ZIMBABWE NATIONAL
ADULT ONCOLOGY
TREATMENT GUIDELINES

2025

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Foreword

The Government of the Republic of Zimbabwe remains steadfast in its commitment to advancing the health and well-being of all citizens, as enshrined in the National Health Strategy (NHS) 2021–2025. This Strategy, a cornerstone of the National Development Strategy 1 (NDS1), positions health as a vital engine of national progress, urging resilience, equity, and innovation. Within this transformative vision, the National Oncology Guidelines emerge as a critical instrument to confront one of our most pressing public health challenges: the rising burden of cancer.

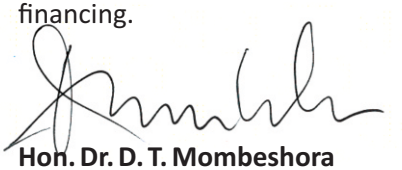
Cancer has become a defining health crisis in Zimbabwe, with over 7,000 new cases documented in 2016 and incidence rates climbing steadily. Driven by factors such as HIV comorbidity, lifestyle changes, environmental risks, and systemic barriers to early diagnosis, this epidemic demands a response rooted in unity, rationality and compassion. These guidelines are not merely a clinical roadmap, they are a declaration of our collective resolve to integrate cancer care into the broader framework of national development, as envisioned by the NHS.

Aligned with the NHS's eleven investment priorities, these guidelines prioritize prevention, early detection, and equitable access to care. They resonate with the Strategy's focus on combating non-communicable diseases (NCDs), strengthening primary healthcare, and fostering multisectoral partnerships. For instance, the emphasis on HPV vaccination and tobacco control aligns with preventive measures under the NHS, while protocols for palliative care and survivorship reflect our commitment to dignity and holistic well-being.

The success of these guidelines, like the NHS itself, hinges on the understanding that no single entity can shoulder this burden alone. From oncologists in Harare to community health workers in Masvingo, from policymakers to development partners, each stakeholder has a role. The guidelines advocate for empowering nurses in rural clinics to timely refer

suspected clients for care, integrate HIV and oncology services to address our dual disease burden, and leverage low-cost innovations like VIAC screening. These strategies mirror the NHS's call for context-driven, resilient solutions, even amid resource constraints.

The COVID-19 pandemic laid bare the fragility of health systems globally, yet it also revealed Zimbabwe's capacity for adaptability. These guidelines build on that resilience, urging investments in radiotherapy infrastructure, chemotherapy supply chains, and training for oncology professionals all critical to achieving the NHS's goal of sustainable domestic health financing.



Hon. Dr. D. T. Mombeshora
Minister of Health and Child Care

Acknowledgements

The development of these National Oncology Guidelines reflects the collective dedication and collaboration of numerous individuals and institutions committed to advancing cancer care in Zimbabwe. The Ministry of Health and Child Care extends its heartfelt gratitude to all who contributed their expertise, time, and resources to bring this vital document to fruition.

We extend our sincere appreciation to the Government Ministries and Departments for their leadership and unwavering support. Their commitment to aligning these guidelines with national health priorities ensured coherence with Zimbabwe's broader development goals and the National Health Strategy 2021–2025.

The Ministry acknowledges the invaluable contributions of its Development Partners, whose technical and financial support played a pivotal role in shaping these guidelines. Their collaboration helped bridge global best practices with Zimbabwe's unique healthcare context, ensuring the guidelines are both aspirational and grounded in local realities.

The National Cancer Registry provided essential data and insights that formed the backbone of these guidelines. Their rigorous work in documenting cancer trends and outcomes has been critical in crafting strategies that address the specific needs of our population.

The Ministry is grateful to the diverse teams of clinicians, public health specialists, and researchers who devoted countless hours to reviewing evidence, drafting recommendations, and refining the guidelines. Their expertise ensured the document remains scientifically robust, patient-centered, and practical for implementation across all levels of care.

The National medicines and Therapeutic Policy Advisory Committee continued to provide guidance on treatment protocols, drug safety. Their

recommendations ensured the guidelines align with national standards for equitable and effective cancer care.

Special thanks to the Editorial Team for their meticulous work in harmonizing contributions, ensuring clarity, and maintaining consistency throughout the document. Their attention to detail transformed complex technical content into a cohesive and accessible resource.

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Acronyms / Abbreviations

5FU	5 Fluorouracil
5HT3	5 hydroxytryptamine 3
AIDS	Acquired Immunodeficiency Syndrome
ADT	Androgen deprivation therapy
ART	Antiretroviral Therapy
AUC	Area under the curve
BCC	basal cell carcinoma
BSA	Body Surface Area
BTCP	Break through cancer pain
BRCA	Breast Cancer Gene
CNS	Central Nervous System
CSF	Cerebral Spinal Fluid
CHD1	Chromodomain Helicase DNA Binding Protein 1
GTR	Complete resection / gross total resection
CT	Computed Tomography scan
DVT	Deep venous thrombosis
DNA	Deoxyribonucleic Acid
DES	Diethylstilbestrol
DDIs	Drug-drug Interactions
ECOG	Eastern Cooperative Oncology Group
ERCP	Endoscopic retrograde cholangiopancreatography
EBV	Epstein-Barr virus
EBRT	External Beam Radiotherapy
FIT	Faecal immunochemical
FOBT	Faecal occult blood test
FAP	Familial adenomatous polyposis
MALT	Mucosa associated lymphoid tumours
MEN	Multi endocrine neoplasia
MLCs	Multileaf collimators
MT-sDNA	Multi-target stool DNA
MAC	Mycobacterium avium complex
NADCs	Non-AIDS-defining cancers
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
OSSN	Ocular surface squamous neoplasia

PPE	Palmar–plantar erythrodysaesthesia
PCNSL	Primary central nervous system lymphoma
PNET	Primitive neuroectodermal tumours
PSA	Prostate Specific Antigen
RET mutation	Rearranged during Transfection mutation
RECIST	Response Evaluation Criteria in Solid Tumour
SCC	Squamous cell carcinoma
STR	Subtotal resection
TSH	Thyrotropin
TNM	Tumour, nodes & metastases
TLS	Tumor lysis syndrome
USS	Ultrasound Scan
UFH	Unfractionated heparin
VIAC	Visual inspection under acetic acid and cardiogram
WBRT	Whole Brain Radiotherapy
ZEPI	Zimbabwe Expanded Programme of Immunization

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Executive Summary

The Government of the Republic of Zimbabwe is committed to the health and well-being of all citizens as enshrined in the National Health Strategy (NHS) 2021–2025. The Ministry of Health and Child Care developed these National Oncology Guidelines to confront the escalating burden of cancer. Cancer has emerged as a defining health crisis, with over 7,000 new cases documented in 2016 and incidence rates rising steadily. This surge is driven by a dual burden: infectious agents such as HIV and HPV contribute to high rates of cervical cancer, Kaposi's sarcoma, and lymphomas, while lifestyle changes and environmental factors fuel increases in breast, prostate, colorectal, and childhood cancers. Tragically, many patients present at advanced stages due to limited screening programs, financial barriers, and low public awareness, resulting in mortality rates that mirror incidence figures.

Central to these guidelines is the recognition that cancer care must be rooted in prevention, equity, and resilience. Prevention efforts prioritize scaling up cost-effective interventions, including HPV vaccination for girls aged 10–14, tobacco control policies, and community education on risk factors. Early detection is reinforced through strengthened screening programs, such as Visual Inspection with Acetic Acid (VIAC) for cervical cancer and clinical breast exams, which are critical in resource-limited settings. Timely and accurate diagnosis is emphasized, with calls to improve pathology services, imaging infrastructure, and mandatory multidisciplinary team (MDT) reviews for all cases to guide tailored treatment planning.

Treatment strategies prioritize context-appropriate therapies (surgery, radiotherapy, and chemotherapy) aligned with Zimbabwe's resource realities. Palliative care is integrated from diagnosis to alleviate suffering and uphold dignity, reflecting a holistic approach to patient well-being. The intersection of HIV and cancer demands urgent attention, with coordinated care models, drug interaction monitoring, and tailored protocols for HIV-

associated malignancies. Survivorship programs are essential to address long-term effects of treatment, promote mental health, and support social reintegration, ensuring patients thrive beyond their diagnosis.

Implementation success hinges on collaboration across sectors. Training clinicians, nurses, and community health workers in oncology basics will strengthen the health workforce, while expanding radiotherapy access and securing chemotherapy supply chains are infrastructural priorities. Policy alignment with the NHS 2021–2025 ensures sustainable funding and integration of cancer care into primary health systems. Community engagement, through partnerships with local leaders and NGOs, is vital to combat stigma, improve health literacy, and foster trust in health services.
These guidelines reflect Zimbabwe's collective resolve. Every stakeholder has a role in this transformative action to solve the challenges.

Introduction to Oncology

Cancer, a condition covering a wide range of malignant diseases, represents a significant disease and economic burden worldwide and is one of the leading causes of death. It is projected that there will be 26 million new cancer cases by 2030 and 17 million deaths per year, most of these being in the low to middle income countries (LMICs) due to limited or lack of access to screening, treatment and low per capita expenditure on healthcare. Overall cancer survival rates can be as low as 25% in LMICs compared to 56% in wealthier nations.

Prevention therefore becomes the key strategy for reducing cancer deaths with the greatest potential impact at reasonable cost. Preventive measures should be directed at lifestyle changes such as dietary changes, physical exercise, and reduction of tobacco and alcohol use and control of infections. This should go hand in hand with awareness/education, access to diagnosis and treatment and provision of palliative and end of life care. Similar to global and regional statistics, the burden of cancer has been increasing in Zimbabwe.

The Zimbabwe National Cancer Registry (2016) reported over 7 000 new cancer cases that were diagnosed in health institutions throughout the country. Trends in the last decade show a steady increase in the incidence of cancer generally. This has been attributed mainly to a continued significant burden of HIV related cancers and lifestyle related predisposing factors amongst others. This increase in incidence can be clearly demonstrated in the commonly occurring cancers in Zimbabwe which include cervical, breast, prostate, colorectal and childhood cancers.

The mortality of cancer in Zimbabwe almost mirrors the incidence in percentages per type of cancer. This may be an indication of non-robust preventive and screening programs such that deaths from curable cancers are still common. It is also well known that the majority of cancers in Zimbabwe are diagnosed late regardless of them being preventable or not.

In such circumstances any treatment intervention would not yield outcomes related to improvement of survival.

Cancers can present in many ways, depending on the system that is affected. In the early stages of cancer development patients are usually asymptomatic as the number of malignant cells will be very small. As progression takes place, localized symptoms may develop due to mass effects and/or invasion of local tissues. As the cancer spreads (development of metastases) symptoms can develop at the affected distant sites or they can result from the effects of production of biologically active hormones by the tumours or immune responses to the tumour by the body (paraneoplastic syndromes).

Common presenting features from local effects include a palpable lump, enlarged locoregional lymph nodes, bleeding, cough, skin changes due to underlying malignancy, change of function (dysphagia, vomiting, constipation, diarrhea, airway obstruction, early satiety) and obstructive symptoms from biliary, urinary, airway, lymphatic and bowel obstruction. Metastatic effects include bone pain/pathological fractures, ascites/effusions, neurological effects and organomegaly such as hepatomegaly. Paraneoplastic syndromes can have neurological, cutaneous, haematological, gastrointestinal, and renal manifestations depending on the hormone or substance responsible. Fever is also a common manifestation of some common tumours particularly haematological cancers.

Many patients with malignant disease can be cured and durable disease control obtained in others. The success of treatment is, however, largely dependent on the stage and extent of disease at first presentation. Early diagnosis, referral and treatment are essential if a good result is to be obtained.

Tremendous cutting-edge advances in treatment approaches to cancer continue to be made with oncology taking a firm position as a strong super-specialty worldwide. Technological advancement in the field has seen the

discipline embrace several scientific fields. Delivery of high-quality radiotherapy and chemotherapy services has become an important political target worldwide. The problems associated with establishing an adequate standard of care for the cancer patient in developing countries are however formidable. Well-planned and coordinated facilities with highly trained staff are necessary to satisfactorily diagnose, stage and treat patients with malignant conditions. Planning of such facilities must be within the context of a National Cancer Control Programme (NCCP).

The multidisciplinary team (MDT) approach has a large and important role in cancer management. The MDT is a group of healthcare professionals who work together to provide high quality clinical services that ensure efficient well-rounded care for the patients. The team must be made up of health professionals directly involved with the care of the patient from all relevant disciplines including those that have an adjunctive role during the patient's journey with cancer.

MDTs have been shown to improve quality of life, lower mortality and reduce the cost of cancer care. Involvement at an early stage is encouraged as it facilitates alignment of patient management to evidence-based standards. Members of the team also benefit from greater job satisfaction and support from other team members. Duplication is avoided thus benefiting the health care system.

The most successful Oncology units are those that incorporate the MDT approach to cancer management. Such units are commonly seen in developed countries where they have been found to offer numerous advantages such as appropriate treatment selection, superior patient care, efficient follow-up arrangements, psychological and practical support for the patient, research opportunities and education for patient, family and public. In Africa, there is a challenge in establishing these MDT units due to limited resources such as finance, staff, equipment and drugs. Despite these limitations, Zimbabwe has taken steps to improve the standard of cancer care through the establishment of MDT units in the central hospitals such as Parirenyatwa, Harare and Mpilo Hospitals. Further steps

are however being taken to improve, co-ordinate and standardize care of patients with malignant disease in this country.
This manual is designed to provide an overview of cancer and guidelines on the general principles of oncological investigation and management. Several protocols are included, giving details of regimens considered appropriate for use in Zimbabwe which are aligned to international standard of care. It is hoped that this manual will be of value to all doctors and other health workers involved in cancer management, and that it will encourage early detection, early referral and management of cancer within the MDT context.

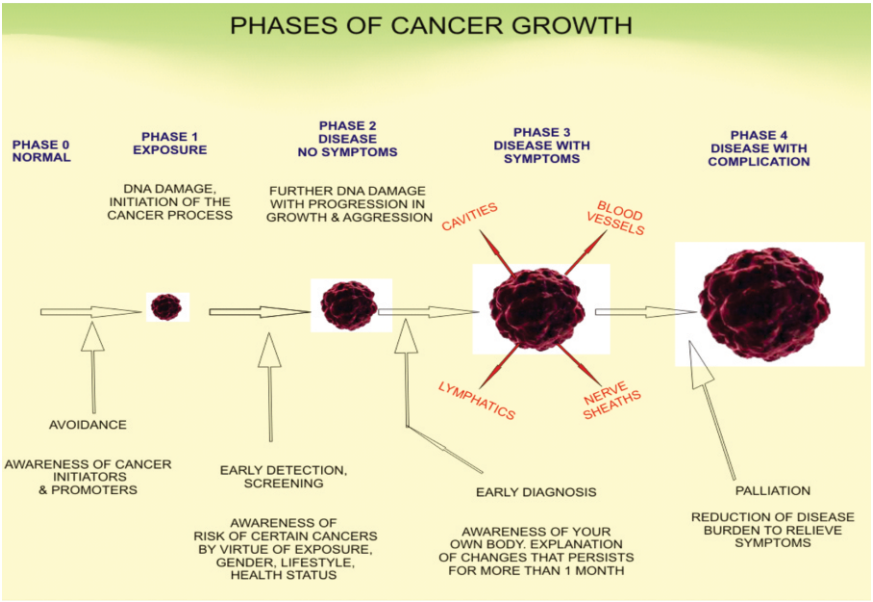
Management of cancer patients is a team effort!

Cancer Prevention

General Note

Cancer development is multifactorial. It is generally linked to personal habits, lifestyles, and environmental conditions. Cancer incidence is increasing worldwide including developing countries like Zimbabwe. The main factors contributing to the increasing incidence of cancer include infectious agents, tobacco and alcohol use, unhealthy diet, physical inactivity, environmental pollution, occupational factors, and in developed countries because of screening.

Prevention of cancer will reduce the number of patients with cancer thereby reducing the morbidity, mortality and costs that are associated with malignancy to individuals, families & the nation.



Risk Factors of Cancer

Cancer is a complex group of diseases each with its own risks, causes and biological behaviour. The causes of cancer initiate the process of carcinogenesis while risk factors promote the development and progression of cancer. Carcinogenesis is a complex process as not all who are exposed to the causes or risks will develop cancer and some without exposure to the known causes/risks can develop cancer. What is known is that the basis of cancer is DNA abnormalities that lead to dis-regulation of cell division and cellular properties, which ultimately gives rise to cancer.

Main factors contributing to the increasing incidence of cancer in Africa include, infectious agents, tobacco use, alcohol consumption, unhealthy diets, physical inactivity, occupational & radiation exposure, and ultraviolet light exposure.

Infectious agents

Infectious agents which predispose to cancers include:

- Human immunodeficiency Virus (HIV)- cervical cancer, non-Hodgkin lymphoma, Kaposi sarcoma and some squamous cell carcinomas of the head and neck such as ocular surface neoplasia.
- Human papilloma virus (HPV) - most squamous cell carcinomas of the cervix, vulva, penis, anus and some of the head and neck cancers.
- Hepatitis viruses B and C (HBV and HCV) - chronic infection causes hepatocellular carcinoma.
- Epstein-Barr virus (EBV) - Burkitt's lymphoma, non-Hodgkin lymphoma, Castleman's disease and nasopharyngeal carcinoma.
- Human herpes virus type 8 (HHV-8) - Kaposi sarcoma.
- Helicobacter pylori (H. pylori) - mucosa associated lymphoid tumours (MALT) and gastric adenocarcinoma
- Schistosomiasis - squamous cell carcinoma of the bladder

Tobacco

Worldwide, tobacco use is the single largest causative factor for cancer, accounting for 30% of all cancer deaths in developed countries. Tobacco smoke contains approximately 4 000 chemical substances, of which at least 438 can cause cancer. The most dangerous substances in tobacco are nicotine, tobacco tar, and carbon monoxide which contain the carcinogenic poly-aromatic hydrocarbon and nitro- compounds. In addition to lung cancer, tobacco consumption causes cancers of the larynx, pancreas, kidneys, bladder, oral cavity, and oesophagus.

The smoking dose intensity, which is the number of cigarettes smoked per day and the duration (years of exposure) are both independent risk factors for lung cancer. Smoking pack years are an accepted method of calculating the risk of lung cancer and chronic obstructive pulmonary disease. This is accepted with the full knowledge that duration and early uptake of tobacco smoking confer a higher risk of lung cancer than cigarettes per day. For regular smokers, the relative risk for development of lung cancer is more than 20 times higher than that of non-smokers. Environmental tobacco smoke (passive smoking) is also carcinogenic although the risk is less than that of active smokers. Cessation of smoking significantly reduces the risk of lung and other tobacco associated cancers even though it remains greater than that of those who never smoked ten or more years after cessation. E-cigarettes (vaping) have fewer toxic chemicals but still carry significant risks. Research into using e-cigarettes as a transition tool to quit tobacco smoking is ongoing in some countries.

Alcohol consumption

Consumption of alcohol is widespread in Zimbabwe and highest among males. Heavy alcohol use is associated with a higher risk for cancer compared to non-drinkers or occasional drinkers. It is also noted that among the alcohol drinking population there is a higher likelihood for active or passive tobacco smoking which further multiples the cancer risk. Heavy alcohol drinkers are also at high risk of micronutrient deficiencies and mental health disorders.

Heavy alcohol consumption increases the risk of cancers of the oral cavity, pharynx, larynx, oesophagus, liver, breast, colon and rectum. Among women even at lower levels of intake, an increase in the risk of breast cancer is noted. Research shows that the more alcohol a person drinks regularly overtime, the higher his/her risk of developing these alcohol-related cancer.

Most studies indicate that stopping alcohol consumption is not associated with immediate reductions in cancer risk. The risk reduction is slow and can only be demonstrated in some cancers after up to 10 years as seen in head and neck cancers.

Diet and nutrition

Between 20-30% of cancer are related to diet and nutrition. A diet high in calories, excessive salts, saturated fats, processed animal meat and sweetened drinks predisposes to colon, breast, prostate, endometrial and other cancers. Specific dietary factors which have been noted to have a protective impact against cancer include consumption of antioxidants, calcium, vegetables, garlic, vitamin D and fluoride.

Health education and deliberate national policies that favour the adoption of healthy diets and nutritional standards in the food manufacturing sector are needed. Nutritional education should be complimented by the availability of affordable and accessible sources of healthy foods.

Obesity and physical inactivity

The obesity epidemic is known to be one of the driving factors for the high cancer incidence. Obesity is mainly due to high calorie intake and unnatural inactive lifestyles. There is a link between obesity and the risk of breast, endometrial, kidney, colon, pancreas, gall bladder and oesophageal cancer. Higher levels of physical activity have been linked to lower risk of cancer.

The general recommendation for the average adult is to engage in at least 150 minutes of moderate intensity aerobic exercises or 75 minutes of vigorous-intensity aerobic exercises every week. A good diet complements

physical activity, and physical activity is made feasible by a healthy diet.

Occupational and Radiation Exposure

Agriculture, agro-processing, mining, manufacturing and health sector activities are all potential sources of exposure to carcinogens. Risk is generally apparent from the age of about fifty years onwards, but maximum risk may not be seen until the post-retirement years due to the long latent period for induction of many occupationally induced cancers.
Substances known to be carcinogenic include asbestos, benzene, cadmium, coal tar, formaldehyde, nickel compounds, soot, wood dust and vinyl chloride.

Exposure to ionizing radiation can result in cellular DNA damage and lead to cancer. Ionizing radiation includes x-rays and gamma rays which are high energy in nature. Lower energy, non-ionizing forms of radiation for example visible light and energy from cell phones do not damage DNA and so far have not been shown to cause cancer. Radon gas is given off by rocks and soil in the environment. People exposed to it have an increased risk of lung cancer. Other sources of gamma rays and x-rays include the nuclear energy, health, agriculture and defense sectors.

Minimal exposure to these workplace carcinogens and radiation is achieved by education, research, use of protective equipment, adequate ventilation, and strict safety standards. These standards must be legislated, and adherence enforced.

Sunlight

Exposure to ultraviolet radiation causes skin damage that over time can lead to skin cancer. People of ALL skin tones should limit the time they spend in the sun. Generally skin cancer is more common in persons of light skin colour but can develop in all skin tones.
To protect the skin from excessive sunlight exposure the following is encouraged:

- Wearing a wide brim hat
- Wearing sunglasses

- Wearing long sleeves and long pants
- Use of sunscreen with a sun protection factor of at least 15

Primary prevention

Primary prevention includes interventions that prevent the development of cancer altogether. It includes health counselling and public education on risks and interventions to reduce exposure to specific carcinogens. Health counselling is when individuals or groups of people are assisted in assessment of their own risk of developing cancer and guided on how best to avoid it. Health counselling results in a more knowledgeable, motivated and committed individual than in the case of population-based education.

Secondary prevention

Secondary prevention includes interventions that focus on early diagnosis and control of cancerous or precancerous processes while still localized. This is done by screening followed by appropriate treatment.

Cervical cancer

- HPV is sexually transmitted, is a major cofactor in cervical cancer, and is responsible for 99% of cervical cancers.
- HIV is strongly associated with cervical cancer.
- Education and health counselling on the causes/risks and the benefits of early diagnosis.
- Women should be made aware of the availability and benefits of screening so that they make informed decision to participate in the programs correctly and consistently. They need to know that all women are at risk, that the impact of the cancer is far reaching and even multigenerational, and that the condition is preventable, screen detectable and amenable to curative treatment.
- Cervical cancer can be detected before it becomes invasive by Pap smear and Visual inspection under acetic acid and cardiogram

cardiogram (VIAC).

- VIAC is feasible for a resource limited country because of its simplicity, low-cost, real-time availability of investigation/treatment, consistently accurate and the training of personnel is simple and at low cost.
- VIAC offers screening, diagnosis and treatment at the same sitting and in clinics accessible to most at-risk women.

For specific details on screening refer to the national guidelines.

Breast cancer

- The cause of breast cancer is not known but many risk factors for it have been identified.
- Modifying risk factors through a healthy diet, physical activity, avoidance of alcohol, breast feeding, genetic counselling for high-risk individuals and appropriate risk reduction therapies.
- Mammography has been shown to reduce the incidence of invasive breast cancer, morbidity, and mortality.
- Before screening, woman should be informed on the burden of the disease, the benefit of primary prevention; the benefits, risks, and pitfalls of screening so they make informed decisions to participate fully in the exercise.
- Ultrasound and P modalities are useful as screening tools for breast cancer in specific cases.
- Breast self-examination (BSE) and clinical breast examination (CBE) detect large tumors and are not considered to be screening methods. BSE increases a woman's breast self-awareness so that she is able to pick up any changes early and seek attention without delay.

Prostate Cancer

- It is not known what specifically causes prostate cancer.
- The commonest risk factor is increasing age (by the age of 65

years, 60% of men will have developed prostate cancer).

- Africans and people with positive family history of prostate cancer also have an elevated risk.
- The role of diet is not clear, but consumption of too much red meat and high fat dairy products and obesity may increase risk for the cancer.
- Prostate Specific Antigen (PSA) assay and digital rectal examination are commonly used for screening. A normal result does not exclude prostate cancer. Digital rectal examination may detect some cancers with normal PSA level.

Colon cancer

- Factors that increase the risk for colon cancer include inherited genetic mutations (e.g. hereditary non-polyposis colon cancer (HNPCC) and familial adenomatous polyposis (FAP)), older age, crohn's disease, diabetes mellitus, low fiber, high fat diets, smoking and alcohol consumption.
- Colon cancers associated with inherited mutations cannot be prevented altogether but can be managed by genetic counselling and testing.
    - Cancer development is prevented by risk reduction procedures such as polypectomy or even colectomy.
    - Use of aspirin or aspirin-like drugs had been shown to reduce risk.
- Diet with high fiber, low fat, plenty of vegetables and fresh fruit, physical activity, maintaining a healthy weight may reduce colon cancer incidence.
- For high-risk persons, screening should start early and done more frequently.
- Colonoscopy is the most effective colon cancer screening tool and on average risk persons it is done every 10 years and more frequently in the high risk.

- CT colonography can be done very 5 years.
- Screening laboratory tests include faecal occult blood test (FOBT), faecal immunochemical (FIT), guaiac faecal (GOT), and multi-target stool DNA (MT-sDNA).

Lung cancer

- Most lung cancers are associated with tobacco smoking.
- Other risk factors occupational exposure to asbestos, cadmium, selenium, silicon, air pollution, family history and chronic obstructive pulmonary diseases
- Smoking cessation and abstinence are the most effective ways of reducing the incidence of lung cancer
- Effective health counselling and public education need to be combined with statutory control on growing and use of tobacco for any success to be achieved in reducing tobacco smoking.
- Effective nicotine replacement with chewing gums, lozenges, transdermal patches, inhalers and nasal sprays can be used in cessation efforts.
- The decision to begin screening should be a result of thorough discussion on the possible benefit, limitations and harms of the procedure and treatment of lung cancer.
- Low dose CT scan (LDCT) appears to be the best option of screening high risk individuals for lung cancer.

Hepatocellular carcinoma

- Hepatocellular carcinoma (HCC) is so prevalent and the results of treatment of symptomatic disease so poor that prevention is an urgent priority.
- Hepatitis B or C is the main cause of HCC in Zimbabwe.
- Childhood vaccination against HBV helps to reduce risk of HCC and is incorporated into the Zimbabwe Expanded Programme of Immunization (ZEPI).

- Therapy with antiviral drugs can reduce viral load and rate of transformation to malignancy but the challenge is early identification of asymptomatic HBV/HCV carriers.
- Screening for HBV and HCV in donated blood and or rational use of viral inactivating steps in the manufacture of blood products reduces risk of iatrogenic spread of the viruses.
- Sexual transmission can be prevented by practicing sex.
- Health counselling among illicit drug users against needle sharing and the hazards of contracting HBV/HCVs among other infections can go a long way in reducing infections
- Aflatoxin- related HCC can be reduced by safe storage of grain harvests.
- Early diagnosis of alcoholism is important to encourage cessation and abstinence to minimize liver damage.
- Six monthly USS scan and serum AFP form the backbone of the screening program for high-risk patients. High risk individuals include:
    - Patients with liver cirrhosis
    - Men with chronic HBV infection without cirrhosis from 40 years of age
    - Women with chronic HBV infection without cirrhosis from 50 years of age
    - Patients with chronic HBV infection and have family history of HCC

NOTE: Primary care physicians play a pivotal role in identifying patients at risk for HCC and ensuring that screening is carried out.

National measures to reduce cancer risk include:

- Regulatory efforts to reduce exposure to cupational/environmental arcinogens
- Health tax on potentially carcinogenic products such as tobacco and alcohol.

- Regulatory standards and enforcement for prevention of environmental and workplace contamination.
- National vaccination programs against common preventable cancers.
    - National HPV vaccination program for girls 10-14 years old
    - Hepatitis B virus vaccination in childhood.
- Increase in availability and accessibility of screening programs for common screen detectable malignancies
- Make available and accessible diagnostic and treatment services for those discovered to have cancer at screening and early detection.

Basic principles of oncology

The management of cancer patients involves multidisciplinary team based accurate diagnosis, staging, treatment and continuing care. The aims of treatment may be cure, prolongation of life, improvement of quality of life, or palliation of symptoms.

Diagnosis

Because of the prognostic implications of cancer and the risk of experiencing treatment related side effects, accurate diagnosis is mandatory. Histological diagnosis is needed. Improved techniques of staining, cell typing and genotyping have increased the accuracy of diagnosis and sub-classification of diseases.

Staging

Staging serves to delineate the extent of disease and assists in therapeutic decision-making. It is also useful in giving an indication of prognosis, in assessing disease response to therapy, in evaluating end results and providing a means of comparison with other studies in a research setting. Methods used in staging include findings of history, physical examination, histological findings, imaging, and surgery. In each given disease entity, there is need to define the minimum diagnostic work-up which establishes the extent of disease. There are four possible steps in staging:

1. Clinical staging
    - Based on physical examination, laboratory testing and where applicable endoscopy

2. Radiological staging
    - Imaging with x-ray, Ultrasound (USS) , Computed Tomography (CT) scan, MRI and radioisotope scanning

3. Surgical staging
    - Procedures to determine disease extent (Invasive & minimally invasive techniques)

4. Pathological staging
    - The use of histological examination of biopsy material to detect tumor spread.

It is important not to over-investigate patients. A variety of staging systems are in use. The international TNM (tumour, nodes & metastases) classification, Federation of Gynecology and Obstetrics (FIGO) classification and Ann Arbor staging system for lymphoma are used widely.

Therapeutic options

Once diagnosis and staging are completed, several questions need to be answered:

1. Is specific treatment appropriate?
2. After full explanation, what are the patient's wishes?
3. What is the most suitable treatment – surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy or a combination of these? Is adjuvant therapy indicated?
4. Are sufficient facilities available to carry out the treatment in a satisfactory manner?

All cancer patients in Zimbabwe should be discussed in a multidisciplinary team meeting (including pathologist, surgeons, dentist, clinical oncologist, pharmacist, oncology nurse, radiologist, rehabilitation specialists, internal medicine specialists, primary care practitioners, palliative care specialists, and social worker) prior to treatment.

Consideration of details relating to each patient is important. These include place of residence, distance from hospital, mode and cost of transport, time off work/school, living conditions and diet. Advice, practical support, and help should be given where appropriate. The aims of treatment must be clearly defined before therapy commences. It can be anticipated that not every patient will respond as expected, and the aims may have to be reassessed and adjusted periodically.

Treatment

Preparation

Optimal preparation and stabilization of the patient before therapy is essential including treatment of pain, infection, anaemia, bleeding, and nutritional rehabilitation. Psychological preparation is equally important. The patient should be fully aware of the diagnosis, treatment aims, details of treatment and possible side effects. Associated services (e.g. social services) should be involved at an early stage. A high level of counselling and emotional support is necessary.

Therapy

Treatment is personalized to each patient and can be unimodal or multimodal including surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy, and supportive therapies. Treatment regimen decided upon by the MDT, should be given in the best possible conditions by qualified personnel. Special consideration should be given to children, the elderly and pregnant women.

Monitoring of patient

As treatment progresses, monitoring for tumour response, side effects/complications, psychological status, and quality of life of the patient should be done. It is a multidisciplinary team effort. The patients' functional performance status must be recorded at all reviews and clinicians can use the Karnofsky Performance Scale (KPS) and Eastern Cooperative Oncology Group (ECOG) scoring systems.

Assessment of tumour response

Response Evaluation Criteria in Solid Tumour (RECIST)

a) Complete response – Complete disappearance of all evident tumours

b) Partial response – ≥30% decrease in the sum of the longest diameters of all measurable lesions, and no new lesions

c) Stable disease- does not meet criteria for partial response or disease progression

d) Progression – ≥20% increase in the sum of the longest diameters of the original lesions or development of new lesions.

Quality of life

Various methods of measuring the extent to which the disease and treatment have affected the patient's lifestyle have been devised. Ideally four functionally domains of quality of life should be assessed, namely physical/somatic, social, psychological, and spiritual function. These will be addressed in the chapter on palliative care.

Continuing care

Continuing applies to the patient who has completed treatment with good result, to the patient on long-term therapy and to the patient in whom treatment is inappropriate or has failed. This will be discussed more fully in the chapter on Survivorship.

WHO/ECOG Performance Scale

Scale	Performance
0	Normal activity
1	Symptoms, but nearly fully ambulatory
2	Some bedtimes , but needs to be in bed less than 50% of normal day time
3	Needs to be in bed more than 50% of normal day time
4	Unable to get out of bed
5	Dead

Karnofsky Scale of Performance Status (KPS)

KPS Score	Description
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activities, minor signs and symptoms of disease
80	Normal activity with effort, some signs and symptoms of disease
70	Cares for self, unable to carry on normal activities or to do active work.
60	Requires occasional assistance, but is able to care for most of his personal needs.
50	Requires considerable assistance and frequent medical care
40	Disabled, requires speci al care and assistance
30	Severely disabled, hospital admission is indicated although death not imminent
20	Very sick, hospital admission necessary, active supportive treatment necessary
10	Moribound, fatal processes progressing rapidly
0	Dead

General Principles of Radiotherapy

Radiotherapy and Multidisciplinary Cancer Care

Radiotherapy can prolong survival, contribute to the preservation of organs affected by cancer, provide palliation and improve patients' quality of life. Approximately 60% of patients with diagnosed cancers would benefit from radiotherapy at some stage of their illness. In Zimbabwe because cancer is diagnosed at an advanced stage the proportion of patients who would benefit from radiotherapy is likely much higher.

The provision of a safe and effective radiation oncology service is complex and highly specialized. It requires a substantial capital investment in radiotherapy equipment and specially designed buildings, an ongoing investment in maintenance and replacement of the equipment, expert

teams of doctors, radiotherapists, oncology nurses and medical physicists, and good access to regular engineering support.

How Radiotherapy Works

- Radiotherapy ionizes chemicals within cells. The crucial lesion is DNA strand breakage which may be repaired or lead to apoptotic or mitotic cell death.
- Different types of normal and malignant cells vary in their susceptibility to ionizing radiation.
- Clinical radiotherapy schedules are designed to exploit the differences between normal tissues and cancer tumours, so that as many malignant cells as possible are killed, while damage to normal tissue is minimized.
- In radical curative treatments, total radiation doses are close to the tolerance of normal tissues. In palliative treatments, usually low doses are used.
- Some tumors are very sensitive to radiotherapy and can be treated with relatively low doses, such as seminoma of the testis and lymphoma. Other tumours, such as melanoma of the skin, are relatively resistant, even to large doses.
- A course of radiotherapy may be spread over days or weeks. This is known as fractionating, and the radiation delivered to a patient in a single treatment session is called a fraction.
- Fractionating allows normal tissues to repair much of the radiation damage, while tumour cells, which are less efficient at repair, do not recover.

- A beam of radiation is called a field. A fraction consists of one or more fields delivered sequentially.
- In general, most modern radiotherapy is delivered with very high-energy, highly focused beams, which can reach deeper tumour tissues while depositing relatively small doses in the normal tissues through which they pass.
- External-beam radiotherapy can be delivered by cobalt machines or linear accelerators, collectively known as megavoltage machines.

Role of radiotherapy in cancer treatment

Radiotherapy acts only on the irradiated tissues and each fraction of radiotherapy kills cells which are mainly in the Mitotic phase (M-phase) of the cell cycles. The use of radiotherapy is not confined to malignant diseases only. Radiotherapy is used for some benign neoplastic condition like intracranial low-grade tumours, benign salivary gland tumours and non-neoplastic conditions like keloids. In cancer management it is used in curative and palliative intent therapy

Curative radiotherapy

- Radiotherapy is prescribed, either alone or combined with surgery and/or chemotherapy for the purposed of cure.
- Because normal tissues recover from radiation damage better than tumours, it is possible to treat a cancer without major injury to the host organ.
- Radiotherapy is used either as neoadjuvant, primary definitive or adjuvant therapy.
- When used as part of multimodality therapy the aim of

radiotherapy is to:

- Where organ preservation is desirable -- for example, breast conservation treatment consisting of lumpectomy and radiotherapy
- Advanced cancer stage or high-risk features indicating high risk of recurrence after initial therapy
- Inoperable cancer conversion treatment to render a tumour operable
- Close or positive surgical margins need treating to prevent local recurrence.

Palliative radiotherapy

- Incurable cancer causes many difficulties for cancer patients due to local tumour effects and the effects of spread to distant organs.
- Radiotherapy can alleviate commonly encountered symptoms like bleeding, pain, spinal cord compression, shortness of breath, cough, superior vena cava obstruction, urinary obstruction, and haemoptysis.
- Short course radiotherapy is an excellent treatment for the palliation of bone pain, brain metastases and compression of vital structures such as the spinal cord.
- Radiotherapy can reverse the effects of spinal cord compression and prevent paraplegia.
- Radiotherapy may be used to prolong the life of patients with advanced incurable cancers.

Side Effects of Radiotherapy

- Radiation side effects can be acute (early) and late (chronic).

- These side effects depend on several factors, including the body site being treated, the volume of normal tissue, the total dose, and the rate of dose accumulation (the amount per week).
- Early side effects result from damage to proliferating tissues, such as the mucosa (lining) of the gastro-intestinal tract or the skin.
- Late side effects occur at least 3 months after a treatment course has ended usually result from damage to non-proliferating differentiated tissues
- Side effects of radiation can be minimized by meticulous planning, verification and delivery of a course of radiotherapy. In Zimbabwe currently we use three- dimensional conformal radiotherapy and working to transition to more advanced and higher conformity modalities.

Ionizing radiation used in radiotherapy

Ionizing radiation is energy sufficiently strong to remove an orbital electron from an atom. This radiation can be an electromagnetic wave, like high-energy photon, or a particulate form, like electron, proton, neutron, or alpha particle.

High-energy photons

The commonest form of radiation used in modern oncology is the high-energy photon. Photons that are released from the nucleus of a radioactive atom are known as gamma rays. When photons are created electronically, such as in a linear accelerator, they are known as x-rays. The only difference between the two terms is the origin of the photon. Three interactions describe photon absorption in tissue: the photoelectric effect, Compton effect, and pair production.

Photoelectric effect

This is process in which an incoming photon undergoes a collision with a tightly bound electron. The photon transfers practically all its energy to the electron and ceases to exist. The electron departs with most of the energy from the photon and begins to ionize surrounding molecules. This

interaction depends on the energy of the incoming photon, as well as the atomic number of the tissue; the lower the energy and the higher the atomic number, the more likely that a photoelectric effect will take place. This is the predominate interaction in diagnostic radiography.

Compton Effect

This is the most important photon-tissue interaction for the treatment of cancer. In this process, a photon collides with a "free electron," i.e, one that is not tightly bound to the atom. In the Compton interaction both the photon and electron are scattered. The photon can then continue to undergo additional interactions, albeit with a lower energy. The electron begins to ionize with the energy given to it by the photon. Compton interaction is independent of the atomic number of the material.

Pair production

In this process, a photon interacts with the nucleus of an atom, not an orbital electron. The photon gives up its energy to the nucleus and, in the process, creates a pair of positively and negatively charged electrons. The positive electron (positron) ionizes until it combines with a free electron. This generates two photons that scatter in opposite directions.

Electron beams

Electrons are a viable option in treating superficial tumours up to a finite depth. Electron depth dose characteristics are unique in that they produce a high skin dose but exhibit a falloff after only a few centimeters. Electron absorption in human tissue is greatly influenced by the presence of air cavities and bone. The dose is increased when the electron beam passes through an air space and is reduced when the beam passes through bone.

Measuring radiation absorption

The dose of radiation absorbed correlates directly with the energy of the beam. An accurate measurement of absorbed dose is critical in radiation treatment. The deposition of energy in tissues results in damage to DNA and diminishes or eradicates the cell's ability to replicate indefinitely.

Gray

The basic unit of radiation absorbed dose is the amount of energy (joules) absorbed per unit mass (kg). This unit, known as the gray (Gy), has replaced the unit of rad used in the past (100 rads = 1 Gy; 1 rad = 1 cGy).

External beam radiotherapy delivery

Linear accelerators

High-energy radiation is delivered to tumours by means of a linear accelerator. A beam of electrons is generated and accelerated through a waveguide that increases their energy to the keV to MeV range. These electrons strike a tungsten target and produce x-rays.

The megavoltage linear accelerator is the modern standard radiotherapy equipment. Its production of x-rays is identical to that of lower-energy machines. However, the energy range of megavoltage units is broad-from 4 to 20 MeV. Most megavoltage units also have electron-beam capabilities, usually in the energy range of about 5-20 MeV.

Shielding normal tissue is essential in radiotherapy. The clinical oncologist may decide to block out some normal tissues in the treatment field. This is accomplished by placing blocks (or alloy) or using multileaf collimators (MLCs) mounted inside the gantry. MLCs provide computerized, customized blocking instead of having to construct a new block for each field.

Pretreatment procedures

Certain imaging procedures must be performed before radiotherapy is commenced.

Pretreatment CT scan

Before any treatment planning can begin, a pretreatment CT scan is usually performed in the preferred treatment position. This scan allows the clinical oncologist to identify both the tumour(s) and surrounding normal structures known as organs at risk (OAR). It is imperative that the patient be treated in a reproducible and comfortable manner each day. To facilitate

this laser alignment should be used to line up the patient during treatment. The patient is then sent for a simulation.

Simulation

The patient is placed on a diagnostic x-ray unit that geometrically simulates an actual treatment machine. With use of the CT information, the patient's treatment position is simulated by means of fluoroscopy

Guides for treatment field placemen

Small skin marks, or tattoos, are placed on the patient following proper positioning in simulation. These tattoos will guide the placement of treatment fields and give the clinical oncology team a permanent record of past fields should the patient need additional treatment in the future.

Treatment planning and delivery

Determining optimal dose distribution

The medical physicist or dosimetrist uses the information from CT and simulation to plan the treatment on a computer. A complete collection of machine data, including depth dose and beam profile information, is stored in the computer. The clinical oncologist and medical physicist decide the number of beams and angles of entry. The goal being to maximize the dose to the tumour while minimizing the dose to surrounding normal structures. The beam-modifying devices such as MLCs and wedges, may be used to optimize the dose distribution around the tumour. Several treatment plans must be generated, and the clinical oncologist chooses the optimal dose distribution taking into account the intent of therapy, specific diagnosis, patients' comorbidities and the radiotherapy units' patient burden.

Establishing the treatment plan

The planning computer will calculate the amount of time each beam should be on during treatment. All pertinent data, such as beam-on time, beam angles, blocks, and wedges, are recorded in the patient's treatment chart and sent to the treatment machine. The radiation therapist will use this information, as well as any casts, tattoos, and lasers, to set up and treat the patient consistently and accurately each day.

Regular port films

As part of departmental quality assurance, weekly port films are taken for each beam. They ensure that the beams are consistently and correctly placed for each treatment. Port films are images generated by the linear accelerator at energies of 6-20 MeV. Because of the predominance of the Compton effect in this energy range, these images are not as detailed as those at diagnostic film energies, but they still provide important information on treatment accuracy and ensure the quality of setup and treatment.

Brachytherapy

Brachytherapy is the term used to describe radiation treatment in which the radiation source is in contact with the tumour. This can be interstitial or Intracavity. This therapy contrasts with external-beam radiotherapy, in which the radiation source is at a distance usually 80-100 cm away from the patient. Commonly used forms of brachytherapy are low-dose–rate (LDR) brachytherapy and high-dose–rate (HDR) brachytherapy. LDR brachytherapy is used in cancer of the oral cavity, oropharynx, sarcoma, and prostate cancer. HDR brachytherapy is frequently used in gynecologic applications with remote after loading techniques. Commonly used radioactive isotopes include radium-226, cesium-137, cobalt-60, Iridium-192, Iodine-125, gold-198 and palladium-103. Cobalt-60 has a half-life of 5.26 years and is currently used for gynaecologic brachytherapy in Zimbabwe.

Types of implants

Brachytherapy procedures can be performed with either temporary or permanent implants. Temporary implants usually have long half-lives and higher energies than permanent implants.

Conformal radiation therapy

Conformal radiation therapy is a geometric shaping of the radiation beam that conforms with the beam's eye view of the tumor. Conformal therapy utilizes the outlining capabilities of the CT simulator. The physician outlines the tumour volume, generates DRRs, and draws an appropriate margin

from 1–2 cm around the tumour. These fields conform closely to the shape of the tumour and shield more critical structures. The margin allows for setup errors of a few millimeters each day. Appropriate immobilization of the target volume must be achieved in each patient.

Intensity-modulated radiation therapy (IMRT)

Intensity-modulated radiation therapy (IMRT), an extension of conformal therapy, allows for shaping of the intensity of the radiation beam. This is an important improvement, especially when the target is not well separated from normal tissues.

A uniform dose distribution can be created around the tumour by either modulating the intensity of the beam during its journey through the linear accelerator or using MLCs. The result is a uniform dose distribution around the tumour and minimal dose to the surrounding normal tissues, often below tolerance levels. This improves the risk-benefit ratio and may allow higher doses to be prescribed to the tumour volume.

General Principles of Chemotherapy

Definition of Chemotherapy

Chemotherapy refers to the therapeutic use of chemical agents to treat any disease. However, the word chemotherapy is generally used to refer to drugs that are used and proved to be effective against cancer. Cytotoxic chemotherapy drugs are systemic therapies that aim to kill or slow the growth of cells. In most malignancies, tumour cells are generally more sensitive to cytotoxic drugs than are their normal parent cells.

Surgery and radiation therapy are often localized treatments, but chemotherapy can work throughout the whole body. It provides a systemic option. This means chemotherapy can kill cancer cells that have metastasized to parts of the body far away from the primary tumor. Chemotherapy agents target different components and phases of the cell cycle of rapidly dividing cells like cancer cells.

Uses of Chemotherapy in Cancer Treatment

Can be delivered in a primary, adjuvant, and neoadjuvant fashion.

1. **Primary chemotherapy:** delivery of chemotherapy alone without any additional therapies such as surgery or radiation therapy (e.g. some hematologic malignancies such as leukemia and lymphoma).
2. **Adjuvant chemotherapy:** given to a patient who has undergone surgery or radiotherapy with curative intent but who is at high risk for relapse (i.e., node-positive breast cancer).
3. **Neoadjuvant chemotherapy:** given to patients before the definitive intervention to "downsize" the tumour.

Goals of chemotherapy treatment

There are three main goals for chemotherapy (chemo) in cancer treatment:

- Cure and eradication.
- Control of disease and remission.
- Palliation of symptoms.

Determining which chemotherapy drugs to use

Choices of drug regimens are based on published scientific peer reviewed international and national guidelines. These are formulated based on scientific studies, committees and expert opinions. Factors to consider when choosing which drugs to use include:

- The type of cancer
- The stage of the cancer (how far it has spread)
- The patient's age
- The patient's overall health and performance status.
- Co- morbidities (such as immunosuppression, heart, liver, or kidney diseases)
- Types of cancer treatments given in the past.

Doctors take these factors into account, along with information published in medical journals and textbooks describing the outcomes of similar patients treated with chemotherapy.

Scheduling and administration of chemotherapy

Chemotherapy is typically given in cycles, which is a treatment followed by a period of rest. A course of chemotherapy is comprised of multiple cycles. Each course is different, but generally consists of four to six cycles. Generally, the scheduling and administration of chemotherapy follow the protocols used in the original clinical trials.

Routes of Administration

- Intravenous drug administration is the commonest administration route for most. This may be infusion or bolus.
- Oral e.g. capecitabine.
- Subcutaneous

Determining chemotherapy doses

Most chemotherapy drugs are strong medicines that have a narrow range for dose safety and effectiveness. Taking too little of a drug will not treat the cancer well and taking too much may cause life-threatening side effects. For this reason, doctors must calculate chemotherapy doses very precisely. Depending on the drug(s) to be given, there are different ways to

determine chemotherapy doses.

- Body Surface Area (BSA), which are calculated using height and weight. BSA is expressed in meters squared (m^2).
- Dose capping. Using the calculated BSA in large and obese patients may lead to relative overdosing of chemotherapy with an associated risk of excess toxicity. Many institutions will use 2.2 m^2 as an upper limit for curative and adjuvant treatments. However, care should be taken when prescribing for tall, non-obese individuals because there is a potential risk of under dosing if the BSA is capped at 2.2m^2.
- Area under the curve (AUC) dosage. Particularly for carboplatin the dose is calculated by the following formula: Dose (mg) = desired AUC × (GFR ml/min + 25)
- Body weight dosing. Bodyweight alone is not used often in calculating doses of cytotoxic drugs. However, some of the newer such as the monoclonal antibody trastuzumab, are calculated on body weight alone.
- Flat dosing e.g. tamoxifen.

Pretreatment investigations and checks before initiating chemotherapy

- **Informed consent**
- **Baseline assessments of tumour:** A baseline measurement and regular objective measurement of response are required to assess whether the patient is benefiting from chemotherapy. This can involve direct physical measurement of the tumour, radiological examination, biochemical tests or measurement of tumour markers, depending on the disease site. Where the principal aim is palliative, one should also monitor symptomatic benefit carefully and balance this against the treatment toxicity.
- **Cardiotoxic drugs:** Pretreatment cardiac assessment is recommended for patients on cardiotoxic drugs such as doxorubicin, previous history of cardiac disease, elderly, previous anthracycline exposure, or mediastinal radiotherapy.
- **Renal function.** An accurate measurement of renal function is generally

required. This entails calculation of the GFR using the Cockcroft–Gault formula. Doses will need to be amended as required.

- **Hepatic function** Most drugs undergo some metabolism by the liver. The treatment protocols in most units include advice on appropriate dose reductions.
- **Central lines** Patients who have chemotherapy through ambulatory infusion devices must have central access before treatment. Patients with poor veins or those who are to receive multiday infusions will also benefit from central lines early on in their treatment.
- **Height and weight.**

Before each cycle

- Full blood count
- Biochemical, renal, liver and bone profile
- Relevant tumour markers and other specific tests to the diagnosis.

Chemotherapy Drug Classes

The traditional classification of chemotherapy drugs is mainly based on the mode of action of the drugs.

1. Alkylating Agents

Alkylating agents are cytotoxic agents which impair cell function by transferring alkyl groups to amino, carboxyl, sulfhydryl, or phosphate groups of Deoxyribonucleic Acid (DNA) and some intracellular proteins. This alkylation results in abnormal nucleotide sequences, miscoding of messenger RNA, cross-linked DNA strands that cannot replicate, breakage of DNA strands and other damage to the transcription and translation of genetic material. The primary mode of action for most alkylating agents is by means of cross-linking of DNA strands and DNA strand breakage.

Commonly used alkylating agents

Cyclophosphamide, cisplatin, carboplatin, oxaliplatin, chlorambucil, dacarbazine, ifosfamide, streptozocin, temozolomide.

2. Mitotic Spindle Agents

Mitotic spindle inhibitors are classically represented by taxanes and vinca-alkaloids. These drugs bind to microtubular proteins, thus inhibiting microtubule assembly (M phase of the cell cycle) and resulting in dissolution of the mitotic spindle structure. Taxanes (paclitaxel and docetaxel) not only bind to microtubules but also promote microtubule assembly and resistance to depolymerization, resulting in the production of nonfunctional microtubules.

Common taxanes: Paclitaxel, docetaxel, cabazitaxel.

Common vinca alkaloids: Vinblastine, vincristine, vindesine, vinorelbine

3. Antitumor Antibiotics

Antitumor antibiotics generally are drugs derived from microorganisms. They are usually cell cycle–nonspecific agents that are especially useful in slow-growing s with low growth fractions. They act by a variety of mechanisms. Several of these drugs interfere with DNA through intercalation, a reaction whereby the drug inserts itself between DNA base pairs. Intercalation with DNA prevents DNA replication and messenger RNA production, or both.

Commonly used antitumor antibiotics

Doxorubicin, actinomycin D, bleomycin, daunorubicin, epirubicin

4. Antimetabolites

Some antimetabolites are structural analogs of normal molecules that are essential for cell growth and replication such as cytidine or uracil analogs. Other antimetabolites inhibit enzymes that are necessary for the synthesis of essential compounds. Their major effect is interfering with the building blocks of DNA synthesis. In general, these agents have been most effective when cell proliferation is rapid.

Common Anti-metabolites

5-Fluorouracil, capecitabine, Gemcitabine, hydroxyurea, Methotrexate, pemetrexed

5. Topoisomerase Inhibitors

DNA is attached at regular intervals to the nuclear matrix at sites called *domains*, which are wound together with their paired DNA molecules. DNA topoisomerases are enzymes that alter DNA topology by annealing and resealing DNA strand breaks. Topoisomerases bind to DNA domains, forming a "cleavable complex," which allows DNA to unwind in preparation for cell division. Topoisomerase I relaxes supercoiled DNA for a variety of crucial cellular processes. Topoisomerase II catalyzes the double-stranded breaking and resealing of DNA, thereby allowing the passage of one double helical segment of DNA through another. Topoisomerases are essential for such events as transcription, replication, and mitosis.

Groups I and II topoisomerases are the targets of cytotoxic agents.

Camptothecin derivatives (irinotecan, topotecan) exert their cytotoxic effect by inhibiting topoisomerase I.

Epipodophyllotoxin derivatives (etoposide, teniposide) inhibit topoisomerase II.

6. Monoclonal Antibodies

Monoclonal antibodies have the advantage of relative selectivity for tissue and relative lack of toxicity.

A. Biological effects.

- Monoclonal antibodies can attack certain cells directly (e.g., malignant lymphocytes exposed to a selective monoclonal antibody are lysed in the presence of complement system).
- Various radioactive and chemotherapeutic agents can be conjugated to monoclones, which deliver these agents specifically to cancer cells.

- Growth factors (e.g., interleukins, epidermal growth factor, tumor growth factor) can sometimes be used as carriers for toxins; these constructs are called *oncotoxins.*

B. Clinical uses

- Imaging of tumors using radioisotope-labeled monoclones
- Selectively purging bone marrow of cancer cells
- Treatment of specific tumors

Common Monoclonal antibodies:
Bevacizumab, brentuximab vedotin, cetuximab, ipilimumab, rituximab, trastuzumab.

7. Hormonal Agents

- Anti-estrogens. Oral e.g. tamoxifen, toremifene.
- Adrenocorticosteroids. Broad indications of oncologic use which include:
  - Component of combination chemotherapy regimens for lymphoproliferative disorders and plasma cell dyscrasias
  - Immune-mediated cytopenias
  - Prevention of chemotherapy-induced vomiting
  - Appetite stimulant and mood elevator in patients with terminal cancer
- Adrenal inhibitors: Mitotane
- Androgens eg. methyltestosterone
- Antiandrogens (bicalutamide, flutamide, nilutamide)
- Estrogens [diethylstilbestrol (DES)]
- Aromatase inhibitors (anastrozole, letrozole, exemestane, aminoglutethimide)
- Gonadotropin-releasing hormone (GnRH) agonists – Zoladex™

General Toxicities and their management

1. Myelosuppression

Neutropenic fever and neutropenic sepsis. The most frequent serious complications of chemotherapy treatment are neutropenic fever and neutropenic sepsis. Although the nadir of neutropenia varies among the chemo regimes, the risk of neutropenia should be always considered during chemotherapy treatment.

Most patients with neutropenic fever will initially appear well, apart from the pyrexia, and they will respond to treatment with oral or intravenous antibiotics. Patients with neutropenic fever or neutropenic sepsis must be treated promptly using the local policies for the empirical treatment. The treatment plan with intravenous antibiotics will usually include an aminoglycoside and an antipseudomonal antibiotic or a cephalosporin and vancomycin. Patients with an apparent site of infection, such as chest infection, urinary tract infection or central-line sepsis, should also receive an antibiotic with appropriate additional cover. However, some patients can rapidly become seriously unwell with hypotension, shock, and end-organ failure. In these patients, rapid assessment and management are essential. Volume replacement with intravenous fluids must be initiated, and consideration should be given to transfer to a high dependency or intensive-care unit. All patients with neutropenic sepsis can deteriorate very quickly, and junior medical staff must be made aware of the need to contact more senior staff, if necessary, for advice on the management of such patients.

Primary and secondary prophylaxis

Patients receiving curative (including adjuvant) treatment should receive Granulocyte-colony stimulating factor (G-CSF) prophylaxis, as secondary prophylaxis, to prevent further episodes of neutropenia and to maintain dose intensity. Primary prophylaxis (i.e. from cycle 1) should be considered for patients on very myelosuppressive regimens, with a greater-than-20% risk of neutropenic sepsis in the first cycle.

2 Anaemia

Some commonly used cytotoxic drugs, including cisplatin cause a gradual reduction in haemoglobin levels over a course of treatment. This does not usually need a dose reduction or delay in treatment, but it can dramatically affect a patient's quality of life. A blood transfusion is standard practice. Erythropoietin may be indicated, but it is expensive.

3. Nausea and vomiting

The problems of chemotherapy-associated nausea and vomiting have become more manageable since the introduction of the 5 hydroxytryptamine 3 (5-HT3) antagonist drugs such as ondansetron and palonosetron. Many new patients still expect nausea and vomiting to be a major problem, but they can be managed with appropriate use of antiemetics.

Predisposing factors

The predisposing factors for an increased risk of nausea and vomiting include the previous poor control of nausea/vomiting, a history of motion sickness, being of a younger age, being female and having a chronic, low alcohol intake. These factors may require increased prophylaxis.

4. Cardiotoxicity

Cumulative cardiac toxicity is a problem associated with the anthracyclines, and treatment should remain generally within the standard guidelines on total lifetime dose. In the case of doxorubicin, this is 450 mg/m2. Cardiac function should be monitored more closely in patients with cardiac problems or in patients who have received previous treatment with anthracyclines or mediastinal radiotherapy. Several other drugs can also occasionally cause cardiotoxicity; fluorouracil is a good example that is linked with cardiac ischemia and arrhythmias.

5. Renal toxicity

Although renal function is monitored before each chemotherapy cycle in most regimens, particular attention is needed for drugs that are either

specifically nephrotoxic or are excreted via the kidneys. Cisplatin is the drug that is most frequently linked to renal toxicity. Appropriate treatment modifications should be made if there is a significant change in renal function.

6. Diarrhoea

Diarrhoea can be a dose-limiting toxicity with the fluoropyrimidines such as capecitabine and 5 Fluorouracil (5-FU). Diarrhoea can also occur as part of the cholinergic syndrome, which is seen with irinotecan. It is important to recognize the symptoms early and to start treatment with fluids, rehydration salts and loperamide.

7. Palmar–plantar erythrodysaesthesia (PPE)

PPE is the dose-limiting toxicity with capecitabine and liposomal doxorubicin. Patients should be encouraged to use emollients, but effective prevention is difficult. A dose delay is usually required for grade 2 or greater PPE. Pyridoxine 50 mg three times a day is often used as treatment. Avoidance of heat can help to prevent PPE.

8. Alopecia

Alopecia can be a very distressing side effect of chemotherapy treatment for some patients. The problem can be minimized to some extent using scalp hypothermia in patients receiving bolus injections or short infusions of doxorubicin, epirubicin and docetaxel. However, many chemotherapy patients do develop significant alopecia, and they need to be aware of this possibility. Arrangements should be offered for wigs and other cosmetic supports such as head scarves.

9. Fertility and fetal abnormalities (contraception)

Chemotherapy can affect the patient's fertility. Good practice is to offer sperm storage for men undergoing chemotherapy. The situation for women is less satisfactory because techniques for the preservation of oocytes or ovarian tissue are not yet reliable or widely used. Patients are advised to defer pregnancy for 12 months after the completion of treatment.

10. Phlebitis and local reactions

Phlebitis is a common problem with irritant drugs such as dacarbazine, the alkylating agents and vinca alkaloids. These drugs should always be given as bolus injections via fast-flowing drips or through a central line. Flash the IV access with water for injection, normal saline or 5%dextrose water after chemotherapy administration.

Follow-up

- During treatment, a patient should be examined and assessed for chemotherapy response and toxicity. This should be done prior to every cycle administration and also a scheduled inter-chemo review should be adhered to until completion of chemotherapy cycles.

- Post-chemotherapy, the patient is followed up at the scheduled visits specific for the diagnosis being treated. These are often short term and then long-term visits. Follow-up will entail a thorough history to assess the patients experience and response, a physical examination and in some instances, investigations maybe required as per expected routine. Investigations often include blood tests and imaging investigations.

Principles of Surgery in Oncology

Cancer surgery has evolved over time from a radical approach to a patient-specific, cancer-specific direction. Cancer management can rarely be delivered by a single specialty which means that surgeons rely on their multidisciplinary partners comprising oncologists, pathologists, radiologists, specialist nurses and various therapists in the assessment of patients to formulate a treatment plan. Surgeons are usually the first specialists involved with most solid tumours, therefore familiarity with biopsy collection, pre-operative imaging, staging, patient-selection and careful surgical technique are fundamental to the surgeon's arsenal. Surgery has several roles in cancer management including diagnosis, removal of primary disease, metastatectomy, palliation, prevention and reconstruction.

Pre-operative Imaging and TNM Staging

Most solid tumours require adequate and site-specific imaging. This facilitates diagnosis and staging of the primary tumour and staging for distal metastases. Not all modalities are appropriate for all sites. For example, mammography using the BIRADS system and ultrasound are used in breast cancers to assess a primary breast cancer. Meanwhile, an oesophageal cancer requires a CT scan, and a low rectal cancer will be best assessed with MRI or endorectal ultrasound, whilst a thyroid cancer is best evaluated with neck ultrasound.

The goals of imaging the primary tumour is to assess tumour size, invasion into surrounding structures and operability. Imaging to stage a tumour aims at assessing nodal involvement and distal metastases.

The TNM staging system (American Joint Commission on Cancer AJCC) is devised for cancers to allow an assessment of T- tumour, N- nodal metastases and M- distal metastases. The goal of having a site-specific staging system is to estimate prognosis, facilitate treatment planning including the sequence of treatments and allow comparisons of treatment for different stages. Generally, a combination of different 'T', 'N', and 'M'

allows the cancer to be grouped into stages.

Pathological Biopsy

Despite suggestive imaging, a cancer is not diagnosed until histopathological biopsy analysis. The goals of a biopsy should be to provide a diagnosis without excessive morbidity to the patient.

Biopsies where tissue (as opposed to cells) are provided to the pathologist increase the accuracy of the pre-operative diagnosis but may not always be feasible. Biopsies may be undertaken percutaneously -- for example, a core biopsy of the breast, fine needle aspiration of thyroid or endoscopically such as in gastric cancer or colon cancer.

A biopsy should confirm the tumour type, grade, may show lymphovascular invasion and in some cases, special immunohistochemical stains may be performed to ascertain the diagnosis as well as provide prognostic and or predictive information for specific cancers.

Patient Selection and timing of surgery

Surgery for a cancer patient MUST be done following a multidisciplinary team meeting to consider the patients diagnosis and reasonable treatment option. It is important for the MDT to choose the correct surgery for the correct patient and with the tumour type and biology in mind. Although surgery removes a tumour and provides further pathological information to estimate prognosis and influence adjuvant therapies, the surgery cannot cause more morbidity than the cancer and must achieve surgical goals without compromising tumour biology.

When tumours are locally advanced, a neoadjuvant approach with chemotherapy, radiotherapy or targeted therapies may be important to down-stage a tumour to render it operable. Sometimes the impact of systemic disease risk may outweigh that of local control necessitating neoadjuvant systemic therapy. Similarly, patients with metastatic disease may still require surgery to prevent complications of the primary tumour, such as bowel obstruction from a colon cancer prior to systemic therapy.

The pre-operative MDT including oncologists, anaesthetists, surgeons, dieticians, psychologists and social workers, and tumour-specific specialist nurses often assesses fitness for cancer surgery and the psychosocial impact of surgery.

Surgery of the Primary Tumour

The aims of any cancer surgery are to remove the cancer with an adequate margin of normal tissue with minimal morbidity. Clear margins have an impact on local control. It is therefore important to ensure meticulous surgery taking care not to disrupt the primary tumour at the time of excision and avoid piece-meal resections which increase the risk of local recurrence and make it very difficult for the pathologist to assess for resection margins. Margin requirements differ according to the origin of the tumour and the functional impact must also be considered.

Two examples of margins versus function/cosmesis include rectal cancer and breast cancer. A low-lying rectal cancer requires an adequate margin above the anal sphincters to enable a primary anastomosis (anterior resection) that is not under tension and therefore at risk of anastomotic leak. As a cancer encroaches on the level of the sphincter muscles, the sphincters must be sacrificed in order achieve an adequate margin (abdominoperineal resection). In breast cancer, a wide local excision may be adequate for many breast cancers but if the result is poor cosmesis/ shape, a mastectomy may be a better operation to achieve a clear margin.

Apart from ensuring that the tumour has been resected with adequate margins, adequate lymph node dissection is also of utmost importance in ensuring good locoregional control and prevention metastatic spread via the lymphatics. Certain cancers have a threshold number of lymph nodes that must be resected and examined by the pathologist during surgery to ensure an adequate lymph node dissection for that type of cancer. For example, a minimum of 12 lymph nodes must be assessed for colon cancer, and a minimum of 16 lymph nodes are considered optimal for gastric cancer.

Metastasectomy

In some circumstances, surgical resection of metastatic disease may be appropriate resulting in long term survival in some patients. This is particularly true in patients with low volume liver metastasis arising from colorectal cancer where metastatectomy has proven to be beneficial with 5-year survival rates of 27-39 % or even long-term survival in carefully selected cases.

Palliative Surgery

In some cases, surgery may not be appropriate for curative purposes but may be very valuable for palliation. Surgery may be undertaken in an elective or emergency setting in colorectal cancer to prevent or manage a bowel obstruction, to bypass a segment of small bowel involved with peritoneal disease or to place an endoscopic stent, for example in a metastatic cholangiocarcinoma or esophageal cancer.

Palliative surgery must be undertaken after an MDT meeting due to the consequence of it delaying other forms of treatment for months.

Prophylactic Surgery

Cancer surgery includes managing patients at high risk of cancer in their lifetimes, usually due to an inherited mutation such as Breast Cancer Gene (BRCA) 1 or 2 or Lynch Syndrome. Prophylactic mastectomy in women carrying a BRCA1 or BRCA2 gene mutation may be able to reduce the risk of breast cancer by about 95%. Other organs that can be removed in surgical prophylaxis include the colon in patients with hereditary colorectal cancer syndromes e.g. Familial adenomatous polyposis (FAP), lynch Syndrome; stomach in patients with Chromodomain Helicase DNA Binding Protein 1 (CHD1) mutation and thyroid in patients with Rearranged during Transfection (RET) mutation.

Reconstructive Surgery

Following surgical excision of a solid cancer, reconstruction is often an integral part of the operation. For example, when a gastrointestinal tumour is resected, the continuity of the Gastrointestinal (GI) tract must be

restored. Reconstruction may also be done for cosmetic reasons e.g. breast reconstruction surgery following mastectomy or cosmetic surgery following resection of a head and neck tumour.

Supportive care in cancer management

Interventions used in cancer management have undesirable effects that may affect treatment outcomes. If these adverse effects are not managed well it may lead to premature termination of therapy, poor quality of life, hospitalization, or death.

Adverse Event is defined as: any unfavourable and unintended sign, symptom, or disease temporarily associated with the use of a medicinal product, whether or not it is considered related to the medicinal product.

Serious Adverse Event is any outward medical occurrence that any dose results in death, is life threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect.

This section provides guidelines on how we can manage the common side effects due to chemotherapy and radiation used in management of cancer.

Nausea and vomiting

Nausea and vomiting are described by patients as feared and unpleasant side effects of anti-neoplastic therapy and if severe may result in termination of therapy. The factors outlined below need to be taken into consideration when planning anti-emetic therapy:

Emetogenic potential of therapy

It is recommended to administer anti-emetic prophylaxis according to the classification of the individual drug with the highest emetogenic potential.

Emetogenic potential of selected intravenous antineoplastic agents

Emetogenecity	Incidence of vomiting (%)	Agent
High	>90	Cisplatin, Cyclophosphamide ≥ 1500mg/m^2, Carmustine Darcabazine
Moderate	30-90	Oxaliplatin, Cytarabine>1g/m^2,Carboplatin, Ifosphamide, Cyclophosphamide<1500g/m^2, Doxorubicin, Daunorubicin, Epirubicin, Irinotecan
Low	10-30	Paclitaxel, Docetaxel, Mitoxantrone, Liposomal Doxorubicin, Topotecan, Etoposide, Methotrexate, Gemcitabin,Cytarabine≤1000mg/m^2,5Fluorouracil,Bortezomib,Cetuximab,Trastuzumab
Minimal	<10	Bleomycin, Busulfan, Fludarabine, Vinblastine, Vincristine, Vinorelbine, Bevacizumab

Emetogenic potential of selected per-oral antineoplastic agents

Emetogenecity	Incidence of vomiting (%)	Agent
High	>90	Procarbazine
Moderate	30-90	Cyclophosphamide, Vinorelbine, Imatinib
Low	10-30	Capecitabine, Etoposide, Sunitinib, Everolimus, Lapatinib, Lenalidomide, Thalidomide
Minimal	<10	Methotrexate, Gefitinib, Erlotinib, Sorafenib

Phases of Nausea and Vomiting

Acute vomiting begins during the first 24hours of treatment.

Delayed vomiting begins on day 1 to 5 after initiation of therapy. It is more difficult to manage compared to acute vomiting.

Anticipatory vomiting occurs before initiation of therapy and is psychologically motivated. This is conditioned by previous experiences of nausea and vomiting and is usually very difficult to manage.

Individual risk factors

- Poor management in previous chemotherapy cycles.
- Female
- Low alcohol consumption
- Young age

Prophylactic measures

The following tips can be used as preventive measures for nausea and vomiting:

- Avoid big meals- light frequent meals
- Cold food is easier to digest than hot food, as are cool drinks
- Avoid sweet, very fatty, highly seasoned or fried foods
- Stimulate the appetite with sour sweets, food or drinks
- Plenty of fresh air
- Get by difficult periods with sleep, or relaxing music or walks in the fresh air
- Avoid powerful odours

Therapy guidelines

Antiemetic therapy for different levels of emetogenic potential

Ematogenecity		**Acute Vomiting**	**Delayed Vomiting**
		Agents	**Agents**
High		Day 1:5-HT_3 antagonist+ Dexamethasone + (fos) aprepitant	Day 2-3:Dexamethasone+ aprepitant Day 4:Dexamethasone
Moderate	anthracycline + cyclophosphamide	Day 1:5-HT_3 antagonist + dexamethasone + (fos)aprepitant	Days 2-3:aprepitant
	All other therapeutic regimens	Day 1:palonosetron (or another 5-HT_3 antagonist) + dexamethasone	Day 2-3:Dexamethasone

Low	Day1:single substance e.g. dexamethasone or 5-HT_3 antagonist	No routine prophylaxis
Minimal	No routine prophylaxis	No routine prophylaxis

Pain management

In pain management pharmacotherapeutic approaches may be combined with other types of treatment. Nociceptorial pain is caused by tissue damage. Neuropathic pain is caused by nerve damage or irritation. Paroxysmal pain is pain occurring from a stable level of pain at rest.

Management of pain should be based on the WHO pain ladder (see Palliative Care and Associated Services chapter).

STEP 1: Non opioids and/or co-analgesics

- Diclofenac, Ibuprofen and Naproxen are recommended.
- Combinations of different NSAIDs should be avoided, since the effects are not additive, but the toxicities are.

STEP 2: Weak opioids and /or non-opioids and/or analgesics

- Weak opioids are prescribed if non opioids are insufficient to control pain, or they are contraindicated.
- Non opioids and opioids may be combined.
- Weak opioids are tramadol, dihydrocodeine, tilidine/naloxone

STEP 3: Strong opioids and/or non opioids and/ or co-analgesics

- If drugs in STEP 2 are insufficient to control pain, strong opioids may be prescribed.
- Sustained release morphine may be rationally combined with non-opioids and psychotropics.
- Oral oxycodone, hydromorphone or sublingual buprenorphine may be used.

*Analgesic therapy should preferably be oral. However, if oral administration of medicaments is no longer possible, therapy must be switched to parenteral OR rectal.

Treating breakthrough pain

- Break through cancer pain (BTCP) is a passing exacerbation of pain which occurs unpredictably in patients with relatively stable and controlled persistent pain.
- It is recommended to use opioids with a low first pass metabolism such as fentanyl in special formulations (oral-trans-mucosal, nasal, and buccal) that take effect fast.

Therapy of undesirable side effects of analgesic medications

Possible side effect	Therapeutic approach
Nausea/vomiting	Administer an antiemetic for the first 14 days of opioid therapy Drugs to use are metoclopramide, domperidone
Constipation	Laxatives: bisacodyl, liquid paraffin, sodium picosulphate, lactulose
Perspiration	Anticholinergics, sage preparations, change of opioid
Pruritus	Antihistamines, skin care, change of opioid
Urine retention	Adjust opioid dosage and reduce co-analgesics (especially tricyclic antidepressants)
Xerostomia	Mouth care, lozenges

Therapy of special pain syndromes

Treatment of neuropathic pain

- Consider using tricyclic antidepressants such as amitriptyline, anticonvulsants (carbamazepine, gabapentin, pregabalin), baclofen or dexamethasone for pain due to nerve compression and increased intra-cranial pressure.

Treatment of bone and soft tissue pain

- NSAIDs and opioids maybe used to manage bone pain. Baclofen may be used in case of spasticity.
- Additionally, Ibandronic acid, zolendronic acid or pamindronic acid (all bisphosphonates) may be used in bone pain management.
- Radiation therapy is recommended in many cases for deep duration

pain management which allows a de-escalation of analgesics.

Treatment of visceral pain

- Spasmolytic such as N-butytl-scopolamine or Non-Steroidal Anti-inflammatory Drugs (NSAIDs) with a spasmolytic component and glucocorticoids are used.

NOTE: Should side effects become difficult to manage as per guidelines recommended above, it may be necessary to switch analgesics or routes of administration. Reference to appropriate dose conversion tables is critical when carrying out the switch.

Alopecia (Hair loss)

Alopecia affects the scalp, and even the eyebrows, eyelashes, beard and other body hair. Hair loss can be severe, moderate or mild depending on the drugs used in chemotherapy.

Managing alopecia

The following recommendations are available for management of alopecia:

- Cover the head with scarfs
- Protect the scalp from sunlight as it in sensitive after hair loss
- Use of satin pillow covers that are gentle on the skin
- Wigs can be worn
- Hair can be precut to avoid the traumatic experience of hair falling out
- In the view of eye lashes and eyebrows make up may be used with expert advise

Due to the high regenerative capability of hair follicles, hair usually grows back 1-2 months after completion of chemotherapy. There is no scientific evidence that hair growth after chemotherapy can be promoted by medication.

Mucositis

This is a side effect frequently occurring during chemotherapy and radiotherapy. Mucosal lesions may be extremely painful and strongly affect the quality of life of tumour patients.

Mucositis often occurs in the second week of therapy. Symptoms of mucositis include pain, oedema formation, ulcerations, bleeding and atrophy. Xerostomia may result in difficulty swallowing, loss of taste and in problems speaking or eating.

Measures and substances for management of mucositis

- Oral care programs (check dental status prior to therapy, tooth sanitization as far as required, training of patients on oral hygiene, regular rinsing of the mouth)
- Analgesic therapy
- Adjustment of diet-nutrition
- Anti-infectious therapy
- Physical measures (cryotherapy after 5-FU bolus and high-dosage melphalan therapy)
- Chemical substances (palifermin, benzydamine in radiation patients)
- Symptomatic management (systemic analgesic therapy; antibiotics, antimycotics, antivirals; growth factors for neutropenia treatment; rinsing in xerostomia.

Nutrition Therapy

- Dietary deficiencies in cancer patients can be due to the cancer itself or the therapy.
- Tumour cachexia is associated with a loss of body fat and muscular tissue. Patient in this condition has a poor prognosis.
- Therapeutic aims of clinical nutrition for tumour patients are improving nutritional state and quality of life, enhancing therapeutic effect and alleviating side effects, and improving the prognosis.

Nutritional care for a cancer patient

- Personalized advice from a professional dietician (member of the MDT)
- Managed dietary choice- patient involvement in choosing meals.
- Energy enrichment- use of protein powders, oils rich in omega-3 fatty acids
- Drink supplements-nutritional drinks (must not be considered the main source of nutrient intake-it is a supplement)
- Appetite modulation-appetite can be enhanced by bitter substances such as ginger, ground nuts
- Other advice to the patient and caregivers:
    - lay the food in an appetizing way
    - avoid set mealtimes and follow your appetite/preferences
    - Passive distractions while eating (music, conversation)

Skin toxicities

- The skin is one of the organs most frequently affected by side effects of antineoplastic therapy.
- Surgery, chemotherapy, targeted therapy, radiotherapy, and immunotherapy can all result in adverse skin occurrence.

Management of reactions affecting the dermis

- During chemotherapy and radiation therapy, the skin should not be exposed to direct sunlight.
- Any mechanical irritation must be avoided.
- Early identification and treatment of skin infection especially following surgery or during radiotherapy.
- Moisturizing lotions and sufficient uptake of liquids should be used to protect the skin from drying out.
- In washing, lukewarm water and mild soaps (pH neutral to mildly acid syndets) must be used, gentle drying is recommended.

Fatigue

- This is a persistent, subjective sense of tiredness related to cancer or cancer treatments that can interfere with usual functioning
- It can be severe, distressing and not usually relieved by rest.
- It is the most common and incapacitating side effect in patients with cancer.
- Fatigue affects both the physical and psychosocial function and reduces the patient's quality of life.

Causes of fatigue

- Anaemia
- Cancer treatments
- Depression and anxiety
- Pain
- Inactivity
- Sleep problems
- Poor nutrition
- Medications (antihistamines, antidepressants, narcotics and anti-nausea drugs)
- Other co-morbidities

Managing fatigue

- Increasing activity by exercising
- Psychosocial measures (cognitive therapy, practicing relaxation techniques, counselling, social support, hypnosis, biofeedback)
- Resting
- Distraction (doing things the patients enjoys)
- Sleep therapy to correct disrupted sleep patterns
- Treat underlying cause if medical condition is a factor- e.g. Correction of anaemia.

NOTE: Antidepressants are not recommended to treat fatigue in cancer patients although they may help treat depression and anxiety.

Cancer related osteoporosis

Cancer patients are more frequently afflicted with osteoporosis than patients of the same age without cancer. It can be caused by the cancer itself or be treatment related.

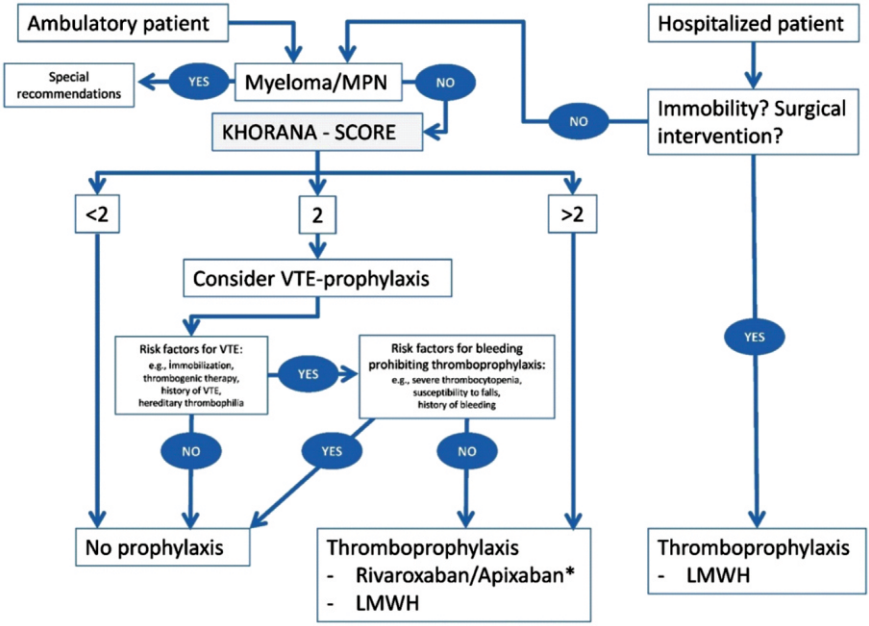
Causes of osteoporosis in cancer patients include effects of systemic therapies, (e.g. methotrexate, cyclophosphamide, ifosphamide), hypogonadism (impaired gonadal function) and prolonged glucocorticoid therapy

Treatment options for osteoporosis

Mechanism		Class/Group	Active ingredient	Dosing for osteoporosis
Antiresoprtive		*Nitrogeneous Biphosphonates	Alendronate	Once 70mg/week(in part with vitamin D 2800,5600IU)
			Ibandronate	Once 150mg per month oral 3mg infusion /3mg injection every 3 months
			Zolendronic acid	Once 5mg per year as infusion
		Monoclonal antibodies	Denosumab	Once 60mg s.c. every 6 months
		Peptide hormones	Calcitonin	Once 100mgIE/day or 50IU 2 times daily s.c/i.m. over 2-4 weeks
Osteoanabolic		Peptide hormones	Parathyroid hormones	Once 100ug/day s.c. over 24 months

Thrombosis

- Cancer patients have increased risk of thromboembolism complications.
- Venous thromboembolism is one of the most frequent complications and present the second most frequent cause of death among cancer patients.



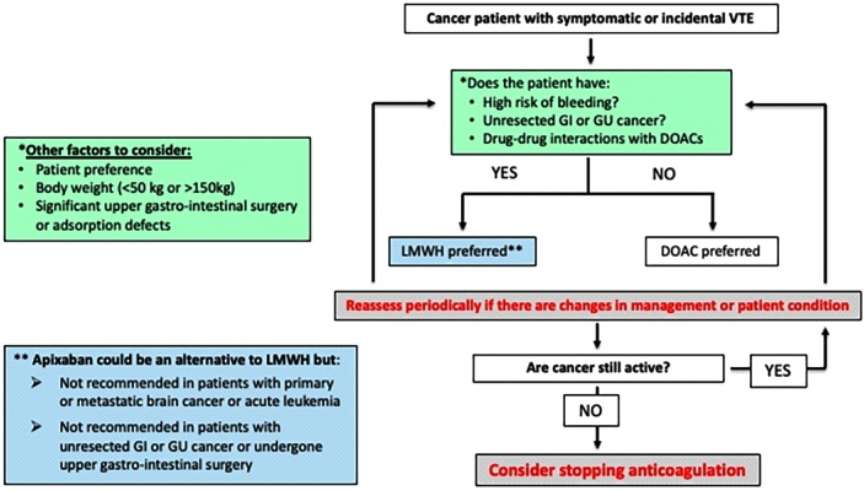
Risk Factors:

1. Chemotherapy for multiple myeloma with lenalidomide or thalidomide
2. Acute hospitalization for internal medical care
3. Tumor surgery with an anticipated duration of ≥ 30minutes

Contraindications:

- Bleeding
- Extended thromboembolism cytopenia with thrombocyte <30 000/ul.

Therapy and secondary prophylaxis as a shown below:



LMWH: Low- molecular weight heparin, DOAC: direct oral anticoagulants

Tumor Lysis Syndrome

- Tumor lysis syndrome (TLS) is a metabolic complication triggered by rapid breakdown of tumor cells and involves massive release of intracellular material over a short period of time.
- It is a potentially life-threatening complication of therapy due to the resultant acute renal failure or cardiac arrhythmia.

Risk factors for the development of TLS

- Rapidly growing tumour
- Large tumor mass
- Increased lactate dehydrogenase (LDH)
- Pre-existing hyperuricemia
- Pre-existing renal insufficiency
- Comorbidities such as:
    - Cardiac insufficiency
    - Obstruction of the urinary passage
    - Condition after kidney transplants

Management of TLS

- Prophylaxis can be given to high-risk patients.
- Patients need to be monitored in terms of their uric acid and electrolyte levels, renal function, and cardiac function.
- The most important measure is balanced hydration. Recommendation: 3l/m^2/d for adults and 200ml/kg/d for children under 10kg.
- Rasburicase is effective treatment for lowering high uric acid levels.

Reporting of Adverse Events

- Adverse events are reported to the Medicines Control Authority of Zimbabwe.
- A link can be found under the Online Services panel.
- The electronic Adverse Drug Reporting (e-ADR) application can be downloaded from a link on the website.

Further information on can be obtained using the details below:

Medicines Control Authority of Zimbabwe
106 Baines Avenue
P.O Box 10559
Harare, Zimbabwe
Telephone; +263-242-736381-5, 708255, 2901327-31
Fax: +263-242-736980
Cellphone: +263 772145191-3
https://www.mcaz.co.zw

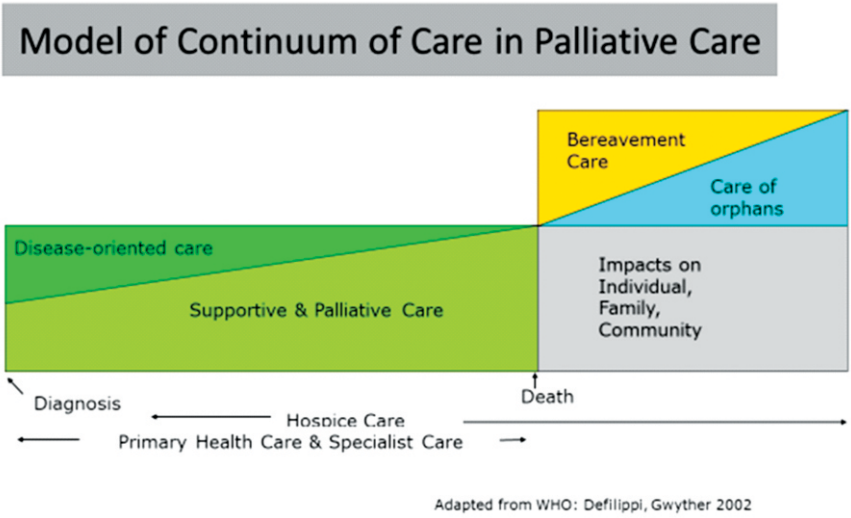
Palliative Care and Associated Services

General note

Palliative Care is an approach that improves the quality of life of patients (adults and children) and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and correct assessment and treatment of pain and other problems, whether physical, psychosocial, or spiritual (WHO, 2005).

Palliative care should start at diagnosis of a life threatening or life limiting illness and should continue across the illness trajectory including the bereavement period. A multi-disciplinary teamwork approach is critical in palliative care.

Continuum of palliative care



Adapted from WHO: Defilippi, Gwyther 2002

Components of Palliative care

Physical care: This includes physical assessment and examination of the patient, management of pain and other distressing symptoms, regular reviews, and general grooming.

Emotional care: This focuses on relief of psychological pain, which could be

due to, fear and anxieties. Good communication from the caring team is very important.

Social care: This emanates from losses due to the illnesses such loss of social status, jobs, finances, body image and functions.

Spiritual care*:* About questioning the meaning of life and issues to do with forgiveness (Why me?).

Principles of palliative care

- Provides relief from pain and other distressing symptoms
- Affirms life and regards dying as a normal process
- Integrates the psychological and spiritual aspects of patient care
- Offers a support system to help patients live as actively as possible until death
- Offers a support system to help the family cope during the patient's illness and their own bereavement
- Intends neither to hasten nor postpone death
- Uses a team approach to address the needs of patients and their families including bereavement counseling, if indicated
- Enhances the quality of life and may also positively influence the course of illness
- Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life such as antiretroviral therapy, chemotherapy, radiation therapy or TB treatment

Models of palliative care

- Hospital - inpatient and outpatient
- Home based palliative care
- Hospice care
- Day care centre
- Outreach – mobile clinics and roadside

Ethical & Legal Aspects of Palliative Care

The commonly used ethical issues are:

1. Respect of Autonomy - Acknowledges patients' rights to self-determination, without prejudice
2. Beneficence - is to produce benefit, to do good, to always act in the best interests of the patient
3. Non-maleficence - is to minimise or do no harm
4. Justice - refers to the equitable allocation of health care resources according to need based on the principle of progressive realisation.

Pain Assessment & Management in Palliative Care

Diagnostic Workup

Pain is complex because it stems from several different factors which include physical, emotional, social, spiritual and cultural problems. This is referred to as "Total Pain". It is subjective and therefore pain is "what the patient says hurts". Pain management involves a multidisciplinary team. The aim of pain management is to allow patients to be pain free as much as possible all the time.

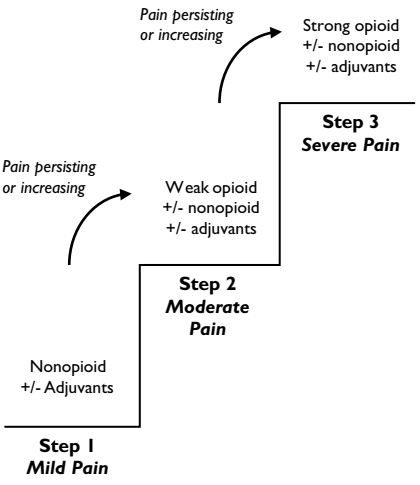
Pain can be classified according to duration, underlying mechanism, and situation. Different types of pain respond differently to different interventions; hence the need to determine the type of pain a person is experiencing to provide the most appropriate intervention.

The **PQRST** tool offers valuable guidelines for questions to help assess and measure pain:

- **P**recipitating and relieving factors:
- **Q**uality of pain (e.g. burning, stabbing, throbbing, aching, stinging):
- **R**adiation of pain: Is the pain in one place or does it move around your body?
- **S**ite and severity of pain: Where is your pain? (use appropriate tool
- **T**iming and previous treatment for pain: How often and when do you get the pain?

Table of Pain Management Medicines

For children and the elderly, dosages to be adjusted according to their ages using the standard guidelines found in EDLIZ. Children will not use WHO level 2 pain medications such as codeine but rather migrate from level 1 to level 3 due to their inability to metabolise the level 2 medications. Most of the level 2 medications are contraindicated in children less than 12 years of age)



The WHO Three -Step Analgesic Ladder

Step 1 Non-opioid (e.g., paracetamol, aspirin) ± adjuvant (e.g., antidepressant).

If pain is not controlled by Step 1 analgesics, move to Step 2 by adding a weak opioid.

Step 2 Opioid for mild to moderate pain (e.g. codeine) ± non-opioid ± adjuvant.

If an opioid for mild to moderate pain has been used to a maximum dose and the patient still has pain, then move to Step 3 by changing to a strong opioid.

Step 3 Strong opioid (e.g., morphine) ± non-opioid ± adjuvant.

(*Source: WHO 1996)*

Basic Communication skills

Effective communication is fundamental to a good relationship between a health service provider and those receiving care and support. Effective communication involves:

- Paying attention to the other person
- Being a good listener
- Being aware of non-verbal messages
- Using appropriate language

- Asking appropriate questions
- Being sensitive to the family culture
- Making sure you understand what the person said
- Making sure they understood what you said
- Self-Awareness will help knowing yourself and your fears

Breaking Bad News

Bad News is any information which drastically alters a patient or relative's view of their future for the worse. The way in which bad news is given has been shown to affect how the patient and family cope in the future.

Basic approach to breaking bad news

- Ask what the patient/relative understands of their situation
- Give a warning phrase/sentence to the patient/relative. By using the patient's own phrases and avoiding medical jargon wherever possible, start to give a range of possibilities
- Avoid assumptions. If a patient/ relative asks a question, never assume that you know what they are referring to.
- Explanations must be clear and simple, in terms that the patient/relative can understand.
- Be positive: optimism is supportive, pessimism is not, confirm that the patient/relative has understood the information so far, allow ventilation of feelings and do not discourage emotions and acknowledge distress

Anxiety and/or depression as well as communication problems are common. Health professionals should never fall into the trap of conspiring with relatives not to tell the truth to the patient.

Bereavement support

Grief is what happens when we experience loss. This can include loss of a life we thought we would live, loss of a limb, a country or a future no longer possible. The death of a loved one is a major loss for anyone, including children. Adults and children react differently to grief, and this is because of different levels of understanding of death and being able to express things differently at various stages of life.

Grief is a normal reaction to loss and most of us will have experienced some form of it. It occurs when we experience any major loss, for example loss of a job or loss of a limb. Grief is however unique to each individual and is influenced by each person's characteristics and circumstances. Loss of a loved one from death is a significant loss for anyone.

Bereavement is the process of healing from loss, and it can take weeks to several years depending on many factors. These include how the death occurred, the nature of the relationship with the deceased, the social support available and the cultural context.

Mourning is the term often used to describe the social expression of grief and includes funeral rites, rituals and memorialisation.
There are three main reasons why knowledge about bereavement is important in palliative care:

1. Patients themselves may have had previous losses.
2. The diagnosis of a life-threatening illness is met with mixed emotions such as disbelief, confusion and anger. The loss of "normal life" begins from this point.
3. The finality of loss through death brings many reactions from bereaved family members. Some people need help to deal with strong emotions and to adapt to the changes in their life after the death of their family member.

What to do to help the bereaved

- Encourage family members to include children in bereavement rituals depending on cultural expectations.
- Adolescents may express their grief by taking more risks, perhaps trying drugs or alcohol, or becoming rebellious. Help them to talk when it is convenient for them.
- Encourage relatives, including children, to talk of the deceased as much as they need. Do not force them to do so but provide an environment where they can do so if they wish.
- Make contact as soon as possible after the death of the loved one

to acknowledge the death and to offer condolences according to personal and cultural norms.

- Give information about the illness and the process of death if the relatives need to understand what happened and how. Use simple terms.
- Acknowledge that some people express grief in tears, and some people feel unable to cry. Each bereaved person needs to find a suitable form of emotional release.
- Encourage discussion of feelings – share memories by asking questions about the deceased and use the name to make it personal.
- You may suggest the family use journals, art, or create a memory book
- Grief can take a long time – prepare the bereaved for that and reassure them when they are still struggling after a time.
- Be there to listen, even when there is repetition – this is necessary for them to do to believe what has happened.
- Help with any necessary documentation such as a will or death certificate or link with organisations that can assist.
- Explain that the purpose of grief is not to forget the past, but to find ways to remember the dead person that are safe, healthy and less painful as time passes. Memories about special people provide roots and a feeling of belonging.
- Discuss with a bereavement professional if you feel a client's grief is especially difficult or complicated

Spiritual & Cultural Aspects in Palliative Care

Spiritual pain happens when people lose a sense of meaning or purpose in life after diagnosis of a life-threatening illness and have unmet emotional or spiritual needs. This pain is usually caused by a major event which challenges their core values and beliefs about how things are supposed to be. Those values and beliefs don't have to be religious, although they can be.

Culture

Each person has his/her own cultural beliefs and practices that are part of their heritage. The palliative care team needs to be sensitive to the fact that people in the same community may interpret culture in their own way and not assume "they" are all the same. The level to which an individual accepts or interprets traditions needs to be explored. Culture is also dynamic and what used to be the "norm" may no longer be the case.

Additional palliative care services

- Counselling
- Support Groups
- Young carers
- Nutritional guidance
- Stoma care
- Complimentary Therapy: (Relaxation, massage, reflexology, meditation, positive visualization and energy classes).
- Post Mastectomy care clinic
- Lymphoedema
- Childhood cancers psychosocial support

Cancer Survivorship

An individual is considered a cancer survivor from the time of diagnosis through the balance of his or her life. Survivorship begins at the time of diagnosis and includes the periods of initial treatment with intent to cure, cancer-free survival, chronic or intermittent disease, and end of life care. Family members, friends, caregivers and the greater community is greatly affected by the survivorship experience as well.

The diagnosis and treatment of cancer can have persistent impact on the health, physical and mental states, health behavior, identity, sexuality and financial security of a survivor.

Some sequelae become evident during treatment whereas others manifest months or years after treatment. The problems range from being mild to severe, debilitationg or life-threatening. Some problems are temporary and may improve with time while others may be progressive or permanent. Commonly encountered problems include depression, pain and fatigue.

Transition from active treatment to follow up care r referral needs to be carefully and clearly documented so that the physician to follow up the survivor has a full report .

Key components of the treatment summary

1. Contact information of the treating institutions and managing doctors/specialist firm
2. Specific diagnosis (e.g., breast cancer), including histologic subtype (e.g., non-small-cell lung cancer) when relevant
3. Stage of disease at diagnosis (e.g., cervical cancer FIG stage 2B)
4. Surgery (yes versus no); if yes:
    a. Surgical procedure with location on the body
    b. Date of surgery
    c. Any complications encountered

d. Attach copy of operation sheet if referring for adjuvant therapy

5. Chemotherapy (yes versus no); if yes:
    a. Names of systemic therapy agents administered (listing individual names rather than regimens)
    b. End date of chemotherapy treatment
    c. Toxicities encountered
6. Radiotherapy (yes versus no); if yes:
    a. Anatomic area treated with radiation
    b. End date of radiation treatment (year required, month optional, day not required)
7. Ongoing toxicity or adverse effects of all treatments received (including those resulting from surgery, systemic therapy, and/or radiotherapy) at the completion of treatment; any information concerning the likely course of recovery from these toxicities should also be covered
8. For selected cancers, genetic or hereditary risk factors or predisposing conditions and genetic testing results if performed

The Essential Components of a Survivorship Care Plan

- Prevention of new and recurrent cancers and late effects
- Surveillance for cancer spread, recurrence or second cancers
- Assessment of late psycho-social and medical effects
- Intervention for consequences of the disease and its treatment (e.g. medical problems, symptoms)
- Co-ordination of care between primary care providers, rehabilitation practitioners and clinical specialists to ensure that all of the survivor's health needs are met.

Surveillance for Cancer Recurrence

This is performed by the oncology team. Where surveillance is being overseen by the primary care physician, the oncologist should provide

evidence-based guidelines to be followed for that particular patient when transferring the patient.

Screening for the effects of cancer and its treatment

The following should be assessed:

1. Current disease status
2. Functional performance status
3. Current medications
4. Co-morbidities
5. Prior treatment history

Physical effects

These include pain, fatigue, urinary/bowel problems, lymphoedema, premature menopause, sexual dysfunction and cognitive deficits. The problems experienced depend on the treatment received. For example, hysterectomy and bilateral salpingo-oophorectomy or pelvic irradiation in a young patient will result in premature menopause.

Second primary cancers

The overall incidence of second primaries has been noted to be higher in survivors. This is attributed to

- Genetic susceptibilities (cancer syndromes)
- Shared causative factors e.g. smoking, obesity, environmental exposures
- Mutagenic effects of cancer treatment: specific chemotherapeutic agents and radiation

Chemotherapy-related leukemia's can occur 2 to 5 years after treatment with alkylating agents, platinum agents and topoisomerase inhibitors. The risk usually declines after 10 years. Alkylating agents have also been associated with development of solid tumors including lung, breast, gastro-intestinal and bladder cancers as well as sarcomas.

Radiation-induced malignancies have a longer latency period at least 5 to

10 years after treatment. The cumulative dose received, irradiated field and age at time of treatment influence the development of second malignancies.

Screening for second primaries should be a shared responsibility between primary care physicians and oncologists. Lifestyle modifications such as smoking cessation, weight loss and physical activity should be encouraged.

Psycho-social Effects

Some positive effects have been reported by some cancer survivors and these include improved relationships, a sense of gratitude or empowerment and an increased appreciation for life. However, individuals may experience psychological distress after active treatment because of fear of recurrence or death, and practical and social problems pertaining to employment, finances, health and life insurance. Some survivors may experience a combination of positive and negative psychological effects.

Fear of recurrence or death may cause significant and enduring distress, and these fears may cause patients and their caregivers to either default on appropriate follow up or to demand more intensive surveillance than that supported by available evidence. In addition, high levels of depression and lower quality of life are more likely in those with high levels of fear of recurrence.

Work status, performance and satisfaction are often adversely affected by cancer and its treatment. Survivors often take long breaks during treatment. Some may be left with disabilities or long-term effects that decrease employment prospects or capabilities. Survivors who do return to work may encounter difficulties such as fatigue physical or cognitive limitations, depression, anxiety and discrimination, which may be real or perceived.

The financial burden on survivors is great, because of lost wages and increased expenses. This can result in increased psychological distress and an adverse impact on adherence to prescribed treatment.

Cognitive Function

Patients have reported cognitive dysfunction associated with cancer treatment. Symptoms reported include difficulty paying attention, finding words or remembering things and slowed thinking. There is growing evidence to support these patient- reported experiences with neuro-psychological testing and brain imaging having shown abnormalities in patients who had chemotherapy. However, there is little evidence to guide management of this condition. The patient's symptoms should be acknowledged and thoroughly evaluated, with screening for potentially reversible factors such as depression, fatigue ad sleep disturbance carried out.

General strategies for management include use of organizational aids such as notebooks, smart phone technology, keeping items in the same place, and relaxation of stress management skills such as meditation are recommended. Limiting alcohol intake and engaging in routine physical activity are encouraged.

Cancer- Related Fatigue

This is a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or its treatment that is not proportional to recent activity and interferes with usual functioning.

It is a common problem in cancer survivors undergoing cancer therapy and can persist months or years after treatment. While the time course differs with everyone, fatigue that initially presents or worsens months after completion of treatment warrants further investigation.

Management includes a thorough history and physical examination. The onset, duration and pattern of fatigue as well as associated or alleviating factors should be elicited. Co-morbidities including anaemia, alcohol or substance abuse, cardiac, endocrine, pulmonary and renal dysfunction should be enquired about. Nutritional issues such as weight and calorie intake as well as use of medication should be assessed.

Laboratory investigations mainly full blood count, urea and electrolytes as well as liver function tests should be carried out. Endocrine evaluation including thyroid function tests are performed if clinically indicated.

Definitive management includes:

- Treatment of contributing factors e.g. pain, distress, anaemia and sleep disturbances
- Patient and family education and counselling
- Physical activity
- -Psycho-social interventions e.g. cognitive behavioural therapy, support groups, journal writing
- Other interventions such as acupuncture, acupressure
- Pharmacologic agents e.g. psycho-stimulants

LYMPHOEDEMA

Lymphoedema is the abnormal accumulation of interstitial fluid and fibro-adipose tissue. It may occur as a result of:

- Lymphatic dissection at surgery- commonest cause.
- Compression of lymphatic channels or nodes
- Infiltration of lymphatic vessels by cells (lymphangitis carcinomatosis)
- Regional lymph node irradiation (however radiation therapy alone is rarely enough to result in development of lymphoedema)

Conditions that need to be ruled out include chronic venous insufficiency, acute deep vein thrombosis, post-thrombotic syndrome and myxedema. Lymphoedema is graded as mild, moderate or severe.

Mild

- Oedema that may pit on touching and resolves on limb elevation
- Maximum girth difference between affected and unaffected limb is <3cm

Moderate

- Does not pit and does not resolve with limb elevation alone
- Maximum girth difference 3-5cm

Severe

- Non-pitting with visible trophic skin changes-fat deposits, acanthosis
- Maximum girth difference >5cm

Management of lymphoedema

Lymphoedema is often difficult to treat with the aim being to improve patient comfort and reduce limb volume. Management consists of general measures for self-care, compression therapy and physiotherapy.

General measures:

- Minimal lymph node dissection whenever possible e.g. sentinel nodal sampling
- Physiotherapy interventions should begin before surgery with patient assessment and counselling
- Self-monitoring with prompt reporting of changes in size, sensation, colour, temperature or skin condition
- Limb elevation
- Maintenance of ideal body weight using diet and exercise
- Avoid skin injury and infection
- Avoid tight fitting clothing

Compression therapy includes use of compression bandaging, compression garments and intermittent pneumatic compression. Physiotherapy interventions may involve manual lymphatic drainage and complete decongestive therapy.

PERIPHERAL NEUROPATHY

This is a type of nerve damage that develops when the nerves that carry information back and forth between the brain and spinal cord are damaged. The damage can be caused by cancer treatment surgery, radiotherapy, chemotherapy therapy and sometimes by the cancer itself. Symptoms of nerve damaged are numbness, tingling sensation, pain, muscle weakness, constipation, or dizziness. Most patients usually recover from these symptoms after many months or a few years after treatment.

MENOPAUSE-RELATED SYMPTOMS IN FEMALES

Surgical removal of a woman's ovaries, chemotherapy, hormonal therapy, and radiation therapy to the pelvic area may cause a woman to have lighter and fewer regular menstrual periods or stop menstruating completely. Menstrual periods may return for some younger women after treatment, but women older than 40 are less likely to have their menstrual periods return. Many people recover over the course of many months or a few years. Sometimes, the condition may be more difficult to cure and may require long-term management.

Menopause is defined as no menses for one year in the absence of prior chemotherapy, tamoxifen use or surgical removal of all ovarian tissue. Serial estradiol levels may help to confirm post-menopausal status in patients who received prior chemotherapy, pelvic irradiation or those on tamoxifen. Many survivors may have symptoms without meeting the definition of menopause.

Menopausal Symptoms and Signs

- Vasomotor symptoms: hot flushes, night sweats
- Vaginal dryness
- Sexual dysfunction
- Sleep disturbances
- Mood disturbance and depression
- Cognitive dysfunction
- Arthralgia's/myalgia's
- Fatigue

Health-related risks

- Osteoporosis/ bone fracture
- Cardiovascular disease

ANDROGEN DEPRIVATION THERAPY (ADT) -RELATED SYMPTOMS IN MALES

Patients treated for non-prostate malignancies who have received radiation chemotherapy or undergone surgery may have hypogonadism.

Those with prostate cancer who have received androgen-deprivation therapy (ADT) may experience menopausal symptoms and sexual dysfunction.

ADT-related symptoms

Anaemia	Arthralgia/myalgia
Cognitive dysfunction	Decreased muscle (sarcopaenia) and increased fat
Decreased penile size	Mood disturbance and depression
Fatigue	Gynaecomastia
Sexual dysfunction	Sleep disturbance
Testicle atrophy	Thinning body hair
Vasomotor symptoms	
Anaemia	

ADT-related health risks

- Acute kidney injury
- Osteoporosis/ bone fractures
- Venous thrombo-embolic disease
- Diabetes mellitus new onset
- Cardio-vascular disease

Management

NON-HORMONAL PHARMACOLOGIC TREATMENT OF VASOMOTOR SYMPTOMS

- Low dose anti-depressants- caution with use of selective serotonin re-uptake inhibitors (SSRIs) in patients on tamoxifen
- Anti-convulsants
- Neuropathic pain relievers
- Certain anti-hypertensives

Non-Pharmacologic Treatment of Vasomotor symptoms

- Acupuncture
- Exercise
- Lifestyle modifications

- Weight loss if overweight or obese
- Cognitive behavioural therapy
- Vitamin E, black cohosh- limited data

Hormonal therapies

For females:

- Combination estrogens and progestins (intact uterus) or estrogen alone (in survivors without a uterus)

For males:

- Medroxyprogesterone
- Cyproterone acetate
- Estrogen (e.g. diethylstilbestrol)

NB: Contra-indicated in survivors of hormonally mediated cancers

Management of Gynaecomastia

- Prophylactic irradiation (must be delivered prior to breast tissue development)
- Tamoxifen
- Reduction mammoplasty

General Principles of Healthy Lifestyles

Survivors should be encouraged to achieve and maintain a healthy lifestyle. This consists of engaging in safe physical activity, healthy dietary habits and weight management.

Physical Activity

- General physical activity daily.
- 150 minutes of moderate or 75 minutes of vigorous activity per week spread out over the course of the week
- Avoid prolonged sitting

Diet

- Survivors should eat a diet high in vegetables, fruits and whole grains, and low in sugars and fats
- Limit red meat and avoid processed meat

Weight Management

- Achieve and maintain a normal body mass index (BMI)
- Weigh self regularly, at least once a week to monitor weight.

Recreational habits

- Minimize alcohol intake (≤1 drink per day for women and ≤2 drinks per day for a man)
- Smoking cessation with the aid or both pharmacological and non-pharmacological aids.

Sun safety

- Avoid direct sun during peak hours
- Use physical barriers: hats, shirts with sleeves
- Use sunscreen SPF 30 or more- apply generously and re-apply every 2 hours or after swimming/ excessive sweating
- Avoid tanning beds

HIV and Cancer

Overview of cancer and HIV infection

HIV is the virus that causes acquired immunodeficiency syndrome (AIDS). HIV does not cause cancer itself, but infection with HIV facilitates an increased likelihood of oncogenesis in the host. Multiple factors may contribute to the increased incidence of malignancy in patients infected with HIV. These include immunosuppression, direct effects of the HIV virus itself and co-infection with other oncogenic viruses.

HIV immunosuppression

HIV immunosuppression results in reduced immune surveillance of cells with non-lethal genetic defects and cancer cells. It depresses the antigen presentation of -specific antigens to effector cells and therefore suppresses immune activation against malignant cells. The T-cells are heavily suppressed resulting in diminished activation of phagocytic neutrophils, natural killer cells and macrophages. HIV immunosuppression therefore permits the proliferation of genetically defective mutagenic cells thereby promoting subsequent carcinogenesis.

Chronic Immune activation

Besides immunosuppression, chronic immune activation (a hallmark of HIV pathogenesis) plays a critical role in HIV-related carcinogenesis. The production of type II cytokines such as IL-4, IL-13, and TGF-β, which drive cell activation results in the production of growth factors (e.g., EGF, FGF-2), angiogenic factors (e.g., VEGF, MMP-9), and inflammatory cytokines (e.g., TNF-α, IL-1). These are collectively exploited by the tumorigenic clones towards a tumour-promoting state.

Age and HIV-related cancers

Among people living with HIV, certain cancers are diagnosed at younger ages, possibly reflecting accelerated cancer promotion and progression or exposure to risk factors. It has been postulated that HIV induces an accelerated ageing process despite virologic control with ART. This overall ageing process could simply be resulting in an “earlier” onset of cancers in this population. It has been observed in some studies that HIV infected

persons had a younger median age at presentation than HIV-negative patients for the same cancers. People diagnosed with AIDS during childhood remain at elevated risk for malignancy into adulthood, despite the management of their HIV infection with ART.

Co-Infections

People with HIV/AIDS also have increased risks of cancers that are caused by infectious agents. Interactions among co-infecting viruses may increase cellular transformation and oncogenesis. In Zimbabwe, common infections include Kaposi's sarcoma-associated herpes virus (KSHV) infection whose complex interplay with HIV dramatically elevates the risk for development of Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman disease. Human papillomavirus (HPV) is also a common infection, and it is associated with cervical, anal, oropharyngeal, vulva, penile and other cancers. Epstein-Barr virus (EBV) infection results in Hodgkin's Lymphoma whilst hepatitis B and C viral (HBV and HCV) infections may cause liver cancer. Though uncommon, Human T-lymphotropic virus 1 (HTLV-1)can cause an aggressive adult T-cell leukemia/lymphoma (ATLL).

Human Immunodefiency Virus (HIV) infection is also associated with increased risks of cancers that are not known to be caused by infectious agents, such as lung cancer.

Effect of Antiretroviral Therapy (ART) on Cancer

Spectrum of Cancer in the ART-Era

Immune reconstitution induced by highly active antiretroviral therapy, with improved life expectancy, has modified patterns of morbidity and mortality for most HIV-associated cancers. . The resulting improved life-expectancy of HIV-infected persons has produced an extra burden of comorbid conditions, cancers and polypharmacy. The spectrum of neoplasia in HIV infected patients is therefore progressively changing. The interaction between anticancer and antiretroviral drugs has consequently become exceedingly complex.

The incidence of AIDS defining malignancies like KS and NHL has decreased markedly, but there has been a relative increase in tumor types that collectively are referred to as non-AIDS-defining cancers (NADCs) compared with the general population. NADCs include HIV-associated cancers such as anal, hepatocellular, vulva, lung and oro-pharyngeal cancers.

Antiretroviral drugs and timing of cancer development

ART extends the life expectancy of patients with HIV. This makes them more likely to develop certain cancers as they age. Certain malignancies such as KS or lymphoma may occur soon after the initiation of ART, arguing that the treatment itself, rather than the increased life expectancy it confers, may predispose towards these cancers. This was attributed to the phenomenon of immune reconstitution in the more severe immunosuppressed patients with subsequent unmasking of sub-clinical KS.

Drug-drug Interactions (DDIs) and polypharmacy (ART and chemotherapy)

Most cytotoxic chemotherapies are used safely in HIV positive patients. However, the possibility that drug-drug Interactions (DDIs) with ART, may enhance treatment toxicity or decreased efficacy should be considered. This may occur via the CYP450 pathway e.g. ART with NNRTIS, protease inhibitors or pharmacologic boosters like ritonavir; such interactions could potentially alter anti-cancer drug metabolism and physiologic availability. Each patient should be considered individually, and management of ART should be discussed by the treating oncologist and the HIV clinician e.g. ART with integrase inhibitors without pharmacologic boosters may be favored in the setting of malignancy due to a lower potential of DDI. Conversely, ART metabolism may be induced or inhibited by chemotherapy drugs which are nephrotoxic or alter hepatic metabolism. The use of novel therapies such as immunotherapies in immune-compromised patients is an area of on-going research.

Approach to an HIV patient with cancer

- Confirm patient has cancer.
- Confirm the HIV status for all cancer patients.
- Refer the patient to an appropriate specialist – oncologist, physician/OI Clinic, gynecologist, and surgeon.
- Thorough history: Onset of symptoms, timing of diagnoses, ART history, co-morbidities such as opportunistic infections, previous treatments, screening
- Examination – for extent and possible spread of cancer disease. Severity of HIV-related/AIDS defining stigmata.
    - Performance status, nutritional status
    - Co-morbidities
- Investigations – baseline bloods: FBC, U&E, LFT, CD4, viral load
    - Relevant imaging for staging and baseline were needed to rule out HR OIs.
    - Relevant reviews of histology, immunohistochemistry (IHC)
- Management: overall management decision is based on the cancer type, stage, prior management (if any), overall well-being and performance status of the patient, severity of immune-suppression, presence and severity of co-morbidities. Regimen and sequence of treatment is best chosen in a multi-disciplinary team setting.
- When therapy is initiated, the patients need close follow-up and alterations to initial prescriptions may be made depending on toxicity profile and response to treatments. Ensure patients sustain ART intake whilst on cancer treatments.
- Supportive treatment – nutritional support, pain control, infection management and other supportive measures should be used to minimize radiotherapy interruptions.

Principles of HIV Management while undergoing Cancer Therapy

- In Zimbabwe, all patients with cancer should be screened for HIV.
- All PLWH with cancer, should be co-managed by an oncologist and

an HIV physician/OI Clinic.

- HIV therapy should be offered immediately and/or continued during cancer therapy. Consider starting ART at east 7days prior to commencement of cancer treatment.
- ART may require modification during chemotherapy to minimize drug interactions and toxicities.
- Frequent viral loads (3 monthly for the 1st year, then every 6 months thereafter where possible) may be needed due to potential interactions between ART and cancer-related drugs leading to diminished effectiveness of ART
- Avoid zidovudine

Principles of Radiation Therapy

- HIV status alone should not be a criterion for decision-making regarding radiation therapy. Radiotherapy should be offered as part of the cancer management approach when indicated.
- Older (pre-ART era) studies showed increased RT-related toxicity in patients with CD4+ count less than 200cells/µL. This may not be the case in the ART-era.
- Extra-caution and monitoring is required with concurrent chemoradiotherapy.

Principles of Systemic/Chemotherapy in PLWHIV

- Oncologists, HIV clinicians and pharmacist should review proposed cancer therapy, supportive medication, cotrimoxazole prophylaxis and ART for possible DDIs and overlapping toxicities prior to initiation.
- Cancer treatment is expected to be myelosuppressive, zidovudine is contraindicated.

Principles of Surgery in PLWHIV

- HIV status alone is not a criterion for decision making regarding surgical intervention, regardless of procedure. All surgical candidates should be treated with universal precautions.

- Overall health (e.g. organ dysfunction, nutritional state) has been found to be a more reliable predictor of surgical outcome than CD4+ count or viral load in PLWH. The data showing that low CD4 counts are associated with poorer prognosis have been inconsistent.
- Surgery in PLWH for common malignancies is safe and should be part of cancer management as indicated for that condition (e.g. prostate cancer, colon cancer).

Supportive Care

- Infections – good HIV control and infection prophylaxis, reduce the risk of infectious complications in People Living With HIV (PLWHIV). All patients should be on cotrimoxazole. Other prophylaxis to be considered include:

  Quinolones e.g. ciprofloxacin - for gram negative bacteria
  Acyclovir – Herpes simplex or varicella viruses
  Nystatin +/- fluconazole – candida.
  Azithromycin – mycobacterium avium complex (MAC)
- Neutropenia – myeloid growth factors are strongly recommended. They are required in the use of high-risk regimens for febrile neutropenia.
- Nausea and vomiting (N&V) – agents for N&V should be used as indicated. However, general use of steroids for anti-emesis should be limited. Steroids can be used briefly as premedication before or after chemotherapy administration.

Screening in HIV patients

Background

Although the rates of many NADC are higher in HIV-infected individuals, in general, screening recommendations for most cancers are the same as for HIV-uninfected individuals. However, screening recommendations should be based on individual patient risk factors and available resources. Prostate cancer, breast cancer and colorectal cancer screening in HIV infected individuals is the same as in the HIV-negative patients.

Primary intracranial tumours.

General Note

Brain tumours are a diverse group of neoplasms arising from different cells within the central nervous system (CNS) or from systemic cancers that have metastasized to the CNS. Risk factors include inherited genetic mutations such as neurofibromatosis, tuberous sclerosis, multiple endocrine neoplasia (type 1), a prior history of irradiation and retinoblastoma. HIV infection increases the risk of primary CNS lymphoma. Metastatic disease to the brain arise mainly from lung, breast, malignant melanoma and colon cancers

History & symptoms

- Personality change
- Dementia
- Altered mental status
- Seizures Visual disturbances
- Difficulty walking
- Vomiting
- Signs of raised intracranial pressure (ICP) morning headaches, vomiting, visual impairment

Physical Examination

- General examination- performance status
- CNS examination- level of consciousness (LOC); cranial nerve deficits; limb tone, power and reflexes.

Diagnostic workup

- MRI scan preferred
- CT scan (and other investigations to exclude other primaries should also be done)
- Tissue biopsy to be obtained for histology and molecular studies

Staging workup

- Full Blood Count (FBC), Urea & Electrolytes (U& E), Liver Function Tests (LFTs), Lactate Dehydrogenase (LDH)and HIV tests
- Appropriate hormonal tests
- Coagulation studies
- Steroids to be avoided if a diagnosis of a primary CNS Lymphoma is suspected

Histology

World Health Organization (WHO) classification of central nervous system tumours

Type
Diffuse astrocytic and oligodendroglial tumours
Other astrocytic tumours
Ependymal tumours
Other gliomas tumours
Choroid plexus tumours
Neuronal and mixed neuronal glial tumours
Embryonal tumours
Meningiomas
Mesenchymal non meningothelial tumours
Tumours of the pineal region
Tumours of the cranial and paraspinal nerves
Melanocytic tumours
Lymphomas
Histiocytic tumours
Germ cell tumours
Tumours of the sellar region
Metastatic tumours

General treatment

ALL patients with a neoplastic intracranial tumour should be discussed in a multidisciplinary team meeting (including nutritionist, pathologist, neurosurgeons, neurologist, clinical oncologist, pharmacist, oncology nurse, radiologist, palliative care specialist, rehabilitation specialists and social worker) prior to treatment.

- Management varies greatly depending on location, tissue type, age and comorbid conditions
- Throughout treatment the patient's quality of life should remain the highest priority and guide clinical decision-making.
- Other indicators of success such as overall well-being, function in day-to-day activities, social and family interactions, nutrition, pain control, long-term consequences of treatment and psychological issues must be considered.

Surgical principles

- The goals of surgery are to obtain a diagnosis, alleviate symptoms related to increased intracranial pressure or compression, increase survival, and decrease the need for corticosteroids
- Frozen section analysis where possible help with intraoperative decision-making
- Aim at maximal safe resection, minimize surgical morbidity, and ensuring an accurate diagnosis by providing sufficient representative tumour tissue.
- Surgical treatment options may include tumour removal or debulking, installation of a ventricular shunt, and placement of radioactive implants
- The surgical options include open biopsy, stereotactic biopsy, subtotal resection (STR), or complete resection (gross total resection: GTR)
- A postoperative MRI scan, with and without contrast, should be obtained 24 to 72 hours after surgery to document the extent of disease after surgical intervention.

Medical management of symptoms

Raised intracranial pressure

Medicine	Codes	Adult dose	Frequency	Duration
Dexamethasone	C V	16 mg IV stat then taper down		

Anti-seizure drugs

Anti-seizure medicines are not generally recommended in patients who have never had a seizure, aside from perioperative prophylaxis in patients undergoing craniotomy for resection.

Medicine	Codes	Adult dose	Frequency	Duration
Phenobarbitone	B E	60-180mg PO	Daily	
Phenytoin	A E	150mg PO	Daily	

Management of specific tumours

Low-grade infiltrative astrocytomas and oligodendrogliomas

- Surgical resection is the preferred first line of treatment. If GTR is achieved
    - Low-risk patients can be observed with close follow-up.
    - High-risk patients require adjuvant radiotherapy and/or chemotherapy

Low-risk features for low-grade gliomas include	**High-risk features for low-grade gliomas include**
Age <40 years,	Age ≥40 years
Karnofsky Performance Status (KPS) ≥70	KPS under 70
Minor or no neurologic deficit	Preoperative neurologic deficit of more than minor degree
Oligodendroglioma or mixed oligoastrocytoma	Tumour crossing midline
dimension <6 cm	Dimension ≥6 cm

1p and 19q co-deleted IDH1 or 2 mutated	Other adverse factors to consider include increased perfusion on imaging and one or no deletion on 1p and 19q, wild -type IDH1 or 2

IDH- isocitrate dehydrogenase (test must be done whenever possible)

- Patients with high-risk features following open biopsy or subtotal excision should be treated with fractionated EBRT or chemotherapy.
- Chemotherapy may be used as adjuvant therapy for recurrence or progressive disease

Medicines

Medicine	Codes		Adult dose	Frequency	Duration
Temozolamide	S	V	150mg/m^2 PO OD DI-D5	4 weekly	
Lomustine	S	V	90-110 mg/m^2 D1	6 weekly	
Procarbazine, Lomustine (CCNU) & vincristine (PCV)	S	V	Procarbazine 100mg/m^2 PO D1-D10 CCNU 100mg/m^2 Vincristine 1.5 mg/m^2 (max 2mg)	6-8 weekly	

Follow up

- Patients should be followed using MRI every 3 to 6 months for 5 years and then annually thereafter.

At recurrence surgery is recommended (if resectable) followed by chemotherapy if patient was treated previously with radiotherapy

Anaplastic gliomas and glioblastoma

ALL patients with anaplastic gliomas and glioblastoma should be discussed in a multidisciplinary team meeting (including pathologist, neurosurgeons, neurologist, clinical oncologist, pharmacist, oncology nurse, radiologist, palliative care specialist, rehabilitation specialists and social worker) prior to treatment. Early integration of palliative care **strongly recommended**

Treatment

Maximal safe resection if feasible with goal for image verified complete resection should be considered. If maximal safe resection is not feasible open biopsy or subtotal resection should be done. Adjuvant treatment is given in the following:

- EBRT for patients with high-grade astrocytomas.
- EBRT followed by PCV for anaplastic oligodendroglioma or oligoastrocytoma.
- Concurrent chemoradiation with temozolamide followed by adjuvant single agent temozolamide for patients with glioblastoma and good performance.
- EBRT, chemotherapy or best supportive care for patients with glioblastoma and KPS <60

Medicines

Medicine	Codes	Adult dose	Frequency	Duration
Temozolamide	S V	Temozolamide 75 mg/m^2 daily concurrent with radiotherapy then 150 mg/m^2 post-irradiation on a 5-day schedule every 28 days	4 weekly	6
Procarbazine, Lomustine (CCNU) & vincristine (PCV)	S	V Procarbazine 100mg/m^2 PO D1-D10 CCNU 100mg/m^2 Vincristine 1.5 mg/m^2 (max 2mg)	6- 8 weekly	

Follow-up.

- Patients should be followed closely with serial MRI scans at 6 weeks post-irradiation, then every 3 months for 2 years

Intracranial and spinal ependymomas

Treatment

- Maximal safe resection is the preferred intervention.

- For intracranial tumours contrast enhanced brain imaging within 24-72 hours post-op.
- Spine MRI should be delayed by at least 2 -3 weeks after surgery to avoid post-surgical artifacts.
- If MRI shows that initial resection is incomplete multidisciplinary team review and re- resection (if possible) should be considered.
- Grade I ependymomas are non-infiltrative and can be treated with resection alone.

Adjuvant treatment

- Depends on the extent of surgical resection, histology, and disease stage
- Cerebral Spinal Fluid (CSF) cytology, delayed at least 2 weeks after surgery, should be performed for anaplastic ependymoma and/or if resection is suboptimal
- CSF analysis is also indicated for grade II ependymomas following GTR if spine MRI is negative. However, lumbar puncture may be contraindicated in some cases (for example, posterior fossa mass).
- Patients who have undergone GTR and have negative findings for MRI and CSF may:
    - Observed for supratentorial or spinal tumour
    - Consider adjuvant fractionated External Beam Radiotherapy (EBRT) for intracranial or myxopapillary tumours.
- Limited-field fractionated EBRT is the appropriate postoperative management for patients with anaplastic ependymoma and/or STR, provided MRI and CSF findings are both negative
- Craniospinal radiotherapy is mandatory when MRI spine or CSF results reveal metastatic disease, regardless of histology and extent of resection.

Follow up

- For localized disease, contrast-enhanced brain and spine MRI (if initially positive) should be done 2 to 3 weeks postoperatively and then every 3 to 4 months for one year
- For **recurrent disease** options include RT (including SRS or re-irradiation of previously irradiated sites), chemotherapy for patients who are refractory to surgery and palliative or best supportive care

Medulloblastoma and supratentorial primitive neuroectodermal tumours (PNET)

- Cranial PNETs are embryonal neoplasms showing varying degrees of differentiation. They are described by their location as infratentorial (medulloblastomas) and supratentorial (cerebral neuroblastoma, pineoblastoma or esthesioneuroblastoma)
- All PNETs of the brain are WHO grade IV- rapidly growing, highly invasive and have the tendency to disseminate through the CSF.

Treatment

- Surgical resection should be the routine initial treatment to establish diagnosis, relieve symptoms, and maximize local control.
- CSF sampling should be done because of the propensity of PNET to have CSF seeding.

Radiation Therapy

- Adjuvant radiotherapy following surgery is standard of care
- Radiotherapy is administered according to recurrence risk stratification
- High risk patients include those with:
    - Large cell or anaplastic medulloblastoma
    - Supratentorial PNET

- Disease dissemination
- Unresectable tumours
- Residual tumours more than 1.5 cm^2 post-surgery

- High risk patient should undergo irradiation of the neuraxis followed by chemotherapy.
- Average risk patients can undergo craniospinal radiotherapy alone or craniospinal radiotherapy +/- chemotherapy followed by post-irradiation chemotherapy.

Follow up

- Brain MRI 3 monthly for the first 2 years, then 6 monthly for the next 3 years, then yearly thereafter.
- Concurrent spinal imaging should be done when clinically indicated for patients with previous spinal disease.
- Bone scans, CT scans and bone marrow biopsies should be conducted as indicated

Primary CNS Lymphoma

- It is an aggressive form of non-Hodgkin's lymphoma that develops within the brain, spinal cord, eye, or leptomeninges usually without evidence of systemic involvement.
- Non-immunosuppressed patients have a better prognosis than AIDS-related cases.
- If contrast enhanced MRI or contrast CT scan suggests primary central nervous system lymphoma (PCNSL), clinicians are advised to withhold the use of steroids if possible before diagnosis is established, since the imaging and histologic features of PCNSL can be profoundly affected by these drugs.

Treatment

Systemic Therapy

- HIV-positive patients should be safely started on ART

Medicine	Codes		Adult dose	Frequency	Duration
Methotrexate, vincristine, procarbazine & rituximab (R-MPV)	S	V	Methotrexate 3.5 g/m^2 IV D2 & D16 Vincristine 1.4mg (max 2mg) IV D2 & D16 Procarbazine 100mg/m^2 PO OD D7-d13 Rituximab 500mg/m^2 D1 & D15	4 weekly	
Methotrexate, temozolamide and rituximab (MTR)	S	V	Methotrexate 8g/m^2 IV D1 & D15 Temozolamide 150mg/m^2 PO OD D7-D11 Rituximab 3750mg/m^2 weekly starting on D3 of cycle 2 for 6 total doses.		

Radiotherapy

Radiotherapy may be given after systemic chemotherapy depending on the responsiveness of the disease to chemotherapy or if patient is not a candidate for systemic chemotherapy.

Primary Spinal Cord Tumours

Optimal management requires a **multidisciplinary team approach**. Early integration of palliative care and pain management specialists is **strongly recommended**

Treatment

- Surgery is the preferred treatment when the tumour is symptomatic Asymptomatic tumours especially grade I meningiomas and peripheral nerve sheath tumours, follow an indolent course and can be followed by observation without immediate intervention

- Radiotherapy is not recommended as primary therapy because of limited response, unknown histology without surgery and low radiotherapy tolerance of the spinal cord proper
- Adjuvant radiotherapy benefits are not clear, but it can be considered appropriate if:
    - Persistent symptoms after incomplete resection or biopsy for patients with asymptomatic, intramedullary, low-grade glioma
    - Incompletely resected myxopapillary ependymoma

Meningiomas

Meningiomas are extra-axial CNS tumours arising from the arachnoid cap cells in the meninges.

Treatment

- Asymptomatic patients with small tumours (<30 mm) can be observed with serial brain imaging until significant growth or symptoms are noted
- Symptomatic surgically accessible meningioma should be resected.
- Post-operative radiotherapy to enhance local control should be considered in the following cases:
    - Residual disease for a large asymptomatic grade I or II s
    - Asymptomatic grade II tumours
    - ALL grade III meningiomas including those with GTR

Follow up

- Malignant (grade 3) or recurrent meningiomas are followed more closely than grade I and II tumours.
- MRI every 3 months in year 1, then every 6-12 months for another 5 years
- Upon detection of recurrence,

- Resectable tumours should be excised followed by radiotherapy
- Non-surgical candidates should receive radiotherapy (if not previously given) or chemotherapy.
- Observation is an option if there is no clinical indication for treatment at recurrence.

Brain Metastases

The presenting signs and symptoms of metastatic brain lesions are similar to those of other mass lesions in the brain.

Treatment

- Can be surgery, chemotherapy and radiotherapy depending on histology, KPS and patient's choice.
- Upfront resection followed by radiotherapy is the standard of care for solitary brain metastases when possible or Stereotactic radiotherapy (if available)
- For multiple metastases whole brain radiotherapy is indicated.
- The standard regimens for Whole Brain Radiotherapy (WBRT) are 30 Gy in 10 fractions or 37.5 Gy in 15 fractions. For patients with poor neurologic performance, a more rapid course of RT can be considered (20 Gy, delivered in 5 fractions)
- Chemotherapy for chemo-sensitive tumours.

Head and Neck Cancers

General Notes

Head and neck cancers are a group of malignancies occurring above the clavicles but excluding the brain, base of skull and skin. They arise from the oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, nasal cavity, paranasal sinuses, salivary glands and thyroid.

Risk factors for head and neck cancers include alcohol intake, smoking, chewing or snuffing tobacco, previous head and neck malignancy, family history of malignancy, chronic irritants e.g. ill-fitting denture and practising oral sex.

This section is an overview of head and neck cancers in general. Management details of the more common malignancies namely laryngeal, nasopharyngeal and thyroid are outlined in this following section.

History and symptoms

- Painless mass
- Dysphagia and/or odynophagia.
- Hoarse voice
- Ear or tooth pain
- Loose teeth or ill-fitting dentures
- Epistaxis or nasal blockage
- Non-healing oral sores

Physical examination

A complete physical examination is paramount. Some signs that can be elicited include

- Primary site or neck mass
- Skin or mucosal ulceration
- Cranial nerve deficits
- Trismus
- Loss of weight

Diagnostic workup

- Core biopsy of accessible site- direct biopsy, endoscopic biopsy etc.
- Fine Needle Aspiration (FNA) cytology of neck masses.
- HPV DNA assay if indicated.

Staging workup

- FBC, U&E, LFT and HIV test.
- Pan-endoscopy
- CT scan head, neck, chest and abdomen (if available).
- If CT not available- CXR and USS neck, abdomen, and pelvis.
- Baseline speech, dental, swallowing, and nutrition evaluations.
- Baseline audiometry.

General Treatment

All patients with head & neck cancers should be discussed in a multidisciplinary team meeting (including pathologist, oncologist, surgeons, dentist, pharmacist, oncology nurse, radiologist, rehabilitation specialists and social worker) prior to treatment.

The following treatment is specific for squamous cell carcinomas of the head and neck region.

Stage	Treatment Options
Early (stage I & II)	Surgery or Radiotherapy
Locally advanced, resectable (III & IVA)	Surgery followed by radiotherapy Or chemo-radiation
Locally advanced, unresectable (IVB)	Definitive chemo-radiation (preferred) Or Induction chemotherapy followed by radiotherapy ± chemotherapy
Metastatic disease	Depends on performance status: • ECOG 0-1 Combination or single agent chemotherapy or surgery/RT/ chemo -radiation if limited metastases • ECOG 2 Single agent chemotherapy/ palliative RT or best supportive care • ECOG 3 Best supportive care

Surgery

The nature of the surgical procedure is determined primarily by the size of the tumour and the structures involved with the goal of achieving histologically negative resection margins. In general, a tumour is unresectable if the surgeon anticipates that all gross tumours cannot be removed. Typically, these tumours involve the cervical vertebrae, brachial plexus, and deep muscles of the neck or carotid artery. Ipsilateral neck dissection is recommended for patients undergoing surgery for the primary tumour with bilateral neck dissection recommended for lesions that approximate or cross the midline and those with bilateral node involvement.

Medicines

Chemotherapy Regimens Used

Medicine	Codes		Adult dose	Frequency	Duration
Chemoradiation					
High dose Cisplatin single agent	S	V	Cisplatin 100mg/m^2 IV D1, D22 & D43 during radiotherapy	3 weekly	
Cisplatin and 5-FU	S	V	Cisplatin 60mg/m^2 IV D1 5-FU 750mg/m^2 continuous infusion IV D1-D4 and D29-D32 of radiotherapy.	3 weekly	
Weekly Cisplatin	S	V	Cisplatin 35-40mg/m^2 iv D1 Weekly during radiotherapy	Weekly	
Combination chemotherapy in metastatic disease					
Cisplatin and 5-FU	S	V	Cisplatin 100mg/m^2 IV D1 5-FU 1000mg/m^2 continuous infusion D1-D4	3 weekly	As per oncologist
Cisplatin and paclitaxel	S	V	Cisplatin 75-100mg/m^2 IV D1 Paclitaxel 175mg/m^2 IV D1	3 weekly	As per oncologist
Single agent therapy					
Cisplatin	S	V	Cisplatin 100mg/m^2 iv D1	3 weekly	
Paclitaxel	S	V	Paclitaxel 175mg/m^2 IV D1	3 weekly	
5-FU	S	V	5-FU 1000mg/m^2 continuous infusion D1-D4.	3 weekly	
Capecitabine	S	V	Capecitabine 1000-1250mg/m^2 PO D1-D14	3 weekly	

Follow Up

The aim of follow up is early detection of recurrence, second primary malignancies as well as the sequelae of the disease and treatment received.

- History and physical examination including a complete head and neck exam with mirror and fibre-optic examination 3 monthly for 2 years then 6 monthly for 3 years then annually thereafter.
- Repeat pre- treatment baseline imaging within 6 months of treatment completion .
- Annual imaging for sites difficult to visualize on examination.
- Thyroid function tests every 6-12 months if the neck was irradiated.
- Dental evaluation for oral cavity and sites exposed to significant intra-oral radiation treatment.
- Nutritional, speech, swallowing evaluation and rehabilitation.

Laryngeal cancer

General note

Laryngeal cancer has a special importance because of its significant impact on voice, swallowing and quality of life. Risk factors include smoking tobacco, alcohol intake, deficiencies of iron, vitamin B12, and vitamin C.

History and symptoms

- hoarseness of voice
- Stridor
- Throat pain
- Dysphagia
- Odynophagia
- Otalgia
- Trismus.
- Neck mass

Physical examination.

- General examination- assess for respiratory distress and performance

status.

- Neck- assess for lymphadenopathy.
- Indirect laryngoscopy.

Diagnostic workup

- Nasopharyngolaryngoscopy and biopsy.
- Accessible abnormal lymph node(s) biopsy.

Staging workup

- FBC, U&E, LFTs, baseline TSH and HIV test.
- CT and/or MRI of the head and neck and chest x-ray
- Bronchoscopy (if clinically indicated).
- Dental assessment.
- Baseline speech, swallowing, and nutrition evaluations.
- Baseline audiometry

Treatment

All patients with laryngeal cancer should be discussed in a multidisciplinary team meeting (including pathologist, clinical oncologist, surgeons, dentist, pharmacist, oncology nurse, radiologist, speech therapist, physiotherapist and social worker) prior to treatment.

Glottic larynx

Stage	Treatment options
I-II	• Radiotherapy (preferred) • Surgery + adjuvant radiotherapy for patients with high-risk features- close or positive margins, lymph node metastases and extranodal extension. • Laser ablation
III-IV	• Surgery followed by radiotherapy or che moradiation depending on features of pathological assessment • Concurrent chemoradiation • Induction chemotherapy followed by radiotherapy. • Palliative surgery/ radiotherapy/ systemic chemotherapy for patients with metastatic disease aimed at quality-of-life improvement

Supraglottic larynx

Stage	Treatment
I-II	• Radiotherapy • Chemoradiation • Surgery +/- adjuvant chemoradiotherapy depending on features of pathological assessment.
III-IV	• Surgery followed by adjuvant radiotherapy +/- concurrent chemotherapy. • Chemoradiation • Induction chemotherapy followed by radiotherapy. • Radiation alone if pat ient is not a candidate for concurrent systemic chemotherapy and radiotherapy • Palliative surgery/ radiotherapy/ systemic chemotherapy for patients with metastatic disease aimed at quality of life improvement

Supraglottic larynx

Stage	Treatment
I-II	• Radiotherapy • Chemoradiation • Surgery +/- adjuvant chemoradiotherapy depending on features of pathological assessment.
III-IV	• Surgery followed by adjuvant radiotherapy +/- concurrent chemotherapy. • Chemoradiation • Induction chemotherapy followed by radiotherapy. • Radiation alone if pat ient is not a candidate for concurrent systemic chemotherapy and radiotherapy • Palliative surgery/ radiotherapy/ systemic chemotherapy for patients with metastatic disease aimed at quality of life improvement

Medicines

Chemotherapy Regimens

Medicine	Codes	Adult dose	Frequency	Duration
Chemoradiation				
High dose Cisplatin single agent.	S V	Cisplatin 100mg/m^2 IV D1, D22 and D43 during radiotherapy.	3 weekly	3
Weekly cisplatin	S V	Cisplatin 35-40mg/m^2 IV D1	weekly	
Cisplatin and 5-FU	S V	Cisplatin 60mg/m^2 IV D1 5-FU 750mg/m^2 continuous infusion IV D1- D4 and D29-D32 of radiotherapy.	3 weekly	

Induction and palliative chemotherapy					
Cisplatin and 5 FU	S	V	Cisplatin 100mg/m2 IV D1 5-FU 1000mg/m2 continuous IV infusion D1-D4	3 weekly	4
Docetaxel + Cisplatin and 5-FU	S	V	Docetaxel 75mg/m^2 IV D1 Cisplatin 75m/m^2 IV D1 5-FU 1000mg/m^2 continuous iv infusion D1-D4	3 weekly	4

Nasopharyngeal cancer

General note

The diagnosis of nasopharyngeal carcinoma depends on a thorough history and physical examination. Risk factors include smoking tobacco, heavy alcohol consumption, EBV infection, exposure to wood and salted fish consumption.

History and symptoms

- Nasal symptoms-bleeding, obstruction and discharge
- Ear symptoms- pain, tinnitus and discharge
- Headache
- Neck swelling/mass

Physical examination

- Oral and nasal examination.
- Neck examination: neck lymph node involvement is often bilateral
- Cranial nerve palsies.
- Symptoms of metastases e.g. bone pain, chest symptoms.

Diagnostic work up

- Nasopharyngoscopy and biopsy
- Epstein Barr virus (EBV) titers including immunoglobin A (IgA) and IgG antibodies to the viral capsid antigen where available

Staging workup

- FBC, U&E, LFT and HIV test.
- MRI scan head and neck to assess intracranial and base of skull extension (preferred)
- CT scan head and neck (base of skull to thoracic inlet).
- CT scan chest, abdomen, and pelvis. (USS Abdomen & pelvis plus chest X-ray if resources are limited).

Treatment

All patients with nasopharyngeal cancer should be discussed in a multidisciplinary team meeting (including pathologist, oncologist, surgeons, dentist, pharmacist, oncology nurse, radiologist, speech therapist and social worker) prior to treatment.

Radiation therapy is the mainstay of treatment with or without chemotherapy. Surgical therapy for these patients is often utilized for biopsy specimen collection and treatment of locally recurrent disease.

Stage	Radiotherapy	Chemotherapy	Surgery
I	Radiotherapy alone		
II	Chemoradiation	Concurrent chemotherapy	
III	• Chemo-radiation followed by adjuvant chemotherapy • Chemoradiation after induction chemotherapy	• Adjuvant chemotherapy • Induction chemotherapy	
IVA	• Chemo-radiation followed by adjuvant chemotherapy • Chemoradiation after induction chemotherapy	• Adjuvant chemotherapy • Induction chemotherapy	
IVB	• Palliate radiotherapy • Radical radiotherapy retreatment if feasible.	• Palliative chemotherapy	
Recurrent disease	• Palliate radiotherapy • Radical radiotherapy retreatment if feasible	• Palliative chemotherapy	Resection if amenable to surgery.

Medicine	Codes	Adult dose	Frequency	Duration
Chemoradiation				
High dose Cisplatin single agent.	S V	Cisplatin 100mg/m^2 IV D1, D22 and D43 during radiotherapy.	3 weekly	3
Weekly cisplatin	S V	Cisplatin 35-40mg/m^2 IV D1	weekly	
Cisplatin and 5-FU	S V	Cisplatin 60mg/m^2 IV D1 5-FU 750mg/m^2 continuous infusion IV D1- D4 and D29-D32 of radiotherapy.	3 weekly	
Induction and palliative chemotherapy				
Cisplatin and 5 FU	S V	Cisplatin 100mg/m2 IV D1 5-FU 1000mg/m2 continuous IV infusion D1-D4	3 weekly	4
Docetaxel + Cisplatin and 5-FU	S V	Docetaxel 75mg/m^2 IV D1 Cisplatin 75m/m^2 IV D1 5-FU 1000mg/m^2 continuous iv infusion D1-D4	3 weekly	4

Para-nasal sinuses

General Note

The paranasal sinuses consist of the ethmoid, frontal, maxillary, and sphenoid sinuses. Tumours commonly occur in the maxillary and ethmoid sinuses. Histologic subtypes include squamous cell carcinoma, adenocarcinoma, esthesioneuroblastoma (olfactory neuroblastoma) minor salivary gland s, sinonasal undifferentiated carcinoma (SNUC), small cell or sinonasal neuroendocrine carcinoma (SNEC), melanoma and sarcoma.

History and symptoms

- Central/facial headaches
- Pain to the nasal or retrobulbar region
- Nasal blockage or discharge
- Epistaxis
- Impaired sensation of the cheek

- Ill-fitting dentures
- Impaired vision

Physical examination

- General examination.
- Ear, eye, nose, and oral cavity assessment
- Facial and neck masses.
- Cranial nerve deficits
- Diplopia
- Paresthesia
- Trismus

Diagnostic workup

- Core biopsy for histology
- FNA neck lymph nodes

Staging workup

- FBC, U&E, LFT and HIV test.
- CT or MRI base of skull to clavicle
- CT scan chest & abdomen as clinically indicated (if available) or chest x-ray and USS abdomen.
- Pan-endoscopy if indicated
- Dental assessment
- Nutritional, speech and swallowing evaluation

Treatment

All patients with para-nasal sinus tumours should be discussed in a multidisciplinary team meeting (including pathologist, oncologist, surgeons, dentist, pharmacist, oncology nurse, radiologist, speech therapist and social worker) prior to treatment.

Stage	Surgery	Radiotherapy/ chemotherapy
TI-T2, N0 (except adenoid cystic)	Complete surgical resection If margins negative proceed to follow up. If close or positive margins, consider re-resection and adjuvant radiotherapy	Adjuvant radiotherapy or chemoradiation for close or positive margins, peri-neural or LVSI
TI-T2, N0 adenoid cystic	Complete surgical resection	Adjuvant radiotherapy (preferred) *Consider observation for margin negative and no peri-neural spread.
T3-T4a, N0	Complete surgical resection	Adjuvant radiotherapy or chemoradiation
T1-T4a, N+	Surgical resection + neck dissection	Adjuvant radiotherapy or chemoradiation
T4b, N0-3		Definitive radiotherapy Or chemoradiation
M1		• RT/chemoradiation • Induction chemotherapy followed by radiotherapy • Palliative chemotherapy • Palliative radiotherapy • Best supportive care

Medicines

Medicine	Codes	Adult dose	Frequency	Duration
Chemoradiation				
High dose Cisplatin single agent.	**S V**	Cisplatin 100mg/m^2 IV D1, D22 and D43 during radiotherapy.	3 weekly	
Weekly cisplatin	**S V**	Cisplatin 35-40mg/m^2 IV D1	weekly	
Cisplatin and 5-FU	**S V**	Cisplatin 60mg/m^2 IV D1 5-FU 750mg/m^2 continuous infusion IV D1 - D4 and D29 -D32 of radiotherapy.	3 weekly	
Systemic chemotherapy				
Cisplatin and paclitaxel	**S V**	Cisplatin 75-100mg/m^2 IV D1 Paclitaxel 175mg/m^2 IV D1	3 weekly	
Cisplatin and 5 FU	**S V**	Cisplatin 100mg/m2 IV D1 5-FU 1000mg/m2 continuous IV infusion D1-D4	3 weekly	

Follow Up

The aim of follow up is early detection of recurrence, second primary malignancies as well as the sequelae of the disease and treatment received.

- History and physical examination including a complete head and neck exam and fibre-optic visualisation if indicated 3 monthly for 2 years then 6 monthly for 3 years then annually thereafter.
- Repeat pre- treatment baseline imaging within 6 months of treatment completion.
- Annual imaging for sites difficult to visualize on examination
- Thyroid function tests every 6-12 months if the neck was irradiated
- Dental evaluation for oral cavity and sites exposed to significant intra-oral radiation treatment.
- Nutritional, speech, swallowing evaluation and rehabilitation.

Salivary gland tumours

General note

The salivary glands consist of the three large, paired major glands-parotid, submandibular, and sublingual and many smaller, minor glands located throughout the upper aero-digestive tract. 80% of parotid gland s are benign whereas 50% of submandibular and 80% of minor salivary glands are malignant. Histologic subtypes include muco-epidermoid, acinic cell, adenoid cystic carcinoma, myoepithelial tumours and rarely squamous cell carcinomas.

History and symptoms

- Rapidly enlarging painless mass
- Facial pain
- Dysphagia
- Loss of weight

Physical examination

- General examination
- Oral cavity and dental examination

- Cervical lymphadenopathy
- Cranial nerve palsies
- Skin involvement
- Trismus
- Nutritional assessment

Diagnostic workup

- FNA and cytology
- Image guided biopsy prior to surgery only when appropriate
- CT or MRI with contrast of skull base to clavicle (were appropriate)

Staging workup

- FBC, U&E, LFT and HIV test.
- CT chest and abdomen (if clinically indicated)
- Dental evaluation
- Nutrition, speech and swallowing assessment.
- Smoking cessation

Treatment

All patients with salivary gland tumours should be discussed in a multidisciplinary team meeting (including pathologist, oncologist, surgeons, dentist, pharmacist, oncology nurse, radiologist, speech therapist, nutritionist, and social worker) prior to treatment.

Stage	Surgery	Adjuvant therapy
T1-2; N0	• Complete surgical resection	• Adjuvant radiotherapy for patient with high risk features*
T3-4a N0	• Surgical resection +/- neck nodal dissection	• Adjuvant radiotherapy or chemoradiation.
T4b	• Not recommended	• Definitive radiotherapy Or chemoradiation
Any T N+ M0	• Surgery and neck nodal dissection	• Adjuvant radiotherapy or chemoradiation.

Any T any N M1	• Selected cases consider primary resection & mastectomy.	• Palliative radiotherapy • Palliative syste mic chemotherapy • Androgen receptor therapy e.g., Bicalutamide if AR positive • Trastuzumab if HER2 positive • Best supportive care

* High risk features include low grade tumours with spillage or perineural invasion or intermediate or high-grade adenoid cystic tumours, positive margins, nodal metastases, extranodal extension

#Patients with the following adverse features should get adjuvant radiotherapy or chemoradiation-e adenoid cystic, intermediate-high grade, close or positive margins, neural or peri-neural invasion, lymph nodes metastases and LVI

Follow Up

The aim of follow up is early detection of recurrence, second primary malignancies as well as the sequelae of the disease and treatment received.

- History and physical examination including a complete head and neck exam with mirror and fibre-optic examination 3 monthly for 2 years then 6 monthly for 3 years then annually thereafter.
- Repeat pre- treatment baseline imaging within 6 months of treatment completion
- Annual imaging for sites difficult to visualize on examination
- Thyroid function tests every 6-12 months if the neck was irradiated
- Dental evaluation for oral cavity and sites exposed to significant intra-oral radiation treatment
- Nutritional, speech, swallowing evaluation and rehabilitation

Thyroid cancer

General note

Thyroid cancer can occur at any age but is more common after the age of 30 years. Its aggressiveness increases significantly with age. It is estimated that a significant percentage of the general population will have a thyroid nodule at some point in life and it's important to note that the majority are benign. Risk factors for thyroid malignancies include prior radiation exposure and genetic syndromes e.g. multi endocrine neoplasia (MEN).

History and symptoms.

- Incidental finding
- Neck mass
- Local pain
- Hoarse voice
- Dysphagia
- Symptoms from distant metastases
    - Bone pain/ pathological fracture
    - Cough
    - Dyspnea

Physical examination

- Neck mass
- Cervical lymphadenopathy
- Signs of thyroid hormonal imbalance.
- Respiratory distress
- Tenderness over involved bones

Indications for FNA of a thyroid nodule

- Nodule > 5mm, with high-risk features such as history of thyroid cancer or radiation exposure, family history for thyroid cancer, MEN syndrome calcitonin > 100pg/ml
- Suspicious USS characteristics include:
    - Internal hypervascularity
    - Irregular borders

- Nodule > 1cm, with microcalcifications or solid and hypoechoic
- Nodule > 1.5cm, if iso- or hyper-echoic
- Nodule > 2cm, mixed cystic and solid

- Nodules that are fixed to adjacent structures or associated with regional lymphadenopathy
- Symptomatic nodules (pain, hoarseness, and/or dysphagia)

Diagnostic workup

- Fine needle aspiration and cytology

Staging Workup

- FBC, U&E, LFT, HIV test and TFTs
- Indirect or fiberoptic laryngoscopy
- MRI scan neck (USS thyroid and neck)
- Radioisotope scan post-surgery

General Treatment

All patients with thyroid cancer should be discussed in a multidisciplinary team meeting (including pathologist, oncologist, surgeons, radiologist, nuclear medicine specialists, pharmacist, oncology nurse, speech therapist and social worker) prior to treatment.

Surgery

Procedure	Indications
Total thyroidectomy	• >4cm in diameter • Extra-thyroidal extension • Cervical lymph node metastases • Poorly differentiated disease • Prior radiation exposure • Bilateral nodularity • Known distant metastases
Unilateral lobectomy with en bloc resection of	• ≤4cm • Modified radical neck dissection should be done for regional lymph node metastases

	• No extra-thyroidal extension • No cervical lymph node metastases • No prior radiation exposure • No distant metastases

Note: Thyroidectomy should be performed in patients with distant metastases to permit treatment with radioiodine, which can still be curative.

Post-surgery histology must assess and report on:

- Tumour size
- Histology and grade
- Margin status
- Extrathyroidal extension
- Capsule rupture
- Lymph node involvement and extra-nodal extension
- Lymphovascular invasion
- Perineural invasion

Histologic types

1. Differentiated: Papillary, follicular, hurthle cell
2. Medullary carcinoma
3. Anaplastic

Adjuvant therapy

Treatment	Indications
Radioactive iodine (I-131, RAI) Absolute indications	Ablation of residual normal thyroid tissue Gross extra-thyroidal extension Primary >4cm Extensive vascular invasion Post-operative unstimulated thyroglobulin > 5 -10ng/L Distant metastases Note: For differentiated thyroid cancers.
Radioactive iodine (I-131, RAI) Relative indications	Microscopic residual disease 2-4cm Minimal vascular invasion Post-operative unstimulated thyroglobulin <5 -10ng/ml

Thyroid Hormone Suppression	After initial thyroidectomy, whether or not radioiodine therapy is administered, thyroid hormone (T4 [levothyroxine]) therapy is required in most patients to prevent hypothy roidism and to minimize potential TSH stimulation of growth
External beam radiotherapy	Poor iodine uptake Gross or microscopic residual disease Visible extra-thyroidal extension Locally recurrent disease not amenable to surgery or radioiodine therapy

Systemic therapy

This can be considered for s that are not surgically resectable, not responsive to iodine-131 in patients who are not amenable to EBRT with significant disease progression.

Response rates to conventional cytotoxic chemotherapy in metastatic differentiated thyroid disease are low. Single agent doxorubicin can be considered.

Targeted therapies **lenvatinib, sunitinib, everolimus** and **sorafenib** are recommended for RAI-refractory differentiated thyroid cancer patients.

Follow up

- History, physical examination, serum TSH, thyroglobulin and antithyroglobulin antibodies at 6 and 12 months after treatment then annually if disease free.
- CT or MRI (USS neck) as clinically indicated
- Thyrotropin (TSH)-stimulated radio-iodine whole body imaging in high-risk patients, patients with previously RAI- avid metastases or abnormal thyroglobulin levels, stable or rising anti-thyroglobulin antibodies or abnormal ultrasound during follow –up.

Medullary Thyroid Carcinoma

Workup of medullary carcinoma includes measurement of baseline serum calcitonin and CEA levels. Serum calcium and screening for

phaeochromocytoma are also performed to rule out multiple endocrine neoplasia syndromes- MEN 2A and 2B. Where available, the patients are also screened for RET proto-oncogene mutations.

Treatment

A. For tumours ≥1cm in diameter or bilateral thyroid disease, treatment options are as follows:
    - Total thyroidectomy with bilateral central neck dissection (level VI)
    - Therapeutic ipsilateral or bilateral modified neck dissection for clinically or radiologically detected disease (levels II-V)
    - EBRT may be considered for grossly incomplete resection when additional resection is not possible but adjuvant EBRT is rarely recommended

    Post-operative levothyroxine should be given to normalize TSH.

B. For tumours <1.0cm in diameter and unilateral thyroid disease, total thyroidectomy should be confirmed with consideration of level VI node dissection.

C. Systemic therapy

The oral kinase inhibitors vandetanib and cabozantinib, where available, may be used in the treatment of unresectable locally advanced or metastatic disease.

Follow up

- History and physical examination 3 months post-surgery
- Serum calcitonin and Carcinoembryonic antigen (CEA) assay
    - If elevated- neck USS and bone scan & MRI scan.
- For patients with MEN2B or 2A annual biochemical screening for phaeochromocytoma and for patients with MEN2A screening for hyperthyroidism is performed as well.

Anaplastic Thyroid Carcinoma

Anaplastic carcinomas are aggressive undifferentiated s with a disease-specific mortality of almost 100%. Fifty percent of these patients have a previous or co-existent differentiated carcinoma. Iodine deficiency is associated with anaplastic thyroid carcinoma with 80% of patients having a history of goiter.

Extent of disease especially in the larynx, trachea and neck, should be assessed thoroughly before attempts at resection. Airway patency should be assessed throughout the patient's course. Most patients have unresectable or metastatic disease at presentation. Total thyroidectomy with attempted complete resection has only been found to improve survival in a few patients with small s entirely confined to the thyroid or readily excised structures.

External beam radiotherapy (EBRT) may be used to improve local control and for palliation (e.g. to prevent asphyxiation) or for management of isolated skeletal metastases.

Ocular surface squamous cell neoplasia

General note

Ocular surface squamous neoplasia (OSSN) consists of a wide range of conjunctival and corneal lesions ranging from dysplastic lesions to invasive squamous cell carcinoma. Risk factors include immunosuppression chiefly from HIV infection, HPV infection, tobacco smoking and ultraviolet (UV-B) radiation.

History and symptoms

- Appearance of a mass in the eye
- Ocular irritation
- Painful eye
- Visual disturbances
- History of precancerous lesion

Physical examination

- General examination- performance status, lymphadenopathy, and facial swelling.
- Examine for orbital masses, ulcerations and facial disfigurement- abnormal appearance, size, shape or location of pigmented or non-pigmented tissue with aberrant surrounding vasculature
- Ophthalmological examination of both eyes including snellen visual acuity, pupil reactivity, tonometry, and slit lamp biomicroscopy (fundoscopy) should be done.
- Tumor depth and presence of scleral penetration can be detected by ultrasound biomicroscopy (UBM)

Diagnostic Work Up

- Biopsy for histological assessment.

Staging Workup

- FBC, U&E, LFT and HIV test (+/-CD4 count & viral load)
- Baseline CXR and USS abdomen (for locally advanced disease)
- Where available fine cut orbit and neck CT/MRI should be included

Treatment

ALL patients with OSSN must be discussed in a multidisciplinary team meeting (including, pathologist, ophthalmologist, neurosurgeons if needed, clinical oncologist, pharmacist, oncology nurse, radiologist, HIV specialist (if needed), rehabilitation specialists and social worker) prior to treatment. Surgery and radiotherapy are the essential components of treatment. Chemotherapy is used in select cases.

Stage	Surgery	Radiotherapy	Other interventions
1	Complete surgical excision with minimum of 2 to 3 mm margin	Brachytherapy with Strontium-90 within 24hrs of surgery	Adjuvant therapies include Cryotherapy Topical chemotherapy e.g. Mitomycin C, 5FU and interferon alpha 2b
IIA	Removal of the with a 3mm margin, lamella sclerectomy and keratectomy Enucleation is an option where the above is not possible.	Adjuvant therapy with beta plaque applications to the excision bed	
IIB	Enucleation is recommended. (best done performed with frozen section control to ensure negative margins)	External beam radiotherapy +/- concurrent chemotherapy is indicated for close or positive margins post enucleation Definitive chemoradiation may be used in advanced, unresectable, or recurrent lesions.	
III	Enucleation or exenteration adjuvant RT is recommended with	Adjuvant external beam radiotherapy +/- chemotherapy followed by external beam radiotherapy. Definitive chemoradiation may be used in advanced, unresectable, or recurrent lesions.	
IV	Palliative surgery to improve quality of life used	Palliative radiotherapy can be used for large unsightly, painful, bleeding or septic lesions and metastasis to other extra orbital sites	Palliative chemotherapy Give appropriate supportive treatment

Medicines

Medicine	Codes		Adult dose	Frequency	Duration
Chemoradiation					
High dose Cisplatin single agent.	**S**	**V**	Cisplatin 100mg/m^2 IV D1, D22 and D43 during radiotherapy.	3 weekly	
Weekly cisplatin	**S**	**V**	Cisplatin 35-40mg/m^2 IV D1 during radiotherapy	Weekly	
Cisplatin and 5-FU	**S**	**V**	Cisplatin 60mg/m^2 IV D1 5-FU 750mg/m^2 continuous infusion IV D1- D4 and D29-D32 of radiotherapy.	3 weekly	
Systemic chemotherapy					
Cisplatin and paclitaxel	**S**	**V**	Cisplatin 75-100mg/m^2 IV D1 Paclitaxel 175mg/m^2 IV D1	3 weekly	6
Cisplatin and 5 FU	**S**	**V**	Cisplatin 100mg/m2 IV D1 5-FU 1000mg/m2 continuous IV infusion D1-D4	3 weekly	6
Carboplatin and paclitaxel	**S**	**V**	Carboplatin AUC5/6 IV D1 Paclitaxel 175mg/m^2 IV D1	3 weekly	6

Follow up

- Close monitoring for tumor recurrence or new lesions in the affected or contralateral eye is paramount.
- First review is 6 weeks post-treatment then 3 monthly for the first 2 years, 6 monthly for year 3-5years and annually thereafter.

Lung cancer

General note

Lung is a leading cause of cancer related death in the world and ranks 9th in Zimbabwe. The main risk factor for lung cancer is tobacco smoking.

History and symptoms

- Weight loss
- Cough
- Dyspnoea, haemoptysis
- Chest pain
- Hoarseness of voice (left recurrent laryngeal nerve involvement)
- Smoking status.

Physical examination

- Performance status
- Finger Clubbing
- Lymphadenopathy
- Signs of pleural effusion
- Signs of superior vena cava syndrome
- Superior sulcus (Pancoast) tumor triad = shoulder pain, brachial plexus palsy, and Horner's syndrome.
- Since some of the symptoms of TB are similar to those of lung cancer, one should always think of lung cancer as a potential differential.
- In small cell carcinoma- paraneoplastic syndromes: SIADH, ACTH production syndrome, and Eaton–Lambert syndrome. Therefore, assess for symptoms of paraneoplastic syndromes

Diagnostic workup

- For central lesions, perform bronchoscopy and biopsy.
- For peripheral lesions, perform image-guided biopsy.
- Sputum cytology (65–80% sensitivity).
- Thoracentesis for cytology (if pleural effusion present)
- Immunohistochemistry (if needed).
- Genetic testing where applicable.

Non-Small Cell Lung Cancer (NSCLC)

Staging workup

- Laboratories: FBC, U&E, LFTs, LDH and HIV test.
- CT scan chest and abdomen with contrast.
- MRI of brain for:
    - Lymph node positive non-squamous.
    - All stage III–IV patients.
    - For patients with neurologic symptoms.
- Pulmonary function testing for pre-surgical and/or pre-radiotherapy evaluation.

- Pan-endoscopy for all smokers to exclude secondary malignancy.
- Smoking cessation advice, counselling and pharmacotherapy.
- Genetic mutations (EGFR, ALK, BRAF) and PD-L1 score if available.

Treatment.

All lung cancer patients should be discussed in a multidisciplinary team meeting (including pathologist, clinical oncologist, surgeon, pharmacist, oncology nurse, radiologist, physiotherapist and social worker) prior to treatment.

Stage	Surgery	Radiotherapy	Chemotherapy
Stage I –II (operable)	• Lobectomy preferred to pneumonectomy if anatomically feasible. • LN sampling or resection is indicated.	For close/+margin, re - resect or consider adjuvant radiotherapy	Adjuvant chemotherapy if: Node positive, >4 cm and completely resected T3N0
Stage I –II (Marginally operable)	Neoadjuvant chemotherapy then consider surgery as stage I-II as above.	For close/+margin, re - resect or consider adjuvant radiotherapy	Neoadjuvant and adjuvant chemotherapy.
Stage I –II (inoperable)		• Definitive radiotherapy +/ - concurrent chemotherapy is indicated. • If patient can tolerate it, give chemotherapy (sequential or, concurrent) if T3N0 or N1.	Chemotherapy can be give sequentially or concurrently with radiotherapy.
Stage IIIA (operable or marginally operable)	Consider surgery after neoadjuvant chemotherapy or chemoradiation. Surgery as above	• Concurrent chemoradiation, restage then consider surgery +/- adjuvant chemotherapy. • For patient who did not receive neoadjuvant	Chemotherapy alone restage then consider surgery Chemotherapy after surgery for high-risk feature*

		radiotherapy consider post - surgery radiotherapy if high risk feature present.*	
Stage IIIA (inoperable) / IIIB		• Concurrent chemoradiation. • If unacceptable risk of pneumonitis with upfront RT, consider induction chemo for down - staging then	• Adjuvant chemotherapy post chemoradiation. • Induction chemotherapy

* close margins (<5 mm), positive margin, nodal extra capsular nodal extension and or N2 disease

Medicines

Medicine	Codes		Adult dose	Frequency	Duration
Systemic/palliative chemotherapy					
Cisplatin and docetaxel	**S**	**V**	Cisplatin 75mg/m^2 IV D1 Docetaxel 75mg/m^2 IV D1	4 weekly	8
Cisplatin and etoposide	**S**	**V**	Cisplatin 100mg/m^2 IV D1 Etoposide 100mg/m^2 IV D1-D3	4 weekly	8
Carboplatin and paclitaxel	**S**	**V**	Carboplatin AUC 6 D1 Paclitaxel 175mg/m^2 D1	3 weekly	
Chemoradiation					
Paclitaxel and carboplatin	**S**	**V**	Paclitaxel 45-50mg/m^2; Carboplatin AUC 2	Weekly	

Consider targeted therapy and immunotherapy when available

Small Cell Lung Cancer (SCLC)

Staging workup

- FBC, U&E, LFTs, LDH and HIV test.
- CT scan chest and abdomen with contrast.

- MRI of brain.
- Pulmonary function testing for pre-surgical and/or pre-radiotherapy evaluation.
- Smoking cessation advice, counselling and pharmacotherapy.

Treatment.

All lung cancer patients should be discussed in a multidisciplinary team meeting (including pathologist, oncologist, surgeon, pharmacist, oncology nurse, radiologist and social worker) prior to treatment.

Stage	Surgery	Radiotherapy	Chemotherapy
Limited stage	For cT1 -2N0 disease with negative mediastinoscopy consider surgery.	Concurrent chemoradiation if complete response or near complete response consider prophylactic cranial irradiation.	Chemotherapy can be concurrent or give alone.
Extensive stage		Palliative radiotherapy to symptomatic sites For patients with partial response or complete response to chemotherapy, consider prophylactic cranial irradiation	Palliative chemotherapy.

Medicines

Medicine	Codes	Adult dose	Frequency	Duration
Cisplatin and etoposide	S V	Cisplatin 75mg/m^2 D1 Etoposide 100mg/m^2 D1-D3	4 weekly	8
Cisplatin and etoposide	S V	Cisplatin 25mg/m^2 D1-D3 Etoposide 100mg/m^2 D1	3 weekly	8

Carboplatin and etoposide.	S	V	Carboplatin AUC5/6 D1 Etoposide 100mg/m^2 D1-D3	Weekly	8

Follow Up

- History and physical examination every 3-4 months for 2 years.
- CXR every 3–4 months for 2 years, then every 6 months for 3 years, then annually
- CT scan chest annually.

Breast Cancer

General Note

Breast cancer is the second most common cancer in females in Zimbabwe. Family history of breast cancer is important, particularly if a patient is premenopausal. High risk families need genetic counselling. Note details of menstrual history, parity, and use of hormonal therapy.

Signs and Symptoms

- Breast lump or lump in the axilla
- Breast discomfort or pain
- Change in size or shape of the breast
- Spontaneous nipple discharge.
- Nipple inversion
- Skin puckering or rash
- Redness of the skin

Physical Examination

- Location of tumor in breast
- Size and consistency
- Fixation to skin or deep tissues
- Peau d'orange or ulceration of skin
- Nipple changes- nipple retraction, inversion
- Axillary and supraclavicular nodes
- Signs of possible distant metastasis – hepatomegaly, pleural

effusion etc.
- Opposite breast findings.

Diagnostic work-up

Whenever possible, a breast cancer diagnosis should be achieved by triple assessment:

- Detailed clinical examination
- Breast ultrasound scan and/or mammogram
- Pathologic diagnosis by core needle biopsy and/or fine needle aspiration

If imaging is not available and the patient has a palpable lump, a core needle or FNA biopsy can be done. If clinically suspicious without a palpable lump, refer to tertiary institution for further assessment and management. If asymptomatic refer for triple assessment. As soon as you diagnose breast cancer refer for specialist care.

Staging Work-Up

Pathology Review

Histology report of core needle biopsy should reveal:

- Histological subtype
- Grade of (Bloom-Richardson-Scarff score)
- Lymphovascular space invasion
- Hormone receptor status
- Her2-neu overexpression

Blood Tests

- FBC, U&E, LFT and HIV screen

Imaging

- CT scan chest, abdominal + pelvic with contrast (if available)
- USS abdomen + pelvis and chest x-ray +/- skeletal survey.
- For stage III and above include bone scan (if available)

Treatment

All breast cancer patients should be discussed in a multidisciplinary team meeting (including pathologist, clinical oncologist, surgeon, pharmacist, oncology nurse, radiologist and social worker) prior to treatment.

Stage	Surgery	Radiotherapy	Chemotherapy
0- DCIS	- Total mastectomy +/ - sentinel lymph node biopsy OR - Wide local excision to negative margins +/- sentinel lymph node biopsy +/- whole breast radiation therapy	Adjuvant w hole breast radiotherapy is an option	
0- LCIS	- Classic LCIS- counselling regarding risk reduction +/- tamoxifen - Pleomorphic LCIS- perform surgical excision and if LCIS without invasive cancer then manage as above. - If DCIS or invasive cancer is noted then manage accordingly	-	-Tamoxifen for chemopreventio n
I	- Modified radical mastectomy with level II axillary node dissection or modified radical mastectomy with sentinel lymph node biopsy (if clinically node negative) OR - Wide local excision to negative surgical margins (no ink at) with level II axillary node dissection or sentinel lymph node biopsy (if clinically node negative)	-Adjuvant Radiotherapy if breast conservative surgery is done.	Adjuvant hormone and or chemotherapy if presence of high risk features *
II	As for stage I	Adjuvant Radiotherapy if breast conservative surgery is done OR - Radiotherapy if high risk features ψ	Adjuvant chemotherapy and hormone therapy depending on the prognostic factors Φ
III	As for stage 1 unless if T3/T4 or clinical N2 or N3 disease which requires neoadjuvant chemotherapy prior to surgery.	Adjuvant r adiotherapy if breast conservative surgery is done OR Radiotherapy if high risk features ψ	Adjuvant chemotherapy if neoadjuvant chemotherapy was not given plus hormonal therapy

IV	Toilet mastectomy if required or metastatectomy in rare instances following an MDT discussion.	Palliative radiotherapy to - whole breast if necessary - metastatic sites e.g. bone, spinal cord	Palliative hormonal therapy +/ - chemotherapy

Footnotes

High risk features: high grade disease, lymphovascular invasion, high Ki-67, high recurrence score on gene testing e.g. Mammaprint or Oncotype DX.

High risk features: high grade disease, positive LVSI, positive margins, positive lymph nodes.

Prognostic Factors; **Patient related factors** – age, menopausal status, comorbid conditions, family history or BRCA mutations, previous treatments. **Disease related factors-** tumour size, nodal status, grade , Ki-67, Recurrence score, hormonal status, Her2- neu status.

Medicines

Medicine	Codes	Adult dose	Frequency
Doxorubicin and Cyclophosphamide (4) followed by Docetaxel (4)	S V	Doxorubicin 60mg/m^2 IV Cyclophosphamide 600mg/m^2 Docetaxel 60-80mg/m^2	3 weekly
Doxorubicin and Cyclophosphamide (4) followed by weekly paclitaxel (12)	S V	Doxorubicin 60mg/m^2 IV and Cyclophosphamide 600mg/m^2 IV followed by Paclitaxel 80mg/m^2 IV weekly	3 weekly weekly
Doxorubicin and Cyclophosphamide (4) followed by Paclitaxel (4)	S V	Doxorubicin 60mg/m^2 IV and Cyclophosphamide 600mg/m^2 followed by Paclitaxel 175mg/m^2 IV 3 weekly	3 weekly
Cyclophosphamide /Doxorubicin/ 5-FU (CAF)	S V	Cyclophosphamide 600mg/m^2 IV Doxorubicin 60mg/m^2 IV 5- FU- 600mg /m^2 IV	3 weekly
Cyclophosphamide / methotrexate/ 5-FU (CMF)	S V	Cyclophosphamide 600mg/m^2 IV Methotrexate 40mg/m^2 IV 5- FU 600mg /m^2 IV	3 weekly

*Consider dose dense chemotherapy were appropriate

Other Therapies

Medicine	Codes		Adult dose	Frequency	Duration
Trastuzumab	S	V	600mg sc.	Every 3 weeks	1 year
Capecitabine	S	V	1000-1250mg/m^2 PO BD D1-D14	Every 3 weekly	
Navelbine	S	V	6mg/m2	Weekly	
Carboplatin	S	N	AUC 5-6	3 weekly	
Tamoxifen	S	V	20mg PO OD	Daily	5-10 yrs.
Anastrozole	S	V	1mg PO OD	Daily	5yrs.
Letrozole			2.5mg PO OD	Daily	5 yrs.

Follow Up

Monthly self-exam.

History and physical examination every 3 months for 1–2 years, then every 6 months for 5 years, then annually.

- Breast USS, mammograms and MRI (where available) annually.
- Imaging and lab investigations not indicated in the absence of signs and symptoms of recurrence.
- Median time to breast cancer recurrence is 5–7 years for women receiving adjuvant hormonal and/or chemotherapy, but is shorter for triple negative breast cancers (<3 years).
- Women on tamoxifen- annual gynecological assessment if uterus is present.
- Active lifestyle, healthy diet, limited alcohol intake and achieving/maintaining an ideal body weight (BMI 20-25) may lead to optimal breast cancer outcomes

Esophageal and GEJ cancers

General Note

Esophageal cancer accounts for 5% of all GI cancers. It is the sixth leading cause of death from cancer in Zimbabwe. Incidence increases with age and peaks in sixth to seventh decade.

History and symptoms.

- Progressive dysphagia and odynophagia,
- Coughing
- Weight loss
- Hoarseness of voice (laryngeal nerve involvement)
- History of tobacco smoking.
- Alcohol intake.
- History of GERD

Physical examination

- General examination- nutrition assessment, anaemia, dehydration and lymphadenopathy.
- Chest and abdominal examination- assess for signs distant metastases.

Diagnostic workup

- Barium swallow.
- Upper GIT endoscopy: allows direct visualization and biopsy.

Staging workup.

- FBC, U&E, LFTs and HIV test
- Endoscopic USS (where available) to assess the depth of penetration and LN involvement
- CT chest and abdomen (if available)
- Chest x-ray and USS Abdomen
- Bronchoscopy: rule-out fistula in mid-esophageal lesions
- Pulmonary function test: to evaluate whether medically operable and

serve as baseline lung function for chemoradiation.

- Nutritional assessment.
- Her2-neu overexpression assay.

Treatment

- All esophageal and GEJ cancer patients should be discussed in a multidisciplinary team meeting (including nutritionist, pathologist, oncologist, cardiothoracic & general surgeons, pharmacist, oncology nurse, radiologist and social worker) prior to treatment.
- Most patients have poor nutritional status, nutritional support is an important part in the management of patients. For patients with significant obstruction dilation of the esophagus with or without stenting is preferred, if not possible gastrostomy feeding tube insertion should be considered.

TNM stage	Surgery	Radiotherapy	Chemotherapy
Tis & T1a	• Endoscopic resection or ablation (if available) • Esophagectomy		
T1b N0	• Esophagectomy		
T2-T4a, N0/N+	• Surgery following chemoradiation is recommended.	• Neoadjuvant chemoradiation then reassess and consider surgery. • Definitive chemoradiation for inoperable patients. • Adjuvant chemoradiation for patient who had upfront surgery	• Concurrent chemotherapy. • Perioperative chemotherapy can be considered for esophageal adenocarcinoma.

T4b, any N		• Definitive chemoradiation and reassess disease status.	Chemotherapy alone for patients with invading the trachea, the great vessels or the heart
Unresectable or metastatic disease		Palliative radiotherapy	Palliative chemotherapy.

Medicines

Medicine	Codes	Adult dose	Frequency	Duration
Neoadjuvant & definitive chemoradiation				
Carboplatin and Paclitaxel	S V	Carboplatin AUC2 IV D1 Paclitaxel 50mg/m^2 IV Day 1	weekly	5
Cisplatin and 5-FU	S V	Cisplatin 75-100mg/m^2 IV D1 and D29 5-FU 750-1000mg/m^2 IV 24 hour continuous infusion D1-D5 and D29-32.	3 weekly	3
Oxaliplatin and capecitabine	S V	Oxaliplatin 85mg/m^2 on days 1,15, 29 for 3 doses Capecitabine PO 625mg/m^2 BD D1-D5 for 5 weeks		3
Adjuvant chemoradiation				
Capecitabine	S V	Capecitabine 750-100mg/m^2 PO BD D1-D14. 1 cycle before and 2 cycles after chemoradiation.	3 weekly	
5-FU and Leucovorin	S V	Cycles 1,3 and 4 before and after radiotherapy: Leucovorin 20mg/m^2 IV bolus D1-D5 5-FU 425mg/m^2 IV bolus D1-D5 Cycle 2 given with radiation Leucovorin 20mg/m^2 IV bolus D1-D4 and D31-D33 5-FU 400mg/m^2 IV bolus D1-D4 and D31-D33	4 weekly	

Systemic therapy for metastatic or locally advanced disease				
Oxaliplatin and capecitabine	S	V	Oxaliplatin 130mg/m^2 IV D1 Capecitabine PO 1000mg/m^2 BD. D1-D14	3 weekly
Cisplatin and Fluorouracil	S	V	Cisplatin 75-100mg/m^2 D1 5-FU 750-1000mg/m^2 IV 24 hour continuous infusion D1-D4	4 weekly
Cisplatin and capecitabine	S	V	Cisplatin 80mg/m^2 IV D1 Capecitabine 1000mg/m^2 PO BD D1- D14	3 weekly

Follow Up

- History and physical examination every 3-6 months for 1-2 years and then every 6-12 months for 3-5 years then annually.
- Nutritional assessment and counselling.
- Imaging as clinically indicated.
- Upper GI endoscopy and biopsy as clinically indicated.

Gastric Cancer

General note

Adenocarcinoma make up 95% of all gastric cancer cases. Risk factors for gastric cancer are nutritional (high salt, low vit A & C), smoked food, occupational carcinogen exposure (rubber industry & coal mine workers), tobacco smoking, *Helicobacter pylori* infection, genetic factors (pernicious anaemia, family history, hereditary nonpolyposis colon cancer & Li-Fraumeni syndrome) and precursor lesions (adenomatous gastric polyps & chronic atrophic gastritis)

History and symptoms

- Abdominal pain
- Dysphagia
- Loss of appetite
- Early satiety
- Nausea
- Vomiting/ hematemesis
- Unexplained weight loss

- Melena stool
- History of long-standing, unconfirmed peptic ulcer disease

Physical Examination

- General appearance- cachexia; hydration status, nutritional status
- Pallor
- Jaundice
- Lymphadenopathy (Virchow's nodes)
- Abdomen
    - Distension; masses; tenderness; sister Mary Joseph nodule.
    - Digital rectal examination.

Diagnostic workup.

- Upper GI endoscopy and biopsy- at least 6-8 specimens
- Endoscopy report should indicate
    - Location of tumour(s).
    - Morphological description of
    - Bleeding status
    - Distance from gastro-oesophageal junction (GEJ) for Siewert classification.
- Laparoscopy/laparotomy and biopsy

Staging work up

- FBC, U&E, LFTs and HIV test.
- Ascitic fluid cytology (if available)
- CT Scan chest, abdomen & pelvis (if available)
- Chest x-ray+ USS abdomen and pelvis if CT scan not available
- Endoscopic USS (where available) to assess the depth of penetration and LN involvement
- Her2-neu overexpression (if metastatic disease)

Treatment

All patients with gastric cancer should be discussed in a multidisciplinary

team meeting (including nutritionist, dietician, pathologist, oncologist, surgeons, pharmacist, oncology nurse, radiologist and social worker) prior to treatment.

Stage	Treatment
Stage 0 (Tis)	Endoscopic resection Or Surgery
Stage I (T1 N0 M0)	Endoscopic resection OR Surgery then follow up
Stage II -III (resectable)	Perioperative chemotherapy and Surgery (preferred) OR Preoperative Chemoradiation followed by surgery. OR Upfront surgery in cases of obstruction or bleeding followed by adjuvant chemotherapy/chemoradiation
Stage II-III (unresectable)	Chemoradiation then re-assess for resectability OR Palliative management (systemic therapy)
Stage IV	• Systemic chemotherapy • Palliative surgery • Palliative radiotherapy • Best supportive care

Medicines

Medicine	Codes	Adult dose	Frequency	Duration
Perioperative chemotherapy		**3 cycles pre-surgery and 3 cycles post-surgery**		
Cisplatin and 5-FU	**S V**	Cisplatin 75-80 mg/m^2 IV day 1 5-FU 800mg/m^2 IV continuous infusion over 24 hours D1-D5	4 weekly	6
Capecitabine and oxaliplatin	**S V**	Oxaliplatin 130mg/m^2 IV D1 Capecitabine 1000mg/m^2 PO BD D1-D14	3 weekly	6
Pre-operative chemoradiation				
Carboplatin and Paclitaxel	**S V**	Carboplatin AUC2 IV D1 Paclitaxel 50mg/m^2 IV Day 1	Weekly	5
Cisplatin and 5-FU	**S V**	Cisplatin 75 -100mg/m^2 IV D1 and D29 5-FU 750 -1000mg/m^2 IV 24 hour continuous infusion D1 -D5 and D29-32.	3 weekly	3

Oxaliplatin and capecitabine	**S**	**V**	Oxaliplatin 85mg/m^2 on days 1,15, 29 for 3 doses Capecitabine PO 625mg/m^2 BD D1-D5 for 5 weeks	
Adjuvant chemoradiation				
Capecitabine	**S**	**V**	Capecitabine 750-1000mg/m^2 PO BD D1-D14. 1 cycle before and 2 cycles after chemoradiation. With radiation: 625 -825mg/m^2 PO BD days 1 -5 or 1 -7 weekly for 5 weeks	3 weekly
5-FU and leucovorin	**S**	**V**	Cycles 1,3 and 4 before and after radiotherapy Leucovorin 20mg/m^2 IV bolus D1-D5 5-FU 425mg/m^2 IV bolus D1-D5 Cycle 2 given with radiation Leucovorin 20mg/m^2 IV bolus D1-D4 and D31-D33 5-FU 400mg/m^2 IV bolus D1-D4 and D31-D33	4 weekly
Systemic therapy for metastatic or locally advanced disease				
Oxaliplatin and capecitabine	**S**	**V**	Oxaliplatin 130mg/m^2 IV D1 Capecitabine PO 1000mg/m^2 BD. D1-D14	3 weekly

Follow up

The aim of follow up is to assess for and manage disease recurrence and sequelae of disease and previous treatment.

- History and physical examination every 3 months for the first 2 years then 6 monthly up to 5 years then annually thereafter.
- Markers (if initially raised) every 3-6 months for the first 2 years the 6 monthly up to 5 years then annually thereafter
- Upper GI endoscopy
    - Tis s :6 monthly for 1 year then annually up to 3 years
    - Post gastrectomy when clinically indicated
- Imaging: CT scan chest, abdomen and pelvis (if available)
    - For stage I- where clinically indicated
    - Stage 2 and higher: every 6-12 months for the first 2 years

then annually thereafter.

- Patients who have had surgical resection should be monitored for nutritional deficiencies and post-gastrectomy syndrome.

Colon cancer

General Note

Colon cancer is one of the top 10 causes of cancer morbidity and mortality in Zimbabwe. It is also one of the most curable, particularly, if caught early. Risk factors include Age >50 years, family history of malignancies, inflammatory bowel disease tobacco smoking, consumption of processed meats, alcohol consumption, diabetes mellitus, physical inactivity, obesity, metabolic syndrome and low fiber diet. Adenocarcinomas make up 95% of colon cancers.

History and symptoms

- Change in bowel habits
- Abdominal pain
- Unexplained weight loss
- Fatigue
- Unexplained iron deficiency anaemia
- Early satiety
- Symptoms of intestinal obstruction: nausea, vomiting, constipation, abdominal distension

Physical examination

- General examination- pallor, oedema, hydration status, nutritional status, and performance status.
- Abdominal examination including digital rectal assessment.
- Rest of systems for metastatic disease.

Diagnostic workup

- Colonoscopy and biopsy
- Laparotomy (for presentation with obstruction or perforation)

- Screening with CT colonography can be used for routine screening of patients.

Staging work up

- FBC, LFTs, U&Es and HIV test
- Serum CEA and CA 19-9
- CT chest, abdomen and pelvis preferred if available
- or chest x-ray + USS abdomen and pelvis
- Gene mutation- KRAS, NRAS, BRAF and MSI/MMR testing if available
- Her2-neu overexpression

Treatment

All colon cancer patients should be discussed in a multidisciplinary team meeting (including nutritionist, dietician, pathologist, oncologist, physicians, surgeons, pharmacist, oncology nurse, radiologist and social worker) prior to treatment

Stage	Surgery	Chemotherapy
0	Polypectomy or mucosal resection then follow up	
I	Colectomy with en bloc resection of regional lymph nodes.	
II	Colectomy with en bloc resection of regional lymph nodes .	If high risk features* present adjuvant chemotherapy is indicated Neoadjuvant chemotherapy can be considered for T4b s
III	Colectomy then adjuvant chemotherapy.	Adjuvant chemotherapy indicated Neoadjuvant chemotherapy can be considered for T4b s.
IV Resectable synchronous liver and/or lung metastases	Surgery depending on response to neoadjuvant chemotherapy	Neo-adjuvant chemotherapy 2 -6 cycles followed by surgery then adjuvant chemotherapy
IV unresectable metastases	Palliative surgery e.g. colostomy diversion for intestinal obstruction	Palliative ch emotherapy +/ - targeted or immunotherapy. Palliative radiotherapy where indicated.

*High risk features: T4 s (stage IIB, IIC), poorly differentiated histology, peri-neural invasion, lymphovascular invasion, bowel obstruction, positive or inadequate margins, <12 nodes sampled.

If tumour is obstructing, consider resection with diversion.

Medicines

Medicine	Codes		Adult dose	Frequency	Duration
Chemotherapy					
FOLFOX 4	**S**	**V**	Oxaliplatin 85mg/m^2 IV D1 Leucovorin 200mg/m^2 IV D1-D2 5-FU 400mg/m^2 Bolus IV D1-D2 5-FU 600mg/m^2 IV continuous infusion over 22 hours D1-D2	2 weekly	12
FOLFOX 6	**S**	**V**	Oxaliplatin 85mg/m^2 IV D1 Leucovorin 400mg/m^2 IV D1 5-FU 400mg/m^2 IV BOLUS D1 5-FU 2400mg/m^2 IV over 46-48 hours continuous infusion.	2 weekly	12
Oxaliplatin and capecitabine	**S**	**V**	Oxaliplatin 130mg/m^2 IV D1 Capecitabine 1000mg/m2 PO BD D1-D14	3 weekly	8
FOLFIRI	**S**	**V**	Irinotecan 180mg/m^2 IV D1 Leucovorin 400mg/m^2 IV D1 5-FU 400mg/m^2 IV D1 5-FU 1200mg/m^2 IV D1-D2	2 weekly	12
FOLFOXIRI	**S**	**V**	Oxaliplatin 85mg/m^2 IV D1 Irinotecan 165mg/m^2 IV D1 Leucovorin 400mg/m^2 IV D1 5-FU 2400mg/m^2 IV over 48 hours.	2 weekly	
5-FU and Leucovorin (MAYO clinic regimen)	**S**	**V**	5-FU 425mg/m^2 IV BOLUS D1-D5 Leucovorin 20mg/m^2 IV BOLUS D1-D5	4-5 weekly	

Targeted and immunotherapy for patients with metastatic disease if available

Follow up

Follow up care aims at assessing for and managing disease recurrence and sequelae of disease and treatment

- History and physical examination every 3 months for the first 2 years then every 6 months for 5 years then annually thereafter.
- CEA (if available) every 3-6 months for the first 2 years then every 6 months for 5 years then annually thereafter.
- CT chest, abdomen, pelvis (if available) every 6-12 months for 5 years or CXR, USS abdomen & pelvis if CT scan unavailable then annually thereafter.
- Completion colonoscopy (if available) within 6 months of treatment if not done initially then at 1 year every 3 years if no abnormalities.
- Long term surveillance should encourage a healthy lifestyle and wellness which include leading a physically active lifestyle, healthy diet consumption, smoking cessation and limiting alcohol intake

Rectal cancer

General Notes

The commonest histology is adenocarcinoma (95%). Risk factors for rectal cancer include age > 50 years, personal or family history of cancer, inflammatory bowel disease, smoking, processed meats consumption, alcohol consumption, diabetes mellitus, physical inactivity, obesity and low fiber diet.

History and symptoms

- Change in bowel habits (for proximal s)
- Abdominal pain, discomfort
- Bleeding per rectum
- Tenesmus
- Mucoid discharge
- Unexplained weight loss
- Unexplained iron deficiency anaemia
- Symptoms of intestinal obstruction: nausea, vomiting, constipation, abdominal distension

Physical exam

- General examination- performance, pallor, nutritional status, hydration and lymphadenopathy.
- Abdominal examination and digital rectal assessment
- Assess for signs of metastases.

Diagnostic workup

- Biopsy at colonoscopy
- Degree of rectal obstruction must be stated at colonoscopy

Staging work up

- FBC, LFTs, U&Es and HIV test.
- CEA & CA 19-9 if available
- Gene status- KRAS, NRAS, BRAF and MSI/MMR testing if available
- MRI pelvis or Endo-rectal ultrasound where available
- CT chest, abdomen and pelvis (preferred) or chest x-ray and USS abdomen and pelvis (if CT not available)
- Nutritional assessment

Treatment

All rectal cancer patients should be discussed in a multidisciplinary team meeting (including nutritionist, dietician, pathologist, oncologist, surgeons, gynaecology (female patients), pharmacist, oncology nurse, radiologist and social worker) prior to treatment.

Stage	Surgery	Radiotherapy	Chemotherapy/ targeted therapy
Stage 0 (Tis)	Local excision		
Stage I (cT1-2 N0)	• Trans abdominal resection • Transanal excision for selected cases	• Adjuvant chemoradiation is indicated for high-risk features*	
Stages II-III (T3-4 N0, any T N1-2)	• Surgery following neoadjuvant radiotherapy or	• Neo-adjuvant long course chemoradiation	• Concurrent chemotherapy with pelvic

	chemoradiotherapy	OR • Short course neoadjuvant radiotherapy alone followed by surgery 1 week later. (not to be used for T4 s)	chemotherapy • Adjuvant chemotherapy post-surgery.
Stage IV (any T, any N, M1)	• Patients with resectable synchronous metastases may have primary & metastatic site resection. •Surgery may be used to palliate symptoms	• Radiotherapy may be used to palliate symptoms from primary disease or the metastatic s	• Systemic therapy in the form of chemotherapy (+ targeted therapy where available) are used

- High risk features e.g. intestinal obstruction or perforation, positive margins, inadequate
  TME, LVSI, positive margins, poorly differentiated tumour and sm3 invasion.

Medicines

Chemotherapy regimens

Medicine	Codes		Adult dose	Frequency	Duration
Chemoradiation.					
Capecitabine	S	V	Capecitabine 825mg/m^2 PO BD 5 days per week during radiotherapy		
5-FU	S	V	5-FU 400mg/m^2 IV bolus Leucovorin 20mg/m^2 IV bolus For D1-D4 during week 1 and 5 of radiotherapy		
Chemotherapy					
FOLFOX 4	S	V	Oxaliplatin 85mg/m^2 IV D1 Leucovorin 200mg/m^2 IV D1-D2 5-FU 400mg/m^2 Bolus IV D1-D2 5-FU 600mg/m^2 IV continuous infusion over 22 hours D1-D2	2 weekly	12
FOLFOX 6	S	V	Oxaliplatin 85mg/m^2 IV D1 Leucovorin 400mg/m^2 IV D1 5-FU 400mg/m^2 IV BOLUS D1 5-FU 2400mg/m^2 IV over 46-48 hours continuous infusion.	2 weekly	12

Oxaliplatin and capecitabine	S	V	Oxaliplatin 130mg/m^2 IV D1 Capecitabine 1000mg/m2 PO BD D1-D14	3 weekly	8
FOLFIRI	S	V	Irinotecan 180mg/m^2 IV D1 Leucovorin 400mg/m^2 IV D1 5-FU 400mg/m^2 IV D1 5-FU 1200mg/m^2 IV D1-D2	2 weekly	12
5-FU and Leucovorin (MAYO clinic regimen)	S	V	5-FU 425mg/m^2 IV BOLUS D1-D5 Leucovorin 20mg/m^2 IV BOLUS D1-D5	4-5 weekly	

Targeted and immunotherapy for patients with metastatic disease.

Follow up

- Follow up care aims at assessing for and managing disease recurrence and sequelae of disease and treatment with referrals to other specialties e.g. urology, gynaecology as necessary.
- History and physical examination every 3 months for the first 2 years then every 6 months for 5 years then annually thereafter.
- CEA (if available) every 3-6 months for the first 2 years then every 6 months for 5 years then annually thereafter.
- CT chest, abdomen, pelvis (if available) every 6-12 months for 5 years or CXR, USS if CT unavailable then annually thereafter.
- Completion colonoscopy (if available) within 6 months of treatment if not done initially then at 1 year, then every 3 years if no abnormalities. Long term surveillance should encourage a healthy lifestyle and wellness which include leading a physically active lifestyle, healthy diet consumption, smoking cessation and limiting alcohol intake.

Anal cancer

General note

Anal cancer is linked to HPV infection in most cases. Risk factors include immunosuppression, history of anogenital warts, cigarette smoking, practicing ano-receptive sexual intercourse and history of prior HPV-associated cancer e.g. cervical, vulva cancers etc.

History and symptoms.

- Anorectal bleeding
- Non-healing peri-anal ulcer
- Tenesmus
- Pain during defecation
- Peri-anal itching
- Anal discharge
- Change in bowel habits (proximal s)
- Faecal incontinence
- Weight loss

Physical exam

- General examination- pallor, nutritional status and lymphadenopathy (inguinal).
- Abdominal examination including rectal exam is mandatory.
    - Assess lesion for site, size, distance from anal verge of lesion, anal sphincter tone, fixation
- Gynecologic exam for females

Diagnostic workup

- Anal lesion biopsy
- HPV testing if available

Staging workup

- FBC, U&E, LFT, HIV test +/- CD4 count and viral load
- Inguinal lymph node evaluation: FNA or biopsy of suspicious nodes
- CT scan chest, abdominal and MRI pelvis (if available) or chest x-ray and USS abdomen and pelvis (including assessment of inguinal nodes)
- Screening for cervical cancer in females

Treatment

All anal canal and peri-anal margin cancer patients should be discussed in a

multidisciplinary team meeting (including nutritionist, dietician, pathologist, oncologist, surgeons, gynaecology (female patients), pharmacist, oncology nurse, radiologist and social worker) prior to treatment.

Stage	Radiotherapy	Chemotherapy	Surgery
Stage 0			Surgical resection of the lesions.
Stage I	Chemoradiation	Concurrent chemotherapy	Wide local excision of small anal margin s which are well differentiated.
Stages II to IIIB	Chemoradiation (preferred)	Concurrent chemotherapy.	
Stage IV	Radiotherapy	Systemic chemotherapy	
Recurrence		Systemic chemotherapy	Surgery if recurrent site is amenable to surgery.

Medicines

Medicine	Codes		Adult dose	Frequenc y	Duration
Chemoradiation.					
5-FU and mitomycin with radiotherapy	S	V	5-FU 1000mg/m^2 IV continuous infusion D1-D4 and D29-D32 Mitomycin 10mg/m^2 iv bolus (max 20mg) D1 & D29 or Mitomycin 12mg/m^2 iv bolus D1	4 weekly	2
Cisplatin and 5-FU with radiotherapy	S	V	Cisplatin 75mg/m^2 IV D1 5-FU 1000mg/m^2 IV continuous infusion D1-D4	4 weekly	2
Capecitabine and mitomycin with radiotherapy	S	V	Capecitabine 825mg/m2 orally twice daily D1-D5 weekly (on each day of radiotherapy-typically 28 days) Mitomycin 10mg/m2 iv bolus D1 and D29 Or Mitomycin 12mg/m2 iv bolus D1		

Systemic chemotherapy					
Carboplatin and Paclitaxel	S	V	Carboplatin AUC5 IV D1 Paclitaxel 175mg/m² IV D1	3 weekly	6
Cisplatin and 5-FU	S	V	Cisplatin 75mg/m² IV D1 5-FU 100mg/m² IV D1-D4	3 weekly	6
Cisplatin and 5-FU	S	V	5-FU 1000mg/m² continuous infusion D1-D4 Cisplatin 60mg/m² IV D1 OR 5-FU 750mg/m² continuous infusion D1-D5 Cisplatin 75mg/m² IV D1	4 weekly	6
FOLFOX 4	S	V	Oxaliplatin 85mg/m² IV D1 Leucovorin 200mg/m² IV D1-D2 5-FU 400mg/m² Bolus IV D1-D2 5-FU 600mg/m² IV continuous infusion over 22 hours D1-D2	2 weekly	
FOLFOX 6	S	V	Oxaliplatin 85mg/m² IV D1 Leucovorin 400mg/m² IV D1 5-FU 400mg/m² IV BOLUS D1 5-FU 2400mg/m² IV over 46-48 hours continuous infusion.	2 weekly	

Follow up

Evaluate 8-12 weeks after treatment

If complete remission

- DRE and Inguinal node palpation every 3-6 months for 5 years then annually thereafter
- Proctoscopy every 6-12 months for 3 years
- CT chest, abdomen + pelvis with contrast annually (if T3-T4 or inguinal node positive)

If persistent disease

- Re-evaluate in 4 weeks
- If there's regression or no progression on serial exams, continue observation and re-evaluate at 3 monthly intervals
- If complete remission, follow up as above
- If progression/persistent disease (after 6 months), manage as progressive disease below

If progressive disease

- Biopsy
- Re-stage
- If localized disease- Abdomino-perineal resection (APR) + groin dissection (for positive inguinal nodes)
- If distant metastases- manage as for stage IV above with palliative intent.

Hepatocellular carcinoma

General note

Diagnosis of hepatocellular carcinoma is based on taking a detailed history, complete physical examination, imaging, and histopathology and biochemical analysis. Risk factors include viral infections (hepatitis B & hepatitis C virus), liver cirrhosis, heavy alcohol intake, metabolic diseases (hemochromatosis, galactosemia, Wilson's disease & glycogen storage disease), tobacco smoking and aflatoxin exposure.

History and symptoms

- Fatigue
- Anorexia
- Weight loss
- Unexplained fever
- Vomiting; haematemesis
- Jaundice
- Abdominal distension or mass
- Right subcostal pain
- History of viral hepatitis or chronic liver disease

Physical examination

- General examination- nutritional and performance status.
- Pallor, jaundice and lymphadenopathy
- Abdomen:
    - Distension, visible superficial veins, hepatomegaly,

splenomegaly, signs of ascites, hepatic bruit, DRE

- Signs of liver failure including encephalopathy

Diagnostic workup

- Multiphasic contrast enhanced CT scan abdomen (or MRI scan if available)
- USS abdomen if CT not available
- Serum Alpha –fetoprotein test
- Tissue biopsy for histology if necessary

Staging workup

- CT scan chest, abdomen & pelvis (MRI scan if available) or chest x-ray and USS abdomen & pelvis if CT not available
- FBC, U&Es, LFTs, RBS, clotting profile, hepatitis infection screen and HIV test

Treatment

All hepatocellular cancer patients should be discussed in a multidisciplinary team meeting (including nutritionist, dietician, pathologist, oncologist, surgeons, gastroenterologist, pharmacist, oncology nurse, radiologist, palliative care specialist and social worker) prior to treatment. Early integration of palliative care **strongly recommended**

Localized and resectable

The MDT must assess the patient for resectability. Resectability is based on:

- Presence of localized disease
- The site and size of the tumour within the liver
- Extent of macrovascular invasion if present
- Reserve liver function estimation [Child-Pugh score]
- The patient's performance status and co-morbidities

Localized and non-resectable disease

- Pre-operative modality treatment followed by surgery
- Microwave ablation
- Radiofrequency ablation
- Highly conformal radiotherapy
- Trans-catheter arterial chemo-embolization
- Percutaneous intra-lesional installation of absolute ethanol

Non resectable metastatic disease

- Systemic chemotherapy therapy
- Targeted therapy
- Hormonal therapy
- Viral hepatitis patients should be treated with appropriate antiviral /interferon therapy

Medicines

Medicine	Codes	Adult dose	Frequency	Duration
Systemic chemotherapy				
Doxorubicin	**S** **V**	Doxorubicin 75mg/^{m2} IV D1	3 weekly	
Sorafenib (if available)		Sorafenib 400mg PO BD	daily	

Follow up

Follow up aims to prevent and treat hepatic decompensation.

- Patients to be followed up with history, physical examination and liver imaging every 3-6months in the first 2 years then every 6 months for 5 years.
- Routine serum AFP and LFT.

Pancreatic cancer

General note

Malignancies of the pancreas may arise from exocrine or endocrine tissue. Exocrine carcinoma of the pancreas accounts for 95% of pancreatic cancers. Risk factors age (7th and 8th decade), heavy alcohol consumption, diabetes mellitus, obesity, tobacco smoking and exposure to carcinogens

including heavy metals, benzidine, pesticides, asbestos, benzene and chlorinated hydrocarbons.

History and symptoms

- Nausea & vomiting
- Weight loss
- Anorexia
- Epigastric/abdominal/back pain
- Jaundice
- Steatorrhea
- Diarrhea
- Symptoms of small bowel or gastric outlet obstruction:

Physical exam

- General examination- performance, hydration and nutrition status
    - Jaundice and oedema.
- Abdominal examination- hepatomegaly, courvoisier's sign and ascites. Pancreatic cancer patients are high risk for deep venous thrombosis (DVT).

Diagnostic workup

- Pancreatic protocol CT scan abdomen (where available)
- Endoscopic USS and endoscopic retrograde cholangiopancreatography (ERCP) where available
- Biopsy if metastatic disease

Staging workup

- CT scan chest, abdomen & pelvis (MRI scan if possible)
- Chest x-ray and USS abdomen & pelvis
- FBC, U&E, LFTS, RBS, CA 19-9 and HIV tests
- Nutritional assessment

Treatment

ALL pancreatic cancer patients should be discussed in a multidisciplinary team meeting (including nutritionist, pathologist, oncologist, surgeons, pharmacist, oncology nurse, radiologist, palliative care specialist and social worker) prior to treatment. The MDT should assess the resectability of the tumour and operability of the patient. Early integration of palliative care is **strongly recommended.**

Management of pancreatic cancer depends on resectability of the tumour. Resectability depends on:

- Involvement/contact with major vessels: celiac axis, superior mesenteric artery, or common hepatic artery, superior mesenteric vein or portal vein and inferior vena cava.
- location: head, body or tail
- Presence of metastases

	Surgery	Chemotherapy	Radiotherapy
Resectable	Definitive surgery	Adjuvant chemotherapy	
Borderline Resectable	Resection following neo-adjuvant chemotherapy	Neo-adjuvant chemotherapy as conversation therapy (preferred)	Chemoradiation is an option for neoadjuvant therapy
Unresectable	Palliative interventions: • Jaundice- biliary bypass or stenting • Pain- celiac nerve blocks • Gastric outlet obstruction- gastrojejunostomy	Neoadjuvant chemotherapy followed by chemoradiation or radiotherapy alone	Upfront radiotherapy/chemoradiation or post induction chemotherapy radiation.
Metastatic (stage IV)	Palliative interventions	Palliative chemotherapy	Palliative radiotherapy

Medicines

Medicine	Codes		Adult dose	Frequency	Duration
Neo-adjuvant chemotherapy					
Cisplatin and Gemicitabine	**S**	**V**	Cisplatin 25-50mg/m^2 IV D1 Gemicitabine 750mg/m^2 IV D1	2 weekly	2-6
FOLFIRINOX (used as adjuvant chemotherapy as well)	**S**	**V**	Oxaliplatin 85mg/m^2 IV D1 Irinotecan 165mg/m^2 IV D1 Leucovorin 400mg/m^2 IV D1 5-FU 1600mg/m^2 IV over 48 hours	2weekly	2-6
Chemoradiation					
Capecitabine	**S**	**V**	Capecitabine 825mg/m^2 PO BD five days per week during radiotherapy	weekly	
Adjuvant and palliative chemotherapy					
Gemicitabine and capecitabine	**S**	**V**	Gemicitabine 1000mg/m^2 IV D1, D8 & D15 Capecitabine 830mg/m^2 PO BD for 3 weeks (D1-D21)	4 weekly	
Gemicitabine (single agent)	**S**	**V**	Gemicitabine 1000mg/m^2 IV D1, D8 & D15	4 weekly	
Capecitabine	**S**	**V**	Capecitabine 850-1250mg/m^2 PO BD for 14 days	3 weekly	

Follow up

- History and physical examination every 3 to 6 months for 2years then every 6 to 12 months.
- CT scan review every 3 to 6 months for 2 years (if available0
- CA 19-9 every 3-6 months for 2 years
- Nutritional review by nutritionist.

Gynaeclogical cancers

Cervical Cancer

General note

Cervical cancer is the leading cause of cancer morbidity and mortality among black Zimbabwean women accounting for 33.2% of all cancers in black women. Risk factors include early sexual debut, multiple sexual partners, high parity, smoking and immunosuppression. Persistent infection with HPV is the most significant cause of cervical cancer and is detected in 99% of cervical s. Globally, HPV 16/18 account for at least two-thirds of cervical carcinomas in all continents; while HPV 31, 33, 35, 45, 52 and 58 are the next most common types associated with cancers. Cervical cancer can be prevented by practising safe sex, HPV vaccination and cervical cancer screening. All women who should have cervical cancer screening using either VIAC or PAP smear.

History and symptoms.

- Watery PV discharge.
- Contact bleeding
- Intermenstrual bleeding
- Persistent/ significant pelvic pain
- Asymptomatic (Lesion noted at screening)

Physical examination

- General examination- includes signs of anaemia and lymph nodes.
- Abdominal exam.
- Pelvic Exam (Mandatory)
    - speculum exam to visualise the cervix.
    - Digital vaginal and rectal exam, to determine size of , involvement of vagina, parametrium, pelvic side wall, rectum and bladder.

All women with above signs and symptoms should be referred to the next level centre of care with a specialist.

Diagnostic Workup

- Cervical biopsy

Staging Workup.

- FBC, LFT, U&E, HIV test.
- Chest x-ray and USS abdomen & pelvis.
- CT scan Abd/pelvis (if affordable in place of USS)
- MRI recommended in early-stage disease to determine extent of parametrial involvement when contemplating primary surgery (if available)

FIGO Staging

Staging is determined by clinical and radiological investigations.
Note: Refer to FIGO staging.

Treatment

All cancer patients should be discussed in a multidisciplinary team meeting (including pathologist, oncologist, gynecologist, pharmacist, oncology nurse, radiologist and social worker) prior to treatment.

The primary treatment for early-stage disease is either surgery or chemoradiation. Appropriate surgery is reserved for stages 1A, 1B1 and selected 2A1 patients and **should be done at tertiary institutions by a gynaecologist**. Concurrent chemoradiation is the treatment of choice for stages 1B2 to 4A and patients must be referred accordingly.

Stage	Surgery	Radiotherapy	Chemotherapy
$1A_1$	Excisional conisation or simple hysterectomy	If childbearing not desirable	Not recommended
$1A_2$	Bilateral pelvic lymphadenectomy + modified (type II) radical hysterectomy	Consider radiotherapy for the following: • LVSI. • Deep stromal invasion • Adenosquamous, clear cell, small cell and undifferentiated histology.	Concurrent chemotherapy indicated for: • Positive surgical margin • Positive lymph node

		Consider chemoradiation for the following: • Positive surgical margin • Positive lymph node • Parametrial involvement	• Parametrial involvement
1B1, 1B2 & IIA1	Radical hysterectomy + pelvic lymph node dissection	Definitive pelvic radiother apy plus brachytherapy boost +/ - concurrent chemotherapy.	Concurrent chemotherapy
1B3-IIIC1	Not recommended	Pelvic radiotherapy plus brachytherapy boost +/- concurrent chemotherapy.	Concurrent chemotherapy
IIIC2	Not recommended	Extended field rad iotherapy plus brachytherapy boo st +/- concurrent chemotherapy	Concurrent chemotherapy
1VA	Not recommended	Pelvic radiotherapy plus brachytherapy boost +/ - concurrent chemotherapy	Concurrent chemotherapy
IVB	Not recommended	Palliative radiotherapy if needed	Palliative chemotherapy

Medicines

Medicine	Codes	Adult dose	Frequency	Duration
Chemoradiation				
Cisplatin.	**S** **V**	Cisplatin 35-40 mg/m ^{2}	weekly	
Carboplatin	**S** **V**	Carboplatin AUC2	3 weekly	
Systemic chemotherapy				
Cisplatin and Paclitaxel +/ - Bevacizumab	**S** **V**	Cisplatin 50mg/m ^{2} IV D1 Paclitaxel 175mg/m ^{2} IV Day 1	3 weekly	
Carboplatin and Paclitaxel +/- Bevacizumab	**S** **V**	Carboplatin AUC5 -6 IV D1 Paclitaxel 175mg/m ^{2} IV D1	3 weekly	

Follow up.

- Should be done at the treatment facility.
- History and examination 6 weeks post chemoradiation or surgery.
- CT scan chest, abdomen & pelvis (if available) or USS abdomen & pelvis and Chest X-ray within 3-6 months of completion of therapy.
- Review clinically every 3 months for 2 years then every 6 months till 5 years then annually.
- Vault/Pap smear screening maybe considered a year post treatment.

Recurrent Disease

- Management depends on previous treatment modality and performance status of the patient.
- **Local recurrence post treatment can be successfully managed by a modality not previously utilised**
- **Pelvic exenteration:** A pelvic exenteration can be considered for central pelvic recurrent disease after primary RT when spread is confined to the bladder or rectum. Metastatic cancer outside the pelvis and poor medical condition of the patient are contraindications to exenteration.
    - **Chemotherapy** for metastatic disease is not curative. Drugs that could be considered following multidisciplinary team consultation include, cisplatin, carboplatin and paclitaxel. Appropriate palliative care should be considered for all the patients.

Uterine Cancer

General note

This is the second most common gynaecologic malignancy developing countries (cervical cancer is more common). Risk factors include unopposed estrogen levels (caused by obesity, diabetes mellitus, and high fat diet), early menarche, nulliparity, late menopause, tamoxifen use and hereditary conditions e.g. Lynch syndrome. Histological subtypes of uterine cancer include malignant epithelial, mesenchymal or mixed epithelial and mesenchymal.

Epithelial type 1 tumours

- Endometrioid carcinoma,

Epithelial Type 2 tumours

- Uterine papillary serous carcinoma (UPSC)
- Clear cell carcinoma,
- Carcinosarcoma
- Undifferentiated carcinoma.

Mesenchymal tumours

- Uterine Leiomyosarcoma,
- Endometrial stromal sarcoma,
- Undifferentiated uterine sarcoma (previously called undifferentiated high grade endometrial sarcoma)
- Adenosarcoma

History and symptoms.

- Abnormal uterine bleeding (75-90%)
- Incidental finding on imaging, after hysterectomy or during abdomino pelvic surgery.
- Abnormal findings on Pap smear
    - Adenocarcinoma
    - Atypical glandular cells

Physical Examination

- General examination- including signs of anaemia and palpable lymph nodes
- Abdominal exam- note extra-uterine masses and ascites.
- Pelvic Exam (Mandatory)
    - speculum exam to visualise the cervix
    - Digital vaginal and rectal exam- size and mobility of the uterus.

Diagnostic work up

- **Transvaginal USS –** Any post- menopausal women with an endometrial thickness (ET) ≥5mm should have endometrial sampling. ET is not very helpful in premenopausal women.
- **Endometrial sampling** with or without hysteroscopy is the gold standard (Pipelle, D & C).

Staging workup

- FBC, U&Es, LFTs, HIV test and baseline CA 125.
- Other tests to be guided by the patient's comorbidities.

- Expert pelvic USS or MRI should be done for local staging and risk stratification prior to surgery
- Chest x-ray and USS abdomen.
- Other imaging modalities e.g. PET +- CT scan

can be used when available

to assess for metastatic disease

- Histological confirmation of diagnosis

Note: Any woman with suspicion of endometrial cancer should have histological diagnosis prior to surgery. If endometrial sampling is not possible, frozen section should be used to guide the appropriate surgery.

Treatment

All uterine cancer patients should be discussed in a multidisciplinary team meeting (including pathologist, clinical oncologist, gynecologist, surgeon, pharmacist, oncology nurse, radiologist and social worker) prior to treatment.

Surgery

Laparotomy involving:

- POD washings for cytological examination.
- Careful exploration of abdominal cavity.
- If resectable: extra-fascial total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH, BSO) & where indicated pelvic lymphadenectomy (PL), including common iliac nodes.
- Omentectomy is recommended in patients with clear cell, carcinosarcomas and UPSC tumours
- Laparoscopic hysterectomy (LH) and BSO with or without pelvic lymphadenectomy may be considered in selected patients and depending on the skill of the surgeon
- Pelvic lymphadenectomy is indicated in case of high-risk factors:
    - Grade 3 endometrioid carcinoma
    - UPSC, clear cell carcinoma and carcinosarcoma histological types
    - Cervical involvement

- > 50% invasion based on preoperative expert USS or MRI or frozen section

Post op Histopathologic assessment should include:

- Uterus
  - Ratio of depth of myometrial/stromal invasion to myometrial thickness
  - Cervical involvement (including depth of stromal invasion)
  - size
  - location (fundus vs. lower uterine segment/cervix)
  - Histologic subtype with grade
  - Lymphovascular space invasion
- Fallopian tubes/ovaries
- Peritoneal cytology (Although cytology by itself does not affect FIGO staging, cytology results should still be obtained because positive cytology is an adverse risk factor.
- Nodes (when resected)
  - Level of nodal involvement (i.e., pelvic, common iliac, para-aortic)
  - Size of metastasis (isolated cells, micrometastasis, macrometastasis)
- Estrogen receptor testing in setting of stage III, IV and recurrent disease.

Treatment for patients deemed medically unfit for surgery.

- For Stage I-IV with a reasonable prognosis from co-morbid condition: whole pelvic radiotherapy plus intracavitary brachytherapy
- Elderly, frail, morbidly obese: Intracavitary brachytherapy only
- For **Stage IV patients -** individualise, e.g. chemotherapy, hormonal

(medroxy-progesterone acetate), palliative radiotherapy, symptomatic treatment.

Treatment for patients with initially unresectable disease

These are patients with vaginal, bladder, bowel/rectum, parametrial or nodal involvement at diagnosis. Treatment options include:

- EBRT +/- brachytherapy +/- systemic therapy followed by re-evaluation for possible surgery
- Systemic therapy followed by re-evaluation for surgery and/or RT depending on response.

Risk group stratification

Endometrial cancer risk groups

Risk group	Description
Low risk	- Grades 1 and 2 with < 50% myometrial invasion (FIGO IA) - No lymphovascular space invasion.
Intermediate risk-low	- Grades 1 and 2 with ≥ 50% myometrial invasion
Intermediate risk	- Grade 1 and 2 with LVSI regardless of depth of invasion - Grade 3 with < 50% myometrial invasion.
High Risk	- FIGO stage 1, grade 3 endometrioid carcinoma with ≥ 50% myometrial invasion - Non-endometrioid histological types - FIGO stage II endometrioid carcinoma - FIGO stage III endometrioid carcinoma with no residual disease
Advanced disease	- FIGO stage III with residual disease - FIGO stage IVA
Metastatic disease	- FIGO stage IVB

Adjuvant treatment

After histological evaluation of the uterus, adnexa and lymph nodes with respect to, depth of myometrial invasion, grade of differentiation, cervical

involvement and adnexal involvement, proceed with adjuvant treatment where indicated. When administering adjuvant RT, it should be initiated as soon as the vaginal cuff has healed, no later than 12 weeks after surgery. Adjuvant treatment according to risk groups as defined above

Risk group/ stage	Recommended interventions
Low risk	Observation.
Intermediate risk-low	• Observation an option for <60 years. • Adjuvant vaginal brachytherapy
Intermediate risk- high	• Lymph node negative- adjuvant vaginal brachytherapy • Lymph node positive- pelvic EBRT and vaginal brachytherapy.
High risk- stage I & II	Pelvic EBRT and vaginal brachytherapy +/- systemic chemotherapy(for grade 3 or LVSI cases)
High risk- stage IIIC1	Systemic therapy and/or pelvic EBRT ± vaginal brachytherapy.
High risk- stage IIIC2	Systemic therapy and/or extended field EBRT ± vaginal brachytherapy
Stage IV	Palliative chemotherapy (single or combination)

Carcinosarcoma (MMMT) Treatment

Surgery as stated above for uterine cancers.

Postoperative treatment:

Chemotherapy +/- EBRT and vaginal brachytherapy is recommended.

Medicines

Medicine	Code	Adult dose	Frequency	Duration
Carboplatin and Paclitaxel	S V	Carboplatin AUC5/6 IV D1 Paclitaxel 175mg/m^2 IV D1	3 weekly	
Cisplatin and Paclitaxel	S V	Cisplatin 50mg/m^2 IV D1 Paclitaxel 175mg/m^2 IV Day 1	3 weekly	
Carboplatin and Doxorubicin	S V	Carboplatin AUC5-6 IV D1 Paclitaxel 175mg/m^2 IV D1	3 weekly	
Carboplatin (single agent)	S V	Carboplatin AUC5/6 IV D1	3 weekly	

Other uterine malignancies

a. Leiomyosarcoma.
b. Endometrial stromal sarcoma (ESS).
c. Adenosarcoma.

Treatment

- Surgery: Total abdominal hysterectomy (Lymphadenectomy and bilateral salpingoopherectomy not indicated).
- Cytoreductive surgery where feasible.

Postoperative treatment

a. Leiomyosarcoma & high-grade ESS.

Stage/ risk group	Adjuvant treatment.
Stage I- Low risk	observation
Stage I- high risk (>15 mitoses/10 HPF)	Consider systemic chemotherapy
Stage II & III	Consider systemic therapy and/or EBRT
Stage IVA	Systemic therapy and/or EBRT
Stage IVB	Palliative chemotherapy therapy +/- palliative EBRT

Incompletely excised: Consider chemotherapy + radiation therapy. Radiotherapy can be considered for local control. And chemotherapy can be considered for advanced or recurrent disease.

b. Low grade ESS.

Late recurrences occur in this disease thus long-term follow-up is recommended. Treatment for low grade ESS include:

Stage	Adjuvant treatment.
Stage 1	• Observation especially in post-menopausal patients. • Estrogen blockade
Stage II- IV	• Postoperative estrogen blockade. • Adjuvant EBRT may be added for stage II-IVA • Palliative RT may be added to estrogen blockade for patients with stage IVB disease • Typical hormone therapy includes aromatase inhibitors (preferred), megestrol acetate, or medroxyprogesterone acetate (MPA). Gonadotropin - releasing hormone [GnRH] analogs are also an option

In cases of incomplete resection and recurrence: consider high dose MPA or aromatase inhibitors.

c. Adenosarcoma

Consider adjuvant radiotherapy or chemotherapy where there is sarcomatous overgrowth or myometrial invasion.

Medicines

Medicine	Codes		Adult dose	Frequency	Duration
Doxorubicin	**S**	**V**	Doxorubicin 60-100mg/m^2 IV D1.	3 weekly	4
Docetaxel and Gemcitabine	**S**	**V**	Docetaxel 75mg/m^2 IV D1 Gemicitabine 675mg/m^2 IV Day 1	3 weekly	4
Anti- estrogen hormone therapy for low grade ESS.					

Follow up

Follow up visits every 3 monthly months for 2 years, then every 6 months for 3 years, then once a year after 5 years with:

- Physical examination including a pelvic exam
- CT scan chest, abdomen & pelvis every 3-6mnths depending on histology, grade and stage for 2 years or CXR and USS abdomen & pelvis.
- Imaging should be based on clinical concern for metastatic disease.
- CA-125 assay or other markers if initial results were high.

Vulva cancer

General note

Risk factors for vulva cancer include HPV infection, cigarette smoking, inflammatory conditions, immunosuppression, multiple sexual partners, history of genital warts and low socioeconomic status.

History and symptoms

- Persistent pruritus and pain/irritation on the vulva.
- Vulva mass which may be ulcerated, leukoplakia, fleshy, or warty.
- vulvar bleeding or discharge.

- Difficulty in defecation or micturition due to invasion of regional structures.

Physical Examination

- General examination- including signs of anaemia and palpable lymph nodes (note inguinal and supraclavicular regions)
- Abdominal exam.
- Pelvic Examination
    - Vulva- describe the abnormal lesion- size, number, extension to other perineal structures, presence of infection and examination of the vagina, cervix, perianal skin and anal canal should be done. This is so as to identify any synchronous lesions as well as the extent of the disease.

Diagnostic workup

- Biopsy of all suspicious areas.
- HPV testing if available may be done.

Staging workup.

- FBC, U&Es, LFTs and HIV test
- PAP smear.
- EUA with cystoscopy or proctoscopy when indicated.
- CT scan chest, abdomen & pelvis if available for large s or if metastasis is suspected.
- Chest X-ray and USS abdomen & pelvis (including inguino-femoral region)
- Pelvic MRI may be used to delineate the extent of and/or to aid in surgical and/or radiation treatment planning

Staging of vulva cancer using FIGO and TNM classifications.

Treatment

All vulva cancer patients should be discussed in a multidisciplinary team meeting (including pathologist, gynecologist, surgeon, pharmacist, oncology nurse, radiologist, HIV care specialist and social worker) prior to treatment. Treatment is based on the stage and histology. The guidelines here focus on squamous cell histology which is more common in Zimbabwe.

Early stage	Surgery	Radiotherapy
T1 with ≤ 1 mm depth of invasion	• Wide local resection or radical resection recommended. • Inguino-femoral nodal dissection not necessary due to low risk of metastases	
T1 or smaller T2 s (<4cm) with depth >1 mm	• Primary treatment is dictated by tumour location. • Lateralized lesions located ≥2 cm from the vulvar midline can undergo radical local resection or modified radical vulvectomy plus ipsilateral groin node dissection. • Midline lesions can undergo radical local resection or modified radical vulvectomy accompanied by bilateral groin node dissection. • If close or positive surgical margin -re-resection or adjuvant radiotherapy	• Adjuvant EBRT for patient with: ○ positive margins ○ Node positive disease. ○ Tumour size >4cm. ○ Depth of invasion >5mm and pattern of invasion (spray or diffuse). ○ • Definitive EBRT for patient who decline surgery.
Local advanced disease- large T2 & T3	• Consider for post chemoradiation residual disease.	• Chemoradiation. • For those with clinical complete response c onsider biopsy of tumour bed at 3 months to confirm pathological response. • Biopsy positive patients may need additional surgery, additional EBRT and/or systemic therapy or best supportive care.

Metastatic disease (stage IVB)	•	• EBRT for locoregional control or symptom palliation f or symptoms such a fungating or bleeding masses • Palliative systemic chemotherapy.

Medicines

Medicine	Codes	Adult dose	Frequency	Duration
Chemoradiation.				
Cisplatin	S V	Cisplatin 35-40mg/m^2 IV D1.	Weekly	5
Carboplatin	S V	Carboplatin AUC2 IV D1	Weekly	5
Systemic chemotherapy.				
Cisplatin and 5-FU	S V	Cisplatin 75-100mg/m^2 IV D1 5-FU 1000mg/m^2 IV D1-D4	3 weekly	As per oncologist.
Cisplatin and paclitaxel	S V	Cisplatin 50mg/m^2 IV D1 Paclitaxel 175mg/m^2 IV Day 1	3 weekly	As per oncologist.

Follow-up

- History & physical examination 6 weeks post treatment, then 3 monthly for 2 years, then every 6–12 months for 3–5 years, then annually based on patient's risk of disease recurrence.
- Cervical/vaginal cytology screening as indicated.
- Imaging as indicated based on symptoms or examination findings suspicious for recurrence.

Epithelial Ovarian Cancer

General note

Diagnosis is often delayed as symptoms are non-specific.

History & symptoms

Frequent symptoms

- persistent abdominal distension
- abdominal bloating
- early satiety
- loss of appetite
- pelvic or abdominal pain
- urinary urgency and/or frequency

Less frequent symptoms are
- postmenopausal bleeding
- unexplained weight loss
- fatigue
- changes in bowel habit e.g. constipation

Diagnostic Work-up
- Serum CA-125 assay.
- FBC, U&E, LFT and HIV test.
- USS scan abdomen and pelvis.
    - Features suggestive of ovarian cancer include complex cysts with papillary projections, septations, mural nodularity, solid ovarian masses, bilateral lesions and ascites
- CT scan chest, abdomen and pelvis (if available).

Treatment

All ovarian cancer patients should be discussed in a multidisciplinary team meeting (including pathologist, oncologist, surgeon, pharmacist, oncology nurse, radiologist and social worker) prior to treatment. Histological diagnosis is not required before offering a patient primary debulking surgery for suspected ovarian cancer but is required before chemotherapy. The mainstay of therapy for early stage ovarian cancer is surgical treatment. Surgery should be performed by experienced specialist gynaecologists with experience in managing ovarian cancer and fertility sparing surgery should be offered to appropriately selected patients.

Surgical staging for ovarian cancer involves:

- Midline laparotomy
- Peritoneal washings/ascitic sampling taken prior to manipulation of the
- Bilateral salpingo-oophorectomy
- Total hysterectomy
- Multiple peritoneal biopsies from the para-colic & sub-diaphragmatic spaces
- Infracolic omentectomy
- Pelvic and para-aortic lymph node assessment
- Retroperitoneal lymph node assessment (sampling of retroperitoneal lymphatic tissue from the para-aortic area and pelvic side walls if there is palpable abnormality, or random sampling if there is no palpable abnormality).

Early-stage disease management.

Adjuvant systemic chemotherapy for high risk early stage disease in the following cases:

- Histological grade 3
- FIGO stage 1c

Management of advanced ovarian cancer.

- Debulking surgery then adjuvant chemotherapy is preferred.
- Neo-adjuvant chemotherapy with interval debulking surgery after three cycles of platinum-based chemotherapy is non-inferior to primary upfront debulking surgery and adjuvant platinum-based chemotherapy.
- A “second look” operation following debulking surgery and chemotherapy has no survival benefit and is not recommended.
- For metastatic disease (stage IV) intervention should be aimed at improving quality of life (palliative care).
- Hormonal and targeted therapies can be considered were appropriate.

Medicines

Medicine	Codes	Adult dose	Frequency	Duration
Carboplatin and Paclitaxel (standard)	S V	Carboplatin AUC6 IV D1 Paclitaxel 175mg/m^2 IV D1	3 weekly	
Carboplatin and paclitaxel (alternative)	S V	Carboplatin AUC6 IV D1 Paclitaxel 175mg/m^2 IV D1, B8 & D15	3 weekly	

Follow up.

Patients with ovarian cancer need monitoring during and after treatment. Follow up visits every 3 monthly months for 2 years, then every 6 months for 3 years, then once a year after 5 years with:

- Physical examination including pelvic exam.
- Serum CA-125 assay or other markers if initial results were high.
- CXR, USS or CT scan when indicated.

Gestational Trophoblastic Neoplasia

General Note

Gestational trophoblastic neoplasia (GTN) is a group of malignant neoplasms that arise from abnormal placental trophoblastic proliferation. The pathologic entities that constitute this group are invasive mole (IM), choriocarcinoma (CC), placental site trophoblastic tumour (PSTT) and epitheloid trophoblastic tumour (ETT). GTN always arise from some form of pregnancy with molar pregnancies being the commonest (50%) followed by miscarriages, term or preterm births and ectopic pregnancies. For this reason, patients who are managed for molar pregnancies should be closely followed up in order to readily identify those developing GTN before the disease has advanced. It is possible to have GTN in patients without a prior pregnancy event as some patients may have early pregnancy losses that they may not be aware of therefore clinicians should always have a high index of suspicion if the history is suggestive. Nearly all forms of GTN secrete human chorionic gonadotrophin hormone (hCG) which is a reliable marker both in the follow up of molar pregnancy and in the diagnosis of GTN.

History and symptoms

- Half of GTN develop from non-molar pregnancies common symptoms include:
    - Abnormal uterine/vaginal bleeding
    - Bleeding from a metastatic lesion e.g. vulva, vagina, abdomen, lung or brain.
    - Symptoms of metastatic disease -coughing, shortness of breath, chest pain and neurologic deficits
- History of repeated uterine curettage (result of low suspicion of GTN by clinicians). It is therefore recommended that a patient should not have repeated uterine curettage unless consultation with an experienced gynaecologist has been made and histology of the whole tissue obtained at curettage is followed up.
- Commonest presentation is in asymptomatic women under hCG surveillance post suction curettage of molar pregnancy
    - Serum hCG should normalise to <5mIU/ml by day 56 therefore a woman has GTN until proven otherwise if hCG has not normalised as expected or it is rising or plateauing as tabulated below.

• When the plateau of hCG lasts for four measurements over a period of 3 weeks or longer; that is, days 1, 7, 14, 21. • When there is a rise in hCG for three consecutive weekly measurements over at least a period of 2 weeks or more; days 1, 7, 14. • When the hCG level remains elevated for 6 months or more. • If there is a histologic diagnosis of choriocarcinoma.

- PV bleeding following an EVAC should be managed with re-EVAC twice, pregnancy test and a referral to a facility where hCG testing can be done.

Physical examination

- General examination- pallor, performance status and oedema
- Abdomino-pelvic examination
  - Bulky uterine size
  - Vaginal or vulva mass/nodules
  - Hepatomegaly
  - Ascites (intra-abdominal bleeding)
- Chest - signs of lung consolidation or pleural effusion collection
- CNS- hemiplegia/hemiparesis due to CNS haemorrhagic metastases

Diagnostic Workup

All women with suspected GTN should have tests that help confirm the disease, assess acuity/ complications and to stage the disease.

- Quantitative serum hCG test (preferred)
- Qualitative serum/urine hCG may be used if quantitative test is unavailable

Histology is not routinely recommended to confirm GTN even in patients with superficial metastatic lesions. There is significant risk of post-procedure haemorrhage and biopsy for histologic evaluation may add to diagnostic delays.

Staging workup.

- FBC, U&E, LFT, blood grouping and HIV test.
- Chest x-ray (size and number of metastatic lesions)
- USS abdomen & pelvis- size of the uterus and number of intra-abdominal metastases
- CT scan abdomen (if available)
- CT scan Chest or brain done for patients with hepatic, lung or vulva metastases found during initial evaluation or those with CNS symptoms.

Risk Scoring

It is vital to allocate every woman diagnosed with GTN a risk score based on the WHO/FIGO prognostic scores. These prognostic scores are based on the finding that women with poor prognostic scores tend to be resistant to monotherapy hence require multi-agent chemotherapy to achieve response.

Risk factor	0	1	2	4
Age (years)	<40	>40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval months from end of index pregnancy to diagnosis of GTN	<4	4 ≤ 7	7 ≤ 13	>13
Pre-treatment serum Bhcg (IU/L)	$<10^3$	$10^3 \leq 10^4$	$10^4 \leq 10^5$	$>10^5$
Largest tumour size, including uterus (cm)	<3	3 ≤ 5	>5	–
Site of metastases	Lung	Spleen, kidney	Gastro-intestinal	Liver, brain
Number of metastases	–	1–4	5–8	>8
Previous failed chemotherapy	–	–	Single drug	Two or more drugs

- Low risk GTN score ≤ 6
- High risk GTN score > 7

Treatment

All gestational trophoblastic neoplasia patients should be discussed in a multidisciplinary team meeting (including radiologist, gynaecologist, clinical oncologist, pharmacist, oncology nurse, pathologist and social worker) prior to treatment to ensure standardized care and better outcomes. Treatment is primarily chemotherapy with either single agent or multiple agents depending on whether the disease is low or high risk respectively.

Classification	Treatment
Low risk	• Single agent chemotherapy
High risk	• Combination chemotherapy • Radiotherapy (site specific e.g. brain metastases)
Chemotherapy refractory disease	• Radiotherapy • Surgery
Acute haemorrhage unresponsive to chemotherapy	• Radiotherapy

Medicines

Chemotherapy regimens.

Medicine	Codes	Adult dose	Frequency	Duration
Low risk disease				
Methotrexate (8-day regimen)	S V	Methotrexate 50mg IM on D1, D3, D5 & D7 Leucovorin 15mg PO D2, D4, D6 & D8	2 weekly	
Methotrexate (5-day regimen)	S V	Methotrexate 0.4mg/m^2 (max 25mg) IV or IM D1- D5	2 weekly	
Methotrexate (weekly IM regimen)	S V	Methotrexate 30-50mg/m^2 IM D1	weekly	
Methotrexate	S V	Methotrexate 300mg/m^2 IV (infusion) D1	2 weekly	
Actinomycin-D (pulsed)	S V	Actinomycin 1.25mg/m^2 IV D1	2 weekly	
Actinomycin - D	S V	Actinomycin 0.5mg IV D1-D5	2 weekly	
High risk disease				
Etoposide, methotrexate, actinomycin-D, cyclophosphamide & vincristine (oncovin) (EMACO regimen)	S V	Day 1 (EMA) • Actinomycin-D 0.5mg IV • Etoposide 100mg/m^2 IV • Methotrexate 300mg/m^2 IV continuous infusion over 12h Day 2 (EMA) • Actinomycin-D 0.5mg IV • Etoposide 100mg/m^2 IV • Leucovorin 15 mg PO/IM 12hourly x 48h; initiate 24hurs after starting of MTX Day 8 (CO) • Vincristine 1mg/m^2 IV bolus (max 2mg) • Cyclophosphamide 600 mg/m2 IV	Alternate weekly	6

Before starting each cycle, a patient should have history taken physical examination, and FBC, U&E, LFT and serum hCG testing. Patients require a minimum of six cycles of chemotherapy but it is more important to ensure that there has been at least two consolidation cycles give following a β-hCG of <5mIU/ml.

Follow up

- It is recommended that for a minimum of 12 months patients must be under surveillance with monthly serum hCG testing while on effective contraception.
- Conception if desired may occur after GTN and following pregnancy it is important to screen for relapse or recurrence of GTN by serum hCG at six weeks postpartum which should be <5mIU/ml.
- Care of women with GTN should be comprehensive with inclusion of general medical care and reproductive and sexual health counselling including HIV testing.

Prostate cancer

General Note

Prostate cancer is the most common cancer in men and the most common cause of cancer-related mortality in males. Ninety-five percent of prostate cancer cases are diagnosed between 45 and 89 years of age (mean: 72 years). The incidence of prostate cancer increases with age, and the risk of developing it is 1/10,000 before 40 years of age, 1/103 between 40 and 59 years of age, 1/8 between 60 and 79 years of age. The lifetime risk of prostate cancer is approximately 10%.

History and symptoms

- Most patients are asymptomatic in the early stages
- Irritative or bladder outlet obstructive symptoms
- Hematuria
- Hematospermia due to seminal vesicle invasion
- Uremic symptoms from ureteral obstruction
- Erectile dysfunction
- Metastatic disease
    - Anorexia
    - Weight loss
    - Metastatic bone pain
    - Pathologic bone fractures
    - Spinal cord compression (Oncological emergency)

Physical examination

- General examination- cachexia, oedema, lymphadenopathy
- Digital rectal examination- firm and irregular prostate is typical of prostate cancer.

Diagnostic workup

- Serum PSA
- Prostate biopsy :>8 separate cores is recommended (Trans-rectal USS guided-biopsy is preferred)

Staging workup

- Pathology review- Gleason score, percentage involved with tumour and lobes involved
- Serum PSA, FBC, U&E, LFT and HIV test.
- Bone scan and CT scan or MRI are usually ordered for T3–T4, Gleason score ≥8, PSA≥ 20, or if symptomatic (if available)
- USS abdomen & pelvis, chest x-ray and skeletal survey if more advanced

imaging is not available

Treatment

All patients with prostate cancer MUST be discussed in a multidisciplinary team meeting (including pathologist, radiologist, clinical oncologist, urologist, physiotherapist, occupational therapist, pharmacist, oncology nurse and social worker) prior to any treatment being initiated.

Localized tumours are stratified by T stage, Gleason score and PSA into three prognostic groups.

Risk classification	T-stage	Serum PSA level	Gleason score
Low	T1–T2a	<10 ng/mL	≤ 6
Intermediate – favourable*	T2b	10–20 ng/mL	7 (3+4)
Intermediate-unfavourable*	T2b	10–20 ng/mL	7 (4+3)
High	T2c–T4	>20 ng/mL	8–10

*The risk is higher in an intermediate risk patient who has GS 4 + 3 than with GS 3 + 4.

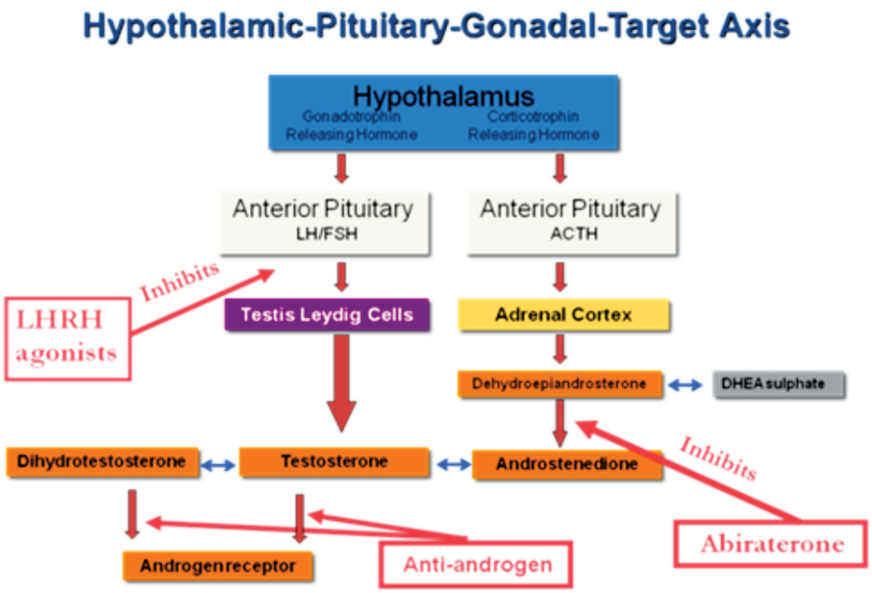
Patients can be offered appropriate treatment options by an MDT according to stage of disease, prognostic risk group and estimated survival considering performance status and comorbidity. Treatment of localized prostate cancer includes external beam radiotherapy, interstitial brachytherapy and surgery for the curative treatment. These modalities have equivalent outcomes but different side effect profiles. Patients must be referred to a centre where all the expertise are present and discussed with the patient.

Prostate cancer stage/risk group	Treatment options
Localised low risk (T1–T2a), PSA <10ng/mL, GS 6)	• Active surveillance • Watchful waiting • External beam radiotherapy + ADT (4-6 months) • Interstitial prostate brachytherapy • Radical prostatectomy
Localised Intermediate risk- favourable (T2b or PSA 10–20 or GS 7 (3+4))	• Watchful waiting • Interstitial prostate brachytherapy • External beam radiotherapy + ADT (4-6 months) • Radical prostatectomy

Localised Intermediate risk- unfavourable (T2b or PSA 10–20 or GS 7 (4+3))	• External beam radiotherapy+ ADT (4-6 months) • External beam radiotherapy and brachytherapy boost + ADT • Radical prostatectomy
Localised high risk: (T2c–T4 or PSA >20 or ≥GS 8)	• External beam radiotherapy+ ADT (2-3years) • External beam radiotherapy and brachytherapy boost + ADT (2-3v years) • Radical prostatectomy and pelvic lymph node dissection (PLND) ○ Adjuvant ADT +/- radiotherapy • Can consider ADT + chemotherapy OR ADT alone in some cases.
Metastatic disease	• Pelvic radiotherapy + ADT for oligometastatic disease • ADT + systemic chemotherapy • ADT alone • Palliative radiotherapy • Palliative surgery • Radio-isotope therapy Ra-233 for patients with no bone metastases. • Best supportive care

Principles of prostate cancer surgery

- Radical prostatectomy is appropriate for patients with localized prostate cancer that can be completely excised surgically, who have a life expectancy of ≥10yrs and no contraindications to surgery.
- An extended pelvic lymph node dissection (PLND) provides more complete staging and may cure some men with microscopic metastases therefore it is preferred when pelvic node dissection is performed
- PLND can be excluded in patients with <2% prediction of prostate cancer of nodal spread.
- Salvage radical prostatectomy is an option for highly selected patients with local recurrence after external beam radiotherapy, interstitial brachytherapy or cryotherapy in the absence of metastases. It has a high morbidity and should be performed by experienced urologists at a tertiary hospital.



Primary ADT options include:

- Surgical castration (bilateral orchiectomy)
- Medical castration with GHRH agonist/antagonists

Secondary ADT options include:

- Anti-androgens (bicalutamide, enzalutamide)
- Androgen metabolism inhibitor (Abiraterone acetate; ketoconazole)
- Corticosteroids (hydrocortisone, prednisolone, dexamethasone)
- Diethylstilbestrol (DES) or other estrogens

ADT for clinically localized disease:

- Neoadjuvant ADT for RP is strongly discouraged outside of a clinical trial
- ADT should generally not be used as monotherapy in clinically localized prostate cancer

Tumour Flare

- When gonadotropin hormone releasing hormone agonists (GHRH) (e.g. Goserilin) are first given, testosterone levels go up briefly before falling to very low levels. This effect is called ***flare***
- Men whose cancer has spread to the bones may have bone pain.
- If the cancer has spread to the spine, even a short-term increase in tumor growth as a result of the flare could result is spinal cord compression (Oncological emergency)
- Flare can be avoided by giving GHRH together with anti-androgens for a few weeks when starting treatment
- GHRH antagonists do not cause a tumour flare.

Medicines

Medicine	Codes		Adult dose	Frequency	Duration
Docetaxel	S	V	Docetaxel 75mg/m^2 IV D1	3 weekly	6-10
Paclitaxel	S	V	Paclitaxel 135-175mg/m^2 IV D1	3 weekly	6-10
Bicalutamide	S	V	Bicalutamide 50mg PO	Daily	
Abiraterone acetate	S	V	Abiraterone 1 000mg PO OD	Daily	

Follow-up

- History and physical examination with DRE and PSA every 6 month for 5 years and then annually thereafter
- In the first 1–3 years after definitive radiotherapy, PSA may be ordered more frequently (e.g. every 3–6 month)

Bladder cancer

General note

Bladder cancer originates from the urothelium. The most common subtype globally is a transitional cell carcinoma (urothelial carcinoma) but in Zimbabwe squamous cell carcinoma is the prevalent subtype. Risk factors include male sex, tobacco smoking, personal & family history of

bladder cancer, pelvic radiation, environmental/occupational exposures, chronic infections (schistosomiasis), chronic irritations (e.g. bladder stone) and medical conditions like obesity & diabetes.

History and symptoms

- Hematuria
- Urinary frequency
- Dysuria
- Lower abdominal pain
- Lower back pain
- Recurrent urinary tract infections

Physical examination

- General examination- performance status, fever, oedema and lymphadenopathy
- Abdomino-pelvic examination

Diagnostic workup

- Cystoscopy and transurethral resection of the bladder tumour (TURBT) or tissue biopsy
- Urine cytology

Staging workup

- FBC, U&E, LFT, Urinalysis including m/c/s, RBS and HIV tests.
- Histology review
- MRI or CT scan (if available) or USS abdomen & pelvis and chest x-ray.
- Bone scan is symptomatic
- Examination under anesthesia

Treatment

All patients with bladder cancer MUST be discussed in a multidisciplinary team meeting (including pathologist, radiologist, clinical oncologist, urologist, rehabilitation specialist, pharmacist, oncology nurse and social worker) before any treatment intervention.

	Surgery	Radiotherapy	Systemic therapy
cTa (low grade)	TURBT then observation		
cTa (high grade)	TURBT with BCG		
cT1	TURBT with BCG or cystectomy (in high grade)		
cT2, N0 (cystectomy feasible)	• Radical cystectomy after neoadjuvant chemotherapy (preferred) • Cystectomy alone if not candidate for neoadjuvant chemotherapy	• Adjuvant radiotherapy for patients with pT3-4 or positive lymph nodes • Upfront concurrent chemoradiation (patient preference)	Neoadjuvant chemotherapy then surgery
cT2 N0 (cystectomy non-feasible)		• Upfront concurrent chemoradiation	• Adjuvant chemotherapy if residual disease after 3 months
cT3-cT4a, N0-N1	• Radical cystectomy after neoadjuvant chemotherapy	• Adjuvant radiotherapy for patients with pT3-4 tumours, residual disease or positive lymph nodes • Upfront concurrent chemoradiation	• Neoadjuvant chemotherapy then surgery • Adjuvant chemotherapy for patients with residual disease, pT3-4 tumours or positive lymph nodes if no neoadjuvant chemotherapy given • Upfront systemic chemotherapy/immunotherapy
cT1-T4a, N2-3		• Concurrent chemoradiation (preferred) following neoadjuvant chemotherapy	• Neoadjuvant chemotherapy followed by chemoradiation • Upfront systemic chemotherapy/immunotherapy
cT4b or M1a		• Concurrent chemoradiation (preferred) following neoadjuvant chemotherapy	• Neoadjuvant chemotherapy followed by chemoradiation • Upfront systemic chemotherapy/immunotherapy

Medicines

Medicine	Codes	Adult dose	Frequency	Duration
Neoadjuvant or adjuvant chemotherapy				
Cisplatin and gemicitabine	S V	Cisplatin 75mg/m2 IV D1 Gemicitabine 1000mg/m^2 D1, D8 & D15	4 weekly	4
MVAC (dose dense)	S V	Methotrexate 30mg/m^2 IV D1, D15 & D22 Vinblastine IV 3mg/m^2 IV D2, D15 & D22 Doxorubicin 30mg/m^2 D2 Cisplatin 70mg/m^2 IV D2	4 weekly	2-3
For cisplatin ineligible chemotherapy				
Carboplatin and gemicitabine	S V	Carboplatin AUC4 IV D1 Gemicitabine 1000mg/m^2 D1 &D8	3 weekly	6
Gemicitabine single agent	S V	Gemicitabine 1200mg/m^2 D1, D8 & D15	4 weekly	
Gemicitabine and paclitaxel	S V	Gemicitabine 1000mg/m^2 D1, D8 & D15 Paclitaxel 200mg/m^2 IV D1	3 weekly	
Paclitaxel single agent	S V	Paclitaxel 80mg/m^2 IV weekly x 3 weeks	4 weekly	

Follow up

- For patients who have uundergone bladder preserving treatment review with history, physical examination, urine cytology and cystoscopy 3 monthly for the first 2 years, then 6 monthly up to the 5th year and annually thereafter. Imaging as clinically indicated.
- Post cystectomy review with history, physical examination and CT scan or MRI scans every 3 months for 2 years, then 6 monthly up to 5 years and annually thereafter.

Soft Tissue Sarcomas

General Notes

Sarcomas are malignant tumours originating from mesenchymal tissue. They can develop at any site in the body. Extremity (45%) > trunk (30%) > upper extremity (15%) > Head & neck (8%). Soft sarcomas (STS) are rarely seen among adults and they constitute about 1% of all cancers. STS are a diverse group of malignancies with different biological behaviours. They are classified histologically according to their cellular origin. Malignant STSs include:

- Malignant fibrous histiocytoma (MFH)
- Liposarcoma
- Leiomyosarcoma
- Fibrosarcoma
- Synovial cell sarcoma
- Rhabdomyosarcoma
- Malignant peripheral nerve sheath tumor/malignant schwannoma (5%).
- Angiosarcoma
- Epithelioid sarcoma
- Clear cell sarcoma
- Neuroectodermal tumor
- Dermatofibrosarcoma
- Hemangiopericytoma
- Myxoid chondrosarcoma
- Synovial chondrosarcoma

History and symptoms

- Painless growing mass which may fungating. Gradually becoming painful, may interfere with movement and other functions depending on site of lesion
- Metastatic symptoms may develop such as cough, shortness of breath
- Common sites
  - Extremity = liposarcoma, MFH, synovial, fibrosarcoma, myxoid

liposarcoma (upper medial thigh).

- Retroperitoneal = liposarcoma (fewer DM) > leiomyosarcoma (increased DM).
- Head &neck =malignant fibrous histiocytoma (MFH), usually high-grade (except myxoid MFH = intermediate grade).
- Chronic lymphedema of upper extremity for lymphangiosarcoma.
- Near (but not within) joints in tendon sheaths, bursae, and joint capsules - synovial sarcoma.

Diagnostic workup

- Incisional biopsy or core needle biopsy preferred
- Incision for biopsy should be along future resection axis with minimal dissection and careful attention to haemostasis to ensure proper excision at definitive surgery.
- If possible, biopsy should be performed by the surgeon/at the institution where definitive surgery will be performed.
- Immunohistochemistry for definitive diagnosis confirmation

Staging workup

- FBC, U&E, LFT, LDH and HIV test.
- CT/MRI of primary site (if available) or plain x-ray and/or USS of primary site.
- CT chest for all patients (or chest x-ray)
- Genetic testing when appropriate e.g. c-*KIT* for GIST

Treatment

All patients with soft tissue sarcomas cancer MUST be discussed in a multidisciplinary team meeting (including pathologist, radiologist, clinical oncologist, surgeons, physiotherapist, occupational therapist, pharmacist, oncology nurse and social worker) before any treatment intervention.

General treatment recommendations

Stage/site	Treatment options
Stage I extremity	Surgery alone (unless close (< 1 cm) or + margin post -op radiotherapy).
Stage II–III extremity •	Surgery + post-op radiotherapy OR Pre-op radiotherapy →surgery. • Consider neoadjuvant/adjuvant chemo for large deep high-grade tumors
Stage IV	• Chemotherapy, and/or palliative surgery. • For controlled primary, with <4 lung lesions and/or extended disease-free interval, consider surgical resection. • Chemotherapy, and/or palliative radiotherapy. • Best supportive care,
Retroperitoneal	• R0 resection – Observe • R1 resection post-op radiotherapy 45–50 Gy or boost if pre-op radiotherapy was given. • R2 resection - Consider re-resection if technically feasible OR treat as unresectable: Unresectable - pre-op radiotherapy +/- chemo → resection.
GIST	• Completely Resectable: → Surgery +/- imatinib • If marginally resectable/: consider further surgery +/- imatinib Consider pre-op imatinib (often 6months or more to achieve significant response) Unresectable: Imatinib Imatinib response is more likely if the is c-KIT positive
Desmoid tumours	• Operable: Surgery. If positive margin, post -op RT (50 Gy). • If inoperable: RT (56–60 Gy). • Consider chemotherapy (methotrexate/vinblastine) in certain cases as about 1/3 can have stable disease or a response

Principles of Surgery in STS

- A wide en-bloc resection with 2 cm margin in all directions should be preferably undertaken.
- A radical resection removes entire anatomic compartment

including neurovascular structures. Wide excision removes cuff of normal tissue.

- Clips should be placed to delineate tumour bed to aide adjuvant radiotherapy planning.

Chemotherapy for STS

Medicines

Medicine	Codes	Adult dose	Frequency	Duration
Systemic therapy with activity in soft tissue sarcoma with non–specific histology				
Gemcitabine & docetaxel		Days 1 and 8: Gemcitabine 900mg/m2 IV Day 8: Docetaxel 100mg/m2 IV.	3 weekly	6
Doxorubicin + ifosfamide + mesna (AIM)	**S V**	Days 1 and 2: Doxorubicin 30mg/m2/day IV ifosfamide 3,750mg/m2/day IV Mesna 750mg/m2 IV immediately preceding and then 4 and 8 hours after ifosfamide administration	3 weekly	6
Mesna + doxorubicin + ifosfamide + dacarbazine (MAID)	**S V**	Days 1–3: Doxorubicin 20mg/m2/day Ifosfamide 2,500mg/m2/day Dacarbazine 300mg/m2/day as continuous IV infusion over 72 hours Mesna 2,500mg/m2/day IV for 84 to 96 hours.	3 weekly	4-6
Doxorubicin single agent	**S V**	Doxorubicin 60–75mg/m2 IV	3 weekly	4-6
Gemcitabine single agent		Days 1 and 8: Gemcitabine 1,200mg/m2 IV	3 weekly	4-6
Ifosfamide	**S V**	Ifosfamide 5 000mg/m^2 IV Mesna 5 000mg/m^2 continuous IV (24 hours) followed by additional mesna 400–600mg/m2 IV over 2 hours after completion of ifosfamide administration.	3 weekly	4-6

Dacarbazine	S V	Dacarbazine 250mg/m^2/day IV D1-D5 OR Dacarbazine 800–1,000mg/m^2 IV D1	3 weekly	4-6
Imatinib (For GIST)		Imatinib 400mg PO OD May gradually increase up to 800mg daily if no response or if recurrence		

Other drugs to consider if available Trabectedin, Pazopanib, Eribulin, Trabectedin, Everolimus, Sunitinib, nilotinib, sorafenib, regorafenib

Follow up.

- Evaluate for rehabilitation (OT, PT) on completion of treatment and continue OT/PT until maximal function is achieved
- History and physical examination every 3months for 2 year, every 6 months for 3– 5years, then annually thereafter
- CT/MRI of primary site +/- CT chest/CXR every 3-6 months for 2 – 5 years, then annually thereafter (may be less frequent in low grade subtypes)

Kaposi Sarcoma

General notes

Kaposi Sarcoma (KS) is a tumour of endothelial cell origin. It is characterized by abnormal angiogenesis, inflammation and proliferation of spindle cells infected with the Kaposi sarcoma herpes virus (KSHV) or human herpesvirus-8 (HHV-8). It remains one of the common malignancies in people living with HIV, especially in sub-Saharan Africa. The roll-out of antiretroviral therapy (ART) has had a profound influence on the epidemiology of HIV-associated KS and has been associated with a substantial reduction in KS incidence and improvement of survival.

History and symptoms.

Clinical presentation is site dependent.

Cutaneous lesions: Flat, painless spots that are red or purple on white skin

and bluish, brownish, or black on darker skin. The lesions are not itchy.

Oedema. Severe swelling in the arms, legs, face, trunk and genitalia. This is often woody-hard and warm to touch.

Gastrointestinal tract: difficulty eating or swallowing, nausea, vomiting, loss of weight, haematemesis, haematochezia, and abdominal pain. Some patients may have asymptomatic oral/palatal lesions found only at physical examination**.**

Muco-cutaneous or visceral regions: Common sites of involvement include lungs, liver, stomach, intestines, and lymph nodes. KS may be extensive and can be life-threatening, particularly with visceral involvement

Chest: Coughing, dyspnoea, chest pain, haemoptysis. Some cases are asymptomatic and incidental lung lesions are found on chest x-ray imaging.
Genitourinary system (GUS): Swollen penis, scrotum, and inguinal lymphadenopathy. In women, KS can affect the perineum and vulva.

KS immune reconstitution inflammatory syndrome (IRIS): This may be characterized by an abrupt clinical worsening of KS.

Physical examination.
General Examination

- Examination of the oral cavity and skin

Local area - thoroughly examine the affected regions and document the following:

- Affected sites.
- Number of lesions
- Size, shape, colour, consistency, flatness, and presence of ulceration.
- State of surrounding skin
- Presence of oedema.
- Measure the circumference of the limb at a specific point e.g.

10 cm distal to the tibial tuberosity.
Regional – examine regional lymph nodes to the affected area.

Diagnostic workup.

- Tissue biopsy for histological diagnosis.
- Immunohistochemistry – KSHV should be done. CD31 and CD34 may be done in uncertain cases.

Staging workup.

A patient with suspected KS (even if unconfirmed) or with insufficient investigations may still be referred to the relevant oncologist. Investigations should not delay the patient from getting a specialized assessment. Treatment should however only be commenced when a tissue diagnosis has been made.

- FBC, U&E, LFT and HIV test.
- CD4 and HIV viral load.
- CXR
- Photography of oral and cutaneous lesions (where available)
- Echocardiogram (if anthracycline use is planned or there is a suspected pericardial effusion)

Useful in Select Cases:

- Stool haemoccult
- Endoscopy – upper GI or colonoscopy
- Bronchoscopy
- USS Abdomen and pelvis
- CT with contrast (or MRI) of chest, abdomen and pelvis

Staging systems than can be used include the AIDS Clinical Trials Group (ACTG) staging classification and the staging system for aids-related KS (paediatric).

Treatment

Principles of Therapy

- Individual KS lesions may be distinct clones as opposed to metastases. Treatment of existing disease does not prevent occurrence of future clones.
- In advanced or widely extensive disease, complete remissions are rare. Treatment is typically continued until unacceptable toxicity or plateau in response. When a plateau has been established, maintenance therapy beyond 2 cycles of systemic therapy after determination of plateau is not recommended.
- Reconstitution of immune function, maintenance of viral suppression and avoidance of additional immunosuppression are critical to prevent additional KS lesions and maintain response to treatment.
- Collaborate with an HIV specialist/OI clinic in AIDS-related KS.

Treatment Options:

- ART alone in HIV-related KS with asymptomatic or limited cutaneous
- Patients with limited cutaneous disease that is asymptomatic and cosmetically acceptable may be observed while continuing ARVs. Patients rarely present with mild/limited KS
- Symptomatic or cosmetically unacceptable but limited disease should use the most minimally invasive and least toxic therapy to control disease. Topical options or a limited number of cycles (e.g. 3 - 4) may be sufficient for some cases.
- Moderate/Advanced symptomatic, visceral, nodal, oral or widely extensive disease will require systemic chemotherapy.
- All topical and systemic therapies are given concurrently with ART in HIV related KS. 1 or 2 cycles of chemotherapy should be used prior to ART initiation; this may prevent a serious IRIS response.
- For second line/refractory disease and if patient tolerated >3 months to 1st line systemic therapy, then repeat 1st line using 6 cycles or use alternate 1st line
- imatinib, nab-paclitaxel and bevacizumab can also be considered

Medicines

Medicine	Codes	Adult dose	Frequency	Duration
Topical Therapy				
*Imiquimod 5% cream	S V	Apply under occlusion 3 times weekly	2 weekly	
Intralesional Chemo				
**Vinblastine	SV	0.2mg.ml solution with a volume of 0.1ml per 0.5cm^2 of lesion		

*Titrate dose to effect tolerability

**Pain from injection is common and may persist for several days. NSAID may be useful to relieve pain from injection

Medicine	Codes	Adult dose	Frequency	Duration
First Line therapy				
Paclitaxel	**S V**	Paclitaxel 100mg/m^2 IV D1	2-3 weekly	6
Liposomal doxorubicin	**S V**	Liposomal doxorubicin 20mg/m^2 IV D1	3 weeks	6
Second Line therapy				
Bleomycin and vincristine (BV)	**S V**	Bleomycin 15 u/m^2 IV D1 Vincristine 1.4mg/m^2 IV(max 2mg) D1	3 weekly	
Doxorubicin, bleomycin: & vincristine.	**S V**	Doxorubicin 15–20 mg/m2 IV; Bleomycin 10–15 mg/m2 IV; Vincristine 1 mg–1.4 mg/m2 (max 2 mg) IV.	3-4 weekly	
Pomalidomide	**S V**	Pomalidomide 5mg PO OD for 3 weeks	4 weekly	
Gemcitabine	**S V**	Gemcitabine 1000mg/m2 IV D1	2 weekly	
Vinorelbine	**S V**	Vinorelbine 30mg/m2 IV D1	2 weekly	
Thalidomide	**S V**	Thalidomide 200mg PO OD		

Radiotherapy Dosing

- Dosing schema range from 6-8Gy single fraction to 30Gy in 10-15 fractions.

  Alternative dosing: 20 - 24 Gy in 10 - 12 fractions.

- For most limited superficial skin lesions, electrons or superficial X-rays can be used. For deeper lesions, conformal photon RT or mixed photon-electron treatment plans may be utilized. Use of bolus may be necessary to achieve adequate skin dose.

Supportive therapy

- Common symptoms such as pain, breathlessness, lymphoedema should be managed in the standard way.
- Symptom control must start at the outset of treatment.
- Ulcerated lesions should be dressed and receive appropriate antibiotic therapy as necessary.
- Assess patient and watch for other HIV -related cancers and opportunistic infections.

Follow-up

- Any patient with AIDS-KS should be on ART. Every patient should be seen monthly after ART initiation, particularly if there is mild/limited disease and a decision not to use chemotherapy has been made.
- All patients with moderate/extensive KS should be given 1-2 cycles before ART initiation. Follow all patients every 3 months after chemotherapy is completed, for the first 1 -2 years.
- After 2 years, if the KS is stable/quiescent and the viral load (VL) is controlled, patients may be seen every 6 months. HIV viral load is measured every 6 months if affordable (at least once a year if resource constrained).
- If HIV viral load is detectable, all patients should be reviewed by an HIV clinician and reviewed monthly until virological suppression is achieved.

Non-Melanoma Skin Cancers

General Notes

The most frequent types of epithelial skin cancers in Zimbabwe are squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Most of the early symptoms of non-melanoma skin cancers mimic those of other non-malignant skin conditions and allergies. The doctor therefore needs to have a high index of suspicion particularly in situations of non-resolving/persistent skin lesions, despite other treatment modalities. For patients with albinism and xeroderma pigmentosum in our community, we encourage a thorough investigation of all skin lesions. Patient education should begin in childhood for individuals with XP and albinism. The Caucasian population in Zimbabwe is at higher risk of developing skin malignancies due to the climate. Risk factors include UV radiation exposure, history of burns, light complexion, family or personal history of BCC, SCC, actinic keratosis, familial dysplastic nevus syndrome, or atypical nevi, chronic cutaneous inflammation, immunosuppression and environmental exposures to carcinogens.

History and symptoms

- Skin nodule/lump which could be of variable pigmentation.
- Scaly, patchy, crusting or scabbing skin appearance
- Chronic ulcers

Physical examination

- General examination
- Local area - document the site, size, shape, colour, consistency, number of lesions, presence of ulceration and describe the surrounding skin.
- Regional lymphadenopathy
- Examine the entire skin surface

Diagnostic workup

- Biopsy can be a shave biopsy, excisional or incisional biopsy
- FNA or core-biopsy of suspected involved lymph nodes

- Biopsy should performed by an appropriate surgical specialty or dermatologist

Staging workup

- MRI scan with contrast to assess the local extent of (if available)
- CT scan with contrast or plain x-rays may be used where bone invasion is suspected
- Chest x-ray and USS abdomen & pelvis to rule out distant metastasis in locally advanced cases.
- FBC, U&E, LFT, serum calcium and HIV test.

Risk Factors for Local Recurrence or Metastases in the Post-Op Setting

Cutaneous squamous cell carcinoma risk stratification	
Low Risk	• < 2 cm on trunk and extremities • < 1 cm on cheek, forehead, scalp, neck, shins (location independent of size may constitute high risk) • Well defined borders • Primary tumour • Immunocompetent status • No prior radiation therapy • Moderately or well-differentiated histologic features w ith no high risk histologic subtype • No perineural, lymphatic, or vascular invasion • No neurologic symptoms • Depth ≤ 2 mm and no invasion beyond subcutaneous fat
High Risk	• ≥ 2cm on trunk and extremities (L-zone) • ≤ 1 cm for o M-zone - cheek, forehead, scalp, neck, shins, central face, o H-Zone - nose, eyelids, periorbital area, ear, periauricular area, lips and perioral area, chin, mandible, hands, feet, genitalia • Ill -defined borders • Recurrent tumour • Immunocompromised status (HIV, Transplant) • Genetic syndrome (Albinism, XP) • Prior radiation therapy • Poorly differentiated histologic features (acantholytic, adenosquamous, desmoplastic, metaplastic histologic subtype) • Perineural, lymphatic or vascular involvement

	• Rapid growth • Neurologic symptoms • Thickness ≤ 2 mm, or Clark level IV/V.
Basal cell carcinoma risk stratification	
Low Risk	• < 2 cm on trunk and extremities • < 1 cm on cheek, forehead, scalp, neck, shins (location independent of size may constitute high risk) • Well defined borders • Primary tumour • Immunocompetent status • No prior radiation therapy • Nodular, superficial histologic pattern • No perineural invasion
High Risk	• ≥2cm on trunk and extremities (L-zone) • ≥1 cm on M-zone and H-Zone • Ill -defined borders, • Recurrent tumour • Immunocompromised status (HIV, Transplant) • Genetic syndrome (Albinism, XP, Gorlin) • Prior radiation therapy • Aggressive histologic pattern (Morpheaform, micro nodular, basosquamous) • Perineural invasion

Treatment

ALL patients with skin cancer MUST be discussed in a multidisciplinary team meeting (including, pathologist, surgeons, dermatologists, clinical oncologist, pharmacist, oncology nurse, radiologist, rehabilitation specialists and social worker) prior to treatment.

Decision of modality is based on the skin cancer histologic subtype, clinical stage of the disease, general condition of the patient, comorbidities, previous treatments given and patient preference. Treatment options include cryotherapy, curettage/electrodessication, chemotherapy, surgical excision, Mohs micrographic surgery and radiotherapy.

Local Treatment Options	
Topical Options	Topical chemotherapy: imiquimod or topical 5 -FU (e.g. efudex) Used for premalignant or superficial lesions confined to epidermis
Cryotherapy and laser therapy	For small, superficial BCC and well-differentiated SCC with distinct margins
Curettage and electrodesiccation	Same indications as cryotherapy, but typically not used for recurrences or cancers overlying scar tissue, cartilage, or bone
Surgery	Mohs micrographic surgery Complete surgical excision with post-op margin assessment +/- grafting or cosmetic surgery If persistent positive margins or perineural invasion should be followed by post-op radiotherapy
Radiotherapy	Radiotherapy can be deployed as primary treatment, adjuvant therapy or palliative treatment. Primary treatment is given for cases of carcinoma -in-situ, unresectable lesions, special areas or patient preference. Post-operative adjuvant therapy indications include: Positive margins Extensive perineural invasion or lymphovascular space invasion High risk histological subtypes >3 cm primary diameter Extensive skeletal muscle invasion Bone/cartilage invasion Palliative – advanced/destructive, unresectable or recurrent lesions which are not amenable to complete sterilization.
Cytotoxic chemotherapy	Chemotherapy is used in chemoradiation or as chemotherapy alone. Neoadjuvant/ adjuvant treatment – advanced, unresectable, or multiple lesions.
Other medical treatments	EGFR inhibitors such as cetuximab may also be used in SCC. SMO inhibitors can be used for BCC

Follow up

- Post-surgery and adjuvant therapy patients must be reviewed 6 weeks post-treatment, then 3 monthly in the first 2 years, then 6 monthly for year 3-5 and annually thereafter.
- Monthly self-examination of all skin surfaces is recommended especially in high risk patients with underlying predisposing conditions.
- Patients must be encouraged to seek health assistance and assessment at the onset of any suspicious spots, itchiness, ulceration or bleeding.

Melanoma

General Notes

Melanoma is a skin cancer which is relatively more common amongst caucasian compared to Africans. Melanoma has subtypes which include superficial spreading, nodular, lentigo maligna and acral lentiginous. These subtypes have differing prognoses. The most significant prognostic factor for recurrence and survival is lymph node involvement. Other prognostic factors include: ulceration, thickness, anatomic site, gender, age and number of involved nodes.

Signs and symptoms

ABCDE rule outlining warning signs for most common types of melanoma:

A Asymmetry,
B Border irregularity,
C Color change, usually getting darker.
D Diameter > 6 mm.
E Evolution of moles/lesions.

Pain, itchiness, bleeding, scabbing and crusting lesions.

Diagnostic workup

- Core biopsy for histology
- Evaluation of suspicious nodes

Staging workup

- FBC, U&E, LFT and HIV test.
- CT scan chest, abdomen & pelvis; include brain if indicated (if available)
- Chest x-ray, USS abdomen, pelvis and regional lymph node sites (if CT scan not available)

Treatment

ALL patients with melanoma should be discussed in a multidisciplinary team meeting (including, pathologist, surgeons, dermatologists, clinical oncologist, pharmacist, oncology nurse, radiologist, rehabilitation specialists and social worker) prior to treatment.

Treatment options	

Surgery	• WLE with sentinel lymph node biopsy (SLNB) followed by completion of regional LN dissection if SLN is positive.
	• Minimum surgical margins for primary tumour:
	  ○ Tis = 5 mm,
	  ○ T1 = 1 cm,
	  ○ T2–T4 = 2 cm
	Note: Studies show no benefit in LC, DFS & OS with >2cm margin
	• Predictors of regional recurrence after nodal dissection alone include extracapsular extension, ≥4 lymph nodes positive, lymph node size >3 cm in diameter, and recurrent disease.. Presence of 1 of these factors has a 30 –50% rate of regional rrecurrence

Radiotherapy	• Adjuvant radiotherapy to primary site for:
	  ○ close or positive margins
	  ○ recurrent disease,
	  ○ Breslows >4 mm with ulceration or satellitosis.
	• Adjuvant nodal irradiation after nodal dissection for:
	  ○ Extracapsular extension
	  ○ ≥4 lymph nodes positive
	  ○ Lymph node size >3 cm
	  ○ Recurrent disease.
	• Primary radiotherapy can be c0nsidered for:
	  ○ Lentigo maligna melanomas on the face that would cause severe cosmetic/functional deficits with surgery
	  ○ Unresectable tumour
	  Palliative cases

Systemic therapy	• Indicated for advanced, unresectable, or metastatic disease. • Immunotherapy: such as ipilumimab, nivolumab and pembrolizumab • Targeted therapy - BRAF V600 gene inhibitors such as vemurafenib or dabrafenib. • C-Kit target agent such as imatinib • Chemotherapy has limited response rates: dacarbazine, paclitaxel

Follow up

- History and physical examinations including a total skin evaluation every 3 months for 2 years then 6 monthly for 3-5years the annually thereafter.

Malignant tumours of the Bone

General note

Sixty percent of bone sarcoma cases occur between 10-20 years of age which is the most active age of skeletal growth. Eighty percent of cases occur in the long bones until epiphyseal closure

Prevalence:Osteosarcoma>chondrosarcoma>Ewing's>malignant fibrous histiocytoma

Osteogenic sarcoma

History and symptoms

- 75% occur in metaphysis of long bones with local pain/ swelling.
- Skin redness over the site
- Fatigue
- Unexplained weight loss
- Fracture of affected bone
- Most common affects the femur, tibia and humerus bone
- Distant metastasis is most common in lung
- Associated withLi-Fraumeni syndrome (p53) and retinoblastoma

Physical Examination

General Examination: pyrexia, pallor, respiratory distress and performance status**.**

Local area (depends on location): site, size, shape, consistency, tenderness, overlying skin status, pulsatile and state of the distal limb (skin colour, warmth, oedema and pulse presence)

Respiratory system: evaluate for signs of lung metastases

Diagnostic work-up

- Biopsy lesion after complete radiologic evaluation and avoid incision over area not to be irradiated or reexcised
- Biopsy should be core needle biopsy or surgical biopsy.

• Biopsy should be performed at institution where treatment will occur

Staging work-up

- FBC, U&E, LFT, serum calcium, urinalysis, ESR and HIV test
- Plainfilms(primaryregionandchest x-ray) codman's triangle, periosteal bone spicules, 1° tumor often seen as cloudlike density.
- CT scan/MRI scan (primary area and chest if available)
- Bone scan: synchronous sites
- Consider PET scan where resources permit

Treatment

ALL patients with osteogenic sarcoma should be discussed in a multidisciplinary team meeting (including, pathologist, radiologist, orthopedic surgeons, clinical oncologist, physiotherapist, occupational therapist, pharmacist, oncology nurse and social worker) prior to treatment. Limb-saving intervention should be pursed whenever possible due to better functional outcomes. Assessment by physiotherapist BEFORE any treatment is instituted

	Surgery	**Chemotherapy**	**Radiotherapy**
Low grade osteosarcoma intramedullary + surface	Wide local excision	Adjuvant chemotherapy if histology shows high grade features	
Periosteal osteosarcoma	Wide local excision following neoadjuvant chemotherapy	**Neoadjuvant chemotherapy (preferred)** Adjuvant chemotherapy if histology shows high grade features.	
High grade osteosarcoma intramedullary		**Neoadjuvant chemotherapy then reassess for resectability (preferred)**	

	Wide local excision after neoadjuvant chemotherapy and now considered resectable	Adjuvant chemotherapy if margins are negative with good response to neoadjuvant chemotherapy	
		Adjuvant chemotherapy (consider switching chemotherapy regimen) if negative margins with poor response to neoadjuvant chemotherapy	
		Adjuvant chemotherapy if positive margins with poor pathological response (consider switching chemotherapy regimen)	Adjuvant radiotherapy can be given
Metastatic/ Unresectable s	Palliative surgery aimed at quality-of-life improvement	Primary systemic chemotherapy	Local or distant site radiotherapy

Medicines

Medicine	Codes	Adult dose	Frequency	Duration
First line regimens (primary/neoadjuvant/adjuvant therapy)				
Cisplatin and Doxorubicin	S V	Cisplatin 100mg/m^2 IV D1 Doxorubicin 25mg/m^2 IV D1-D3	3 weekly	6
Second line regimens (relapsed/refractory or metastatic disease)				
Docetaxel and Gemicitabine	S V	Gemcitabine 675mg/m^2 IV D1, D8 Docetaxel 75-100mg/m^2 D8	3 weekly	13
Cyclophosphamide and Etoposide	S V	Cyclophosphamide 4000mg/m^2 IV D1 + mesna	3-4 weekly	2

			1400mg/m^2 before and 4 and 8 hours after starting of cyclophosphamide Etoposide 100mg/m^2 twice daily for 3 days on D2, D3 and D4 (total dose 600mg/m^2 Repeat in 21-28 days for 2 cycles		
Carboplatin, etoposide and Ifosfamide	S	V	Carboplatin 400mg/m^2 D1 and D2 Ifosfamide 1800mg/m^2 IV + mesna Etoposide 100mg/m^2 D1-D5 Cycle every 3 weeks for up to 12 weeks	3 weekly	4
Gemicitabine (single agent)	S	V	Gemcitabine 1200mg/m^2 IV D1and D8	3 weekly	As per oncologist

Follow-up

- Intensive physical rehabilitation is very important, especially for paediatric cases.
- History and physical examination with functional assessment every 3 months for 2 years, 6 months up to 5 year and thereafter annually.

Hodgkin's Lymphoma

General Note

Hodgkin's lymphoma is a cancer of the lymphatic system, which is part of the immune system. It affects people of all ages but has a bi-modal incidence distribution i.e. more common between 20-40 years of age and > 65 years. In Zimbabwe, Hodgkin's lymphoma consists about 0.8% of cancers reported annually.

History and symptoms

- Painless swelling of lymph nodes in the neck, armpits or groin
- Persistent fatigue
- Fever
- Night sweats
- Unexplained weight loss
- Pruritus
- Increased sensitivity to the effects of alcohol or pain in the lymph node regions

Physical examination

- General examination- cachexia, fever, jaundice, performance status and lymphadenopathy
- Chest examination
- Abdominal examination- hepatomegaly, splenomegaly

Diagnostic workup

- Biopsy- excisional lymph node biopsy preferred over core needle biopsy
- Bone marrow to be done in all cases

Staging workup

- FBC, U&E, LFT, RBS, ESR, LDH and HIV test
- CT scan chest, abdomen & pelvis (if available) or USS abdomen & pelvis and chest x-ray.

Treatment

ALL patients with Hodgkin's lymphoma MUST be discussed in a multidisciplinary team meeting (including pathologist, radiologist, haematologist, clinical oncologist, surgeons, physiotherapist, pharmacist, oncology nurse and social worker) prior to treatment. Treatment recommendations by stage (Lugano classification)

Stage	**Treatment**	
	Chemotherapy	Radiotherapy
I (favorable)	Chemo alone	Chemo----> Radiation RT alone (e.g. nodular lymphocyte predominant Hodgkin's lymphoma [NLPHL])
I (unfavorable)	Chemo alone	Chemo----> Radiation
IIA (favorable)	Chemo alone	Chemo----> Radiation RT alone (e.g. nodular lymphocyte predominant Hodgkin's lymphoma [NLPHL])
II (unfavorable)	Chemo alone	Chemo----> Radiation
IB, IIB		Chemo----> Radiation
III	Chemo alone	Chemo----> Radiation
IV	Chemo alone	Chemo ± Radiation (PET +, initially bulky disease)

Medicines

Medicine	Codes	Adult dose	Frequency	Duration
Stage IA, IIA favourable (No Bulky Disease, <3 Sites of Disease, ESR <50, and No E-lesions)				
Doxorubicin, bleomycin, vinblastine, Dacarbazine (ABVD) followed by radiotherapy	**S V**	Doxorubicin 25mg/m^2 IV Bleomycin 10units/m^2 IV Vinblastine 6mg/m^2 IV Dacarbazine 375mg/m^2 IV Days 1 and 15 Repeat cycle every 4 weeks for 2 cycles followed by radiation therapy.	4 weekly	2
ABVD Preference to treat with chemotherapy alone)	**S V**	ABVD as above Repeat cycles every 4 weeks for 3 cycles.	4 weekly	3

Doxorubicin, Vinblastine, Mechlorethamine, Etoposide, Vincristine, Bleomycin & Prednisone (Stanford V) followed by radiotherapy	**S V**	Days 1 and 15: Doxorubicin 25mg/m^2 IV Vinblastine 6mg/m^2 IV Day 1: Mechlorethamine 6mg/m^2 IV Days 8 and 22: Vincristine 1.4mg/m^2 (max 2mg) IV Bleomycin 5units/m^2 IV Days 15 and 16: Etoposide 60mg/m^2 IV Days 1–28: Prednisone 40mg/m^2 orally every other day. Taper prednisone dose by 10mg every other day beginning Day 15 of **Cycle 2.** Repeat cycle every 4 week for 2 cycles followed by radiation therapy, optimally within 3 weeks of chemotherapy completion.	4 weekly	2
Stage I–II Unfavourable (Bulky or Non-bulky Disease)				
ABVD (For Bulky Disease)	**S V**	ABVD as above Days 1 and 15 OR 4 cycles of AVD with or without subsequent radiation therapy	4 weekly	4-6
Stanford V (with or without subsequent radiation therapy)	**S V**	Stanford V as above Note: Prednisone 40mg/m^2 orally every other day. Taper prednisone dose by 10mg every other day beginning Day 15 of **Cycle 3**.	4 weekly	3
Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine and Prednisone (Escalated BEACOPP) (In selected patients if IPS≥4, age <60)	**S V**	Day 1: Cyclophosphamide 1,250mg/m^2 IV Doxorubicin 35mg/m^2 IV Days 1–3: Etoposide 200mg/m^2 IV Days 1–7: Procarbazine 100mg/m^2 orally. Day 8: Vincristine 1.4mg/m^2 (max 2mg) IV Bleomycin 10units/m^2 IV Days 1–14: Prednisone 40mg/m^2 orally daily.	3 weekly	2

		Repeat cycle every 3 weeks for 2 cycles followed by ABVD for 2 cycles and then by radiation therapy.		
Stage III–IV				
ABVD	**S V**	ABVD as above Repeat cycle every 4 weeks for 2 cycles followed by 4 cycles of AVD or 4 cycles of escalated BEACOPP , cycles with or without subsequent radiation.	4 weekly	2
Stanford V (In selected patients if IPS ≤3)	**S V**	Stanford V as above Repeat cycle every 4 weeks for 3 cycles with or without subsequent radiation therapy.	4 weekly	3
Escalated BEACOPP (In selected patients if IPS≥4, age <60)	**S V**	Escalated BEACOPP as above Repeat cycle in selected patients (IPS≥4, aged <60 years) every 3 weeks for 6 cycles, with or without subsequent radiation therapy.	3 weekly	6
Brentuximab Vedotin, Doxorubicin, Vinblastine, Dacarbazine (BV + AVD) in select patients if IPS>4, bleomycin contraindicated, no known neuropathy)	**S V**	Days 1 and 15: Brentuximab vedotin 1.2mg/kg IV Doxorubicin 25mg/m^2 IV Vinblastine 6mg/m^2 IV Dacarbazine 375mg/m^2 IV Repeat cycle every 4 weeks for up to 2 cycles.	4 weekly	2

For subsequent second line therapies when indicated consider Bendamustine, C-MOPP, Everolimus, GCD, lenalidomide, Mini-BEAM and MINE.

Radiation therapy dose

Stage	Radiation dose
I-II -favourable	20Gy ISRT in 1.8-2Gy/fx
I-II unfavourable	30GY ISRT in 1.8-2Gy/fx
I-II bulky	30-36Gy ISRT 1.8-2Gy/fx
III-IV	30-36Gy ISRT 1.8-2Gy/fx
For radiotherapy alone 30Gy involved-site radiotherapy (ISRT) in 1.8-2Gy/fx (Consider 36Gy for bulky disease)	

Follow up

- History and physical examination and blood tests every 3 months for years 1 - 2, then every 6 months until year 3, then annually.
- Serum TSH every 6 months if radiotherapy to the neck, upper mediastinum.

- CT scan after treatment once within 12 months, then as clinically indicated.
- Females start breast cancer screening 8 years after radiotherapy or age 40 (whichever comes first) after mediastinal treatment.

Non-Hodgkin's Lymphoma

General Note

Non-Hodgkin's lymphoma (NHL) is a cancer that originates in lymphocytes. NHL mostly affects adults. In Zimbabwe, NHL consists about 7.9% of all cancers annually.

History and symptoms

- Chest pain, coughing or shortness of breath
- Persistent fatigue
- Night sweats
- Unexplained weight loss
- Fever and chills
- Abdominal pain
- Easy bruising and bleedin
- Painless swollen lymph nodes in your neck, armpit or groin

Physical examination

- Enlarged lymph nodes

Diagnostic workup

- Biopsy: Excisional lymph node biopsy preferred over core-needle biopsy, immunophenotping of specimen
- Bone marrow in all cases

Staging workup

- FBC, U&E, LFT, LDH, HIV tests and hepatitis screen
- CT scan chest, abdomen & pelvis
- If Gastric MALT- oesophago-gastroscopy with biopsy, H.*pylori*
- If Burkitt lymphoma- Lumbar puncture, HIV, Hep B and C screen
- If Extranodal NK/T Cell lymphoma (Nasal type)- EBV viral load

Treatment

ALL patients with Non-Hodgkins lymphoma MUST be discussed in a multidisciplinary team meeting (including, pathologist, radiologist, haematologist, clinical oncologist, surgeons, physiotherapist, pharmacist, oncology nurse and social worker) prior to treatment.

Treatment options by disease and site

Condition	Stage	Treatment
Chronic lymphocytic leukaemia (CLL) /Small Lymphocytic Lymphoma (SLL)	I	I: Observe or radiation therapy (RT [palliation])
	II – IV	II-IV: Observe OR systemic therapy OR transplant
Follicular lymphoma (Gr 1-2)	I-II	Radiotherapy OR immunotherapy ± chemotherapy OR Observe
	III- IV (asymptomatic)	Observe
	III-IV (symptomatic)	Chemo-immunotherapy OR palliative radiotherapy
Gastric Marginal Zone Lymphoma (MZL)	I-II (H. pylori positive)	Antibiotic therapy
	I-II (H.Pylori negative or t11:18 positive)	Radiotherapy
	III-IV	Observe
	III-IV (symptomatic):	Chemo-immunotherapy OR palliative radiotherapy
Non- gastric Marginal zone lymphoma	I-II	Radiotherapy OR surgery or immunotherapy OR observe (if asymptomatic)
	III-IV	Manage as per stage IV follicular lymphoma
Mantle cell	I-II	Radiotherapy OR Chemo-radiation
	III-IV	Chemotherapy

Diffuse large B cell lymphoma (DLBCL)	I-II	Chemo ---> radiotherapy OR chemotherapy alone
	IB, IIB	Chemo--->± radiotherapy
	III-IV	Chemo ---> radiotherapy (bulky tumour or incomplete response) OR Chemotherapy alone
PMBL/GZL		Chemo ---> radiotherapy OR Chemo--->± radiotherapy
Burkitt Lymphoma		Chemo--->± palliative radiotherapy
AIDS-related B Cell Lymphoma		Burkitt: Chemotherapy DLBCL: Chemotherapy Plasmablastic: Chemotheapy PCNSL: Chemotherapy OR palliative radiotherapy
ALCL (ALK+).	I-II	Chemo ---> radiotherapy OR Chemo--->± radiotherapy
	II-IV	Chemo--->± radiotherapy
Other PTCL		Clinical trial or Chemo ---> ± radiotherapy
Extranodal NK/T-cell (nasal type)	I	Radiotherapy OR Chemo----- radiotherapy
	I (with risk factors),II	Chemo radiotherapy
	III-IV	Chemo radiotherapy
Extranodal NK/T-cell (extranasal type)	I-IV	Chemo radiotherapy

Radiation dosing

Medicines

Medicine	Codes	Adult dose	Frequency	Duration
First Line				
R-CHOP (Note: Rituximab only for those with CD20+ histology)	S V	Days 1, 22 & 43: Rituximab 375mg/m^2 IV 7 days prior to beginning CHOP regimen Day 1: Cyclophosphamide 750mg/m^2 IV	3 weekly	3

	Doxorubicin 50mg/m^2 IV bolus Vincristine 1.4mg/m^2 IV bolus (max dose 2mg) Days 3, 24 & 45: Prednisone 100mg orally 5 days. Radiotherapy begins 3 weeks after last cycle of R-CHOP		
Bortezomib-CHOP	Days 1 and 4: Bortezomib 1.3mg^2 iv CHOP as above	3 weekly	3
Dose-adjusted EPOCH + rituximab	Days 1–4: Etoposide 50mg/m^2 IV Doxorubicin 10mg/m^2 IV Vincristine 0.4mg/m^2 IV Day 5: Cyclophosphamide 750mg/m^2 IV Days 1–5: Prednisone 60mg/m^2 orally twice daily. Administer G-CSF 5 mcg/kg SQ daily until an ANC >5 × 10^9/L above nadir level starting day 6.	3 weekly	6

For frail patients and those >80years of age with comorbidities			
R-mini-CHOP	Days 1: Rituximab 375mg/m^2 IV Cyclophosphamide 400mg/m^2 IV Doxorubicin 25mg/m^2 IV bolus Vincristine 1mg/m^2 IV bolus Days 1-5 Prednisone 40mg orally	3 weekly	6
Concurrent presentation with CNS disease			
Parenchymal	Systemic methotrexate 3g/m^2 or more on day 15 of a 21-day R-CHOP cycle that has been supported by growth factors.	3 weekly	
Leptomeningeal	Methotrexate/cytarabine IT: Consider Ommaya reservoir placement and/or systemic methotrexate 3-3.5mg/m^2	3 weekly	
Second line and subsequent therapy			
ESHAP +/- rituximab	Days 1-4: Etoposide 40-60mg/m^2 IV Days 1-5: Methyprednisolone 250-500mg IV	3-4 weekly	3

Day 5: Cytarabine
2g/m^2 IV 2-3 hours

Days 1-4: Cisplatin
25mg/m^2 IV 24-hr
infusion

Day 1 or Day 5
Rituximab 375mg/m^2
IV

For patients with poor left ventricular function consider RCEPP, RCDOP, RGCVP, DA-EPOCH + Rituximab and RCEOP.

Radiation Therapy Dosing

	Stage	
Indolent lymphomas (FL, MZL, SLL, and MCL)	I-II:	• 20 – 30 Gy in 1.8 – 2 Gy/fx
	III-IV:	• 4Gy in 2 Gy/fx local RT, repeat if needed for further palliation •
Aggressive lymphomas (DLBCL, PTCL)		• CR after chemo: 30 – 39.6 Gy in 1.8 – 2 Gy/fx • PR after chemo: 40 – 50 Gy in 1.8 – 2Gy/fx • Definitive (no chemo): 45 – 55 Gy in 1.8 – 2 Gy/fx
Primary CNS Lymphoma (PCNSL)		• CR after chemo: 23.4 – 24 Gy in 1.8 – 2 Gy/fx • PR after chemo: 36 – 45 Gy in 1.8 – 2Gy/fx • Definitive (no chemo): 40 – 50 Gy in 1.8 – 2 Gy/fx
Eye		• Primary intraocular lymphoma: 36 Gy in 1.8 Gy/fx • Orbital: 24 – 30 Gy in 1.5 – 2 Gy/ fx, Consider 4 Gy in 2 Gy/fx for palliation (may be repeated) •
Nasal cavity and Paranasal Sinus		• CR after chemo: 30 Gy in 1.8 – 2 Gy/fx • PR after chemo: 40 Gy in 1.8 – 2Gy/fx
Extranodal NK/T-cell		• Concurrent Chemorad: 50 Gy in 2Gy/fx • Definitive: 50 Gy in 2 Gy/fx with 5 – 10 Gy in 1.8 - 2 Gy/fx boost • CR after chemo: 45 – 50 Gy in 1.8 – 2 Gy/ fx
Gastric MALT		• Definitive: 30 Gy in 1.5 – 1.8 Gy/fx •

Follow up

- If asymptomatic, generally clinical follow up every 3-6 months up to 5 years, then annually or as clinically indicated
- MALT lymphoma: History and physical examination every 3- 6 months for 5 years, then as clinically indicated; if gastric, endoscopy every 6 months for 5 years, then annually
- Follicular lymphoma (grade1 -2): History and physical examination with blood tests every 3- 6 months for 5 years; CT scan of the site of disease no more than every 6 months up to 2 years
- Burkitt lymphoma: History and physical examination with blood tests every 2 – 3 months for 1 year, then 3 months for 1 year, then every 6 months
- Extranodal NK/T-cell Lymphoma (nasal type): repeat initial imaging post-radiotherapy (e.g. CT, MRI and PET-CT), endoscopy (annually) with visual biopsy, and EBV viral load

Cutaneous lymphoma

General note

Cutaneous lymphoma is a rare subtype of Non-Hodgkin's lymphoma that starts in the skin but is not classified as a skin cancer because the cancer cells originates in white blood cells called lymphocytes. They can be sub classified into B-cell and T- cell cutaneous lymphoma.

History and symptoms

- Skin lesions
    - Round skin patches
    - Papules, nodules, plaques
- Skin itchiness
- Unexplained weight loss
- Profuse night sweats

Physical examination

- Total skin examination
- Lymphadenopathy

Diagnostic workup

- Biopsy – excisional, incisional, or punch biopsy with immunophenotyping

Staging workup

- FBC, U&E, LFTs, LDH, hepatitis screen and HIV tests
- CT scan chest, abdomen & pelvis (if available)
- For Mycosis Fungoides (MF)/ Sézary Syndrome: Biopsy of suspicious lymph nodes, peripheral blood assessment for Sézary cells.
- Bone marrow aspirate

Treatment

ALL patients with cutaneous lymphoma MUST be discussed in a multidisciplinary team meeting (including, pathologist, radiologist, dermatologist, haematologist, clinical oncologist, surgeons, physiotherapist, pharmacist, oncology nurse and social worker) prior to treatment.

Treatment recommendations by disease and stage

Disease	Stage	Intervention options
Primary cutaneous B-cell lymphoma (PCBCL) (PCMZL/PCFCL)	T1-T2	Radiotherapy OR Surgical excision OR Topical therapy
	T3	Observation OR Local radiotherapy OR Topical therapy
Diffuse large B cell lymphoma (DLBCL) leg type		RCHOP ± local radiotherapy OR Radiotherapy
PCTCL Anaplastic large cell lymphoma (ALCL)	Localised	Radiotherapy OR Surgery ± radiotherapy
PCTCL (ALCL)	Multifocal	Radiotherapy OR Systemic therapy OR Observation

MF/ Sézary Syndrome	IA- IIA (localised)	Radiotherapy OR Topical therapy
	IA-IIA (extramedully)	Total skin electron beam therapy (TSEBT) OR Topical therapy
MF/ Sézary Syndrome	IIB: (localized)	Radiotherapy OR Topicals
	IIB (extramedully)	Systemic therapy
MF/ Sézary Syndrome	III: (no blood involvement)	Total skin electron beam therapy (TSEBT) OR Topical therapy
MF/ Sézary Syndrome	III (blood involvement)	Systemic chemotherapy ± radiotherapy
MF/ Sézary Syndrome	IV	Systemic chemotherapy ± radiotherapy

PCFCL- Primary cutaneous follicular center lymphoma; PCMZL- Primary cutaneous marginal zone lymphoma.

Radiation dosing

Disease	Radiation dose
PCMZL/PCFCL	24 to 30 Gy in 1.8 – 2 Gy/fx
Primary Cutaneous DLBCL, leg type	• 36 to 40 Gy in 1.8 Gy- 2 Gy/ fx
PCTCL (ALCL)	• 24 to 36 Gy in 1.8 Gy – 2 Gy/fx
MF/ Sézary Syndrome	• 20 to 24 Gy in 1.8 to 2 Gy/fx for local therapy • For TSEBT 12 to 36 Gy in 1 to 2 Gy/fx (daily, or twice per week if higher dose per fx)

Follow up

- History and physical examination, labs every 3 months for years 1 and 2, then every 6 to 12 months until year 3, then annually.
- Patients must have total skin exam at each review
- Thyroid stimulating hormone assay (TSH) if appropriate every 6 months (e.g. patients who received TSEBT)

Multiple Myeloma/ Plasmacytoma

General note

Multiple myeloma (MM) is a cancer that forms in a type of white blood cell called plasma cell. MM causes cancer cells to accumulate in the bone marrow, where they crowd out healthy blood cells and also release chemicals that trigger other cells to dissolve bone (resulting in lytic lesion of the bone). MM consist about 1.1% of all cancers diagnosed in Zimbabwe annually.

Plasmacytoma refers to a tumor consisting of abnormal plasma cells that grows within the soft tissue or bony skeleton. It can present as a discreet solitary mass of abnormal plasma cells, in which case it's termed a "solitary" plasmacytoma or it can be present as part of myeloma.

History and symptoms

- Bone pain
- Nausea
- Constipation
- Fatigue
- Frequent infections
- Weight loss
- Excessive thirst

Physical examination

- General examination- performance status, pallor, purpura
- Abdomen- hepatomegaly, splenomegaly
- CNS- signs of spinal cord compression

Diagnostic workup

- FBC, U&Es, Ca2+, LFTs, serum beta-2-microglobulin, serum free monoclonal light chain (FCL), 24-hour urine protein, serum/urine protein electrophoresis and immunofixation
- Skeletal survey, and when indicated non contrast CT scan, PET-CT scan and/or MRI scan

- Biopsy- unilateral bone marrow aspiration and biopsy with immunophenotyping, cytogenetics and FISH analysis

Treatment

ALL patients with multiple myeloma should be discussed in a multidisciplinary team meeting (including pathologist, radiologist, haematologist, clinical oncologist, surgeons, physiotherapist, pharmacist, oncology nurse and social worker) prior to treatment.

Treatment recommendations.

	Chemotherapy	**Radiotherapy**
Solitary Plasmacytoma (SP)		Bone: Radiotherapy alone Extramedullary: Radiotherapy and/or Surgery
Smoldering MM (High risk smoldering & Low risk smoldering)	Systemic therapy recommended	
Active MM (up to 40% cases will need radiotherapy)	Systemic therapy + bisphosphonate (evaluate response at two cycles) then consider for stem cell transplant ±RT ± Surgery ± maintenance systemic therapy	Consider radiotherapy and surgery in addition to chemotherapy. Radiotherapy Indications: • Uncontrolled pain • Impending pathologic fracture • Spinal cord compression
Monoclonal gammopathy of undetermined significance (MGUS)	Surveillance	Surveillance

Medicines

Medicine	Codes	Adult dose	Frequency	Duration
Bortezomib, Lenalinomide and dexamethasone	**S V**	Day 1, 8 & 15 Bortezomib 1.3mg/m^2 SC or IV Day1- Day 14 Lenalinomide 25mg PO D1-D14	3 weekly	
Bortezomib, thalidomide, dexamethasone	**S V**	Day 1, 8, 15 & 22 Bortezomib 1.3mg/m^2 SC or IV Dexamethasone 40mg PO OD Thalidomide 100mg PO OD D1 - D14 then 200mg PO OD D15-21	4 weekly	
For elderly patients consider the following combination				
Daratumumab, Bortezomib, Lenalinomide, and dexamethasone				

Radiation therapy dose

Solitary plasmacytoma	• 45 Gy in 1.8 -2 Gy/fx
Multiple myeloma	• Single fraction 8Gy • 10 -30 Gy in 2 – 5 Gy/fx, boost to 36 Gy for bulky disease, cord compression, or partial response • 20Gy in 10 fractions for palliation

Follow up

Solitary Plasmacytoma

- Myeloma specific blood tests every 3 months, bone marrow aspirate and biopsy and imaging if indicated (>50% patients with one SP progress to MM, <50% patients with xtramedullary SP progress to MM).

Multiple myeloma

- Myeloma specific blood tests every 3 months, skeletal survey annually or with symptoms, one marrow aspirate and biopsy and imaging if indicated.

Leukemia

General note

Leukemia is a group of cancers that usually begin in the bone marrow and result in high numbers of white blood cells. These white blood cells are not fully developed and are called blasts or leukemia cells. Many types of leukemia exist, they are grouped into acute (rapidly developing) and chronic (slowly developing). Some forms of leukemia are more common in children. Other forms of leukemia occur mostly in adults. Leukemia accounts for about 2.5% of all cancers in Zimbabwe annually. Acute lymphoblastic leukemia (ALL) and acute myeloid leukemia are the most common leukemia in children.

History and symptoms

- Fever or chills
- Persistent fatigue, weakness
- Frequent or severe infections
- Unexplained weight loss
- Easy bleeding or bruising
- Recurrent nose bleeds
- Pain in the bones or joints
- Excessive sweating especially at night

Physical examination

- General examination- performance status, cachexia
- Skin- petechial lesion
- Lymphadenopathy
- Abdominal examination- hepatomegaly, splenomegaly

Diagnostic workup

- Bone marrow biopsy, cytogenetic

Staging workup

- FBC, U&E, LFTs, CSF analysis and HIV test
- Neuroimaging if symptomatic

Classification of bone marrow involvement

- M_1: <5% lymphoblast
- M_2:5% to 25% lymphoblasts
- M_3: >25% lymphoblasts

Classification of central nervous system involvement

- CNS_1: negative cytology
- CNS_2: positive cytology <5 WBC/mcL
- CNS_3: positive cytology >=5 WBC/mcL

Treatment

ALL patients with leukaemia should be discussed in a multidisciplinary team meeting (including haematologist, pathologist, paediatricians, clinical oncologist, surgeons, physiotherapist, pharmacist, oncology nurse and social worker) prior to treatment.

In general, treatment consists of induction, consolidation, delayed intensification, and maintenance phases of chemotherapy. Treatment response monitoring must be threaded throughout treatment.

Medicines

Medicine	Codes	Adult dose	Frequency	Duration
Chemoradiation.				
Induction therapy Age < 65 years				
Anthracycline and Cytarabine	**S** **V**	Days 1–3: Anthracycline. Daunorubicin 60–90mg/m^2 IV OR idarubicin 12mg/m^2 Days 1–7: Cytarabine 100–200mg/m^2 continuous IV		
Daunorubicin, Cytarabine & Cladribine	**S** **V**	Days 1–3: Daunorubicin 60mg/m^2 IV Days 1–7: Cytarabine 200mg/m^2 continuous IV Days 1–5: Cladribine 5 mg/m^2		
Induction therapy Age ≥65 years				
De novo AML without unfavourable cytogenetics or molecular markers; no antecedent hematologic disorder; and no therapy-related AML				

S	V	Days 1–3: Anthracycline. Daunorubicin 60–90mg/m^2 IV OR idarubicin 12mg/m^2 IV OR mitoxantrone 12mg/m^2IV Days 1–7: Cytarabine 100–200mg/m^2 continuous IV.

CNS and testicles considered sanctuary sites

- In ALL, recent trials have preserved RT for CNS prophylaxis in certain risk groups, CNSdisease, T-cell ALL, or recurrence
- In AML, recent trials have largely eliminated cranial RT. In recurrent AML, intrathecal and systemic chemotherapy can be used
- Bone marrow failure often rapidly follows apparent isolated CNS failure in AML. Palliative RT useful for chloromas.
- Total body irradiation (TBI) is used as part of conditioning regimens prior to stem cell transplant and may be myeloablative or non-myeloablative

Treatment recommendations:

For ALL, risk categories as defined in AALL

- Standard risk: B- precursor, WBC <50K, age 1-10 years
- High risk: all others not in standard or very high- risk groups
- Very high risk: PH+, t (9; 22) (q34; q11), hypodiploid clone, induction failure, or mixed- lineage leukemia (MLL) rearrangement with SER after induction.
- T-cell ALL: It has separate classification system.

All patients will typically receive systemic and intrathecal chemotherapy, the following table includes only the radiation therapy recommendations.

When recommended, cranial radiotherapy is typically given during delayed intensification or at the start of maintenance chemotherapy depending on study protocol or institutional practice. ALL with CNS_3 -any risk group	Therapeutic cranial radiotherapy

When recommended, cranial radiotherapy is typically given during delayed intensification or at the start of maintenance chemotherapy depending on study protocol or institutional practice. ALL with CNS_3 -any risk group	Therapeutic cranial radiotherapy
Standard risk ALL – CNS_1 or CNS_2	No prophylactic cranial radiation
High-risk ALL – all slow early responder patients, patients with MLL rearrangements, patients pre-treated with steroids	Prophylactic cranial irradiation (PCI)
High-risk ALL - CNS_1 or CNS_2 and not meeting the preceding criteria	No prophylactic cranial radiation
Very high risk ALL - CNS_1 or CNS_2	Prophylactic cranial radiation
T-cell ALL – intermediate and high risk – $CNS_{1/2}$	Prophylactic cranial radiation
CNS relapse	Early relapse: craniospinal radiation Late (>= 18months): cranial radiotherapy only
Testicular involvement or relapse	Bilateral testicular radiation if disease persistent at the end of induction or re-induction chemotherapy
Ocular involvement or relapse	If anterior chamber: electron beam radiotherapy If retina or choroid: consider as CNS failure. Local eye and optic nerve radiotherapy or cranial radiotherapy with eye boost
Symptomatic chloroma	Involved site radiation
Transplant conditioning	Myeloalative TBI* may be used for ALL and AML patients requiring transplant such as those with very high risk or recurrence. Nonmyeloablative TBI is occasionally used in patients with poor performance status, but its role is not well established in paediatric patients

Radiotherapy dose

Prophylactic cranial irradiation	12 Gy in 1.5 Gy/fx
Therapeutic cranial irradiation	18 Gy in 1.8 Gy/fx
CNS relapse	24 Gy to whole brain and 15 Gy to spine in 1.5 Gy/fx, Dose may be reduced to 15 Gy if there has been prior cranial radiation to >20Gy
Testicular radiotherapy	24 Gy in 2 Gy/fx
Anterior chamber of eye	12 Gy in 2Gy/fx en-face electrons
Retina or choroid involvement	24 Gy in 1.2 Gy/fx to eye, consider cranial RT as posterior recurrence considered CNS failure
Chloroma	24 Gy in 2 Gy/fx
Myeloablative TBI	12-14.4 Gy in 2 to 2.2 Gy/fx BID at low dose rate <10 to 12cGy/min
Non myeloablative TBI	2- 4 Gy in single fraction at low dose rate

TBI- Total body irradiation

In patients receiving cranial irradiation and planned to receive TBI, subtract the TBI dose from the planned cranial radiotherapy dose. E.g. For a very high-risk patient with CNS_3 disease planned for 12 Gy TBI in preparation for transplant, 6 Gy in 3 fractions just prior to TBI is adequate for a patient who otherwise would have received 18Gy cranial dose.

Follow up

If asymptomatic: History and physical with labs weekly during induction, start of consolidation and delayed intensification, q4 weeks in maintenance.

Paediatric tumours

This guideline contains paediatric neuroblastoma and rhabdomyosarcoma guidelines. Please refer to the Zimbabwe National Paediatric Oncology Treatment Guidelines for guidelines on paediatric Acute Lymphoblastic leukemia, paediatric Hodgkin's Lymphoma, Burkitt's Lymphoma, Retinoblastoma and Low-Grade Glioma.

Neuroblastoma

General note

Neuroblastomas are embryonal tumours of the sympathetic nervous system arising from primitive ganglion cells. They have broad spectrum of clinical behavior which can range from spontaneous regression to maturation to benign ganglioneuroma or aggressive disease with metastatic determination leading to death. They are heterogeneous varying in terms location, histo-pathothological appearance and biological characteristics. It has the capacity to synthesize and secret catechol amines.

History and symptoms

Symptoms depend on the location of the tumour. Common symptoms include the following:

- A mass in the abdomen (commonest), neck or pelvis
- Difficulty breathing, cough
- Symptoms of bowel obstruction- constipation, nausea, vomiting
- Symptoms of urinary obstruction
- Headache
- Backache, weakness of lower limbs in spinal cord compression
- Sweating, flushing, palpitations in excess catecholamine secretion
- Diarrhoea in excess vaso-active intestinal peptide secretion
- Bone pain in the case of bone metastases

Physical examination

- General examination- general failure to thrive, fever, weight loss, weakness, and hypertension
- Abdominal examination- mass in the abdomen
- Respiratory compromise
- Neurologic deficits
    - Horner's syndrome
    - Opsoclonus-myoclonus syndrome
- Eye- peri-orbital ecchymoses

- Urinary retention
- Blueberry muffin syndrome in neonates with skin metastases

Diagnostic workup

- CT scan or MRI scan of primary site (if available)
- Urinary catecholamine metabolites (vanillylmandelic acid (VMA) and homovanillic acid (HMVA)

Staging workup

- FBC, U&E, LFT
- CT scan chest, abdomen and pelvis (if available)
- Chest x-ray or USS abdomen & pelvis if CT scan not available
- Bilateral bone marrow aspirate and biopsy
- I-131 MIBG scan where available

Treatment

ALL patients with neuroblastoma should be discussed in a multidisciplinary team meeting (including radiologist, pathologist, surgeons, pediatrician, clinical oncologist, pharmacist, oncology nurse and social worker) prior to treatment. Treatment of depends on risk stratification.

Low risk disease

Includes the following patients:

1. International neuroblastoma staging system (INSS) stage 1
2. Stage 2A/2B non-amplified MYCN
3. Stage 4S disease with favourable histology, non-amplified MYCN, and aneuploidy tumours

Treatment of low-risk disease

- Gross surgical excision- typically do not require adjuvant therapy
    - Patients with MYCN amplification or low DNA index (where available) may require adjuvant therapy
- Unresectable tumours that are otherwise of low stage (INSS stages 1, 2, and 3 with negative lymph nodes) may require preoperative

chemotherapy and occasionally radiation therapy to convert them to a resectable status

Intermediate-risk disease

Includes the following patients:

1. All stage 2A/2B disease except patients with amplified MYCN and unfavorable histology unless they are younger than age 1 year.
2. Children younger than 18 months with stage 3 disease without MYCN amplification.
3. Children older than 18 months of age with stage 3 disease without MYCN with favourable histology
4. Infants with stage 4 disease without MYCN amplification

Treatment on intermediate-risk disease

- Infants younger than 1 year of age should undergo complete resection of the primary tumour and receive adjuvant chemotherapy
- In unresectable cases, chemotherapy may be administered initially, and surgery can be performed after response to systemic treatment
- In older children with lymph node metastases, adjuvant radiation therapy to the primary and regional lymph nodes has improved the disease-free and overall survival rates

High-risk disease

Includes the following patients:

1. Older children with INSS stages 2 to 3
2. Unfavorable Shimada histology
3. Amplified MYCN
4. Metastatic disease (INSS stage 4). The majority of patients with neuroblastoma present with metastatic disease.

Three phases of treatment:

- Induction therapy with chemotherapy followed by delayed surgery or radiotherapy for local control of bulky disease

- High dose marrow ablative therapy followed by haematopoetic stem cell transplant.

Medicines

Pre-op chemotherapy administer 2 cycles of carboplatin and etoposide.
Post-operative chemotherapy administers 3 cycles of carboplatin and etoposide.

Follow up

- Close follow up is needed as survivors are at increased risk of long-term treatment related toxicities.
- Low and intermediate risk patients review every 3 months for at least the first 2 years and annually thereafter
- High risk patient review on a patient-to-patient basis
- Urinary catecholamine's testing, physical examination and diagnostic imaging.

Rhabdomyosarcoma

Rhabdomyosarcoma are malignant tumours arising from mesenchymal tissue at anybody site. They are thought to originate from immature cells that are destined to form striated skeletal muscle; however, these tumors can arise in locations where skeletal muscle is not typically found (e.g. the urinary bladder).They can arise in any part of the body with the most common primary sites being the head and neck region (35 -40%), the genitourinary tract (25%), and the extremities (20%)

History and symptoms

These depend on site of primary and presence or absence of distant metastases.

- Enlarging mass head and neck region or extremities
- Muco-purulent or sanguinous discharge
- Protruding eye or ophthalmopegia with orbital tumours
- Haematuria and urinary obstruction from bladder tumours
- Urinary frequency or constipation from extrinsic compression of the

bladder or intestinal tract from large pelvic primaries
- Discharge or a polypoid mass from a vaginal primary
- Scrotal or inguinal enlargement from para-testicular tumours

Physical examination
- General examination- general failure to thrive, fever, weight loss and weakness
- Local examination of tumour site and all potential metastatic locations.

Diagnostic workup
- CT or MRI scan of primary tumour region
- Plain radiographs of primary site
- Core needle biopsy
- Immunohistochemistry: myoD and myogenin
- Where available, molecular cytogenetics

Staging workup
- FBC, U&E, LFT
- CT scan of chest, abdomen and pelvis (if available)
- CXR, Ultrasound abdomen and pelvis (if CT scan not available)
- Bone scan
- Bilateral bone marrow aspirate and biopsy
- Lumbar puncture (para-meningeal primary)

Children's oncology Group (COG) Rhabdomyosarcoma surgico-pathologic grouping.

Group I	Localized disease that has been completely resected (a) Confined to muscle or organ of origin (b) Infiltration outside the muscle or organ of origin
Group II	Complete resection with: (a) Microscopic residual disease (b) Regional lymphatic spread that has been resected (c) Both
Group III	Gross residual disease: (a) After biopsy only (b) After major resection (greater than 50% resected)
Group IV	Distant metastatic disease present at Diagnosis

Risk Stratification

Risk group	Histology	Site	Stage	Group
Low	Embryonal	Favourable	I	I-III
		Unfavourable	II-III	I-II
Intermediate	Embryonal	Unfavourable	II-III	III
	Alveolar	Any	I-III	I-III
High	Any	Any	Any	IV

Treatment

ALL patients with rhabdomyosarcoma should be discussed in a multidisciplinary team meeting (including radiologist, pathologist, surgeons, pediatrician, clinical oncologist, pharmacist, oncology nurse and social worker) prior to treatment.

- Complete excision for localized disease is recommended as long as functional and/or cosmetic results are acceptable. Where complete resection is not possible or if disease involves the orbit, vagina, bladder, or biliary tract, initial diagnostic biopsy followed by induction (neoadjuvant) chemotherapy and then definitive local therapy are performed.
- Palpable or radiologically enlarged lymph nodes should be excised and submitted for histologic evaluation.

- Radiotherapy is recommended to enhance local control in ALL patients except those with low-risk disease who undergo a complete resection with negative margins.
- Radiotherapy is a major treatment modality for rhabdomyosarcoma, particularly for achieving local control in patients with residual microscopic or gross disease following surgery and chemotherapy.
- Chemotherapy is utilized in addition to local therapy for all patients with RMS. All patients typically receive VAC or VAI (vincristine, dactinomycin, and cyclophosphamide or ifosfamide) based chemotherapy.

Medicines

Standard chemotherapy regimens for newly diagnosed patients with rhabdomyosarcoma

Prognosis group	Definition	Regimen	Dose	Schedule
Low risk				
Subset A Excellent prognosis (>85% EFS)	Embryonal and alveolar fusion-negative tumors: • Stage 1 CG I/II • Stage 1 CG III orbital • Stage 2 CG I/II	VA per subset A regimen D9602 × 15 cycles (45 weeks)[1]		
		Vincristine	1.5 mg/m^2 (max 2 mg)	Weekly during weeks 0 to 8, 12 to 20, 24 to 32, 36 to 44
		Dactinomycin	0.045 mg/kg (max 2.5 mg)	Every three weeks during weeks 0 through 45
		OR		
		VAC/VA per subset A regimen ARST0331 × eight cycles (24 weeks)		
		Vincristine	1.5 mg/m^2 (max 2 mg)	Weekly during weeks 1 to 9, 13 to 21
		Dactinomycin	0.045 mg/kg (max 2.5 mg)	Every three weeks during weeks 1 to 22◊
		Cyclophosphamide	1200 mg/m^2 with mesna and as needed hematopoietic growth factor support	Every three weeks during weeks 1 to 10 for a total of four doses

Subset B Very good prognosis (70 to 85% EFS)	Embryonal and alveolar fusion-negative tumors: • Stage 1 CG III non-orbit • Stage 3 CG I/II	VAC × 14 cycles (40 weeks)		
		Vincristine	1.5 mg/m^2 (max 2 mg)	Weekly during weeks 1 to 13, 16, 19 to 25, 28, 31 to 37
		Dactinomycin	0.045 mg/kg (max 2.5 mg)	Every three weeks during weeks 1 through 40◊
		Cyclophosphamide	1200 mg/m^2 with mesna and hematopoietic growth factor support	Every three weeks during weeks 1 through 40
Intermediate risk				
		VAC × 14 cycles (40 weeks)		
Good prognosis (50 to 70% EFS)	Embryonal and alveolar fusion-negative tumors: • Stage 2, 3 CG III • Metastatic disease, age <10 years Alveolar fusion-positive tumours • CG I to III	Vincristine	1.5 mg/m^2 (max 2 mg)	Weekly during weeks 1 to 13, 19 to 25, 31 to 37, 40
		Dactinomycin	0.045 mg/kg (max 2.5 mg)	Every three weeks during weeks 1 through 40
		Cyclophosphamide	1200 mg/m^2 with mesna and hematopoietic growth factor support	Every three weeks during weeks 1 through 40
		OR		
		VAC/VI 14 cycles (40 weeks)		
		Vincristine	1.5 mg/m^2 (max 2 mg)	On weeks 1 to 13, 16, 17, 19, 20, 22 to 26, 28, 31 to 34, 37, 38, 40
		Dactinomycin	0.045 mg/kg (max 2.5 mg)	On weeks 1, 7, 13, 22, 28, 34, 40
		Cyclophosphamide	1200 mg/m^2 with mesna and hematopoietic growth factor support	On weeks 1, 7, 13, 22, 28, 34, 40

		Irinotecan	50 mg/m^2 days 1 to 5	On weeks 4, 10, 16, 19, 25, 31, 37
High risk				
Poor prognosis (<30% EFS)	Embryonal and alveolar fusion-negative tumors: • Metastatic disease, age >10 years Alveolar fusion-positive tumors:	VAC × 14 cycles (40 weeks)		
		Vincristine	1.5 mg/m^2 (max 2 mg)	Weekly during weeks 1 to 13, 19 to 25, 31 to 37
		Dactinomycin	0.045 mg/kg (max 2.5 mg)	Every three weeks during weeks 1 through 40$^{\lozenge}$
		Cyclophosphamide	1200 mg/m^2 with mesna and hematopoietic	Every three weeks during weeks 1 through 40
	• Metastatic disease, any age		growth factor support	

Follow Up

- Follow up involves monitoring for recurrence and long-term sequelae of the disease as well as treatment.
- History and physical examination plus chest x-ray every 2 months for the first year with repeat images studies that were positive at diagnosis every 3 months.
- History and physical examination plus chest x-ray every 4 months for year 2 and 3 thereafter annually.

ZIMBABWE NATIONAL

ADULT ONCOLOGY TREATMENT GUIDELINES

2025