed to exclude occult metastatic disease. Other studies that may be useful, depending on the clinical presentation, will be colonoscopy or air contrast barium enema to exclude other causes of lower GI tract bleeding, and transrectal ultrasonography.

The American Joint Committee on Cancer (AJCC) staging system for anal carcinoma is:

### **PRIMARY TUMOUR (T)**

- TX Primary tumour cannot be assessed
- T0 No evidence of primary tumour
- Tis Carcinoma in situ
- T1 Tumour  $\leq 2$  cm in greatest dimension
- T2 Tumour  $> 2$  cm but  $\leq 5$  cm in greatest dimension
- T3 Tumour  $> 5$  cm in greatest dimension
- T4 Tumour of any size invades adjacent organ(s), which should be specified (i.e. vagina, urethra, bladder); involvement of the sphincter muscle(s) alone is not classified as T4

### **REGIONAL LYMPH NODES (N)**

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in perirectal node(s)
- N2 Metastasis in unilateral internal iliac or inguinal lymph node(s)
- N3 Metastasis in perirectal and inguinal lymph node(s), bilateral internal iliac or inguinal lymph node(s)

## DISTANT METASTASIS (M)

Stage grouping	TNM
0	Tis N0 M0
I	T1 N0 M0
II	T2-3 N0 M0
III(A)	T4 N0 M0 T1-3 N1 M0
III(B)	T4 N1 M0 Any T N2-3 M0
IV	Any T Any N M1

### 8.5. Management of HIV related anal cancer

The conventional management of anal cancer in HIV negative patients is, nowadays, with chemo-radiation: using 5-fluorouracil and mitomycin C synchronously with radical doses of radiation. The major issue in the management of HIV positive patients with anal cancer is whether, against a background of increased susceptibility to infection and, possibly, increased sensitivity of the normal tissues, such treatment can safely be given.

There have been several studies, all of them small, which have reported on the management of anal cancer in HIV positive people [5–12]. The results of the studies using chemo-radiation can be summarised as follows:

- There is no evidence that tumour control is any worse, stage for stage, in HIV positive patients than would be expected in HIV negative patients.
- There is no evidence that chemo-radiotherapy accelerates the progression of HIV infection.
- Acute toxicity is greater in HIV positive patients than would be expected in HIV negative patients. There is no evidence that HIV status has any influence on late morbidity.
- Patients with AIDS and anal cancer fare worse than HIV positive patients with anal cancer. This is due to progression of the HIV related problems rather than failure to control the tumour.
- There is some evidence that patients with CD4 counts less than 200 per dL experience more severe acute effects from chemo-radiation than patients with CD4 counts greater than 200 per dL. CD4 count has no apparent effect on the probability of achieving local control of the tumour with chemo-radiation.

Local surgery may have a role to play in patients with early tumours. Experience is limited but Lorenz et al. report encouraging results in a small series of HIV positive patients treated by local excision of their anal cancers [13].

On the basis of these reports, guidelines for treatment can be proposed.

### **8.5.1. *Fit patients with early tumours***

Patients with HIV infection who have not been incapacitated by opportunistic infections or other sequelae of HIV infection (i.e. dementia), who have good performance status, and adequate physiologic parameters should be treated with aggressive chemo-radiation. When available, anti-retroviral therapy should be given. When appropriate, prophylaxis against opportunistic infections such as pneumocystis carinii should be considered during chemo-radiation and any subsequent period of neutropenia or immuno-suppression.

Radiotherapy techniques may vary somewhat upon the equipment available and the physical factors involved in the treatment of any one individual patient, such as patient girth. Radiotherapy fields will initially encompass the low pelvis including the primary site and regional perirectal, inguinal, and internal iliac for the first 30 Gy of radiotherapy. This dose can be given at 1.8–2.0 Gy per fraction over approximately 3 weeks. Unless patients have a very wide AP-PA separation resulting in a dose inhomogeneity of >10%, anterior-posterior (AP-PA) megavoltage beam arrangements are appropriate. These AP-PA fields can be designed to place the superior border of the field at the bottom of the sacroiliac joints, the inferior border 2 cm below the anus, and lateral borders 1 cm beyond the acetabulum. For obese or other patients with a large AP-PA separation, megavoltage beam energy may need to be  $\geq 10$  MV if AP-PA fields are to be employed without excessive dose inhomogeneity. If these higher energy megavoltage beams are not available, 3-field (PA and lateral fields), 4-field (AP, PA, and lateral fields), or other beam arrangements may be necessary. If these multiple field techniques are employed, dose calculations should include the doses to the primary site as well as perirectal, internal iliac, and inguinal nodes. Bolus over the primary site and any superficial inguinal nodes may be necessary to ensure adequate build-up for these areas to receive full dose.

The initial 30 Gy to the primary site and regional nodes can be given concurrently with 5-FU 1000 mg/ m<sup>2</sup>/day on days 1–4 by infusion with Mitomycin at 10 mg/m<sup>2</sup> on day 1. Boost radiotherapy to the primary site and any grossly involved nodes, possibly with a second course of 5-FU can be considered for patients with  $\geq T3$  lesions or less than complete responders.

Following the initial 30 Gy in 15 to 18 fractions, and after a gap of 7 to 10 days to allow any acute reaction to settle, a boost should be given to the local tumour and anal canal. Boost doses may be in the range of 15–25 Gy at 1.8–2.5 Gy per daily fraction. Boost treatment techniques can include 3-field (PA, lateral fields) photons or en face photons or electrons of appropriate energy. Again, bolus over the primary site or inguinal nodes may be necessary.

### **8.5.2. *Unfit patients and/or advanced disease***

For patients with anal carcinoma and evidence of progressive HIV disease such as major opportunistic infections, HIV dementia, or other incapacitating manifestations of HIV infection, several treatment options seem reasonable. For patients with lesions of the anal verge (i.e. perianal skin), excision can be done if negative margins can be obtained with preservation of anal sphincter function. For patients with carcinomas of the anal canal less than 2 cm, excision can also be considered. Otherwise, localised radiotherapy alone to the primary site can be given. Dose schedule chosen will depend in part upon the extent of HIV disease, equipment availability, and patient/family preference, but the schedule should balance the need to adequately control pain, bleeding, and infection related to the anal carcinoma with the usual goals of palliative radiotherapy (i.e. to deliver treatment in the fewest number of

fractions that will provide palliation without causing treatment induced complications). Appropriate schedules might include:

- (1) 30 Gy in 10 fractions with a plan to reassess after the acute reaction has settled, and deliver an additional 10–20 Gy at 2.5–3 Gy per fraction.
- (2) 3.7 Gy b.i.d. (separated by 6 hours) or 3.7 daily to 14.8 Gy in 4 fractions, with re-assessment approximately 3 and 6 weeks later to repeat this dosing 1 to 2 times, if necessary, to bring the total dose to a maximum of 44.4 Gy in 12 fractions over a total treatment time of 10 to 12 weeks.

Whether to employ any chemotherapy in this situation is a decision that must be set against the overall clinical status of the patient. If a decision is made to give chemotherapy, continuous infusion 5-FU at the above-mentioned doses with or without Mitomycin could be given. If chemotherapy is given in these circumstances, then the radiation dose and dose per fraction may need to be modified in the light of the evolving acute effects.

## **8.6. Outcome and prognosis**

Survival beyond two years, without colostomy, should be achievable for the majority of patients who have T1 or T2 tumours, who are in good general condition and who do not have AIDS.

## **8.7. Future developments**

These treatment recommendations for the treatment of anal carcinoma in HIV infected patients have been made after review of the relatively sparse data available on this subject. There are relatively few published reports available and these include only a small number of patients treated by experienced (and often academic expert) clinicians in developed nations. It is important to collect and analyse data from centres in developing nations on the regimens employed for treatment of these patients, as well as treatment efficacy and toxicity. After review of this data, revision of the treatment recommendations and or modification of suggested treatment programs might be indicated.

Oral 5-FU analogues are now available [14]. These agents are being tested, in combination with radiotherapy, for treatment of a variety of gastrointestinal malignancies [15]. If dose schedules with comparable efficacy to continuously infused 5-FU can be established, their usage in the treatment chemo-radiation treatment of these patients with anal carcinoma might offer significant benefits in terms of both quality of life and cost.

The addition of cis-Platinum to 5FU-based chemo-radiotherapy schedules is now being tested in randomised trials in HIV negative patients. If platinum proves to confer significant benefit, then there is no reason not to use the drug, with caution, in HIV positive patients with anal cancer.

The issue of screening high risk populations, such as HIV positive men and women, or people who practice receptive anal intercourse is also important. The sensitivity of anal cytology, in a population of homosexual and bisexual men, for the diagnosis of anal squamous intraepithelial lesions was 69%, in HIV positive men, and 47%, in HIV negative men [16]. Although a recent analysis suggests that annual screening with anal cytology in HIV positive homosexual men may be an effective strategy, the cost was not trivial: \$16,600 per quality adjusted life year gained [17].

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## 9. MALIGNANCIES IN HIV INFECTED CHILDREN

### 9.1. Introduction

#### 9.1.1. General

Before the AIDS epidemic, childhood cancers were generally uncommon in most developing countries notably those in Africa. However, some tumours such as Burkitt's lymphoma (BL) predominantly occurred in Equatorial Africa accounting for about 1/3 of all childhood cancers in Uganda. With the advent of HIV/AIDS, an increase in some malignancies has been observed, albeit to a lesser extent compared to HIV infected adults.

The identification of HIV associated tumours in children has been hampered by the scarcity of data — particularly from the developing world. Diagnosis and case-identification is difficult and it is entirely possible that, amongst the children of Africa and Asia, many HIV related tumours are going unreported.

#### 9.1.2. Aetiology and pathogenesis

The tumours that develop in HIV infected children are, in their origins and appearance, little different from those that affect adults. Smooth muscle tumours, which are the second most prevalent tumour in children with AIDS, are the exception. There is strong evidence linking these tumours to infection with Epstein-Barr virus (EBV) [1].

#### 9.1.3. Epidemiology

In the developed world, only about 2% of HIV positive children develop malignancy as an AIDS defining diagnosis. In the UK, BPA surveillance series there have been 9 malignancies in 302 HIV positive children: 7 cases of NHL and 2 cases of Kaposi's sarcoma (KS) [2]. The pooled experience of AIDS related malignancy in children from Europe and the USA shows that, in contrast to HIV infection in adults, lymphomas are more common than KS. The distribution of tumour types in 64 HIV positive children with cancer in one series from the USA was as follows: 65% had NHL; 17% had soft tissue tumours; 8% had leukaemia; 5% had KS. Other tumours included: Hodgkin's disease (2 children), in situ vaginal carcinoma (one child) and tracheal neuroendocrine tumour (one child) [3].

In Africa, the position is entirely different: childhood Kaposi's sarcoma, previously rare, has increased 40-fold since the beginning of the AIDS epidemic and clinically resembles the condition seen in adults infected with HIV. In Zimbabwe, 27 of 64 (42%) consecutive children assessed by the paediatric oncology service were HIV positive: the most common tumours were NHL, Wilm's tumour, acute leukaemia and KS [4]. The data from Uganda fail to show any increase in soft-tissue tumours in children associated with the AIDS epidemic [5].

There has been no demonstrable increase in Burkitt's lymphoma in African children since the start of the AIDS epidemic. This is a provocative observation for several reasons. Burkitt's lymphoma is an EBV associated tumour and there has been an HIV related increase in another group of EBV related tumours, smooth muscle tumours, during this period. There has also been, in the developed world, an increased incidence of Burkitt's lymphoma and other EBV related lymphomas in HIV infected adults. Only 15% of Burkitt's lymphoma in African children is associated with HIV. This may simply be because, since Burkitt's is a

tumour of later childhood and adolescence, HIV infected children in Africa do not live long enough to develop the condition.

## **9.2. Management of HIV related tumours in children**

### **9.2.1. General principles of management**

HIV infected children are susceptible to a multitude of problems. These include: psychosocial difficulties, infections, including TB; frequent attacks of diarrhoea cause weight loss, impaired growth and further immunosuppression. All these issues need to be addressed in order to improve the child's quality of life. Palliative management may often be the only treatment that is appropriate, available or affordable.

### **9.2.2. Radiotherapy for HIV related tumours in children**

Sadly, most of these children can only be treated palliatively. Radiotherapy has an important role to play in the relief of symptoms. It is often effective and, provided it is given judiciously, toxicity and disruption can be kept to a minimum.

Dyspnoea resulting from pulmonary Kaposi's sarcoma can be controlled with 3 Gy in a single fraction to the lungs.

### **9.2.3. Chemotherapy in general**

The majority of these children present with advanced disease (both HIV and cancer). In view of this, their bone marrow reserve is limited, their performance status is poor and the likelihood of further immunosuppression on conventional doses of chemotherapy is very high. Chemotherapy regimens should be given, using doses that are 75% of those that are used in conventional practice. Frequent monitoring of blood counts and careful monitoring for adverse effects of treatment is essential. Blood transfusions should be given when indicated and antibiotics rationally used. Those who can afford the cost of anti-retroviral drugs should not be denied the opportunity to use them, knowing fully well that increased myelosuppression may occur. The Pediatric Oncology Group (POG) has developed protocols for the management of children with HIV related malignancies and this provides a potential source of further information.

### **9.2.4. Chemotherapy for Kaposi's sarcoma in childhood**

Kaposi's sarcoma in children usually presents as a generalised disease with involvement of mucus membranes, lymph nodes and the skin. The majority of the children are anaemic, malnourished, thrombocytopenic and febrile. Their general condition can be improved by: ensuring adequate nutrition; treating any infection that is present; using blood transfusions to correct any anaemia. Palliative chemotherapy may be given using a marrow-sparing regimen:

vincristine (1.4 mg/m<sup>2</sup>/IV) + bleomycin (10 mg/m<sup>2</sup>/IV)

given every 2 to 3 weeks



### **9.2.5. Chemotherapy for NHL in childhood**

These patients should be treated with reduced (75%) dosage of CHOP along with intrathecal methotrexate as CNS prophylaxis.

## **9.3. Future developments**

### **9.3.1. Control of HIV infection**

A reduction of the prevalence of HIV infection in children will follow any reduction in the prevalence of HIV in women of childbearing age. The vast majority of children (90%) with HIV acquired their infection by maternal–child transmission at and around the time of birth: during labour or breast-feeding.

### **9.3.2. Control of HIV associated malignancies**

In the current state of knowledge, secondary prevention appears to be an unrealistic goal.

### **9.3.3. Provision of adequate data**

We simply do not know enough about the incidence and prevalence of HIV related malignancies in children living, and dying, in the developing world. There is an urgent need for a systematic approach for identifying, registering and tracking outcomes in children with HIV related tumours. Until we know the nature and extent of the problem, there is too little that we can do to tackle it.

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## **10. RADIOTHERAPY TREATMENT OF THE MEDICAL COMPLICATIONS OF HIV INFECTION**

### **10.1. Thrombocytopenia**

Severe Zidovudine-resistant, HIV associated thrombocytopenia can be a significant problem with HIV infected patients. Low dose splenic radiotherapy has been given in these patients in an attempt to reverse or ameliorate thrombocytopenia. Soum et al. [1] reported a prospective study of 17 patients who met the entry criteria of haemorrhagic symptoms or platelet count below or equal to  $50 \times 10^9$  /L and normal numbers of megakaryocytes on bone aspiration. The mean baseline platelet count was  $20.3 (+/- 14.4) \times 10^9$  /L; four patients had a platelet count inferior to  $10 \times 10^9$  /L. Splenic volume was defined by ultrasonography. A total dose of 9 Gy was given in 9 fractions of 1 Gy using a parallel opposed pair of fields. Treatment was given three times per week: total dose 9 Gy in 9 fractions over 3 weeks. One month after the end of treatment, six patients had a significant rise in their platelet count. Clinically, haemorrhagic symptoms stopped for all patients that were symptomatic. Unfortunately, duration of response was short because platelet count was maintained for only one patient at 6 months. All patients were still alive. At the time of last evaluation, four of eight patients were receiving combination anti-retroviral therapy and had a platelet count above  $50 \times 10^9$  /liter. They were disappointed with the duration of palliation, but did recommend that splenic irradiation be considered for the minority of patients with severe bleeding that was not responsive to standard medical treatment. A report from Australia corroborated this experience [2].

Hence, it would be useful to keep radiotherapy in mind as a potentially useful treatment for the minority of patients with severe bleeding in the setting of HIV associated thrombocytopenia not responsive to standard medical treatment. Radiotherapy offers, of course, an excellent palliative option for patients with bleeding from a variety of tumour sites with doses of approximately 20 Gy at 2–5 Gy per fraction effective in stopping bleeding over 1–2 weeks in the majority of patients.

### **10.2. Benign parotid hypertrophy**

Benign parotid hypertrophy due to multicystic, benign lymphoepithelial lesions either unilateral or more commonly bilateral results in cosmetic deformity in HIV+ patients.

An early study of 4 to 5 fractions to 8–10 Gy in 1.5 Gy gave a median control of 9.5 months [3]. Subsequently, 24 Gy in 1.5 Gy fractions has shown to give lasting local control in 68% of cases [4]. This is administered by parallel opposed photon fields for bilateral lesions and by electrons for unilateral lesions.

No studies have been reported on dose fractionations between these extremes.

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## LIST OF PARTICIPANTS

Asavametha, N.	Division of Radiation Oncology, Chulalongkorn University, Bangkok, Thailand
Ateenyi-Agaba, C.	Department of Ophthalmology, New Mulago Hospital, Kampala, Uganda
Calaguas, M.	Division of Radiation Oncology, St. Lukes Medical Center, Quezon City, Philippines
Curren, W,	Dept. of Radiation Oncology, TJ Univ. Hospital Bodine Ctr for Cancer Treatment, Philadelphia, USA
Delaney, T.	Dept. of Radiation Oncology, Boston University Medical Center, Boston, USA
Kasese, J.	Radiotherapy Centre, Mpilo Hospital, Bulawayo, Zimbabwe
Levin, V.	Division of Human Health, International Atomic Energy Agency, A-1400 Vienna, Austria
Kirova, Y.	Cancerology Department, University Hospital Henri Mondor, Créteil, France
Mbidde, E.	Uganda Cancer Institute, Kampala, Uganda
Munro, A.	Radiation Oncology, Ninewells Hospital and Medical School, Dundee, Scotland, United Kingdom
Parkin, M.	International Agency for Research on Cancer, Lyon, Cedex 08, France





