NATIONAL GUIDELINES
FOR CANCER MANAGEMENT
KENYA

August, 2013
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Comments or inquiries from readers and users of these Guidelines, that could be of use in improving cancer management is welcome, and can be sent directly to:

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Foreword

Cancer is one of the major non-communicable diseases (NCDs) which together with cardiovascular, diabetes and chronic respiratory diseases cause over 60% of global mortality every year. Cancer alone is estimated to annually kill over 7.9 million people globally. This constitutes close to 13% of deaths worldwide. While communicable diseases still remain the leading causes of death in many developing countries, the incidence and mortality from non-communicable diseases is rising rapidly. This has resulted in a “double burden of disease” further straining the existing health systems.

This pattern is true in Kenya where cancer ranks third as the leading cause of death after infectious and cardiovascular conditions. In Kenya, it is estimated that the annual incidence of cancer is about 28,000 new cases with an annual mortality of 22,000 cases. Over 60% of those affected are below 70 years while the risk of getting cancer before 75 years of age is 14% and the risk of dying of it is estimated at 12%. The leading cancers in women are breast, cervical and oesophagus. In men, oesophagus, prostate cancer and Kaposi’s sarcoma are the most common.

Following the development of National Health Policy Framework, 2013-2030 and based on the National Clinical Management and Referral Guidelines Volume III and the Cancer Control Strategy 2011 – 2016, it was deemed necessary to develop comprehensive cancer management guidelines. The guidelines are intended to be facilitative, enabling, and foundational, providing a firm bases for the attainment of high standards in the management of cancers. Development of the Guidelines has been a highly consultative process, evidence- based, incorporating recent advances in cancer management and emerging opportunities and challenges of the 21st Century.

The Ministry of Health will systematically disseminate these Guidelines, based on an agreed dissemination strategy and curriculum. In addition, the ministry will implement a monitoring and evaluation strategy that ensures and promotes the use of the Guidelines. This will also inform subsequent evidence based reviews. It is the expectation of the Ministry of Health that these guidelines will serve the users well (both public and private health sectors) as a guide for appropriate care of cancer patients delivered at the respective level of healthcare. The regular and consistent use of the guidelines by clinicians countrywide, will improve the management of cancer in Kenya, and thus help reduce the morbidity and mortality attributed to cancers.
Finally, on behalf of the Ministry of Health, I would like to appreciate the Technical Working Group, all the experts, reviewers and editors (below) who have worked hard to make these guidelines a reality. I would also like to acknowledge the technical assistance and financial support provided through funding from the United States Agency for International Development (USAID) by Management Sciences for Health/Health Commodities and Services Management (MSH/HCSM) Program. The contributions of the Africa Cancer Foundation (ACF) and the World Health Organization are acknowledged.

James Macharia,
Cabinet Secretary,
Ministry of Health,
Kenya.
Preface

In Kenya, cancer ranks third as the cause of morbidity and mortality after infectious and cardiovascular diseases. Formulation of these Guidelines was therefore prompted by this fact as well as the need to achieve some of the strategic objectives of the Cancer Control Strategy 2011-2016. The Cancer Control Strategy is the roadmap developed by the Government to reduce the incidence of cancer, improve its management and ultimately improve the quality of life of those who develop cancer and their care givers. A standardized approach to management was necessary hence the development of the National Guidelines for Cancer Management.

These Guidelines are designed to contribute to the reduction of the incidence and mortality from cancer and improve the quality of life of cancer patients by adopting best practice. Application of the guidelines is expected to improve early detection, timely diagnosis, harmonize and standardize treatment of cancer. The Guidelines should be utilized by all health care professionals at the four levels of care in both public and private sectors. In addition, they should be utilized by the pre-service training institutions. Further, the Guidelines will facilitate the development of the lists of essential medicines, non pharmaceuticals and equipment for cancer treatment.

The National Guidelines for Cancer Management contains information on selected common cancers in Kenya. It provides key information on their prevalence, data availability, presentation, methods and tools for diagnosis, management options for treatment (surgery, chemotherapy, and radiotherapy), follow-up and palliation.

The Guidelines are organized into four parts:

Part 1: Health System in support for cancer management.
This part contains a brief introduction to cancer, giving global, regional and national statistics. It highlights the multidisciplinary approach in cancer management and the roles of various cadres. Additionally, it deals with health system issues that include policy requirements, leadership and governance, financing, health products (diagnostics, pharmaceuticals and equipments), information and service delivery. These are required to facilitate optimum delivery and access to cancer treatment and care services.

Part 2: Site Specific tumor management in Adults.
The site specific cancers are arranged both alphabetically and anatomically. Management of site specific tumors is detailed in this part and is described in the following sequence: Introduction, Epidemiology, Diagnosis, Staging and risk management, commonly used medicines, prognosis and references.

Part 3: Pediatric Cancers.
Pediatric cancers are handled separately since the presentation and management differs from that of adults in various aspects. The commonly occurring cancers in children in Kenya were chosen.

Part 4: Supportive Care for cancer patients.
Supportive care is crucial as it ensures the quality of life of patients is at an optimal level to improve outcomes. This includes nutritional support, palliative care, handling of oncologic and palliative emergencies and pain management.
In order to improve cancer management through early detection and standardized management of cancer, implementation of these Guidelines is crucial. This will require wide dissemination of the Guidelines and its utilization in all health facilities in this country including public, private and faith based organizations. Its applications will provide relevant information that will guide future revisions of the Guidelines to suit the national needs for cancer management.

The Guidelines are mainly adopted from European Society of Medical Oncology (ESMO) Guidelines and will be reviewed at defined time intervals. In addition an accompanying booklet on treatment protocols will be developed and implemented.

The two health Ministries (Ministry of Medical Services and Ministry of Public Health and Sanitation) spearheaded the writing of the Guidelines giving the responsibility to experts in various clinical and supportive fields. In recognition of the urgent need for the Guidelines, the Technical Working Group was formed to oversee the process of their development.

The development process received technical and financial support from the USAID funded Management Sciences for Health/ Health Commodities and Services Management (MSH/ HCSM) program.

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PART 1

HEALTH SYSTEM IN SUPPORT OF CANCER MANAGEMENT
1. Introduction

Mueke S, Waihenya P, Odongo I, Kochollah L, Ogaja E, Korir A, Nato J.

1.1 Background

Cancer is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues. It is not just one disease but many diseases with more than 100 different types named for the organ or type of cell they begin in. Cancer results from internal and external risk factors working together and/or in sequence to trigger the process. People may be exposed to risk factors or cancer-causing agents in their environment and/or from their lifestyles.

Cancer is a leading cause of death worldwide accounting for 7.6 million deaths [around 13% of all deaths] in 2008. About 70% of these deaths occurred in low and middle income countries. It is projected that deaths from cancer will continue to rise with an estimate of 13.1 million deaths in 2030. Currently lung, stomach, liver, colon and breast cancer cause the most cancer deaths each year globally. In the past, cancer has received low priority for healthcare services in Sub-Saharan Africa, the reason partly being the undoubtedly overwhelming burden of communicable diseases. In Kenya, cancer ranks third as a cause of death after infectious diseases and cardiovascular disease. It causes 7% of the total national mortality each year.

Cancer is a major source of psychiatric morbidity, with about 50% of cancer patients suffering from a psychiatric disorder as well. The common disorders are adjustment disorder, depressive illnesses, anxiety and cognitive disorders.

Emerging trends point to the fact that non-communicable diseases such as cancers are growing health problems that need to be dealt with appropriately to sustain health advances that have already been achieved. This implies that the future country policies need to comprehensively address these twin epidemics of communicable and non-communicable diseases. Significantly, the new Kenya Health Policy [2012-2030] seeks to ensure significant reduction in the overall ill health in the Kenyan population by guaranteeing reductions in death due to communicable diseases and containing increases in death due to non communicable conditions below levels of public health importance without losing focus on emerging conditions. Therefore one of the policy objectives of the KHPF is to halt and reverse the rising burden of NCDs. The policy lays out the following strategies for achieving this goal:

- Ensuring universal access to interventions addressing recognized non communicable conditions in the country
- Ensuring that services relating to non communicable diseases are of high quality standards with a view to maximize utilization of services the population has access to
• Put in place programs for non-communicable diseases and control. To this end, the country has developed a National Cancer Control Strategy [2011-2016] to guide efforts in addressing this disease. The strategy proposes several interventions including the development of clinical protocols and QA guidelines for cancer treatment. Therefore, development of these Guidelines is a key strategic objective for the implementation of the Cancer Control Strategy.

1.2 Rationale
These Guidelines are designed to contribute to the reduction of the incidence and mortality of cancer and improve the quality of life of cancer patients. Application of the Guidelines is expected to improve early detection, timely diagnosis and standardise treatment of cancer. Additionally, this will improve accessibility to quality and safe cancer treatment and enhance capacity in all fields of cancer management. Further, the Guidelines will facilitate the development of an essential cancer medicines list and equipment for cancer treatment. The Guidelines seek to harmonise and standardise cancer care across the public and private sectors through mechanisms such as sharing of resources and information. Also, it will enable the Government to plan for the required resources (human, financial, infrastructural, essential products and technologies).

1.3 Description and organization of the Guidelines
The Guidelines describe the management of various site specific cancers organized as per the specific sites where it occurs. Each monograph in the Guidelines describes the following:
• Introduction
• Epidemiology
• Diagnosis
• Staging and risk management
• Management
• Commonly Used Medicines
• Prognosis
• References
The site specific cancers are arranged both alphabetically and anatomically. In addition, the Guidelines contain general chapters dealing with health system issues required to facilitate optimum delivery and access to cancer treatment and care services addressing policy requirements, financing, management and service delivery by level of care and referral pathways. The Guidelines also include a list of essential cancer medicines, diagnostics and equipment required for the provision of cancer treatment and care services at the different tiers of the health system.
1.4 Process of Developing the Cancer Management Guidelines
The process was initiated by the Ministries of Health, (MOMS &MOPHS) whereby a technical working group (TWG) was formed to oversee the development of the guidelines on 18th January, 2012. This was followed by a breakfast consultative forum organized by the Ministries in collaboration with ACF at Serena Hotel on 4th July 2012. During the meeting, presentations on local cancer management and prevention were made. Efforts to chart the way forward for a guideline was debated, but no consensus was reached. A second meeting (‘Experts’ Forum’) was convened at the KICC on 17/07/2012 and chaired by Prof Anyang Nyong’o who appointed the DMS and Prof Othieno-Abinya to lead the guideline development process (Prof Abinya headed the Secretariat of the Sub-Saharan Africa Task Force on adoption of National Comprehensive Cancer Network (NCCN) guidelines. Thereafter, several meetings were held, starting at Afya House (Ministry of Health headquarters) on 24th August, 2012 followed by several others at Panafric Hotel, Nairobi. The USAID funded Management Sciences for Health (MSH) was co-opted into the process in November 2012.

These preparatory meetings culminated in the first retreat to formulate the guidelines which was held in Naivasha in January 2013. Fifty six experts attended the retreat and the product was a first draft of the Guidelines. At the same time a roadmap to ensure completion of the work was agreed and an editing committee appointed.

Post Naivasha, and after compilation of the site-specific cancer management monographs, part of the retreat team was recalled for a meeting to review the content of the Draft. This was named Draft 1 and handed over to the national Cancer TWG to complete. The TWG reviewed and sent it to the External Reviewers. The final incorporation of comments towards a print ready draft was done by the TWG, following a stakeholders meeting held in June, 2013.

1.5 General Practice Guidelines
According to best practice, cancer is most effectively diagnosed, treated and prevented by a multiplicity of experts in different fields of specialization. For the benefit of the patient, standard practice, where there are adequate numbers of trained personnel, requires that the following practice disciplines (principles) be observed as much as possible.

Treatment modalities depend on the extent of the cancer and are usually combined as depicted below.

- Localised cancer is mainly treated by surgery.
- Loco-regional disease by radiotherapy.
- Widespread disease by chemotherapy, hormonal therapy, or biotherapy.

Before any cancer treatment is instituted, there must be clear justification. This must be for the benefit of the patient. Most of cancer treatments administered in low-income
countries with an aim to cure do not achieve this benefit because the patients usually present at the late stages with terminal disease requiring only palliative approaches. There should always be careful consideration concerning cancer treatment on:

- When to offer,
- When to abandon,
- When to avoid altogether.

The Ministry strongly recommends that appropriate multidisciplinary approach to cancer management should be adopted to achieve the safest and most cost-effective care. As such, all facilities treating cancer should establish “Multidisciplinary Tumour Boards”. This will avoid wastage of scarce resources and facilitate consideration of all aspects of the patient’s condition. Further, the multidisciplinary approach creates a framework for selecting patients for clinical trials, continuous professional development, audit and research.

1.6 Roles of Various Disciplines in Cancer Management

The roles of the various disciplines need to be clearly defined. This helps in:

- Referral for maintenance of the best standards of care;
- Regulation;
- Accountability.

The era of “Jacks of all trades” in cancer care should be easing off. Roles should follow the order given. Where the group that comes first is inaccessible then the next should apply. There should be systems/criteria for verifying competencies of the experts in each area. This should be done with regulatory and professional bodies taking a lead in the verification processes to protect patients from abuse and exploitation.

Biopsies should be carried out in the order given:

- Surgeons/gynaecologists
- Surgical/gynaecologic oncologists
- Internists (physicians)
- Paediatricians
- General duty medical officers
- Haematopathologists/haematologists
- Imaging experts
- Clinical officers

Fine needle aspiration (FNA)

- Pathologists
- Imaging experts
- Surgeons
- Surgical/Gynae-oncologists
- Haematopathologists
- Haematologists
• Internists (physicians)
• Paediatricians
• General duty medical officers
• Clinical officers

Diagnostic imaging
• Imaging specialists
• Others with the appropriate expertise.

Cancer Staging
• Imaging specialists
• Surgical/gynae-oncologists
• Surgeons
• Gynaecologists
• Histopathologists
• Adult/paediatric medical oncologists
• Haematologists
• Haematopathologists
• Radiation oncologists
• Clinical oncologists
• Internists (physicians)
• Paediatricians

Chemotherapy
• Medical oncologists (adult and paediatric)
• Haematologists/haematopathologists
• Clinical oncologists
• Radiation oncologists
• Internists (physicians)
• Paediatricians
• Surgeons
• Clinical Pharmacists

Radiotherapy
• Radiation oncologists
• Clinical oncologists

Nuclear medicine
• Nuclear medicine specialists
Palliative care
- Palliative care specialists.
- All the rest, depending on the required modality.

End of life issues
- Trained counsellors
- Palliative care specialists
- Spiritual leaders

All the other disciplines as required for the chosen modality. It’s acknowledged that such experts are in short supply in our country and effort should be made to train more.

1.7 Principles of Cancer Staging
The value of carrying out staging in cancer is to determine how wide the cancer has spread. Staging information assists the clinician in several ways including:
1. For selection of modalities of therapies
2. For prognostication purposes
3. Evaluating the success of therapy on patient’s disease
4. Facilitating the sharing of information between practitioners and treatment centres
5. Contributing to the enhancement of local knowledge base about cancer

Staging Systems
Globally there are a number of staging systems that are used in clinical practice. Generally they all provide information on the tumour extent which also determines treatment options and guides the prognosis of the disease.

Of the available systems the most widely applied is the TNM System developed by UICC (International Union Against Cancer). For proper cancer management it is critical that cancer staging systems are well understood and uniformly applied by all concerned in the clinical team.

The TNM system uses an alphanumeric notation which defines the stages as follows:
T Stage = The local disease extent with the use of numerical subsets which indicates the progressive extent of the malignant process (T0, T1, T2, T3, T4)
N Stage = Nodal status which indicates the presence or absence of regional lymph node metastases (N0, N1, N2, N3).
M Stage = Metastasis stage which defines the presence or absence of distant metastasis (M0, M1).

Surgical resection margin evaluation (R classification)
The R classification is a system that evaluates the completeness of the surgical excision of the primary tumor and regional nodes in reference to T and N above.
It does not refer to the presence of metastasis. Complete removal of all local disease corresponds to resection margins that are free of tumor. This R classification also assists the pathologist to evaluate the margin of surgical excision.

**Table 1: The R classification**

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<thead>
<tr>
<th>RX</th>
<th>Presence of residual tumor cannot be assessed</th>
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<tbody>
<tr>
<td>R0</td>
<td>No residual tumor</td>
</tr>
<tr>
<td>R1</td>
<td>Microscopic residual tumor</td>
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<tr>
<td>R2</td>
<td>Macroscopic residual tumor</td>
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</table>
2. Cancer Prevention


2.1 Introduction

Prevention means eliminating or minimizing exposure to the causes of a disease, and includes reducing individual susceptibility to the effect of such causes. Approximately 40% of cancers are preventable through interventions such as tobacco control, environmental controls, promotion of healthy diets and physical activity. Prevention offers the most cost-effective long-term strategy for the control of cancer. Prevention of cancer can be categorised into two - Primary prevention and secondary prevention.

- Primary prevention refers to a set of interventions that keeps a cancerous process from developing and includes health counselling, education and environmental controls.
- Secondary prevention is that set of interventions leading to the discovery and control of cancerous or precancerous lesions.

2.2 Primary prevention

Interventions aimed at reducing levels of the above risk factors in the population will not only reduce the incidence of cancer but also that of the other conditions that share these risks. Among the most important modifiable risk factors for cancer are: tobacco use; overweight, and obesity; harmful alcohol use; sexually transmitted human papilloma virus (HPV) infection, HIV/AIDS; air pollution, both outdoor and indoor; and occupational carcinogens.

2.2.1 Public health education

Health education involves raising public awareness on the risk factors for cancer and providing education on ways of reducing these risks. This should result in behaviour change, which often occurs over a long period of time and may be difficult to quantify. Education on the benefits of early diagnosis, ways of detection and screening should also be provided. These preventive measures should be highly promoted.

Increased awareness of warning symptoms and signs of cancer and taking prompt action, by the general public as well as physicians, nurses and other health care providers, can have a great impact on the disease through early diagnosis and hence more effective management.

Some early signs of cancer include lumps, sores that fail to heal, abnormal bleeding, persistent indigestion, and chronic hoarseness. Examples related to these afore mentioned symptoms include cancers of the breast, cervix, mouth, larynx, colon, rectum, and skin.
2.2.2 Tobacco control
Tobacco use is the single greatest avoidable risk factor for cancer mortality worldwide, causing an estimated 22% of cancer deaths per year. Tobacco smoking causes many types of cancer, including cancers of the lung, esophagus, larynx (voice box), mouth, throat, kidney, bladder, pancreas, stomach and cervix. Over 70% of the lung cancer burden can be attributed to smoking alone. Second-hand smoke (SHS), also known as environmental tobacco smoke, has been proven to cause lung cancer in nonsmoking adults and exposes children to cancers. Smokeless tobacco (also called oral tobacco, chewing tobacco, khat and pan) causes' oral, oesophageal and pancreatic cancers.
Health workers should inform patients of the dangers of smoking and encourage them to stop.

2.2.3 Healthy diets and physical activity
There is a link between overweight and obesity and many types of cancer such as oesophagus, colorectum, breast, endometrium and kidney.
Health care professionals should inform clients that regular physical activity, combined with a healthy balanced diet, prevent obesity and can reduce the risk of developing cancer.

2.2.4 Avoidance of alcohol use
Harmful (excessive) use of alcohol is a risk factor for many cancer types including cancer of the oral cavity, pharynx, larynx, oesophagus, liver, colorectum and breast. The risk of cancer increases with the amount of alcohol consumed. Therefore, health personnel should encourage their clients to stop or moderate alcohol consumption.

2.2.5 Avoidance of environmental pollution
Exposure to carcinogenic chemicals in the environment can occur through drinking water, pollution of indoor and ambient air and via the contamination of food by chemicals, such as aflatoxins or dioxins. Environmental carcinogens (aflatoxins, asbestos, vehicle emissions, lead, ultraviolet (UV) light and ionizing radiation,) are also culprits. Indoor air pollution, like smoke arising from use of charcoal and firewood in poorly ventilated houses, and, fumes from cars, dust, and garbage pollution increase the risk of lung cancer.

2.2.6 Prevention of Infections
Infectious agents contribute to significant proportion of cancer deaths. Viral hepatitis B and C cause cancer of the liver; human papilloma virus infection causes cervical cancer; Helicobacter pylori increases the risk of stomach cancer. HIV/AIDS is associated with cancers including aggressive lymphoma subtypes, Kaposi’s sarcoma, anorectal cancer, cervical cancer. In some countries schistosomiasis increases the risk of bladder cancer and in other countries, liver fluke increases the risk of cholangio-carcinoma.
Preventive measures include vaccination, prevention and treatment of infection and infestation.
2.2.7 Vaccination

HPV VACCINATION

At present, two types of HPV vaccines are available: a quadrivalent type that protects against the high risk HPV types 16 and 18 as well as low risk types 6 and 11 that are responsible for genital warts and a bivalent type which protects against HPV types 16 and 18. Both vaccines have shown more than 90% efficacy to prevent precancerous lesions in females naive to vaccine specific HPV types and who have completed all three doses. Out-of-school population should be reached through nearby health care facilities or through outreach campaigns. Catch-up vaccination for older girls and women up to age of 26 years is recommended.

HEPATITIS B VACCINATION

Chronic HBV is related to approximately 60%-90% of hepatocellular carcinomas (HCC) in adults and nearly 100% of childhood HCC in areas endemic for HBV infection. Hepatitis B vaccine is offered to all infants in the routine immunization schedule in the country. Treatment of certain infections and infestations (HIV/AIDS, schistomiasis, H. pylori, and hepatitis B&C) is also a preventive measure.

2.2.8 Minimising exposure to radiation

Ultraviolet (UV) radiation, and in particular solar radiation, is carcinogenic to humans, causing all major types of skin cancer, such as basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma. Ionizing radiation is also associated with leukemia and other solid tissue tumours. Proper disposal of highly radioactive isotopes is an effective preventive measure.

People with albinism are at a much higher risk of skin cancer and health workers should encourage them to wear protective clothing and wide brimmed hats.

Health workers should employ a multi-sectoral approach to addressing environmental and occupational exposures through the relevant government and non-governmental authorities.

2.3 Secondary Prevention

EARLY DETECTION OF CANCER AND SCREENING

Early detection of cancer greatly increases the chances for successful treatment. It comprises early diagnosis in symptomatic populations and screening in asymptomatic high risk populations.

Screening refers to the use of simple tests across a healthy population in order to identify individuals who have disease, but do not yet have symptoms. Based on existing evidence, mass population screening is advocated for breast and cervical cancer. Other cancers that are commonly screened for include prostate and colon.

2.3.1 Screening for Breast Cancer

Screening for breast cancer involves breast self examination (BSE), clinical breast examination (CBE) and breast imaging (mammography and/or ultrasound scanning).
BREAST SELF EXAMINATION (BSE)
This is a simple, quick examination done by the client herself, that improves breast self-awareness and allows individuals who detect breast lumps early enough to present themselves to clinicians in good time for evaluation. Where cancer is detected, the possibility of complete cure is greater. Regular and correct technique of breast examination is important and easy to teach and carry out.

CLINICAL BREAST EXAMINATION (CBE)
CBE is performed by a trained and skilled health care provider. It can be done at any KEPH level; and includes taking a detailed history and conducting a physical examination. All breast quadrants must be examined in detail. During CBE, the provider inspects the skin for changes and swellings, for tethering of the breast on the chest wall, palpates for lumps, checks for nipple discharge and advises clients on the next steps. A suspicious lump or bloody nipple discharge requires additional evaluation by mammography or ultrasonography as well as core needle biopsy.

MAMMOGRAPHY
A mammogram is a low-dose x-ray of the breast. Mammography is the test of choice for screening of early breast cancer when the lumps are not palpable by the patient or the doctor. However, although relatively fast and accurate, it is a specialised test and requires personnel and elaborate equipment.

BREAST ULTRASOUND
Ultrasound alone is not used as a screening test, but is useful as an additional tool in characterizing palpable tumours and taking of image-directed biopsies. In some instances, it has been used as a screening tool in lactating women, small-breasted women and in males.

2.3.2 Screening for Cervical Cancer
Screening for cervical cancer aims to detect precancerous lesions that are then treated to prevent progression to invasive cancer. The following methods are recommended for cervical cancer screening in the country:

VISUAL INSPECTION WITH ACETIC ACID (VIA)
This procedure involves applying 3-5% freshly prepared acetic acid to the cervix and observing after one minute. The VIA results are generally categorized into three subsets: suspicious for cancer, VIA negative and VIA positive. VIA uses instrument sets and equipment usually available at healthcare centers. It does not require a laboratory and provides an immediate result. Healthcare providers are encouraged to initiate counseling and screening for eligible women at all points of contact. The following recommendations should be considered when using VIA as a screening method:
Women under 25 years of age should be screened only if they are at high risk for disease. Women at high risk for cervical abnormalities are those who have had early sexual exposure, multiple partners, previous abnormal screening results or CIN, or are HIV positive.

VIA is not appropriate for women over 50 years. These women should be screened at five-year intervals using cytology or HPV testing.

Annual screening is not recommended at any age for the general population.

**VISUAL INSPECTION WITH LUGOL’S IODINE (VILI)**

VILI involves looking at the cervix with the naked eye or low magnification after swabbing with Lugol’s iodine. VILI has a sensitivity and specificity of about 92% and 85%, respectively; Test results are available immediately thus decreased loss to follow-up. Recommendations and timings of VIA outlined above also apply to VILI.

**CYTOLOGY TESTING BY PAP SMEAR**

A Pap smear is a microscopic examination of cells scraped from the opening of the cervix. The Pap smear is best taken around mid cycle. It should be postponed in case of cervicitis until after treatment; otherwise the pus cells obscure clarity of the smear and affect interpretation. It generally costs more than the other screening methods. It can however be cost effective if screening targets the population at highest risk for disease, and the infrastructure is in place.

**HPV TESTING**

HPV testing is a useful triage tool that allows visual or cytological testing for women who test positive for oncogenic HPV types.

Health workers should utilize every encounter with a member of the public at health facilities, to create awareness and promote screening.
3. The National Health System for Cancer Management


3.1 Leadership and governance

Cancer screening, treatment and care is complex and requires clear leadership at all levels of care. The division of Non-Communicable Diseases at the Ministry of Health provides national leadership on implementation of cancer prevention, care and treatment. To achieve the desired outcomes of the National Cancer Control Strategy, the National Cancer Institute will be established to provide technical leadership in planning for diagnosis, treatment, resource mobilization, palliation, research and data management for cancer.

At the county levels, county health coordinators will be in charge of their counties while hospitals and health centres will be represented by the respective in-charges working closely with their health management teams.

Roles and Responsibilities for each Level:

National level:
- Assess the cancer epidemiological and health delivery patterns in the country.
- Develop national level policies, strategic plans and planning guides for lower levels.
- Support resource mobilisation.
- Coordinate stakeholders and partners on cancer management in the health sector.
- Consolidate, analysis and dissemination of cancer data.
- Support human resource development and deployment for cancer management.
- Support infrastructure and equipment procurement for cancer.

County coordinators:
- Coordinate cancer management at county level.
- Advocate for resource allocation for county health care needs.
- Consolidate data from the county facilities.
- Monitor service delivery and ensure quality and responsiveness of cancer management.
- Support supervision and training coordination.
- Plan for management and utilisation of available resources for service delivery.
- Management of inputs including staff, equipment and pharmaceuticals.
- Organising service coverage, collection of data and appropriate referral management.
Community unit:
- Patient referral and follow-up.
- Advocacy for prevention and control of cancers.
- Provision of palliative care.
- Integration of cancer issues into other community-based programmes e.g. Microfinance.

### 3.2 Comprehensive Service Delivery

#### 3.2.1 Organization

Previously under the KHPF (1994-12) the country’s health system had been organized into six levels of care namely
- Level 1- Community Level
- Level 2- Dispensary & Clinics
- Level 3- Health Centres, private medical centres and nursing homes
- Level 4- District and Sub-district hospitals
- Level 5- Provincial General Hospitals and high volume district hospitals
- Level 6- National referral and teaching hospital

However, under the new Kenya Health Policy Framework 2012-2030, the health system has now been reorganized into 4 tiers to facilitate coordination and more efficient and effective service delivery. These tiers are
- Level 1- Community level
- Level 2- Primary Health Care level
- Level 3- Secondary level- 1st referral level
- Level 4- Tertiary – National Referral & Teaching Hospital.

The categorization of the healthcare system into 4 distinct tiers is primarily meant to rationalize the delivery of health services within the health system for efficiency in the use of existing resources. The responsibilities for the various levels of care for cancer management are:
- Health promotion- at all levels
- Prevention- at all levels
- Screening for early detection- all levels
- Treatment – secondary and tertiary level
- Palliative care- all levels
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<tr>
<th>HEALTH CARE</th>
<th>TIER PERSONNEL</th>
<th>SERVICES OFFERED</th>
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<tr>
<td>Community Service</td>
<td>- Community Health Worker</td>
<td>- IEC/BCC /community mobilization</td>
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<td></td>
<td>- Community Health Extension Worker</td>
<td>- Screening and treatment during outreach.</td>
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<td></td>
<td>- Trained health personnel</td>
<td>- Home based and palliative care</td>
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<td>- Community Health</td>
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<td>- Information Systems</td>
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<td>- Contact tracing</td>
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<td>- Referral and linkages.</td>
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<td>County Referral Service (Primary Referral Services)</td>
<td>- Nurse</td>
<td>- IEC/BCC</td>
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<tr>
<td></td>
<td>- Clinical Officer</td>
<td>- Screening using VIA/VILI or clinical examination</td>
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<td></td>
<td>- MO</td>
<td>- Centre for in- and outreach screening services</td>
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<tr>
<td></td>
<td>- Public Health Officer/Public Health Technician</td>
<td>- Cryotherapy</td>
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<td></td>
<td>- CHEW</td>
<td>- Referral for screen-positive clients for further management</td>
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<td>- Follow-up care</td>
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<td>- Palliative care</td>
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<td></td>
<td>- Research</td>
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<tr>
<td>Primary Care Service (Dispensary and Health Centre)</td>
<td>- Public Health Officer</td>
<td>- IEC/BCC</td>
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<tr>
<td></td>
<td>- Health Education Officer</td>
<td>- Screening e.g. with VIA/VILI or Pap smear, for cervical cancer.</td>
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<tr>
<td></td>
<td>- CHEW</td>
<td>- Diagnosis using imaging modalities,</td>
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<td></td>
<td>- Nurse</td>
<td>- Staging and biopsy for suspected cancer</td>
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<tr>
<td></td>
<td>- Clinical Officer</td>
<td>- Treatment within their capabilities --Referral for further management</td>
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<td></td>
<td>- Medical Officer</td>
<td>- Palliative care</td>
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<tr>
<td></td>
<td>- Family Physician</td>
<td>- Coordination/M&amp;E</td>
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<td></td>
<td>- Physician (Internist)</td>
<td>- Research</td>
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<tr>
<td></td>
<td>- Pathologists</td>
<td>- Cancer Registry</td>
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<tr>
<td></td>
<td>- Gynaecologist</td>
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<tr>
<td></td>
<td>- Surgeon</td>
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<td></td>
<td>- Peadiatrician</td>
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</tbody>
</table>
National Referral Services (Tertiary Referral Services)

- Nurse
- Clinical officer
- Medical Officer
- Physician (Internist)
- Pathologists
- Gynecologist
- Surgeons
- Pediatrician
- Radio-oncologist
- Medical oncologist
- Clinical Pharmacist

- Same as County Referral Services plus
- All modalities of therapy including Surgery
- Radiation Therapy
- Chemotherapy
- Research

Existing comprehensive cancer treatment facilities are found only in Nairobi at the Kenyatta National Hospital (public sector), Aga Khan Hospital, Nairobi Hospital and Kenya Cancer Care (all private sector). Cancer treatment to varying degrees, but excluding radiotherapy, is offered at Moi Teaching and Referral Hospital in Eldoret, all Level five Hospitals in the public sector and various private and faith-based hospitals in urban centers spread across the country.

3.2.2 Referral System

A referral system is a mechanism instituted to enable clients’ health needs to be comprehensively managed using resources beyond those available at the point where clients are accessing care. Establishment of an effective referral chain provides linkages needed across the different levels of care from level 1 to 4 ensuring that a given health care need of a client can be addressed irrespective of the level of the health system at which the client first accesses care. Cancer management spans all the tiers of the healthcare system, but with specific services offered dependent on the availability, quality, capability of human resource and functional infrastructure and equipment.

Management of cancer entails both physical and indirect referral upward and downward of the health care system. The key referral elements are patients/clients, expertise, specimens and information. Physical referral refers to the movement of the client or patient or the service or expertise. Indirect referral refers to the movement of the specimens of client parameters. Movement of client parameters is further facilitated by e-health. In view of limited infrastructure, equipment and human resources, the utilization of telemedicine to improve access is necessary. It is therefore imperative that the e-health Strategy be implemented.
3.2.3 Surveillance and Reporting

Cancer surveillance and reporting provide quantitative data on cancer and its determinants in a defined population by providing cancer incidence, morbidity, survival and mortality for persons with cancer. It tells where the national effort to reduce the disease burden lies and informs research and interventions for cancer prevention and control. A cancer registry is a surveillance tool and is a systematic continuous collection of data on cancers. According to the Cancer Prevention and Control Act all medical institutions (both government and private hospitals and some specified laboratories) should notify the National registry within 60 days of diagnosis.

Regional population-based registries should be established to consolidate data from hospital-based registries and provide data to the National Cancer Registry. All hospitals (level 4 and above) including cancer centres, should establish hospital-based registries in their institutions and should channel their data to regional population based registries

Health care institutions at all levels should capture and maintain comprehensive screening data for both disease and risk factors and should make periodic follow up.

The following variables should be captured in all patient information:

**Patient Details:** First name, given/maiden name, last name (surname), ID number, age/date of birth, gender, concurrent illness, current residence, place (district) of birth, religion and tribe/ethnicity.

**Tumour:** Incidence date, basis of diagnosis, primary site/topography (ICD-10) code, histology/morphology (ICD-10) code, behaviour, grade and stage at diagnosis (TNM).

**Treatment(s):** Initial and subsequent treatments – surgery, radiotherapy, chemotherapy, hormone therapy & symptomatic.

**Sources of data:** Hospital/laboratory name, hospital number, laboratory report number, date of abstraction.

**Follow-up:** Patient status (alive or dead) as at date of incidence, last date of contact with physician/health-care provider or if dead - date of death and cause of death, hospice number.

**Genetics and cancer:** document history of family members who have had a history of cancer (family tree).
**Quality Indicators**

All new diagnoses should be notified and registered. A disease registry championed by the Ministry and maintained by this task force will trend the disease for presentation characteristics, R0 resections, treatment related morbidities, repeat surgeries, lengths of hospital stays, recurrences and mortality. A trial data base established for different treatment regimen including newer ones will ensure that we no longer say ‘available local data not existent.

Since cancer occurrence and treatment outcomes differ by region, it is necessary to have research at all levels to support policy formulation and evaluate outcomes.

### 3.3 Financing

Cancers, being chronic illnesses require long term follow-up with chemotherapy or radiotherapy and are therefore financially intensive.

Options for financing include insurance through the National Social Health Insurance Fund (N.H.I.F), private insurance or Out of Pocket (O.O.P) expenditure. The latter is usually not sustainable. Health providers should educate clients on these options and guide them on how best to access financing.

**Public Private Partnerships (PPP)**

In view of the fact that the Government has limited resources to effectively implement the Cancer Control Strategy, a multisectoral approach, embracing PPP, will be effected. Several areas of cancer management are amenable to implement PPP e.g. prevention strategies, capacity building, optimizing use of radiotherapy machines and equipment, diagnostic facilities, pharmaceutical firms for subsidized costs of health products etc. Other modalities, such as placement of equipments in the public sector by the private sector, will be employed.

### 3.4 Human Resource Development - Paediatric and Clinical Oncology nurses

Cancer management requires highly skilled manpower, but currently there is a severe shortage of human resource to manage cancer in the country. The required specialists include medical radiation, gynaecology, paediatric & clinical oncologists, oncology nurses, surgeons, pharmacists medical physicists, therapy radiographers, and palliative care specialists.

In view of this current gap, the proposed expanded services and the envisaged new centres, additional human resource will be required to conform with the standard norms of operation in line with the Cancer Prevention and Control Act, 2012. The proposed establishment is 15 radiation oncologists, 25 medical oncologists, 15 gynaecology, 15 surgical oncologists, 10 radiation therapy technologists (RTTs), 50 oncology nurses, 10 medical physicists, 8 nuclear medicine physicians, 8 oncology pharmacists and 12 nuclear medicine technologists.
The training of these cadres is not available locally, and is expensive for the country. The duration of training ranges from one to four years; the latter being for radio oncologists. This will require planning with a phased approach. The medium - long term goal would be to establish the training programmes locally.

3.5 Health Products and Technologies

Diagnostics

Diagnostics play a critical role in the management of patients with cancer and are applied at every step in the patient care process. These steps include the following:

1. Establishing diagnosis and staging
2. Monitoring response to treatment
3. Evaluation of presence or absence of residual disease following treatment (response)
4. Confirmation of remission of disease
5. Identification of complications of treatment
6. Surveillance for relapse

Diagnostics include:

a) Imaging
b) Laboratory Work-up

3.5.1. Imaging In Cancer Management

Within the past few decades medical imaging has evolved very rapidly, now becoming an indispensable tool in the diagnosis, treatment, and follow-up of patients with cancer. Multiple imaging modalities are available for the assessment of cancer patients, each one with different advantages and limitations that are important to consider at the time of ordering a diagnostic study or planning an image-guided procedure.

Conventional Radiography and Fluoroscopy

These modalities use X-rays; one of the oldest forms of medical imaging. Despite all the newer, more sophisticated forms of scanning, conventional radiography is still one of the most sensitive ways of detecting many of the primary or metastatic bone and pulmonary lesions.

Fluoroscopy entails use of radiopaque substances like barium and iodine to x-ray hollow organs like the oesophagus, stomach or colon.

Locally, conventional radiography and fluoroscopy are available in many centres, both in the public and private sectors, and though not very good in characterising lesions to a high degree of specificity, the modalities are useful in diagnosis, treatment and follow up especially in a resource constrained environment like ours.

Angiography is the fluoroscopic X-ray visualization of blood vessels after injection of a radiopaque dye and is a useful modality in characterising the vascularity of tumours.

Angiography is also useful in therapy (interventional procedures like embolization) of tumours.
Mammography
This modality uses low-energy X-rays to examine the breast. It is the primary imaging modality for breast cancer screening, detection and diagnosis. The modality is very useful in identifying small calcified lesions in the breast (the goal of a screening mammography programme is to detect small; <1 cm tumours, typically through identification of characteristic masses and/or microcalcification). Mammographic screening is generally suggested to the asymptomatic 40–45-year-old female population at 2-year intervals.

Ultrasonography
This is the second oldest imaging method and the second most widely used worldwide. It uses high frequency non-ionizing sound waves (2 – 20 MHz) to generates images from the echoes received from the tissues. Nowadays, sonography is increasingly and routinely being used in many centres as an essential compliment to physical examination for the evaluation of palpable masses.

This modality is fairly widely distributed and its relatively lower cost, high temporal resolution, real-time imaging and lack of ionizing radiation make ultrasound an ideal modality for use mainly in the abdomen for anatomical identification and localization of cancerous lesions. It is good for characterisation and guiding biopsy or fine needle aspiration (FNA) of tumours, treatment planning and follow-up of patients with not only abdominal malignancy but also tumours in the small superficial organs like the thyroid gland and breast.

The biggest advantage of sonography is that one avoids the potential harmful effects of X-rays and the portability of the equipment allows ease of use in bedside scanning and emergency departments. This makes it the modality of choice for guiding percutaneous interventional procedures on tumours, from needle biopsy to ablation in many centres.

Computerised Tomography (CT)
Formerly known as CAT scan, computerised tomography (CT) uses the lowest practicable X-ray doses in a more sophisticated manner to produce finely detailed cross-sectional images of the body. When the image slices are reassembled by computer, the result is a very detailed, three dimensional view of the body’s interior. Computerised tomography is useful for anatomical identification and localization of lesions at all stages of a patients’ illness. CT is the workhorse of medical imaging particularly for the assessment, treatment planning and follow-up of cancer patients.

Nuclear Medicine
Nuclear medicine is a form of molecular imaging where a radioactive material (radiopharmaceutical) is administered to a patient and the radiation emitted by the radiopharmaceutical is detected by sensitive radiation detectors (PET detectors and gamma Cameras) placed outside the patient’s body. Combination of gamma camera and CT (in
SPECT scanner) and the combination of PET and CT (in PET/CT scanner) is a major advance in improving detection and localisation of lesions. Radionuclide imaging is broadly divided into two:

**a) Single Photon Emission Computerised Tomography (SPECT)**

This modality uses single photon radionuclides like technicium-99m, Iodine-131, Galium-67 and others that emit gamma rays (energy ranges 75 – 360 Kev). SPECT is a functional scan and is specific for organ of interest. It can also be applied to the whole body, is relatively safe in terms of radiation dose and is good in detection of primary and metastatic tumours; especially skeletal. Iodine-131 is both diagnostic and therapeutic for thyroid cancer. This modality is available in Nairobi.

**b) Positron Emission Tomography (PET/CT)**

In terms of radiation dose, PET/CT is also relatively safe and uses positron emitting radionuclides like carbon-11, Fluoride-18, Oxygen-15 and others. The most commonly used tracer in PET is a radioactive form of glucose; [18F]fluoro-2-deoxy-D-glucose. Tissues with increased metabolic demand like growing cancer cells, show enhanced uptake of the tracer and show up on the scan. By combining PET and CT, important information about many conditions affecting the different organs of the body is easily mapped. PET/CT is highly sensitive and specific for detecting occult and additional sites of loco-regional lymph nodal spread and/or distant metastases not detected by standard imaging, thus changing staging in up to 25% of the cases.

This modality is used for treatment planning by determining extent of primary disease. It is also used in re-staging post treatment disease recurrence and management follow up. The modality is not available in Kenya at the moment.

**Magnetic Resonance Imaging (MRI)**

This is an imaging modality that uses radiofrequency pulses to generate images from hydrogen atoms in the body of a patient while the patient is lying in a strong magnetic field. The modality has a superb tissue contrast and can obtain very high anatomical delineation of a tumour, especially in the central nervous system. MRI is the method of choice in detection of primary or metastatic brain and spinal tumours. Compared to computerised tomography (CT), MRI has the advantage of using non-ionizing radiation, but has the disadvantage of inferior resolution where there is body motion or close points, particularly, in the chest, abdomen and pelvic studies.

The development of fusion imaging technology allows combination of information from CT or MRI with images from real-time ultrasound scan. This is very useful when performing invasive procedures like percutaneous biopsies and radiofrequency ablation of tumours. In these procedures, Ultrasound guidance is preferred to perform the procedure, but the more detailed tissue characterisation from a contrasted CT and MRI is also critical. Currently, there are only a few available MRI machines with most concentrated in the
private sector, in Nairobi, Mombasa and Eldoret. Thus, the routine use of MRI is limited by access (geographical) human resource capacity, cost and availability constraints.

3.5.2 Laboratory

Biochemistry analysers
Used to carry out biochemical tests required in relation to chemotherapy treatment including renal function tests, alkaline phosphatase (ALP) and liver function tests. Automated analysers are preferred for accuracy and precision.

Immunooassay analysers (Serology & Tumour Markers)
To conduct specific serological tests related to oncological diagnosis and management (e.g. HIV ELISA, hepatitis B surface antigen and hepatitis C antibodies). Others are tumour markers related to oncological diagnosis and follow-up including beta-HCG and alfa-fetoprotein (AFP). The analyser uses enzyme-linked immunosorbent technology, and should preferably be automated.

Haematology Analysers
For full blood count (five-part differential) essential in diagnosis of haematological malignancies and status examination of all cancer patients for oncological treatment.

Bone marrow kits
Bone marrow needles for aspirate and trephine biopsy together with the procedure packs for conducting bone marrow procedures useful in diagnosis, staging and follow-up of haematological malignancies are available.

Histopathology and cytopathology equipment
These are required to prepare stained slides of specimens for microscopic examination by histopathologists. They include cutting stations, tissue processors, embedding stations, microtomes, staining equipment, cover slips and accessioning systems.

Immunohistochemistry set-up
Used for demonstration of specific antigens and phenotypes in tumours, thus used to demonstrate the histogenesis (cell of origin of cancers) which helps in distinguishing various cancers such as lymphomas and carcinoma. It also identifies characteristic markers related to treatment outcomes (predictive factors) such as hormone receptors and Her2 for breast cancer treatment and prognostication. The set-up includes immunohistochemistry stainers for primary antibodies with detection kits having the secondary antibodies.

Flow cytometry
This is a technique similar to immunohistochemistry, but applied on cells suspended in a stream of fluid and passing them by an electronic detection apparatus (flow cytometer), whereby the primary antibodies and detection system allows phenotyping of the cells such as leukaemia and lymphoma.
Molecular PCR platforms

These are used to detect and quantify specific genetic mutations characteristic of certain cancers such as the BCR:ABL translocation for diagnosis of chronic myeloid leukaemia (CML).

Radiotherapy Machines and Technologies

1. Co 60 units – Cobalt therapy or cobalt-60 therapy is the medical use of external beam gamma rays from cobalt-60 radioisotopes to treat conditions such as cancer.
2. Linear Accelerator (LINAC) machines produce external beam, high energy x-rays (photons) used for X-ray therapy. A linear accelerator machine is designed to be a general purpose radiation delivery machine able to treat all areas of the body from head to toe. It has better precision than a cobalt machine and most often used in multi-session treatments in order to avoid damaging healthy surrounding tissue with too high a dose of radiation.
3. Brachytherapy- is a form of radiotherapy where a radiation source is placed inside a body cavity (intracavitary) or next to the area requiring treatment. It is commonly used as an effective treatment for cervical, prostate, breast and skin cancer and can also be used to treat tumours in many other body sites.
4. Radioisotope therapy – Radioisotope therapy is a type of internal radiotherapy using systemic radioactive substances or radioisotopes, used for the management of certain malignant and non malignant conditions, for example, the use of radioactive iodine for management of thyroid disorders.

The above equipment are broadly used for diagnostics and treatment. These are not the only equipment used in the management of cancer as the choice depends on the condition being addressed. Chemotherapy and surgery are complementary modalities.

3.5.4 Essential Medicines (Appendix 1)

Essential medicines, are defined by the WHO as “those drugs that satisfy the health care needs of the majority of the population; they should therefore be available at all times in adequate amounts and in appropriate dosage forms, at a price the community can afford”. For cancer management, meeting this requirement involves strategizing to improve access and equity. This is achieved through availing an essential medicines list for the public sector and a more expanded one for the country. The list is intended to guide the development, production, procurement and supply, prescribing, dispensing and use in order to attain high standards of cancer care in the country.

Handling Cytotoxic Medicines

Storage and dispensing

Cytotoxic drugs should be stored in a restricted area or lockable cabinet and/or fridge away from other drugs. Chemotherapy should be dispensed by trained personnel. Prepared chemotherapy should be comprehensively and clearly labelled with details
such as patient name, medicine name, strength and volumes, and stability. Cytotoxics for intrathecal use should be indicated as such.

**Training for safe handling of cytotoxics**
Personnel should be trained in aseptic technique, infection control and proper disposal, so as to protect the patient and protect themselves.

**Use of personnel protective equipment (PPE Gowns, chemo gloves, mask)**
Personnel preparing and administering chemotherapy should wear protective equipment which includes:
- A low-permeability, closed-front gown with long sleeves and elastic cuffs,
- Nitrile, vinyl or powder-free latex gloves,
- Face mask and goggles,
- Closed footwear.

**Use of biologic safety cabinet (class II)**
Chemotherapy cabinet – also known as biological safety cabinet, is used for compounding chemotherapy drugs to ensure their safe handling during re-constitution.
Chemotherapy medicines/agents should be prepared in centers that have a biological safety cabinet, by trained and qualified medical personnel, using aseptic technique. The cabinets should be in a restricted area and should be serviced bi-annually.

**Transportation**
Chemotherapy preparations should be transported from the preparation unit to the administration unit by a nurse or trained personnel in a leak-proof plastic bag placed in a sturdy container.

**Management of spills (small and large volume)**
All personnel involved in preparation and administration of chemotherapy products should be trained in the management of cytotoxic spills. The preparation area as well as administration area will have a spill kit that shall include:-
- Alkaline soap
- Isopropyl alcohol
- Absorbent mats
- Niosh Mask
- 2 pairs of powder-free gloves
- Gown with closed front and snug cuffs
- 2 Cytotoxic Disposal bags
- Sharps container
- Dust pan and brush
- A pair of goggles
Management of cytotoxic waste
Cytotoxic waste shall be transported in dedicated leakproof cytotoxic waste containers and disposed off via incineration at temperature not less than 1100°C

Specialty training for providers
Physicians- oncology and radiotherapy, pharmacists, nursing staff, counselors. All personnel handling chemotherapy have to undergo competency training. Re-assessment shall be required for personnel involved in admixture and administration.

Pre- and Post-Chemotherapy
The patient needs to be well prepared with pre-and post hydration and pre-and post medication to improve tolerability of the regimen and prevent adverse effects.

Adverse drug reaction reporting (physician, pharmacist, nurse)
The World Health Organization defines an adverse drug reaction (ADR) as “A response to a drug which is noxious and unintended, and which occurs at doses normally used or tested in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function”. Chemotherapy agents have been associated with safety concerns including serious ADRs, short and long term adverse effects which include cardiotoxicity, neuropathy, renal and hepatotoxicity, neutropenia, to mention but a few. All personnel involved in chemotherapy treatment shall be required to document any observed or suspected adverse drug reactions in the specified form. Reports on adverse reaction to a medicine should be made using a “yellow form” (Form for Reporting Suspected Adverse Drug Reactions) which is available at http://www.pharmacyboardkenya.org/assets/files/Suspected ADR Notification Form.pdf or report electronically at www.pv.pharmacyboardkenya.org

Procurement (including quality control)
All medicines/HPTs procured and used in chemotherapy should be authentic and of proven quality as well as being cost effective. Reports on poor quality medicine, sub-standard medicine or counterfeit medicine, should be made using a “pink form” (Form for Reporting Poor Quality Medicinal Products) which is available at http://www.pharmacyboardkenya.org/assets/files/Form for Reporting Poor Quality Medicinal Products.pdf or reported electronically at www.pv.pharmacyboardkenya.org

3.6 Physical Infrastructure
(Comprehensive cancer treatment facilities)
There is limited capacity for cancer management, hence the proposal to expand facilities for early detection, diagnosis and treatment services for cancer in Kenya. In collaboration with IAEA and development partners in the public sector, KNH will be upgraded through installation of additional equipments for diagnostic and radiotherapy services. Four new regional centres (i.e. Coast General Hospital, New Nyanza Provincial General Hospital, Nyeri
Provincial General Hospital and Moi Teaching and Referral Hospital) will be established to improve access (geographical) and quality of care locally and regionally (East and Central Africa).

3.7 Information System

A requisite cancer information system will integrate data collection, processing and presentation of information to enable evidence-based decision-making for managing cancer services at all levels of the health system. The Cancer Prevention and Control Strategy envisages establishment of hospital and regional population-based registries to provide and consolidate information on cancer. Further, a cancer information system will facilitate collation and summarization of information on various components of the health system that contribute to effective management of cancer. This will include policy and legal framework, service delivery (including referral networks), products and technologies, human and financial resources.
PART 2

SITE- SPECIFIC GUIDELINES
4. Breast Cancer


4.1 Introduction
Breast cancer is the commonest cause of cancer related mortality in women, and a leading cancer in Kenya and globally. It is noted to have a more aggressive behavior in black African women. It also affects men, however majority of patients affected (>99%) are women.

4.2 Epidemiology
Breast cancer in Kenyan women occurs more commonly in younger women (age <50 years). It’s the leading cancer in women in Kenya with the rate of 33.5/100,000 population according to the Nairobi Cancer Registry. The known risk factors include female sex, age, and a family history of breast cancer, prolonged exposure to oestrogens, obesity, smoking and alcohol.

BRCA1 and 2 gene mutations are specific genetic abnormalities that are associated with high risk for breast and ovarian cancers that may be familial. Such candidates may be investigated using genetic tests for the BRCA1 & 2 gene mutation. If confirmed, affected subjects may be offered prophylactic mastectomy after child bearing and achieving desired family size.

Screening for early detection is recommended as lesions treated in the early stages have a high cure rate. Screening for breast cancer includes breast self examination (BSE), clinical breast examination (CBE) and breast imaging (mammogram and/or ultrasound scanning). BSE is recommended at day 10 of the menstrual cycle. For post menopausal women, a monthly BSE schedule should be established. All patients with clinical suspicious lesions should have imaging as part of early detection. Mammogram is recommended for women over 40 years, while ultrasound is the imaging of choice for younger women. MRI may be used where possible for screening and early detection in patients at high risk of breast cancer such as those with BRCA1 & 2 gene mutations.

4.3 Diagnosis

4.3.1 Clinical Features and Initial Presentations
During early stages the following symptoms and signs may be present:

- A painless lump in the breast (in majority of patients)
- Nipple retraction
- Skin changes such as darkening and dimpling (appearance like the skin of an orange)
- Nipple discharge that may be bloody
In late stages, common presentations include:

- ulceration
- enlarged lymph nodes in the armpit and neck
- uniform breast enlargement
- Symptoms and signs of distant metastases such as un-resolving cough, bone pains and pathological fractures

Pain is usually a late symptom.

### 4.3.2 Imaging

- Mammogram is recommended for women over 40 years, while ultrasound is the imaging of choice for younger women.
- MRI may be of value in select group of women who have had equivocal mammogram/ultrasound.

The imaging examination should include the axilla.

### 4.3.3 Pathology Diagnosis

- A core needle biopsy obtained manually, or preferably by ultrasound or stereotactic guidance is recommended
  - FNA should only be used as a screening test where core biopsy services are not possible / available. Any atypical/suspicious or malignant cytology on FNA must be confirmed on histopathological examination. Surgery should not be done on the basis of FNA results, except where triple assessment (clinical, radiological and cytological findings) is definitive for malignancy.

* Preoperative or diagnostic open incision biopsy is not recommended.

- The histopathological reporting should be done according to WHO classification, specifying the histological type of breast cancer, grade, lymphovascular invasion, tumour dimensions, number of nodes sampled and number of nodes involved and presence of necrosis.
  - It is recommended that histopathology be reported by specialist pathologists, and if reported by a non-specialist pathologist that this is reviewed as referral before treatment is instituted at a specialist treatment center.
- Immunohistochemistry (IHC) for estrogen receptor (ER) and progesterone receptor (PR) must be done.
- Fluorescence in situ hybridization (FISH)/chromogenic in situ hybridization (CISH) test is required for equivocal HER2 on IHC (HER2 2+) for confirmation of HER2 overexpression.
  - It is recommended that immunohistochemistry should be undertaken.
4.4 Staging and Risk Assessment

Preoperative related disease staging includes clinical, radiological and pathological information.

Clinical examination includes the size of tumour (T stage), axillary and supraclavicular node examination (N), symptoms and signs of metastases (M).

An attempt should be made to stage all breast cancers before any operative treatment.

### Table 3: Tumor Node Metastases (TNM) staging system for cancer of the breast

#### Primary tumor (T)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>in-situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor &lt;20 mm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt;20 mm but &lt;50 mm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt;50 mm in greatest dimension</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)</td>
</tr>
</tbody>
</table>

#### Regional lymph nodes (N)

**Clinical**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed (e.g. previously removed)</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastases</td>
</tr>
<tr>
<td>N1</td>
<td>Metastases to movable ipsilateral level I, II axillary lymph node(s)</td>
</tr>
<tr>
<td>N2</td>
<td>Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases</td>
</tr>
<tr>
<td>N3</td>
<td>Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement</td>
</tr>
</tbody>
</table>
### Pathological (pN)

<table>
<thead>
<tr>
<th>pNX</th>
<th>Regional lymph nodes cannot be assessed (e.g. previously removed, or not removed for pathological study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN0</td>
<td>No regional lymph node metastasis identified histologically</td>
</tr>
<tr>
<td>pN1</td>
<td>Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected</td>
</tr>
<tr>
<td>pN2</td>
<td>Metastases in 4–9 axillary lymph nodes; or in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases</td>
</tr>
<tr>
<td>pN3</td>
<td>Metastases in &gt;10 axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected; or in ipsilateral supraclavicular lymph nodes</td>
</tr>
</tbody>
</table>

### Distant metastasis (M)

| M0          | No clinical or radiographic evidence of distant metastases                                          |
| M1          | Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven >0.2 mm |

#### 4.4.1 Radiology & Imaging for Staging

- In early disease (clinical T1 and T2 tumours), there is no need for further imaging.
- In locally advanced disease (clinical T3 and T4 tumours), chest x-ray and abdominal ultrasound are recommended. Further imaging such as bone scans is guided by clinical presentation.

#### 4.4.2 Laboratory Investigations

- Full blood count (FBC)
- Biochemistry including liver and renal function tests, alkaline phosphatase (ALP), calcium and urate.
- Viral serology for HIV (recommended).
- Tumour markers have no role in diagnosis, treatment or prognostication of breast cancer.
4.5 Management

Treatment is stratified according to the extent of the disease, with surgery, chemotherapy, radiotherapy and hormonal therapy as treatment options. A multidisciplinary treatment planning involving at least a breast surgeon, radiologist, pathologist, medical oncologist and radiation oncologist should be used to integrate local and systemic therapies and their sequence.

4.5.1 Surgery

**T1 & T2 tumours**

- Surgery is the mainstay of treatment for any localized disease (lesions <5cm)
  - T1 should be treated through breast conserving surgery or simple mastectomy, then followed by radiation therapy*
  - T2 should be treated through breast conserving surgery, or simple mastectomy, then followed by radiation therapy* Large T2 tumours where negative margins may be difficult to achieve should be treated with breast conserving surgery after downsizing with neoadjuvant chemotherapy, or simple mastectomy, then followed by radiation therapy*.

* Where radiotherapy services cannot be easily accessed, the preferred surgical procedure is modified radical mastectomy

- Sentinel lymph node mapping should be done where possible for clinically non-palpable nodes, and if negative no axillary dissection should be undertaken. If positive, axillary node dissection should be undertaken and at least 12-15 nodes harvested and submitted for histopathological examination.
  - Sentinel lymph node mapping is not indicated for clinically palpable nodes.

- The margins should be confirmed through histopathology, for which the entire specimen should be sent to the laboratory for examination.

- If initial excision shows a positive margin at histopathology, early re-excision should be considered if the residual site of the lesion is amenable to repeat surgery.
  - If not amenable to repeat surgery (re-excision), radiation therapy of the tumour bed is recommended.

- It is recommended that all other tumours be given adjuvant chemotherapy, except for T1 tumours that are grade 1 ER+, PR+, Her2-, node negative. These can be given hormonal therapy. Her2+ node negative tumours regardless of ER status should get chemotherapy.

- In situation where both adjuvant radiotherapy and chemotherapy are indicated, radiotherapy should follow completion of the chemotherapy.

- Where breast conserving surgery has been undertaken, adjuvant radiotherapy is mandatory.

- Axillary irradiation should be given for node positive in T1 and T2 tumours; where the axillary nodes are negative in T1 and T2 tumours there is no role for axillary irradiation.
• Axillary nodal irradiation can now be safely administered instead of axillary dissection where sentinel node is positive especially in T1/T2 tumours. If sentinel nodal mapping cannot be carried out, good imaging of the axilla, by ultrasonography for example may be used to detect nodal involvement. If positive then axillary irradiation should be considered as a replacement for axillary dissection. This should be more attractive in our set-up where practitioners generally find axillary dissection quite challenging. The only problem is limited radiotherapy facilities.
• Hormonal therapy should be given after completion of chemotherapy and radiotherapy for ER+ tumours

T3 & T4 tumours
• Surgery, either simple mastectomy or modified radical mastectomy, is the mainstay of treatment.
• Neoadjuvant chemotherapy is recommended for downstaging before surgery.
• Lymph nodes are handled the same way as for T1-T2 tumours.
• The margins should be confirmed through histopathology, for which the entire specimen should be sent to the laboratory for examination.
• Chest wall irradiation is mandatory for T3 and T4 tumours.
• Axillary irradiation is indicated for lymph node positive T3 and T4 tumours.
• In situation where both adjuvant radiotherapy and chemotherapy are indicated, radiotherapy should follow completion of the chemotherapy.
• Hormonal therapy should be given after completion of chemotherapy and radiotherapy for ER+ tumours.

4.5.2 Chemotherapy
A multiplicity of chemotherapy regimens are in use for adjuvant treatment.

4.5.3 Metastatic Disease
• There is no standard approach to treatment of metastatic disease, which is mainly palliative.
• Hormonal therapy is preferred unless there is life threatening disease for which chemotherapy is preferred.
• Chemotherapy regimens, singly or in various combination or sequentially, may be used
• Radiation therapy for localized disease may be given to control symptoms, and may also be used for localized bone and CNS metastases.
• Biphosphonates should be offered for patients with bone metastases, since they have been shown to reduce incidence of skeletal related events.
4.5.4 Non-Invasive Tumours (DCIS, LCIS)
Non-invasive tumours (intraductal carcinoma, ductal carcinoma in situ, DCIS) may be treated with breast conserving surgery providing negative tissue margins >10mm can be achieved (<1mm is considered inadequate excision on pathological specimens). Adjuvant radiation therapy decreases the risk of local recurrence, and should be used for high-risk DCIS. Low risk DCIS (focus size <10mm, low/intermediate nuclear grade with adequate surgical margins) may not require radiation therapy. Hormonal therapy may be considered for ER+ DCIS.
Where possible, breast reconstructive surgery should be considered for all patients who have had mastectomy.

4.5.5 Breast Reconstruction
Reconstruction mammoplasty in properly selected patients following mastectomy for cancer does not adversely affect the prognosis or the physician's ability to follow the patient for metastatic disease. The reconstruction may include the breast mound alone or also the nipple-areolar complex. The plastic surgeon performing the reconstruction should be in close contact with the surgeon who performed the original mastectomy for details of the patient's previous treatment and prognosis. This should only be undertaken by a qualified surgeon in a facility with the capacity for adequate care and follow-up.

4.5.6 Management of Male Breast Cancer
Investigation of breast cancer in the male is identical to that of the female patient. Because the male breast is very small, it is common for even small tumours to involve both skin and deep tissues with the result that they present as locally advanced disease. Surgery should be planned so that there will be wide margins on both the skin and deep tissues, and this may require removal of some underlying muscle.
Axillary dissection is also required.
It is important to assess the hormone receptor status since most carcinomas of the male breast are hormone receptor positive thus amenable to hormonal therapy.
Adjuvant radiotherapy is often recommended owing to the size of the breast and locally advanced disease. The indications for post-mastectomy radiation for males are essentially the same as those for females.

4.5.7 Follow-Up
There is no standard sequence or protocol for follow-up. The key aim of follow-up is to detect early in-breast and local recurrences or contralateral breast cancer, and to evaluate therapy related complications (such as osteoporosis and second cancers). Mammography is recommended yearly for premenopausal women and for postmenopausal women who have had breast conserving surgery. Laboratory and imaging tests (e.g. blood counts, routine chemistry tests, chest X-rays, bone scans, liver ultrasound exams, CT scans or any
tumor markers such as CA15-3 or CEA) are not indicated in asymptomatic patients as they provide no benefit supported by literature.

4.5.8 Relapsed or Refractory Disease
Tissue diagnosis through biopsy for histopathological plus or minus immunohistochemical verification should be obtained whenever possible, as this is relevant to rule out biological change or different disease entity.

4.5.9 Palliation and End of Life
[See Chapter 40 – 41 on palliation and cancer pain].

4.6 Medicines commonly used
Anthracyclines, cyclophosphamide, methotrexate, taxanes, trastuzumab, lapatinib, capecitabine, vinorelbine, carboplatin, gemcitabine, ixabepilone; tamoxifen, anastrazole, letrozole, exemestane. In resource limited settings, doxorubicin and cyclophosphamide is the standard treatment. A combination of cyclophosphamide/methotrexate and 5FU is also use in some centers, though combination of cyclophosphamide and an anthracycline with or without 5-fluorouracil is still preferred by many despite concerns about cardiotoxicity of anthracyclines. Patients with tumours that are Her2+ (over-expressing, or amplified) should, in addition to adjuvant chemotherapy, receive traztuzumab for 12 months. Other chemotherapy regimens in the adjuvant setting use combinations of doxorubicin/cyclophosphamide, and a taxane, either simultaneously or sequentially. Platinum agents such as carboplatinum and cis-platinum are also used in combination. Hormonal therapy should be given after completion of chemotherapy and radiotherapy for ER/PR+ tumours. Tamoxifen with or without a luteinizing hormone releasing hormone (LHRH) analogue is preferred in premenopausal women. Those who cannot access tamoxifen can undergo ovarian ablation, either surgically or by irradiation. Postmenopausal women should be offered an aromatase inhibitor (anastrazole, letrozole or exemestane), or tamoxifen.

4.7 Prognosis
Early breast cancer is curable in the majority of cases if treated appropriately. Advanced breast cancer is generally incurable.
REFERENCES
5. Central Nervous System (CNS) Tumours

Mwang’ombe N J M, Narayanan V, Gatei D, Kalebi A

5.1 Introduction
Central nervous tumours are tumours of the brain and spinal cord. Global data suggests this disease having a lower incidence in less developed countries, among the less affluent, and people of African and Asian descent compared to Caucasian descent.

5.2 Epidemiology
The annual global age standardized incidence of primary malignant brain tumours is 2.8 to 5.8 and 2 to 4.1 per 100,000 for males and females respectively. In Kenya the higher male incidence is well recorded.
Brain tumours rank 13 out of 15 malignancies in the Nairobi Cancer Registry, with gliomas as the commonest followed by meningiomas.
Known risk factors include age, gender, inherited familial syndromes, irradiation and ethnicity. Immunosupression due to AIDS is a well recognized cause of cerebral lymphoma.

5.3.1 Clinical Features and initial Presentations
The most frequent symptoms of brain tumors include:
• Headaches that tend to be worse in the morning and ease during the day
• Seizures or convulsions
• Nausea or vomiting
• Weakness or loss of feeling in the arms or legs
• Stumbling or lack of coordination in walking
• Abnormal eye movements or changes/loss in vision
• Drowsiness
• Changes in personality or memory
• Changes in speech
Diagnostic tests should be performed to determine if these symptoms are that of a brain tumor and if it is a primary or secondary one.

5.3.2 Imaging
For diagnostic work-up, an MRI is the investigation of choice and is superior to CT scan due to better contrast resolution, further characterization and assessment of full extent of disease. If not accessible unenhanced computerised tomography (CT) scan is mandatory to evaluate for most intracranial mass lesions. The initial imaging is useful for surgical planning and forms a basis for follow up. The patient with suspected brain tumour on imaging should be referred, with the CT-scan or MRI, to a specialist referral center without delay.
5.3.3 Neurosurgical review
An urgent neurosurgical review should be done with MRI where possible for emergency surgery, otherwise the patient should be seen by a pre-operative multidisciplinary team for review and surgical management planning (biopsy/debulk/resection). A preoperative biopsy for planning management should preferably be obtained stereotactically.

5.3.4 Pathology diagnosis
- Tissue obtained at emergency or planned surgery should be submitted to histopathology for examination.
- Diagnostic biopsy is required before initiation of any chemotherapy or radiotherapy, except for high-risk cases where biopsy cannot be done and emergency radiotherapy is required (see under management).
- The histopathological reporting should be done according to WHO classification, specifying the histological type and sub-type of brain tumour and grade as per WHO criteria.
  - The WHO grading system is 4-tier system (grade I to IV) and must be reported applied in all brain tumours.
- It is recommended that histopathology be reported by specialist pathologists, and if reported by a non-specialist pathologist that this be reviewed as referral before treatment is instituted at a specialist treatment center.
- Immunohistochemistry (IHC) is recommended for confirmation of diagnosis, being mandatory for high-grade or equivocal tumours where the histogenesis is unclear. The IHC should be undertaken at a duly accredited laboratory by a specialist pathologist.
Table 4: Histological Types and Common Sub-Types of Brain Tumours

<table>
<thead>
<tr>
<th>TUMOUR TYPE</th>
<th>EXAMPLE OF SUB-TYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroepithelial</td>
<td>Tumors Astrocytic tumors, Oligodendrogial tumors, Ependymal cell tumors</td>
</tr>
<tr>
<td>Tumors of the choroid plexus</td>
<td>Choroid plexus papilloma and choroid plexus carcinoma</td>
</tr>
<tr>
<td>Neuronal and mixed neuronal-glial tumors</td>
<td>Gangliocytoma, Ganglioglioma</td>
</tr>
<tr>
<td>Pineal Parenchyma Tumors</td>
<td>Pineocytoma, Pineoblastoma, Mixed tumours</td>
</tr>
<tr>
<td>Embryonal tumors</td>
<td>Primitive neuroectodermal tumors with multipotent differentiation eg medulloblastoma</td>
</tr>
<tr>
<td>Tumours of the Sellar Region</td>
<td>Pituitary adenoma, Pituitary carcinoma, craniopharyngioma</td>
</tr>
<tr>
<td>Hematopoietic tumors</td>
<td>Primary malignant lymphomas, plasmacytoma</td>
</tr>
<tr>
<td>Germ Cell Tumors</td>
<td>Dysgerminoma</td>
</tr>
<tr>
<td>Meningeal tumours</td>
<td>Meningiomas,</td>
</tr>
<tr>
<td>Cranial and Spinal Nerves tumours</td>
<td>Schwannoma, Neurofibroma, Malignant peripheral nerve sheath tumor</td>
</tr>
<tr>
<td>Metastatic tumours</td>
<td>Metastatic carcinoma</td>
</tr>
</tbody>
</table>

5.5 Management

- Emergency cases (those with life threatening or rapidly deteriorating neurological symptoms and signs) should have a neurosurgical review.
- Otherwise refer to pre-operative multidisciplinary team (MDT) for review and surgical management planning.

5.5.1 Early & Emergency Management Care

- Acute cerebral oedema due to raised intracranial pressure
  - Commence dexamethasone 4-8mg bd, p.o/i.v (2-3 times a day) with a proton pump inhibitor for gastric protection. Mannitol may be used if immediately prior to surgery.
  - If patient already on dexamethasone double the dose initially to a maximum of 24-30mg.
- Seizures:
  - New onset seizures: start anticonvulsants, usually phenytoin (iv if rapid control is needed), carbamazepine or lamotrigine as first line treatment. Contact neurosurgical service if surgery is indicated. Contact oncology team for advice on further treatment.
- Established seizures: Start the patient on treatment; po/iv phenytoin (15mg/kg/24 hours) or sodium valproate. These two drugs can be given iv at the same dose as the patient’s usual oral dose for rapid response. For long term treatment, carbamazepine or lamotrigine may be used for focal onset seizures and sodium valproate or lamotrigine for primary generalized seizures.
- Prophylactic antiepileptic therapy before or after surgery is not needed. After tumour resection, the indication for anti-seizure therapy should be revisited.

Table 5: Commonly used antiepileptic Medicines

<table>
<thead>
<tr>
<th>MEDICINE</th>
<th>START DOSE/DAY</th>
<th>COMMON MAINTENANCE DOSE/DAY</th>
<th>DOSAGE INTERVAL</th>
<th>INTERACTIONS</th>
<th>COMMON SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine SR</td>
<td>200 mg</td>
<td>400-1200 mg</td>
<td>Bd</td>
<td>Enzyme inducer</td>
<td>Dizziness, diplopia, nausea, rash</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>200 mg</td>
<td>250-450 mg</td>
<td>Od</td>
<td>Enzyme inducer</td>
<td>Rash, gum hypertrophy, hirsutism</td>
</tr>
<tr>
<td>Valproate</td>
<td>600 mg</td>
<td>600-2000 mg</td>
<td>Bd</td>
<td>Enzyme inhibitor</td>
<td>Weight gain, tremor, hairloss, platelet dysfunction</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>25 mg (if patient on Valproate, use 25 mg on alternate day)</td>
<td>100-400 mg</td>
<td>Bd</td>
<td>Probable enzyme inducer</td>
<td>If rash discontinue, fatigue, headache, dizziness, diplopia</td>
</tr>
</tbody>
</table>

5.5.3 Emergency Surgical Intervention for Brain and CNS Tumours

- Review patient examination, history taking, neurological examination and imaging using approved protocols and guidelines.
- Manage cerebral oedema. For primary brain tumour, contact neurosurgical team on call.

5.5.4 Surgical Resection

- Rationale for radical resection
  - Improve the chances of removing the whole tumour
  - Decrease intracranial hypertension.
  - Improves outcomes in conjunction with adjuvant radiochemotherapy.
• Low grade glioma (LGG, WHO Grade 1 and 2)
  - It is important to identify those patients who will benefit from “watchful waiting” and those who will need early surgical intervention using the European Organization for Research and Treatment of Cancer Guidelines (EORTC) on factors associated with poor prognosis for survival.
  - Patients with LGG at increased risk of deterioration who may benefit from early intervention include age 40 years and above, tumour diameter 6 cm and above, tumour crossing the midline, astrocytoma histology, and presence of neurological deficit.
• High Grade Glioma (HGG, WHO Grade 3, 4)
  - These tumours including glioblastoma, anaplastic astrocytoma, anaplastic ligodendroglioma and anaplastic ependymomas are usually associated with a poor prognosis.
  - Other risk factors influencing prognosis include age, performance status, comorbidity factors, and presence or absence of seizures.
  - Defined management should include any of the following
    -- Urgent surgical intervention (emergency decompression or shunt insertion for hydrocephalus)
    -- Elective surgery followed by management plan based on MDT review.
    A Patient considered not fit for any surgical intervention should undergo radiotherapy.
    --Radical Radiotherapy without histological diagnosis may be considered where neuroscience MDT feels surgery would put the patient at unacceptable risk (e.g. brain stem glioma).

5.5.5 Radiotherapy
• The aim of radical treatment in high grade gliomas is to deliver a high dose of radiation with a margin such that the disease free interval and survival are extended compared to surgery alone.
• LGG may be treated with radiotherapy or observation depending on the individual circumstances.

5.5.6 Chemotherapy
• Exclusive chemotherapy with temozolamide (TMZ) should be offered for elderly patients.
• For high grade gliomas/glioblastomas, concomitant chemoradiotherapy is the standard of care
• TMZ improves average survival of patients with 12-14 months.
• TMZ (at a low dose of 75 mg/m2) is administered daily (7 days/week), 1–1.5 hours before radiotherapy from the first to the last day of radiotherapy (usually 40–49 days).
During the adjuvant phase, the blood counts should be monitored weekly, and chemotherapy should be temporarily suspended in the case of thrombocytes <75/mm^3 or a neutrophil count of <1500/mm^3.

• During the maintenance phase TMZ (150–200 mg/m2) is administered on a daily x 5 schedule every 28 days; blood counts should be checked on days 21 and 28.

5.5.7 Primary Paediatric CNS Tumours

• Paediatric brain tumours are treated as their adult counterparts with dose reduction where appropriate unless otherwise specified in the paediatric radiotherapy guidelines.

5.5.8 CNS Metastases

• Multiple brain metastases receive whole brain irradiation.
• Solitary brain metastases may be treated with stereotactic radiotherapy or surgery.

5.5.9 Relapsed or Refractory Disease

Post therapy recurrence of malignant CNS tumor is a therapeutic challenge. Best supportive care is the recommended option. Temozolomide may be considered or implantable intratumoural chemotherapy if available. Where possible, tissue diagnosis through biopsy and histopathological verification should be obtained, as this is relevant to rule out transformed disease or new disease. Immunohistochemical verification needed thus image guided core biopsy may be appropriate in this context.

5.5.10 Palliation and End of Life

(See chapter on palliation).

5.6 Medicines commonly used

Temozolomide, carmustine, procarbazine, lomustine, vincristine, irinotecan, bevacizumab, etoposide, carboplatin, hydroxyurea, imatinib.

In resource limited settings, a combination of CCNU and Vincristine is the recommended first line. Where resources are available, Temozolomide is the drug of choice.

5.7 Prognosis

Prognosis varies widely; overall survival for high grade gliomas is dismal.
REFERENCES


GASTROINTESTINAL CANCERS

These are cancers of the alimentary canal and include those of the oesophagus, stomach, hepatobiliary system, colon and rectum.

6. Oesophageal Cancer

Ogendo SW, Othieno-Abinya NA, Nyongesa CN, Musibi AM, Waweru W.

6.1. Introduction

Oesophageal cancer follows malignant transformation of oesophageal tissue. Transformation may affect the epithelium giving rise to the two main forms, squamous cell carcinoma and adenocarcinoma.

6.2 Epidemiology

It is a common malignancy worldwide and main areas of high incidence span China, across to Caspian Sea and down the eastern coast of Africa to South Africa. Eighty to eighty five percent of cases are found in the developing world. Worldwide male to female ratio is 15:1. The incidence according to the Nairobi Cancer Registry is 9.1/100,000.

Risk factors

Heredity factors, achalasia of the oesophagus, tobacco smoking, heavy alcohol consumption, gastroesophageal reflux disease (GERD) and associated obesity, Barrett’s oesophagus, as well as other sources of inflammation such as hot beverages, Plummer–Vinson syndrome e.t.c. Human papillomavirus (HPV) is also emerging as a major risk factor for oesophageal cancer. Others are corrosive injury to the esophagus by swallowing strong alkalines (lye) or acids. Particular dietary substances, such as nitrosamines that may contaminate stored foods are also associated with a high risk. Radiotherapy to the chest also increases the risk of oesophageal carcinoma.

6.3 Diagnosis

The main symptom is progressive dysphagia. Others are heart burn, and odynophagia. In advanced cases with trache-oesophageal fistula – coughing and choking on drinking fluids may be a feature.

Table 6: Grading of Dysphagia

<table>
<thead>
<tr>
<th>GRADE</th>
<th>FEATURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal swallowing</td>
</tr>
<tr>
<td>1</td>
<td>Difficulty with solids</td>
</tr>
<tr>
<td>2</td>
<td>Difficulty with semi solids</td>
</tr>
<tr>
<td>3</td>
<td>Difficulty with liquids</td>
</tr>
<tr>
<td>4</td>
<td>Total dysphagia</td>
</tr>
</tbody>
</table>
• Signs include wasting, dehydration, and anaemia.
• Radiological evaluation should include barium swallow, chest radiograph, chest CT scan.
• CT scan is also valuable for tumour staging. It detects evidence of distant tumour spread.
• Endoscopy is also used in diagnosis and staging. Endoscopic biopsy is used in diagnosis and endoscopic ultrasound for determination of loco-regional spread.
• Histology is the ultimate diagnostic procedure. Tissue is obtained at endoscopy, and iodine staining is useful in picking very early stages (T0 and Tis) or severe dysplasia.

6.4 Staging and Risk Assessment
Staging is essential and has a bearing on the management options and prognosis. Oesophageal carcinoma may be staged using the TNM classification or equivalent anatomic staging systems. TNM classification is illustrated in tables below;

Table 7: TNM staging for oesophageal cancer—Primary tumour (T)

<table>
<thead>
<tr>
<th>T</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>The primary tumour can’t be assessed.</td>
</tr>
<tr>
<td>T0</td>
<td>There is no evidence of a primary tumour.</td>
</tr>
<tr>
<td>Tis</td>
<td>Limited to epithelium. High-grade dysplasia.</td>
</tr>
<tr>
<td>T1</td>
<td>Invaded the lamina propria, muscularis mucosa, or submucosa.</td>
</tr>
<tr>
<td>T1a</td>
<td>Invaded the lamina propria or muscularis mucosa</td>
</tr>
<tr>
<td>T1b</td>
<td>Invaded into the submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>Invaded thick muscle layer (muscularis propria).</td>
</tr>
<tr>
<td>T3</td>
<td>Invaded the adventititia.</td>
</tr>
<tr>
<td>T4</td>
<td>Invaded nearby structures.</td>
</tr>
<tr>
<td>T4a</td>
<td>Invaded pleura, pericardium, or diaphragm, but resectable surgically.</td>
</tr>
<tr>
<td>T4b</td>
<td>Invaded trachea, aorta, or other crucial structure and surgically unresectable.</td>
</tr>
</tbody>
</table>

Nodes (N)

<table>
<thead>
<tr>
<th>N</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Nearby lymph nodes can’t be assessed.</td>
</tr>
<tr>
<td>N0</td>
<td>The cancer has not spread to lymph nodes immediately surrounding oesophagus.</td>
</tr>
<tr>
<td>N1</td>
<td>Cancer has spread to 1 or 2 nearby lymph nodes.</td>
</tr>
<tr>
<td>N2</td>
<td>Cancer has spread to 3 to 6 nearby lymph nodes</td>
</tr>
<tr>
<td>N3</td>
<td>Cancer has spread to 7 or more nearby lymph nodes.</td>
</tr>
<tr>
<td>N0</td>
<td>Not metastasised to distant nodes, organs or tissues</td>
</tr>
<tr>
<td>N1</td>
<td>Has metastasised to distant nodes, organs or tissues</td>
</tr>
</tbody>
</table>
It is important to also look at the histological grading of tumours when evaluating the stage of oesophageal cancer. Poorly differentiated tumours tend to grow as well as spread faster.

**Table 8: Histological grading (G) of Oesophageal Cancer**

|GX| Not possible to assess |
|G1| Well differentiated |
|G2| Moderately differentiated |
|G3| Poorly differentiated |
|G4| Undifferentiated |

Relationship of tumour classification and the TNM system for both squamous cell carcinoma and adenocarcinoma area is illustrated;

**Table 9: Comparison of TNM and grading systems (Squamous cell carcinoma) of Oesophageal Cancer**

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM (G)</th>
<th>LEVEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0:</td>
<td>Tis, N0, M0, GX or G1;</td>
<td>any location</td>
</tr>
<tr>
<td>Stage IA:</td>
<td>T1, N0, M0, GX or G1;</td>
<td>any location</td>
</tr>
<tr>
<td>Stage IB:</td>
<td>T1, N0, M0, G2 or G3;</td>
<td>any location</td>
</tr>
<tr>
<td></td>
<td>T2 or T3, N0, M0, GX or G1;</td>
<td>lower oesophagus</td>
</tr>
<tr>
<td>Stage IIA:</td>
<td>T2 or T3, N0, M0, GX or G1;</td>
<td>Upper or middle</td>
</tr>
<tr>
<td></td>
<td>T2 or T3, N0, M0, G2 or G3;</td>
<td>lower oesophagus</td>
</tr>
<tr>
<td>Stage IIB:</td>
<td>T2 or T3, N0, M0, G2 or G3;</td>
<td>upper or middle</td>
</tr>
<tr>
<td></td>
<td>T1 or T2, N1, M0, any G;</td>
<td>any location</td>
</tr>
<tr>
<td>Stage IIIA:</td>
<td>T1 or T2, N2, M0, any G;</td>
<td>any location</td>
</tr>
<tr>
<td></td>
<td>T3, N1, M0, any G;</td>
<td>any location</td>
</tr>
<tr>
<td></td>
<td>T4a, N0, M0, any G;</td>
<td>any location</td>
</tr>
<tr>
<td>Stage IIIB:</td>
<td>T3, N2, M0, any G;</td>
<td>any location</td>
</tr>
<tr>
<td>Stage IIIC:</td>
<td>T4a, N1 or N2, M0, any G;</td>
<td>any location</td>
</tr>
<tr>
<td></td>
<td>T4b, any N, M0, any G;</td>
<td>any location</td>
</tr>
<tr>
<td></td>
<td>Any T, N3, M0, any G;</td>
<td>any location</td>
</tr>
<tr>
<td>Stage IV:</td>
<td>Any T, any N, M1, any G;</td>
<td>any location</td>
</tr>
</tbody>
</table>
Table 10: Comparison of TNM and grading system (adenocarcinoma) of Oesophageal Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM (G)</th>
<th>LEVEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0:</td>
<td>Tis, N0, M0, GX or G1; any location</td>
<td></td>
</tr>
<tr>
<td>Stage IA:</td>
<td>T1, N0, M0, GX or G1; any location</td>
<td></td>
</tr>
<tr>
<td>Stage IB:</td>
<td>T1, N0, M0, G2 or G3; any location</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2 or T3, N0, M0, GX or G1; lower oesophagus</td>
<td></td>
</tr>
<tr>
<td>Stage IIA:</td>
<td>T2 or T3, N0, M0, GX or G1; Upper or middle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2 or T3, N0, M0, G2 or G3; lower oesophagus</td>
<td></td>
</tr>
<tr>
<td>Stage IIB:</td>
<td>T2 or T3, N0, M0, G2 or G3; upper or middle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T1 or T2, N1, M0, any G; any location</td>
<td></td>
</tr>
<tr>
<td>Stage IIIA:</td>
<td>T1 or T2, N2, M0, any G; any location</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3, N1, M0, any G; any location</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T4a, N0, M0, any G; any location</td>
<td></td>
</tr>
<tr>
<td>Stage IIIB:</td>
<td>T3, N2, M0, any G; any location</td>
<td></td>
</tr>
<tr>
<td>Stage IIIC:</td>
<td>T4a, N1 or N2, M0, any G; any location</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T4b, any N, M0, any G; any location</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any T, N3, M0, any G; any location</td>
<td></td>
</tr>
<tr>
<td>Stage IV:</td>
<td>Any T, any N, M1, any G; any location</td>
<td></td>
</tr>
</tbody>
</table>

6.5 Management

Multidisciplinary approach to patient management is essential. All patients should be staged prior to multidisciplinary consultations. Supportive treatment consists of:

- Fluid management; ensuring daily fluid and electrolyte needs are met.
- Nutritional management; ensuring daily nutritional needs met,
- Counselling and other supportive services.
- For advanced disease palliative care services should be enlisted.

Definitive treatment options vary between surgery, radiotherapy and chemotherapy. Choice of treatment modality is dependent on tumour stage and general fitness of the patient. The role of curative resection in oesophageal cancer is only considered in cases of early disease. Curative surgery is applied to stages 0, I, and II oesophageal cancers. For Stage III, surgery is applied as palliative care.
6.5.1 Surgical Options

Resection: Sub-endothelial for high grade dysplasia
Oesophagectomy: Preoperative radiotherapy is recommended for stages II and III to shrink tumour and render it amenable to resection. Preoperative chemotherapy may also confer some benefit.

For patients not fit for surgery, chemoradiotherapy (Cisplatin, 5FU-based) is recommended and Chemoradiotherapy for upper third tumours.

Late squamous cell carcinoma:
Surgical resection has little influence on survival. If considered, it must have clear indications outweighing the lack of improved survival.

Stenting/intubation: These are preferably carried out endoscopically when and where possible. In most cases, stents are inserted for restoration of swallowing and also to relieve symptoms in presence of tracheo-oesophageal fistulae.

Percutaneous endoscopic gastrostomy or other form of gastrostomy may be performed.

6.5.2 Follow-up

All patients require regular follow up to assess recurrence or development of signs of distant disease. Regular clinic visits should be scheduled (every 3-6 months during which time radiological (chest radiographs, CT scans repeat barium swallow), weight, and other investigations should be performed. Ideally, visits should be as close as possible to the patient’s home.

6.6 Commonly Used Medicines

5-fluorouracil, cisplatin, vinblastine, epirubicin, interferon alpha-2a, paclitaxel, docetaxel, irinotecan, vinorelbine.

The standard regimen is a combination of 5FU and cisplatin with or without radiotherapy. Where resources are available, a platinum compound and a taxane can be used.

6.7 Prognosis

The occasional patient who presents with early disease can be cured by surgery. But in our setting, where most patients present with late disease, the prognosis is poor.
REFERENCES


7. Gastric Cancer

Njuguna E, Musibi A, Saidi H, Weru I, Amayo A

7.1 Introduction
Cancer of the stomach is one of the major causes of death worldwide.

7.2 Epidemiology
This is the third most common GI malignancy in Kenya after oesophageal and colorectal cancer. The disease seems to be increasing in incidence especially amongst males, probably because of better diagnosis. The anatomical sites involved are body, antrum and proximal parts in that order of frequency. The mortality from gastric cancer is high; it is the second commonest cause of cancer mortality worldwide. Known etiologic and risk factors documented include alcohol consumption, atrophic gastritis and gastric ulcer disease, male gender, H pylori, tobacco, and family history.

7.3 Diagnosis
The disease is diagnosed based on history, physical examination, endoscopic or surgical biopsy and histopathology. Common presenting symptoms include epigastric pain, dysphagia and feature of gastric outlet obstruction.

7.3.1 Histopathological Diagnosis
Histopathology provides definitive diagnosis of gastric carcinoma, and it is strongly recommended that reporting be done according to WHO criteria including classification (e.g. diffuse signet-ring cell type versus intestinal type), presence or absence of dysplasia, lymphovascular invasion, tumour dimension and pathological stage (TNM). Immunohistochemistry may be of value to exclude metastatic disease. Her2 testing is a new field that may be considered where possible, particularly for advanced intestinal type carcinoma.

7.4 Staging and Risk Assessments
This is based on tumour invasion nodal involvement and distant metastases. Staging investigations should include CXR/CT chest, CT scan abdomen and pelvis. Laparascopy should be performed in those considered resectable to exclude all peritoneal and other metastases. PET scan where available, is offered to all with potentially curable disease. TNM classification is most widely adopted.
Table 11: TNM Clinical Classification for Gastric Cancer

<table>
<thead>
<tr>
<th>Primary Tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX primary tumor cannot be assessed</td>
</tr>
<tr>
<td>TO No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis carcinoma in situ: intraepithelial tumor without invasion of the lamina propria, high grade dysplasia</td>
</tr>
<tr>
<td>T1 Tumor invades lamina propria, muscularis mucosae or submucosa</td>
</tr>
<tr>
<td>T1a tumor invades lamina propria or muscularis mucosae</td>
</tr>
<tr>
<td>T1b tumor invades submucosa</td>
</tr>
<tr>
<td>T2 tumor invades muscularis propria</td>
</tr>
<tr>
<td>T3 tumor invades subserosa</td>
</tr>
<tr>
<td>T4 Tumor perforates serosa or invades adjacent structures</td>
</tr>
<tr>
<td>T4a tumor perforates serosa</td>
</tr>
<tr>
<td>T4b tumor invades adjacent structures</td>
</tr>
</tbody>
</table>

Notes:
1. The adjacent structures of the stomach are the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestines, and retroperitoneum.
2. Intramural extensions to the duodenum or oesophagus is classified by the depth of the greatest invasion in any on these sites, including stomach.
3. Tumor that extends into gastrocolic or gastrohepatic ligaments or into greater or lesser omentum, without perforation of visceral peritoneum, is T3

Regional lymph nodes (N-)

<table>
<thead>
<tr>
<th>Regional lymph nodes (N-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0 no regional lymph nodes metastasis</td>
</tr>
<tr>
<td>N1 metastasis in 1 to 2 regional lymph nodes</td>
</tr>
<tr>
<td>N2 metastasis in 3 to 6 regional lymph nodes</td>
</tr>
<tr>
<td>N3 metastasis in 7 or more regional lymph nodes</td>
</tr>
<tr>
<td>N3a metastasis in 7-15 regional lymph nodes</td>
</tr>
<tr>
<td>N3b metastasis in 16 or more regional lymph nodes</td>
</tr>
</tbody>
</table>

Note: The regional lymph nodes of the stomach are the perigastric nodes along the lesser and the greater curvatures, the nodes along the left gastric, common hepatic, and celiac arteries and the hepatoduodenal nodes. Involvement of other intra-abdominal lymph nodes such as retropancreatic, mesenteric and Para-aortic is classified as distant metastasis.

| M0 no distant metastasis |
| M1 distant metastasis |

Note: distant metastasis includes peritoneal seeding, positive peritoneal cytology and omental tumor not part of continuous extension.
The pT and pN categories correspond to the T and N categories pN0 histological examination of regional lymphadenectomy specimen will ordinarily include 14 or more lymph nodes.

If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

**Table 12: Stage Grouping of Gastric Cancer**

<table>
<thead>
<tr>
<th>Stage 0</th>
<th>Tis</th>
<th>N0</th>
<th>MO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td>T1</td>
<td>NO</td>
<td>MO</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2</td>
<td>N0</td>
<td>MO</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N1</td>
<td>MO</td>
</tr>
<tr>
<td>Stage II A</td>
<td>T3</td>
<td>N0</td>
<td>MO</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>MO</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N2</td>
<td>MO</td>
</tr>
<tr>
<td>Stage II B</td>
<td>T4a</td>
<td>N0</td>
<td>MO</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>MO</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N2</td>
<td>MO</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N3</td>
<td>MO</td>
</tr>
<tr>
<td>Stage III A</td>
<td>T4a</td>
<td>N1</td>
<td>MO</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N2</td>
<td>MO</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N3</td>
<td>MO</td>
</tr>
<tr>
<td>Stage III B</td>
<td>T4b</td>
<td>N0, N1</td>
<td>MO</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N2</td>
<td>MO</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N3</td>
<td>MO</td>
</tr>
<tr>
<td>Stage III C</td>
<td>T4a</td>
<td>N3</td>
<td>MO</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
<td>N2, N3</td>
<td>MO</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

**7.5 Management**

**7.5.1 Treatment of localized disease**

Treatment modalities include surgery, neo-adjuvant chemotherapy/ radiotherapy, adjuvant chemotherapy, radiotherapy. Surgery is applicable to all T groups and includes resection and lymphadenectomy. Features of non-resectable (curative) tumors at staging include encased vessels, extensive lymph nodes and advanced local involvement. Lymphadenectomy should aim to submit 14 -25 nodes.
7.5.2 Neoadjuvant chemotherapy and radiotherapy
Pretreatment with chemotherapy +/- radiotherapy may be applied in bulky T2 tumours to improve resectability.

7.5.3 Adjuvant chemo/radiotherapy
Chemotherapy +/- radiotherapy is applicable for node positive, large T or positive surgical margins.

7.5.4 Treatment of metastatic disease
Chemotherapy is the treatment of choice for palliation of metastatic disease. Active agents include platinum compounds, fluoropyrimidines, anthracyclines, taxanes and topoisomerase inhibitors. Targeted therapy with trastuzumab is useful in HER2 positive gastric cancer. 
Chemotherapy agents are administered in duplet or triple combination. Common combinations include: 1) cisplatin + epirubicin 2) oxaliplatin +5FU 3) Irinotecan +5FU 4) docetaxel+cisplatin 5) capecitabine +oxaliplatin 6) epirubicin+cisplatin+5FU.

7.5.4 Emergencies in gastric cancer
Perforation and gastric outlet obstruction are managed surgically. Bleeding gastric tumor is managed by either radiotherapy or surgery.

7.5.5 Palliative care
See Chapter 40 on Palliative Care.
- Obstruction (managed by stenting or by-pass surgery)
- Nutrition – may require supplementing pancreatic enzymes.

7.5.6 Response evaluation
- Clinical evaluation
- Serial imaging

7.5.7 Follow up
Follow up is driven by the symptoms. Radiological investigations are recommended for patients being considered for palliative chemo- or radiotherapy.

7.6 Commonly Used Medicines
5-fluorouracil, folinic acid, capecitabine, epirubicin, doxorubicin, cisplatin, oxaliplatin, paclitaxel, docetaxel, trastuzumab, irinotecan, bevacizumab, cetuximab,
In resource limited setting, 5-fluorouracil without or with folinic acid can be used. The most commonly used combinations are doxorubicin or epirubicin, cisplatin and 5FU where resources are available. Trastuzumab may be included in Her 2 overexpressing tumours.
7.7 Prognosis
By the time patients with gastric cancer present with symptoms, the disease is advanced and incurable. Treatment is basically palliative.

REFERENCES
8. Biliary Tract Cancer

Busakhala N, Othieno-Abinya NA

8.1 Introduction
Cholangiocarcinoma is one of the commonest liver cancers worldwide.

8.2 Epidemiology
Three to five cases are reported in the Eldoret Cancer Registry annually with a slight female proponderance. Similar numbers are reported for carcinoma of the gall bladder.

8.3 Diagnosis
8.3.1 Presentation
The commonest presenting symptoms are abdominal pain, pruritis and yellowness of eyes. Physical examination reveals jaundice and an abdominal mass.

Investigations include imaging by ultrasound, CT scan and magnetic resonance imaging (MRI). Others are per cutaneous cholangiography, endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography (MRCP) can be used for diagnosis.

Biopsy, fine needle aspiration or biliary brush cytology. A final pathological diagnosis has to be obtained before any chemotherapy, radiotherapy or other non-surgical oncological therapy, but is not critical for planning surgery in patients with characteristic findings of resectable biliary cancer.

8.4 Staging & Risk Assessment
Staging consists of complete history and physical examination, blood counts, liver function tests, chest X-ray, imaging of the abdomen by sonography and CT scan or MRI, endoscopic retrograde or percutaneous transhepatic cholangiography and possibly endoscopic ultrasonography, cholangioscopy and laparoscopy.

Upper and lower GI endoscopy has to be performed in patients with an isolated intrahepatic mass. The staging is to be given according to the TNM 2010 system separately for gallbladder cancer, intrahepatic, perihilar and distal cholangiocarcinoma). Hilar cholangiocarcinoma (Klatskin’s tumor) is clinically staged depending on the involvement of the hepatic ducts according to the Bismuth–Corlette classification.
### Table 13: TNM Staging of Gallbladder Cancer

#### Primary Tumor (T)

<table>
<thead>
<tr>
<th>T</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades lamina propria or muscular layer</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor invades lamina propria</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor invades muscular layer</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum or extrahepatic bile ducts</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures</td>
</tr>
</tbody>
</table>

#### Regional Lymph nodes

<table>
<thead>
<tr>
<th>N</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastases to nodes along the cystic duct, common bile duct, hepatic artery and/or portal vein</td>
</tr>
<tr>
<td>N2</td>
<td>Metastases to periaortic, pericaval, superior mesenteric artery and/or celiac artery lymph nodes</td>
</tr>
</tbody>
</table>

#### Distant metastasis (M)

<table>
<thead>
<tr>
<th>M</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

### Table 14: Stage Grouping for Cholangiocarcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis, N0, M0</td>
</tr>
<tr>
<td>1</td>
<td>T1, N0, M0</td>
</tr>
<tr>
<td>II</td>
<td>T2, N0, M0</td>
</tr>
<tr>
<td>IIIa</td>
<td>T3, N0, M0</td>
</tr>
<tr>
<td>IIIb</td>
<td>T1-3, N1, M0</td>
</tr>
<tr>
<td>IVa</td>
<td>T4, N0-1, M0</td>
</tr>
<tr>
<td>IVb</td>
<td>Any T, N2, M0</td>
</tr>
<tr>
<td></td>
<td>Any T, Any N, M1</td>
</tr>
</tbody>
</table>
8.5 Management

Treatment after incidental finding of gallbladder cancer on pathological review;

8.5.1 Resectable tumors

Complete surgical resection is the only potentially curative treatment available. Resection of gallbladder cancer consists of extended cholecystectomy including en bloc hepatic resection and lymphadenectomy (porta hepatis, gastrohepatic ligament, retroduodenal) with or without bile duct excision. Major hepatectomy including caudate lobectomy such as extended right lobe resection with portal vein resection increases resectability and radicality for stage 3 and 4 hilar cholangiocarcinomas and has been associated with higher 5-year survival rates. Preoperative transarterial or portal vein embolization increases the remnant liver volume in patients with estimated postresection volumes of <25% and appears to reduce postoperative liver dysfunction.

8.5.2 Adjuvant chemotherapy

Gallbladder cancers; 5-fluorouracil, gemcitabine and oxliplatin-based chemotherapy can be used after non-curative resection.

Cholangiocarcinoma; Radiotherapy may be considered but the role of chemotherapy is controversial.

Neoadjuvant chemo/radiotherapy confers survival benefit in both gallbladder and biliary duct cancer, and postoperative chemoiirradiation may be considered as an option.

8.5.3 Unresectable tumors

Palliation of jaundice can be accomplished by endoscopic or percutaneous stenting of the biliary tree or by operative biliary–enteric bypass. Urgent biliary drainage and broad-spectrum antibiotics are crucial in patients with cholangitis due to obstructive jaundice. Gemcitabine with or without cisplatin/oxaliplatin have a clear survival advantage without added clinically significant toxicity.

The biologicals erlotinib and bevacizumab are also useful.

Neoadjuvant therapy is not a routine option in biliary cancers. However, if restaging in patients with locally advanced disease shows potentially resectable tumors, resection should be considered.

8.5.4 Response evaluation

In a phase II trial of palliative chemotherapy in patients with advanced biliary cancer, decreases in SUV (max) on [18F] fluorodeoxyglucose-positron emission tomography (FDG-PET) scans after 8 weeks of treatment were associated with disease control and increases progression-free and overall survival.
8.5.5 Follow up
Follow-up visits after complete resection should be restricted to history and physical examination considering symptoms, nutrition and psychosocial problems.

8.6 Medicines commonly used:
5-fluorouracil, oxaliplatin, docetaxel, gemcitabine, capecitabine, cisplatin, erlotinib.
The combination of 5FU and cisplatin is the preferred first line. Where resources are available, gemcitabine and oxaliplatin may be used.

8.7 Prognosis
Even in patients undergoing aggressive surgery, 5-year survival rates are 5–10% for gallbladder cancer and 10–40% for cholangiocarcinoma.

REFERENCES
9. Hepatocellular Carcinoma


9.1 Introduction
This is a common malignancy in the developing world which carries high case mortality because of late diagnosis and the commonly associated liver cirrhosis.

9.2 Epidemiology
There is a steady increase in the incidence of hepatocellular carcinoma (HCC). Liver cancer represents the sixth most common cancer in the world (749,000 new cases) and the third cause of cancer-related deaths (692,000 cases). It ranks sixth in males and fifth in females according to the Nairobi Cancer registry.

The current 5-year overall survival rate for patients with very early-stage liver cancer who undergo surgical resection or liver transplantation is 50%-70%. Thus, the 5-year overall survival rate for patients with liver cancers of any stage is about 15%. Two patients with the same stage of liver cancer, but differing health in the rest of the organ, would likely need different treatments thus management must be personalized to both conditions.

Risk factors
Ninety percent (90%) of patients diagnosed with HCC have underlying cirrhosis from chronic alcohol consumption, exposure to aflatoxins and chronic viral hepatitis (hepatitis B and C). Liver disease caused by environmental exposure or autoimmune or hereditary conditions is less common.

9.3 Diagnosis
Symptoms and signs of hepatocellular cancer include abdominal pain and swelling, loss of appetite, weight loss and eventually jaundice, ascites, encephalopathy, splenomegaly and hepatomegaly.

Ultrasonography is often the first line of investigation, CT and MRI are the most sensitive and specific imaging techniques for evaluating the liver. Tissue specimen (biopsy) is used to confirm diagnosis.

Elevated alfa-fetoprotein level above 40ug/l with positive ultrasonographic findings is also diagnostic. A negative biopsy does not rule out malignancy.

There is no indication for biopsy of a focal lesion in a cirrhotic liver:
(i) When the patient is not a candidate for any form of therapy because of serious comorbidity;
(ii) In case of decompensated cirrhosis and the patient is on the waiting list for liver transplantation.
(iii) When the patient is a candidate for resection that can be carried out with an acceptable morbidity and mortality risk.

### 9.4 Staging & Risk Assessment

Staging of HCC includes assessment of tumor extent, liver function, portal pressure and clinical performance status. The staging systems include pTNM system which is based on the pathology report. The Barcelona Clinic Liver Cancer (BCLC) staging system classifies patients into early HCC who may benefit from curative therapies (stage 0 and A), those at intermediate (stage B) or advanced stage (stage C) who may benefit from palliative treatments and those with a very poor life expectancy (stage D). Median survival without therapy is >36 months for stage 0 and A, 16 months for stage B, 4–8 months for stage C and <4 months for stage D.

**Table 15: TNM staging of Hepatocellular Carcinoma**

**Primary Tumour T**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>The primary tumor cannot be evaluated</td>
</tr>
<tr>
<td>T0</td>
<td>There is no evidence of a primary tumor.</td>
</tr>
<tr>
<td>T1</td>
<td>The tumor is 2 centimeters (cm) or smaller. It does not involve nearby blood vessels.</td>
</tr>
</tbody>
</table>
| T2   | Either of these:  
|      | • Any tumor that involves nearby blood vessels.  
|      | • More than one tumor, but none larger than 5 cm |
| T3a  | There is more than one tumor, and at least one is larger than 5 cm. |
| T3b  | The tumor (of any size) involves the major veins around the liver. |
| 4    | Either of these:  
|      | • The tumor has spread to the organs near the liver (except the gallbladder).  
|      | • The tumor has broken through the visceral peritoneum (layer of tissue that lines the abdomen). |

**Node (N)**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>The regional lymph nodes cannot be evaluated.</td>
</tr>
<tr>
<td>N0</td>
<td>Cancer has not spread to the regional lymph nodes.</td>
</tr>
<tr>
<td>N1</td>
<td>The cancer has spread to the regional lymph nodes.</td>
</tr>
</tbody>
</table>

**Distant metastasis (M)**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>The tumor cannot be evaluated.</td>
</tr>
<tr>
<td>M0</td>
<td>The cancer has not spread to other parts of the body.</td>
</tr>
</tbody>
</table>
Table 16: Stage Grouping for Hepatocellular Carcinoma.

<table>
<thead>
<tr>
<th>Stage</th>
<th>T1, N0, M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage II</td>
<td>T2, N0, M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T3a, N0, M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T3b, N0, M0</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>T4, N0, M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>any T, N1, M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>any T, any N, M1</td>
</tr>
</tbody>
</table>

Table 17: Risk classification by Child-Pugh

<table>
<thead>
<tr>
<th>MEASURE</th>
<th>1 POINT</th>
<th>2 POINTS</th>
<th>3 POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin, µmol/l (mg/dl)</td>
<td>&lt;34 (&lt;2)</td>
<td>34-50 (2-3)</td>
<td>&gt;50 (&gt;3)</td>
</tr>
<tr>
<td>Serum albumin, g/l</td>
<td>&gt;35</td>
<td>28-35</td>
<td>&lt;28</td>
</tr>
<tr>
<td>PT INR</td>
<td>&lt;1.7</td>
<td>1.71-2.30</td>
<td>&gt; 2.30</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Mild</td>
<td>Moderate to Severe</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>None</td>
<td>Grade I-II (or suppressed with medication)</td>
<td>Grade III-IV (or refractory)</td>
</tr>
</tbody>
</table>

Table 18: Cirrhotic classification by Okuda

<table>
<thead>
<tr>
<th>DEFINITION OF THE OKUDA STAGING SYSTEM FOR HEPATOCELLULAR CARCINOMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Points</td>
</tr>
<tr>
<td>Tumour size</td>
</tr>
<tr>
<td>Ascites</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
</tr>
</tbody>
</table>

9.5 Management

9.5.1 Local disease: radical therapies
Radical treatments include surgical resection, liver transplantation and local destruction methods radiofrequency ablation (RFA) or percutaneous ethanol injection (PEI) and external-beam radiation therapy (EBRT).

1. Resection is the recommended treatment in patients without advanced fibrosis, as long as an R0 resection is achieved and remnant volume adequate for liver function. In cirrhosis, resection is advised for early BCLC stages (0 and A) when the lesion is single, performance status good with no portal hypertension.
2. Local ablation techniques (RFA and PEI) are alternatives for surgery especially for small nodules (<2cm). The number and diameter of lesions treated by RFA should not exceed five and 5 cm, respectively. Neo-adjuvant or adjuvant therapies are not recommended.

3. Liver transplantation should be considered in patients with a solitary lesion of <5 cm or three nodules <3 cm that are not suitable for resection.

4. External-beam radiation therapy (three-dimensional conformal, stereotactic, or proton therapy) is indicated for patients with poor performance status and severe comorbidities.

9.5.2 Locally advanced/metastatic disease: palliative treatments

Local therapy

Transcatheter devices, systemic therapy and external beam radiotherapy are palliative techniques. Agents administered intra-arterially include chemotherapy (e.g. doxorubicin, cisplatin), embolizing material (e.g. coils, gelatin sponge particles) or radioactive particles. Transarterial chemoembolization (TACE) is recommended for multi-nodular BCLC stage B with good liver function.

9.5.3 Systemic therapy

In the resource limited settings, various chemotherapeutic agents can be used in combination. Sorafenib is the standard systemic therapy for patients with advanced HCC and well-preserved liver function (BCLC stage C) and those with intermediate-stage HCC who progress following TACE. It is expensive and only given where resources are available.

9.5.4 Follow-up

Response evaluation and follow-up of patients after radical treatments should consist of the clinical evaluation of liver decompensation and the early detection of recurrence by dynamic CT or MRI studies every 3 months for the first 2 years and surveillance every 6 months later on. Patients with more advanced stages of HCC who are treated with TACE or systemic agents (e.g. sorafenib) are evaluated clinically for signs of liver decompensation and by dynamic CT or MRI for tumor progression every 2 months to guide therapy decisions.

9.5.5 Prevention

Immunization against the Hepatitis B virus should be done, while reduction in exposure to hepatitis B and C viruses should be emphasized through safe injection practices and screening of donated blood for the presence of the viruses. Treatment of active hepatitis should also be emphasized. Reduction of the exposure to aflatoxin B1 should also be
instituted.

9.6 Commonly Used Medicines

Doxorubicin, 5-fluorouracil, capacitabine, interferon alpha, cisplatin, oxaliplatin, gemcitabine, sorafenib.

Most patients in resource limited settings are diagnosed late and the best treatment option is supportive care. If chemotherapy has to be applied doxorubicin as a single agent or combined with 5FU and/or cisplatin can be applied. Where resources are available, sorafenib is considered the standard of care.

9.7 Prognosis

Most patients with liver cancers present late and the outcome is generally poor. The occasional patient with solitary small tumours (less than 2-3-cm), in absence of liver cirrhosis, can be cured by surgical resection alone.

REFERENCES

10. Pancreatic cancer

Nebayosi T, Saidi H, Musibi A, Njuguna E, Busakhala N.

10.1 Introduction
Cancer of the pancreas has had a markedly increased incidence over the last decade and carries a very high mortality rate.

10.2 Epidemiology
The incidence of pancreatic cancer increases with age and the majority of cases are diagnosed above the age of 65 years. Smoking, obesity and dietary factors such as high consumption of processed meat increase the risk for pancreatic cancer. There are some genetic conditions that are associated with an increased risk of pancreatic cancer, e.g. hereditary pancreatitis, Peutz–Jeghers syndrome, familial malignant melanoma, hereditary breast and ovarian cancer syndrome and Lynch syndrome. Hereditary conditions account for 5%–10% of pancreatic cancers.

Regular endoscopic ultrasound (EUS) that allows the detection of small lesions and magnetic resonance imaging (MRI) are recommended in patients with hereditary pancreatitis, Peutz–Jeghers syndrome, familial malignant melanoma, hereditary breast and ovarian cancer syndrome and Lynch syndrome.

10.3 Diagnosis
Pancreatic head tumors present with painless jaundice. Abdominal pain, back pain or weight loss are usually signs of late-stage disease. Tail and body tumors may present with newly diagnosed diabetes.

10.3.1 Imaging
Contrast enhanced CT scan is the investigation of choice. MRI abdomen and pelvis is also an alternative for detection of pancreatic tumor and evaluation of invasion of vessels and metastasis (e.g. lymph nodes, liver, peritoneal cavity).
Abdominal ultrasound is also useful for the initial evaluation of biliary system.
EUS allows biopsy and/or fine needle aspiration cytology.
Positron emission tomography scanning (PET scan) has no role in the diagnosis of pancreatic cancer.
Endoscopic retrograde cholangiopancreatography (ERCP) only has a role in relieving bile duct obstruction.

10.3.2 Pathology Diagnosis
Histological proof of malignancy is mandatory for unresectable cases before chemotherapy is planned.
Pre-operative histological diagnosis is not required for resectable disease.
The diagnosis is established through EUS-guided FNA and cytology wash-outs or percutaneous image-guided FNA/core biopsies when unavailable. Open biopsies (laparotomy and laparascopy) should only be considered when a sample cannot be obtained with the other methods. Pathology reporting on resection specimens should be done using the WHO criteria and should include details on grading, resection margins, lymphovascular and perineural invasion and lymph node ratios. Immunohistochemistry should be considered for undifferentiated tumours.

10.4 Staging & Risk Assessment

Staging is done by the TNM System. The American Joint Committee on Cancer (AJCC) system is also popular.

Table 19: TNM Staging Classification for Pancreatic Cancer

**Primary Tumour (T)**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>The primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of a primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ (very few tumors are found at this stage)</td>
</tr>
<tr>
<td>T1</td>
<td>The cancer has not spread beyond the pancreas and is &lt;2 cm (0.75 inch) across</td>
</tr>
<tr>
<td>T2</td>
<td>The cancer has not spread beyond the pancreas but is &gt;2 cm across</td>
</tr>
<tr>
<td>T3</td>
<td>The cancer has spread from the pancreas to surrounding tissues near the pancreas but not to blood vessels</td>
</tr>
<tr>
<td>T4</td>
<td>The cancer has extended further beyond the pancreas into nearby large blood vessels</td>
</tr>
</tbody>
</table>

**Regional Lymph Nodes - N**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>Regional lymph nodes (lymph nodes near the pancreas) are not involved.</td>
</tr>
<tr>
<td>N1</td>
<td>Cancer has spread to regional lymph nodes.</td>
</tr>
</tbody>
</table>

**Distant Metasis M**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Spread to distant organs cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>The cancer has not spread to distant lymph nodes or to distant organs</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis is present</td>
</tr>
</tbody>
</table>

10.5 Management

10.5.1 Surgery

The only curative treatment of pancreatic cancer is radical surgery (duodenopancreatectomy,
distal or total pancreatectomy) for stage I and some stage II. The aim of surgery is margin negative (R0) resection. Criteria for resectability include size, infiltration of duodenum, portal or superior mesenteric vein, celiac artery, common hepatic and superior mesenteric artery.

Standard lymphadenectomy should remove nodes along hepatoduodenal ligament, common hepatic artery, and the portal vein, celiac and superior mesenteric arteries. Extended lymphadenectomy is not beneficial.

**10.5.2 Adjuvant treatment**

Postoperatively, with R0/R1 margins 6 months of gemcitabine (GEM) or 5-fluorouracil (5-FU) chemotherapy are recommended. Adjuvant chemoradiation has no advantage over chemotherapy alone.

**10.5.3 Neoadjuvant chemotherapy or chemoradiotherapy**

Neoadjuvant strategies may be employed in patients with potentially resectable tumors (e.g. abutting rather than encasing blood vessels, borderline size).

**10.5.4 Treatment of unresectable local disease and stage IV disease**

Gemcitabine (GEM) is recommended in patients with non-metastatic unresectable tumors. Metastatic disease may be treated using Gemcitabine, 5-FU with folinic acid/irinotecan/oxaliplatin (FOLFIRINOX) or combination of Gemcitabine and erlotinib.

**10.5.5 Palliative therapy**

Endoscopic retrograde cholangiopancreatography (ERCP) is used to relieve bile duct obstruction by stenting (with metal or plastic stents). Transhepatic percutaneous biliary drainage or surgical bypasses (in same order of preference) are other options for biliary obstruction management.

**10.5.6 Response evaluation in the palliative setting**

Patients should be followed up at each cycle of chemotherapy for toxicity and evaluated for response to chemotherapy every 8 weeks. Clinical benefit and ultrasound may be useful tools to assess the course of disease in the metastatic setting. When performing abdominal ultrasound patients should be monitored for the presence of ascites that can indicate peritoneal disease.

**10.5.7 Follow up after surgical treatment**

Follow-up investigations include tumour marker CA 19.9 every 3 months for 2 years and abdominal CT scan every 6 months.

**10.6 Commonly Used Medicines**

Gemcitabine, 5-fluorouracil/folinic acid, capecitabine, cisplatin, oxaliplatin, irinotecan, erlotinib.

In resource limited settings, 5-fluorouracil, without or with folinic acid, can be used. Even
where resources are available, gemcitabine monotherapy may be used.

10.7 Prognosis

In our set-up, most patients are diagnosed late and will not survive beyond 5 years.

REFERENCES


11. Colon Cancer

Saidi H, Njuguna E, Musibi A, Weru I, Amayo A, Othieno-Abinya NA; Odongo I

11.1 Introduction
Colon cancer is one of the commonest cancers world wide and also one of the most curable, particularly, if caught early.

11.2 Epidemiology
Cancers of the colon are common in Kenya, constituting 40-50% of all cancers of the large bowel. The mean age of diagnosis is around 50 years. It is highly curable when localized in the bowel. Known risk factors include personal history of colon or other cancer, tobacco, inflammatory bowel diseases, family history of ovarian, endometrial, breast cancer, familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer. Fecal occult blood test (FOBT) is recommended for screening at risk population; this reduces mortality from colorectal cancer by up to 25% when used correctly. Colonoscopy is advised after a positive FOBT. The screening interval should be every 3 years. CT colonography (virtual colonoscopy) may be used to screen high risk patients with polyps.

11.3 Diagnosis
Early clinical features are not specific (discomfort, weight loss, change in bowel habits, tiredness). Symptomatic disease is diagnosed using history, physical examination, double contrast barium enema, and colonoscopy. Biopsy for histopathology is taken during endoscopy.

11.4 Staging And Risk Management
TNM classification is used in staging the disease. Radiological investigations should include Chest Xray, CT scans of chest, abdomen and pelvis. Malignant polyps should be classified according to the Haggit system.
### Table 20: TNM classification of Colon Cancer

#### Distant Metastases (M)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>no evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ: intraepithelial or invasion of lamina propria.</td>
</tr>
<tr>
<td>T1</td>
<td>tumor invades submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>tumor invades muscularis propria</td>
</tr>
<tr>
<td>T3</td>
<td>tumor invades through muscularis propria into subserosa or into nonperitonealized pericolic or perirectal tissues</td>
</tr>
<tr>
<td>T4</td>
<td>tumor directly invades other organs or structures and/or perforates visceral peritoneum</td>
</tr>
</tbody>
</table>

#### Regional Lymph Nodes (N)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>no regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>metastasis in one to three regional lymph nodes</td>
</tr>
<tr>
<td>N2</td>
<td>metastasis in four or more regional lymph nodes</td>
</tr>
</tbody>
</table>

#### Distant Metastases (M)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>no distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>distant metastasis</td>
</tr>
</tbody>
</table>

### Table 21: Stage Grouping for Colon Cancer

#### AJCC Classification

<table>
<thead>
<tr>
<th>Stages</th>
<th>AJCC Classification</th>
<th>Dukes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis N0 M0</td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>T1 N0 M0 A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2 N0 M0 B1</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>T3 N0 M0 B2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T4 N0 M0 B2</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>T1, T2 N1 or N2 M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3, T4 N1 or N2 M0</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T Any N M1 D</td>
<td></td>
</tr>
<tr>
<td>Stage V</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 22: Duke’s Staging System for Colorectal Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage A</td>
<td>Limited to mucosa</td>
</tr>
<tr>
<td>Stage B1</td>
<td>Extending into muscuaris propria but not penetrating through it; nodes not involved.</td>
</tr>
<tr>
<td>Stage B2</td>
<td>Penetrating through muscularis propria; nodes not involved.</td>
</tr>
<tr>
<td>Stage C1</td>
<td>Extending into muscularis propria but not penetrating through it. Nodes involved.</td>
</tr>
<tr>
<td>Stage C2</td>
<td>Penetrating through muscularis propria. Nodes involved.</td>
</tr>
<tr>
<td>Stage D</td>
<td>Distant metastatic spread.</td>
</tr>
</tbody>
</table>

This staging gives valuable information for the prognosis and management of the particular cancer.

Table 23: Haggitt system for polyps with invasive cancer

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 0</td>
<td>Carcinoma in situ, not invading muscularis mucosa</td>
</tr>
<tr>
<td>Level 1</td>
<td>Invasion into submucosa, limited to head of polyp</td>
</tr>
<tr>
<td>Level 2</td>
<td>Cancer invades neck of polyp</td>
</tr>
<tr>
<td>Level 3</td>
<td>Cancer invades stalk of polyp</td>
</tr>
<tr>
<td>Level 4</td>
<td>Cancer invades submucosa of bowel wall = T1</td>
</tr>
</tbody>
</table>

All sessile polyps with invasive cancer are level 4 by Haggitt’s criteria. Level 1-3 are limited to polyp wall and do not involve normal bowel wall. For proper nodal staging at least 12 nodes should be submitted.

Prognostication
Clinico-pathologic factors related to prognosis which should be considered during patient evaluation include (i) disease stage (ii) grading (iii) lymphatic or venous or perineural invasion (iv) lymphoid inflammatory response (v) involvement of resection margins (vi) bowel obstruction and perforation (vii) pre-treatment elevated levels of CEA.

11.5 Management
The mainstay of treatment of colon cancer is surgery which removes the lesion with wide margins and loco-regional nodes. Operations include open or laparoscopic segmental resections, hemicolecotomies, and anterior resections as appropriate. Adjuvant treatment is given to for stage III and high risk stage II patients [A]. The definition of high risk in stage II disease include (i) lymph nodes sampling <12 (ii) poorly differentiated tumour (iii) vascular or lymphatic or perineural invasion (iv) tumour presentation with obstruction or (v) tumour perforation and (vi) pT4 stage
## Table 24: Strategy of treatment by stage

<table>
<thead>
<tr>
<th>STAGE</th>
<th>TREATMENT</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant polyp, no risk of invasion</td>
<td>Polypectomy</td>
<td>Assess for invasiveness; this suffices for pedunculated polyp with invasion to head.</td>
</tr>
<tr>
<td>Malignant polyp, with risk of invasion</td>
<td>Resection and lymph node excision</td>
<td>High risk features: lymphatic or venous invasion, grade 3 differentiation, level 4 invasion (invades the submucosa of the bowel wall below the polyp) or involved margins of excision; sessile polyp with invasion</td>
</tr>
<tr>
<td>Stage 0 (Tis N0 M0, T1 N0 M0)</td>
<td>(i) local excision OR (ii) segmental resection</td>
<td>High risk features: lymphatic or venous invasion, grade 3 differentiation, level 4 invasion (invades the submucosa of the bowel wall below the polyp) or involved margins of excision; sessile polyp with invasion</td>
</tr>
<tr>
<td>Stage II (T3 N0 M0, T4 N0 M0) (old staging: Dukes’ B and B2)</td>
<td>Wide surgical resection</td>
<td>In high-risk patients adjuvant therapy could be considered in clinical practice.</td>
</tr>
<tr>
<td>Stage III (any T, N1 M0, any T, N2 M0) (old staging: Dukes’ C)</td>
<td>Colectomy</td>
<td>Adjuvant therapy with: Oxaliplatin and 5FU/folinic acid (LV) (FOLFOX4 or FLOX) [I, A] OR FU/LV infusion OR oral fluoropyrimidines (capecitabine)</td>
</tr>
</tbody>
</table>
Metastatic disease

| Metastatic disease | Resection of liver and lung secondary Downsize unresectable ones and assess Palliative chemo (1st line, 2nd line, MDT) | Perioperative FOLFOX improves survival Combination of 2 drugs with cetuximab & bevacizumab increases resection rate in kras pts |

Obstructive colorectal cancers

| Obstructive colorectal cancers | (i) Colostomy first followed by colonic resection, or (ii) Hartmann’s procedure first followed by colostomy closure and anastomosis OR (iii) one-stage procedure with either subtotal colectomy and ileorectal anastomosis or in selected cases, segmental resection after intraoperative colonic lavage OR Endoscopic stenting to relieve obstruction and allow subsequent one-step resection. |

11.5.2 Follow-up

The primary goal of follow up is to detect relapse and improve survival. The follow up recommendations for colon cancer include (i) history and physical examination and CEA determination every 3–6 months for 3 years and every 6–12 months at years 4 and 5 after surgery (ii) colonoscopy at year 1 and thereafter every 3–5 years and (iii) CT scan of chest and abdomen every 6–12 months for the first 3 years [II, B].

CEA is restricted to patients who would be candidates for resection of lungs and liver. Its routine use outside this is not recommended.

11.5.3 Prevention

Prevention practices for colon cancer include:

- Maintaining healthy weight (obesity is a risk)
- Periodic sigmoidoscopy for those at risk (family history) at least annually initially.
- Avoidance of tobacco and alcohol
- Use of aspirin for high risk population

11.6 Commonly used Medicines

5-fluorouracil, folinic acid, capecitabine, oxaliplatin, irinotecan, bevacizumab, cetuximab, panitumumab.

In resource limited settings, 5-fluorouracil, without or with folinic acid, can be used. Where possible, oxalipatin should be added to 5-fluorouracil/folinic acid.
11.7 Prognosis

Early colonic cancer is curable with appropriate treatment. Advanced disease is generally incurable though patients with limited metastasis, particularly in the liver, can be cured. In our setting, most patients present at the late stage.

REFERENCES

12. Rectal Cancer


12.1 Introduction
Rectal carcinoma is relatively rare and tends to be associated with HIV infection.

12.2 Epidemiology
Colorectal cancer is the fifth most common malignancy in Kenya. Rectal cancer forms 55.3% of the total colorectal cancer burden and peaks in the fifth decade. The male to female ratio is 1.5:1). The disease presents late (average delays of 33 weeks). Hospital studies show poor documentation of pathology and follow up data.

12.3 Diagnosis
Dominant symptoms include rectal bleeding (70.3%), change in bowel habits (66.4%), abdominal pain/discomfort (60.0%), intestinal obstruction (43.6%), mucus discharge (24.3%) and tenesmus (30.8%). Majority (91%) are palpable on digital rectal examination. Proctoscopic/Sigmoidoscopic biopsy and histopathology completes the diagnosis.

12.4 Staging and Risk Assessment
For local staging of rectal cancer MRI and EUS (or Contrast enhanced CT pelvis if not available) are recommended. Chest X ray with liver US or CT Chest and abdomen are recommended for distant metastases.
Complete colonoscopy should be done before or after surgery. The surgical specimen is evaluated for surgical margins (proximal, distal, circumferential), examination of at least 12 nodes and vascular and nerve invasion.
Rectal cancer is staged using the TNM system (table 1). Stalked and sessile adenomas should be classified using the Haggit system (Table 27)
Table 25: TNM Staging for Rectal Carcinoma

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>no evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>carcinoma in situ: intraepithelial or invasion of lamina propria</td>
</tr>
<tr>
<td>T1</td>
<td>tumor invades submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>tumor invades muscularis propria</td>
</tr>
<tr>
<td>T3</td>
<td>tumor invades through muscularis propria into subserosa or into nonperitonealized pericolic or perirectal tissues</td>
</tr>
<tr>
<td>T4</td>
<td>tumor directly invades other organs or structures and/or perforates visceral peritoneum</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional Lymph Nodes (N)</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>no regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>metastasis in one to three regional lymph nodes</td>
</tr>
<tr>
<td>N2</td>
<td>metastasis in four or more regional lymph nodes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant Metastases (M)</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>no distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>distant metastasis</td>
</tr>
</tbody>
</table>

Table 26: Stage Grouping AJCC Staging for Rectal Carcinoma

<table>
<thead>
<tr>
<th>TNM Classification</th>
<th>Dukes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stages</td>
<td></td>
</tr>
<tr>
<td>Stage 0</td>
<td>Tis</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1</td>
</tr>
<tr>
<td></td>
<td>T2</td>
</tr>
<tr>
<td>Stage II</td>
<td>T3</td>
</tr>
<tr>
<td></td>
<td>T4</td>
</tr>
<tr>
<td>Stage III</td>
<td>T1, T2</td>
</tr>
<tr>
<td></td>
<td>T3, T4</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
</tr>
<tr>
<td>Stage V</td>
<td></td>
</tr>
</tbody>
</table>
### Table 27: Haggitt system for polyps with invasive cancer

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Carcinoma in situ, not invading muscularis mucosa</td>
</tr>
<tr>
<td>1</td>
<td>Invasion into submucosa, limited to head of polyp</td>
</tr>
<tr>
<td>2</td>
<td>Cancer invades neck of polyp</td>
</tr>
<tr>
<td>3</td>
<td>Cancer invades stalk of polyp</td>
</tr>
<tr>
<td>4</td>
<td>Cancer invades submucosa of bowel wall = T1</td>
</tr>
</tbody>
</table>

All sessile polyps with invasive Cancer are level 4 by Haggitt’s criteria.

Level 1-3 are limited to polyp wall and do not involve normal bowel wall.

#### 12.5 Management

**12.5.1 Treatment of localised disease**

The aim of treatment is complete (R0) resection with sphincter preservation. The treatment is planned in a multidisciplinary setting. Surgical options include local, anterior and abdominoperineal resections. Total Mesorectal Excision (TME) must be performed to remove all mesorectal fat and all involved nodes and reduce local recurrence.
Table 28: Treatment Options by Stages

<table>
<thead>
<tr>
<th>STAGE</th>
<th>TREATMENT OPTIONS</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant polyps; (Haggit 1-3; T1 sm1 N0)</td>
<td>Local resection</td>
<td>Avoided in Haggit &gt; 3; T1 sm 2; LV invasion and high grade</td>
</tr>
<tr>
<td>Early cancer (cT1–2, some cT3, N0) and clear crm</td>
<td>TME</td>
<td></td>
</tr>
<tr>
<td>Intermediate (most cT3, some cT4,N+)</td>
<td>Preoperative chemoradiation + TME</td>
<td></td>
</tr>
<tr>
<td>Locally advanced (cT3 crm+, cT4, involvement of organs not easily resectable)</td>
<td>Preoperative radio-chemotherapy + radical surgery</td>
<td>Surgery after 6-8 weeks CRT + 5FU/Leucovorin infusion) OR oral capecitabine OR Oral 5FU</td>
</tr>
<tr>
<td>Disseminated disease</td>
<td>Local treatment and + systemic treatment or reverse Surgery for isolated liver or lung met Palliative radiotherapy Colostomy or stenting if unresectable Palliative chemotherapy</td>
<td>1st line: 5FU/leucovorin in +/- oxaliplatin or irinotecan +/- antibody</td>
</tr>
</tbody>
</table>

12.5.2 Postoperative Therapy
Adjuvant chemotherapy and radiotherapy is recommended for stages III disease or ‘high risk’ stage II disease.

12.5.3 Local recurrences
For patients not given radiotherapy earlier, preoperative radiotherapy with concomitant chemotherapy should be given. For those previously irradiated, additional radiotherapy (brachytherapy) could be tried. Attempts at radical surgery should take place 6–10 weeks after radiotherapy. Systemic chemotherapy is offered to patients with prior radiotherapy.
for whom salvage surgery is not an option.

12.5.4 Follow-up
Follow up identifies patients who may need salvage surgery and palliative care. The follow up protocol should include
(i) History and rectosigmoidoscopy every 6 months for 2 years
(ii) Completion colonoscopy within the 1st year if not done initially
(iii) History and colonoscopy every five years with resection of colonic polyps
(iv) Imaging of the liver and lungs at 1 and 3 years for those treated with curative intent.

12.5.5 Prevention
Prevention practices for colon cancer include:
• Periodic sigmoidoscopy for those at risk (family history)
• Aspirin for very high risk FAP.

12.6 Commonly used Medicines
5-fluorouracil, folinic acid, capecitabine, oxaliplatin, irinotecan, bevacizumab, cetuximab, panitumumab.
In resource limited settings, 5-fluorouracil without or with folinic acid is the first line treatment. Where resources are available, a combination of 5FU, folinic acid and oxaliplatin for early disease or 5-fluorouracil, folinic acid and irinotecan for advanced disease are the preferred treatments.

12.7 Prognosis
Early rectal carcinoma is curable when appropriately managed. In our set-up, however, diagnosis is usually late.
REFERENCES
13. Gastrointestinal Stromal Tumour (GIST)

Saidi H, Musibi A, Njuguna E, Weru I, Amayo A; Odongo I.

13.1 Introduction
This is a rare sarcoma found in the GI tract mainly driven by KIT and platelet derived growth factor (PDGF) mutations.

13.2 Epidemiology
GISTs are rare malignancies. The exact local incidence is unknown. Common sites include the stomach (60%), small intestine (30%), and colorectum (4%).

13.3 Diagnosis
The clinical presentation depends on the site. GISTs present with GI bleeding, abdominal pain and swelling, intestinal obstruction. Further evaluation is by endoscopy (EUS if available is very useful), imaging (CT or MRI) and biopsy. Histopathology should evaluate morphology, immunohistochemistry (CD 117 positive in 95% of GIST lesions), mitotic count and known mutations. Mutational analysis should be done in a central laboratory.

13.4 Staging and Risk Assessment
The imaging procedures of choice in staging GIST is contrast enhanced abdominal and pelvic CT (or MRI) and chest CT or Xrays.

Table 29: TNM system staging of GIST

<table>
<thead>
<tr>
<th>T- Primary tumor</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>primary tumour cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 2cm or less</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Tumor 2cm-5cm in greatest dimension</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Tumor 5cm-10cm in greatest dimension</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Tumor more than 10cm in greatest dimension</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N- Regional Lymph Nodes</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional nodes cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
<td></td>
</tr>
</tbody>
</table>

Distant metastasis

<table>
<thead>
<tr>
<th>M0</th>
<th>No distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>
The risk of relapse is determined on the basis of:

(i) Mitotic rate  
(ii) Tumor size  
(iii) Tumor site  
(iv) Surgical margins  
(v) Tumor rupture

These prognostic factors should be documented. Low mitotic rate refers to 5 or fewer per 50 high power fields (hpf) while high rate refers to over 5.

13.5 Management

13.5.1 Treatment of localised disease
This is planned in a multidisciplinary setting. The aim of treatment is to achieve a complete (R0) resection. If incomplete (R1) resection, re-excision is recommended when this is possible. Imatinib pre-treatment may be recommended for the purpose of cytoreduction before surgery 6-12 months later. During imatinib pre-treatment, tumor response may be monitored using PET or PET CT scans. Adjuvant treatment is recommended in high risk GIST e.g. those with tumour size > 3-5 cm, and high mitotic rates.

13.5.2 Treatment of extensive disease
Imatinib is the standard treatment in inoperable disease. The treatment is continued indefinitely. Imatinib dose escalation should be entertained in case of disease progression. When the treatment fails, the patient should be enrolled in a clinical trial of new therapy combinations.

13.5.3 Follow-up
Follow up with CT scan every 3 months for 3 years for high risk patients then every 6 months until 5 years and yearly afterwards is recommended. Low risk GIST has very low risk of recurrence and this does not warrant routine follow up.

13.6 Commonly used Medicines
Imatinib, sunitinib.
First line treatment is Imatinib. Those who fail and can afford should be put on sunitinib.

13.7 Prognosis
Early disease is curable by surgery. The rest is palliated on imatinib.
REFERENCES


Gynaecological Cancers

14. Cervical Cancer

Ndirangu G, Mueke S, Muchiri LM, Ojwang’ SBO

14.1 Introduction
Human papillomavirus (HPV) is the primary cause of 99.7% of all cervical cancers. Infection with one or more of the 15 high-risk oncogenic types leads to invasive cervical cancer after 10-20 years. Globally, about 70% of all cases of cervical cancer are caused by HPV types 16 and 18. Lesions that are limited to the cervical epithelium are referred to as pre-invasive lesions, whereas those that have penetrated beyond the epithelium are invasive.

14.2 Epidemiology
Cancer of the cervix is the second most common cancer among women worldwide. Incidence is highest in developing countries where it is the leading cause of cancer deaths. In 2008, 529,409 new cases occurred globally, about 274,883 women died in the same year. About 86% of new cases occur in developing countries, where 80-90% of deaths occur. Data from hospital-based registries in Kenya in the 10-year period, 1981-1990 indicate that cancer of the cervix accounted for 8-20% of all cancer cases and 70-80% of all genital tract cancers. The incidence of cervical cancer in Kenya is estimated to be 2,454 women per year with annual number of deaths estimated at 1,676 women. In the absence of accelerated interventions for screening, detection and early treatment, the incidence of cervical cancer is projected to rise to 4,261 resulting in 2,955 deaths in 2025. Peak age for cervical cancer is 35-45 years, but occurs a decade earlier in women with HIV/AIDS.

14.2.1 Primary Prevention
- Promote abstinence or delayed sexual debut for adolescents.
- Promote faithfulness to one partner for those in relationships.
- Promote Condom use: Allows faster HPV clearance, increases regression of cervical lesions, reduces the risk of genital warts as well as pre-cancer and cancer, protects against other STIs that are cofactors for cervical cancer, and protects against HIV which facilitates high risk HPV infection and progression into high grade squamous intraepithelial lesion.
- Promote HPV Vaccination.
- Promote male circumcision

HPV Vaccination
At present, two types of HPV vaccines are available: a quadrivalent type that protects against the high risk HPV types 16 and 18 as well as low risk types 6 and 11 that are
responsible for genital warts and a bivalent type which protects against HPV types 16 and 18. Both vaccines have shown more than 90% efficacy to prevent pre-cancerous lesions in females naive to vaccine specific HPV types and who have completed all three doses. Both vaccines are licensed for use in Kenya.

The target population is young adolescent girls aged 9-13 years using a school-based approach; out-of-school population will be reached through nearby health care facilities or through outreach campaigns. Catch-up vaccination for older girls and women up to age of 26 years is recommended.

14.2.2 Secondary Prevention
Cervical cancer has a long precancerous period that usually takes more than 10 years to progress to invasive cancer. Secondary prevention aims at preventing invasive cervical cancer by detecting and treating precancerous lesions of the cervix thereby interrupting progression to invasive cancer.

**Screening and Early Diagnosis**
- Visual inspection with acetic acid (VIA)
- Visual inspection with Lugol's iodine (VILI)
- Cytology using conventional and liquid based Pap smear
- HPV testing

* Women at high risk for cervical abnormalities are those who have had early sexual exposure, multiple partners, previous abnormal screening results or CIN, or are HIV positive.

Screening cycle
- Once every 5 years except for HIV-infected women and those with abnormal tests.
  - If screening has been normal, it can be stopped at 65 years of age. If results have been abnormal or the client has undergone treatment, rescreening should be provided in a year.
- Annual screening is not recommended for the HIV negative population.

Screening for HIV-infected Women
- All HIV-positive women aged 18 years and above should be screened for cervical cancer. Screening should begin at diagnosis of HIV, 6 monthly in the first year, then yearly thereafter.

Screening during Pregnancy and Puerperium
- Screening during pregnancy until 20 weeks gestation is recommended. No treatment should be given for premalignant lesions during pregnancy, unless there is evidence of a malignant lesion. Patients should return at 6-12 weeks post partum for treatment. Since most women also bring their children for immunization at 6 weeks post partum, eligible
women will be offered screening at that time and managed accordingly.

Screening done by VIA or VILI.
1. Negative cases: wait for 5 years for another screening.
2. Positive cases: Those suitable for cryotherapy should be offered the procedure.
   Those not suitable should be referred for colposcopy and biopsy.
3. Those found suspicious at screening should also be referred for colposcopy and biopsy.

After colposcopy:
1. Precancer cases should be treated with LEEP or cold knife conisation.
2. Invasive cancer cases should be treated as outlined below.
3. Negative cases should be rescreened after 5 years.

Screening with cervical cytology
1. Pap smear is performed, but if found unsatisfactory for evaluation, it should be repeated after correcting the cause of its being unsuitable.
2. Those with normal tests should be rescreened after 5 years.
3. Those with ASCUS /LSIL should have a repeat after 6-12 months.
4. Those with LSIL should be referred for colposcopy and biopsy.
5. Those with AGUS or malignant cells should be referred for further investigations and management.

Screening with HPV DNA Test
1. Negative cases should be retested after 5 years
2. Positive cases should go for VIA
3. VIA cases if HIV-positive, should be re-tested in 6 months but HIV-negative cases should be re-screened in 5 years.
4. Those positive on VIA should be managed as outlined above.

14.3 Diagnosis
The standard method for diagnosis of cervical precancerous lesions is histopathological examination of tissue obtained through colposcopically-directed biopsy.

Colposcopy
The most common reason for referral of women for colposcopy is abnormal cervical cytology. Indications for colposcopy include suspicious-looking cervix, HSIL, persistent ASCUS/LSIL (12-18 months), persistently unsatisfactory cytology, positive VIA or VILI, to map abnormalities before cryotherapy or LEEP.
Methods of Treatment of Precancerous Cervical Lesions

Cryotherapy

This method involves freezing abnormal tissues with a probe cooled by liquid nitrous oxide or carbon dioxide. It has an overall effectiveness rate of 80-90% in women with suitable lesions. It is simple, safe, and major complications are uncommon. It is also inexpensive; does not require electricity, and is practical for low-resource settings. It has been safely performed by nurses and other non-physicians in low level facilities and even primary care level in Kenya and elsewhere. Cryotherapy is not suitable for lesions that are larger than the cryoprobe tip or for lesions that extend into the cervical canal. Micro invasive cancers are usually asymptomatic, and may be detected only on cytology or histological evaluation of a biopsy specimen.

Table 30: Common Symptoms and Signs of Invasive Cervical Cancer

| Early | • Vaginal discharge, sometimes foul smelling  
|       | • Irregular vaginal bleeding  
|       | • Post coital bleeding in women of any age  
|       | • Post menopausal bleeding (especially that which does not respond to appropriate treatment)  
| Late  | • Urinary frequency and urgency  
|       | • Backache  
|       | • Lower abdominal pain  
| Very late | • Severe back pain  
|         | • Weight loss  
|         | • Oliguria (due to ureteric obstruction or renal failure)  
|         | • Urinary/ fecal incontinence  
|         | • Edema of lower limbs  
|         | • Dyspnoea (due to anemia, metastasis or pleural effusion)  

Any woman presenting with any of the above symptoms should have a speculum examination to visualize the cervix, and any visible lesions should be biopsied. If the woman is pregnant, she should be referred to a specialist for biopsy and follow-up. The definitive diagnosis of cancer is confirmed by histopathological examination of the biopsy specimen and is mandatory before any therapies, or even extensive investigations, are started.

14.4 Staging and Risk Assessment

The classification of the International Federation of Gynecology and Obstetrics (FIGO), which is based on tumor size and the extent of spread of disease in the pelvis and distant organs, is recommended for staging invasive cervical cancer.
In many low-resource settings, speculum, vaginal and rectal examinations are the only feasible approaches to staging; these will often provide sufficient information when performed by experienced clinicians. Attention should be paid to the size of the tumor and possible involvement of the vaginal fornices, the parametria (transverse cervical and uterosacral ligaments), the pelvic walls, the bladder and the rectum. This can be performed without anesthesia. General anesthesia is recommended in case of doubtful diagnosis or if the patient is too tense or in pain. Suspected bladder and rectal involvement should be confirmed histopathologically.

Imaging
- Chest X-ray
- X-ray of skeleton
- IVU
- Cystoscopy
- For diagnosis and staging of pelvis and abdomen, magnetic resonance imaging (MRI) is the modality of choice. However, CT scan can also be used.
### Table 31: FIGO Staging for Invasive Cervical Cancer

<table>
<thead>
<tr>
<th>STAGE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Carcinoma in situ, cervical intraepithelial neoplasia grade III. This is not considered invasive cancer, since the lesion has not gone beyond the basement membrane.</td>
</tr>
<tr>
<td>Stage I</td>
<td>Carcinoma strictly confined to the cervix (Extension to the corpus is disregarded)</td>
</tr>
<tr>
<td>IA</td>
<td>Micro invasive carcinoma strictly confined to the cervix</td>
</tr>
<tr>
<td>IA₁</td>
<td>Stromal invasion ≤3mm in depth and extension ≤7mm</td>
</tr>
<tr>
<td>IA₂</td>
<td>Stromal invasion 3-5mm and extension ≤7mm</td>
</tr>
<tr>
<td>IB</td>
<td>Clinically visible lesion confined to the cervix or clinical cancer greater than stage IA₁</td>
</tr>
<tr>
<td>IB₁</td>
<td>Clinically visible lesion ≤4cm diameter</td>
</tr>
<tr>
<td>IB₂</td>
<td>Clinically visible lesion &gt;4cm diameter</td>
</tr>
<tr>
<td>Stage II</td>
<td>Cancer extends beyond the cervix but has not reached the pelvic wall and/or carcinoma involves the upper part of the vagina but not the lower third</td>
</tr>
<tr>
<td>IIA</td>
<td>Spread beyond the cervix, including upper two-thirds of the vagina, but not to tissues around the uterus (parametria).</td>
</tr>
<tr>
<td>IIB</td>
<td>Spread beyond the cervix, with parametrial invasion, but not as far as the pelvic wall or the lower third of the vagina</td>
</tr>
<tr>
<td>Stage III</td>
<td>Carcinoma has extended to the pelvic wall. On rectal examination, there is no cancer-free space between the tumour and the pelvic wall. The tumour also involves the lower third of the vagina. Clients may also have hydronephrosis or non-functioning kidneys.</td>
</tr>
<tr>
<td>IIIA</td>
<td>Invasion of the lower third of the vagina, with no extension to the pelvic wall</td>
</tr>
<tr>
<td>IIIB</td>
<td>Extension to the pelvic wall, or hydronephrosis or nonfunctioning kidney</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Carcinoma extended beyond the true pelvis or clinically involves mucosa of the bladder or rectum.</td>
</tr>
<tr>
<td>IVA</td>
<td>Spread to involve the mucosa of the bladder or rectum.</td>
</tr>
<tr>
<td>IVB</td>
<td>Spread to distant organs, such as extra pelvic lymph nodes, kidneys, bones, lungs, liver and brain</td>
</tr>
</tbody>
</table>
14.5 Management

Treatment options are pegged on the stage of invasive cancer and comprise of surgery, radiotherapy, and chemotherapy, singly or in combination. Consideration should be given to the best interest of the patient, the overall assessment of the patient, the availability and quality of surgery, radiotherapy and oncology services, and the other support systems available to the patient. Women should be given all the information about the procedure (including the benefits, risks, potential side effects, recovery time, cost, chances of success, 5 year survival rates etc) before it is performed.

14.5.1 Treatment Options for Invasive Cervical Cancer

Stage 0: If uterine function is to be preserved: cone biopsy, or LEEP/LLETZ. Simple hysterectomy should be considered in case of other gynecologic pathology, poor follow up, or if family has been completed.

Stage IA1: Hysterectomy and pelvic lymphadenectomy if LEEP/LLETZ cone biopsy margins are clear and there is no vascular or lymphatic invasion. Radical hysterectomy and pelvic lymphadenectomy should be considered if vascular and/or lymphatic invasion are present or if the depth is uncertain due to growth at the LEEP/LLETZ/cone margin. Radical hysterectomy and pelvic lymphadenectomy are strongly recommended in case of adenocarcinoma. For lesions ≤4cm, radical hysterectomy and pelvic pelvic lymphadenectomy are strongly recommended, but the approach should be individualized for age, obesity, and other co-morbidities.

External beam irradiation and intracavitary brachytherapy should be offered for patients unfit for surgery.

Stage IA2: External beam irradiation and intracavitary brachytherapy should be offered. Re-assess after 6 weeks and consider salvage hysterectomy if viable tumor is still present.

Stages IB1 and IB2 - Treat as IA2.

Stage IIA: If lesion ≤4cm; radical hysterectomy and pelvic lymphadenectomy, if there is minimal involvement of upper vagina. If unfit for surgery, tumour >4cm or extensive involvement of upper vagina should be treated with radiotherapy.

Stage IIB: External beam irradiation and intracavitary brachytherapy should be applied.

Stage III: Radical radiotherapy, external and intracavitary brachytherapy. Palliative radiotherapy should be administered to control symptoms if general condition of the patient is poor, or there are co-morbidities, poor performance status, or there are large bilateral hydronephrosis.

Stage IVA: In fit patients with low volume tumour, full radiotherapy to be decided. Most patients are given palliative radiotherapy to control symptoms.

Stage IVB: should be treated with radiotherapy to the pelvis and symptomatic metastatic areas.
14.5.2 Adjuvant therapy: is recommended for stage I-IIA with histologically proven pelvic lymph nodes, positive margins or parametrial involvement, and involve pelvic irradiation and platinum-based chemotherapy. For stages IIB and above (locally advanced cancer) platinum-based chemotherapy and external and intracavitary radiotherapy are strongly recommended.

14.5.3 Invasive cancer in pregnancy
Management should be individualized, taking into consideration the woman’s concerns, health and the impact on the outcome of the pregnancy. The patient should be counseled on all available options and allowed to make an informed consent. Management by surgery or by radiotherapy depends on the stage of the cancer but is also related to the gestational age of the pregnancy. In early pregnancy, radiotherapy is appropriate for management and should begin with pelvic irradiation to cause fetal death and abortion followed by uterine evacuation and brachytherapy. An ultrasound scan must be done to verify that the fetus is no longer viable. In the third trimester, definitive treatment is usually delayed until the foetus is mature/able to survive outside the uterus, upon which the baby is delivered by classical Caesarean section followed immediately by surgery or radiation as determined by the stage of the cancer. For radiotherapy, it must be started after involution of the uterus.

14.5.4 Invasive Cervical Cancer in HIV positive women:
HIV positive women with CD4 counts <200/mm3 are at risk of complications irrespective of treatment methods. Where possible, surgery is preferable. Treatment with radiotherapy and chemotherapy should be tailored to the individual.

14.5.5 Palliative Care:
Refer to Chapter 40

14.6 Medicines commonly used
5FU, Cisplatin, paclitaxel, navelbine, topotecan, carboplatin, docetaxel, gemcitabine, ifosfamide, hydroxyurea, mitomycin C. In resource limited settings, 5FU without or with cisplatin is recommended treatment. Where resources are available, a platinum compound and a taxane can be used.

14.7 Prognosis
With timely diagnosis and optimal treatment, the following are the five (5) year survival rates by stage of cancer:
- Stage 1A – 95 -98%
In our setting, majority of patients present at an advance stage.

If relapse occurs after conservative treatment, salvage hysterectomy may be considered. This approach is however unlikely to alter the survival rate, but is associated with a longer disease free interval and possibly a better quality of life. Chemotherapy is also an option in case of recurrence after radiation.

Finally, radiation can be used to treat non-pelvic or distant metastases, e.g. in the bones, lung or other organs.

REFERENCES

15. Endometrial Cancer

Ndirangu G, Muchiri LM, Mueke S, Ojwang’ SBO

15.1 Introduction
Endometrial cancer is a common gynecological malignancy.

15.2 Epidemiology
Prevalence in Kenya is unknown but hospital based data show that for every 30 cases of cervical cancer, there is one case of endometrial cancer. Lifetime risk of developing endometrial cancer is approximately 2%. In USA, it causes approximately 6000 deaths. About half of patients with endometrial cancer have risk factors for the disease, including obesity; unopposed estrogen exposure (exogenous or endogenous e.g. estrogen secreting ovarian tumours such as granulosa and theca cell tumors; older age; chronic anovulation; low parity/nulliparity; early menarche (onset below 12 years); late menopause (above 52 years); use of tamoxifen; diabetes mellitus; and history of breast or ovarian cancer.

15.3 Diagnosis
Abnormal vaginal bleeding including postmenopausal bleeding/spotting occurs in 90% of patients. Though most patients are postmenopausal, about a quarter of them are premenopausal with 5% below 40 years of age. Majority of young patients are obese or have high levels of unopposed endogenous estrogen from chronic anovulation from polycystic ovary disease.
Initial evaluation should include full physical examination, (pelvic examination noting the size, position and contour of the uterus). Screening for cervical cancer should be performed. Diagnosis requires histopathological evaluation of endometrial tissue. One should consider primary endocervical adenocarcinoma or extension of cervical carcinoma into the endometrium. Therefore, both endocervical and endometrial sampling should be performed. Devices for use in the office allow endometrial sampling and accurate diagnosis. Hysteroscopic evaluation and biopsy may be performed where facilities are available. Pelvic ultrasonography may be suggestive of disease. More than 90% of all cancers are endometroid in type. Other types are serous, clear cell, mucinous, mixed cell, transitional cell and sarcomas.

15.4 Staging and Risk Assessment

15.4.1 Degree of Differentiation
Histological differentiation is important in determining treatment and prognosis. Response to treatment decreases with increasing grade. WHO grading (grade 1: non-squamous, non-morula solid growth pattern in ≤5% of tumour; grade 2: non-squamous, non-morula solid growth pattern in 5-50% of tumour; grade 3: non-squamous, non-
morula solid growth pattern in >50% of tumour).

Pre-operative Evaluation and Preparation

- Laboratory investigations: total blood count, renal function tests, liver function tests, blood sugar, others as necessary.
- Imaging: chest X-ray, pelvic ultrasonography (transvaginal), pelvic and abdominal CT scan, MRI scan (contrast-enhanced dynamic MRI) for uterine and pelvic spread

The most popular staging classification for endometrial cancer is the FIGO system. This is a surgical staging system

Table 32: FIGO Staging for Endometrial Carcinoma

<table>
<thead>
<tr>
<th>STAGE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Confined to the uterus</td>
</tr>
<tr>
<td></td>
<td>IA: Confined to the endometrium</td>
</tr>
<tr>
<td></td>
<td>IB: Invasion to &lt;50% myometrium</td>
</tr>
<tr>
<td></td>
<td>IC: Invasion to &gt;50% myometrium</td>
</tr>
<tr>
<td>Stage II</td>
<td>Extension to uterine cervix</td>
</tr>
<tr>
<td></td>
<td>IIA: Endocervical glandular involvement only</td>
</tr>
<tr>
<td></td>
<td>IIB: Cervical stromal invasion</td>
</tr>
<tr>
<td>Stage III</td>
<td>Extension beyond the uterus</td>
</tr>
<tr>
<td></td>
<td>IIIA: Tumour invades serosa and/or adnexa positive peritoneal cytology</td>
</tr>
<tr>
<td></td>
<td>IIIB: Vaginal involvement</td>
</tr>
<tr>
<td></td>
<td>IIIC: Metastasis to pelvic or para-aortic lymph nodes</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Spread to neighbouring organs or distant metastasis</td>
</tr>
<tr>
<td></td>
<td>IVA: Invasion to bladder and/or bowel mucosa</td>
</tr>
<tr>
<td></td>
<td>IVB: Distant metastasis including intraabdominal oringuinal lymph nodes</td>
</tr>
</tbody>
</table>

Prognostic Factors

- Surgical stage
- Histological grade
- Depth of myometrial invasion
- Histological type
- Tumour diameter
- Invasion of lymphovascular space
- Age of patient
- Endocervical stromal invasion
### Table 33: Risk Categorization for Endometrial Carcinoma

<table>
<thead>
<tr>
<th>Risk Categorization</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk:</td>
<td>Stage IA/IB, grade 1 or 2, endometrioid histopathological type</td>
</tr>
<tr>
<td>Intermediate risk:</td>
<td>Stage IC, grade 1 or 2, endometrioid histopathological type</td>
</tr>
<tr>
<td></td>
<td>Stage IA/IB, grade 3, endometrioid histopathological type</td>
</tr>
<tr>
<td>High risk:</td>
<td>Stage IC, grade 3, endometrioid histopathological type</td>
</tr>
<tr>
<td></td>
<td>Stage IA/IB/IC, serous, clear cell, small cell or undifferentiated histopathological type</td>
</tr>
</tbody>
</table>

### 15.5 Management

Surgery is the mainstay of treatment. This involves total abdominal hysterectomy (TAH) and bilateral salpingoopherctomy (BSO).

Chemotherapeutic regimens containing doxorubicin, cis-platin, carboplatin, paclitaxel, docetaxel, topotecan, ifosfamide, 5-fluorouracil, methotrexate. These are usually administered in various combinations but single agents can also be administered. High dose medroxyprogesterone acetate may also be included in steroid-receptor positive cases.

### 15.6 Commonly used Medicines

Cisplatin, carboplatin, paclitaxel, docetaxel, doxorubicin, topotecan, ifosfamide, vinorelbine, tamoxifen.

In resource limited settings, cisplatin with doxorubicin is the preferred treatment option.

Where resources are available taxane and a platinum compound are used.

### 15.7 Prognosis

Early stage presentation is curable with surgery alone.

### REFERENCES

16. Ovarian Cancer

Ndirangu G, Muchiri LM, Mueke S, Ojwang’ SBO

16.1 Introduction
Ovarian cancer is the second most common gynaecologic cancer. More than 90% of primary ovarian cancers are epithelial in origin. Other types include germ cell, sex cord-stromal and mixed cell types.

16.2 Epidemiology
Ovarian cancer accounts for 6.3% of all cancers in women globally. One in every 56 women will develop the disease in their lifetime. At Kenyatta National Hospital, ovarian cancer represents about 20-25% of all gynecological cancers. The incidence increases with age.

16.3 Diagnosis

Clinical Presentation
There are no symptoms and signs that are specific to ovarian cancer. As such 75-85% of cases are advanced at the time of presentation. It can present as a surgical problem or medical problem.

The following symptoms may indicate the presence ovarian cancer:
• Vague abdominal discomfort e.g. pressure, gas, bloating, constipation, early satiety, poor appetite, nausea, vomiting
• Urinary frequency
• Pelvic pressure
• Mass or masses in the abdomen; if mass >15cm in 40-69 years, suspect ovarian cancer
• Abdominal distension
• Irregular vaginal bleeding
• Low back pain
• Fatigue
• Dyspareunia
• Weight loss

Physical examination
Any woman presenting with any of the above symptoms should have pelvic examination to rule out ovarian cancer. The presence of a solid, irregular, fixed pelvic mass is highly suggestive of ovarian malignancy. The diagnosis is even more likely, if in addition to the above, there is upper abdominal mass and/or ascites. Additional signs depend on the stage of presentation. A high index of suspicion in women between 40 and 69 years with
persistent gastrointestinal symptoms is important for early diagnosis. The definitive diagnosis for ovarian cancer involves histopathological evaluation of a surgical specimen. Such patients quite often require laparotomy to confirm the diagnosis.

Other diagnostic tests include:
- Pelvic ultrasonography (sensitivity of 62-100% and specificity of 77-95%)
- Liver ultrasonography
- An elevated serum tumour marker CA-125 in a woman with a pelvic mass may be suggestive of ovarian cancer.
- Other tumour markers that may be elevated include hCG, alpha-fetoprotein, carcinoembryonic antigen (CEA).
- Ultrasonography combined with elevated CA-125 can help distinguish between malignant and benign pelvic tumours.
- Other radiological tests may include CT scan, MRI, and PET where available to stage the primary tumour.
- Chest X-ray is necessary for evaluation of patients before treatment.
- Ascitic tap for cytology, chemistry and microscopy to rule out Tuberculosis.
<table>
<thead>
<tr>
<th>STAGE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
</table>
| Stage I | Tumour confined to one or both ovaries  
IA: Confined to one ovary; capsule intact, no malignant ascites; no tumour on the external surface  
IB: Confined to both ovaries; capsules intact, no malignant ascites; no tumour on the external surfaces  
IC: Tumour on one or both ovaries with ruptured capsule, or tumour on surface of malignant or ascites with positive peritoneal washings |
| Stage II | Growth involves one or both ovaries with pelvic extension.  
IIA: Extension and/or metastasis to the uterus and/or tubes  
IIB: Extension to other pelvic organs  
IIC: Stage 1A or 1B with tumour on the surface of one or both ovaries; with ruptured capsule/s; or with malignant ascites or positive peritoneal washings |
| Stage III | Tumour involves one or both ovaries with peritoneal implants outside pelvis and/or positive retroperitoneal or inguinal nodes; superficial liver metastasis; tumour is limited to the true pelvis but with histologically proven malignant extension to small bowel or omentum  
IIIA: Tumour grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seedlings of abdominal peritoneal surfaces  
IIIB: Tumour of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2cm in diameter. Nodes negative.  
IIIC: Abdominal implants >2cm in diameter and/or retroperitoneal or inguinal nodes. |
| Stage IV | Growth involving one or both ovaries with distant metastasis. If pleural effusion present, there must be a positive cytology result; parenchymal liver metastasis |
16.5 Management

16.5.1 Surgical Management
Pre-operative work up:
- Tests -
  - Full blood count
  - Urea/electrolytes
  - Liver enzymes (AST, ALT, GGT, ALP)
  - Serum calcium
  - Albumin
- Preoperative procedures:-
  - Where available, book for frozen preparations.
- Definitive treatment includes simple hysterectomy with bilateral salpingo-
  ophorectomy (BSO) and omentectomy.
- Cytoreduction of macroscopic tumor (<1cm diameter)
- Maximum effort to reduce the size of tumor(s) if optimal surgery is not possible.
- Careful documentation of size and site of residual disease and histopathological
  evaluation is necessary.

16.5.2 Chemotherapy
- Combination of platinum-based (cisplatin or carboplatin) and taxanes e.g. paclitaxel
  and docetaxel
- Cyclophosphamide and platinum-based compounds
- Additional chemotherapeutic agents include topotecan, gemcitabine and
  bevacizumab
- Intra-peritoneal chemotherapy

16.5.3 Persistent and Recurrent Disease
- On treatment: stop chemotherapy
- <6 months after stopping chemotherapy: supportive care
- >6 months after stopping chemotherapy: restart original regimen for 6 cycles
- Rising CA-125 without clinical or radiological evidence of recurrence, assume
  recurrence.

16.6 Commonly used Medicines
These include carboplatin, cisplatin, paclitaxel, docetaxel, doxorubicin,
cyclophosphamide, topotecan, gemcitabine, ifosfamide, vinorelbine, 5-fluorouracil/
leucovorin, bevacizumab, oxaliplatin, tamoxifen, etoposide.
In resource limited settings, cyclophosphamide/doxorubicin in combination is preferred.
Cisplatin/carboplatin and a taxane (paclitaxel, docetaxel) may be used where resources
are available.
16.7 Prognosis
Curable with surgery in early disease, but advanced stage is incurable.

REFERENCES
17. Vulvar Cancer

_Ojwang S.B.O., Ndirangu G G., Muchiri L., Mueke S._

17.1 Introduction
The majority of all vulvar cancers are squamous cell types. Since the vulva is covered by skin, any malignant changes that appear elsewhere on the skin can occur in this area.

17.2 Epidemiology
Vulvar cancer accounts for 5% to 8% of all female genital malignancies. It occurs most commonly among women aged between 65 – 75 years, but can also occur in younger women below 40 years.
The causes of vulvar cancer are unknown, but there is some association with condylomata acuminata and HPV infections.
Associated clinical conditions include dystrophies like, atrophic vulvitis, diabetic vulvitis, leukoplakia, kraurosis. Patients tend to be obese, diabetic, hypertensive, and have arteriosclerosis.

17.3 Diagnosis
Diagnosis requires careful inspection in good light. One may observe vulvar pruritus which occurs several years before actual cancer in up to 67% of patients. Ulcer, pain, oozing of serous fluid, bleeding, and inguinal lymphnode enlargement are important findings. Colposcopy may be useful after application of 2% acetic acid. Excisional biopsy is the preferred method for obtaining tissue. Fine needle aspiration cytology of suspicious inguinal lymph nodes may be performed in the background of suggestive clinical scenario.
Imaging evaluation includes chest X-ray, pelvic X-ray, CT and MRI scan if necessary.
Laboratory work up should include full blood counts, renal function tests, liver function tests, VDRL, HIV test, random blood sugar.
Pathological tumour types include epidermoid cysts, melanoma, sarcoma, basal cell carcinoma, squamous cell carcinoma, adenocarcinoma, undifferentiated carcinoma.
Squamous cell carcinoma accounts for 86% of all cases.
Indications for excisional biopsy include changes in surface area, elevated, raised, thickened/or nodular lesions on the vulva. These may be new lesions, or old lesions, but with recent changes. There may also be change in colour of the skin to brown or black, change in surface from smooth to scaly or ulcerated or even change in sensation to itchy or tingling.
17.4 Staging and Risk Assessment

Table 35: TNM System staging for Vulvar Carcinoma

**Primary Tumour (T)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in-situ (preinvasive carcinoma)</td>
</tr>
<tr>
<td>T1a</td>
<td>Lesions ≤ 2 cm, confined to the vulva or perineum, and with stromal invasion ≤ 1.0 mm.</td>
</tr>
<tr>
<td>T1b</td>
<td>Lesions &gt; 2 cm in size, or any size with stromal invasion &gt; 1.0 mm, confined to the vulva or perineum.</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour of any size with extension to adjacent perineal structures.</td>
</tr>
</tbody>
</table>

**Regional lymph nodes (N)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>NO</td>
<td>No regional lymph node metastasis.</td>
</tr>
<tr>
<td>N1</td>
<td>One or two regional lymph nodes with the following features</td>
</tr>
<tr>
<td>N1a</td>
<td>One or two lymph node metastases each 5 mm or less.</td>
</tr>
<tr>
<td>N1b</td>
<td>One lymph node metastasis 5 mm or greater.</td>
</tr>
<tr>
<td>N2</td>
<td>Regional lymph node metastases with the following features:</td>
</tr>
<tr>
<td>N2a</td>
<td>Three or more lymph node metastases each less than 5 mm.</td>
</tr>
<tr>
<td>N2b</td>
<td>Two or more lymph node metastases each 5 mm or greater.</td>
</tr>
<tr>
<td>N2c</td>
<td>Lymph node metastasis with extracapsular spread.</td>
</tr>
<tr>
<td>N3</td>
<td>Fixed or ulcerated regional lymph node metastasis.</td>
</tr>
</tbody>
</table>

**Regional lymph nodes (N)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNM</td>
<td>FIGO</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis (including pelvic lymph node metastasis).</td>
</tr>
</tbody>
</table>

17.5 Management

In situ lesions are preferably treated by local excision while superficially invasive (<3 mm full thickness) lesions should be treated by wide local excision only.

**Invasive Disease**

Early invasive disease should be treated by surgical excision. If inguinal lymph nodes are not palpable, radical excision of the vulva can be achieved without sacrificing the sphincter.

If excision margin is less than 1 cm, then re-operation should be considered if frozen section available and positive. In this case, contralateral inguinal lymphadenectomy should also be considered.
**Advanced disease**

If suspicious lymphnodes are present, the sphincter must be sacrificed. Unfavorable features are presence of two or more lymphnodes, one metastatic lymphnode after 5cm. or there is extra capsular spread. This requires wide local excision. The excision should extend down to deep perineal fascia and clear the tumour by a margin of at least 1cm in all directions.

**Advanced or recurrent vulvar cancer**

If the node is irresectable, but the primary tumour is resectable, adjuvant radiotherapy should be administered. If the excision margin is less than 1cm, then the vulva should be included in the radiation field.

Irresectable primary tumour should be treated with concomitant radiochemotherapy. If nodes are clinically negative consider lymph node dissection. If they are pathologically involved, then pelvic radiotherapy should be considered. Attempts should be made to debulk large mobile nodes before radiotherapy.

Individualization of patients is important in relation to age, obesity and other parameters. If nodal disease is not a problem and sufficient regression of primary tumour has occurred, attempt at wide local excision is recommended. If the disease is advanced and the patient’s performance status is poor, then palliative irradiation should be considered.

**16.6 Commonly used Medicines**

Bleomycin, cisplatin, 5-fluorouracil, paclitaxel, mitomycin-C.

In resource limited settings, 5-fluorouracil and mitomycin-c or 5FU and cisplatin.

**17.7 Prognosis:**

Early disease is curable in a significant number of cases.

**REFERENCES.**

1. American Cancer Society. *Cancer Facts and Figures 2009*
18. Gestational Trophoblastic Diseases (GTD)

Othieno-Abinya N.A., Ndirangu G, Mueke S, Nyongesa C

18.1 Introduction
These tumours and neoplasms are rare but highly curable diseases arising from the products of conception in the uterus. They result from abnormal fertilization and are divided into distinct clinicopathologic entities:
- Hydatidiform mole, partial or complete
- Invasive mole
- Gestational trophoblastic neoplasias (choriocarcinoma, placental site trophoblastic tumour, epithelioid trophoblastic tumour).

18.2 Epidemiology
Broadly, these tumours represent less than 1% of all tumours, though there are no clear local data. The most common risk factor is molar pregnancy; they can also complicate normal or ectopic pregnancies, and spontaneous or induced abortions.

18.3 Diagnosis
Women with GTD may present with pelvic pain or sensation of pressure, anemia, hyperemesis gravidarum, hyperthyroidism, and preeclampsia in early pregnancy. However, abnormal and excessive vaginal bleeding is the commonest mode of presentation. Other symptoms and signs depend on the site of metastasis e.g. lungs, liver and brain. Examination includes speculum pelvic examination which may show vaginal deposits. Further diagnostic work up includes laboratory estimation of $\beta$-hCG in urine and/or blood, pelvic ultrasound, chest X-ray. Chest and brain CT scan or MRI are of value. Imaging modalities are primarily used for the evaluation of metastatic disease.

18.4 Staging and Risk management

Table 36: FIGO Anatomical Staging for GTD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumour confined to the uterus.</td>
</tr>
<tr>
<td>II</td>
<td>Tumour extending to the adnexa or vagina but limited to the genital structures (adnexa, vagina, broad ligament).</td>
</tr>
<tr>
<td>III</td>
<td>Tumour extending to the lungs, with or without known genital tract involvement.</td>
</tr>
<tr>
<td>IV</td>
<td>All other metastatic sites.</td>
</tr>
</tbody>
</table>
Table 37: FIGO (WHO) Risk Factor (Prognostic) Scoring with FIGO Staging

<table>
<thead>
<tr>
<th>SCORE</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>&lt;40</td>
<td>≥40</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Antecedent pregnancy</td>
<td>mole</td>
<td>abortion</td>
<td>term</td>
<td>–</td>
</tr>
<tr>
<td>Interval months from index pregnancy</td>
<td>&lt;4</td>
<td>4–6</td>
<td>7–12</td>
<td>&gt;12</td>
</tr>
<tr>
<td>Pretreatment serum hCG (iu/l)</td>
<td>&lt;10³</td>
<td>10³–10⁴</td>
<td>10⁴–10⁵</td>
<td>&gt;10⁵</td>
</tr>
<tr>
<td>Largest tumor size (including uterus)</td>
<td>&lt;3</td>
<td>3–4 cm</td>
<td>≥5 cm</td>
<td>–</td>
</tr>
<tr>
<td>Site of metastases</td>
<td>lung</td>
<td>spleen, kidney</td>
<td>gastrointestinal</td>
<td>liver, brain</td>
</tr>
<tr>
<td>Number of metastases</td>
<td>–</td>
<td>1–4</td>
<td>5–8</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Previous failed chemotherapy</td>
<td>–</td>
<td>–</td>
<td>single drug</td>
<td>≥2 drugs</td>
</tr>
</tbody>
</table>

The total score is obtained by adding individual scores. A score of 0-6 is low risk while a score of ≥7 is high risk.

18.5 Management
18.5.1 Hydatidiform mole
- Suction curettage is the standard treatment; sharp curettage two weeks later is then done for histopathological diagnosis.
- Provide combined oral contraceptive pill for at least one year after treatment.
- Monitor by serum -hCG levels monthly until three negative values.
- Hysterectomy is an alternative in special cases that should be decided by gynecology oncologists and discussed with the patient.
- Administer anti-D after uterine evacuation.

18.5.2 Choriocarcinoma
- Perform pretreatment laboratory work up that includes total blood count, renal and liver function tests.
- For nonmetastatic disease (FIGO stage I) and low risk metastatic disease (FIGO stages II and III, score 0-6), use single agent chemotherapy with methotrexate or actinomycin D. Hysterectomy may be indicated in the presence of persistent heavy bleeding or when fertility is not desired.
- For high risk metastatic disease (FIGO stage III-IV, score ≥7– combination of etoposide, methotrexate, actinomycin D, cyclophosphamide and vincristine (EMA/CO) protocol is most commonly used.
- For refractory disease second-line chemotherapy with cisplatin replacing vincristine in the EMA/CO protocol (EMA/EP) is recommended. Paclitaxel containing chemotherapy has a role. High dose chemotherapy with bone marrow stem cell rescue has a role in refractory cases.
• The role of surgery in metastatic GTD lies mainly in the control of complications that result from the disease or chemotherapy such as haemorrhage or infection. However, judicious use of surgery, in extirpating the sites of disease, can not only be life saving, but may also reduce the amount of chemotherapy given and decrease the chance of drug resistance. Adjuvant radiotherapy or surgery may be considered for refractory cases. Palliative radiotherapy can be used for women with severe vaginal bleeding, those with brain and liver metastasis.

18.5.3 Follow-up
Follow up identifies women who may relapse, develop early menopause or secondary cancer.
Monitor by serum β-HCG levels monthly until three negative values. Besides clinical examination, all patients should have weekly β-HCG estimation until the levels return to normal. Thereafter, β-HCG estimation is done at monthly intervals. In low-risk disease, this is carried on for a year. In high-risk patients, this should be performed for at least 2 years. During this period of monitoring, it is important to prescribe effective contraception e.g. combined oral contraceptive pill.

18.6 Commonly used Medicines
Methotrexate, etoposide, actinomycin-D, cisplatin, vincristine, cyclophosphamide, doxorubicin.
The first line treatment in low risk disease is methotrexate monotherapy; in high risk disease a combination of etoposide, methotrexate, actinomycin-D, cyclophosphomide and vincristine (EMA/CO) can be used.

18.7 Prognosis
The prognosis for cure is usually good, even when the disease has metastasized

REFERENCES
19. Acute Leukaemia

Leukaemias are a heterogenous group of cancers arising from blood cells that involve the bone marrow and peripheral blood, and may be lymphoid or myeloid. It is broadly categorized into acute leukaemia and chronic leukaemia.

19.1 Introduction

Acute leukaemia is characterized by the presence in the bone marrow and/or peripheral blood circulation of immature cells (blast or promyelocytes). Lymphoblasts are found in acute lymphoblastic leukaemia (ALL) while myeloblasts are found in acute myeloid leukaemia (AML). Both myeloblasts and promyelocytes are found in a subset of AML known as acute promyelocytic leukaemia (APML). All have aggressive biological behavior with rapid progression to fatality if not properly treated.

19.2 Epidemiology

Even though acute myeloid leukemias (AMLs) are infrequent they are highly malignant yet curable in a sizeable proportion of cases if treated appropriately making them significant in clinical practice.

AML shows 2 peaks in occurrence, one in early childhood with the majority occurring later in adulthood.

ALL is on the other hand most common in childhood with a peak incidence at 2–5 years of age, with a smaller peak in old age.

There is a slight male preponderance in both AML and ALL.

19.3 Diagnosis

Patients with the following symptoms (history) should be further evaluated:

- Recurrent infections
- Bleeding or easy bruising
- Unexplained Weight loss
- Drenching night sweats
- Persistent fever
- Bone pains

The following clinical signs should be looked for in a full physical examination:

- Pallor (anaemia)
- Splenomegaly
- Hepatomegally
- Bruising (purpura)
- Gum hypertrophy
- Lymphadenopathy (All groups of lymph nodes)
19.3.1 Laboratory Evaluation
- Bone Marrow Aspirate (mandatory) and trephine (recommended) for diagnosis, with relevant cytochemistry and immunophenotyping as applicable.
- FBC, with differential count and peripheral blood film examination
  - Where the blood count is abnormal, or there are abnormal cells are seen on peripheral film, the slides must be reviewed by a specialist pathologist (haematopathologist or clinical pathologist with haematology experience)
  - Stained slides and unstained slides should be prepared at site and sent with the whole blood to the pathology laboratory for review, if initially reported by a technologist only
- The following ancillary tests are recommended where possible: flow cytometry/immunophenotyping and cytogenetics/molecular studies are recommended for establishing sub-type of acute leukaemia for purposes of risk stratification and prognostication.

19.4 Staging and Risk Assessment
- Biochemistry including liver and renal function tests, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), urate, and liver enzymes.
- Viral serology for HIV (mandatory), Hepatitis B and Hepatitis C (strongly recommended).
- Diagnostic tap (Lumbar puncture) is mandatory for all patients with ALL, and is recommended for other acute leukaemias with clinical suspicion of CNS involvement.
  Radiology & Imaging
  Generally not required, but may be guided by the clinical presentation.

19.5 Management
Treatment is divided into supportive and definitive treatment

19.5.1 Supportive Treatment
- Treatment of infections with relevant antimicrobial agents.
- Provision of prophylactic antimicrobials at a specialized centre.
- Transfusion of blood components (packed cells and platelet concentrates) as needed.
- Hydration.
- Correction of abnormal blood chemistries such as hyperuricaemia, lactic acidosis and renal failure.
- Prevention and management of tumour lysis syndrome.
19.5.2 Specific Treatment
The treatment is stratified according to the specific type of acute leukaemia, and it is recommended that such treatment should only be initiated by an oncology specialist at a specialized treatment center.

19.5.3 AML other than APML
Treatment options include induction and consolidation chemotherapy with a curative intent. Patients older than 65 years are more susceptible to treatment complications than young patients because of other co-morbidities such as diabetes mellitus, hypertension and coronary artery disease.

• Induction:
  - Chemotherapy regimen options includes Cytarabine, Anthracyclines (e.g. Daunorubicin) in 7+3 regimen as the standard recommended regimen

• Consolidation:
  - Involves use of high-dose cytarabine (HIDAC) which has various toxicities including non-haematological toxicities such as cerebellar ataxia that should prompt immediate discontinuation of the chemotherapy. Steroidal eye drops must be instilled from the initiation of therapy.

19.5.4 APML
APML (AML M3) is treated differently from other AMLs.
The treatment includes induction with differentiation agents like all trans retinoic acid (atrazine®) and anthracyclines (such as daunorubicin) which should be given as emergency treatment by a specialist at a specialist treatment centre. These patients are at high risk for developing life threatening coagulopathies hence the need for prompt consultation to a specialist and referral to a specialist centre.

Maintenance therapy is part of standard of care for APML, and may go up to 24 months, given by a specialist.

If promptly diagnosed and therapy initiated early, this is the AML with the best prognosis. Arsenic trioxide should be considered for relapsed APML.

19.5.5 ALL
Treatment of ALL follows the same pattern of induction, consolidation, CNS prophylaxis and maintenance chemotherapy. There are various and varying protocols for treatment for ALL available.
Owing to high toxicity of these regimens, supportive therapy is paramount in the management, hence the need for prompt and continued care at a specialized referral centre during and after treatment.

Radiation therapy for CNS prophylaxis is recommended after consolidation/during maintenance.
19.5.6 Relapsed or Refractory Disease
Management of relapses depends on the specific sub-type of the acute leukaemia, and this should be referred to a specialist at a specialized cancer treatment center for salvage chemotherapy, and consideration for bone marrow stem cell transplant where possible.

19.6 Commonly used Medicines
Anthracyclines and anthracenediones, cytosine arabinoside, methotrexate, etoposide, 6-thioguanine, 6-mercaptopurine, cyclophosphamide, vincristine, L-asparaginase, prednisone/prednisolone, dexamethasone.
In resource limited settings, a combination of doxorubicin or daunorubicin, vincristine, cytosine arabinoside and prednisone is commonly used. Where resources are available, other combinations such as the United Kingdom Acute Leukaemia (UKAL), Linker, Cancer and Leukaemia Group B (CALGB) and Hyper-fractionated cyclophosphomide, vincristine, adriamycin HD dexamethasone (Hyper-CVAD) [+ or – high dose methotrexate and high dose cytosine arabinoside] amongst others, are used. These combinations can only be administered in specialized centers with adequate support facilities.

19.7 Prognosis
Childhood ALL is curable in a majority of cases if treated appropriately whereas adult ALL carries almost as poor a prognosis as AML.
REFERENCES


20. Chronic Leukaemia

Kalebi A, Abwao H, Chite F, Maina M., Othieno-Abinya N.A., Odongo I

20.1 Introduction
The chronic leukaemias are broadly classified into chronic lymphocytic leukaemia (CLL) and chronic myeloid leukaemia (CML) based on the cell lineage they are derived from i.e. lymphocyte and myelopoietic lineages respectively. CML is a myeloproliferative disease characterised by the Philadelphia (Ph) chromosome and/or the BCR/ABL fusion gene from translocation of the ABL gene from chromosome 9 to 22 (9;22) 9934; 911). The disease progresses in three phases: chronic phase (CML-CP), accelerated phase (CML-AP) and blast phase (CML-BP)

20.2 Epidemiology
CLL is the most common leukemia globally and in the western world with an incidence of 4.2/100 000/year, seen in elderly patients with a mean age at diagnosis of 72 years.

20.3 Diagnosis
Clinical Features and Initial Presentations
Patients with the following symptoms (history) should be further evaluated
- Recurrent infections
- Bleeding or easy bruising
- Unexplained Weight loss
- Drenching night sweats
- Persistent fever
- Waxing and waning lymph node enlargement (CLL)
- Swelling and discomfort in the left flank due to massive splenomegally (CML)

The following clinical signs should be looked in a full physical examination:
- Pallor (anaemia)
- Splenomegally
- Hepatomegally
- Bruising (purpura)
- Lymphadenopathy

Laboratory Evaluation
- Full blood count (FBC), with differential count and peripheral blood film examination
- Where the blood count is abnormal, or there are abnormal cells seen on peripheral film, the slides must be reviewed by a specialist pathologist (haematopathologist or clinical pathologist with haematology experience).
- Stained slides and unstained slides should be prepared at site and sent with the whole
V blood in to the pathology laboratory for review, if initially reported by a technologist.

- Bone Marrow Aspirate (mandatory) and trephine (recommended) for diagnosis, with relevant immunophenotyping as applicable.
- Quantitative BCR-ABL assay using polymerase chain reaction (PCR) is mandatory for CML
- Immunophenotyping is recommended for CLL on trephine (immunohistochemistry) or blood (flow cytometry)

The diagnosis of CLL is established by the presence in the peripheral blood of >5000 monoclonal lymphocytes/μl for the duration of at least 3 months. It is recommended that the clonality of the circulating B lymphocytes be confirmed by flow cytometry and also to distinguish from other lymphoid proliferations that can present with leukaemic phase e.g. mantle lymphoma. Small lymphocytic lymphoma (SLL) and CLL are considered to be the same entity. The diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly, with the number of B lymphocytes in the peripheral blood not exceeding 5000. SLL cells show the same immunophenotype as CLL cells so diagnosis is confirmed by histopathological evaluation of a lymph node biopsy.

The hallmark of CML is leukocytosis with basophilia and with immature granulocytes, mainly metamyelocytes, myelocytes and promyelocytes, and few occasional myeloblasts. The diagnosis must be confirmed by cytogenetics tests through polymerase chain reaction (PCR) showing BCR-ABL transcripts.

**Pre-Treatment Risk Assessment**

- Biochemistry including liver and renal function tests, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), urate, and liver enzymes.
- Viral serology for HIV (mandatory), Hepatitis B and Hepatitis C (strongly recommended).

**Radiology & Imaging**

CXR, Abdominal ultrasound/CT Scan and ECG are recommended.

**20.4 Staging and Risk Assessment**

Staging, Treatment and Follow-Up

**Chronic Myeloid Leukaemia**

Staging is not applicable in CML. The Sokal and Hassford scores are not uniformly applied. There are three phases of CML: Stable, Accelerated and Blast crisis. BCR-ABL targeting tyrosine kinase inhibitors are used for treatment of CML, with Imatinib as the standard (Nilotinib and Desanitib are other inhibitors used). Hydroxyurea is an option for patients that cannot access imatinib. Treatment should be given by a specialist at a referral centre.
BCR-ABL monitoring is done for patients on treatment. Blast crisis is managed as acute leukaemia requiring prompt referral and treatment. Allogeneic bone marrow transplant is potentially curative for CML and should be considered where possible.

**Assessment of Response**

**Criteria**

- **Complete Hematologic Response (CHR):** complete normalization of peripheral blood white count (< 10 x 10⁹), and platelet count (< 450 x 10⁹) sustained for at least 4 weeks.
- **Major Cytogenetic Response (MCR):** < 35% Philadelphia positive bone marrow metaphases by conventional cytogenetic analysis. This is equivalent to a 1 log reduction in BCR/ABL transcripts from baseline as measured by quantitative PCR.
- **Complete Cytogenetic Response (CCR):** No Philadelphia positive bone marrow metaphases by conventional cytogenetic analysis. This is equivalent to a 2 log reduction in BCR/ABL transcripts from baseline as measured by quantitative PCR.
- **Major Molecular Response (MMR):** Greater than or equal to a 3 log reduction in BCR/ABL fusion transcripts compared to baseline by PCR analysis.
- **Complete Molecular Response (CMR):** No detectable BCR/ABL transcript.

The goal of therapy is to reach a complete cytogenetic response (> 2 log reduction in BCR/ABL transcripts) and preferably a major molecular response (> 3 log reduction in BCR/ABL transcripts) with minimal toxicity within 18 months of starting therapy.

**Follow-Up Evaluation**

**Tests & Intervals**

- **Full blood count (FBC) and differential -** weekly until CHR, then monthly.
- **Serum creatinine, uric acid, liver function tests -** weekly until stable then monthly.
- **Peripheral blood quantitative PCR -** every 3 months until MMR achieved and maintained for at least 6 months, then quantitative PCR is measured every 6 months, if available.
- **Bone marrow aspirate and biopsy -** at diagnosis, then as clinically indicated.

**Chronic Lymphocytic Leukaemia**

The Modified Rai staging system used for CLL (Hallek, Guidelines for the diagnosis and
### Table 38: Modified Rai Staging Classification

<table>
<thead>
<tr>
<th>RISK CLASSIFICATION</th>
<th>RAI STAGE</th>
<th>FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>0</td>
<td>Peripheral blood lymphocyte count &gt; 5.0 x 10^9 /L. Bone marrow, if done, contains &gt; 30% lymphocytes*</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>1</td>
<td>Stage 0 + lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Stage 0 + hepatomegaly and splenomegaly</td>
</tr>
<tr>
<td>High risk</td>
<td>3</td>
<td>Stage 0 + anemia (Hgb &lt; 110 g/L)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Stage 0 + thrombocytopenia (Platelets &lt; 100 x 10^9 /L).</td>
</tr>
</tbody>
</table>

### Table 39: Binet Classification

<table>
<thead>
<tr>
<th>STAGE</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>&lt; 3 node-bearing areas.</td>
</tr>
<tr>
<td>B</td>
<td>≥ 3 node-bearing areas</td>
</tr>
<tr>
<td>C</td>
<td>Anaemia and/or thrombocytopenia</td>
</tr>
</tbody>
</table>

### 20.5 Management

#### 20.5.1

Treatment is not recommended for asymptomatic patients merely because of lymphocytosis, splenomegaly or lymphadenopathy. An elevated white blood cell count, even to markedly high levels, does not require treatment by itself as long as the hemoglobin and platelet count remain satisfactory, the patient does not become symptomatic and the lymphocyte doubling time remains greater than 6 months. Treatment should be considered for patients who develop one or more of the following, due to the CLL.

1. Anaemia
2. Thrombocytopenia
3. Symptomatic splenomegaly
4. Symptomatic lymphadenopathy
5. Lymphocyte doubling time < 6 months
6. Autoimmune hemolytic anemia
7. Autoimmune thrombocytopenia
8. Otherwise unexplained fatigue or constitutional symptoms sufficient to interfere with work or normal daily activity.

#### 20.5.2

Treatment of advanced stage small lymphocytic lymphoma (SLL) is identical to that of CLL. Chemotherapy options include various combinations of drugs such as fludarabin,
cyclophosphamide, rituximab, bendamustine and chlorambucil which should be prescribed by a specialist at a specialized treatment centre/clinic. Relapsing patients may be given the same combination of drugs aforementioned, whereby the same regimen used on initial treatment can be used if the relapse occurs <12 months; different drugs combinations if <12 months.

20.6 Commonly used Medicines
Imatinib mesylate, hydroxyurea, nilotinib, dasatinib, busulphan, decitabine, interferon-alpha for CML. chlorambucil, cyclophosphamide, fludarabine, anthracyclines/anthracenediones, vincristine, bendamustine, cladribine, pentostatin, lenalidomide, rituximab for CLL. In resource limited settings, chronic myeloid leukaemia should be managed with hydroxylurea monotherapy. Where imatinib is available in an access program, it is the treatment of choice. In resource limited settings cyclophosphamide, vincristine and prednisone (CVP) is also useful. Chronic lymphocytic leukaemia is managed upfront with chlorambucil with or without prednisone. Combinations of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) are also commonly used.

20.7 Prognosis
Chronic myeloid leukaemia is controllable for years with oral medication alone and curable with bone marrow transplant. CLL also runs an indolent course over years, but is incurable.

REFERENCES
21. Lymphomas in Adults

Kalebi A, Abwao H, Chite F, Maina M, Othieno-Abinya NA, Odongo I.

21.1 Introduction
Lymphomas are cancers of lymphocytes that represent clonal proliferation derived from various lymphocytic cell -line, mainly B cells and also T-cells or NK cells at different stages of differentiation and/or activation. These tumours have variable clinical courses depending on the sub-type, typified by accumulation of neoplastic cells in lymph nodes, and may affect extra-lymphoid tissues bone marrow and organs such as the skin, viscera and bone. Lymphomas are broadly classified as Hodgkin’s Lymphoma and Non-Hodgkin’s Lymphoma (NHL).

Classical Hodgkin’s lymphoma (CHL) is characterised by specific abnormal cells called Hodgkin’s cells (if mononuclear), and Reed-Sternberg cells (if bi- or multinucleated), which have characteristic cytology and are admixed with non-neoplastic inflammatory, stromal and accessory cells. The abnormal cells in Hodgkin’s Lymphoma are considered to be derived from germinal centre B cells.

NHL are very heterogeneous comprising over thirty sub-types derived from B- or T-lymphocytes and rarely from NK (natural killer cells).

21.2 Epidemiology
World wide non-Hodgkins lymphomas occur more commonly than Hodgkin’s disease with a male preponderance for both groups. The peak age of occurrence for Hodgkin’s disease tends to be in the teenage and young adults for most populations, whereas for non Hodgkins, there is a wide age distribution depending on the pathological sub-types. Diffuse large B-cell lymphoma (DLBCL) constitutes 30%–60% of lymphoma series worldwide including Kenya. Other lymphomas in order of frequency of occurrence include small lymphocytic lymphoma (SLL), follicular lymphoma and Burkitt’s lymphoma. Below is a clinically oriented classification of the more frequently encountered lymphomas based on similar natural histories, modes of presentation and response to treatment using the terminology of the REAL/WHO classification scheme.
Table 40: Lymphoma types most frequently encountered

<table>
<thead>
<tr>
<th>GRADE</th>
<th>B-CELL</th>
<th>T-CELL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indolent</td>
<td>Small lymphocytic</td>
<td>Mycoses fungoides</td>
</tr>
<tr>
<td></td>
<td>Lymphoplasmacytic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follicular, grade 1, 2 or 3 A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Marginal zone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• MALT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• nodal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• splenic</td>
<td></td>
</tr>
<tr>
<td>Aggressive</td>
<td>Follicular, grade 3</td>
<td>Peripheral T cell, unspecified</td>
</tr>
<tr>
<td></td>
<td>Mantle cell</td>
<td>Peripheral T-cell, specified</td>
</tr>
<tr>
<td></td>
<td>Diffuse large cell+, any type</td>
<td>Angioimmunoblastic (AIL)</td>
</tr>
<tr>
<td></td>
<td>Burkitt’s-like</td>
<td>Nasal T/NK cell</td>
</tr>
<tr>
<td></td>
<td>(small noncleaved cell).</td>
<td>Subcutaneous panniculitic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enteropathy associated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anaplastic large cell (CD30 positive) including</td>
</tr>
<tr>
<td></td>
<td></td>
<td>null cell</td>
</tr>
<tr>
<td>Highly</td>
<td>Burkitt’s</td>
<td>Lymphoblastic</td>
</tr>
<tr>
<td>aggressive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

21.3 Diagnosis
Clinical Features and Initial Presentations

Patients with the following symptoms (history) should be further evaluated:

- Progressive lymph node enlargement
- Unexplained Weight loss
- Drenching night sweats
- Persistent fever

The following clinical signs should be looked at in a full physical examination:

- Pallor (anaemia)
- Lymphadenopathy (All groups of lymph nodes including the Waldeyers
- Splenomegaly Hepatomegally

Pathology
Biopsy

Diagnosis is made through histopathological evaluation of a surgical specimen of the tissue affected, commonly a lymph node excision biopsy.

Fine needle aspirations (FNA) are inappropriate for a reliable diagnosis and may only be done as a screening test.
It is recommended that a surgical excision biopsy of a significantly enlarged lymph node (>2cm) should be carried out in patients clinically suspected to have lymphoma, without a prior FNA, and referred for histopathological evaluation in order to reduce delay in diagnosis as FNA doesn’t add value in such instances.

Core biopsies should only be performed in patients without easily accessible lymph nodes e.g. retroperitoneal or intra-abdominal sites, but are not preferred owing to tissue heterogeneity of lymphomas that warrant full architecture for proper assessment.

* Biopsies should preferably be carried out by designated clinicians who undertake surgical excisions, mainly surgeons or experienced medical officers/physicians.

Request forms accompanying the specimen should have all relevant clinical information and other laboratory test results already done.

The histopathological report should give the diagnosis according to the World Health Organization (WHO – REAL) classification.

**Guidelines on Ancillary Tests**

**NHL Immunohistochemistry**

- For NHL, a minimum of CD45 (pan-) CD20 (B-) and CD3 (T-) cell lymphoid markers should be done as part of the mandatory evaluation.
- Where lymphoblastic lymphoma is suspected, a TDT is mandatory for diagnosis.
- For follicular lymphoma, Bcl2 stain is strongly recommended in addition to the minimum panel of CD45, CD3 and CD20. For Burkitt’s lymphoma, TDT (to exclude ALL) and Ki67 (to exclude Burkitt’s like lymphoma) are strongly recommended in addition to the minimum panel of CD45, CD3 and CD20
- For T-cell lymphomas, CD30 is recommended in addition to the minimum panel of CD45, CD3 and CD20. The latter excludes B-cell lymphoma.

**CHL IMMUNOHISTOCHEMISTRY**

- Immunohistochemistry using CD15 and CD30 is recommended for diagnosis.

**MOLECULAR STUDIES**

Molecular studies are optional investigative modalities that may be helpful in diagnosis where morphology and immunohistochemistry are inconclusive, particularly where they have specific predictive such as T-cell gene rearrangement for confirmation of T-cell lymphoma.

**21.4 Staging And Risk Assessment**

- Full blood count for all lymphomas;
- Bone marrow aspirate is mandatory, and trephine is strongly recommended) for lymphoma staging.
- Erythrocyte sedimentation rate (ESR) for Hodgkin’s lymphoma.
- Biochemistry including liver and renal function tests, lactate dehydrogenase (LDH), urate, alkaline phosphatase (ALP) and liver enzymes.
• Thyroid-stimulating hormone (TSH) is recommended for patients with Hodgkin’s lymphoma.
• Viral serology for HIV (mandatory), Hepatitis B and Hepatitis C (strongly recommended).
• Diagnostic tap (Lumbar puncture) is indicated if there is clinical suspicion of CNS involvement, CNS symptoms or for high-risk blastic leukaemia/lymphoma that have propensity for involving CNS (paranasal sinus, testicular, parameningeal, orbit disease).

21.4.1 Radiology and Imaging
CT-Scan of chest, abdomen and pelvis is strongly recommended.
If CT-scan is unavailable, then CXR and abdomino-pelvic ultrasound should be done.
MRI is the investigation of choice for suspected CNS musculoskeletal and marrow lymphoma. Also, MRI should be the initial investigation in children.

21.4.2 Staging
The internationally adopted staging system for lymphoma is the Ann Arbor system.

Table 41: Ann Arbor Staging Classification for Lymphomas

<table>
<thead>
<tr>
<th>STAGE</th>
<th>INVOLVEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Single lymph node region or one extralymphatic site.</td>
</tr>
<tr>
<td>2</td>
<td>Two or more lymph node regions, same side of the diaphragm or local extralymphatic extension plus one or more lymph node regions same side of the diaphragm.</td>
</tr>
<tr>
<td>3</td>
<td>Lymph node regions on both sides of the diaphragm (3) which may be accompanied by local extralymphatic extension.</td>
</tr>
<tr>
<td>4</td>
<td>Diffuse involvement of one or more extralymphatic organs or sites.</td>
</tr>
</tbody>
</table>

Systemic Symptoms

A = no B symptoms
B = presence of at least one of these

1) unexplained weight loss > 10% baseline during 6 months prior to staging
2) recurrent unexplained fever > 38 o C
3) recurrent night sweats

In addition to the above, note is taken of bulky tumour (measuring more than 10cm in at least one dimension or more than one third of the mediastinum, for mediastinal location)
Further risk assessment and prognostication using International Prognostic Index should be done by the specialist team at the specialized cancer treatment center.
21.5 Management
Treatment strategy should be stratified according to the specific type/grade of lymphoma.

Treatment for Non-Hodgkin's Lymphoma
NHL is a heterogenous group of histological sub-types each requiring tailored therapy, thus referral to a specialized centre for treatment is strongly recommended for the appropriate regimen to be determined.

- DLBL is the commonest sub-type lymphomas for which the standard therapy is CHOP 6-8 cycles. If CD20 positive, Rituximab added to the regimen is highly recommended for each cycle.
- BL is a highly aggressive NHL that is more common in children and HIV positive adults. It requires prompt treatment, whose regimen varies widely and are highly toxic, thus must be handled by specialists in specialized treatment centre.
- Other lymphomas, including apparently low grade lymphomas and skin lymphomas, must be referred to a specialized cancer treatment center for care.

In selected patients, radiotherapy may be used in the treatment of NHL, including palliation.

If there is CNS involvement, proven on CSF cytology, intrathecal chemotherapy and craniospinal radiation is recommended – to be done at a specialized treatment center.

Treatment for Hodgkin's Lymphoma

Limited disease:
- Chemotherapy with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) two cycles followed by involved field radiation therapy.
  - If radiation therapy is unavailable, 2-4 additional cycles of ABVD should be given.

Intermediate disease
- Chemotherapy with ABVD 4 cycles followed by involved field radiation therapy.
  - If radiation therapy is unavailable, 2 additional cycles of ABVD should be given.

Advanced disease
- Chemotherapy with ABVD 6 – 8 cycles should be given.
  - If there are any residual nodes, radiation therapy is recommended

21.5.4 Relapsed or Refractory Disease
Tissue diagnosis through biopsy and histopathological verification should be obtained whenever possible, as this is relevant to rule out transformed disease or new disease. Biopsy is particularly mandatory for suspected relapses >12 months after the initial diagnosis. Immunohistochemical verification is needed.
Laboratory work-up for treatment is similar to that for new disease. Management of relapses depends on the specific histological sub-type of the lymphoma, and this should be referred to a specialist at a specialized cancer treatment center for salvage chemotherapy, which may include bone marrow stem cell transplant.

21.5.5 Follow Up

Most patients with Hodgkin’s lymphoma, especially those below the age of 65 years at diagnosis, can potentially be cured with the treatments described above. Most cured patients experience minimal long-term toxicity from the treatments; however, certain predictable and occasional, rare and unpredictable late effects may occur and require preventive measures and/or recognition and treatment.

Some follow-up tests and examinations should be performed on all patients after treatment of lymphoma. Visits should be every 3 months for 2 years, then every 6 months for 3 years, then annual thereafter. Laboratory tests include FBC and routine chemistry including LDH every 6 months for 2 years, then only as needed for evaluation of suspicious symptoms. TSH monitoring is recommended in patients who have had irradiation to the neck for Hodgkin’s lymphoma at 1, 2 and 5 years. Regular CT scans are not required unless clinically indicated when relapse is suspected from clinical or laboratory test results. The following late effects of Hodgkin’s lymphoma or its treatment should be considered when patients are reviewed in follow-up.
### Table 42: Hodgkin’s Lymphoma

<table>
<thead>
<tr>
<th>RISK/PROBLEM</th>
<th>INCIDENCE/RESPONSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>10% to 30% of patients relapse depending on stage and bulk of presentation. Careful attention should be directed to Z lymph node sites, especially if previously involved with disease.</td>
</tr>
<tr>
<td>Dental caries</td>
<td>Neck or oropharyngeal irradiation may cause decreased salivation. Patients should have careful dental care follow-up and should make their dentist aware of the previous irradiation.</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Follows external beam thyroid irradiation in at least 50% of patients treated for Hodgkin’s lymphoma. Thyroxine replacement therapy to maintain euthyroidism is recommended.</td>
</tr>
<tr>
<td>Infertility</td>
<td>Current chemotherapy regimens and radiation fields used don’t cause infertility problems, except for direct radiation to gonads. In general, after treatment, women who continue menstruating are fertile, but men may require semen analysis to provide a specific answer.</td>
</tr>
<tr>
<td>Secondary neoplasms</td>
<td>Although uncommon, certain secondary neoplasms occur with increased frequency in patients who have been treated for Hodgkin’s lymphoma. These include acute myelogenous leukemia, thyroid, breast, lung and upper gastrointestinal carcinoma and melanoma and cervical carcinoma-in-situ. It is appropriate to screen for these neoplasms for the rest of the patient’s life because they may have a lengthy induction period.</td>
</tr>
</tbody>
</table>

#### 21.5.6 Palliation

Refer to Chapter 40

#### 21.6 Commonly used Medicines

Doxorubicin, cyclophosphamide, chlorambucil, vincristine, dacarbazine, bleomycin, methotrexate, cytosine arabinoside, procarbazine, prednisone/prednisolone, dexamethasone, etoposide, rituximab, vinblastine, mustine hydrochloride, vinorelbine, gemcitabine, mitoxantrone, bendamustine, fludarabine, oxaliplatin, cladribine, cisplatin, bortezomib, thalidomide, temsirolimus, lenalidomide, methylprednisolone, carmustine, melphalan.
For Hodgkin’s lymphomas, a combination of Doxorubicin, bleomycin, vinblastine and dacarbazin is standard in all settings. If not feasible, then a combination of cyclophosphamide, vincristine, prednisone and procarbazine (COPP) can be used. For non-Hodgkin’s lymphomas of aggressive phenotype the CHOP protocol is still standard even in resource limited settings. Where resources are available, rituximab is added to CHOP (R-CHOP) for the B cell group. For the indolent sub-group, chlorambucil with or without prednisone, can be given upfront, but other combinations including CHOP can be used.

21.7 Prognosis

Hodgkin’s disease generally runs a good prognosis. Non-Hodgkins lymphomas consist of 70 different sub-types with varying prognosis.

REFERENCES


22. Myeloma

Kalebi A, Abwao H, Chite F, Maina M., Othieno-Abinya N.A.

22.1 Introduction

Myeloma is a cancer of plasma cells

22.2 Epidemiology

It is a disease that occurs almost exclusively in the middle-aged to elderly population all over the world with a male preponderance.

22.3 Diagnosis

Clinical Features & Initial Presentations

Patients with the following symptoms (history) should be further evaluated

- Bone pain
- Fractures following trivial trauma (pathological)

The following clinical signs should be looked in a full physical examination:

- Pallor (anaemia)
- Bone tenderness
- Repeated infections
- Vertebral collapse/spinal cord compression

Laboratory Evaluation

- Full blood count (FBC) and erythrocyte sedimentation rate (ESR)
- Bone Marrow Aspirate (mandatory) and trephine (recommended) for diagnosis
- Serum protein electrophoresis with quantification
- Urea, creatinine and electrolytes

The diagnostic criteria of myeloma by the International Myeloma Working Group (Anonymous BJ Hematology 2003; 121:749-757). All three of the following must be present:

1. Monoclonal paraprotein.
2. Bone marrow plasmacytosis or biopsy proven plasmacytoma.
3. At least one end organ consequence not due to another detectable cause (note mnemonic CRAB)
   - Hypercalcemia
   - Renal failure
   - Anaemia
   - Lytic Bone lesions

The following additional findings can be helpful supportive evidence for the diagnosis of myeloma if present:

- depression of the levels of the uninvolved immunoglobulins
Remember that 2-5% of myeloma patients have no abnormal protein detectable in urine or serum, so-called non-secretory myeloma. Such cases should be accepted as myeloma only if criteria 2 and 3 above are present plus lytic bone lesions or two of the CRAB criteria. For such patients a serum free light chain level test should be requested as a significant number of these patients will have abnormal values.

- Biochemistry including liver and renal function tests, alkaline phosphatase (ALP), calcium, albumin, B2 microglobulin
- Viral serology for HIV (mandatory), hepatitis B and hepatitis C (strongly recommended).

**22.4.1 Radiology and Imaging**

Skeletal survey (X-ray).
- CT of a specific area is required for decisions concerning radiotherapy and/or surgery, or if extraosseous plasmacytoma is suspected.
- MRI, without and with contrast, of the cervical, thoracic, and lumbar spine and pelvis.

Any other imaging is as per the clinical presentation.

Nuclear bone scan is not relevant in multiple myeloma.

Both the traditional Durie and Salmon staging and the International Staging System (ISS) (Greipp, J Clin Oncol, 2005;23:3412) are widely in use.

**Table 43: Myeloma - Durie Salmon Staging**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hgb &gt; 10 g/dl Calcium &lt; 2.88 mmol/L Bones = no more than 1 lytic lesion</td>
</tr>
<tr>
<td></td>
<td>M-protein: IgG &lt; 50 g/L IgA &lt; 30 g/L</td>
</tr>
<tr>
<td></td>
<td>Total urinary light chain &lt; 4 g/24 h</td>
</tr>
<tr>
<td>2</td>
<td>Between 1 and 3</td>
</tr>
<tr>
<td>3</td>
<td>Any one of these:</td>
</tr>
<tr>
<td></td>
<td>Hgb &lt; 85 g/L Calcium &gt; 2.88 mmol/L Bones = multiple lytic lesions</td>
</tr>
<tr>
<td></td>
<td>M-protein: IgG &gt; 70 g/L IgA &gt; 50 g/L</td>
</tr>
<tr>
<td></td>
<td>Total urinary light chain &gt; 12 g/24 h</td>
</tr>
<tr>
<td></td>
<td>A = creatinine &lt; 180 mmol/L</td>
</tr>
<tr>
<td></td>
<td>B = creatinine &gt; 180 mmol/L</td>
</tr>
</tbody>
</table>
Table 44: Myeloma International Staging System

<table>
<thead>
<tr>
<th>STAGE</th>
<th>FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Serum beta-2microglobulin &lt; 35 g/L and serum albumin ≥ 35 g/L</td>
</tr>
<tr>
<td>2</td>
<td>Serum beta-2microglobulin &lt; 35 g/L and serum albumin &lt; 35 g/L or Serum beta-2microglobulin 35 to &lt; 55 g/L</td>
</tr>
<tr>
<td>3</td>
<td>Serum beta-2microglobulin ≥ 55 g/L</td>
</tr>
</tbody>
</table>

22.5 Management

Chemotherapy options include various combinations of drugs such as Thalidomide, Melphalan, Dexamethasone, Lenalidomide, and Bortezomib which should be prescribed by a specialist at a specialized treatment centre/clinic.

Local radiation should be considered for patients with any of the following:

- A symptomatic lytic bone lesion or soft tissue plasmacytoma which is not responding to systemic treatment.
- Threatening or actual pathological fracture.
- Spinal cord compression (recall that spinal cord compression is an emergency; a radiation oncologist should be contacted immediately to discuss treatment plans)

Biphosphonate is strongly recommended in patients with bone disease.

Autologous and allogeneic transplant are treatment options that can be considered where possible. Melphalan should not be used in transplant eligible candidates.

Assessment of Treatment

Criteria for Adequate Response

- Reduction of serum paraprotein to less than 50% of the pretreatment level and urine paraprotein to less than 10% of pretreatment level is required to be considered a partial remission.
- Improvement or stabilization of bone marrow function.
- Improvement or stabilization of kidney function.
- Normalization of serum calcium.
- No new osseous or extra-osseous lesions.
- Resolution of all symptoms.

Criteria for Relapse or Progression

- Progressive rise in level of paraproteinemia and/or paraproteinuria by more than 25%.
- Development of hypercalcemia.
- Appearance of new osseous or extra-osseous lesions.
- Progressive bone marrow failure.

Development of anemia, thrombocytopenia or neutropenia singly or in combination usually reflects one of two problems, drug toxicity or progressive disease. Concurrent
assessment of bone marrow (aspiration + biopsy) and paraproteins (serum + urine) will usually resolve the question. If progressive disease, bone marrow examination shows heavy infiltration with abnormal plasma cells and rising paraprotein levels. If drug toxicity, bone marrow examination shows hypocellular marrow, usually with residual myeloma. Paraprotein levels are either falling or remaining stable. Pancytopenia developing unexpectedly in patients on long-term therapy with alkylating agents may be due to secondary leukemia or myelodysplasia.

The development of a falling paraprotein level and separate signs of progressive disease (such as new bone lesions) suggest that the myeloma is becoming non-secreting and the paraprotein may not be as useful to follow disease. For such patients, serum free light chain levels may be helpful to follow disease.

**Duration of Treatment**

For non-transplant eligible patients, initial treatment may be stopped after attainment and maintenance of the deepest response for at least four months. Treatment should be changed to secondary regimens if progressive disease develops during primary treatment. If treatment has been stopped because of an adequate response it should be resumed on the first objective evidence of progressive disease.

**Table 45: Evaluation during treatment**

<table>
<thead>
<tr>
<th>TESTS</th>
<th>INTERVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC with platelets serum creatinine, calcium</td>
<td>1 month</td>
</tr>
<tr>
<td>Serum protein electrophoresis (if available).</td>
<td></td>
</tr>
<tr>
<td>Urine 24hr protein</td>
<td>3 monthly (if it’s the only means of detecting abnormal protein)</td>
</tr>
<tr>
<td>Skeletal survey</td>
<td>at least once yearly or as clinically indicated</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>only as needed to assess marrow function</td>
</tr>
</tbody>
</table>

**Evaluation Off treatment**

The same tests should be performed as when the patient is on treatment, but the interval can be up to 3 months between lab tests and yearly for the skeletal surveys, as indicated.

**Palliation and End of Life**

*Refer to Chapter 42*
22.6 Commonly Used Medicines
Melphalan, prednisone, thalidomide, dexamethasone, bortezomib, lenalidomide, doxorubicin, vincristine, cyclophosphamide, BCNU, arsenic trioxide.
In resource limited settings, combination of melphalan and prednisone is standard treatment. Vincristine, doxorubicin and dexamethasone can also be used as a first line regimen.
Where resources are available, patients should be started on thalidomide or lenalidomide and dexamethasone or cyclophosphamide and dexamethasone followed by bone marrow or peripheral blood stem cell transplant.

22.7 Prognosis
Multiple Myeloma runs a chronic and variable course and is incurable unless allogeneic bone marrow transplant is performed.

REFERENCES
23. Head and Neck Cancers

Opiyo A, Obura H, Macharia I, Guthua S, Kiarie G, Shah H, Kalebi A, Adamali A

23.1 Introduction

Head and neck cancers include a heterogeneous group of malignant tumours arising in all structures cephalad to the clavicles, except for the brain, spinal cord, base of the skull and usually the skin. A meaningful understanding of these malignant tumours requires anatomic separation into those cancers arising in the oral cavity, oropharynx, hypopharynx, larynx, nasal fossa, paranasal sinuses, thyroid and salivary glands.

23.2 Epidemiology

- Cancers arising in the head and neck constitute about 3% of all newly diagnosed cancers worldwide, but in Kenya, they contribute about 10% of all cancers. This is largely contributed by the high prevalence of nasopharyngeal cancers in the region.
- In 2007, an estimated 45,500 newly diagnosed cancers of the oral cavity, pharynx, and larynx resulted in 11,200 related deaths.
- Cigarette smoking and substantial alcohol intakes are the major risk factors.
- 20% those who survive cancer of the head and neck cancer will develop another head and neck primary.

Prevention includes

- Abstinence from the use of alcoholic beverages and tobacco is recommended.
- Elimination of chronic irritants, such as an irregular sharp tooth or ill-fitting denture, is desirable.
- Appropriate, life style modification is recommended.

23.3 Diagnosis

23.3.1 Common symptoms and signs

- Painless mass
- Local ulceration with or without pain
- Referred pain to teeth or ear
- Dysphagia
- Alteration of speech, such as difficulty pronouncing words (tongue) or change in character (larynx, nasopharynx)
- Persistent hoarseness (larynx)
- Unilateral tonsillar enlargement in an adult
- Persistent unilateral “sinusitis”
- Persistent unilateral nosebleed or obstruction
- Unilateral hearing loss
- Cranial nerve palsies
- Loosening of the teeth
23.3.2 **Physical examination**
Complete physical examination with special emphasis on the ear, nose, oral cavity, pharynx and neck with emphasis on presence and location of swellings, ulcers and neurological defects.

23.3.3 **Indications for referral**
- Red or red and white patches of the oral mucosa which persist for more than three weeks at any particular site.
- Ulceration of oral mucosa or oropharynx which persists for more than three weeks.
- Oral swellings which persist for more than three weeks.
- Unexplained tooth mobility not associated with periodontal disease.
- Persistent, particularly unilateral, discomfort in the throat for more than four weeks.
- Pain on swallowing persisting for three weeks that does not resolve with antibiotics.
- Dysphagia which persists for more than three weeks.
- Hoarseness which persists for more than three weeks.
- Stridor (requires same day referral).
- Unresolved head or neck mass which persists for more than three weeks.
- Unilateral serosanguineous nasal discharge which persists for more than three weeks particularly with associated symptoms.
- Facial palsy, weakness or severe facial pain or numbness.
- Orbital masses.
- Ear pain without evidence of local ear abnormalities.

23.3.4 **Pathology.**
- All primary and metastatic cancers must be documented histologically or cytologically. Additional investigations such as immunohistochemistry may be required to confirm the diagnosis.
- FNA cytology is advised for cervical masses as a screening test to be confirmed by histology if malignant.
- Open biopsies of metastatic neck disease is not recommended.
- In some circumstances, where there is cervical lymph node metastasis and no obvious primary tumour found on physical or imaging examinations, guided biopsies of regions drained by the nodes are appropriate.
23.3.5 Imaging
- Chest x-rays and other relevant x-rays remain part of the evaluation,
- Computed tomography (CT) or/and Magnetic resonance imaging (MRI) from the base of skull to the thoracic inlet are essential in establishing the local or regional extent of the tumour.
- Ultrasound should be considered in determining the nature of the neck mass.

23.3.6. Endoscopy.
- Visualization of the oral cavity, nasal cavity, nasopharynx, oropharynx, hypopharynx, larynx, cervical oesophagus, and trachea is essential in establishing the presence and extent of tumour.
- Biopsies should be done at the time of endoscopy if a lesion is identified.

23.3.7 Evaluation of masses in the neck.
- A firm, usually non-tender mass or masses, in the head and neck, either unilateral or bilateral, especially in adults should raise suspicion of cancer.
- Before a neck mass biopsy is done, a search for the primary cancer in the head and neck region should be done.
- Initial direct biopsy of suspicious, enlarged cervical lymph node should be done by fine-needle aspiration.

23.4 Staging and Risk Assessment
- Staging should be based on clinical information, imaging, endoscopy or information found at surgery. Clinical staging determines the treatment strategy.
- Blood investigations including total blood count, U/E/C, LFT and HIV test are recommended.
- The TNM system proposed by the AJCC/UICC is the most frequently used system.
Table 46: TNM Staging for Head and Neck Cancer

<table>
<thead>
<tr>
<th>PRIMARY TUMOUR (T)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour &lt; 2 cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour &gt; 2 cm but &lt; 4 cm</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour &gt; 4 cm</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour invades adjacent structures (defined under specific site)</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumour invades adjacent structures, but is potentially resectable</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumour invades adjacent structures, but is unresectable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, &lt; 3 cm</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in single ipsilateral lymph &lt; 3 cm but &lt; 6 cm</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none &gt; 6 cm</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none &gt; 6 cm</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node &gt; 6 cm in greatest dimension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant metastasis (M)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mx</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>
Table 47: Stage groupings for Head And Neck Cancers

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T1-3</td>
<td>N1</td>
<td>M0, T3</td>
</tr>
<tr>
<td>IVA</td>
<td>T4a</td>
<td>N0-2</td>
<td>M0, T1-3</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>IVC</td>
<td>Any T</td>
<td>any N</td>
<td>M1 (advanced distant, metastatic disease).</td>
</tr>
</tbody>
</table>

Notes

a Excludes nasopharynx cancers

b N staging, M staging I T1 N0 M0, and stage groupings are identical for the other carcinomas, of the head and neck (lip, oral cavity, oropharynx, hypopharynx, larynx, nasal cavity, paranasal sinuses, and major salivary glands)

c T staging for carcinomas of the hypopharynx and major salivary glands has the same definitions for tumour size but also depends on local tumour extension

d Carcinomas of the larynx and paranasal sinuses have specific definitions for all T stages that depend on tumour location rather than on tumour size.

Adapted from the AJCC Cancer Staging Manual.

23.5 Management

Before commitment to a management program for a specific patient, there should be input from all members of the multidisciplinary oncology team (Surgeons, radiation oncologists, medical oncologists, dentists, nurses, social workers, and rehabilitation personnel.)

Based on the stage of disease, treatment of the primary tumour may include removal of the tumour and its local and regional extensions.

Management of the primary cancer

1. T1 and T2 primary cancers ,
   - Single modality using surgery or radiation treatment (RT) is recommended.
     - The choice of treatment may be influenced by tumour site, accessibility, histological grade, the patient’s health status, vocation, or preference.

2. T3 and T4 primary cancers
   - A combination of surgery, RT and chemotherapy is recommended.
   - If resection is not possible, high dose RT and adjuvant chemotherapy may be useful.

23.5.1 Surgical Management

- En block dissection of the primary should be attempted whenever feasible.
- Surgical dissection should be planned based on the extent of the primary tumour as defined by clinical examination and appropriate radiographic images.
Principal goal of oncologic surgery is complete tumour resection with histologic verification of tumour free margins.

Ipsilateral neck dissection is recommended for patients undergoing surgery for the primary tumour.

Bilateral neck dissection is recommended for lesions that approximate or cross midline and those with bilateral node involvement.

In continuity, en block tumour resection and neck dissection should be done where feasible.

### 23.5.2 Radiotherapy

- Radiotherapy is indicated in many cancers of the head and neck often with better cosmetic and functional outcomes.
- In treatment of primary cancer of the head and neck, radiotherapy is used as the initial and possibly only therapy, sometimes substituting surgery for resectable tumours for preservation of organs and functions.
- Adjuvant radiotherapy is indicated for use before or after surgery in presence of close or inadequate resection margins, poorly differentiated cancers, involvement of lymphatics including cervical nodes and perineural invasion.
- Combined chemoradiotherapy is the treatment of choice in most of the T3 T4 tumours.
- Tumour control and toxicity is related to the radiation technology, technique and chemotherapy options used.
- Decision on whether to use radical or palliative radiotherapy should be based on the extent of the disease.

### 23.5.3 Chemotherapy

- The choice of chemotherapy should be individualised based on patient's characteristics performance status and goals of treatment.
- The standard therapy for patients with locally advanced disease remains is concurrent cisplatin and RT.
- Concurrent chemoradiotherapy using Cisplatin alone, Cisplatin with 5-FU, and Carboplatin with 5-FU in patients with locally advanced SCCHN has a statistically significant improvement in overall survival.
- The cisplatin based induction chemotherapy can be used followed by radiation based locoregional treatment (that is sequential chemo- RT).

**Occult Primary Cancer**

If the primary has not been identified it is recommended to treat the neck disease appropriately as the search for the primary continues.
23. 5. 6 Supportive Management
Nutritional management including assessment, counselling and supplementary feeding is very important in head and neck cancer patients many of who lose weight as a result of their disease, health behaviours and treatment related toxicities. Prophylactic feeding tube placement should be strongly considered for patients with:
- Severe weight loss prior to treatment, 5% weight loss over prior 1 month, or 10% weight loss over 6 months;
- Ongoing dehydration or dysphagia, anorexia, or pain interfering with the ability to eat/drink adequately;
- Significant comorbidities that may be aggravated by poor tolerance of dehydration, lack of caloric intake, or difficulty swallowing necessary medications;
- Severe aspiration; or mild aspiration in elderly patients or in patients who have compromised cardiopulmonary function; or
- Patients for whom longterm swallowing disorders are likely, including those anticipated to receive large fields of highdose radiation to the mucosa and adjacent connective tissues. However, consideration of other risk factors for swallowing dysfunction must be taken into account as well.

Maintenance of swallowing and speech functions is very important especially in cases where these functions have been compromised by the disease process.

Adverse effects of treatment.
All treatments of cancer, even when properly administered by current standards, may have unintended adverse consequences including cosmetic changes, functional disabilities, inflammatory changes.

Local, regional or metastatic recurrence.
- Persistent or ‘recurrent’ cancers usually occurs within 2 years of completion of treatment
- Surgery or re-irradiation may be considered.
- In most cases palliative treatment only will be required.
- Referral to a centre with advanced facilities is recommended.
- The standard care for patients with recurrent unresectable disease in a previously irradiated field is palliative chemotherapy.

23.5. 6 Follow Up
- The aim of follow up is the early detection of the potential curable locoregional recurrence and second primary tumours.
- Physical examination along with radiological imaging should be included in the follow up.
- Treatment response should be evaluated by clinical examination, CT scan or MRI of the head and neck depending on the procedure.
• Chest X-ray should be included.
• If available, PET scanning may be useful in the presence of doubtful findings particularly after combined chemoradiation.
• Special attention should be paid to the treatment sequelae that include swallowing and respiratory impairment and nutritional status.
• After chemoradiation or radiotherapy, appropriate clinical assessment should be undertaken 4 to 8 weeks.
• Further follow up should be done 3 monthly for the first year, 4 monthly for the second year, 6 monthly from year 3 to 5 and thereafter annually.
• Evaluation of thyroid function tests in patients with irradiation to the neck is recommended at 1, 2, and 5 years.

23.5.8 Palliative care
All modalities of treatment should be considered as options for the palliation of head and neck cancer.
• Palliative Chemotherapy
  - Patients of adequate performance status should be considered for palliative chemotherapy which may reduce tumour volume.
  - Single agent methotrexate, single agent cisplatin, or cisplatin/5FU combination should be considered for palliative chemotherapy in patients with head and neck cancer.
  - Excessive toxicity from intensive chemotherapeutic combination regimes should be avoided.
• Palliative Radiotherapy
  - Radiotherapy may be considered for palliative treatment in patients with locally advanced, incurable head and neck cancers.
• Palliative Surgery
  - Appropriate surgical procedures should be considered for palliation of particular symptoms, taking local expertise into consideration.

23.6 Commonly Used Medicines
Cisplatin, 5-fluorouracil, cetuximab, docetaxel, epirubicin, bleomycin, carboplatin, oxaliplatin, mitomycin-C, paclitaxel, methotrexate, capecitabine, ifosfamide, gemcitabine, erlotinib.
In resource limited settings, 5FU can be used with or without cisplatin. Where resources are available, cisplatin and taxanes are preferred.

23.7 Prognosis
These are different types' cancers with varying prognosis depending on site and stage.
REFERENCES


24. Nasopharyngeal cancer


24.1 Introduction

Nasopharyngeal cancer arises in the fossa of Rosenmuller in the nasopharynx and spreads directly into the lymph nodes of the neck and anterior and superior to the upper airways and base of skull. It carries a much better prognosis than the rest of head/neck cancers despite the fact that it is usually diagnosed late.

24.2 Epidemiology

Though rare in developed countries but it is common in Eastern and Southern Africa and Asia. It is by far the commonest head and neck malignancy in Kenya. Distinct racial, ethnic and geographical distribution is important in etiology. There is an interaction between genetic predisposition and environmental pollution. Smoking, alcohol consumption and Epstein Barr Virus (EBV) virus infection are important factors in its causation. Incidence is higher in men than women.

24.3 Diagnosis

24.3.1 Symptoms

- Neck Swelling
- Nasal Blockage
- Bloody Nasal Discharge/Epistaxis
- Unilateral hearing loss
- Ear Blockage
- Facial pains and paraesthesia

Complete physical examination with special emphasis on ear, nose, throat and head and neck is important.

Imaging – Similar to head and neck cancers.

24.3.2 Pathology

- Definitive diagnosis is made by biopsy of the nasopharyngeal tumor obtained by endoscopic examination or examination under anesthesia.
- The histological type should be classified according to World Health Organization criteria.
- Immunohistochemistry may be done for tumour classification and Epstein Barr Virus (EBV) identification.
- Neck biopsy and/or neck nodal dissection is not recommended since it may reduce cure probability and have an impact on late treatment sequelae.
24.4 Staging and Risk Assessment

- NPC is clinically staged according to the International Union against Cancer (UICC) and American Joint Committee on Cancer (AJCC) staging system.
- Routine staging procedures include history, physical examination including cranial nerve examination, complete blood cell count, serum biochemistry (including liver function test), chest X-ray, nasopharyngoscopy, computed tomography (CT) scan or magnetic resonance imaging (MRI) of nasopharynx and base of skull and neck.
- MRI is generally preferred if available for use in staging.
- Imaging for distant metastases including isotope bone scan and CT scan of chest and upper abdomen could be considered for at-risk subsets (node positive, especially N3 stage) and for those patients with clinical or biochemical abnormalities detected.
- Positron emission tomography (PET) CT scan if available can be used for detection of distant metastatic disease.

Table 48: TNM Staging for Nasopharyngeal Carcinoma

<table>
<thead>
<tr>
<th>TX</th>
<th>Primary tumour cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour confined to nasopharynx</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour extends to tissues of oral pharynx or nasal</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades bony structure or paranasal sinuses</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour with intracranial extensions or involvement of cranial nerves, infratemporal fossa, hypopharynx, masticator space or orbit.</td>
</tr>
</tbody>
</table>

Regional lymph nodes (N)

<table>
<thead>
<tr>
<th>Nx</th>
<th>Regional lymph nodes cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No regional node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Unilateral metastasis in lymph nodes less than 6cm above supraclavicular fossa</td>
</tr>
<tr>
<td>N2</td>
<td>Bilateral metastasis in lymph nodes less than 6cm above supraclavicular fossa.</td>
</tr>
<tr>
<td>N3a</td>
<td>Metastasis in a lymph node &gt; 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N3b</td>
<td>Extension to supraclavicular fossa.</td>
</tr>
</tbody>
</table>

Distant metastasis (M)

<table>
<thead>
<tr>
<th>Mx</th>
<th>Distant metastasis cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis.</td>
</tr>
</tbody>
</table>
Table 49: Stage groupings for Head and Neck Cancers

<table>
<thead>
<tr>
<th></th>
<th>TI</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T1, 2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T1-3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1,</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T4</td>
<td>any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

24.5 Management

- Radiation therapy (RT) is the mainstay of treatment and is an essential component of curative-intent treatment of non-disseminated NPC.
- Stage I disease is treated by RT alone, while stage II, III, IVA, IVB disease are treated by chemoradiotherapy.
- Use of 3-D conformal radiotherapy/intensity-modulated radiation therapy (IMRT) is recommended if available to reduce toxicity and improve on accuracy of treatment.
- Elective nodal irradiation is recommended for N0 stage disease.
- Use of concurrent chemotherapy-RT is recommended as this provides benefit in overall survival and both loco regional and distance control.
- Cisplatin based induction chemotherapy improves disease-free survival and may be considered in locally advanced disease.

24.5.1 Follow-up

- Documentation of complete remission in the nasopharynx and neck through clinical and endoscopic examination and/or imaging studies is important.
- CT/MRI is often used to evaluate the response to RT or chemoradiotherapy, especially for T3 and T4 tumors.
- Follow-up for patients includes periodic examination of the nasopharynx and neck, cranial nerve function and evaluation of systemic complaints to identify distant metastasis. For T3 and T4 tumors, MRI /Endoscopy might be used on a 6- to 12-monthly basis to evaluate the nasopharynx and the base of the skull at least for the first few years after treatment.
- Evaluation of thyroid function (TSH) in patients with irradiation to the neck is recommended at 1, 2 and 5 years.

24.5.2 Treatment of Recurrent or Metastatic disease

- Small local recurrences should be treated using the following options: nasopharyngectomy, brachytherapy, radiosurgery, stereotactic RT, IMRT or a combination of surgery and RT, with or without concurrent chemotherapy.
- Regional recurrence is managed by radical neck dissection if resectable and the primary is controlled.
- In metastatic NPC, palliative chemotherapy should be considered for patients with adequate performance status.
24.6 Commonly Used Medicines
Cisplatin, 5-fluorouracil, cetuximab, docetaxel, epirubicin, bleomycin, carboplatin, oxaliplatin, mitomycin-C, paclitaxel, methotrexate, capecitabine, ifosfamide, gemcitabine, erlotinib.
In resource limited settings, 5FU monotherapy can be used, but Platinum combination regimens, with or without taxanes are prefered as first line therapy.

24.7 Prognosis
Early nasopharyngeal carcinoma carries a reasonably good prognosis.

REFERENCES
25. Oral Squamous Cell Carcinoma

Dimba EAO, Guthua SW.

25.1 Introduction
Oral squamous cell carcinoma (OSCCA) is the most common malignancy of the oral cavity. Cancers arising from the epithelial linings of the oral cavity and upper aerodigestive tract constitute over 90% of neoplasms within this anatomical area. Other cancers, such as minor salivary gland tumours and lymphomas more commonly present as masses but can also occur as an ulcer, which is the typical clinical appearance of OSCCA. Approximately 97% of cancers in the oral cavity are histologically proven cases of OSCCA; adenoid cystic carcinomas constitute 2%, while the remaining 1% is other cancers such as osteosarcoma, lymphoma, fibrosarcoma and Kaposi’s sarcoma.

25.2 Epidemiology
Oral squamous cell carcinoma characteristically affects older males but the incidence in women and in younger adults is increasing. Lifestyle factors, specifically the habitual use of tobacco and alcohol have a synergistic or multiplicative effect on the levels of risk in development of oral cancer. Cultural habits such as betel quid or areca nut chewing also increase risk in some populations. The main risk factor for cancer of the lip is exposure to ultraviolet light. There is a growing body of evidence for the role of particular strains of human papilloma viruses (HPVs) in oropharyngeal cancers, HPV 16 DNA being consistently demonstrated in over 70% of biopsies derived from such cancers. Nutritional deficiencies also contribute to the incidence of oral squamous cell carcinoma, with the absence of vitamins A, C and E which are important for mucosal integrity increasing the risk of malignant transformation of the epithelium. Other risk factors include the presence of potentially malignant lesions of the oral mucosa, such as erythroplakia and leukoplakia and various general mucosal disorders in which mucosal atrophy occurs.

Given the strong association of this cancer with habits such as alcohol and tobacco consumption, public health approaches involving the reduction of consumption of these substances at the primary levels tend to constitute the most effective method of reducing the incidence of oral cancers.

25.3 Diagnosis
Oral squamous cell carcinoma typically presents as a non-healing painless ulcer, although varying presentation in the early stages can lead to misdiagnosis. Carcinoma may develop in clinically normal mucosa or in an area of clinically altered oral mucosa such as leukoplakia and erythroplakia, which are by definition white or red lesions exhibiting histological features of dysplastic change on microscopic examination. In advanced cases, infiltration of the malignant growth beneath the oral mucosa results in palpable induration around the ulcer or a mass that may ulcerate through the skin or cause
fixation of mobile oral tissues. Neural involvement may cause pain and paraesthesia. Additional symptoms are trismus, dysphagia, dysphonia, halitosis and enlarged lymph nodes.

A systematic oral/peri-oral examination in combination with imaging is mandatory for patients presenting with oral ulcerations so as to properly identify oral cancers. The radiographic estimate of deep tissue extension and nodal involvement is usually more accurate than clinical inspection and palpation. Panoramic radiographs may need to be supplemented by computed tomography (CT), magnetic resonance imaging (MRI) and ultra-sound scans. Several experimental trials are ongoing to evaluate methods for rapid diagnosis and early detection of oral squamous cell carcinoma. These new methodologies include diaelectrophoresis, a non-invasive method of determining electrophysiological parameters of cellular cytoplasm.

25.4 Staging And Risk Assessment
The gold standard for staging is the pTNM system, where p indicates pathology, which is currently considered in tandem with tumour characteristics, extent of nodal involvement and metastases (Tables 47).

Table 50. TNM classification of lip and oral cavity carcinomas

<table>
<thead>
<tr>
<th>TNM PARAMETER</th>
<th>CODE</th>
<th>CLINICAL OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumour (T)</td>
<td>TX</td>
<td>Primary tumour cannot be assessed.</td>
</tr>
<tr>
<td></td>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td></td>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>Tumour &lt; 2 cm in maximum dimension</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>Tumour &gt; 2 cm in maximum dimension</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>Tumour &gt; 4 cm in maximum dimension</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>Tumour invades into adjacent structures</td>
</tr>
<tr>
<td>Regional lymph nodes (N)</td>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td></td>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td></td>
<td>N1</td>
<td>Metastasis to a single ipsilateral lymph node &lt; 3 cm in maximum dimension</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>Metastases in single ipsilateral, bilateral or contralateral lymph nodes</td>
</tr>
<tr>
<td></td>
<td>N3</td>
<td>Metastases to a lymph node &gt; 6 cm in diameter</td>
</tr>
<tr>
<td>Metastases (M)</td>
<td>MX</td>
<td>Presence of metastases cannot be assessed</td>
</tr>
<tr>
<td></td>
<td>M0</td>
<td>No distant metastases</td>
</tr>
<tr>
<td></td>
<td>M1</td>
<td>Distant metastases present</td>
</tr>
</tbody>
</table>
25.5 Management
Prognostication and treatment of OSCCA is based on the TNM staging. Surgical resection remains the main method of curative management in oral squamous cell carcinomas, partnered with adjunctive radiotherapy and chemotherapy regimens.

Table 51: Staging and treatment of OSCCA

<table>
<thead>
<tr>
<th>STAGE</th>
<th>TNM GROUPING</th>
<th>MODE OF MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis, N0, M0</td>
<td>Surgery and close monitoring</td>
</tr>
<tr>
<td>1</td>
<td>T1, N0, M0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>T2, N0, M0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>T3, N0, M0/ T1, T2, M0</td>
<td>Surgery and chemo/radiotherapy</td>
</tr>
<tr>
<td>4</td>
<td>T4, N0, M0/ any mets (M1)</td>
<td>Surgery, chemo/radiotherapy and palliative treatment.</td>
</tr>
</tbody>
</table>

25.6 Commonly Used Medicines
Cisplatin, 5-fluorouracil, cetuximab, docetaxel, epirubicin, bleomycin, carboplatin, oxaliplatin, mitomycin-C, paclitaxel, methotrexate, capecitabine, ifosfamide, gemcitabine, erlotinib.
In resource limited settings, 5FU can be used with or without cisplatin. Where resources are available, cisplatin and taxanes are preferred.

25.7 Prognosis
Prognosis is good with a mean 5-year survival rate of 80% for Stage 1 and 2 disease. However, in the case of advanced disease (Stage 3 - 4) survival rates range between 20 - 40%.
REFERENCES


26. Lung Cancer

Ogendo SW, Othieno-Abinya, Nyongesa CN, Musibi AM, Waweru W.

26.1 Introduction
The most common forms of primary lung cancer arise from bronchial epithelium. There are two types of primary lung cancer, non-small cell type (NSCLC) accounting for 80% of cases and small cell lung cancer (SCLC). The latter usually results from smoking and rarely affects non-smokers. The main difference between NSCLC and SCLC is that the latter grows, and spreads rapidly and has nonmetastatic endocrine effects. This property ultimately affects its treatment options.

26.2 Epidemiology
Lung cancer incidence is one of the highest accounting for 12.7% of all cancers worldwide. Disease incidence varies greatly with highest rates in United States and Europe (46.8 – 81/100,000) and lowest in the African region (2.8 – 3.1/100,000). Males are more affected than females (3-4:1) and forms the leading cancer among males. The Nairobi cancer registry reports an incidence of 3.4/100,000 with male to female ratio of 2.1. Locally, this malignancy is the seventh and tenth most common for male and females respectively. Worldwide, it is the second most common cause of mortality amongst cancer sufferers. Predisposing factors include smoking; both active and passive is responsible for up to 80 – 90% of cases. Others are asbestos exposure, family history of lung cancer, chronic lung diseases, prior history of lung cancer and air pollution. Smoking cessation must be advised. Reduction in exposure to other risk factors also required. This may require enactment of laws to enforce Health education campaigns to start from school level. National programmes to monitor pollution levels within environment should be enforced.

26.3 Diagnosis
Most patients will present with clinical signs on first visit, but a minority (20%) may be diagnosed incidentally. Symptoms may be directly related to local effects (tumour itself or pressure effects) of the cancer or to endocrine or metastatic effects. Presentations due to local effects include chronic cough with haemoptysis, shortness of breath, chest pain. Symptoms and signs can be due to local effects of tumour, effects of metastatic tumour, or paraneoplastic effects. Those due to local tumour are chronic cough with haemoptysis, chest pain, shortness of breath, wheezing, hoarseness of voice, pancoast's syndrome, dysphagia, fatigue, weight loss, and superior venacaval obstruction. Symptoms due to distant spread depend on the organ involved.
26.3.1 Pathological subtypes are
- Small cell is further subdivided into oat cell and combined small cell.
- Non small cell, subdivided into squamous cell types which tend to be central, and adenocarcinoma, which are usually peripheral. Non-epithelial lung cancer sub-types include glandular and carcinoid tumours.

26.3.2 Imaging findings are
Chest radiograph is the main investigation in the resource limited settings. Most clinical cases will have radiological features of mass or enlarged lymph nodes.
Coin lesion (solitary pulmonary nodule) usually > 3cm diameter.
Multiple nodules with cavitation arising from necrosis of centrally located malignant tissue may be observed.
Mediastinal mass: Various locations possible like superior sulcus (Pancost tumour) or hilar Peripheral lung mass
Features of consolidation
• CT provides more detail and enables staging of disease. In high risk and symptomatic patients CT screening is indicated. MRI can assess extent of Pancost’s tumour or brain metastasis and should be considered. Positron Emission Tomography (PET) scan to assess extent of systemic disease is recommended where available. It is the most accurate modality for staging intra and extrathoracic disease involvement in a single study
Tissue diagnosis is obtainable through:
Biopsy can be done either through bronchoscopy or may be ultrasound guided. Tissue can also be obtained FNA cytology, mediastinoscopy, core needle biopsy, open biopsy, biopsy of metastasis of secondary deposit.
Sputum, lavage, brushes or thoracocentesis specimens may also be obtained for cytology.

26.4 Staging And Risk Assessment
Staging is carried out according to the TNM system. Adverse prognostic factors are advanced stage, weight loss and markers of large sizes tumours (LDH)
Table 52: TNM staging for Lung Cancer

<table>
<thead>
<tr>
<th>Primary Tumour (T)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed, or the tumour is proven by the presence of malignant cells in sputum or bronchial washing but is not visualized by imaging or bronchoscopy</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, no bronchoscopic evidence of invasion, more proximal than the lobar bronchus (not in the main bronchus); superficial spreading of tumour in the central airways (confined to the wall of the trachea or mainstem bronchus)</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour &gt; 3 cm but ≤ 7 cm or tumour with any of the following:</td>
</tr>
<tr>
<td></td>
<td>Invades visceral pleura</td>
</tr>
<tr>
<td></td>
<td>Involves the main bronchus ≥ 2 cm distal to the carina</td>
</tr>
<tr>
<td></td>
<td>Associated with atelectasis/obstructive pneumonitis extending to hilar region but not involving the entire lung</td>
</tr>
<tr>
<td></td>
<td>Tumour &gt; 7 cm or one that directly invades any of the following:</td>
</tr>
<tr>
<td>T3</td>
<td>Chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, or parietal pericardium</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, or carina; separate tumour nodule(s) in a different ipsilateral lobe</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in the ipsilateral mediastinal and/or subcarinal lymph node(s)</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in the contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes</td>
</tr>
</tbody>
</table>
### Distant Metastasis (M)

<table>
<thead>
<tr>
<th>MX</th>
<th>Distant metastasis cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural (or pericardial) effusion</td>
</tr>
<tr>
<td>M1b</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

### Table 53: Stages of lung cancer

<table>
<thead>
<tr>
<th>STAGE</th>
<th>DESCRIPTION</th>
<th>TNM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis N0 M0</td>
<td></td>
</tr>
<tr>
<td>Ia</td>
<td>Invaded the underlying lung tissue but hasn't spread to the lymph nodes.</td>
<td>T1a N0 M0, T1b N0 M0</td>
</tr>
<tr>
<td>Ib</td>
<td>T2a N0 M0</td>
<td></td>
</tr>
<tr>
<td>IIa</td>
<td>Spread to neighbouring lymph nodes or invaded the chest wall or other nearby structures.</td>
<td>T1a N1 M0, T1b N1 M0, T2a N1 M0, T2b N0 M0</td>
</tr>
<tr>
<td>IIb</td>
<td>T2b N1 M0, T N0 M0</td>
<td></td>
</tr>
<tr>
<td>IIIa</td>
<td>Spread from the lung to lymph nodes in the centre of the chest.</td>
<td>T1 N2 M0, T2 N2 M0, T N2 M0, T N1 M0, T4 N0 M0, T4 N1 M0</td>
</tr>
<tr>
<td>IIIb</td>
<td>Spread locally to areas such as the heart, blood vessels, trachea and oesophagus — all within the chest — or to lymph nodes in the area of the collarbone or to the tissue that surrounds the lungs within the rib cage (pleura).</td>
<td>T4 N2 M0, T1 N M0, T2 N M0, T N M0, T4 N M0</td>
</tr>
<tr>
<td>Extensive disease IV</td>
<td>Spread to other parts of the body, such as the liver, bones or brain.</td>
<td>T Any N Any, M1a or 1b</td>
</tr>
</tbody>
</table>
### Table 54: TNM staging of small Cell lung cancer

<table>
<thead>
<tr>
<th>STAGING</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited</td>
<td>Confined to the ipsilateral hemithorax, which can be safely encompassed within a tolerable radiation field</td>
</tr>
<tr>
<td>Extensive</td>
<td>Beyond ipsilateral hemithorax, which may include malignant pleural or pericardial effusion or haematogenous metastases</td>
</tr>
</tbody>
</table>

#### 26.5 Management

This should always be multidisciplinary. Counselling (education, assurance, informed consent, family involvement e.t.c.) essential to maintain a positive attitude of both patient and family.

Early Non-Small Cell Lung Cancer:

Clinical assessment of patients for suitability of surgery and includes staging, physical fitness and lung function test.

### Management of NSCLC

Surgery is the mainstay for curative treatment of NSCLC. Stages of NSCLC that may be considered for surgical resection are illustrated below (shaded):

#### Table 55: Suitability of lung cancer for surgical resection based on TNM classification

<table>
<thead>
<tr>
<th>Nodes (N)</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>M1</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>IA</td>
<td>IB</td>
<td>II B</td>
<td>IIIB</td>
<td>IV</td>
</tr>
<tr>
<td>N1</td>
<td>IIA</td>
<td>II B</td>
<td>III B</td>
<td>III B</td>
<td>IV</td>
</tr>
<tr>
<td>N2</td>
<td>III A</td>
<td>III A</td>
<td>III A</td>
<td>III B</td>
<td>IV</td>
</tr>
<tr>
<td>N3</td>
<td>III B</td>
<td>III B</td>
<td>III B</td>
<td>III B</td>
<td>IV</td>
</tr>
<tr>
<td>Mets (M)</td>
<td>M1</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
</tbody>
</table>

Surgical resection may be either lobectomy or pneumonectomy with node resection. These procedures are usually performed through open resection however VATS is a possibility where facilities available.

Postoperative chemotherapy (Cisplatin based) is recommended for stages IB (T > 4), II and IIIA

Radiotherapy may be offered to operable patients who are not medically fit for surgery.
26.5.2 Late NSCLC
The treatment approach is concomitant chemoradiotherapy (cisplatin based).

26.5.3 Management of limited SCLC
Small Cell Lung Carcinoma is very sensitive to many chemotherapeutic agents and to radiotherapy. Because it is usually disseminated at presentation, the mainstay of treatment is chemotherapy and radiotherapy.
For limited disease chemotherapy (platinum and etopside) in combination with thoracic radiotherapy.
There is very limited role for surgery in very early disease. This should be followed with chemotherapy and radiotherapy if mediastinal nodes are involved.

26.5.4 Management of advanced SCLC
Cisplatin or caboplatinin combination with etopside is the commonly used first-line.
Response is quick, but brief. Prognosis is poor with median survival of ten months and two year survival of 10%.
Prophylactic cranial irradiation (PCI) for patients with any response to first line treatment irrespective of stage is offered by many oncologists though its benefit is controversial.
Second-line chemotherapy may include topotecan, Cyclophosphamide, doxorubicin and vincristine, either singly or in combination.

26.5.5 Follow-up
Followups are recommended at 3 to 6 monthly for the first two years and 6 to 12 monthly thereafter. During review detailed physical and radiological examination performed. When clinically indicated specific investigations should be carried out.

26.6 Commonly Used Medicines
Cisplatin, etoposide, vinorelbine, paclitaxel, docetaxel, carboplatin, vinblastine, gemcitabine, pemetrexed, bevacizumab, erlotinib, gefitinib, cetuximab, irinotecan, topotecan.
In resource limited settings there is no justifiable combination chemotherapy for advanced non-small cell lung cancer. Small cell lung cancer can be treated with various agents including vincristine, cyclophosphomide, etoposide, doxorubicin, cisplatin either singly or in combination.

26.7 Prognosis
Prognosis for both SCLC and non SCLC is poor even in early disease.
REFERENCES

1. GLOBOCAN 2008.

27. Malignant Pleural Mesothelioma

Ogendo SW, Othieno-Abinya NA, Nyongesa CN, Musibi AM, Waweru W.

27.1 Introduction
Malignant pleural mesotheliomas arise from the protective lining of lungs (pleura). Usually commences growth as small plaques, often in the dependent portions of the lung near the diaphragm. With time they expand and coalesce to form a covering. Invasion into adjacent organs follows with time.

27.2 Epidemiology
This is considered to be a fairly rare tumour. Current international incidences vary between 1 and 3 per 100,000 with a 3:1 male to female ratio. Extrapolated incidence from Kenya is 0.94 per 100,000

Risk factors
Exposure to asbestos is the main etiological factor and 80% of cases have positive history of asbestos exposure.
Exposure to radiation may also have a role.

27.3 Diagnosis
Signs may be nonspecific and thus a high index of suspicion is required. A history of occupation in asbestos industry is important. Chest pain, difficulty in breathing, shortness of breath, chronic cough and dysphagia are some of the more common presentations. Examination findings may be limited to those associated with pleural effusion (90% of cases).
Imaging evaluation
Chest radiograph may show obliterated diaphragm, pleural effusion, thickened pleura, and loculated effusion. Chest CT scan gives more detail than plain radiographs. PET helps differentiate malignant from benign mesothelioma.
Tissue confirmation should be obtained before instituting therapy.

27.4 Staging And Risk Assessment
This should include CT and MRI scans. Pathology specimens can be obtained through thoracoscopy, Pleuroscopy, laparoscopy, and biopsy from the diaphragm. Cytological evaluation can be performed on peritoneal collection.
The tumours are staged according to the TNM system shown in the table below.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>The primary tumour cannot be assessed.</td>
</tr>
<tr>
<td>T0</td>
<td>There is no evidence of a primary tumour.</td>
</tr>
<tr>
<td>T1a</td>
<td>The tumour is limited to the ipsilateral parietal pleura as well as the mediastinal and diaphragmatic pleura. However, there is no involvement of the visceral pleura.</td>
</tr>
<tr>
<td>T1b</td>
<td>The tumour has involved the ipsilateral parietal and visceral pleura along with the mediastinal and diaphragmatic pleura.</td>
</tr>
<tr>
<td>T2</td>
<td>The ipsilateral pleural surfaces, which include the parietal, mediastinal, diaphragmatic and visceral pleura, have been invaded by the tumours. At least one of the following features is also included in this stage: The diaphragmatic muscle is involved. The tumour has extended into the visceral pleura and the underlying pulmonary parenchyma.</td>
</tr>
<tr>
<td>T3</td>
<td>The tumour has expanded locally, but is potentially resectable. It has invaded all of the ipsilateral pleural surfaces, which include the parietal, mediastinal, diaphragmatic and visceral pleura. One or more of the following features will be displayed: The endothoracic fascia is involved. Extension into the mediastinal fat. The tumour has extended into the soft tissues of the chest wall and is solitary and completely resectable. Nontrasmural involvement of the pericardium.</td>
</tr>
<tr>
<td>T4</td>
<td>The tumour is locally advanced and is unresectable. It has involved all of the ipsilateral pleural surfaces including the parietal, mediastinal, diaphragmatic and visceral pleura. These tumours will also display at least one of the following features: A diffuse extension or multifocal masses into the chest wall, with or without rib destruction. The tumour has direct transdiaphragmatic extension into the peritoneum. A direct extension of the tumour into the contralateral pleura. The tumour has directly extended into one or more of the mediastinal organs. The spine has experienced a direct extension of the tumour. The tumour has extended through the internal surface of the pericardium with or without a pericardial effusion. The tumour has involved the myocardium.</td>
</tr>
</tbody>
</table>
MX | The presence of metastasis cannot be assessed.
M0 | The tumour has not metastasized to other parts of the body.
M1 | The presence of metastasis into other parts of the body.

**Table 57: Stage grouping for Malignant Pleural Mesothelioma**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>PRIMARY TUMOUR (T)</th>
<th>REGIONAL LYMPH NO DES (N)</th>
<th>METASTASIS (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T1, T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1, T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0, N1, N2</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

**Table 58: Stage grouping and TNM for Malignant Pleural Mesothelioma**

<table>
<thead>
<tr>
<th>Stage IA</th>
<th>T1a N0 M0</th>
<th>Completely resected within the capsule of the parietal pleura without adenopathy (ie, ipsilateral pleura, lung, pericardium, diaphragm, or chest wall disease limited to previous biopsy sites)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IB</td>
<td>T1b N0 M0</td>
<td>All stage I characteristics, with positive resection margins, intrapleural adenopathy, or a combination</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2 N0 M0</td>
<td>Local extension of disease into the chest wall or mediastinum, into the heart, through the diaphragm or peritoneum, or extrapleurally to involve the lymph nodes</td>
</tr>
<tr>
<td>Stage III</td>
<td>T1, T2 N1 M0</td>
<td>Distant metastatic disease</td>
</tr>
<tr>
<td></td>
<td>T1, T2 N2 M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3 N0, N1, N2 M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any T N3 M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any T Any N M1</td>
<td></td>
</tr>
</tbody>
</table>
27.5 Management
All modalities of cancer therapy have a role in management of malignant mesothelioma (multimodality treatment). Single modality therapy results in poor outcome. Surgery in combination with adjuvant chemotherapy seems to offer the most promising results. This however is among those patients with good prognostic indicators.

27.5.1 Early Disease
This is mainly treated by surgery. The goal is to provide macroscopic resection of lesions. Surgery, as the single modality, is wrought with high recurrence rates. Its indications are in superficial disease. Pleurodesis is carried out for pleural effusions. Less than 30% success rates are reported with this approach. It is mainly indicated in patients with advanced disease with recurrent collections, and who are poor candidates for surgical resection.

27.5.2 Late disease
- In advanced locally invasive disease both lung and pleura are affected. Surgical management is extrapleural pneumonectomy. This involves removal of the lung tissue without traversing the pleural space, pericardial sac and diaphragm on affected side.

27.5.3 Follow-up
This is recommended to be carried out every 3 – 6 weeks and then 6 monthly if all is well. Follow-up involves clinical evaluation, looking at symptoms of recurrence, and a thoracic CT scan as needed.

27.6 Commonly Used Medicines
Cisplatin, etoposide, vinorelbine, paclitaxel, docetaxel, carboplatin, vinblastine, gemcitabine, pemetrexed, bevacizumab, erlotinib, gefitinib, cetuximab, irinotecan, topotecan.
In resource limited settings there is no justifiable combination chemotherapy for advanced non-small cell lung cancer. Small cell lung cancer can be treated with various agents including vincristine, cyclophosphomide, etoposide, doxorubicin, cisplatin either singly or in combination.

27.7 Prognosis
Prognosis for all types of lung cancer is poor.
REFERENCES
28. Prostate Cancer

Ngugi PM, Nyongesa CN, Rogena E, Muchiri L, Chite FA, Kasina M, Muthaka C.

28.1 Introduction
This is the most common cancer among elderly male population all over the world, with a slight preponderance in blacks.

28.2 Epidemiology
The Nairobi cancer registry places prostate cancer as the commonest cancer in males at 17.3%. This compares well with 15% reported in developed countries. Prostate cancer is a disease of the aging male, the majority presenting after 65 years.

28.3 Diagnosis
Most of the patients present with lower urinary tract symptoms:
- Urge to urinate often, especially at night.
- Difficulty in starting or stopping the urine flow, inability to urinate;
- Weak, decreased or interrupted urine stream, a sense of incompletely emptying the bladder.
- Burning or pain during urination, blood in the urine or semen, painful ejaculation.

Screening and Early Detection
1. The standard method of early detection for prostate cancer is the digital rectal examination (DRE) which should be done annually in fit men 50-70 years or if obstructive or other urinary tract symptoms are present.
2. Serum PSA is of unknown value as a population screening test. Although there is good evidence that it increases the detection rate of early stage clinically significant prostate cancers, there is little evidence to date that such early detection leads to reduced mortality; the “gold standard” for evaluating screening tests.
3. Fit men age 50-70 (men with at least 10 years life expectancy) should be made aware of the availability of PSA as a detection test for prostate cancer. They should be aware of the potential benefits and risks of early detection so they can make an informed decision as to whether to have the test performed.
- The main diagnostic tools to obtain evidence of PCs include DRE, serum PSA and transrectal ultrasonography (TRUS) guided biopsy. Its definite diagnosis depends on the histopathologic verification of adenocarcinoma in prostate biopsy cores or operative specimens.
- Most prostate cancers are located in the peripheral zone of the prostate. The patient’s biological age, potential co-morbidities and the therapeutic consequences should also be considered. Transrectal approach is used for most prostate biopsies but a transperineal approach can be used.
Antibiotics administered prior to biopsy. Oral or intravenous antibiotics are state-of-the-art treatment. Quinolones are the medicines of choice, e.g. ciprofloxacin or equivalent alternative.

28.4 Staging And Risk Assessment
Investigations for Staging
Assessment should consist of history and physical examination, CBC, BUN, creatinine, urinalysis PSA (which should be done prior to biopsy). Radionuclide bone scan is indicated only in patients with intermediate or high-risk disease.

Table 59: TNM Staging System for Prostate Cancer

<table>
<thead>
<tr>
<th>TX</th>
<th>primary tumour cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>TO</td>
<td>no evidence of primary tumour</td>
</tr>
<tr>
<td>T1</td>
<td>clinically inapparent tumour not palpable or visible by imaging</td>
</tr>
<tr>
<td>T1a</td>
<td>tumour incidental histological finding in 5% or less of tissue resected</td>
</tr>
<tr>
<td>T1b</td>
<td>tumour incidental histological finding in more than 5% of tissue resected</td>
</tr>
<tr>
<td>T1c</td>
<td>tumour identified by needle biopsy (e.g., because of elevated PSA)</td>
</tr>
<tr>
<td>T2*</td>
<td>tumour confined within the prostate</td>
</tr>
<tr>
<td>T2a</td>
<td>tumour involves one lobe</td>
</tr>
<tr>
<td>T2b</td>
<td>tumour involves both lobes</td>
</tr>
<tr>
<td>T3**</td>
<td>tumour extends through the prostatic capsule</td>
</tr>
<tr>
<td>T3a</td>
<td>extracapsular extension (unilateral or bilateral)</td>
</tr>
<tr>
<td>T3b</td>
<td>tumour invades seminal vesicle(s)</td>
</tr>
<tr>
<td>T4</td>
<td>tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall</td>
</tr>
</tbody>
</table>

* Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging is classified as T1c
** invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.

N - Regional Lymph Nodes  The regional lymph nodes are the nodes of the true pelvis which essentially are the pelvic nodes below the bifurcation of the common iliac arteries. Laterality does not affect the N classification.

<table>
<thead>
<tr>
<th>NX</th>
<th>regional lymph nodes cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td>no regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>regional lymph node metastasis</td>
</tr>
</tbody>
</table>
M - Distant Metastasis

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>MO</td>
<td>no distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>non-regional lymph node(s)</td>
</tr>
<tr>
<td>M1b</td>
<td>bone(s)</td>
</tr>
<tr>
<td>M1c</td>
<td>other site(s)</td>
</tr>
</tbody>
</table>

Note: when more than one site of metastasis is present, the most advanced category should be used.

Table 60: Risk categories

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk:</td>
<td>- PSA ( \leq 10 \text{ ng/mL} ),</td>
</tr>
<tr>
<td></td>
<td>- Gleason ( \leq 6 ),</td>
</tr>
<tr>
<td></td>
<td>- Stage T1/T2a</td>
</tr>
<tr>
<td>Intermediate Risk:</td>
<td>- PSA ( &gt; 10 \text{ ng/mL} ),</td>
</tr>
<tr>
<td></td>
<td>- Gleason ( = 7 ),</td>
</tr>
<tr>
<td></td>
<td>- Stage T2b</td>
</tr>
<tr>
<td>High Risk:</td>
<td>- PSA ( &gt; 20 \text{ ng/mL} )</td>
</tr>
<tr>
<td></td>
<td>- Gleason ( \geq 8 ),</td>
</tr>
<tr>
<td></td>
<td>- Stage T3a or worse</td>
</tr>
</tbody>
</table>

28.6 Management

a) Low Risk: options,
   - Watchful waiting, active surveillance
   - Radical prostatectomy
   - Radical Radiotherapy

b) Intermediate Risk: Options
   - Radical Surgery,
   - Radical radiotherapy (3DCRT, IMRT, Brachytherapy)

c) High Risk
Depending on the patient’s age, general health, and disease-related parameters, a variety of therapeutic approaches may warrant consideration including combined radiation and androgen deprivation therapy, radical prostatectomy, radiotherapy alone, or androgen deprivation therapy alone.

Castration-resistant PCA (CRPC)
The term castration-resistant prostate cancer (CRPC) has become more used than the term hormone refractory or androgen independent. Docetaxel is the mainstay of treatment is administered.
Docetaxel administered weekly at 75 mg/m² and prednisone 5 mg twice a day.
**Metastatic disease**

- Androgen suppression using bilateral orchiectomy or an LHRHa should be first-line treatment. A short-course antiandrogen should be used to prevent disease flare-up on starting an LHRHa. Mature results are awaited of intermittent hormone therapy approaches though early results suggest equivalence with continuous hormone ablation.

- External beam radiotherapy should be offered for patients with painful bone metastases from castration-refractory disease (1 x 8 Gy has equal pain-reducing efficacy to multifraction schedules).

- Radioisotope therapy with strontium-89 or samarium-153 should be considered for patients with painful bone metastases.

- Intravenous bisphosphonates should be considered for patients with bone pain resistant to palliative radiotherapy and conventional analgesics. The primary objective is to reduce skeletal-related events (SRE) such as pathological fracture, spinal cord compression, surgery or radiotherapy for bone pain or a change in anticancer treatment for bone pain.

MRI of the spine to detect subclinical cord compression should be considered in men with castration-refractory prostate cancer with vertebral metastases and back pain. Spinal cord compression is a devastating complication of metastatic disease.

**Follow up**

A rising PSA profile is indicative of recurrent disease, but does not distinguish local from metastatic relapse.

**28.6 Medicines Commonly Used**

Goserelin, luteolide, buserelin, bicalutamide, flutamide, docetaxel, estramustine, abiraterone acetate, diethylstilboestrol.

In resource limited settings, diethylylstilboestrol is the first line treatment. Where resources are available, any of the leutenizing hormone releasing hormone (LHRH) agonists like goserelin, with or without an antiandrogen like bicalutamide and flutamide are used.

**28.7 Prognosis**

Early disease is curable with surgery or radiotherapy with or without hormonal manipulation. Advance disease is incurable.
REFERENCES

3. Pickles T and Prostate Cohort Outcomes Initiative. Low risk prostate cancer carries a minimal risk of prostate mortality and intensification of treatment should be questioned. ASCO-ASTRO Prostate Symposium. 2006.
29. Soft Tissue and Bone Sarcomas

Kalebi A, Abwao B, Chite F, Maina M, Othieno-Abinya NA, Mulimba JAO

29.1 Introduction
Sarcomas are a heterogenous group of cancers arising in mesenchymal connective tissue such as muscle, nerves, fat, blood vessels (soft tissue), and bone/cartilage. Most soft tissue tumours are benign and curable with surgical excision. There are more than 50 histological sub-types of soft tissue tumours as per WHO classification and these are often associated with unique clinical, prognostic and therapeutic features.

29.2 Epidemiology
Sarcomas comprise less than 1% of cancer burden worldwide with a global annual incidence of soft tissue sarcoma at around 3/100,000 per year. Kaposi’s sarcoma is the commonest sarcoma in sub-Saharan Africa and almost invariably associated with HIV infection. Kaposi’s sarcoma is a blood vessel sarcoma of low to intermediate grade that is commonly associated with HIV, caused by HHV8. Other than HIV driven Kaposi’s sarcoma, there are no significant geographical variations in the distribution of incidence of sarcomas.

29.3 Diagnosis
Soft tissue sarcomas may occur anywhere in the body but three quarters are located in the extremities, followed by the trunk wall and retroperitoneum. There is a slight male predominance. They are generally more common with older age (median 65 years) though age distribution varies with sub-type.
About 30% of sarcomas, other than Kaposi’s, which are superficial have a median diameter of 5 cm, the rest are deep seated with a median diameter of 9 cm. Retroperitoneal tumours are often much larger before they become symptomatic.
About 10% of patients with sarcomas, other than Kaposi’s, have detectable metastases at presentation and a third die of metastatic disease. Three out of four are histologically classified as high grade (highly malignant).
Patients with progressive soft tissue swelling, with or without pain, should be further evaluated, particularly if there is no history of trauma to the site and no evidence of infection.
The following clinical signs should be looked at in a full physical examination and patients referred accordingly:
• All patients with unexplained mass within deep soft tissues identified clinically or radiologically.
• All patients with superficial lesion of soft tissues having a diameter of >5 cm, or arising in paediatric age.
• Any soft tissue mass that is rapidly growing or clinically infiltrative.
29.3.1 Laboratory Evaluation

Triple assessment with clinical examination, imaging and biopsy is required for diagnosis. Imaging should preferably be done as relevant before or to guide biopsy.

29.3.2 Imaging

- MRI is the recommended imaging for superficial trunk lesions and soft tissue tumours in the extremities.
- Ultrasound may be of value as a screening test in superficial lesions and abdominopelvic masses where MRI is not available.
- XRay and CT-scan are indicated for bone lesions.
- CT-scan may have a role in calcified lesions of soft tissue.
- CT scan and MRI have the same value for abdominopelvic and retroperitoneal sarcomas.
- It is recommended that where possible all imaging of suspected cancers should be read and reported by a radiologist.

Biopsy/Tissue Sampling

- Biopsies should only be done preferably after multidisciplinary discussions including clinical and radiological correlation, and involvement of the patient/relatives for minors.
- A diagnostic biopsy (multiple cores, excision biopsy, or open biopsies) confined to tissue planes is recommended for all soft tissue masses >5 cm, as incomplete excisional biopsy or ‘shelling out’ of a sarcoma is inappropriate owing to ensuing difficulties in further patient management.
- Excisional biopsies with a 2-3cm rim of uninvolved tissue is advisable only for obvious subcutaneous small lumps preferably <2cm*.
- All sub-fascial or deep-seated masses, irrespective of size, should have core biopsies recommended rather than excision biopsy.
- Open incision biopsy is not recommended unless minimal extension to other tissue planes is guaranteed. If performed, this should be located in such a way as to allow complete excision of the tract at definitive surgery.
- For bone, open incision biopsy is recommended. These bone lesions bleed easily thus ensure blood for transfusion is available during the procedure.
- FNA is generally not recommended as it is of limited value in making a diagnosis of sarcoma, and should only be used as a screening test where core biopsy or excisional biopsy (for superficial lesions) is not possible/available.

* Excision biopsy of larger lumps should preferably be carried out only by specialist surgeons.
Histopathological Evaluation and Grading

- The biopsy specimen should be placed in buffered 10% formalin and sent to a histopathology laboratory.
- Pathological diagnosis of sarcomas relies on morphology and immunohistochemistry, as these ubiquitous tumours can mimic each other and other non-soft tissue tumours.
- The histopathological reporting should be done according to WHO classification, specifying the type of soft tissue or bone sarcoma i.e. histogenesis.
- Immunohistochemistry is used to confirm histogenesis. It is recommended in all cases where morphological diagnosis is not absolute, and for all cases of non-specific high-grade/undifferentiated sarcomas.
- A panel of markers is selected by the specialist pathologist as appropriate.
- Immunohistochemistry should be complemented by molecular pathology [fluorescent in situ hybridisation, reverse transcription–polymerase chain reaction]. This is an optional route especially when the specific histological diagnosis is doubtful after immunohistochemistry and clinical-pathologic-radiological correlation and the diagnosis has a predictive relevance.
- If the biopsy is seen or reported by a non-specialist pathologist and diagnosed as sarcoma, it is recommended that the case be subsequently referred to a specialist histopathologist for review.
- All FNA reports need confirmation with biopsy for histopathological reporting.
- The histopathological report should give the diagnosis according to the World Health Organization (WHO) classification. A pathological expert’s second opinion is strongly recommended in all cases being attended to at specialist centers.

Minimum Pathology Data Set

Each tumour should have the following assessments:

- The histology type and malignancy grade as per NCI grading system, which distinguish malignancy grades based on differentiation, necrosis and mitotic rate into grade 1 (low), grade 2 (intermediate) and grade 3 (high) grades.
- Tumor site should be properly recorded.
- Tumor size and tumor depth (in relation to the superficial fascia) should also be recorded, since they entail a prognostic value.
- Tumor margins are used for assessment of completeness of surgical resection and should be at least 3 cm. i.e. there should be a distance of at least 3cm of healthy tissue to the edge of the tumour.

If preoperative treatment was carried out, the pathology report should include an assessment of the histological response of the tumor.
### Table 61: TNM Staging System for Bone and Soft Tissue Sarcomas

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Bone Sarcoma</th>
<th>Soft-tissues sarcomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor ≤ 8 cm in greatest dimension</td>
<td>Tumor ≤ 5cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt; 8 cm in greatest dimension</td>
<td>Tumor &gt; 5cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Discontinuous tumor in the primary site</td>
<td></td>
</tr>
</tbody>
</table>

#### Regional lymph nodes (N)

<table>
<thead>
<tr>
<th>N0</th>
<th>No clinical regional lymph node metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis present</td>
</tr>
</tbody>
</table>

#### Distance Metastases (M)

<table>
<thead>
<tr>
<th>M0</th>
<th>No distant metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>Distant metastases present</td>
</tr>
</tbody>
</table>

(for bone sarcomas, M1a has metastasis to the lung and Mb has metastasis to other distant sites.)

### 29.4 Staging And Risk Assessment

Staging of soft tissue sarcomas is based on histological, clinical and radiological information. The major staging systems used are the TNM and AJCC. In sarcomas, these staging systems incorporate histological grade as well tumour size and depth.

#### Radiology and Imaging for Staging

- Chest CT-scan is mandatory for all sarcomas, including bone sarcomas.
- Abdominal CT-scan is recommended.
- FBC
- Routine biochemistry including urate, and renal function.
- Viral serology for HIV (mandatory), hepatitis B and hepatitis C (strongly recommended).
29.5 Management

Treatment is stratified according to the extent of the disease. Patient education and counseling on treatment options is important. Healthcare providers should be educated on recognition and prompt referral of patients that they encounter, as time is of essence in the progression of sarcomas.

29.5.1 Localised Tumour Amenable To Excision

- Surgery is the mainstay of treatment for any localized disease (lesions <5cm or those compartmentalized in clear tissue planes on radiology), subcutaneous or intramuscular high grade soft tissue sarcoma smaller <5 cm, or any size low grade sarcoma. Surgery alone should be considered if a wide excision with a negative 2-3 cm cuff of surrounding fat and muscle can be achieved.
- The margins should be confirmed through histopathology, for which the entire specimen should be sent to the laboratory for examination.
- If initial excision shows a positive margin at histopathology, early re-excision should be considered if the residual site of the lesion is amenable to repeat surgery.
- If not amenable to repeat surgery (re-excision), radiation therapy of the tumour bed should be considered.
- For selected sarcomas, depending on the tumour histological sub-type and grade, chemotherapy may be indicated. All grade 2 and 3 sarcomas should be referred to a specialist treatment centre where they are to be considered for further appropriate chemotherapy as may be indicated.

For localized bone tumours, limb sparing surgery should be considered instead of amputation where possible, and should be offered to the patient. Limb sparing surgery should be done by specialist surgeons in a specialized treatment center.

29.5.2 Locally advanced tumour without evident metastases, is amenable to surgery.

- The treatment of these sarcomas should be individualized depending on the histological sub-type and the stage of the tumour, and it is strongly recommended that this be determined by a multidisciplinary team.
- For low grade and selected cases of intermediate grade sarcomas that are locally advanced, attempt at surgical excision should be made in centres where reconstruction can be done for mutilating surgeries.
- For high grade locally advanced sarcomas, available options are chemotherapy and/or radiotherapy; surgery should only be attempted for down-staged tumours where there is possibility of better outcome from excision followed by reconstruction.
- The value of systemic chemotherapy depends on the specific histological subset of the sarcoma.
- Chemotherapy is usually indicated as primary (neoadjuvant) therapy in the treatment of Ewing sarcoma and rhabdomyosarcoma.
29.5.3 Metastatic Disease

- Patients with metastatic disease should be treated with chemotherapy as standard treatment, the regimen of which is dependent on the type and grade of sarcoma.
- Radiation therapy may be used in highly selected cases, taking into consideration the site of metastases and the natural history of the specific tumour type.

29.6 Commonly Used Medicines

Doxorubicin, ifosfamide, methotrexate, actinomycin-D, cyclophosphamide, vincristine, cisplatin, gemcitabine, paclitaxel, dacarbazine, docetaxel, epirubicin, mitomycin-c, trabecetin, topotecan, irinoteca.
Standard first line treatment monotherapy is high dose doxorubicin. Where resources are available doxorubicin with or without ifosfamide is used.

29.7 Prognosis

Except in very early disease, where surgery without or with adjuvant treatment, is curative, sarcomas have a poor prognosis.

Kaposi's Sarcoma (Ref: Cap 37)

Introduction

This is the commonest soft tissue sarcoma, especially in sub-Sahara Africa, particularly so in association with HIV/AIDS. In the majority of cases presence of HHV8 can be demonstrated.

- This is a tumour which is commonly found in HIV/AIDS and often presents as multicentric disease involving the skin and mucosal sites as well as visceral sites. It also commonly presents with lymphoedema of the lower limbs.
- Patients with occasional lesions can respond to HAART only. Patients with extensive disease should be offered chemotherapy, as the tumour is highly responsive to chemotherapy and radiation therapy.
- Radiation therapy may be used for localized disease.
- Chemotherapy regimens in single or combination include bleomycin, vincristine, vinblastine, doxorubicin, liposomal daunorubicin, etoposide and gemcitabine.
  It is recommended that these drugs should only be given in specialized treatment centers.

Relapsed Or Refractory Disease

Tissue diagnosis through biopsy and histopathological verification should be obtained whenever possible, as this is relevant to rule out transformed disease or new disease. Immunohistochemical verification is needed thus image guided core biopsy may be appropriate in this context.
Palliation
Refer to Chapter 42

Commonly Used Medicines
Vincristine, bleomycin, doxorubicin, actinomycin-D, cyclophosphamide, paclitaxel, dacarbazine, docetaxel, epirubicin, topotecan.
In resource limited settings, vincristine and bleomycin is the first line treatment, even with resources its still the preferred regimen.

Prognosis
Prognosis is usually good unless in advanced cases with lymphoedema.

REFERENCES
30. Skin cancer

Nyongesa C, Rogenia E, Othieno-Abinya NA.

30.1 Introduction
These are arguably the most common cancers in sub-Sahara Africa. There are various types of skin cancer which include Kaposi’s sarcoma, squamous cell carcinoma (SCC), malignant melanoma and basal cell carcinoma (BCC). Dermatofibrosarcoma protuberans, Merkel cell carcinoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, others. In our set up the first three are the most common.

30.2 Epidemiology
Chronic skin infections (including HPV) and chronic skin ulcers are key causes of skin cancer. Ionizing radiation, environmental carcinogens, artificial UV radiation, sun exposure, aging, and light skin color predispose one to developing various types of skin cancer. Other risk factors include albinism and other genetic syndromes such as congenital melanocytic nevi syndrome, characterized by the presence of nevi (birthmarks or moles), xeroderma pigmentosa.

Non-melanoma (basal and squamous cell carcinoma) skin cancers (NMSC) are the most common types of skin cancer in our environment, but melanomas are also not uncommon. Minimizing exposure to sources of ultraviolet radiation (the sun and sunbeds), following sun protection measures include wearing sun protective clothing (long-sleeved shirts, long trousers, and broad-brimmed hats). This is especially true for persons with albinism. A good rule of thumb for decreasing ultraviolet light exposure is to avoid the sun between the hours of 9 a.m. and 3 p.m.

30.3 Diagnosis
Symptoms include changes in skin colour, non-healing ulcers and changes in existing moles (melanoma).

Melanoma
Most melanomas are brown to black looking lesions. A few melanomas are pink, red or fleshy in color and may be difficult to recognize. Warning signs of malignant melanoma include changes in the size, shape, color or elevation of a mole. Other signs are the appearance of a new mole during adulthood or pain, itching, ulceration or bleeding. An often-used mnemonic is “ABCDE”, where A= asymmetrical, B= “borders” (irregular), C= “color” (variegated), D= “diameter” (larger than 6 mm—the size of a pencil eraser) and E= “evolving.”

Squamous cell carcinoma may occur in chronic ulcers. They may present us scaling, thickened patch on sun-exposed skin. Some are firm or hard nodules which may be dome shaped like keratoacanthomas. Ulceration and bleeding may occur.
**Basal cell carcinoma** usually presents as a raised, smooth, pearly bump on the sun-exposed skin of the head, neck or shoulders. Crusting and bleeding in the center of the tumor frequently develops. It is often mistaken for a sore that does not heal. This form of skin cancer carries the best prognosis and with proper treatment can be completely eliminated, often without scarring.

**Special emphasis on malignant melanoma**
Physical examination with special attention to other suspicious pigmented lesions, tumor satellites, in-transit metastases, regional lymph node and systemic metastases is mandatory. A skin biopsy performed under local anesthesia is often required to assist in making or confirming the diagnosis. Elliptical excisional biopsies may remove the tumor, followed by histological analysis and Breslow scoring.

**Investigations**
Lactate dehydrogenase (LDH) tests are often used to screen for metastases. Others are chest X-rays, and in some cases CT and MRI, scans. Sentinel lymph node biopsies may be performed in patients to assess spread to the lymph nodes. A diagnosis of melanoma is supported by the presence of the S-100 protein marker and HMB-45 monoclonal antibody (Human Melanoma Black).
Confirmation of the clinical diagnosis is done with a skin biopsy.
30.4 Staging And Risk Assessment

Table 62: TNM Staging for Malignant Melanoma

<table>
<thead>
<tr>
<th>Stage 0: Melanoma in situ (Clark Level I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a: Less than 1.0 mm primary tumor thickness, without ulceration, and mitosis &lt; 1/mm²</td>
</tr>
<tr>
<td>T1b: Less than 1.0 mm primary tumor thickness, with ulceration or mitoses ≥ 1/mm²</td>
</tr>
<tr>
<td>T2a: 1.01–2.0 mm primary tumor thickness, without ulceration</td>
</tr>
<tr>
<td>T2b: 1.01–2.0 mm primary tumor thickness, with ulceration</td>
</tr>
<tr>
<td>T3a: 2.01–4.0 mm primary tumor thickness, without ulceration</td>
</tr>
<tr>
<td>T3b: 2.01–4.0 mm primary tumor thickness, with ulceration</td>
</tr>
<tr>
<td>T4a: Greater than 4.0 mm primary tumor thickness, without ulceration.</td>
</tr>
<tr>
<td>T4b: Greater than 4.0 mm primary tumor thickness, with ulceration</td>
</tr>
</tbody>
</table>

Nodal Status N

| N1: Single positive lymph node |
| N2: Two to three positive lymph nodes or regional skin/in-transit metastasis |
| N3: Four positive lymph nodes or one lymph node and regional skin/in-transit metastases |

Distant Metastasis M

| M1a: Distant skin metastasis, normal LDH |
| M1b: Lung metastasis, normal LDH |
| M1c: Other distant metastasis or any distant metastasis with elevated LDH |

Classification

Melanoma is divided into the following types: Lentigo maligna melanoma, superficial spreading melanoma, acral lentiginous melanoma, mucosal melanoma, nodular melanoma, desmoplastic melanoma, amelanotic melanoma, others.

30.5 Management

Treatment is dependent on type of cancer, location of the cancer, age of the patient, and whether the cancer is primary or a recurrence. Options include surgery, radiation therapy (external beam radiotherapy or brachytherapy), topical chemotherapy (imiquimod or 5-fluorouracil) and cryotherapy (freezing the cancer off). In the case of disease that has metastasized, further surgical procedures or chemotherapy may be required.
37.5.1 Surgery
Wide excision of primary tumors with safety margins is recommended. Sentinel lymph node biopsy has been developed to reduce the complications of lymph node surgery. If a lymph node is positive, a radical lymph node dissection will often be performed.

30.5.2 Chemotherapy and immunotherapy
Various chemotherapy agents are used, including dacarbazine (also termed DTIC), immunotherapy (with interleukin-2 (IL-2) or interferon (IFN)), as well as local perfusion. Other drugs used are temozolamide, cisplatin, and cyclophosphamide. The overall success in metastatic melanoma is quite limited.

30.5.3 Radiation therapy
It is often used after surgical resection for patients with locally or regionally advanced melanoma or for patients with unresectable distant metastases.

30.5.4 Patient information and follow-up
Melanoma patients should be instructed on avoidance of sunburns, extended unprotected solar or artificial UV exposure and on lifelong regular self-examinations of the skin and peripheral lymph nodes. Patients have follow-up visits every 3 months during the first 3 years and every 6–12 months thereafter. Serum S-100 may be useful follow-up. Routine imaging techniques are not recommended.

30.6 Commonly Used Medicines
Dacarbazine, temozolamide, cisplatin, cyclophosphamide, interferon-alpha.
In resource limited settings, a combination of cisplatin and dacarbazine can be used. Where resources are available, interferon alpha-2B and dacarbazine can be used.

30.7 Prognosis
Early disease is curable with surgery and adjuvant therapy. Metastatic disease carries a poor prognosis.
REFERENCES
PART 3

PAEDIATRIC CANCERS
Paediatric Cancer


Introduction

Cancers in children may be classified into leukemias (acute and chronic), lymphomas (Hodgkin’s ad Non-Hodgkin’s) and solid tumors. Among the commonest in the latter category are retinoblastoma, brain tumours, nephroblastoma, rhabdomyosarcoma, neuroblastoma and osteogenic sarcoma among others.

Kenya has a population of approximately 40 million people of which nearly 50% are children under the age of 15 years. Children face many health problems including diarrhoeal diseases, pneumonia, malaria, malnutrition and HIV/AIDS which contribute to high mortality rates. According to the latest (2008) Kenya Demographic Health Survey (KDHS), infant mortality rate (IMR) is 52 per 1000, and under-5 mortality rate 74/1000. Incidence of childhood cancers in Kenya is undetermined but Western countries have a rate of about 150 per million children. Considering the under 15 population, the local incidence would be about 3000 new cases per year. Lymphoma, kidney cancer, eye tumors (retinoblastoma) and leukemia constitute about 80% of all childhood cancers in Kenya and majority respond well to treatment.

Unlike adult cancers, about 80% of childhood cancers are potentially curable if diagnosed early and appropriate treatment promptly instituted. However, only an estimated 20-30% of children treated for cancer at the KNH experience long term disease-free survival. Type of cancer, disease stage at time of diagnosis and quality of care are also important determinants of treatment outcome.

Most cancer cases are easily confused with other common medical diseases like malaria and other causes of fever, anaemia, large glands, liver and spleen thus prompting many to die before definitive diagnosis is made.

Most children with cancer are noticed because of an enlarging mass, but other signs and symptoms can be subtle or confusing, leading to delays in early diagnosis and commencement of treatment. Most malignant solid tumours are found at the time of physical examination, which may present at any age from birth to later childhood. For children of any age, clinical manifestations of cancer vary according to the body tissues involved. For example, leukemias often present as recurrent infections, bleeding tendencies and anaemia whereas enlargement of lymphnodes, hepatosplenomegaly and central nervous system involvement characterize lymphoma presentation. Solid tumors present as visible or concealed lumps. Certain cancers may however present with specific signs like leukocoria (white pupil) in retinoblastoma and associated congenital abnormalities like hemi-hypertrophy in familial nephroblastoma.
Early diagnosis and timely referral of children with cancer from peripheral health care facilities to treatment centres are key prerequisite for a good outcome. Delay in treatment leads to widespread disease and more care costs. Booster vaccines and growth development and endocrine assessments are key part of follow up for all children treated for cancer irrespective of diagnosis.
31. Leukaemias in Childhood

31.1 Introduction
Childhood leukaemias represent a very heterogenous group of malignancies characterized by the accumulation of immature blood cells in the bone marrow and blood. These transformed cells exhibit aberrant differentiation patterns with increased self-renewal capability and ultimately they inhibit the growth of lymphoid, erythroid, granulocytic and megakaryocytic precursors in the bone marrow by direct and indirect mechanisms. They can be acute or chronic, myeloid or lymphoid.

31.2 Epidemiology
The incidence varies throughout the world, but some of the comparative data, not being population-based, especially from the developing countries, must be treated with caution. In the USA and Europe it is quoted as the most common malignancy in childhood and remains the most common cause of cancer related mortality. The AMPATH Eldoret cancer registry, 1998 – 2002, reported the leukaemias to represent 20.7% of all cancers.

Acute Leukaemias
The most common acute leukaemia in childhood is acute lymphoblastic leukaemia (ALL) accounting for about 85% of the cases and the rest are acute myeloid leukaemia (AML).

31.3 Diagnosis
Clinical presentation of acute leukemias is readily explained by myelosuppression emanating from severe reduction in numbers of red blood cells and platelets, or effective numbers of white blood cells. This may manifest in form of anaemia leading to general malaise and easy fatiguability or even frank cardiac failure, recurrent serious bacterial infections and bleeding tendencies. Tissue infiltration may also manifest as organ enlargement, nerve palsies, ostitis, arthritis or peri-orbital and gum chloromatous deposits. Laboratory work-up includes morphological examination of blood and bone marrow samples, cytochemistry, flow cytometry, immunohistochemistry, cytogenetics and molecular typing.

31.4 Staging And Risk Assessment
Investigations needed to determine baseline physiological status and extent of disease include renal function tests, uric acid and LDH, liver function tests, serum calcium and magnesium. Blood cultures if febrile, HIV-ELISA, hepatitis surface antigens. CSF cytology is part of ROUTINE staging for ALL.

Imaging studies including chest X-ray and abdominal U/S, if there is organomegaly, should be undertaken. Other tests should be done as dictated by the clinical presentation. Risk assessment in acute myeloid leukaemia includes age of patient, initial leukocyte count, presence of extramedullary disease, morphological type Karyotype and selected molecular markers.
In Acute lymphoblastic leukaemia poor prognostic features include high WBC on presentation (ranging from standard, intermediate to high and very high risk categories); age if <2 or > 10 years, T cell or mature B cell disease and pre-defined cytogenetic markers where available. Abnormal karyotype (hypo and pseudodiploidy) also signify poor risk disease.

31.5 Management

Treatment plan is divided into specific and supportive care. Specific chemotherapy for AML aims at eradicating the malignant clone of cells by giving short intensive cyto-reduction treatments over 5-7 days with combinations of daunorubicin, cytosine arabinoside and 6-thioguanine. Maintenance treatment is not required in AML unlike ALL. Patients who survive beyond 24 months infrequently relapse. All-trans-retinoic acid (ATRA) reduces risk of DIC-like syndrome associated with a variant of pro-myelocytic (M3v) AML. The options available for patients who do not go into remission are to give two more courses of the same regimen and assess the remission status or to re-induce with different agents (mitoxantrone, fludarabine, cladribine).

Treatment of acute lymphoblastic leukemia [ALL] is divided into three phases including CNS prophylaxis or treatment.

31.5.1 Induction phase

Strategy in this phase is to use non-myelotoxic drugs which will permit rapid blast kill without undue injury of the normal stem cells. Modern protocols advocate an approach with minimum of 3-4 drugs including prednisone, vincristine and L-asparaginase. Doxorubicin is frequently added as the 4th drug. This phase takes about 4 weeks. Evidence shows that the faster the achievement of remission, the better the prognosis; hence intensification of induction. Complete remission is defined as less than 5% of leukaemic blasts in the bone marrow at a time when bone marrow cellularity is restored after induction chemotherapy.

31.5.2 Consolidation phase/Intensification

This aims at elimination of residual disease and entails use of intensive treatment with multiple drugs acting in different stages of the cell cycle. This is followed by cranial irradiation and an 8-week interim maintenance with antimetabolites and re-intensification before maintenance phase. Patients who do not go into remission at this point are considered to be treatment failures and should be considered for myelo-ablative therapy followed by allogeneic stem-cell transplantation where resources and compatible donors are available.

31.5.3 Maintenance phase

Patients are treated with monthly intravenous vincristine, weekly oral methotrexate and daily 6-mercaptopurine for two years. Intra-thecal methotrexate is administered every three months.
31.5.4 Supportive Care:
This is important in managing treatment related morbidity. This includes prevention of tumour lysis syndrome (especially in the rare M4, M5 subtypes) by use of allopurinol or rasburicase (urate oxidase) where available for those with high tumour load. Adequate fluid intake, use of blood products for anaemia and haemorrhage (due to thrombocytopenia), management of bacterial and fungal infections with appropriate antimicrobials, and effective anti-emetics are an essential component of supportive care.

31.5.5 Response Evaluation
Total blood counts and peripheral blood film examination should be done prior to every course of chemotherapy during treatment. Bone marrow examination is used to assess remission status after consolidation, but after clearance of peripheral blood blasts. Cerebrospinal fluid cytology is done on fresh specimen (a delay results in degenerative changes) during every administration of intra-thecal treatment where initial test is positive or suspicious. Testing of CSF sediment for TdT positivity is recommended where available since morphology alone can be misleading.

31.5.6 Follow Up
Monthly follow up after completion of maintenance treatment for one year is necessary. Three monthly reviews for the next two years and thereafter, six monthly reviews are carried out.

31.6 Commonly Used Medicines
Similar to adults except that L-asparaginase seems to be an important addition in childhood ALL.

31.7 Prognosis
Paediatric lymphoid neoplasms carry excellent prognosis if treated appropriately.

Chronic Myeloid Leukaemia
This is rare in children constituting less than 5% of all leukemias. It presents as the classical adult type or juvenile form which is less frequently associated with the Philadelphia chromosome. While hydroxyurea remains the standard treatment, imatinib (glivec) is preferred for Philadelphia chromosome positive cases. In Kenya this drug is available at no cost through the Glivec International Patient Assistance Program (gipap www.gipap@themaxfoundation.org).

Prognosis
It’s the same as in adults.
REFERENCES
3. Kasili EG; Synopsis of Oncology.
4. Paediatric oncology 3rd edition Ross Pinkerton, Piers N. Plowman and Rob Pieters.
32. Lymphomas

32.1 Introduction
Lymphomas are neoplasms arising from lymphoid cells at various stages of maturation. They are classified into two major groups, Hodgkin’s lymphoma and non-Hodgkin’s lymphomas. The non-Hodgkin’s lymphomas are a large group which in children is further sub-classified into three main categories, according to the cell type (B, T or N/K cells). For treatment purposes, they are here categorized into Hodgkin’s Lymphoma, Burkitt’s lymphoma, precursor B-cell and T-cell lymphoblastic lymphomas.

32.2 Epidemiology
Lymphomas represent almost 50% of the childhood tumours in Kenya. In sub-Saharan Africa, disease burden from lymphoma ranks 5th in males and females, with an incidence of 16 and 10.8 per 100,000 respectively. The majority of the lymphomas in childhood are NHL with Burkitt’s lymphoma (BL), a B-cell malignancy topping the list. In those countries where HIV/AIDS occurs in high numbers, the prevalence of NHL is higher in people living with HIV/AIDS. A number of these lymphomas are pathogenetically linked to viruses such as HHV8, EBV and HIV.

32.3 Diagnosis
Clinical presentation
- Lymphomas generally present similarly with lymphadenopathy with or without hepatosplenomegaly. Hodgkin’s lymphoma (HL), often starts as a single node with contiguous spread unlike lymphoblastic lymphoma which may involve different lymphnode groups over a short period.
- HL may also present with symptoms like weight loss, fever and night sweats leading to confusion for tuberculosis.
- CNS involvement is common in NHL unlike HL which rarely affects the system. The endemic type of BL which is closely linked with EB virus infection is found in the tropics and commonly presents as jaw masses or intra-abdominal tumors. Systemic spread is similar to that of lymphoblastic lymphoma, including spread to the bone marrow and liver. Spread to the CNS presents as paraplegia, proptosis or cranial nerve palsies, and even blindness.

Diagnosis involves physical examination chest and nasopharyngeal radiograph; abdominal ultrasound scans, FNA cytology for accessible tumours, biopsy with Immunohistochemistry (IHC), bone marrow aspiration/biopsy, CSF examination, complete blood count, liver function tests and LDH, kidney function tests and Uric acid, HIV, HBV & HCV screening. Imaging studies including gallium bone scan and skeletal survey, CT scan and MRI scans may be undertaken as indicated by clinical manifestations. The diagnosis should give a distinct clinical pathological entity based on morphology, immunophenotype and genotype (WHO classification).
32.4 Staging And Risk Assessment
Paediatric non-Hodgkin’s lymphomas are most commonly staged according to St. Jude’s staging system and Hodgkin’s lymphomas according to modified Ann Arbor system.

Risk Assessment
Outcome depends on histological classification with most favourable being for lymphocyte rich classical and Nodular lymphocyte predominance histology and clinical stages I & II A. Patients with B symptom respond less well to treatment. Elevation of ESR suggests poor prognosis and B-symptoms while alkaline phosphatase may indicate presence of bone involvement requiring radio nuclide studies or skeletal survey.

32.5 Management
• As in other cancers, treatment is divided into supportive and specific. Specific treatment is determined by type of lymphoma.

32.5.1 Burkitt’s Lymphoma
• Current treatment protocols place emphasis on short but intensive treatment without maintenance therapy as was the case in the past.
• It is highly chemo-sensitive and recommended treatment comprises of six courses of a combination of cyclophosphamide, vincristine and methotrexate.
• Intrathecal methotrexate and cytosar are given for CNS prophylaxis and treatment.
• Although highly radio-sensitive, radiotherapy is not effective because of rapid tumour growth.
• Other more intensive protocols offering superior results require high level supportive care as they depend on high dose methotrexate and cytosine arabinoside.

32.5.2 Precursor B-cell Lymphoblastic lymphoma
Approach to treatment is similar to that of B-cell acute lymphoblastic leukemia with induction, consolidation/intensification and maintenance phases and intercalated CNS prophylaxis or treatment. As in acute leukemia methotrexate, cytosine- arabinoside and cranial irradiation are the mainstay for CNS management. Treatment of T-cell lymphoblastic lymphoma also follows similar approach to that of acute lymphoblastic leukemia. Hodgkin’s lymphoma is managed with chemotherapy followed by radiotherapy. The number of courses of chthenotherapy and radiotherapy is dictated by disease stage and risk category. The salvage treatment for relapses and non-responders is autologous stem cell transplant following myeloablative therapy in patients without bone marrow disease. Allogeneic transplant would be offered to those with bone marrow disease and compatible related donors. Alternative but more intensive protocols are available for NHL initial treatment failures though with poor outcome.
32.5.3 Prognosis of Non-Hodgkin’s Lymphoma (NHL)

The prognosis is determined by the stage of disease and the immunophenotype, with T-cell and mature B-cell having a poor prognosis. The presence of certain genotypes such as double Cmyc translocation indicate poor prognosis in Burkitt’s lymphoma which otherwise has long disease free survival of 60-80% with optimal treatment for stages I-III. Cure rate for Stage IV is below 50%. Current protocols for T-cell lymphoma show disease free survival of up to 70%. Hodgkin’s disease is among childhood cancers with best outcome for all clinical stages put at about 70%.

32.5.4 Response evaluation and follow-up

Response to treatment should be gauged by the regression of tumour at disease sites, using imaging modalities including, PET scan where available.

Follow up after treatment should be every 6 weeks in the first year then every 3 months in the second and third year followed by bi-annual reviews till the age of 5 years. Annual visits would be advisable thereafter to monitor growth and development as well other psycho-social and endocrine concerns.

32.6 Commonly Used Medicines

Medicines are similar as for adult lymphoid neoplasms, but protocols have minor variations. Commonly used medications include cyclophosphamide, vincristine, prednisone, procarbazine, doxorubicin, bleomycin, dacarbazine, vinblastine, chlorambucil and etoposide.

In resource limited settings, a combination of cyclophosphamide, vincristine, prednisone and procarbazine can be used. Standard protocol for HL combines doxorubicin, bleomycin, vinblastine and dacarbazine (DTIC) on days 1 & 15 on a 28-day cycle.

32.7 Prognosis

Prognosis is more favourable than in adults.

REFERENCES

33. Nephroblastoma (Wilm’s Tumour)

33.1 Introduction
The commonest solid tissue tumours in childhood include nephroblastoma, retinoblastoma, rhabdomyosarcoma and neuroblastoma. Of these, nephroblastoma is the commonest. It arises from poorly differentiated cells in the kidneys. It is the most common renal tumour in children comprising 90% of all kidney cancers.

33.2 Epidemiology
Globally, the incidence is estimated to be between 5 -10 per million with peak before the age of 5 years. According to the Eldoret (AMPATH) cancer registry, Wilms tumour constitutes 17.4% of childhood cancers.

Retinoblastoma and nephroblastoma have strong familial tendencies; especially varieties that present within the first year of life. Majority of nephroblastoma present without associated physical findings (sporadic). A smaller number (familial) occur in association with congenital anomalies such as aniridia, hemihypertrophy and genitourinary anomalies. These findings in an infant with a positive family history should increase index of suspicion for kidney tumour.

33.3 Diagnosis
Nephroblastoma most commonly presents as painless abdominal swelling though gross or microscopic haematuria and hypertension occur less often. This emphasizes the importance of full physical examination for children even when they present with unrelated clinical problems as most cases are detected by chance.

Nephroblastomatosis, mesoblastic nephroma, bilateral nodular renal blastema and non-malignant conditions like hydronephrosis should be excluded in those less than 2 years with bilateral renal involvement. Very similar presentation to that of neuroblastoma making it difficult to differentiate those with early disease without imaging or laboratory support. A chest radiograph is a valuable diagnostic tool in looking for metastasis in these conditions. Nephroblastoma metastases occur in lung parenchyma, as opposed to those from neuroblastoma that tend to deposit in the posterior mediastinum.

Renal sonography is the preferable imaging study in differentiating the two as it provides better tissue cleavage without ionizing radiation though some may require optimized IVU studies. CT scan of chest at diagnosis is useful.

Definitive diagnosis of nephroblastoma is made histologically on tissue biopsy which also has prognostic implications and classified into classical and atypical. Classical histology is graded as “favourable” or “unfavourable”.

Most tumours exhibit triphasic appearance comprising of blastemal, stromal and epithelial cell types though some may exhibit only two or one.

Line of differentiation determines the designated tumour histiotype.

Malignant rhabdoid tumour (MRTK) and clear cell sarcoma are considered different entities...
from typical nephroblastoma. Predominantly blastemal histology is associated with more aggressive disease while stromal, especially with tendency to differentiation into skeletal muscle, demonstrate good response to treatment.

### 33.4 Staging And Risk Assessment

**Table 63: National Wilms Tumor Study (NWTS):**

(Clinical pathologic staging considers tumour dynamics and resectability and is the most preferred).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I:</td>
<td>Tumour limited to the kidney and completely excised</td>
</tr>
<tr>
<td>Stage II:</td>
<td>Tumour extends beyond the kidney but completely excised. Invasion of renal sinus and/or extra renal vessels and/or peri-renal fat.</td>
</tr>
<tr>
<td>Stage III:</td>
<td>Invasion beyond capsule, any abdominal lymphnodes, tumour rupture, peritoneal tumour implants or incomplete excision.</td>
</tr>
<tr>
<td>Stage IV:</td>
<td>Haematogenous metastasis (lung, liver, bone, brain and lymphnodes) outside abdominal pelvic region</td>
</tr>
<tr>
<td>Stage V:</td>
<td>Bilateral renal tumours at diagnosis</td>
</tr>
</tbody>
</table>

### 33.5 Management

**33.5.1 Supportive Management**

See general guidelines. Majority of children present in fairly good condition though those with stage IV and V may be wasted and septic.

**33.5.2 Specific Management**

National Wilms Tumour Study (NWTS) and Internal Society of Paediatric Oncology (SIOP) guidelines are the most widely used.
### Table 64: Management of Nephroblastoma

<table>
<thead>
<tr>
<th>Stage I</th>
<th>adjuvant Vincristine and actinomycin D without radiotherapy except for patients with unfavourable histology. No need for maintenance and radiotherapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage II</td>
<td>adjuvant vincristine and actinomycin D without radiotherapy except for those with unfavourable histology. No need for maintenance and radiotherapy.</td>
</tr>
<tr>
<td>Stage III and earlier stage disease with unfavourable histology –</td>
<td>Three drug adjuvant treatment with vincristine, actinomycin D and Adriamycin for a longer duration. Radiotherapy of renal bed and whole abdomen for those with positive nodes and tumour spillage. Radiotherapy should be avoided in children under the age of 2 years.</td>
</tr>
<tr>
<td>Stage IV –</td>
<td>Three drug adjuvant treatment with vincristine, actinomycin D and Adriamycin as in stage III. Radiotherapy is limited to residue metastatic lesions, especially in the lungs. Surgical excision should be considered prior to radiotherapy whenever feasible.</td>
</tr>
</tbody>
</table>

Note: Stage II-IV with diffuse anaplastic tumours should have radiotherapy of the tumour bed.

#### 33.5.3 Response Evaluation
- Imaging studies should be advised by disease stage and sites involved. Abdominal ultrasound should be performed after induction and end of maintenance treatment.
- Chest radiograph is preferred for evaluation of those with lung metastasis.
- Long term disease free survival for nephroblastoma in industrialized countries is in excess of 90% as virtually all patients present with early stage disease. Locally, survival is estimated at about 50%.

#### 33.5.4 Follow-up
- Clinical assessments every 2 months in the first year then 6 monthly in the second and third year; including monitoring of blood pressure. Recurrences are uncommon after 3 years hence follow up annually.
- Renal function tests including serum creatinine and protein-creatinine ratio three monthly in the first year then annually for 3 years then every 5 years as risk for renal impairment is lifelong.
33.6 Commonly Used Medicines
Ifosfamide, etoposide, carboplatin, vincristine, actinomycin-D, anthracyclines.
In resource limited settings, Vincristine, actinimycin-D, doxorubicin is the first line treatment. This also applies where resources are available.

33.7 Prognosis
These are curable in a majority of cases if diagnosed early.

REFERENCES
34. Neuroblastoma

34.1 Introduction
This tumour is less common than nephroblastoma. Annual incidence, peak age of presentation and clinical manifestations are similar to that of nephroblastoma but is more frequently associated with wasting. It has tendency of presenting at an earlier age than nephroblastoma with some cases manifesting in utero though majority of those undergo spontaneous regression.

34.2 Epidemiology
Incidence of neuroblastoma is higher in industrialized countries than in the less developed ones. According to the Eldoret Registry it contributes to 8.5% of solid tumours in childhood.

34.3 Diagnosis
- Neuroblastoma like nephroblastoma has peak age of presentation before 5 years though a few cases are seen in older children particularly in association with neurofibromatosis.
- Neuroblastoma may arise from any site with sympathetic nervous tissues. About 60% arise from the abdomen, especially supra-renal gland and present as painless flank swellings.
- General examination may reveal features of neurofibromatosis in those with late onset.
- Major differential diagnoses are similar to those for nephroblastoma but also include quasi-malignant and benign ganglioneuroblastoma and ganglioneuroma.
- Imaging evaluation should include abdominal ultra sound scan, chest radiograph, and/or chest CT/MRI scan. Skeletal survey and bone marrow trephine in two different sites are important in diagnosis and staging.
- MIBG scan is preferred to skeletal survey where available for diagnosis and follow-up. CT scan is used where primary tumour does not take MIBG.
- Tumour markers include vanillylmandelic acid (VMA), homovanillic acid (HVA), neuron specific enolase (NSE), lactate dehydrogenase (LDH), ferritin and N-myc gene amplification where available.
- Histology with immunohistochemistry provides confirmatory diagnosis with positive synaptophysin and CD 99 for neuro-endocrine tumours.

34.4 Staging And Risk Assessment
Clinical staging and N-Myc gene amplification are the most important predictors of prognosis. Infants and Stages II and III with N-Myc amplification and stage IV disease carry poor prognosis.
Widely recommended International Staging System for Neuroblastoma (ISSN) and is as follows:

**Table 65: Staging With ISSN For Neuroblastoma**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Localized tumour with complete gross resection and without lymph nodes involvement.</td>
</tr>
<tr>
<td>II(a)</td>
<td>Localized tumour with incomplete resection but without lymph nodes involvement.</td>
</tr>
<tr>
<td>II(b)</td>
<td>As IIa but has ipsilateral lymph nodes involvement but contralateral are tumour free.</td>
</tr>
<tr>
<td>III</td>
<td>Unresectable unilateral tumour infiltrating across the midline with or without regional lymph nodes involvement</td>
</tr>
<tr>
<td>IV</td>
<td>Primary tumour with dissemination to distant lymphnodes, liver, bone, bone marrow, skin and/or any other organs (excludes those under IVs).</td>
</tr>
<tr>
<td>IVs</td>
<td>Localized primary tumour manifesting as Stage II above in infants below 1 year with dissemination limited to skin and liver and/or bone marrow.</td>
</tr>
</tbody>
</table>

### 34.5 Management

**34.5.1 Surgery**

Surgery is the mainstay of treatment with chemotherapy being reserved for Stage III and IV and those with N-Myc gene amplification. Outcome of stage III and IV neuroblastoma is poor.

- Stage I & II should be treated with surgical resection alone. Localized recurrence should be similarly resected without adjuvant treatment.
- Children above 1 year with Stage III disease should undergo surgical resection. Those with N-myc amplification should be given adjuvant chemotherapy.
- All Stage IV and N-myc amplified tumours in patients above 1 year should receive neoadjuvant chemotherapy followed by surgical resection of the primary. This should be followed by myelo-ablative therapy (MAT) and autologous or allogeneic stem cell transplant where feasible followed by radiotherapy of primary site and 6 months course of intermittent 13 cis-retinoic acid. Where stem cell transplant is not an option, the goal of treatment remains disease control and palliation without toxic radio or chemotherapy.

**34.5.2 Response Evaluation**

- Evaluation relies on monitoring of tumour markers, MIBG and imaging studies. Event Free Survival (EFS) of above 80% is expected for stages I-II with negative amplification.
- Children above 1 year with N-myc amplification and Stage IV disease have worst prognosis with 45% success following above treatment.
34.5.3 Follow-up
Considering de-emphasis on overtreatment of residual disease, close follow-up at 6 weekly intervals during first year and 3 monthly thereafter is recommended.

34.6 Commonly Used Medicines
Cisplatin, doxorubicin, etoposide, cyclophosphamide, ifosfamide, melphalan, carboplatin. In resource limited settings, Cis-platin/carboplatin plus cyclophosphamide, doxorubicin, or etoposide is the first line regimen. The same applies where resources are available.

34.7 Prognosis
Prognosis is good particularly in those diagnosed early.

REFERENCES
35. Retinoblastoma

35.1 Introduction
- Retinoblastoma is the most common primary ocular malignancy (eye cancer) of childhood. Although not often recognised at birth, it is often congenital and usually affects young children. It is widely believed to arise from mutation (chromosome 13) hence prevention by counselling and early detection is important.
- Children with hereditary forms of retinoblastoma are at an increased risk of developing other malignant tumours.

35.2 Epidemiology
Worldwide, the incidence of retinoblastoma is estimated to be 1 case of retinoblastoma per 18,000-30,000 live births, depending on the country. The total number of new cases in Kenya is estimated at 90 per year. At KNH about 50 new cases are seen annually. The average age at diagnosis is about 2 years. There is no significant difference in the incidence of retinoblastoma by sex for children. About 5% of patients will have a family history of the disease.

35.3 Diagnosis
- History should capture family history of retinoblastoma and eye tumours in the family, previous enucleation, or any malignancy in childhood.
- Retinoblastoma may present as a white pupil (leukocoria), squint (strabismus), abnormal red reflex (done in a dimly lit room) or proptosis.
- It is important to differentiate it from congenital cataract, vitreous haemorrhage, retinal detachment and other ocular tumours like Burkitt’s lymphoma, neuroblastoma, rhabdomyosarcoma and chloroma in acute myeloid leukaemia.
- Ultrasound and/or CT/MRI to provide further details on texture and extent of involvement.
- Biopsy for histological and histochemistry for confirmation.
- Other Laboratory investigations should include haemogram, U/E and LFTs and DNA studies for hereditary types.
- Cerebrospinal fluid cytology done for extensive intraocular (stage D, E) or extraocular (metastatic) disease.
- Bone marrow aspirate or trephine should be done when there is systemic involvement.

35.4 Staging And Risk Assessment
- Retinoblastoma is categorized into intraocular and extraocular disease for purposes of treatment.
- Clinical staging is adopted from the American Joint Committee on Cancer (AJCC).
- There are 5 clinical stages:
Table 66: AJCC Staging For Retinoblastoma

<table>
<thead>
<tr>
<th>Group A:</th>
<th>Small intraretinal tumors (&lt; 3mm diameter) away from foveola and disc,</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B:</td>
<td>All remaining discrete tumors confined to the retina.</td>
</tr>
<tr>
<td>Group C:</td>
<td>Discrete local disease with minimal subretinal or vitreous seeding.</td>
</tr>
<tr>
<td>Group D:</td>
<td>Diffuse disease with significant vitreous or subretinal seeding.</td>
</tr>
<tr>
<td>Group E:</td>
<td>Presence of any one or more of several poor prognosis features including Tumor touching the lens, diffuse infiltrating retinoblastoma, tumour necrosis with aseptic orbital cellulites.</td>
</tr>
</tbody>
</table>

- Prognosis for vision in the uninvolved eye in unilateral tumours is excellent.
- Presence of multiple primary tumours or bilateral tumour supports a diagnosis of inherited retinoblastoma. Prognosis for vision in bilateral retinoblastoma depends upon the extent of tumour involvement and the effectiveness of treatment. Outcome for extraocular (metastatic) disease is poor.

35.5 Management

- Management of retinoblastoma is complex and relies heavily on a coordinated team approach which includes the ophthalmologist, oncologist, radiation oncologist and radiologist among others.
- The goals of treatment are to save a child’s life followed by need to save the eye and or vision.
- Supportive management is as for other childhood malignancies with extra need to prepare for loss of an eye from enucleation.
- Specific treatment combines surgery with chemotherapy with or without radiotherapy depending on stage of disease and extent of involvement of the contralateral eye.
- Surgical Enucleation is treatment of choice for advanced intraocular retinoblastoma.
- Pre-enucleation chemotherapy is avoided whenever possible since it may mask features of extraocular extension causing understaging and undertreating of systemic disease.
- Orbital exenteration is used when there is tumour recurrence after the child has received maximal acceptable doses of chemotherapy and radiotherapy.
- Cryotherapy is used in treatment of equatorial and small peripheral disease and pre-chemotherapy (24 – 72 hours) to increase the drug penetration in the eye.
- Laser photocoagulation is reserved for treatment of small posterior disease.
- Late stage disease is treated with neoadjuvant chemotherapy before enucleation and radiotherapy.
- Early insertion of prosthesis after surgery when socket is healed reduces facial deformity.
35.5.1 Response Evaluation and follow up

- Examination under anaesthesia (EUA) is performed to assess the disease prior to surgery and then during follow up according to the stage of disease and whether the contralateral eye is involved.
- Survivors should receive individualized, lifelong follow-up and surveillance, counseling (including genetic) and interventions for late effects of disease and treatment.
- Monthly follow-up is advocated in the first year then 3 monthly for 2 years then every 6 month visits till age of 5yrs and thereafter annually for life as advocated for all other cancers.
- More frequent visits should be advised for a child with proven hereditary retinoblastoma gene mutation associated family history of disease and/or bilateral involvement.
- Survivors of school age with significantly reduced visual fields/visual acuity should be referred to a low vision centre for additional assistance as appropriate.
- Genetic counseling should be done for the family of the affected child.

35.6 Commonly Used Medicines

Etoposide, carboplatin, cyclophosphamide, thiotepa, vincristine, doxorubicin, etoposide, cyclosporine. In resource limited settings, Cisplatin/carboplatin plus etoposide, cyclophosphamide, or doxorubicin, with or without cyclosporine are the first line. The same combination applies where resources are available.

35.7 Prognosis

Prognosis is usually good.

REFERENCES

36. Bone Tumours

Bone tumors are presented in more details in the section on adult tumours.

36.1 Introduction

In childhood, the commonest bone tumours are osteogenic and Ewing’s sarcomas. Although emphasis below is on osteogenic sarcoma, with improvements in immunohistochemistry abilities, Ewing’s sarcoma family of tumors are increasingly being reported from Negroid population. Ewing’s sarcoma manifests as osteolytic lesions in long and flat bones with almost similar frequency which arises in the diaphysis and metaphysis unlike osteogenic sarcoma which predominantly arises from the metaphysis.

36.2 Epidemiology

Osteogenic sarcoma is the commonest bone tumor in children and adults with a childhood peak at 15-19 years. Annual incidence in the general population is 2-3 per million and 1 per million in children. It is about 1.4 times more common in males than females.

36.3 Diagnosis

- Presents as painful swelling associated with history of trauma in about 10% of cases.
  - Common sub-types are osteoblastic, chondroblastic and fibroblastic and most often arise from long bones. Radial proximal soft tissue ossification may show “sunburst appearance” on plain radiographs, but which is not diagnostic. Codman’s triangle is caused by evident lifting up of the cortex by the tumor.
- MRI provides best information on intra-medullary and soft tissue spread.
- Plain radiograph may show lytic or sclerotic changes.

36.4 Staging And Risk Assessment

The staging is done in a similar manner to adults.

36.5 Management

- Primary modality of treatment is surgery but high risk of micro-metastatic spread calls for use of chemotherapy with doxorubicin, ifosfomide, cis-platin and high dose methotrexate or alternative combinations.
- Though without proven better outcome, neo-adjuvant chemotherapy may help contain micro-metastatic disease earlier and improve feasibility of limb salvage surgery.
- Radiotherapy is reserved for inoperable residual disease.

36.5.1 Response evaluation and follow up.

- Alkaline phosphatase and LDH may be elevated in majority of patients, though levels may not accurately reflect extent of disease, but may predict worse outcomes.
36.6 Commonly Used Medicines
Doxorubicin, cisplatin, methotrexate, ifosfamide, actinomycin D, Etoposide, cyclophosphamide, vincristine, bleomycin.
In resource limited settings, a combination of doxorubicin and cisplatin with or without actinomycin D should be first line treatment.

36.7 Prognosis:
These tumours, if diagnosed early, are curable in over 80% cases with surgery and adjuvant chemotherapy. Unfortunately, in our set-up they tend to be diagnosed late. Still, with amputation and chemotherapy the cure rates approach 50%.

REFERENCES
37. Kaposi’s Sarcoma

37.1 Introduction
Kaposi’s sarcoma (KS) is a tumor associated with Human herpesvirus 8 (HHV8), also known as Kaposi’s sarcoma-associated herpes virus (KSHV).

37.2 Epidemiology
KS is one of the most prevalent cancers in children in those regions of Africa with a high prevalence of HIV infection and is an AIDS defining illness. It has been estimated that an HIV-infected individual has a 20,000 times increased risk of developing KS compared with people without HIV. A lymphadenopathic form of Kaposi’s sarcoma is also seen in HIV seronegative pre-pubertal children. In Kenya, childhood KS has an incidence rate 3.6 per million.

- KS presents as a systemic disease with lymphadenopathy, cutaneous lesions, oropalatal and inguinoscrotal disease with or without internal organ involvement.
- Skin lesions are reddish to dark purple multifocal and widespread. They may be flat, raised or nodular. There is tendency to affect groins and genitalia. Facial nodules commonly accompanied by peri-orbital oedema and haemorrhages while oral lesions tend to involve the hard palate, gums or tongue.
- Internal lesions may cause bleeding, intussusception, pain and weight loss and respiratory system involvement may cause cough, shortness of breath, haemoptysis, chest pain or pleural effusions.

37.3 Diagnosis
- KS presents as a systemic disease with lymphadenopathy, cutaneous lesions, oropalatal and inguinoscrotal disease with or without internal organ involvement.
- Skin lesions are reddish to dark purple multifocal and widespread lesions. They may be flat, raised or nodular. There is tendency to affect groins and genitalia. Facial nodules commonly accompanied by peri-orbital oedema and haemorrhages while oral lesions tend to involve the hard palate, gums or tongue.
- Internal lesions may cause bleeding, intussusception, pain and weight loss and respiratory system involvement may cause cough, shortness of breath, haemoptysis, chest pain or pleural effusions.
- Biopsy and histology of lesion confirms the diagnosis.
- Other investigations may include bronchoscopy, endoscopy, Ultra scan (U/S) and CT scan
- Other supportive investigations include haemogram, urea, electrolytes and creatinine and LFTs.
37.4 Staging And Risk Assessment

HIV Screening Risk Assessment
There is no accepted and validated system for staging all types of Kaposi’s sarcoma (KS) in children. The AIDS Clinical Trial Group system was devised pre-HAART era. It considers:
(i) The extent of the tumor,
(ii) The status of the immune system (CD4 count),
(iii) Presence or absence of systemic illness.
Under each of these, 2 subgroups identified by either a zero (0, or good risk) or a 1 (poor risk).

37.5 Management
This depends on whether associated with HIV immunosuppression, number and location of the tumors and symptoms.

37.5.1 General and supportive treatment
- This includes the management of:
  - HIV infection with antiretroviral drugs (may cause tumour regression)
  - Anaemia, thrombocytopenia with blood and blood products
  - Fever, co-infections (including TB) and pain.
  - Poor nutritional state often present.

37.5.2 Specific treatment
- Chemotherapy – for generalized or extensive disease the regimen of choice is a combination vincristine and bleomycin (BV). In those patients with extremely poor status, two drug or single drug regimen may be opted for.
- Few small localised lesions may be treated with cryotherapy alone where available and Radiation therapy used for limited localized disease or for palliation.

37.5.3 Response Evaluation and Follow-up
- Response to HIV treatment with HAART usually improves the outlook of HIV-associated Kaposi’s sarcoma (KS). Reductions in size and number of lesions are evidence of response to treatment. Activity and well-being should also be measured (Lansky score).
- Recurrent disease and sero-negative lymphadenopathic KS seen in young children has a poor prognosis.
Post treatment follow-up should be six weekly for the first year followed by 3-monthly follow-up for the next year then 6-monthly to yearly after that.
37.6 Commonly Used Medicines
Vincristine, bleomycin, doxorubicin, paclitaxel, vinorelbine, etoposide, vinblastine, irinotecan.
In resource limited settings, a combination of bleomycin and vincristine is the treatment of choice. In failing treatment, doxorubicin can be added to the combination.

37.7 Prognosis
Usually very good for HIV infected patients on concurrent antiretroviral medicines (ARVs).

REFERENCES
SOFT TISSUE SARCOMAS

Soft tissue sarcomas comprise a heterogenous group of tumours derived from mesenchymal cells like muscle, connective tissues and fat, the most common being rhabdomyosarcoma. The rest are like in adults.

38. Rhabdomyosarcoma

38.1 Introduction

• Rhabdomyosarcoma (RMS) a highly malignant and the commonest soft tissue sarcoma in children in most populations.
• It is among the group referred to as small round cell tumours of childhood.

38.2 Epidemiology

Soft tissue sarcomas comprise a heterogeneous group of tumors derived from tissues of mesenchymal origin and constitute about 6.5 - 8% of all paediatric malignancies worldwide. Rhabdomyosarcoma is the commonest subtype in the first two decades of life, accounting for 60 - 70% of these diagnoses. About 70% develop before the age of 10 years and shows two peaks of incidence; the first peak in children aged 2 -5 years, and the second during adolescence. Local data lumps it with other soft tissue tumors at 8.5%.

Aetiology of childhood RMS is still unknown. Genetic factors may play an important role. Congenital disorders like neurofibromatosis, fetal alcohol syndrome and Li-Fraumeni cancer family syndrome. Characteristic reciprocal chromosomal translocations involving the PAX3 gene on chromosome 2 and the PAX7 gene on chromosome 1 are found in the majority of tumours with the alveolar subtype.

38.3 Diagnosis

Initial signs depend on the site of origin and on the extension of the tumour to contiguous organs. RMS may arise anywhere in the body. The reported relative frequency of occurrence at primary sites are in decreasing order: genitourinary 23% (bladder and prostate, non bladder prostate), parameningeal head – neck 21%, other sites 22%, extremities 14% orbit 10.5%, headneck non parameningeal 9.5%. Some are asymptomatic, but the commonest presenting symptoms are masses (polypoid protrusion in cavitory sites like bladder, vagina and nasal cavity and scrotum), obstruction (urinary, nasopharynx, gastrointestinal), proptosis, cranial nerve palsies and ascites with peritoneal masses.

• Tissue diagnosis can be obtained preferably through core needle biopsy. Fine needle biopsy can also be performed. Fine needle aspirations have limitation in that they do not provide enough information to distinguish the various sub-types. Incisional biopsy should be through the smallest incision. Biopsy should be performed preferably at the center where definitive treatment will be carried out.
• Immunohistochemistry: Desmin and muscle specific actin are relatively sensitive though not as specific as muscle transcription factors myoD and myogenin, which are preferable.
• Molecular cytogenetics has become an established adjunct to conventional histological analysis in RMS.

38.4 Staging And Risk Assessment

• Investigations depend on the anatomic sites affected and include complete physical examination, Laboratory (TBC, LFTs, RFTs including phosphorus, calcium and magnesium, uric acid and coagulation parameters, bone marrow biopsy and trephine biopsy). Imaging (chest xray, ultra sound, CT, MRI scans and cerebrospinal fluid cytology done when CNS disease is suspected).

• Prognostic factors include primary site of involvement, clinical group/stage using the Intergroup Rhabdomyosarcoma studies (IRS I-IV) system that considers tumor resectability and tumor size, nodal involvement and metastasis.

Table 67: Intergroup Rhabdomyosarcoma Study Staging System

<table>
<thead>
<tr>
<th>STAGE</th>
<th>FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor confined to anatomic site of origin (noninvasive).</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor extension and/or fixation to surrounding tissue (invasive).</td>
</tr>
<tr>
<td></td>
<td>a Tumor ≤5 cm in maximum diameter.</td>
</tr>
<tr>
<td></td>
<td>b Tumor &gt;5 cm in maximum diameter.</td>
</tr>
<tr>
<td>N0</td>
<td>No clinical regional lymph node involvement.</td>
</tr>
<tr>
<td>N1</td>
<td>Clinical regional lymph node involvement.</td>
</tr>
<tr>
<td>NX</td>
<td>Regional lymph nodes not examined; no information.</td>
</tr>
<tr>
<td>M0</td>
<td>No metastatic disease.</td>
</tr>
<tr>
<td>M1</td>
<td>Metastatic disease.</td>
</tr>
</tbody>
</table>

Further prognostication is as below:

Favorable site: Orbit: nonparameningeal head and neck; genitourinary tract other than kidney, bladder, and prostate; biliary tract.

Unfavorable site: Any site other than favorable.

• Favourable prognosis is associated with: complete surgical excision, tumour ≤5 cm without nodal involvement or spread, primary site in orbit and genitourinary (excluding non - bladder or prostate sites) and head & neck excluding para-meningeal involvement. The International classification of RMS recognizes three prognostic categories:

• Superior Prognosis with > 90% event free survival (botryoid, spindle cell subtypes);

Intermediate with 60-80% survival (embryonal) and Poor with < 60% survival (alveolar, pleomorphic and anaplastic).
38.5 Management
- Determination of mode of therapy needed may be challenging in RMS depending on primary site of involvement. Choice must balance probability of cure and treatment-associated morbidity. Surgery is, for example less preferable for neck, orbital and urinary bladder tumours. Radiotherapy as an option, though effective, is less preferable to surgery and chemotherapy except for surgically inaccessible sites. It is otherwise reserved for containing residual disease.
- Second look surgery post chemotherapy or radiotherapy is justified.
- Combinations of vincristine, doxorubicin and cyclophosphamide or ifosfamide have remained standard treatment. Therapy intensification has translated in more toxicity without better disease-free survival. Cisplatin, carboplatin, etoposide and DTIC have led to remission as rescue regimens, but superiority has not been demonstrated.

38.5.1 Response evaluation and follow-up
- Evaluation following treatment involves physical assessment and imaging for local and metastatic disease initially at 6 weekly intervals in the first year then 3-monthly for 2 years then every 6 months till 5 years post treatment. Annual visits would suffice thereafter.
- Booster vaccines and growth development and endocrine assessments are key part of follow up for all children treated for cancer irrespective of diagnosis.

38.6 Commonly Used Medicines
Doxorubicin, ifophosphomide, cyclophosphomide, vincristine, gemcitabine, paclitaxine. In resource limited settings, a combination of vincristine, doxorubicin, and cyclophosphamide is the first line treatment.

38.7 Prognosis
Prognosis is usually good.
REFERENCES


PART 4

SUPPORTIVE CARE FOR CANCER PATIENTS
39. Nutritional Care of the Cancer Patient
Samburu B, Ngaruro R

39.1 Introduction
Nutrition plays a major role in many aspects of cancer development and treatment. Malnutrition is a common problem in cancer and an important component of adverse outcomes, increased morbidity and mortality and decreased quality of life. Depending on the type of cancer, some persons die because of severe malnutrition rather than the malignancy per se. Nutritional support of persons with cancer should be an integral part of any treatment.

Weight loss is an indicator of poor prognosis in cancer patients. At diagnosis, 80% of patients with upper gastrointestinal cancer and 60% of patients with lung cancer have a significant weight loss, defined as at least a 10% loss of body weight in the preceding 6 months. Poor nutrition practices lead to under nutrition, contribute to the incidence and severity of treatment side effects, and increase the risk of infection, thereby hampering chances of survival.

39.2 Goals of Nutrition care:
- Prevention or correction of nutritional deficiencies
- Minimizing weight loss
- Support healing
- Regain muscular strength
- Relief from nutrition impact symptoms and improving quality of life
- Provide nutrition support for those with difficulty feeding

39.3 Initiation of Nutrition care
This should be in the management plan and started in the initial health assessment or on admission. It should include:
1. Nutrition assessment
   - Medical social and nutrition history
   - Anthropometric data
   - Nutrition and drug interaction
   - Biochemical assessment
   - Dietary analysis
2. Nutritional Diagnosis
3. Nutritional Intervention
   - Oral Feeding during the management of cancers
   - Nutritional management of therapy side effects
   - Nutritional support at the rehabilitation stage
4. Nutritional Monitoring and evaluation
   - Routine assessment

**39.4 Cancer cachexia**
This syndrome is defined by a >5% weight loss/month or >10% weight loss over 6 months. It is typified by loss of appetite, inadequate food intake, progressive weight loss, malnutrition, increased and altered metabolism and wasting.
Cancer cachexia is also associated with:
- Decreased immunity and increased risk of infections;
- Decreased resistance to side effects of treatment;
- Multiple organ dysfunction;
- Poor tolerance to treatment.

Nutrition intervention should start soon after diagnosis has been made for longer-term management of the disease.

**39.5 Nutritional Needs For Cancer Patient**
These are general recommendations for adults which should be adjusted to individual patient needs

**Energy**
Persons with a normal nutritional status have an increase of 110 – 130% of the usual energy requirement. On the other hand if the individual is malnourished, 130 – 150% of normal energy requirement is needed.

**Protein**
If the person with cancer has a normal nutritional status, the protein requirement is 1 - 1.25 g/kg body weight (current weight) compared to the malnourished person’s need of 1.5 – 2 g/kg.

**Fats**
Monounsaturated and polyunsaturated fats are preferred to saturated fats or transfats. Monounsaturated fats are found mainly in vegetable oils like olive, canola, and peanut oils, whereas polyunsaturated fats are found mainly in vegetable oils like safflower, sunflower, corn, and flaxseed.

**Vitamins and minerals**
The needs of these depend on the type of therapy used and the presence and the severity of complications. All individuals should be carefully monitored for early signs of nutrient deficiencies. Multivitamins/minerals should be supplemented in most persons with cancer, while guarding against excessive supplementation.
Antioxidants
Patient should be advised and encouraged to eat a variety of fruits and vegetables. Commercial antioxidants under prescription are recommended if the patient intake of fruits and vegetables is poor.

39.6 Methods of feeding
The oral route is the preferred mode of feeding but for persons with eating difficulties or food-related problems, modifications are necessary in the type and consistency of food and its presentation according to individual needs. Frequent, small meals, with emphasis on morning feedings, are suggested. The timing of meals or snacks relative to anti-cancer therapy should be considered.

Enteral feeding
If the oral route fails and food intake remains inadequate or is inappropriate due to the site of the cancer, alternative feeding methods should be used. If the gut is functional, enteral feeding (tube feeding) is an option.

Parenteral nutrition.
This method is used when the gastrointestinal tract is not functioning. Intense monitoring and specialized care is required in such a situation.

Dietary guidelines for adjusting the diet to treat symptoms associated with anti-cancer treatment (Appendix 2)

REFERENCES:
40. Oncologic and Palliative Care Emergencies

Busakhala, AO

Emergencies can result from either the cancer or its treatment or unrelated disease. In emergencies, rapid assessment, evaluation and management of symptoms due to malignancy is required. Major emergencies include: delirium, severe pain, Spinal Cord Compression (SCC), Superior Vena Cava Obstruction (SVCO), hemorrhage, hypercalcaemia, pathological fracture, drug toxicity, chocking, seizures, and stridor. These need to be assessed and treated as emergencies (Refer to Treatment Protocols)

40.1. Neurologic Emergencies typified by

40.1.1 Spinal Cord Compression
The most common presentation is back pain and weakness of the limbs.

Management
Give Dexamethasone at 10 -100 mg intravenously and then 4 - 24 mg every 4 to 6 hours, surgery, and radiotherapy.

40.1.2. Increased intracranial pressure; CSF pressure above 10 mm Hg.
Presentation: Presents as headache, projectile vomiting, altered consciousness, seizures and coma. Pappiloedema is a constant finding.

Treatment ; oral dexamethasone at a dosage of 16 mg/day or 4 mg every 6 hours or 40 to 100 mg intravenously and subsequently 40 to 100 mg/day , mannitol in intact blood–brain barrier at 20 to 25% solution at 0.5 to 2.0 g/kg administered intravenously over 10 to 30 min, hyperventilation,Radiation , Surgery and Chemotherapy.

40.1.3. Seizures
Management: (Refer to 3.5)

40.1.4. Altered mental status
Management: According to CNS Section of the Guidelines

40.2. Cardiac Emergencies

40.2.1
Cardiac Tamponade; cardiac insufficiency due to pericardial effusion. The patient can present with a shock-like syndrome.

Management: Treatment of tamponade includes the administration of oxygen, intravenous fluids, and vasopressors if necessary. Pericardiocentesis under ultrasound guidance, Radiation therapy, chemotherapy and sclerosis.
40.2.2 Superior Vena Cava Syndrome; Impaired blood flow from the SVC to the right atrium
Physical examination often reveals engorgement of veins and collaterals in the upper extremities.
Management: Elevation of the head, corticosteroids, diuretics local lytic therapy or anticoagulation, chemotherapy, radiation, and stents.

40.3. Haematologic Emergencies
40.3.1 Febrile Neutropenia
Any patient with temperature single reading of 38.5°C or 38°C sustained for an hour, absolute neutrophil count of less than 500/mm³ or 1000/mm³ with predicted decline to <500/mm³ over next 48 hrs.
Management: Barrier nursing, antimicrobial therapy and growth factors. Treatment involves initiation of empiric antibiotic treatment usually with fluoroquinolone and amoxycillin/clavulanate. Haematopoietic growth factors such as filgrastim can be initiated prophylactically post-chemotherapy in patients at high risk for severe neutropenia.

40.3.2. Hyperviscosity Syndrome; Serum viscosity exceeds 4.0 Ostwald units.
Treatment; intravenous fluids followed by diuresis, plasma exchange, chemotherapy

40.3.3 Hyperleukocytosis; WBC count in the peripheral blood higher than 100,000/L.
Management: involves lowering the WBC count, which can be accomplished with leukapheresis or chemotherapy.

40.3.4 Thrombosis; Both deep venous thrombosis and pulmonary thromboembolism.
Management: anticoagulation and appropriate mechanical approaches as appropriate.

40.3.5 Bleeding; Prolonged bleeding both internally and externally.
Management: Treat the primary cause and give blood components.

40.4 Genitourinary Emergencies
40.4.1. Hemorrhagic Cystitis; Haematuria
Management: gentle bladder irrigation, prostaglandins E2 or F2, 1% alum, or formalin can be instilled. Formalin instillation is painful and requires general or spinal anesthesia. To correct continued bleeding, some patients require surgery, hypogastric artery embolization, or open surgical intervention.

40.4.2. Urinary Tract Obstruction; Involve ureters, or urethra
Management: Relieve obstruction by catheterization and stenting as appropriate.
40.5. Respiratory Emergencies

40.5.1. Airway Obstruction; both upper and lower airway
Management: Surgical intervention (Intubation and tracheostomy) with or without appropriate medication (steroids, bronchodilators, chemo/radiotherapy)

40.5.2. Hemoptysis; bleeding from the lower respiratory tract.
The most important aspect of managing massive hemoptysis is protecting the airway. This may need intubation through bronchoscopy.
Management: Any coagulopathy should be corrected, and cough suppressed with codeine or other agents.
Bronchial artery embolization or tumor resection external beam radiation therapy (EBRT), local epinephrine injection, laser treatment, electrocautery, APC, photocoagulation, balloon tamponade, or iced-saline lavage.

40.5.3. Toxic Lung Injury; Presents as acute respiratory distress syndrome.
Management: Support as appropriate.

40.6 Chemotherapy-Induced Extravasations;
Can cause skin irritation to skin ulceration, tissue necrosis, nerve damage, and (rarely) loss of limbs due to vesicant chemotherapy.
Management: Depends on the agent and site and quantity. Prompt expulsion of the extravasated agent.

40.7. Metabolic Emergencies

40.7.1. Syndrome of Inappropriate antidiuretic hormone secretion (SIADH)
A paraneoplastic syndrome in which antidiuretic hormone (ADH) is secreted inappropriately from the posterior pituitary gland, despite lower serum osmolality.
Management:
Restricting water to 500 to 1000 mL/day from all sources and treating the underlying disorder.
Demeclocycline (600-1200 mg/day) can be used in divided doses two to four times per day (51).
Slow infusion of 3% normal saline; care must be taken not to increase serum sodium by more than 0.5 to 1 mEq/h to prevent central pontine myelinolysis.

40.7.2. Tumor Lysis Syndrome; Is a combination of hypocalcemia, hyperphosphatemia, hyperkalemia, elevated uric acid, and occasionally acute renal failure.
Management: Supportive management with correction of electrolyte imbalance.

40.7.3. Hypercalcemia; Adjusted serum calcium levels above the upper limit of normal with associated symptoms.
Management: Intravenous saline infusion, steroids and biphosphonates
40.8 Gastrointestinal Emergencies

40.8.1 Gastrointestinal Bleeding

40.8.2 Typhlitis; a syndrome of bowel inflammation, edema, and wall thickening involving the proximal large bowel in patients with neutropenic fever. The organisms most often isolated in cases of typhlitis are Clostridium and gram-negative bacilli. Treatment: bowel rest and intravenous administration of broad-spectrum antibiotics and rarely surgery. Further reading: The MD Anderson Manual of Medical Oncology
41. Support of Treatment Complications

Chite F, Njuguna E, Ng’ang’a W, Musibi A

41.1 Cancer symptoms and side effects of treatment
Common side effects experienced with treatment include nausea, vomiting, mucositis, alopecia, peripheral neuropathy, hand-foot syndrome, bone marrow suppression, diarrhea, anorexia, fatigue, paresthesia, ulceration. Patients should receive preventative supportive medication before and after treatment, to reduce expected adverse effects and improve tolerability. Patients should also be encouraged to report any new problem they experience, to their healthcare provider.

Lymphedema care
Lymphedema is often caused by the interruption of regional lymphatic drainage e.g. following breast cancer it results from interruption of the axillary lymphatic drainage from the arm. To detect lymphedema, circumferential measurements of both extremities should be taken at the metacarpal-phalangeal joints, the wrists, 10 cm distal and 15 cm proximal to the lateral epicondyles. A difference of 2 cm or greater at any point is clinically significant.

It is recommended that a multi-disciplinary team should manage patients with Lymphedema. Options of care include external compression, massage, elevation, exercise, psychosocial support, prompt treatment of infection and avoidance of factors which may aggravate it.

Sterility, infertility and teratogenicity
Prior to any planning for cancer treatment, a care team is strongly advised to discuss with the patient, with or without the family, the effects of the treatment of fertility, potential for sterility and teratogenicity. Options for sperm banking, ovarian relocation, and embryo preservation should be discussed.

Oral: Xerostomia and pain
Patient should maintain a clean and well-hydrated mouth, avoiding any foods such as acidic citrus fruits and juices, hot and spicy products and rough-textured foods, if these cause discomfort. Both topical and systemic analgesics should be used for pain and oral antiseptics gargles for infections.

Patient support groups
Formation of patient support groups should be encouraged. This forms an integral part of survivorship care.
Spiritual and psychosocial counseling (see Chapter 40).
Blood and Blood Products Transfusion
This is indicated in patients with anaemia or thrombocytopenia and other disorders of coagulation and haemostasis. In patients presenting with low haemoglobin and associated symptoms, it is recommended that blood and blood products transfusion is undertaken, appropriately guided by the clinical scenario. These include Hb<10gm/dl prior to chemotherapy or radiotherapy and symptomatic anaemias. Also, erythropoietin and parenteral iron replacement may be used as needed.

Skin care: Wounds and radiation skin reactions
Wound management should be structured around three core principles: treatment of the underlying tumour and management of co-morbid conditions; symptom management; and local wound management.
Radiation skin reactions are a common side effect of radical radiotherapy. Reactions are evident one to four weeks after beginning treatment and can persist for several weeks post treatment. Patients should maintain good skin hygiene, applying aqueous cream and cytoprotective agent e.g. amifostine.

Rehabilitation
Rehabilitation should be considered and addressed prior to any cancer management plan. These include physiotherapy, speech and occupational therapy.

Stoma care
Nurses or health care professionals trained in stoma care should be charged with assisting patients with management of stomas.

Thrombo-embolism management
The risk of thrombosis exists in cancer patients and should be taken into consideration. Prompt referral to a facility that can initiate immediate anticoagulation is key to the survival of patients with thrombosis.
42. Palliative Care

Ali Z, Maara M, Njuguna E, Munyoro E, Makumi D, Mwangura F, Kumar V.

42.1 Introduction

Palliative Care is an approach that improves the quality of life of patients and their families facing the problems associated with a life-threatening illness. It involves the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual (WHO 2002).

Palliative care is patient and family centered, with a goal of supporting the best possible quality of life, regardless of the stage of the disease. This means that palliative care provides comfort even while the patient is on active cancer treatment. (For in-depth understanding, cross reference with various available palliative guidelines e.g. National Palliative Care Guidelines).

Palliative care should be offered right from diagnosis alongside conventional cure-oriented treatment NOT when cure is not possible. This will maximize the benefits of palliative care especially pain management and control of distressing symptoms (Appendix 3).

42.2 Essential components of palliative care

These include:

- Multi-disciplinary Teams (MDT)
- Effective symptom control
- Effective communication
- Psychosocial support
- Spiritual support
- Sexuality concerns
- Rehabilitation to maximize independence
- Continuity of care and coordination between services
- End of Life care
- Support in bereavement
- Education and Research
- Patient and family education and involvement in the care process
- Pain assessment and management

42.2.1 Multi-disciplinary Teams (MDT)

Hospice and palliative care is provided by an interdisciplinary team consisting of physicians, pharmacists, nurses, psychologists, social workers, chaplains, physiotherapists, occupational therapists, volunteers, and, most importantly, the family. The team’s focus is to optimize the patient’s comfort with the patient is the centre of the care process. Care Teams share an obligation to maintain confidentiality of information acquired through the clinician–patient relationship.
42.2.2 Effective symptom control
Distressing symptoms like nausea, vomiting, diarrhoea, hiccups, dyspnoea etc, that negatively impact the quality of life of patients with life threatening illness can be effectively controlled. This aims to improve the quality of life of the patients and enhance their autonomy.

Good symptom management using evidence based tools and protocols are important. Symptom management in palliative care includes, but is not limited to:
- Pharmacological therapies
- Non-pharmacological therapies
- Psychosocial support
- Palliative chemotherapy, radiotherapy and surgery

42.2.3 Communication:
The Care Team should communicate with the patient and family in a timely and sensitive manner. Communication should be done in a way that fosters hope and confidence in the care process. Patients are entitled to all information about their diagnosis, prognosis, treatment options and costs. Patients should be aware that they have a right to this information, and that all symptoms, including pain can be controlled. Patients are a key part of the care team and should have a say in decisions about their care.

42.2.4 Psychosocial support
Patients and their families should be assessed for psychosocial issues such as anxiety and depression since psychiatric co-morbidity has been reported to occur in about one third of the cancer patients. This necessitates the cancer treatment team to work closely with mental health workers in order to comprehensively address the needs of cancer patients. Psychosocial support groups for all patients with life threatening illnesses, including cancer, are therefore necessary to meet patients’ psychosocial needs. Care of children, finances, community support, family relationships and writing a will should be candidly discussed. Grief and bereavement support should be provided after the patient’s death.

42.2.5 Spiritual support
With a cancer diagnosis, patients and families often look more deeply for meaning in their lives and feel the need to mend broken relationships like forgiving and being forgiven. Spiritual care involves being a compassionate presence to patients and it recognizes that healing can take place even though a physical cure is impossible. Clinicians should be able to conduct a spiritual distress assessment using available tools.
42.2.6 Sexuality
Defined as the process of giving and receiving sexual pleasure and is associated with a sense of belonging or being accepted by another. Care Teams should bring up the topic and explain that sexuality is part of quality of life and that it can be discussed freely. This is particularly important especially in cases where the illness affects the sexual organs or impacts on the patient’s sexual performance.

42.2.7 Advanced Directives
Advance directives (advance decision) are legal documents that allow patients to convey their decisions about end-of-life care ahead of time. They provide a way for patients to communicate their wishes to family, friends and health care professionals, and to avoid confusion later on. All health care teams should be made aware of any directives given/signed. The presence of an advance directive should not deny a patient the right to quality health care.

42.3 Appropriate referral
42.3.1 Palliative Care Referral Criteria
Referral can be initiated by the client, the family or through other care providers such as a general practitioner, a medical specialist, community nurse or allied health professional. Referral can be to the hospital based palliative care teams, hospices or to palliative care medical specialists. This referral can be initiated for the following reasons:
- The physician feels the patient is at a point where supportive care should be emphasized.
- Has a life threatening illness with an expected poor prognosis.
- Has a deteriorating medical condition and is at risk of needing symptom control and management.
- Agrees with emphasis of care in the home setting with short term inpatient care.
- Care through the terminal event.
- If more aggressive therapy is needed it will be provided by the primary physician.
- Patient/Family is not agreeable regarding the life threatening diagnosis and prognosis.
- Patient/Family is not agreeable to stopping aggressive therapy.
- Physician is uncertain if the patient will benefit from hospice care.
- For pain assessment and management

42.3.2 When to refer the patient to a hospice
Hospice is the gold standard of end-of-life care. The hospice philosophy of comprehensive holistic care delivered compassionately by a multidisciplinary team greatly improves the quality of life of the dying. Ideally, referral should be when a patient has a life expectancy of six months or less. Hospice improves pain and symptom scores, enhances closure, addresses spiritual needs, and reduces the risk for complicated grief.
Hospice referral should also be considered when:

- There is the lack of treatment efficacy.
- There is a change in the goals of care
- An acute event, such as severe pain, occurs.

The referral discussion should introduce hospice care as what constitutes good medical care.

Patients can also be referred to Palliative Care Units (PCU) Appendix 5 which have been set up in major hospitals across the country so as to incorporate palliative care into the main stream health system.

### 42.4 End-of-Life Care

End-of-life care refers to medical care not only of cancer patients in the final hours or days of their lives, but more broadly, medical care of all those with cancer that has become advanced, progressive and incurable. When a patient’s health care team determines that the cancer can no longer be controlled, active cancer treatment should stop, but other forms of care should continue. Services should be available to help patients and their families with the medical, psychological, and spiritual issues surrounding dying. A care pathway that starts with the identification of people approaching the end of life and initiating discussions about their preferences is central to the end of life care strategy. A hospice provides such services.

#### 42.4.1 Grief and Bereavement Support

Grief and bereavement risk assessment should be done as required. Bereavement support should be provided as needed for as long as necessary. Cultural and religious rituals should be respected to help the family cope with death.

#### 42.4.2 Ethical Issues

The care team should identify existing potential ethical issues. The care team should take into account the laws of the land, cultural and religious beliefs when handling ethical issues. The care process established should observe autonomy and justice to guard against wrong-doing by the care team. Areas of conflicts should be discussed by the multi-disciplinary team (MDT) and if resolution cannot be reached the hospital ethical committee should be involved. Ethical committees should be established in all facilities offering cancer services.

#### 42.4.3 Imminent Death

Symptom control in the last days of life is primarily a continuation of what is already being done. New problems sometimes emerge and existing ones may be exacerbated. These should be promptly identified and appropriately managed. Care goals must be redefined and, when appropriate, certain treatments discontinued.
42.4.4 Laboratory and Imaging Tests
These must be used judiciously and only if they will positively impact the overall management of the patient and enhance the patient’s quality of life taking into account the cost.

42.5 Palliative care in children with cancer
The purpose of paediatric palliative care (PPC) in oncology is to deliver competent, compassionate, and consistent care to children living with cancer and their family members. Paediatric palliative cancer care includes physical, psychological, educational, social, and spiritual goals and is provided concurrently with disease-modifying therapies or as the main goal of care may require. This care aims to enhance life, decrease suffering, optimize function, and provide opportunities for personal and spiritual growth. Interdisciplinary palliative care team includes the child, family, and caregivers from the time of the cancer diagnosis, continuing throughout all cancer treatments into survivorship or cure, or until the end of life.

Primary care providers should be taught to recognize a child’s need for palliative care, to assess the emotional and spiritual needs of the child and family, to facilitate advance care planning, to assess and manage the child’s pain and symptoms, to provide bereavement care to the child’s family, and to recognize the indications for a referral to a specialist.

42.6 Cancer Pain
Pain is a common symptom experienced by patients with cancer either as a result of disease or disease-related treatment. Pain causes significant physical and psychosocial burden impacting the quality of life of the patient. Effective pain management may include pharmacological measures, based on the WHO pain management guidelines, and non-pharmacological measures. (See Chapter 43)
Even with late stage cancer, pain can be reduced, the progression of the cancer slowed, and patients and their families helped to cope.
REFERENCES

1. Adam J. ABC of palliative care: The last 48 hours. 1997;315:1600
43. Cancer Pain Management

Ali Z, Njuguna E, Munyoro E, Makumi D, Kumar Vijay, Kanja J.

43.1 Definitions
Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (International Association for the Study of Pain-IASP).

Pain is a subjective experience, and no objective tests exist to measure it. Whenever possible, the existence and intensity of pain are measured by the patient’s self-report, abiding by the clinical definition of pain.

More than 50% of all patients diagnosed with cancer experience pain and lack of adequate pain control is a persistent problem frequently reported by cancer patients. This inadequacy can be caused by barriers arising from limitations in the health care systems e.g. lack of pain medicines especially opioids; from health care providers e.g. unwillingness to prescribe or dispense opioids or they could be patient-related concerns like unwillingness to take opioids.

Pain associated with cancer increases with progression of the disease. Cancer pain has many dimensions including psychological, physical, social and spiritual which must be addressed in order to improve quality of life. For good pain management, the Clinician should assess spiritual and psychological distress, and treat appropriately. For all these to happen, good communication, planning and trust are fundamental.

43.2 Assessment of Pain
Diagnosis of the cause of pain and its functional and psychosocial impact is achieved by a full assessment (history, physical examination, investigations and standardized assessment tools – Appendix 4).

A comprehensive assessment of pain should consider the following domains:
- Physical effects/manifestations of pain
- Functional effects (interference with activities of daily living)
- Psychosocial factors
- Spiritual aspects

Pain should be assessed in terms of pain intensity, quality, location, radiation, mode of onset, timing, exacerbating factors and relieving factors of pain.

The patient should be the prime assessor of his or her pain where possible. The intensity of pain and the treatment outcomes should be regularly assessed using standardized assessment tools as (Appendix 3).
43.3 Principles of Pain Management

Patients should be given information and instruction about pain and pain management and be encouraged to take an active role. The principles of treatment outlined in the WHO cancer pain relief programme should be followed when treating pain in patients with cancer. Optimum management of pain in patients with cancer requires a multidisciplinary approach.

Table 68: Categorization of pain and appropriate analgesia

<table>
<thead>
<tr>
<th>SCORE NRS 1-10</th>
<th>ANALGESIC OF CHOICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Mild pain</td>
<td>Paracetamol ± NSAIDs ± Adjuvant</td>
</tr>
<tr>
<td>2 Moderate pain</td>
<td>Weak opioids ± paracetamol ± NSAIDs ± Adjuvant</td>
</tr>
<tr>
<td>3 Severe pain</td>
<td>Strong opioids ± paracetamol ± NSAIDs ± Adjuvant</td>
</tr>
</tbody>
</table>

The WHO analgesic ladder has been demonstrated to improve pain in approximately 85% of patients with cancer. Treatment should be adjusted from one step to the next according to increasing or decreasing pain severity, history of analgesic response, and side effect profile. For chronic pain analgesia should be individualized, given regularly by the clock, preferably by mouth and by the WHO ladder for pain management.

Breakthrough pain is pain of moderate or severe intensity arising on a background of controlled chronic pain. Breakthrough pain may be described as spontaneous (unexpected) or incident (expected or predictable). For quality pain control, breakthrough medication must be prescribed.

The extent to which pain responds to opioid analgesics varies depending on both patient and pain characteristics. No pain is predictably unresponsive to opioids. Neuropathic pain can respond to opioids, although the response may be incomplete.

It is advised that the lowest effective dose of NSAID or cyclo-oxygenase-2 (COX-2) selective inhibitor should be prescribed for the shortest period to control symptoms and that the need for long term treatment should be reviewed periodically.

Injections should be avoided to avoid inflicting more pain on the patient. Oral pain medication or transdermal patches are preferred. Also, the patients don’t need hospitalization since the medication can be done in the home environment where the patient is in contact with loved ones. Oral pain medication therefore reduces the cost of treatment and ensures the emotional and psychosocial needs of the patient are properly addressed during the care process.
Pharmacologic approaches to pain management
WHO 3-Step Ladder

<table>
<thead>
<tr>
<th>Step 3, Severe Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
</tr>
<tr>
<td>Hydromorphone</td>
</tr>
<tr>
<td>Methadone</td>
</tr>
<tr>
<td>Levorphanol</td>
</tr>
<tr>
<td>Fentanyl</td>
</tr>
<tr>
<td>Oxycodone</td>
</tr>
<tr>
<td>Nonopioid analgesics</td>
</tr>
<tr>
<td>Adjuvants</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 2, Moderate Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acct or ASA+</td>
</tr>
<tr>
<td>Codeine</td>
</tr>
<tr>
<td>Hydrocodone</td>
</tr>
<tr>
<td>Oxycodone</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
</tr>
<tr>
<td>Tramadol (not available with ASA or Acet)</td>
</tr>
<tr>
<td>+ Adjuvants</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 1, Mild Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (ASA)</td>
</tr>
<tr>
<td>Acetaminophen (Acet)</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs (NSAIDs)</td>
</tr>
<tr>
<td>+ Adjuvants</td>
</tr>
</tbody>
</table>

“Adjuvants” refers either to medications that are coadministered to manage an adverse effect of an opioid or to so-called adjuvants analgesics that are added to enhance analgesia.

In 1986, the World Health Organisation (WHO) developed a 3-step conceptual model to guide the management of cancer pain. It provides a simple, well-tested approach for the rational selection, administration and titration of a myriad of analgesics. Today, there is worldwide consensus favouring its use for the medical management of all pain associated with serious illness.

Treatment of mild pain with non-opioids analgesics (WHO Step 1)
Mild pain can be treated using either of the following analgesics: Paracetamol, Aspirin, Ibuprofen and Diclofenac.
Table 69: WHO Step 2 – Treatment of Moderate and severe Pain with Opioids

<table>
<thead>
<tr>
<th>Substance</th>
<th>Widely Available Forms and Strengths</th>
<th>Widely Available Forms and Strengths</th>
<th>Maximal Daily Dose</th>
<th>Starting Dose Without Pre-Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydrocodeine (DF118)</td>
<td>30mg</td>
<td>4-6</td>
<td>4-6</td>
<td>60-120mg</td>
</tr>
<tr>
<td>Codeine</td>
<td>30mg-60mg</td>
<td>4-6</td>
<td>360mg</td>
<td>15-60mg</td>
</tr>
</tbody>
</table>

**Strong opioids**

The oral route should be used for administration of opioids, if practical and feasible. Continuous subcutaneous infusion of opioids is simpler to administer and equally as effective as continuous intravenous infusion and should be considered for patients unable to take opioids orally. Oral morphine is recommended as first line therapy to treat severe pain in patients with cancer. This can be administered in form of morphine solution or morphine tablets.

**Titrating opioids**

A careful individual assessment of pain control, degree of side effects and total amount of opioid required, including breakthrough doses, in the previous 24 hours must be made daily prior to prescribing. Starting doses of oral morphine in opioid-naive patients are generally of the order of 5 to 10 mg four hourly in young and middle aged people and 2.5 to 5 mg four hourly in the elderly. Conventional practice is to commence an immediate release formulation of opioid, which allows pain to be controlled more rapidly. This also allows earlier assessment and titration up or down if necessary. Once pain has been controlled the four hourly doses may be converted to a 12 hourly modified release dose by dividing the effective total 24 hour dose by two.

**Transdermal Fentanyl**

Other technologies available include the medicated patches. Opioid naive patients should never be prescribed fentanyl patches.

For those with stabilized severe pain who express a preference for a patch formulation or those with swallowing difficulties or intractable nausea and vomiting, fentanyl transdermal patches may be appropriate provided the pain is stable.

The following should be considered when converting from an oral strong opioid to transdermal fentanyl:

- If taking 4 hourly oral opioid, continue for 12 hours after applying transdermal patch.
- If taking 12 hourly oral opioid, give last dose when first transdermal patch is applied.
- If taking 24 hourly oral opioid, apply first transdermal patch 12 hours after last dose.

Patients with Renal Impairment
In patients with poor or deteriorating kidney function, the following are of considerable importance to prevent or manage toxicity:

- Choice of opioids
- Consideration of dose reduction and/or an increase in the dosage interval.
- Change from modified release to an immediate release oral formulation.
- Frequent clinical monitoring and review.

**Bisphosphonates**

Bisphosphonates should be considered as part of the therapeutic regimen for the treatment of pain in patients with metastatic bone disease. As hypocalcaemia is a noted potential complication of administration of intravenous bisphosphonates, calcium levels should be included as part of the routine monitoring of therapy. Calcium and vitamin D supplements may be considered if dietary intake is insufficient.

**43.4 Management of side effects**

Many patients develop adverse effects such as constipation, nausea, vomiting, urinary retention, pruritus and central nervous system (CNS) toxicity (drowsiness, cognitive impairment, confusion, hallucinations, myoclonic jerks and, rarely, opioid-induced hyperalgesia/allodynia). In some cases a reduction in opioid dose may alleviate refractory side effects. This may be achieved by using a co-analgesic or an alternative approach such as a nerve block or radiotherapy. Naloxone is a short-acting opioid antagonist for intravenous use able to revert symptoms of accidental severe opioid overdose.

**43.4.1 Control of opioid-induced nausea and vomiting**

Many opioid-naïve patients will develop nausea and/or vomiting when started on opioids. Tolerance in the majority of patients usually occurs within 5-10 days. Patients commencing an opioid for moderate to severe pain should have access to a prophylactic antiemetic to be taken if required. Haloperidol 1.5mg at night for a week is usually adequate.

**43.4.2 Control of opioid-induced Constipation**

The majority of patients taking opioids for moderate to severe pain will develop constipation. Little or no tolerance develops. The best prophylactic treatment for preventing opioid-induced constipation is a combination of stimulant and softening laxatives (senna tablets). Severe constipation can be managed using senna or bisacodyl tablets.

**43.5 Neuropathic Pain**

Patients with neuropathic pain should be given either a tricyclic antidepressant (e.g. amitriptyline or imipramine) or anticonvulsant (e.g. gabapentin, carbamazepine or phenytoin, Pregabalin) with careful monitoring of side effects. Ketamine is used in selected patients who have persistent pain that remains uncontrolled by other means and is prescribed by specialists in cancer pain. It may be indicated in
neuropathic pain, ischaemic limb pain and refractory pain in cancer. The use of ketamine as an analgesic should be supervised by a specialist in pain relief or a palliative medicine specialist.

43.6 Non-pharmacological treatment
Complementary therapies are defined as the supportive methods used to complement the mainstream treatments for cancer pain. Although these therapies have increased in popularity, the evidence to support their use in the treatment of cancer pain remains weak. These include physiotherapy and complementary therapies like massages, aromatherapy, music therapy, acupuncture, transcutaneous (TENS) electrical nerve stimulation and reflexology.

Radiotherapy
Radiotherapy has specific and critical efficacy in providing pain relief caused by bone metastases. Radiotherapy also has a role in tumours compressing nerve structures and cerebral metastases. All patients with pain from bone metastases which proves difficult to control by pharmacological means should be referred to a clinical oncologist for consideration of external beam radiotherapy or radioisotope treatment.

Surgical Intervention
Pain control can be achieved by decompression of the spinal cord and of hollow organs with stents and other devices. Patients with bone pain from pelvic bone metastases proving difficult to control by pharmacological means and reduced mobility should be considered for percutaneous cementoplasty.

Anaesthetic Intervention
Despite management by multidisciplinary teams according to the principles of the WHO ladder, up to 20% of cancer patients may have poorly controlled pain. Any patient with difficult to control pain despite optimal management with systemic/oral therapy should be assessed by an anesthetist with expertise in pain medicine, for consideration of an appropriate intervention including nerve blocks. Patients most likely to benefit include patients with significant locally advanced disease, neuropathic pain or marked movement-related pain.

43.7 Cancer Pain Management in Children
Children consistently report that they experience more pain from procedures and cancer treatment than from the cancer itself. Therefore, the burden of pain in children with cancer experience can be actively reduced by effectively managing procedural pain. Existing studies demonstrate that children’s procedural pain can be reduced using relatively simple techniques. These techniques include pharmacologic and non-pharmacologic supports, such as distraction and positioning. Research suggests that parental presence is the most important factor in helping children cope with painful and frightening experiences.
Available data suggest use of sucrose is an effective means of alleviating pain for many minor neonatal procedures. Because oral sucrose reduces but does not eliminate pain in neonates, it should be used with other non-pharmacologic measures to enhance its effectiveness.

43.7.1 Pain Assessment in Infants and Children
Observational pain scales have been validated for neonates and infants to allow pain assessment in those unable to verbalize their pain. These scales, though essential, also respond to distress from causes other than pain, such as hunger, fear or anxiety (e.g., from parental separation). Simple self-report scales using facial expressions or small objects to describe pieces of hurt (i.e., Poker Chip Tool) have been devised to allow pre-school and school age children to more accurately describe the intensity of their pain.

43.7.2 Management of Procedural Pain
For all patients, an opioid or a local anaesthetic is needed to reduce the pain. Anxiolytics and sedatives are used specifically to reduce anxiety before and during the procedure. If used alone without anaesthesia, they may just blunt the behavioural response without relieving the pain.

Local anaesthetics may be administered by local infiltration (e.g. into the skin, subcutaneous tissues or periosteum with 1% procaine or 1% lidocaine for bone marrow aspirate (BMA) or topically using eutectic mixture of local anaesthetics (EMLA) cream.

EMLA cream is applied to intact skin (the recommended dose is approximately 1.5 g/10 cm²) and is covered with an occlusive dressing for 60–120 minutes, anaesthesia develops in the underlying tissue. In all instances, maximal development of analgesia is achieved by 120 minutes. After removal of the cream from the skin, analgesia persists in the underlying tissue for several hours.

43.7.3 Preparing children for invasive procedures
• Remember that anxiety and distress can increase pain.
• Explain what will happen clearly, in simple, developmentally appropriate language.
• Emphasize the qualities of the sensations they may experience such as cold, sharp, tingling, and pressure so that the child focuses on what they are feeling, rather than only on the hurting aspect.
• If the procedure will hurt, describe what children might feel using more familiar examples of pains that they have experienced during play and sports.
• Use versatile pain control methods that involve the child such as attention and distraction, deep breathing, counting exercises, or guided imagery.
• Give the child as many choices and as much control as possible such as choosing which arm for injections, whether to watch or look away, and which pain control method to use.
43.7.4 Conscious sedation

The use of conscious sedation is highly recommended for the management of pain and distress associated with procedures such as Bone Marrow Aspirate and Lumbar Puncture. A combination of a benzodiazepine (midazolam) and an opioid (either morphine or fentanyl) is most frequently recommended for intravenous conscious sedation. The recommended dosage ranges are:

- Midazolam, 0.05 mg/kg intravenously, initially up to a maximum total dose of 0.15 mg/kg, diluted to a concentration of 1mg/ml with 0.9% saline.
- Morphine, 0.05–0.1 mg/kg intravenously, diluted to 1 mg/ml with 0.9% saline
- Fentanyl, 0.5–1 mg/kg intravenously, undiluted.

The necessary monitoring of the patient includes the baseline assessment of heart rate, respiratory rate, blood pressure, skin and nail bed colour, level of consciousness, responsiveness and comfort level before sedation, and frequent (every five minutes during the procedure) assessment of heart rate respiratory rate, and blood pressure after conscious sedation. Continuous oxygen saturation monitoring is essential from the time of administration of conscious sedation until the child is fully alert after the procedure. Oxygen, suction and airway management equipment, and emergency drugs and supplies, should all be readily available. A clinical practice protocol is necessary to maximize the efficacy and safety of the interventions selected. Finally, all those involved in these medical procedures should receive continuous emotional support because of the extremely stressful nature of the experience.

43.7.5 General anaesthesia

Some experts maintain that short-acting general anaesthesia is a highly preferable alternative to premedication for outpatient procedures.

43.8 Management of Cancer Pain

Pain in children who are dying of cancer can be complex and challenging to manage. It is important to identify the cause and treat appropriately. As cancer progresses, pain may result from various causes. The majority of cases of cancer pain in children could be managed by the treating physician using non-opioids, opioids and adjuvant as per the WHO guidelines (Appendix 2 & 3)

Table 70: Categorization of pain and appropriate analgesia in children

<table>
<thead>
<tr>
<th>WHO ANALGESIC LADDER</th>
<th>SCORE NRS 1-10</th>
<th>ANALGESIC OF CHOICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Mild pain</td>
<td>1-3</td>
<td>Paracetamol ± NSAIDs ± Adjuvant</td>
</tr>
<tr>
<td>2 Moderate and Severe pain</td>
<td>4-10</td>
<td>Strong opioids ± paracetamol ±±NSAIDs± Adjuvant</td>
</tr>
</tbody>
</table>

Non-opioids

These are used to control mild – moderate pain and include paracetamol, ibuprofen, Diclofenac.
Table 71: Non-opioid drugs to control pain in children

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>10–15 mg kg PO, every 4–6 h</td>
<td>Lacks gastrointestinal and hematological side effects; lacks anti-inflammatory effects (may mask infection-associated fever)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>5–10 mg kg PO, every 6–8 h</td>
<td>Anti-inflammatory activity. Use with caution in patients with hepatic or renal impairment, compromised cardiac function or hypertension (may cause fluid retention, oedema), history of GI bleeding or ulcers, may inhibit platelet aggregation</td>
</tr>
<tr>
<td>Naproxen</td>
<td>10–20 mg kg day PO, divided every 12 h</td>
<td>Anti-inflammatory activity. Use with caution and monitor closely in patients with impaired renal function. Avoid in patients with severe renal impairment Dose limit of 1 g day</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1 mg kg PO, every 8–12 h</td>
<td>Anti-inflammatory activity. Similar GI, renal, and hepatic precautions as noted above for ibuprofen and naproxen Dose limit of 50 mg dose</td>
</tr>
</tbody>
</table>

43.8.1 Opioid Analgesics

The WHO recommends the use of only strong opioids in children. For the vast majority of children, opioids provide excellent analgesia with a wide margin of safety. Developmental differences, however, can make dosing difficult, especially in the first several months of life. Cardio-respiratory monitoring and careful observation is recommended whenever opioids are administered to infants less than 2 to 3 months of age.

Table 72: Opioid analgesics – usual starting doses for children

<table>
<thead>
<tr>
<th>DRUG</th>
<th>STARTING DOSE IV</th>
<th>IV: PO</th>
<th>STARTING DOSE PO/RATIO TRANSDERMAL</th>
<th>DURATION OF ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>0.015–0.02 mg kg every 4 h</td>
<td>1:3</td>
<td></td>
<td>3-4</td>
</tr>
<tr>
<td>bFentanyl</td>
<td>1–2 ug kg as continuous infusion</td>
<td>25 mg patch if on 100ug 0f IV fentanyl</td>
<td>72 hours</td>
<td></td>
</tr>
</tbody>
</table>

bPotentially highly toxic. Not for use in acute pain control.
43.8.2 Principles of opioid administration:

- If inadequate pain relief and no toxicity at peak onset of opioid action, increase dose in 50% increments.
- Avoid parenteral administration.
- Whenever using continuous infusion, plan for hourly rescue doses with short onset opioids if needed. Rescue dose is usually 50–200% of continuous hourly dose. If greater than 6 rescues are necessary in 24-h period, increase daily infusion total by the total amount of rescues for previous 24 h/24. An alternative is to increase infusion by 50%.
- To taper opioids – anyone on opioids over 1 week must be tapered to avoid withdrawal: taper by 50% for 2 days, and then decrease by 25% every 2 days.

43.8.3 Side effects of opioids in children

Side-effects of opioids (e.g. constipation) should be anticipated, aggressively treated and regularly reassessed. Adverse effects which are more common in children include urinary retention (which can be eased by carbachol and bethanechol. Opioid-induced pruritis is less common. Children must be treated for constipation, nausea and vomiting induced by use of opioids.

43.8.4 Neuropathic pain

Neuropathic pain (NP) is pain directly caused by a lesion or disease affecting the somatosensory system. The recommended routine practice is to provide opioids for the treatment of neuropathic pain, in addition to anticonvulsant therapy (gabapentin) and/or a tricyclic antidepressant (amitriptyline).
Table 73: Common medicines used for neuropathic pain

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline and nortriptyline</td>
<td>0.2-.4mg/kg po nocte; titrate upward by .25mg/kg q 5 to 7 days; may divide bid; maintenance 0.2-.3mg/kg</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>5 to 10mg/kg/24hrs divided bid; gradual increase of 10mg/kg/24hrs per week; maximum dose - 12yrs - 1.6 to 2.4 g/24hrs.</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>2 to 3mg/kg divided bid-three times per day gradual increase of .5mg/kg q 3 to 4 wks; maximum dose: 5mg/kg/d (1000 mg/d).</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>5 to 15mg/kg divided once-three times per day gradual increase of 5 to 10mg/kg every 5 to 7 days; maximum dose 60mg/kg/d.</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>5 to 10mg/kg OD, day 2 bid, day 3 three times per day maximum dose 2400 to 3600mg/24hrs.</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>0.15-.6mg/kg/24hrs OD- bid; slow gradual increase over2 weeks.</td>
</tr>
</tbody>
</table>

REFERENCES

### Appendix 1: Essential Medicines List

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE FORM</th>
<th>SIZE / STRENGTH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYTOTOXIC MEDICINES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ALKYLATING AGENTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Chlorambucil</td>
<td>Tablet</td>
<td>2mg</td>
</tr>
<tr>
<td>2 Chlorambucil</td>
<td>PFI</td>
<td>200mg, 500mg, 1gm</td>
</tr>
<tr>
<td>3 Procarbazine</td>
<td>Tablet</td>
<td>50mg</td>
</tr>
<tr>
<td>4 Melphalan</td>
<td>Tablet</td>
<td>2mg</td>
</tr>
<tr>
<td><strong>ANTIMETABOLITES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Cytarabine (Cytosine arabinoside)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 5-Flourouracil</td>
<td>Injection</td>
<td>250mg vials or ampoules</td>
</tr>
<tr>
<td>7 Methotrexate</td>
<td>Injection</td>
<td>50mg (without preservative)</td>
</tr>
<tr>
<td></td>
<td>Tablet</td>
<td>2.5mg</td>
</tr>
<tr>
<td><strong>CYTOTOXIC ANTIBIOTICS AND RELATED MEDICINES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 Dactinomycin [Actinomycin D]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Bleomycin</td>
<td>PFI</td>
<td>15 IU</td>
</tr>
<tr>
<td>10 Daunorubicin</td>
<td>PFI</td>
<td>20mg</td>
</tr>
<tr>
<td>11 Doxorubicin</td>
<td>PFI</td>
<td>10mg, 50mg</td>
</tr>
<tr>
<td>12 Mitomycin - C</td>
<td>PFI</td>
<td>2mg, 10mg, 40mg</td>
</tr>
<tr>
<td><strong>PLATINUM BASED CYTOTOXICS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 Carboplatin</td>
<td>Injection</td>
<td>150mg, 450mg</td>
</tr>
<tr>
<td>14 Cisplatin</td>
<td>Injection</td>
<td>10mg, 50mg</td>
</tr>
<tr>
<td><strong>TOPOISOMERASE INHIBITORS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 Etoposide</td>
<td>Capsule</td>
<td>100mg</td>
</tr>
<tr>
<td></td>
<td>Concentrate for injection</td>
<td>100mg</td>
</tr>
</tbody>
</table>
### Appendices

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE FORM</th>
<th>SIZE / STRENGTH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VINCA ALKALOIDS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 Vinblastine</td>
<td>Injection</td>
<td>10mg</td>
</tr>
<tr>
<td>17 Vincristine</td>
<td>PFI</td>
<td>1mg</td>
</tr>
<tr>
<td><strong>OTHERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 Hydroxyurea [Hydroxy carbamide]</td>
<td>Capsule</td>
<td>2mg</td>
</tr>
<tr>
<td>19 Dacarbazine</td>
<td>PFI</td>
<td>200mg</td>
</tr>
<tr>
<td><strong>PROTEIN KINASE INHIBITORS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 Imatinib</td>
<td>Tablet</td>
<td>100mg</td>
</tr>
<tr>
<td><strong>OTHERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21 Asparaginase</td>
<td>Powder for injection</td>
<td>10,000IU</td>
</tr>
<tr>
<td><strong>HORMONES AND ANTIHORMONES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22 Diethylstilboestrol</td>
<td>Tablet</td>
<td>5mg</td>
</tr>
<tr>
<td>23 Goserelgin</td>
<td>Injection</td>
<td>3.6mg; 10.8mg</td>
</tr>
<tr>
<td>24 Tamoxifen</td>
<td>Tablets</td>
<td>10mg, 20mg</td>
</tr>
<tr>
<td><strong>DRUGS FOR CYTOTOXIC INDUCED SIDE EFFECTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 Calcium folinate</td>
<td>Injection or PFI</td>
<td>50mg</td>
</tr>
<tr>
<td>25 Calcium folinate</td>
<td>Tablet</td>
<td>115mg</td>
</tr>
<tr>
<td><strong>CORTICOSTEROIDS</strong> (Oral and topical steroids)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 Dexamethasone</td>
<td>Injection</td>
<td>4mg</td>
</tr>
<tr>
<td>26 Dexamethasone</td>
<td>Tablets</td>
<td>0.5mg; 2mg</td>
</tr>
<tr>
<td>27 Prednisolone</td>
<td>Tablet</td>
<td>5mg</td>
</tr>
</tbody>
</table>

**ANALGESICS, ANTIPYRETICS AND NON STEROIDAL ANTIINFLAMMATORY MEDICINES** Divide into NSAIMS and OPIODS
# Appendix 2: Guidelines For Adjusting Diet To Manage Symptoms Associated With Anti-Cancer Treatment.

<table>
<thead>
<tr>
<th>PROBLEM</th>
<th>POSSIBLE SOLUTION</th>
<th>REDUCE/AVOID INTAKE OF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased appetite</td>
<td>• Smaller more frequent meals - 5-6 instead of three main meals</td>
<td>• Low energy- and nutrient dense foods and beverages</td>
</tr>
<tr>
<td></td>
<td>• Meals should be appetizing in appearance and taste and provide enough energy and protein</td>
<td></td>
</tr>
<tr>
<td>Sore Mouth or throat</td>
<td>• Eat small, frequent meals</td>
<td>• Spicy, salty or acidic foods</td>
</tr>
<tr>
<td></td>
<td>• Food is best tolerated at cool or room temperature</td>
<td>• Carbonated beverages</td>
</tr>
<tr>
<td></td>
<td>• Eat dry, salty crackers, biscuits and cookies</td>
<td>• Juice, especially citrus</td>
</tr>
<tr>
<td></td>
<td>• Simple foods such as rice, scrambled eggs, toast, noodles, bananas, mashed potatoes, custards may be better tolerated</td>
<td>• Bananas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Crisp or raw foods</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hard / tough meats</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Textured or granular foods</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Coarse bread products</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Extremely hot or cold foods</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>• Clear, cold non-acidic liquids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Light low-fat foods</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Enough liquids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Allow plenty of fresh air in the house</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Eat soft, moist food at cool or room temperature (mashed potatoes, macaroni and casserole)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Drink through a straw</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Thick liquids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Thick hot cereals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dry foods, bread products, tough meats, crackers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Excessively hot foods</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Alcohol</td>
</tr>
<tr>
<td>Condition</td>
<td>Strongly flavoured / spicy foods and supplements</td>
<td>Emphasis on aroma and texture sucking of mints may help</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------------------------------------------</td>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>Mouth blindness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taste alteration</td>
<td>Include many cold foods and milk products</td>
<td>Experiment with foods</td>
</tr>
<tr>
<td>Early satiety</td>
<td>High-calorie diet with calorically dense foods</td>
<td>Meat, fish, poultry, eggs, whole milk, cheese, cream soups, ice cream, whole-milk yoghurt, creamed vegetables, rich desserts</td>
</tr>
</tbody>
</table>
## Diarrhoea

- Eat smaller more frequent meals
- Replace Fluid with water or re-hydration drinks after every loose stool or. (Home recipe for oral rehydration therapy (remember hygiene): 1 litre of cooled cooked water, 8 teaspoons of sugar and 1/2 teaspoon of table salt).
- A low fat and low dairy diet may be indicated (damaged to the surface of the gut may cause intolerance to lactose; drinking milk or eating milk products can cause cramps, abdominal distress and diarrhea in some people).
- Moderate the intake of fibre. Concentrate on soluble fibre (fruit, oats, and legumes).
- Limit the intake of fructose (fruit sugar) by avoiding pear juice as well as grapes, honey, dates, nuts, figs and soft drinks.
- Eat bananas, potatoes, fish, and meat; drink apricot juice, tomato juice to replenish sodium (salt) and potassium.
- Eat foods that have been brought to room temperature.

- Avoid gas forming foods and drinks (e.g. peas, lentils, cabbage, cauliflower, broccoli, onion, nuts, cucumber, beans and bran, garlic, beer).
- Avoid alcohol and caffeine, since both may have a dehydrating effect.
| Constipation | • Regular diet with fibre added (whole grains, dried fruit such as prunes - even prune juice, bran, etc.).  
• Fibre-enriched supplements / bulking agents may be beneficial  
• Extra fluids and exercise can be beneficial | • Gas-forming foods and beverages |
APPENDIX 3: Palliative Care Guideline

Patient presents with a new or existing diagnosis of cancer

The health care Team determines that palliative care is required

Initiate palliative care discussion with patient and family.

Assess patient needs and initiate basic palliative care

Assessment Parameters

Physical Socio-cultural Religious-Spiritual Ethical-Legal Psychological

Establish goals of care through shared decision-making (patient/family and clinical team)

Establish goals of care through shared decision-making (patient/family and clinical team)

Death Remission/resolution
APPENDIX 4: Pain Assessment Tools

Wong-Baker FACES rating Scale

0  2  4  6  8  10
NO HURT  HURTS LITTLE BIT  HURTS LITTLE MORE  HURTS EVEN MORE  HURTS WHOLE LOT  HURTS WORST


Numeric Rating Scale

0  1  2  3  4  5  6  7  8  9  10
None  Mild  Moderate  Severe

FLACC Scale -- Pain Assessment Tool

Observer Rated Pain Scale

<table>
<thead>
<tr>
<th>DATE/TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Face</th>
<th>DATE/TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - No particular expression or smile</td>
<td></td>
</tr>
<tr>
<td>1 - Occasional grimace or frown, withdrawn, disinterested</td>
<td></td>
</tr>
<tr>
<td>Legs</td>
<td>DATE/TIME</td>
</tr>
<tr>
<td>0 - Normal position or relaxed</td>
<td></td>
</tr>
<tr>
<td>1 - Kicking, or legs drawn up</td>
<td></td>
</tr>
<tr>
<td>Activity</td>
<td>DATE/TIME</td>
</tr>
<tr>
<td>0 - Lying quietly, normal position, moves easily</td>
<td></td>
</tr>
<tr>
<td>1 - Squirming, shifting back and forth, tense</td>
<td></td>
</tr>
<tr>
<td>2 - Arched, rigid or jerking</td>
<td></td>
</tr>
<tr>
<td>Cry</td>
<td>DATE/TIME</td>
</tr>
<tr>
<td>0 - No cry (awake or asleep)</td>
<td></td>
</tr>
<tr>
<td>1 - Moans or whimpers; occasional complaint</td>
<td></td>
</tr>
<tr>
<td>2 - Crying steadily, screams or sobs, frequent complaints</td>
<td></td>
</tr>
<tr>
<td>Consolability</td>
<td>DATE/TIME</td>
</tr>
<tr>
<td>0 - Content, relaxed</td>
<td></td>
</tr>
<tr>
<td>1 - Reassured by occasional touching, hugging or being talked to, distractible</td>
<td></td>
</tr>
<tr>
<td>2 - Difficult to console or comfort</td>
<td></td>
</tr>
</tbody>
</table>

TOTAL SCORE
APPENDIX 5: HOSPICES AND PALLIATIVE CARE UNITS IN KENYA
2013

Free standing Hospices
1. Meru Hospice
2. Nairobi Hospice
3. Kisumu Hospice
4. Coast Hospice
5. Nyeri Hospice
6. Eldoret Hospice
7. Nyahururu Hospice
8. Nakuru Hospice
9. Thika Hospice
10. Embu-Mbeere Hospice
11. Kakamega Hospice
12. Catherine Mc Auley Hospice – Muhoroni
13. Murang’a Hospice
14. Pope John Paul II Huruma Hospice - Nanyuki
15. Baraka Medical Centre, Thika Road
16. Siaya Roselyne Hospice and Palliative Care Centre
17. Laikipia Palliative Care Centre, Nanyuki

Hospice and Palliative Care services in the rural community (FBO)
1. Kimbilio Hospice – Kipkaren, Eldoret
2. VIAGENCO (Victoria Agricultural and Environmental Conservation Organization Integrated Comprehensive Care) Mbita, Nyanza
3. Our Lady Hospice - Thigio, Limuru
4. Shepherds of Life (Sol Kenya) - Meru
5. KICOSHEP (Kibera Integrated Community Self-Help Programme)

Mission Hospitals with Palliative Care
1. AIC Kijabe Hospital
2. AIC Litein Mission Hospital
3. PCEA Chogoria Hospital
4. Tenwek Mission Hospital
5. PCEA Maua Methodist Hospital
6. PCEA Kikuyu Mission Hospital
7. Assumption Sisters Integrated Aids Program- Mang’u
8. Catholic Archdiocese of Mombasa Health Centre
9. Christian Medical Fellowship (CMF) Narok
Government Hospitals with Palliative Care
1. Kakamega Provincial General Hospital
2. Coast Provincial General Hospital
3. Embu Provincial General Hospital
4. Nyeri Provincial General Hospital
5. Rift Valley Provincial General Hospital
6. Meru Level Five Hospital
7. Thika Level Five Hospital
8. Garissa Level Five Hospital
9. Kisii Level Five Hospital
10. Machakos Level Five Hospital
11. Jaramogi Oginga Odinga Teaching and Referral Hospital

Teaching and Referral Hospitals
1. Kenyatta National Hospital
2. Moi Teaching and Referral Hospital – Palliative Care Unit (housed in the Oncology Department – AMPATH)

District Hospitals
1. Homabay District Hospital
2. Naivasha District Hospital
3. Nanyuki District Hospital
4. Malindi District Hospital
5. Webuye District Hospital

District Hospitals that are in the process of integrating palliative Care Services
1. Voi District Hospital
2. Hola District Hospital
3. Msambweni District Hospital
4. Mandera District Hospital
5. Wajir District Hospital
6. Isiolo District Hospital
7. Marsabit District Hospital
8. Moyale District Hospital
9. Kitui District Hospital
10. Mwingi District Hospital
11. Makueni District Hospital
12. Kangundo District Hospital
13. Narok District Hospital
14. Kericho District Hospital
15. Lodwar District Hospital
16. Wamba District Hospital
17. Oloitokitok District Hospital
18. Kitale District Hospital
19. Busia District Hospital
20. Siaya District Hospital
21. Nyahururu District Hospital
22. Murang’a District Hospital
23. Kerugoya District Hospital
24. Karatina District Hospital
25. Kiambu District Hospital
### APPENDIX 6: Case Abstract Form (CAF)

**Hospital Based Cancer Registry:**

Name of Hospital__________________________________________

County____________________________________________________

---

### A. PATIENT:

1. **NAME**

<table>
<thead>
<tr>
<th>FIRST</th>
<th>SECOND</th>
<th>FAMILY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Identification No.______________________

3. Marital Status:  
   1 = Single  
   2 = Married  
   3 = Widowed  
   4 = Separated  
   9 = Unknown

4. TEL. NO. [Patient]__________________________

5. TEL. NO. [NEXT OF KIN]_____________________

6. Age ___________  
7. Date of Birth Date / / 

---

9. Place of Residence

<table>
<thead>
<tr>
<th>A. COUNTY</th>
<th>B. DIVISION</th>
<th>C. LOCATION / ESTATE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

10. Place of Birth

<table>
<thead>
<tr>
<th>A. COUNTY</th>
<th>B. DIVISION</th>
<th>C. LOCATION / ESTATE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

11. Tribe / Ethnic background

12. Family History of cancer [1]: Yes  [2]: No

13. Education level [1]: None  [2]: Primary  [3]: Secondary  [4]: Tertiary  [9]: Unknown

14. Occupation

15. Smoking [1]: Never  [2]: Smoker  [3]: Ex-Smoker  [4]: Unknown

16. Alcohol use [1]: Never  [2]: Drinker  [3]: Ex-Drinker  [9]: Unknown

### B. TUMOUR:

17. Incidence date D D M M Y Y

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>

18. Basis of Diagnosis

0 = Death cert only  
1 = Clinical only  
2 = Clinic.Invest./UltraSound  
4 = Biochem. Immuno test  
5 = Cytology/Haematology  
6 = Histology of metastasis  
7 = Histology of primary  
9 = Unknown
19. Primary Site ____________________________________

20. Laterality  Rt.  Lt.  Bil.  Unk.  N/A

21. Histology

22. Behaviour  23. Grade

24. Stage

0 – Benign  1 – Well diff
1 – Uncertain  2 – Moderately diff
2 – In situ  3 – Poorly diff.
3 – Malignant  4 – Undifferentiated/Anaplastic

C. TREATMENT

25. FIRST COURSE OF TREATMENT: [1=YES; 2=NO; 9=UNKNOWN]

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Date</th>
<th>Radiotherapy</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Curative</td>
<td></td>
<td>1. Curative</td>
<td></td>
</tr>
<tr>
<td>2. Palliative</td>
<td></td>
<td>2. Palliative</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Date</td>
<td>Hormone therapy</td>
<td>Date</td>
</tr>
<tr>
<td>1. Curative</td>
<td></td>
<td>1. Curative</td>
<td></td>
</tr>
<tr>
<td>2. Palliative</td>
<td></td>
<td>2. Palliative</td>
<td></td>
</tr>
<tr>
<td>Immuno.</td>
<td>Date</td>
<td>Other</td>
<td>Date</td>
</tr>
</tbody>
</table>

D. HIV SEROLOGY:

26. DOCUMENTATION OF HIV STATUS [Y/N]

27. Specifically (-ve)

28. Specifically (+ve)

29. HAART therapy combination________________________

30. WHO stage________________________
33. Laboratory ____________________________ Lab.No._____________________________
34. Referred from______________________________________________________________
35. Referred to______________________________________________________________

F. FOLLOW UP:

36. Present Status  □ 1=Alive □ 2=Dead  37. Date Last Contact/Date of death: ____ / ____/ _______

38. Method of Case follow up used ________________________________________________

39. Hospice No._____________________ 40. If Dead Cause of Death _______________________
Remarks if any:____________________________________________________________________

G. QUALITY CHECKS

Form filled by__________________________________________ Date_______________________
Data verified & entered by _________________________________Date_______________________