



MINISTRY OF HEALTH

# KENYA NATIONAL CANCER TREATMENT PROTOCOLS



JULY 2019



## Kenya National Cancer Treatment Protocols

Developed by the National Cancer Control Program, Division of Non-Communicable Diseases- Ministry of Health

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# Table of Content

|  |      |
|--|------|
| <b>LIST OF TABLES</b>  | i    |
| <b>LIST OF FIGURES</b>   | iv   |
| <b>FOREWORD</b>  | v    |
| <b>EXECUTIVE SUMMARY</b>   | vii  |
| <b>ACKNOWLEDGEMENT</b>   | viii |
| <br>   |      |
| <b>CHAPTER ONE: INTRODUCTION</b>   | 1    |
| 1.1 General principles of cancer management                                | 2    |
| 1.2 Palliative Care, Supportive Care and End of Life Care                  | 6    |
| 1.3 Survivorship care  | 10   |
| <br>   |      |
| <b>CHAPTER TWO: BREAST CANCER TREATMENT PROTOCOL</b>                       | 11   |
| 2.1 Introduction   | 11   |
| 2.2 Clinical Evaluation  | 12   |
| 2.3 Imaging for Assessment of Breast Lesions                               | 18   |
| 2.4 Pathological Diagnosis   | 19   |
| 2.5 Pre-operative Staging Considerations                                   | 20   |
| 2.6 Treatment  | 21   |
| 2.7 Follow-up and Surveillance   | 31   |
| 2.8 Supportive care for breast cancer                                      | 31   |
| 2.9 Anticipated Care at Various Health Facility Levels                     | 32   |
| <br>   |      |
| <b>CHAPTER THREE: BRAIN AND CENTRAL NERVOUS SYSTEM<br/>TUMORS PROTOCOL</b> | 34   |
| 3.1 Introduction   | 35   |
| 3.2 Clinical Evaluation  | 36   |
| 3.3 Pathological Diagnosis   | 38   |
| 3.4 Management   | 38   |
| 3.5 Supportive and rehabilitative care for brain tumor                     | 45   |
| 3.6 Role of facility levels in the care of patients with brain tumors      | 46   |



|  |     |  |
|--|-----|--|
| <b>CHAPTER FOUR: GASTROINTESTINAL CANCER TREATMENT PROTOCOLS</b>     | 47  |  |
| 4.1 Esophageal cancer  | 49  |  |
| 4.2 Gastric cancer   | 58  |  |
| 4.3 Colorectal cancer  | 57  |  |
| 4.4 Pancreatic cancer  | 61  |  |
| 4.5 Hepatocellular carcinoma   | 65  |  |
| 4.6 Anal carcinoma   | 70  |  |
| <br>   |     |  |
| <b>CHAPTER FIVE: GYNAECOLOGICAL CANCER PROTOCOLS</b>                 | 73  |  |
| 5.1 Ovarian cancer   | 75  |  |
| 5.2 Cervical cancer  | 80  |  |
| 5.3 Vulvar cancer  | 84  |  |
| 5.4 Gestational trophoblastic disease (GTDS)                         | 87  |  |
| 5.5 Endometrial cancer   | 91  |  |
| 5.6 Anticipated services for gynecological cancers per level of care | 94  |  |
| <br>   |     |  |
| <b>CHAPTER SIX: HEAD AND NECK CANCERS PROTOCOLS</b>                  | 95  |  |
| 6.1 Introduction   | 97  |  |
| 6.2 Risk Factors   | 97  |  |
| 6.3 Signs and Symptoms   | 97  |  |
| 6.4 Clinical evaluations   | 98  |  |
| 6.5 Staging  | 99  |  |
| 6.6 Management   | 100 |  |
| 6.7 Supportive management for head and neck cancer                   | 103 |  |
| 6.8 Patient Follow-up  | 104 |  |
| 6.9 Anticipated care at different levels of health system            | 104 |  |
| <br>   |     |  |
| <b>CHAPTER SEVEN: ADULT HAEMATOLOGICAL CANCERS</b>                   | 107 |  |
| 7.1 Acute Leukaemias   | 109 |  |
| 7.2 Chronic Leukaemias   | 119 |  |
| 7.3 Lymphomas  | 125 |  |
| 7.4 Multiple Myeloma   | 136 |  |

**CHAPTER EIGHT: KAPOSÍ'S SARCOMA TREATMENT PROTOCOL** 143

**CHAPTER NINE: LUNG CANCER TREATMENT PROTOCOL** 151

**CHAPTER TEN: UROLOGICAL CANCER TREATMENT PROTOCOLS** 165

10.1 Prostate Cancer 165

10.2 Bladder Cancer 174

**CHAPTER ELEVEN: CHILDHOOD CANCER TREATMENT PROTOCOLS** 178

11.1 Leukaemias 180

11.2 Burkitts lymphoma 187

11.3 Nephroblastoma (Wilms' Tumor) 189

11.4 Brain and Central Nervous System tumours 194

11.5 Osteogenic Sarcoma 198

11.6 Rhabdomyosarcoma 201

11.7 Retinoblastoma 204

**CHAPTER TWELVE: COMMON ONCOLOGIC EMERGENCIES** 210

12.1 Febrile neutropenia and sepsis 211

12.2 Superior vena cava syndrome 213

12.3 Spinal cord compression 214

12.4 Hypercalcaemia of malignancy 214

12.5 Syndrome of inappropriate ADH secretion 214

12.6 Haematological emergencies 215

12.7 Genitourinary emergencies 215

12.8 Respiratory emergencies 215

12.9 Chemotherapy-induced extravasations 216

**APPENDICES** 217

# List of Tables and Figures

## TABLES

|             |   |     |
|-------------|---|-----|
| Table 2. 1: | Breast Imaging Reporting and Data System (BIRADS)                         | 13  |
| Table 2. 2: | AJCC Staging of Breast Cancers  | 15  |
| Table 2. 3: | Molecular Subtyping of Invasive Breast Cancer                             | 18  |
| Table 4. 1: | Barcelona Clinic Liver Cancer (BCLC) staging                              | 61  |
| Table 4. 2: | Child Pugh-Turcotte Score   | 61  |
| Table 4. 3: | Treatment Options for Hepatocellular Carcinoma                            | 63  |
| Table 4. 4: | Factors to consider in treatment<br>decision-making for anal cancer       | 66  |
| Table 5. 1: | FIGO Anatomical Staging for Gestational<br>Trophoblastic Neoplasms        | 85  |
| Table 6. 1: | TNM Staging of Head and Neck Cancer                                       | 97  |
| Table 6. 2: | Stage Grouping of Head and Neck Cancers                                   | 97  |
| Table 6. 3: | Nodal Assessment of Thyroid Cancers                                       | 98  |
| Table 7. 1: | Modified RAI Staging & Classification                                     | 116 |
| Table 7. 2: | Assessment of Response Criteria   | 120 |
| Table 8. 1: | Revised AIDS Clinical Trial Group (ACTG)<br>Staging Classification for KS | 145 |

## FIGURES

|              |  |     |
|--------------|--|-----|
| Figure 1.1:  | Aspects of cancer survivorship   | 13  |
| Figure 2.1:  | Symptoms of breast cancer  | 17  |
| Figure 3.1:  | Common Types and Subtypes of CNS Tumors  | 36  |
| Figure 3.2:  | Flow diagram illustrating of diagnosis of<br>spinal cord tumors                      | 43  |
| Figure 3.3:  | Palliative Care Recommendations Concerning<br>the Treatment of Brain Cancer Symptoms | 45  |
| Figure 11.1: | Common sites of involvement of osteosarcoma<br>in children                           | 198 |



## Foreword

The global cancer burden continues to rise with an estimated 18.1 million new cases in 2018 and 9.6 million deaths. In Kenya there were an estimated 47,887 new cancer cases and 32,987 deaths in 2018. It is the third leading cause of death after infectious and cardiovascular diseases. The increasing cancer burden is due to several factors, including population growth and aging as well as the changing prevalence of certain causes of cancer linked to social and economic development. This is particularly true in rapidly growing economies, where a shift is observed from cancers related to poverty and infections to cancers associated with lifestyles more typical of industrialized countries. Mortality from cancer in Kenya, like in other developing countries, is high mainly because optimal access to timely diagnosis and effective treatment is less common. The Ministry of Health aims to address this challenge through development of these Cancer Treatment Protocols, among other initiatives.

The Cancer Treatment Protocols have been developed in line with the National Cancer Control Strategy 2017-2022 Pillar 3 that focuses on Treatment, Palliative Care and Survivorship. They are aligned with the Ministry of Health's mission of providing the highest standard of health for all Kenyans and the Government of Kenya's Big Four Agenda on universal health coverage. The key areas covered are diagnosis, imaging, pathology, surgery, rehabilitation, palliative care and survivorship. It emphasizes a multi-disciplinary team approach which is paramount for quality cancer care. The specific cancers covered are breast, central nervous system, gastrointestinal, gynecological, head and neck, hematological, Kaposi's sarcoma, lung, prostate and pediatric cancers. They also complement the National Guidelines for Cancer Management in Kenya released in 2013.

These Cancer Treatment Protocols have been developed through an extensive consultative process with various experts in the field of oncology. They are an important tool meant to be used by health workers in Kenya where cancer services are offered. They are presented in a simplified manner using a public health approach to cancer treatment. The aim of this document is to ensure that suspected cancer patients seen in any health facility in Kenya are given due services as per the level of care and are referred in a timely manner to an appropriate management facility, and that their evaluation, treatment, rehabilitation and continuing care through to survivorship or palliation is done in a well co-ordinated manner. It also seeks to ensure best practice in service delivery within the facilities providing any cancer care and treatment services.

I trust this guidance document will provide the much-needed framework and impetus to move towards universal access for cancer services and the agenda of halting and reversing the burden of NCDs by 2030 as a key national health strategic objective.

A handwritten signature in black ink, consisting of a stylized 'SK' followed by a large, rounded flourish that ends in a horizontal line.

---

Sicily K. Kariuki (Mrs), EGH  
Cabinet Secretary  
Ministry of Health



# Acknowledgement

The Ministry of Health appreciates all who contributed to the successful development of these protocols. We thank the top leadership of the Ministry of Health for their support especially The Office of the Cabinet Secretary, Principal Secretary, Director General, Department of Preventive and Promotive Health and the Division of Non-Communicable Diseases, whose guidance led to the successful development of these protocols.

In a special way, we wish to convey our gratitude to the technical working group and the team leads who worked tirelessly to ensure the successful completion of these protocols. We are grateful to Prof. Muthoni Musibi who was the lead consultant in the development process. Special thanks to Dr. Anne Ng'ang'a, the Head of the National Cancer Control Program, who provided impeccable support and strategic leadership in the development process; and Dr. Mary Nyangasi, the Program Officer in charge of Cancer Treatment in the Program who coordinated the entire process. Others included Dr. Joseph Kibachio, Dr. Oren Ombiro, Dr. Joan-Paula Malenya, Dr. Eunice Gathitu, Dr. Valerian Mwenda, Lydia Kirika and Hannah Gitungo.

We would like to recognize and appreciate the technical input, commitment and dedication of various experts from public, private and faith-based institutions. In this regard, we particularly recognize the Kenya Society of Hematology and Oncology (KESHO), Surgical Society of Kenya (SSK), Kenya Association of Radiologists (KAR), Kenya Obstetrical and Gynecological Society (KOGS), Kenya Association of Urological Surgeons (KAUS), Kenya Dental Association (KDA), Gastroenterology Society of Kenya (GSK) and Kenya Ear Nose and Throat Society (KENTS) and the National Cancer Institute of Kenya (NCI-Kenya). We are grateful to Clinton Health Access Initiative (CHAI) for their participation and financial support. We wish to appreciate Takeda Pharmaceuticals for their financial support.

A special tribute goes to the late Dr. Eliud Murugu Njuguna who was supportive, dedicated and passionate about this work. At the time of his demise, he was the team lead for gastrointestinal cancers track.

The development of these protocols has been a lengthy journey with many challenges, but we finally have this document which provides a big milestone in the country's response to cancer.



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Susan N. Mochache, CBS  
Principal Secretary  
Ministry of Health



# Executive Summary

The cancer care continuum involves a series of interventions aimed at curing the disease or prolonging the patient's life considerably while improving the quality of life. These protocols combine evidence-based and best-practice recommendations, with the aim of ensuring availability of equitable, high-quality services for cancer patients. They cover aspects of clinical evaluation, diagnosis, imaging, surgery, radiotherapy, chemotherapy, hormone therapy, psychosocial support, palliative care, rehabilitation, and survivorship at the different healthcare levels.

**Chapter 1** addresses the general principles of cancer management including referral timelines and processes. It sets out the multidisciplinary team (MDT) structure in line with peer review requirements, describes general principles of patient and inter-professional communication, palliative care, end of life care and survivorship.

**Chapter 2-9** are on breast, brain and central nervous system, gastrointestinal, gynaecological, head and neck, haematological, Kaposi's sarcoma, lung and urological cancers, outlining the key generic principles for management of these tumors. Key palliative and supportive care aspects are presented within each section.

**Chapter 10** provides information for managing cancers in paediatric patients. Avoidable deaths from childhood cancers in Kenya result from low awareness, diagnostic challenges, obstacles to accessing care, abandonment of treatment due to cost of care or fatalistic beliefs regarding childhood cancers, inadequate human resource capacity, death from toxicity, and higher rates of relapse, among others. Most childhood cancers lack screening strategies therefore early diagnosis and treatment is critical for good outcomes.

**Chapter 11** addresses the management of oncologic emergencies.

It is my expectation that all health facilities providing cancer care will use these protocols as a guide on the continuum of care required for priority cancers in Kenya.

---

Dr. John Wekesa Masasabi  
Ag. Director General  
Ministry of Health



# INTRODUCTION

## 1.1 General principles of cancer management

Patients with cancer require high levels of specialised complex multimodal care from a multidisciplinary team that includes oncologists, physicians, surgeons, pathologists, radiologists, clinical nurse specialists, dietitians, dermatologists, plastic surgeons, dentists and specialist palliative care physicians from the pre-treatment assessment to the point where rehabilitation is complete and beyond. In line with the National Cancer Control Strategy 2017-2022, these protocols have been developed with input from specialists within the major hospitals treating cancer patients in Kenya.

The protocols will be reviewed regularly, in line with guidance from the Ministry of Health and other national and international guidance, as well as significant new research publications.

Cancer services should be patient centered and should respond to patient and carer feedback. Excellent communication between professionals and patients is particularly important to improve patient satisfaction.

### Early Diagnosis and Referral

There is evidence that patients with cancer attend health facilities a number of times with symptoms related to their cancer and are treated otherwise before onward referral. These protocols recommend that cancer patients be referred appropriately in a timely manner to the appropriate level of care where the specific service required in the care pathway is available. The patients should be triaged before referral based on their signs and symptoms.

These protocols recommend the following minimum timelines in order to minimize delays and improve outcomes:

1. Immediate referral will require admission acutely **within a few hours** of referral such as in oncological emergencies.
2. Urgent referral will require **a 14-day standard** from referral to assessment in a cancer centre with rapid assessment by a designated clinician.
3. **A 31-day standard** from diagnosis to start of treatment (including for recurrent disease).

Designated clinicians should cooperate to ensure that an appropriate diagnostic work-up is provided for patients suspected to have cancer. The definitive diagnosis of cancer is confirmed by histopathological examination of the biopsy specimen. Patients confirmed with cancer should be referred without delay to the appropriate multidisciplinary team (MDT) in the nearest facility providing cancer care. There should be pre-booking systems for appointments at both referring and receiving clinics, where each patient with a new cancer diagnosis should be seen by an oncologist. The referring clinician should also be informed of the diagnosis and decision made.

## Inter-Professional and Patient Communication

Communication needs to be timely and concise. The main communication points along the patient journey must include:

- What the patient has been told about their condition
- What written/other information was offered
- Next steps – when the patient is being seen or treatment started
- Intent of treatment (curative/palliative)
- Summary of medication and alterations to medication
- Contact details for further information/discussion
- Specialist assessment and intervention summary
- Treatment plan summary – when created and when amended
- Written correspondence to be copied to all appropriate team members who have actions to undertake in the patient's care.

Key points at which to communicate include: Diagnosis, multidisciplinary team discussions, assessment clinic, clinic appointment reviews, treatment reviews, decision points for changes in care planning and decision point for end-of-life care planning

## Stages of the Referral Pathway

Referral sources will include Accident and Emergency department, internal referrals from other departments and referrals from outside facilities among others.

### *Assessment and diagnosis*

- Consultant clinic appointment.
- Investigations: of body function (renal, haemogram), imaging, fine needle aspiration cytology, biopsy; must be discussed to ensure individual good care.
- Diagnosis given to the patient.

### *Multidisciplinary team meeting*

- Agree on referral and minimum data for case presentation at the MDT meeting.
- Outline treatment plan recommended (including surgery).
- Communication to patient and referring clinician.
- Paediatric and young adult cases to be discussed at appropriate Paediatric MDT.

### *Treatment planning*

- Treatment plan explained to patient and next of kin with explanation of possible effects, reviews as necessary;
- Contact details in case of oncologic emergencies like febrile neutropaenia;

- Holistic needs assessment done;
- Refer to specialist oncology rehabilitative service provider, as required

#### ***Pre-treatment assessment***

- To include general surgical assessment
- Information prescription
- Clinical assessment

#### ***Treatment***

- Surgery.
- Radiotherapy
- Systemic therapy
- Best supportive care
- After-care and rehabilitation plan agreed with patient
- End of Treatment Summary completed on discharge (including details regarding follow-up)
- Early referral to local support team and community specialist palliative care services
- Communication with referring clinician.

#### ***Follow-up/surveillance***


- Risk-stratified follow-up plan to guide investigation and follow-up
- Function follow-up
- Plan for pregnancy
- Rehabilitation
- Triggers for MDT discussion

### **Multidisciplinary Team Meeting**

Multidisciplinary team (MDT) care is accepted as best practise in the delivery of high quality cancer management globally. They have been shown to improve cancer care delivery to patients. Comorbidities, performance status and staging are assessed and recorded, appropriate diagnostic tests generated and treatment plans developed, reviewed and implemented by MDT members.

It is advised that the MDTs develop terms of reference as a concise summary of their meeting standards and processes. The following should be included as a minimum:

1. Statement of purpose/function of the MDT;
2. List of health care professional membership including core members, disciplines and their roles and responsibilities, chair and co-ordinator;
3. Procedure to maintain attendance records; data management, auditing and reporting on MDT meeting activity.
4. Meeting venue, format, frequency and duration. Having regular MDT meetings helps treating teams better manage waiting lists, lower waiting times and make best use of resources;

- 
5. Communication: referral to MDT process, discussion criteria and documentation;
  6. Patient confidentiality in selection and review of cases and who is responsible.  
Patients should be informed of their case presentation at an MDT meeting.  
The patient has the right to refuse care provided in this way or limit what information is shared.
  7. Education and training. Other health professionals may attend for educational purposes. Industry may give educational presentation before or after the MDT.
  8. Videoconferencing is not essential but desirable to allow regional sites or primary care providers the opportunity to participate in their patient's discussion at the MDT meeting.

Where appropriate, participation in clinical trials, including the process for identifying eligible patients, should also be addressed in the terms of reference.

**Characteristics that result in effective MDT meetings include:**

1. Treatment decisions and care is delivered by specialists with knowledge and skills in the relevant aspects of the particular cancer type;
2. Patients are offered information and support to cope with their cancer;
3. Good communications and continuity of care regardless of who or where care is provided;
4. The MDT has collegial working relationships;
5. The MDT has an educational component;
6. Economic use of resources, such as the use of telehealth
7. Alerts on significant changes to the recommended treatment plan – to provide opportunity to review and record variances and learn from these cases;
8. Auditing and monitoring of MDT processes to drive service improvement and assist service planning, including sustainability of the MDT.

## **1.2 Palliative care, supportive care and end of life care**

Palliative, supportive and end of life care should be offered at any point in the patient journey at all levels of care.

### **1.2.1 Palliative Care**

World Health Organization defines palliative care as an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illnesses, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychological and spiritual (WHO, 2002). Palliative and supportive care must be multi-disciplinary. Integrating palliative care from the time of diagnosis improves patient and family experience, which ultimately leads to better patient reported outcomes (Lancet, 2018). The inclusion of PC as a fundamental health service and right is incorporated in the Kenya Health Act (2017). However, according to WHO (WPCA, 2014), less than 10% of patients who require palliative care in the country do access it.



## Components of Palliative Care

They include:

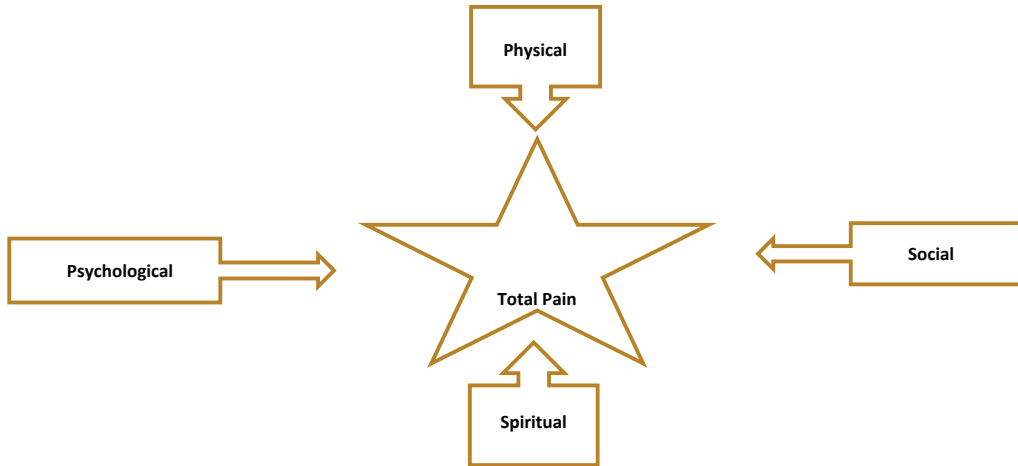
- Treatment navigation – integrates palliative care with standard cancer care
- Assistance in communication to both the patient, family members and caregivers
- Pain and symptom management
- Psycho-social assessment and support e.g. patient's social support system, coping strategies, fears, self-care activities
- Spiritual assessment and support
- Chronic wound and stoma care
- Image and sexuality support
- Anticipatory approach to symptom management
- Ethical-legal support e.g. palliative care as a human right, writing a will
- Advanced directives – a legal document that expresses the desire of the patient in relation to different medical treatments when the patient is unable to make those decisions. It's in three formats: living will, appointment of a healthcare proxy and legal status of preferences.
- Rehabilitation e.g. physical therapy, occupational therapy, speech therapy, prosthetics etc that improve mobility, function, pain relief and other aspects of the patient
- Support groups
- Transition/continuity of care – to improve care, enhance patient and family caregiver outcomes and manage the cost of care.
- Complimentary and alternative therapies
- Home based care.



### 1.2.2 Pain management

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue injury or damage (IASP, 1979). Pain is whatever the experiencing person says it is existing whenever the experiencing person says it does (McCaffery, 1968).

#### ***Holistic Approach is Central to Management.***

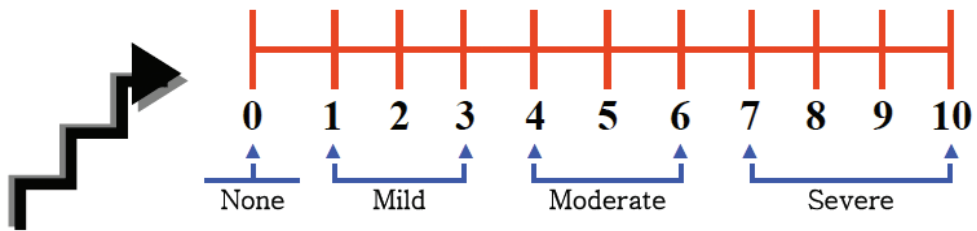


Pain is one of the most frequent and serious symptoms experienced by patients in need of palliative care. 80% of patients with cancer will experience moderate to severe physical pain at one point during their treatment. Pain management requires a multi-faceted approach – total pain treatment approach encompassing physical, social, psychological and spiritual aspects. The use of the WHO pain management ladder is a useful guide in the utilization of various medications.

#### **Pain assessment – History**

- Is the pain limiting activity?
- What does the patient feel about the pain?
- What are the expectations of treatment?
- What are the patient's fears?
- What are the patient's previous experience of pain and illness?

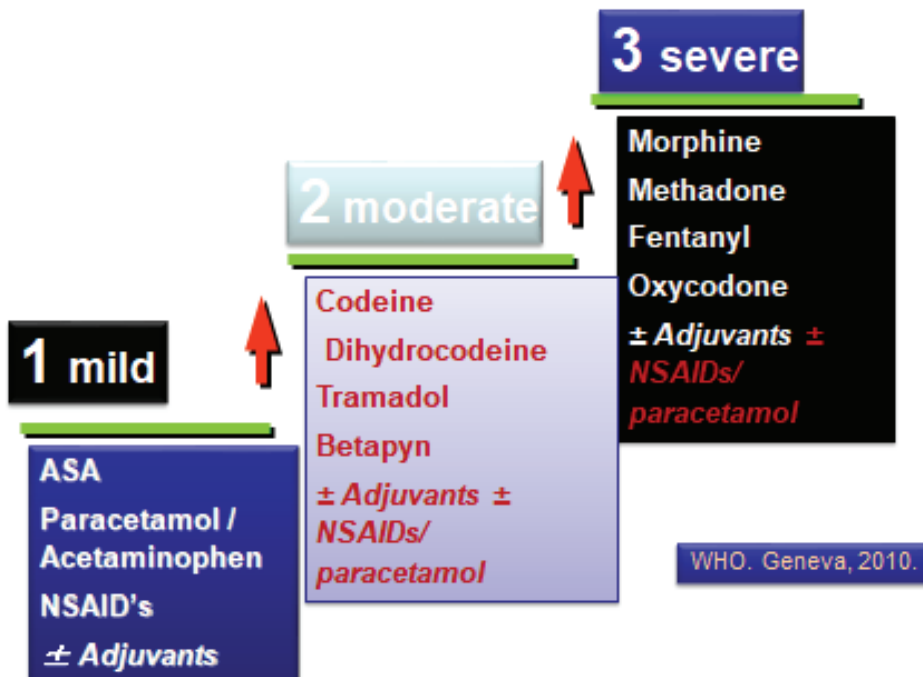
## Numerical Pain scale



### Treatment of Pain

- Non-pharmacological therapy – e.g. pet therapy, aromatherapy
- Pharmacological therapy – NSAIDs, opioids, adjuvants

### 3 Step WHO Adult Pain Management Ladder



## WHO Pain Relief Program



### 1.2.3 Management of other symptoms

#### Depends on:

- Organ affected
- Stage of disease
- How much it affects the nearby organs or structures
- Spread (metastasis) – where symptoms may appear in different parts of the body
- Systemic effects
- Consider psychosocial and spiritual wellbeing of the patient

#### General principles of Symptom Management

1. Assessment always precedes treatment
2. Use assessment tools e.g. Edmonton symptom assessment scale-R (ESAS-R)
3. Regular assessment for
  - a. Setting treatment goals
  - b. Monitoring the response to specific treatment
  - c. Communication
4. Symptom management – For every symptom, consider:
  - Evaluation – diagnosis of each symptom
  - Explanation to the patient before treatment
  - Management – individualized treatment
  - Monitoring – continuing review of treatment impact
  - Attention to details

#### 1.2.4 Supportive care

Supportive care is given to improve the quality of patients with life-threatening disease. The goal is to prevent or treat as early as possible the symptoms of a disease, side effects caused by treatment of a disease, and psychological, social and spiritual problems related to a disease or its treatment. General supportive care includes:

- Management of central venous catheters including chemoports and peripheral venous access
- Hydration
- Blood and blood products transfusion
- Nutritional support
- Management of acute Radiation and chemotherapy side effects including;
  - o Nausea & vomiting
  - o Fever
  - o Mucositis
  - o Constipation
  - o Anorexia & cachexia
  - o Fatigue
  - o Diarrhea
  - o Dehydration
  - o Premature menopause
  - o Keratinization - Skin and hair changes.

#### 1.2.5 End of life care

End of life care is care for those with a life-threatening condition that has become advanced, progressive and incurable. It requires a range of decisions, including patients' right to self-determination (of treatment, life etc), ethics and efficacy of extraordinary medical interventions, efficacy of routine medical interventions, rationing and allocation of resources.

The components of end-of-life care include:

- o Prognostication – giving information to the patient and their family about life expectancy to help plan realistically for their future.
- o Pain and symptom management
- o Spiritual assessment and support
- o Anticipatory approach to symptom management
- o Ethical-legal support
- o Home based care
- o Palliative care emergencies treatment
- o Discussions around goals of care
- o Family conferences
- o Issues around nutrition and hydration

- o Surrogate decision making determination – when patients lack decision making capacity, a surrogate should be identified to make decisions.
- o Do Not Resuscitate (DNR) orders
- o Withdrawal/withholding treatment
- o Futile care
- o Last rites
- o Bereavement and grief support.

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### 1.3 Survivorship care

Survivorship focuses on the health and life of a person with cancer post treatment until the end of life. It covers the physical, psychosocial and economic issues of cancer, beyond the diagnosis and treatment phases. It includes issues related to the ability to get health care and follow-up treatment, rehabilitation, surveillance for late effects of treatment, screening for recurrence & secondary cancers and quality of life. Family members, friends and caregivers are also considered part of the survivorship experience.

**Care of the cancer survivor should include:**

1. Prevention of new and recurrent cancers and other late effects.
2. Surveillance for recurrence/spread of cancer and screening for subsequent primary cancers at least annually.
3. Assessment for late psychosocial and physical effects.
4. Interventions for consequences of cancer treatment such as pain and peripheral neuropathy management, lymphedema management, for those who received anthracyclines, assess for anthracycline-induced cardiotoxicity (evaluate for heart failure signs and symptoms, presence of risk factors), need for immunizations.
5. Care co-ordination between specialists and primary care givers with specific roles delineated to ensure the health needs of the cancer survivor are met.
6. Survivorship care planning: This plan will include a summary of treatment received, follow-up care, surveillance and screening recommended for the survivor, post-treatment needs of the survivor, healthy lifestyle behavior recommendations and information on treatment related side effects and anticipated health risks.

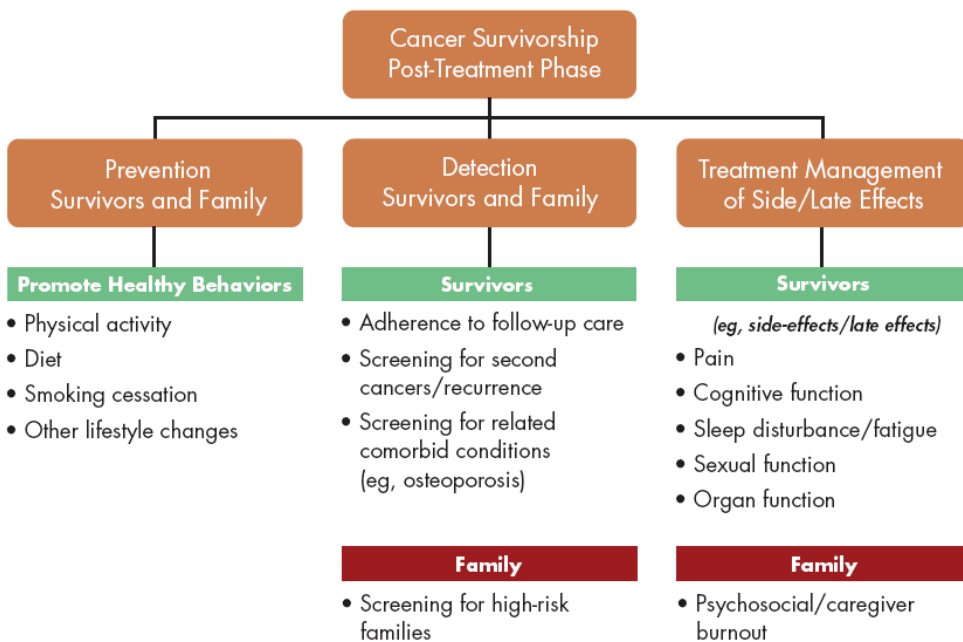


Figure 1.1: Aspects of cancer survivorship (Grant, Marcia & Economou, Denice. (2008). The evolving paradigm of adult cancer survivor care. Oncology (Williston Park, N.Y.). 22.13-22, 27.)

### **Evaluating success of survivorship care will include:**

- Improved communication and care co-ordination: (perceived) patient-physician communication, physician-physician communication.
- Improved understanding of needed follow-up tests, their purpose and timing, and who will conduct them, potential late effects of illness and what symptoms might be important to report.
- Better adherence to recommended follow-up activities; fewer requests for unnecessary tests; reduced duplication of services.
- Improved ability to identify providers and resources to address persistent effects of cancer and its treatment.
- Improved overall survival with decreased cancer-related morbidity.
- Improved healthy lifestyle choices with better quality of life and function.
- Improved knowledge about and ultimately standardization of follow-up care behaviors.
- Improved ability to monitor survivors' health and implement changes in care in response to new information about treatment exposures and follow-up needs.
- Improved access to information necessary to guide follow-up care; less time spent searching for this.
- Enhanced quality of care delivery (such as compliance with evolving quality standards)

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Commission on Cancer: Cancer Standards Program (2016 edition)





# BREAST CANCER TREATMENT PROTOCOL

## List of Abbreviations

|        |   |
|--------|---|
| AD     | Axillary Dissection                                   |
| AI     | Aromatase Inhibitor                                   |
| ALND   | Axillary Lymph Node Dissection                        |
| BCS    | Breast Conserving Surgery                             |
| BIRADS | Breast Imaging Reporting and Data System              |
| BMI    | Body Mass Index                                       |
| BRCA   | Breast Cancer gene                                    |
| CK 5/6 | Cytokeratin antibody 5/6                              |
| CT     | Computerized Tomography                               |
| CXR    | Chest X Ray   |
| DCIS   | Ductal Carcinoma in situ                              |
| ECOG   | Eastern Cooperative Oncology Group performance status |
| EGFR   | Epithelial Growth Factor Receptor                     |
| ER     | Estrogen receptor                                     |
| FNAC   | Fine Needle Aspirate Cytology                         |
| HER2   | Human Epidermal Growth Factor Receptor 2              |
| HRT    | Hormonal Replacement Therapy                          |
| LCIS   | Lobular Carcinoma in situ                             |
| LHRH   | Luteinizing Hormone Release Hormone                   |
| MRI    | Magnetic Resonance Imaging                            |
| MRMR   | Modified Radical Mastectomy                           |
| PR     | Progesterone receptor                                 |
| RT     | Radiotherapy  |
| SLNB   | Sentinel Lymph Node Biopsy                            |
| US     | Ultrasound  |
| WLE    | Wide Local Excision                                   |

## 2.1 Introduction

Breast cancer is the leading cancer both in incidence and mortality among women globally. In Kenya, it is the most common cancer with an age standardized rate of 40.3 per 100,000, and the third leading cause of all cancer deaths annually. Breast cancer tends to occur at a relatively young age (35-50 years) in Kenya, in comparison to Western countries (50-55 years). About 90% of cases occur sporadically, while only 5-10% can be attributed to genetic predisposition. Invasive ductal carcinoma (IDC) is the most common histological type diagnosed accounting for up to 75% of all breast cancers.

## 2.2 Clinical Evaluation

Take a comprehensive history and inquire about the following risk factors:

- Family history of breast/ovarian cancer/previous positive BRCA gene test especially among first degree relatives.
- Reproductive history (estrogen exposure): null parity, early age at menarche and/or later age of menopause, long menstrual cycles (>32 days), history of not breastfeeding, history of hormone replacement therapy (HRT), age at first parity, contraceptive history (type and duration of use).
- Previous abnormal breast biopsy (history of atypical ductal hyperplasia or lobular carcinoma in situ).
- History of irradiation, especially chest wall irradiation.
- Lifestyle - obesity, physical inactivity, tobacco & alcohol use.
- **Symptoms such as breast lump, pain, ulceration, nipple changes/discharge, peau d'orange.**



Figure 2. 1: Symptoms of breast cancer

## Physical examination

- Assess the Body Mass Index (BMI).
- Assess performance status
- Look out for signs such as breast lump, tenderness, ulceration, skin dimpling (peau d'orange), nipple changes (inverted, redness, discharge) and axillary & cervical lymphadenopathy.
- Describe the tumor size, location, asymmetry, chest wall fixation, skin & chest wall changes, and regional lymph node involvement.
- Assess the opposite breast.
- Conduct bimanual palpation of both breasts (See Appendix 3).
- Conduct a complete physical examination.

## 2.3 Imaging for Assessment of Breast Lesions

- Bilateral mammography for those above 35 years.
  - Bilateral breast ultrasound for those below 35 years\*.
  - Breast MRI for younger women and those with a high risk of breast cancer.
- All imaging studies must be accompanied by a report from qualified radiologist.  
\*Ultrasound may be used to guide biopsy and/or as complimentary for patients above 35 years.

Mammography and ultrasound findings, category and recommendations are as tabulated below:

**Table 2. 1: Breast Imaging Reporting and Data System (BIRADS)**

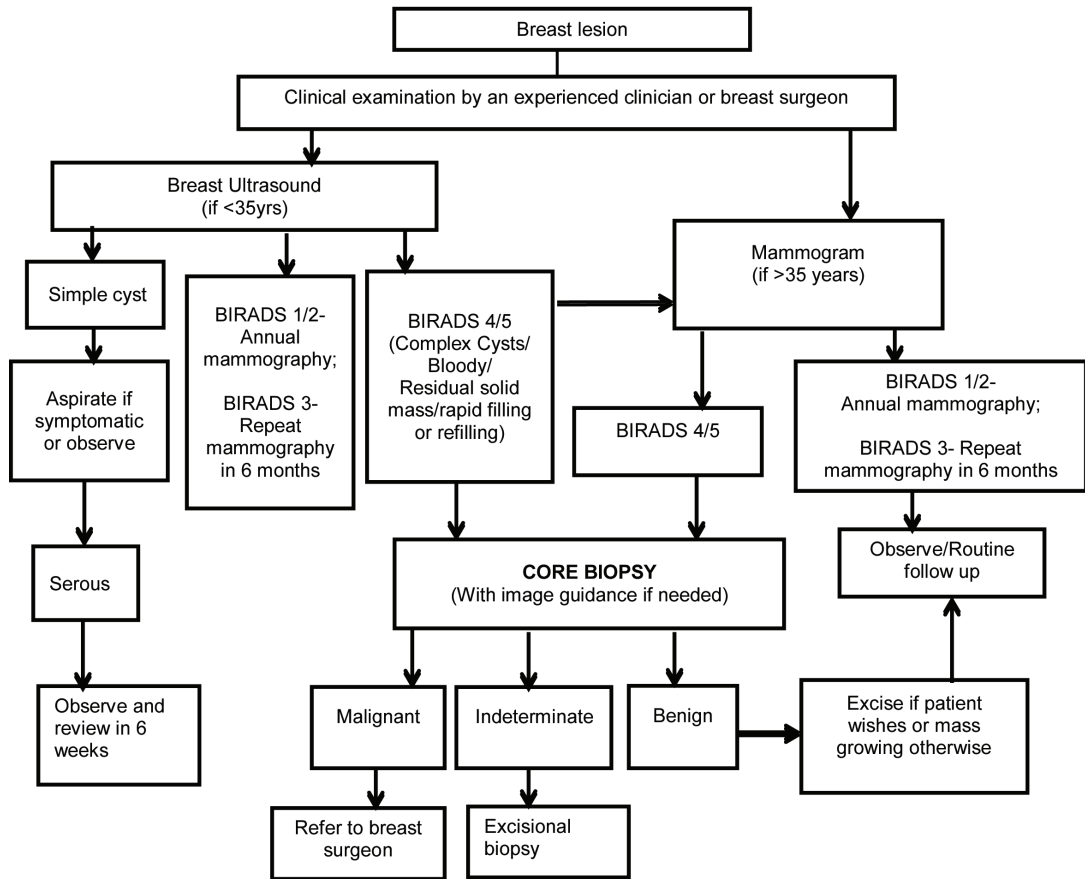
| Assessment | Category   | Recommendation                                       |
|------------|--|--|
| BIRADS 0   | Need additional imaging evaluation                                 | Add views or ultrasound                              |
| BIRADS 1   | Negative   | Annual mammography                                   |
| BIRADS 2   | Benign finding   | Annual mammography                                   |
| BIRADS 3   | Probably benign finding-short interval follow up suggested         | Bilateral mammography 6 month follow-up is suggested |
| BIRADS 4   | Suspicious abnormality   | Biopsy should be considered                          |
| BIRADS 5   | Highly suggestive of malignancy-appropriate action should be taken | Biopsy   |
| BIRADS 6   | Biopsy proven carcinoma  |  |

### **ALL women with a breast lump should undergo a Triple Assessment:**

- **Clinical examination preferably by an experienced clinician or breast surgeon**
- **Bilateral breast imaging: a bilateral mammogram(>35yrs)/ Ultrasound(<35yrs) or an MRI as appropriate**
- **Histopathology: Core biopsy**

*\*Fine needle aspirate cytology (FNAC) role is in the evaluation of lymph nodes prior to intervention and follow up, cytology for nipple discharge and aspirated fluid from simple cyst.*

## Diagnostic Algorithm: Workup of a Breast Lump



## 2.4 Pathological Diagnosis

- Core biopsy and immunohistochemistry (ER/PR/HER2)
- Nipple discharge cytology
- Fine needle aspirate of the axillary node/lump

*All pathology reports should be accompanied by a report from a qualified pathologist.*

**The decision to treat a breast mass, including through surgery, should NOT be based on the results of FNAC alone.  
Core biopsy is mandatory.**

### Laboratory Tests

*Core tests : Full blood count, U/E/Cr, LFTs, HIV test*

*Others (not mandatory): Alkaline Phosphatase, Lactate Dehydrogenase*

*Personalised testing: may include BRCA testing, Oncotype DX and MammaPrint.*

## 2.5 Pre-operative Staging Considerations

All patients **must** be staged before treatment.

Preoperative staging is mainly by imaging and clinical examination.

**T-Staging** – Clinical examination, imaging and surgical specimen

- The initial imaging should indicate the absence or presence of additional lesions in the ipsilateral breast, axilla and the contralateral breast, otherwise, review or repeat the imaging.

**N-Staging** - Clinical examination, imaging and surgical specimen

- Preoperative staging of N is clinical examination and CT scan results .

**M- Staging** - Imaging.

- Early breast cancer (T2 and below)- chest x-ray and abdominal ultrasound
- Locally advanced (T3 and 4) - CT Chest & Abdominopelvic, and bone scan (if necessary).
- Other tests as indicated by clinical evaluation, for instance CT head for CNS symptoms)

**Table 2. 2: AJCC staging of breast cancer**

| <b>T Status</b> | <b>Characteristics</b>  |
|-----------------|---|
| Tx              | Primary tumour cannot be assessed   |
| T0              | No evidence of primary tumour   |
| Tis             | Ductal carcinoma in situ  |
| Tis(Paget)      | Paget's disease not associated with parenchymal disease or ductal carcinoma in situ |
| T1              | Tumour less than 20mm   |
| T1mi            | Tumour less than 1mm  |
| T1a             | Tumour more than 1mm but <5mm   |
| T1b             | Tumour >5 mm but <10mm  |
| T1c             | Tumour more than 10 but less than 20mm  |
| T2              | Tumour more than 20mm but <50mm   |
| T3              | Tumour more than 50mm in the greatest dimension                                     |
| T4              | Tumour of any size with invasion of skin, chest wall or both                        |
| T4a             | Invasion to chest wall (not pectoralis major)                                       |
| T4b             | Invasion to skin (ulceration, macroscopic satellite, peau de orange)                |
| T4c             | Invasion to both chest wall and skin  |
| T4d             | Inflammatory  |

## Nodal status

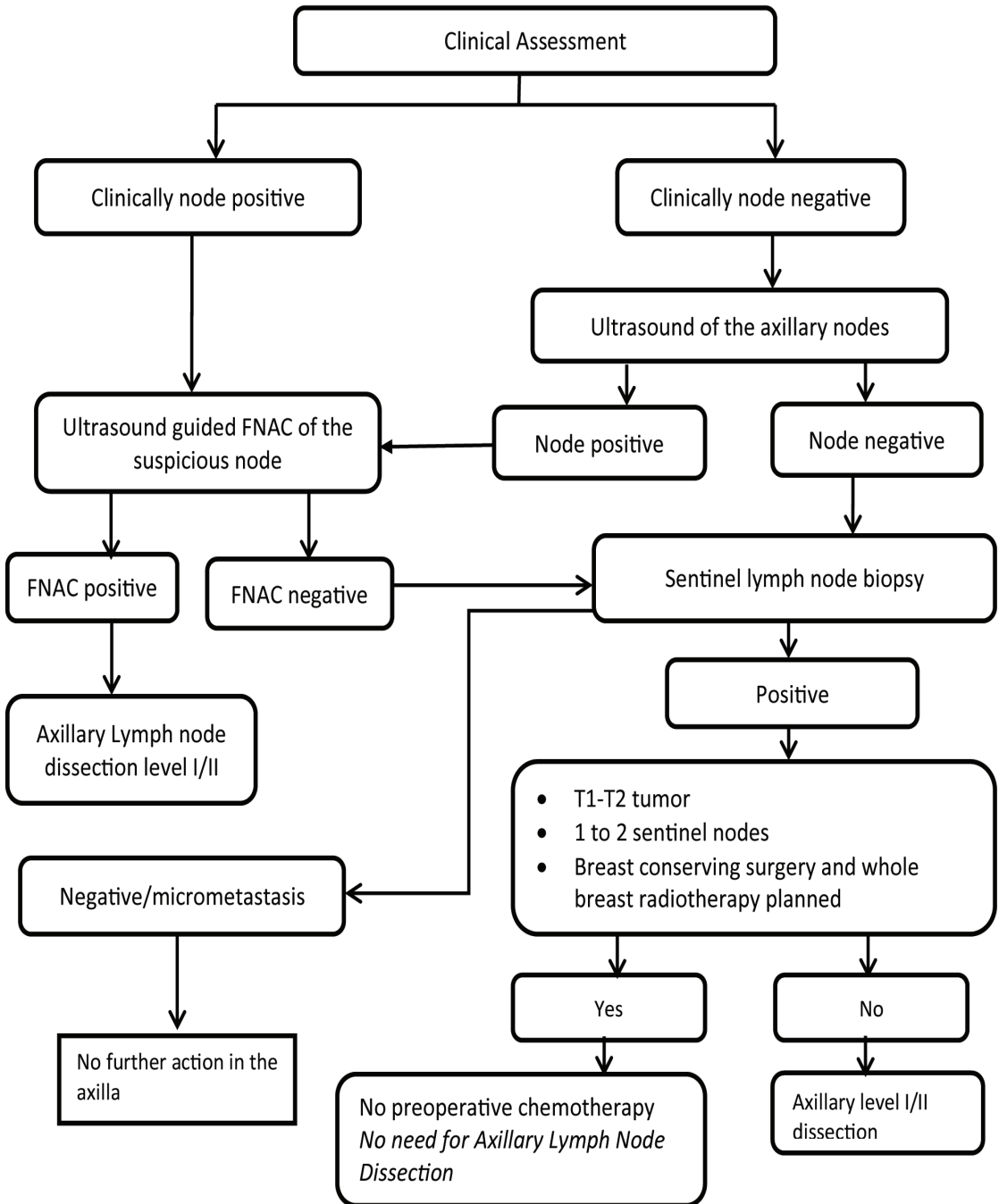
| Clinical |  | Pathology |   |
|----------|--|-----------|---|
| cNx      | Regional nodes cannot be assessed (Previously removed)             | pNx       | Regional nodes cannot be assessed for pathological studies                    |
| cN0      | No evidence of nodal metastasis by imaging or clinical examination | pT0       | No regional lymph node identified or ITCs (isolated tumor cell clusters) only |
|          |  | pN0(i+)   | ITCs only   |
|          |  | pN0(mol+) | Detected by PCR, no ITC   |
| CN1      | Clinically mobile level I/Level II nodes                           | PN1       | 1-3 nodes   |
| CN1mi    | Micro metastasis, less than 2mm, larger than 0.2mm                 | pN1mi     | Micro metastasis  |
| cN2      | Ipsilateral level I/II clinically fixed or matted                  | pN2       | 4-9 nodes   |
| cN3      | Ipsilateral infraclavicular nodes or supraclavicular nodes         | pN3       | More than 10 nodes axillary, infraclavicular node or supraclavicular node     |

## M-status

|        |  |
|--------|--|
| M0     | No clinical or radiological evidence of distant metastasis   |
| M0(i+) | Above but with evidence of less than 0.2mm deposit or bone marrow, or circulating tumor cells without symptoms |
| cM1    | Clinically or radiologically detected distant metastasis   |
| pM1    | Pathologically detected larger than 0.2mm  |

| T     | N     | M  | Stage |
|-------|-------|----|-------|
| Tis   | N0    | M0 | 0     |
| T1    | N0    | M0 | IA    |
| T0    | N1mi  | M0 | IB    |
| T1    | N1Mi  | M0 | IB    |
| T0    | N1    | M0 | IIA   |
| T1    | N1    | M0 | IIA   |
| T2    | N0    | M0 | IIA   |
| T2    | N1    | M0 | IIB   |
| T3    | N0    | M0 | IIB   |
| T0    | N2    | M0 | IIIA  |
| T1    | N2    | M0 | IIIA  |
| T2    | N2    | M0 | IIIA  |
| T3    | N1    | M0 | IIIA  |
| T3    | N2    | M0 | IIIA  |
| T4    | N0    | M0 | IIIB  |
| T4    | N1    | M0 | IIIB  |
| T4    | N2    | M0 | IIIB  |
| Any T | N3    | M0 | IIIC  |
| Any T | Any N | M1 | IV    |

### Algorithm for Axillary Staging





## 2.6 Treatment

**All new breast cancer patients should be reviewed by a multi-disciplinary team (MDT) whose** core members include: designated breast surgeon(s), radiologist, pathologist, oncologist, nursing, palliative care, social worker and MDT co-ordinator. Other disciplines, such as plastic and reconstructive surgeons, speech therapists, occupational/physiotherapists may be included as and when need rises. Treatment is usually guided by molecular subtypes and staging.

### Subtyping of Invasive Breast Cancer

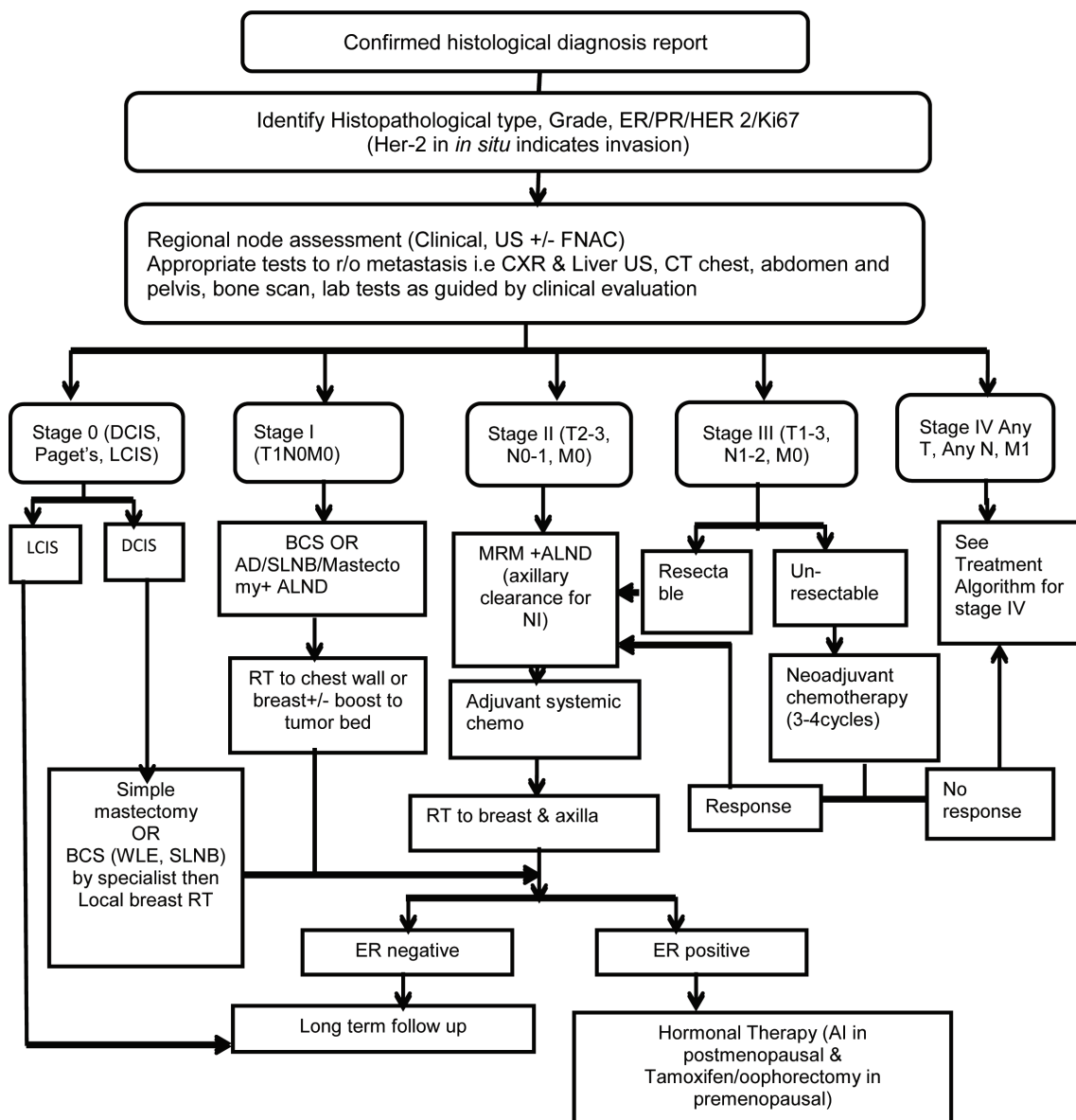
Breast cancer has been traditionally classified based on clinical and morphologic features; the latter takes into account tumour type, size, grade, lymphovascular invasion, the number and extent of lymph node involvement and the expression of hormone receptors; estrogen (ER) and progesterone receptor (PR) and the Human Epidermal Growth Factor Receptor 2 (HER2), the latter a member of the tyrosine kinase receptor family. Various classification systems use a combination of these factors to categorize patients into risk factor and prognostic groups. However, due to the heterogeneous nature of breast cancer, individual patients in the same risk category may have different clinical outcomes. Thus, the advent of molecular classification in recent years has seen a refinement of the traditional classification system to better assess the prognosis and predict response to therapy of Breast Cancer at an individual level.

There are four distinct molecular “intrinsic variants” (Luminal A, Luminal B, HER2-enriched, and Basal-like) and a Normal Breast-like group each with different clinical outcomes. Immunohistochemistry has been used as a surrogate marker for the intrinsic Breast Cancer subtypes as defined by gene expression profiling. Although, three markers Estrogen receptor (ER), Progesterone Receptor (PR) and Human Epidermal Growth Factor 2( HER2), were initially used to define the Luminal A, Luminal B, HER2 enriched and the Basal subtypes of BC, this approach was further modified to include three more antibodies (CK5/6, EGFR and Ki67) that better predict the molecular subtype.

**Table 2. 3: Molecular Subtyping of Invasive Breast Cancer**

| <b>Molecular Intrinsic Variant</b> | <b>ER</b> | <b>PR</b> | <b>HER2</b>       | <b>Ki67</b> | <b>CK5/6</b> | <b>EGFR</b> |
|------------------------------------|-----------|-----------|-------------------|-------------|--------------|-------------|
| Luminal A                          | Positive  | Positive  | Negative          | <14%        | Negative     | Negative    |
| Luminal B                          | Positive  | Positive  | Positive/negative | >14%        | Negative     | Negative    |
| HER2-enriched                      | Negative  | Negative  | Positive          | Any Ki67    | Negative     | Negative    |
| Basal like                         | Negative  | Negative  | Negative          | Any Ki67    | Positive     | Positive    |

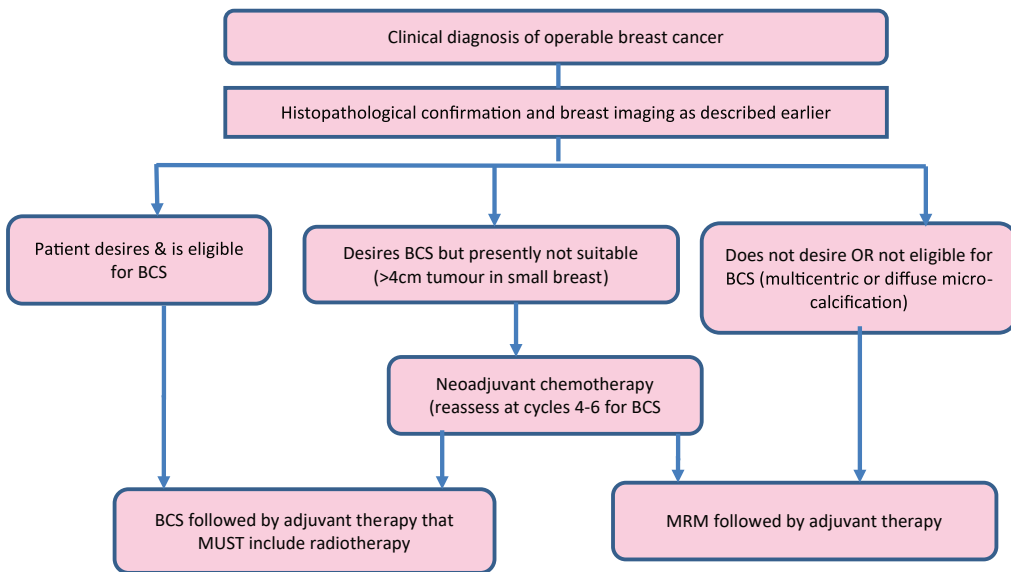
## Treatment Algorithm for Histologically Confirmed Breast Cancer



## 2.6.1 Surgical Management of Breast Cancers

Accurate pre-operative assessment of the size and extent of the tumor through clinical examination and standard breast imaging is essential for deciding whether breast conserving surgery is an option to mastectomy. In difficult cases, particularly lobular cancers, MRI should be used in planning surgical treatment after discussion at the MDT.

### Algorithm for Surgical Management of Breast Cancer



Surgical complications include infection and bleeding in the acute setting, flap necrosis and long term complications such as lymphoedema.

### Margins

- The major surgical factor influencing local recurrence following BCS is completeness of excision, and clear radial margins must be obtained.
- Close margins at the chest wall or near the skin may be less important.
- The specimen should be orientated and marked prior to delivery to the pathologist.
- Acceptable margins are 1mm for Invasive Ductal Carcinoma (Tumor on ink) and 2mm for DCIS.

### Drains

- The use of drains is to be decided by the surgeon at time of surgery, can be avoided in BCS. The drain site should be anterior to the mid axillary line to enable coverage of site by radiotherapy.

**Table 2.4 Summary of Treatment interventions**

| <b>Term</b>                       | <b>Recommendation and Indications</b>  |
|-----------------------------------|--|
| Axillary surgery                  | Performed in all patients with invasive breast cancer in order to stage the axilla and eradicate metastatic disease within the nodes.  |
| Axillary lymph node status        | Most important prognostic indicator for patients with primary breast cancer (breast cancer that hasn't spread beyond the breast or the lymph node under the arm) and has a role in deciding the use of adjuvant therapy.   |
| Simple mastectomy                 | Removal of the whole breast without axillary dissection usually for ductal carcinoma in-situ.  |
| Mastectomy                        | Mainstay of surgical management of breast cancer<br><i>Indications:</i> <ul style="list-style-type: none"> <li>• Patient's choice</li> <li>• Operable tumours &gt; 4cm in diameter in an average sized breast</li> <li>• Operable multi-focal disease in &gt; one quadrant of the breast</li> <li>• Contraindication to radiotherapy</li> <li>• Failed BCS (e.g. local recurrence or positive margins after wide local excision where further wide local excision is not feasible)</li> <li>• Where BCS is unlikely to result in an acceptable cosmetic outcome (e.g. larger tumour in a small breast)</li> <li>• Most cases of central breast cancer</li> <li>• Local recurrence</li> </ul>   |
| Breast conserving surgery (BCS)   | Includes lumpectomy, wide local excision, quadrantectomy or segmentectomy. Must be followed by radiotherapy. May require oncoplastic techniques hence the need for specialist care.<br><i>Indications:</i> <ul style="list-style-type: none"> <li>• Patient choice</li> <li>• Operable tumors up to 4cm in diameter in an average sized breast</li> <li>• Operable multi-focal tumor restricted to a single breast quadrant</li> <li>• Two or more small tumors in different quadrants in a large sized breast</li> <li>• No contraindications to radiotherapy</li> <li>• Larger tumors may be treated when combined with oncoplastic procedures</li> <li>• After neo-adjuvant chemotherapy or hormonal therapy specifically aimed at reducing tumor size</li> </ul> |
| Mastectomy plus Level II/III AD   | Removal of whole breast tissue plus axillary lymph nodes behind the pectoralis minor for level II and above it for level III. Optimal axillary lymph node dissection means removal of a minimum of 10 nodes.   |
| Sentinel lymph node biopsy (SLNB) | A technique of sampling the most likely lymph nodes with metastasis. This can be performed by introduction of methylene blue dye at the sub-cutaneous level at the peri-areolar or peri-lesional. This can be performed just after patient is placed under GA and the breast massaged. The indication is for those with clinically node negative disease, and the optimal number of the nodes is can range between 1-6 nodes. Positive SLNB is usually followed by axillary lymph node dissection.   |
| Neoadjuvant chemotherapy          | Preoperative systemic chemotherapy given to patients who have unresectable locally advanced disease to make it resectable and convert mastectomy to BCS for those that are resectable. They require clinical response at cycle 3.<br><i>Indications:</i> <ul style="list-style-type: none"> <li>• Triple negative breast cancer</li> <li>• HER2 enriched breast cancer</li> <li>• Unresectable locally advanced breast cancer</li> </ul>   |

### 2.6.2 Adjuvant Therapy for Breast Cancer

This will include radiotherapy, endocrine, biological or hormonal therapy. Discuss at MDT meeting for ALL patients and decisions made based on prognostic and predictive factors, potential benefits and side effects of the treatment.

#### Radiotherapy

- Postoperative RT to the breast/ chest wall with or without lymphatic areas is indicated in most cases, except after mastectomy for a DCIS or early node negative cancer.
- Indications for postoperative radiotherapy to chest wall +/- nodal area include:  $\geq 4$  axillary nodes positive, post neoadjuvant chemotherapy for upfront unresectable disease, clinically or pathologically T3 or T4 tumours, positive resection margins and after breast conservative surgery.

#### Endocrine therapy

- Patients receiving adjuvant chemotherapy should defer endocrine therapy until chemotherapy is completed.
- ONLY patients with ER positive disease should receive endocrine therapy. For male patients with ER positive disease: give adjuvant tamoxifen 20mg daily for 5 years.
- All premenopausal ER positive women should receive at least 5 years of tamoxifen 20 mg once a day as their initial adjuvant therapy and thereafter either tamoxifen or an aromatase inhibitor (AI) dependent on menopausal status. Ovarian ablation (LHRH analogues such as goserelin) combined with either exemestane, fulvestrant or tamoxifen has added survival benefit.
- All postmenopausal ER positive breast cancer should be offered an aromatase inhibitor as their initial adjuvant therapy for at least 5 years, unless not tolerated or contraindicated, in which case tamoxifen should be offered. Aromatase inhibitors increase the risk of osteoporosis; therefore, give lifestyle advice, such as regular weight bearing exercise, smoking cessation, high calcium diet; for those at high risk, DEXA Scan should be done and bisphosphonate given as indicated.

#### Biological therapy

For HER2 positive disease, Trastuzumab should be given at 3-week intervals for one year or until disease recurrence, as an adjuvant treatment or till progression in the metastatic setting.

#### Chemotherapy Protocols

Adjuvant chemotherapy should be started as soon as clinically possible, usually within 6 weeks of completion of surgery. Choice of the regime should be left to the oncologist dependent on the patient characteristics, tumour characteristics and system/social-economic characteristics, among others.

### **HER2 negative disease**

- o Doxorubicin/Cyclophosphamide x 4 cycles. Repeat cycle every 21 days.
- o Docetaxel/Cyclophosphamide x 4 cycles. Repeat every 21 days.
- o Cyclophosphamide/Methotrexate/5-Fluorouracil x 6 cycles. Repeat every 28 days.
- o 5-Fluorouracil /Epirubicin /Cyclophosphamide. Repeat every 21 days x 6 cycles
- o Doxorubicin/Cyclophosphamide x 4 cycles every 21 days followed by Taxane x 4 cycles every 21 days.
- o Doxorubicin/Cyclophosphamide x 4 cycles followed by 12 weekly paclitaxel
- o Doxorubicin/Docetaxel/Cyclophosphamide for 6 cycles

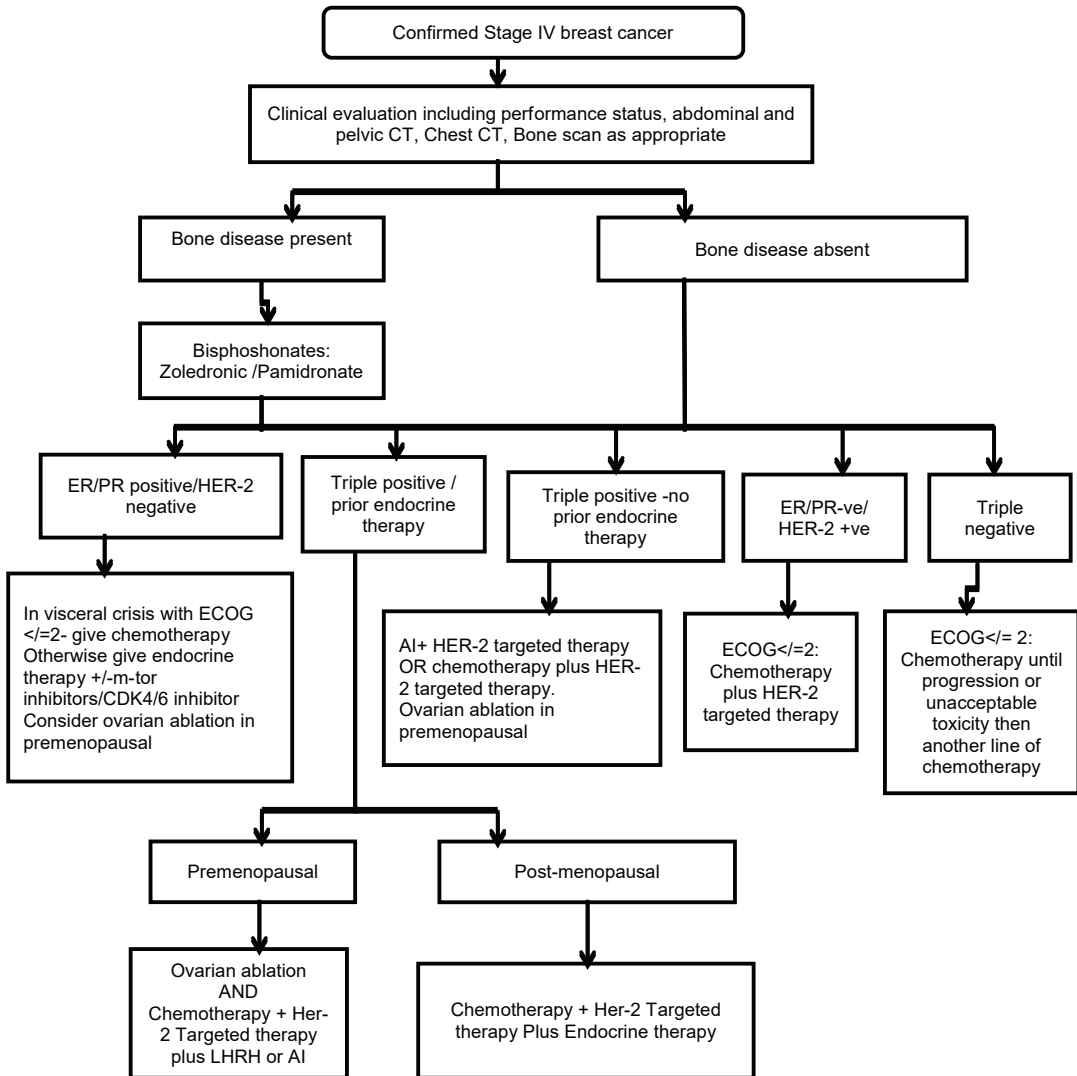
### **HER 2 positive disease**

- o Doxorubicin/Cyclophosphamide x 4 cycles followed by paclitaxel/trastuzumab ± pertuzumab x 4 cycles followed by trastuzumab ± pertuzumab x 18 cycles (9 cycles of trastuzumab ± pertuzumab can be used as an alternative)
- o Docetaxel/carboplatin/trastuzumab ± pertuzumab x 6 cycles followed by trastuzumab ± pertuzumab for 12 cycles
- o Paclitaxel and trastuzumab x 4 cycles followed by trastuzumab x 18 cycles

*If using anthracycline and trastuzumab based chemotherapy, baseline echocardiograph will be required.*

## 2.6.3 Recurrent or Metastatic Breast Cancer

### Treatment Algorithm for Stage IV (Metastatic) Breast Cancer



#### Note

- Palliative therapy may involve chemotherapy/endocrine/ biological agents
- It may also involve surgery for control of wound if will improve quality of life
- It may also include palliative radiotherapy for bleeding ulcers, control of metastasis
- Those with pleural effusion will require drainage of the fluid before chemotherapy either by an interventional radiologist or by chest tube insertion.

### **Hormonal therapy (for ER+ve)**

- Pre-menopausal who have received prior treatment with tamoxifen: LHRH analogue with an aromatase inhibitor should be considered.
- Postmenopausal who have received prior treatment with AI: give tamoxifen or exemestane.
- Other hormonal therapy that can be considered in progressive disease include: fulvestrant, everolimus and the CDK4/6 inhibitors like palbociclib and ribociclib.

### **Chemotherapy**

- The decision will depend on prior treatment, disease free interval, performance status and patient preference.
- Indications for palliative cytotoxic chemotherapy include:
  - Hormone insensitivity
  - Disease progression on hormone therapy
  - If rapid disease control is required (e.g. visceral metastases)
- Combination chemotherapy is preferred in patients with high visceral burden whereby you want a rapid disease control.
- Anthracyclines or taxanes are the preferred first line agents if not used earlier.
- Other chemotherapy agents that can be used include capecitabine, platinum, eribulin, vinorelbine, gemcitabine and ixabepilone.

### **Biological Treatment**

- In HER2 positive patients consider trastuzumab, pertuzumab, ado-trastuzumab and lapatinib either as a monotherapy or combination with chemotherapy.
- Bisphosphonates (e.g. zoledronic acid, denosumab) in patients with skeletal metastases so as to reduce skeletal related events like compression or fragility fractures. Patients on bisphosphonates should be on calcium supplements with monthly monitoring of kidney function. Dosages should be adjusted according to the renal function.

### **Radiotherapy**

Palliative Radiotherapy is given to patients with metastatic disease for symptomatic relief such as:

- **Bone metastasis:**
  - Radiotherapy along with bisphosphonates is the main stay of treatment for symptomatic bone metastasis, impending fracture or cord compression.
  - Established fractures in patients with more than 6 months of life expectancy should be fixed surgically and then given postoperative RT.
- **Brain metastasis:**
  - Most symptomatic patients would benefit from steroids and fractionated whole brain radiotherapy.
  - For single brain metastasis in patients with controlled primary and no other site of systemic disease, consider surgery or radiosurgery of the brain lesion followed by whole brain radiotherapy.



- **Spinal cord compression:**

- Palliative radiotherapy with steroids is the mainstay of treatment.
- Select cases with life expectancy of more than six months presenting with recent onset paraparesis or paraplegia and limited vertebral involvement should be considered for surgical decompression prior to palliative radiotherapy.

## 2.7 Follow up and surveillance

Patients should be counseled on the diagnosis, treatment care plan and anticipated financial implications. The need for regular follow up for timely detection and salvage of recurrences, treatment of contralateral/metastatic disease and management of late sequelae of treatment including quality of life and survivorship plan should be emphasised.

### At follow up visits:

1. Take a detailed history - metastatic symptoms, physical / psychosocial sequelae of treatment
2. Clinical examination
3. Mammogram (bilateral if breast conserving surgery has been done) every 12 – 24 months.
4. No blood tests, imaging or tumor markers unless concerned about tumor recurrence.

The follow-up frequency should be: 3 monthly for 2 years; 6-monthly for 3 years; then annually.

Patients with significant family history of cancer or known BRCA mutation should be kept on lifelong 6-monthly or annual follow up.

## 2.8 Supportive care for breast cancer

1. **Lymphedema management:** often caused by the interruption of regional lymphatic drainage. 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 at baseline and after treatment. A difference of 2 cm or greater at any point is clinically significant. Symptoms will include swelling on the same side of treatment, sensation of heaviness of the limb, fatigue, fullness/tightness of skin or pain. Risk factors for lymphedema include obesity (BMI > 30kg/m<sup>2</sup>), localized infections and increased number of nodes removed.

Early detection is key because stages 0 and 1 are reversible.

Options of care include : external compression garments (such as lymphedema stockings), massage/ manual lymphatic drainage, elevation, exercise, psychosocial support and prompt treatment of infections.

2. **Breast reconstruction:** Every patient undergoing mastectomy should be informed of the option of breast reconstruction for patients with early breast cancer or locally advanced breast cancer as appropriate. For early breast cancer, there must be an option of breast conserving surgery.
3. **Breast prostheses** may be considered for breast cancers survivors who have undergone mastectomy.
4. **Management of hormone-related symptoms:** menopause management in females by appropriate specialist.
5. **Symptom management** – pain, wound management, depression, anaemia, side effects of their medication, loss of appetite, vomiting, numbness.
6. Linkage with support groups.
7. Sexuality support and management should be discussed and if needed patient sent to experts for management.

## 2.9 Anticipated Care at Various Health Facility Levels

| Level     | Function  |
|-----------|---|
| Level 1   | Breast health awareness, appropriate & timely referral, palliative care   |
| Level 2/3 | Breast health awareness<br>Clinical Evaluation - History taking, physical examination including CBE<br>Appropriate & timely referral for those with suspicious history or breast lesions, palliative care.  |
| Level 4   | Breast health awareness<br>Clinical Evaluation - History taking, physical examination including CBE<br>Diagnosis – Imaging (mammogram, ultrasound, Chest x-ray)<br>Pathology (FNAC, biopsy specimen collection)<br>Mastectomy and level I/II axillary lymph node dissection<br>Appropriate & timely referral; MDT including through telemedicine<br>Management of acute surgical complications (infection, bleeding)<br>Palliative care   |
| Level 5   | Breast health awareness<br>Clinical Evaluation - History taking, physical examination including CBE<br>Diagnosis – Imaging (mammogram, ultrasound, Chest x-ray)<br>Pathology (FNAC, Core biopsy, IHC)<br>Mastectomy and level I/II axillary lymph node dissection<br>Chemotherapy, Hormonal therapy by qualified oncologist<br>MDT discussions for all patients<br>Appropriate & timely referral<br>Management of acute surgical complications (infection, bleeding), palliative care |
| Level 6   | All Level 5 functions; all modes of treatment: including BCS and reconstructive surgeries.<br>Support to lower level facilities as appropriate, rehabilitation services<br>Downward referral and palliative care.   |

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# 3

## CHAPTER THREE

### Brain and Central Nervous System Tumors Treatment Protocol

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# BRAIN AND CENTRAL NERVOUS SYSTEM TUMORS TREATMENT PROTOCOLS

## List of abbreviations

|       |                                     |
|-------|-------------------------------------|
| AIDS  | Acquired Immune Deficiency Syndrome |
| CT    | Computerised Tomography             |
| GTR   | Gross Tumor Resection               |
| IGF-1 | Insulin-like Growth Factor 1        |
| MEN   | Multiple Endocrine Neoplasia        |
| MRI   | Magnetic resonance Imaging          |
| MSR   | Maximal Safe Resection              |
| PNET  | Primitive neuroectodermal tumor     |
| RT    | Radiotherapy                        |
| RPA   | Recursive Partitioning Analysis     |
| SRS   | Stereotatic Radio Surgery           |

## 3.1 Introduction

Brain tumors may either be primary (50%), or metastatic. The annual global age-standardized incidence of primary malignant brain tumors is ~3.7/100,000 for males and 2.6/100,000 for females. Rates appear to be higher in more developed countries (males, 5.8 and females, 4.1/100,000) than in less developed countries (males 3.0 and females 2.1/100,000). In adults, two thirds of primary brain tumors arise from supratentorial region with gliomas, metastases, meningiomas, pituitary adenomas and acoustic neuromas accounting for 95% of all brain tumors. They account for approximately 2% of all cancer deaths.

### Risk Factors

- Increasing age
- Male
- Inherited familial syndromes such as MEN1, neurofibromatosis
- History of previous cranial irradiation
- Black ethnicity
- Immunosuppression due to AIDS is a well-recognized cause of cerebral lymphoma

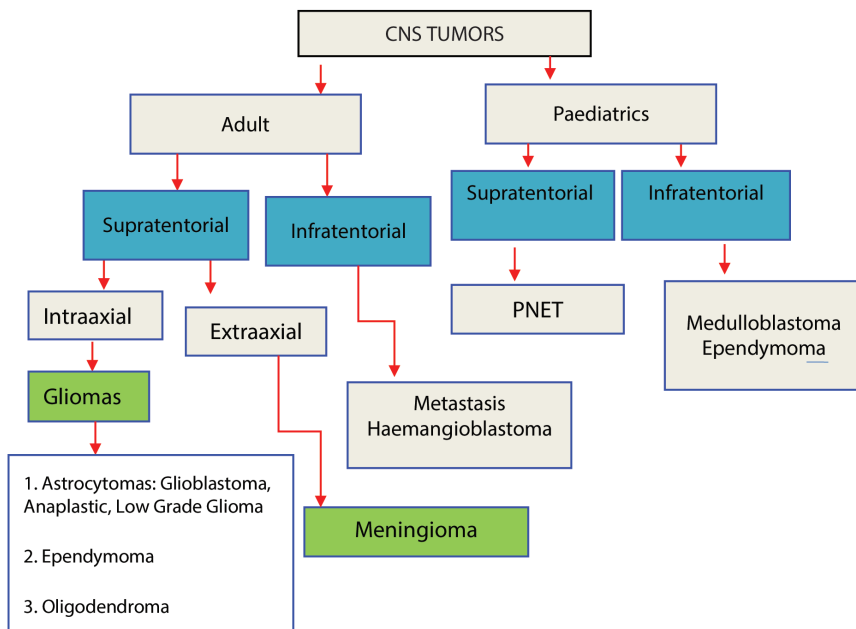


Figure 3.1: Common Types and Subtypes of CNS Tumors

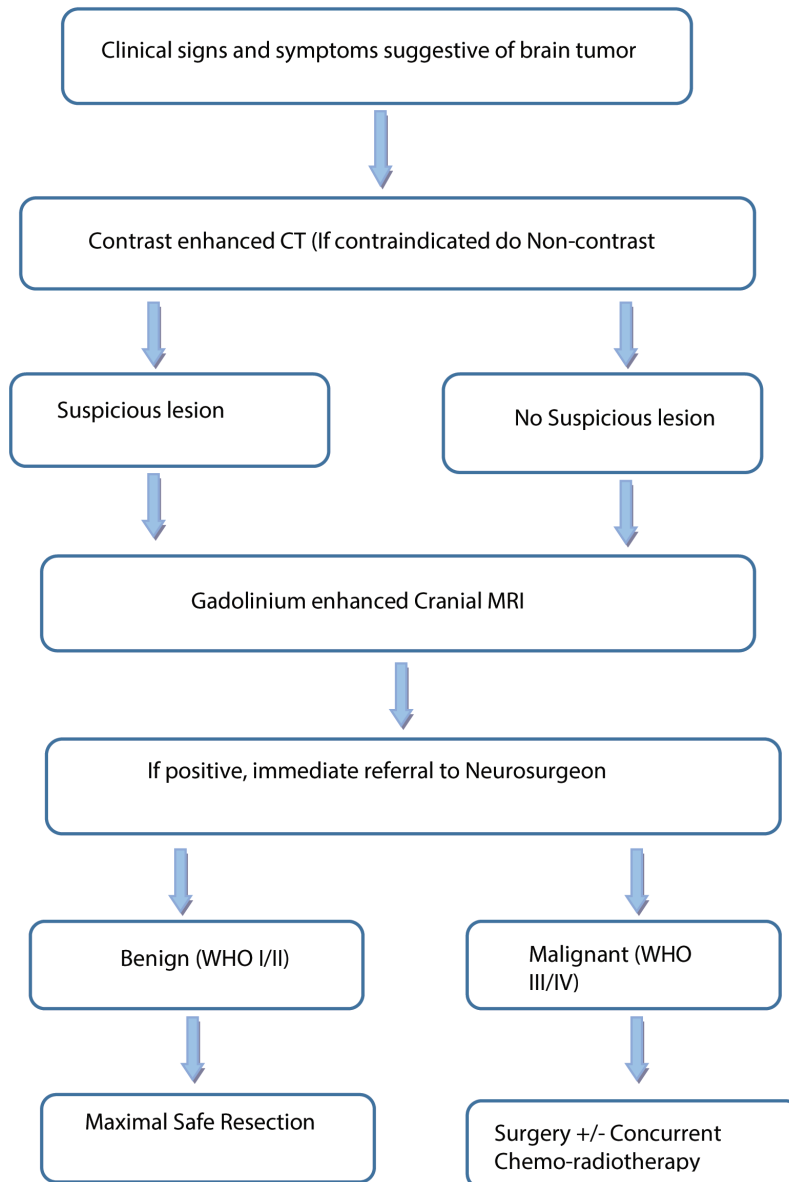
### 3.2 Clinical Evaluation

The signs and symptoms of brain tumors are largely dependent on location and a high index of suspicion is invaluable for early diagnosis which ultimately impacts on patient outcomes.

#### Signs and Symptoms

|   |  |
|---|--|
| <i>Increased intracranial pressure</i>                        | Persistent headache<br>Vomiting<br>Visual blurring<br>Cushing’s Triad (bradycardia, reduced respiration, systolic hypertension)<br>In childhood tumors-hydrocephalus with papilledema, sunsetting eyes, increased head size, tense fontanelle                            |
| <i>Brain Dysfunction</i>                                      | Mental function deterioration<br>Memory disturbance<br>Personality changes<br>Seizures   |
| <i>Focal neurological deficits for supratentorial lesions</i> | Frontal lobe - Personality changes, seizures, headache<br>Temporal lobe – Seizures, speech problems<br>Suprasellar – Endocrinopathies, visual acuity or field loss<br>Occipital- Cortical Visual Deficits<br>Thalamus – Motor sensory deficits                           |
| <i>Focal neurological deficits for infratentorial lesions</i> | Cerebellar – Nystagmus, ataxia, hydrocephalus, resting tremor, incoordination<br>Brainstem – Cranial neuropathies, gait, swallowing incoordination, drooling, breathing dysfunction<br>Posterior fossa – nausea, vomiting, cerebellar signs, gait ataxia, incoordination |

## Diagnostic Imaging Algorithm



**Note:** 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 but if not accessible unenhanced computerised tomography (CT) scan is mandatory to evaluate.

### Indications for Urgent Referral

- Mass lesion on CT scan or suspected, with headache- with increasing drowsiness, increasing weakness or vomiting;
- Tumors associated with midline shift, hydrocephalus or severe deficits;
- Cauda equina syndrome;
- Gradual loss of movement/sensation in an arm or leg;
- Unsteadiness or imbalance, especially if associated with headache;
- A new epileptic seizure, intractable seizure;
- Loss of vision in one or both eyes ( especially if more peripheral), double vision (especially if associated with headache);
- Hearing loss with or without dizziness;
- Speech difficulty of gradual onset;
- Nausea and vomiting, more severe in the morning.

*The referring health care provider should inform the health care provider at the receiving facility about the referral and write a comprehensive medical report to accompany the patient including all scans done.*

### 3.3 Pathological Diagnosis

1. **Biopsy:** Tissue obtained at emergency or elective surgery should be submitted to histopathology for examination.  
Diagnostic biopsy is required before initiation of any chemotherapy or radio therapy, except for high-risk cases where biopsy cannot be done and emergency radiotherapy is required.
2. **Immunohistochemistry** is recommended for confirmation of diagnosis, being mandatory for high-grade or equivocal tumors where the histogenesis is unclear.

### 3.4 Management

#### Emergency Management

- Manage acute cerebral edema due to raised intracranial pressure with Dexamethasone 4-8mg TDS P.O/I.V with a proton pump inhibitor for gastric protection.
- Seizures:
  - o New onset seizures: start phenytoin (IV if rapid control is needed), carbamazepine or lamotrigine as first line treatment and refer to neurosurgical team.
  - o Established seizures: PO/IV phenytoin (15mg/kg/24 hours) or sodium valproate. 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 is not needed.***



### 3.4.1 Glioblastoma

Glioblastoma is the most malignant and frequently occurring type of primary astrocytomas accounting for >60% of all brain tumors.

#### **Definitive Management**

Maximal safe debulking surgery is the initial standard of care to relieve mass effect, obtain diagnostic tissue, reduce tumor burden and to improve or maintain neurological status. Decisions on the need and extent of surgical resection are individualized with considerations based on:

- Performance status (Karnofsky/ECOG status)
- Size of the tumor
- Eloquence of surrounding cortex
- Extension beyond the midline
- Patients age

Imaging is recommended within 72 hours of resection, to assess residual volume of disease or within 21 days to mitigate for post-surgical changes.

Confirmed histological diagnosis and oncology review should be within ten days of surgery due to the rapid doubling time of the tumor. Adjuvant treatment such as radiotherapy with concurrent chemotherapy may be required.

#### **Recurrent Disease/ Progression**

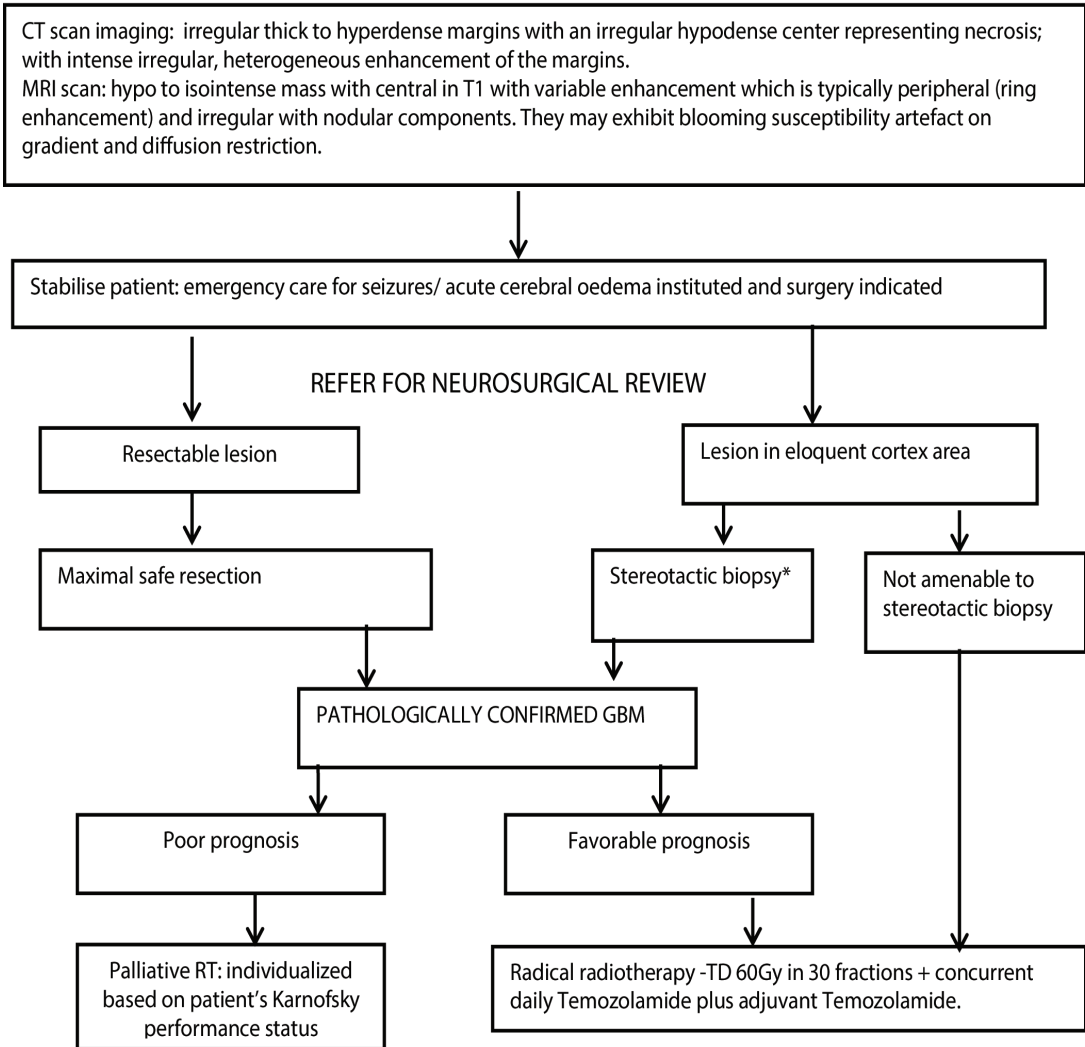
Surgery is indicated in selected patients to relieve symptoms, improve performance status and quality of life. Repeat radiotherapy may be considered, depending on size of lesion, previous dose and the interval since the last radiotherapy treatment. Chemotherapy may also be considered. Active agents include Carmustine, Vincristine, Temozolomide, Irinotecan and Bevacizumab.

Repeat scans should be done after 2-3 cycles to determine response.

#### **Follow up**

A baseline cranial CT scan should be done at 4 months post-radiotherapy as a reference. Thereafter scans are usually done at 6 months and then annually, or if clinically indicated.

## Algorithm for Management of Glioblastoma



\* Stereotactic biopsy is a procedure that uses at least two planes to localize a target in three-dimensional space.

### 3.4.2 Pituitary gland tumors

They include adenomas, carcinomas and other rarer types which constitute 10% of intracranial malignancies. They rarely metastasize but are frequently locally invasive. Morbidity is due to their mass effect as well as endocrine consequences. Etiology is unknown, but may rarely be associated with multiple endocrine neoplasia (MEN) type 1 syndrome.

#### Diagnosis

- Pituitary function: All patients should have baseline pituitary function measured which includes: Thyroid function tests, serum prolactin levels, cortisol levels, growth hormone levels and IGF-1 levels.
- Ophthalmology evaluation –Visual Acuity and Visual Field assessment should be done pre-operatively.
- Imaging as indicated above.

#### Management

Surgery is the primary treatment for most pituitary tumors (except prolactinomas which may be managed medically). MRI is done at 3 months after surgery to assess for residual disease.

Radiotherapy is indicated for sub totally resected tumors, recurrent tumors, patients with persistently elevated circulating hormone levels, and medically inoperable patients. It is very effective for control of growth of pituitary tumors (>95%), but is less effective for decreasing circulating hormone levels of endocrinologically active tumors whose control may take years to achieve after radiotherapy. Consultation with the endocrinologist is therefore mandatory.

### 3.4.3 Meningiomas

They constitute 20% of all intracranial tumors with a male to female ratio of 1:2. Peak incidence occurs in the 7th decade. Possible etiologies include previous exposure to ionizing radiation, trauma, viral infections and exposure to sex hormones (approx. 75% are Progesterone Receptor +ve). They are associated with neurofibromatosis - Type 2 and breast cancer.

#### Imaging

It is typically a well circumscribed, smooth contoured tumor and usually has homogeneously increased density on unenhanced CT and moderate to intense enhancement with contrast. 60% may have surrounding edema. Frequently (15-20%) associated with bony destruction/distortion or hyperostosis, but this usually does NOT represent bony invasion. It is often associated with linear meningeal thickening (“dural tail”), which frequently represents reactive change but may represent spread along meningeal plane. Imaging may give an indication as to the grade of the meningioma with the lesions with predominant surrounding edema being higher grade.



### **Surgery**

Both intracranial and spinal meningiomas are best managed with total excision if possibly achievable with acceptable morbidity. About a third are NOT fully resectable because of location, size and proximity to critical structures.

### **Radiotherapy**

Post-operative radiotherapy significantly improves survival rates and is standard of care. The dose of radiotherapy given is dependent on the grade of meningioma, extent of resection +/- residual disease and site (proximity to dose limiting structures). External beam radiotherapy is used for treatment with few indications for the use of stereotactic radiosurgery in small tumors located next to eloquent areas.

#### **3.4.4 Brain metastases**

They are the commonest diagnosed brain tumors in adults. Tumors that commonly present with brain metastasis include, but are not limited to lung cancer, malignant melanoma, breast and prostate cancer.

### **Definitive Management**

Surgery can be offered to resect solitary brain metastasis or multiple brain metastases with a controlled primary tumor.

Local radiotherapy may be offered thereafter with stereotactic radiosurgery (SRS). Whole brain radiotherapy can be offered but this results in significant neurocognitive decline that needs to be discussed with the patient before the treatment.

| <b>RPA Class</b> | <b>Surgery</b> | <b>SRS</b>                  | <b>Whole Brain Radiotherapy</b> |
|------------------|----------------|-----------------------------|---------------------------------|
| <b>I</b>         | Resection      | Post resection/Unresectable | Discuss post resection          |
| <b>II</b>        | Consider       | If amenable                 | Offer                           |
| <b>III</b>       | Minimal role   | No role                     | Offer                           |

### 3.4.5 Primary Spinal Tumors

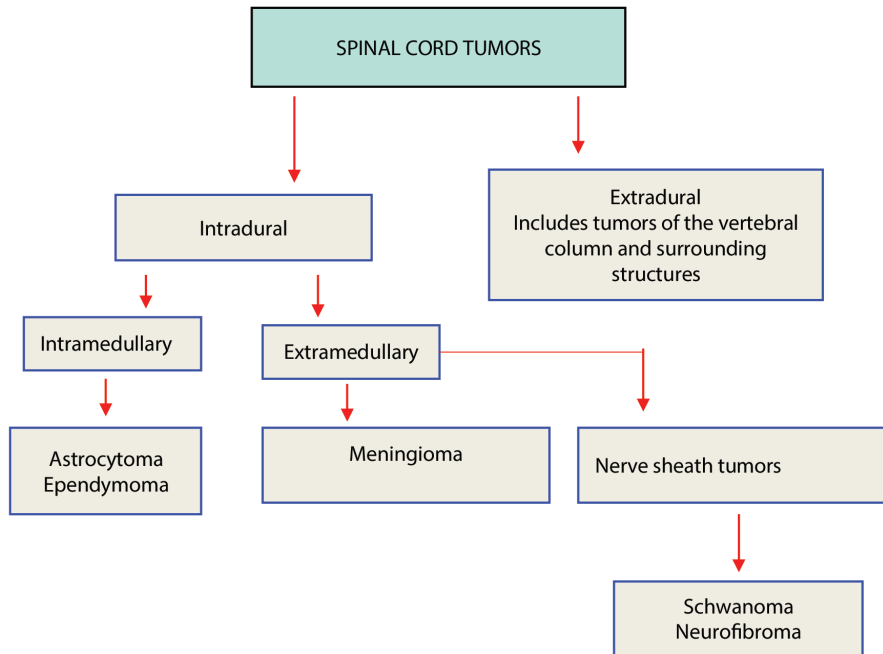


Figure 3.2: Flow diagram illustrating of diagnosis of spinal cord tumors

70% of primary spinal cord tumors are low grade and slow growing so patients **may suffer for months to years with symptoms of back pain** before a diagnosis is made. Patients with Neuro bromatosis type I, II and Von Hippel-Lindau syndrome are more susceptible to developing particular spinal tumors especially- astrocytomas, peripheral nerve sheath tumors, ependymomas and intramedullary haemangioblastomas.

#### Clinical Presentation

Local symptoms corresponding to level of lesion:

- Pain
- Segmental/ nerve root weakness
- Sensory deficit (dermatomal)
- Distal symptoms corresponding to long tract involvement:
- Paresis (diffuse)
- Sensory deficits
- Autonomic dysfunction

#### Management of Spinal Cord Tumors

1. Observation - for asymptomatic patients especially grade I lesions without immediate intervention.
2. Surgery – aim for gross tumor resection (GTR) if the patient is symptomatic and the lesion is amenable to surgery.

3. Radiotherapy – not recommended as either as primary therapy or post-operatively due to low radiotherapy tolerance/recurrence potential. Role of adjuvant RT after a biopsy or surgery remains controversial and is dependent on the histology of the tumor. Therapy should be tailored according to this.
4. Systemic therapy – Minimal role in primary spinal tumors, except for high grade tumors.

### 3.4.6 Spinal cord metastasis

These account for 95% of extradural tumors and are mostly bone metastasis commonly from breast, prostate, lung and renal cancers. Patients can be asymptomatic or present with pain.

Three types of pain patterns have been described;

1. **Local pain** – this is due to tumor growth, presents as a deep ache that improves on steroid use
2. **Mechanical back pain**- varies with movement and spinal position is due to Spinal column instability
3. **Radicular pain** – sharp and stabbing pain. Due to nerve root compression. Spinal cord compression accounts for 5-10% of presentation in oncology patients and can be debilitating especially with prolonged symptoms.

### Imaging

**MRI of Entire spine** is mandatory as multiple areas on the spine maybe involved.

### Management of Spinal Cord Metastasis

Palliative therapy is mostly instituted and depends on performance status, duration of cord compression, site(s) of involvement, structural integrity of the spine and available resources.

Treatment options include:

- a. **Surgery** –for patients with a life expectancy of >three (3) months with solitary metastasis.
- b. **Spine stabilization** – Bone cement (Vertebroplasty) or balloon (kyphoplasty).
- c. **Radiotherapy** – most commonly used mode of therapy.
- d. **Systemic therapy** – use of chemotherapy or hormone therapy to manage the systemic disease in combination with bone targeted therapies including bisphosphonates, RANK ligand antibodies or targeted radiotherapy agents (Radium 223).

### 3.5 Supportive and Rehabilitative care for brain tumors

Palliative care is an often overlooked and underutilized part of comprehensive care for brain tumor patients that should be integrated early after diagnosis for both primary and secondary brain cancers. Despite their differences in management, both primary and secondary brain tumor patients experience similar symptom morbidity that impacts their quality of life.

- Rehabilitation provides patients with a chance to achieve optimal functional capacity within the limits of the disease. By setting realistic goals, they can have a better sense of control and reduce their dependency on others.
- Rehabilitation teams can consist of a physical therapist, occupational therapist, speech therapist, social worker, nurse, dietitian, and psychologist. Cancer rehabilitation goals are not universal but should be set according to the prognosis of each patient.
- Supportive rehabilitation attempts to help patients adapt to permanent functional deficits caused by cancer and to maximize their autonomy. After brain tumor resection, for instance, patients may have cognitive deficits for which they can be taught to compensate with therapy.

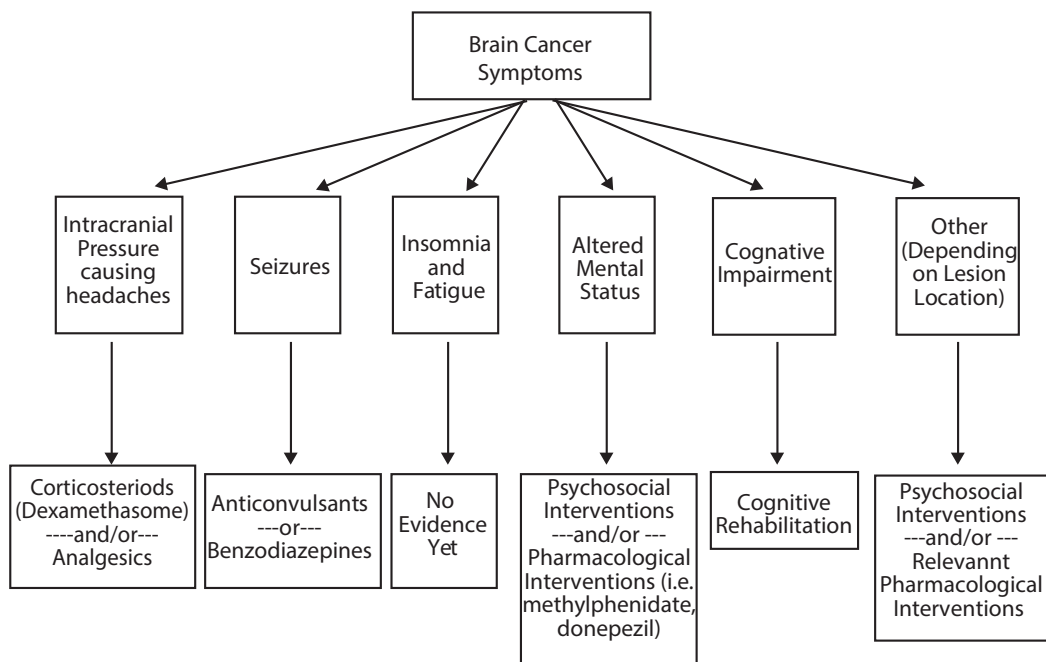


Figure 3.3: Palliative Care Recommendations Concerning the Treatment of Brain Cancer Symptoms

Adopted from the EANO Guidelines for Palliative Care in Adults with Glioma



### 3.6 Role of facility levels in the care of patients with brain tumors

| Level of Health Care | Anticipated Cancer Services  |
|----------------------|--|
| Level 1              | Clinical symptoms and signs, refer to County referral hospital, Rehabilitative post-treatment  |
| Level 2,3 and 4      | Clinical symptoms and signs, refer to County referral hospital, Rehabilitative post-treatment  |
| Level 5              | CT Scan, MRI. Possible tissue biopsy/debulking if Neurosurgical and ICU services available, pathology services available. Refer to Tertiary level for further management |
| Level 6              | All the above plus Comprehensive cancer control services; includes all treatment modalities: radiotherapy, surgery; chemotherapy.  |

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# 4

## **CHAPTER FOUR**

### Gastrointestinal Cancer Treatment Protocols

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# GASTROINTESTINAL CANCER TREATMENT PROTOCOLS

## List of abbreviations

|       |   |
|-------|---|
| BRCA2 | Breast Cancer type 2 susceptibility gene        |
| CEA   | Carcinoembryonic Antigen                        |
| CRT   | Chemoradiation                                  |
| DRE   | Digital Rectal Examination                      |
| ER    | Endoscopic Resection                            |
| ERCP  | Endoscopic Retrograde Cholangio-Pancreatography |
| HBV   | Hepatitis B Virus                               |
| HCV   | Hepatitis C Virus                               |
| MMR   | Mismatch Repair                                 |
| MRCP  | Magnetic Resonance Cholangio-Pancreatography    |
| MSI   | Microsatellite Instability                      |
| NACT  | Neoadjuvant Chemotherapy                        |
| PS    | Performance Status                              |
| RFA   | Radiofrequency Ablation                         |
| SCC   | Squamous Cell Carcinoma                         |
| SEMS  | Self Expanding Metallic Stents                  |
| WHO   | World Health Organisation                       |

## 4.1 Esophageal Cancer

### Introduction

Kenya has one of the highest incidence rates of esophageal cancer (EC) in Africa. There are approximately 4,380 new cases and 4,351 deaths annually. It is the leading cause of cancer mortality in Kenya (GLOBOCAN, 2018). There are two main subtypes – squamous cell carcinoma (SCC) and adenocarcinoma (AC). Squamous cell carcinoma (SCC) accounts for 90% of EC cases in Kenya.

### Risk Factors

- Alcohol intake
- Family history of esophageal cancer
- Age: highest risk is from 45-70years
- Male
- Smoking history
- Overweight and obesity
- Carbon exposure from firewood and other sources
- Barrett's esophagus

### Signs and Symptoms

- Dysphagia (difficulty in swallowing)
- Odynophagia (painful swallowing)
- GIT bleeding with haematemesis or melaena stools
- Recurrent aspiration or emesis
- Post-prandial vomiting
- Weight loss
- Loss of appetite
- Retrosternal pain

### Investigations

1. Upper GIT Endoscopy with biopsies (multiple suspected sites recommended) is the investigation of choice.  
*Request for immunohistochemistry (if WHO poorly differentiated and undifferentiated carcinoma on biopsy).*
2. Barium swallow (if there is no obstruction, where endoscopy is not available).

### Investigations for Staging

CT scan of the chest and abdomen is recommended for staging



## TNM Staging

| <b>Primary Tumour (T)</b>  |
|--|
| <ul style="list-style-type: none"><li>▪ Tis (carcinoma <i>in situ</i>) - abnormal cells that haven't grown beyond the epithelium</li><li>▪ T1 tumours have invaded the lamina propria, muscularis mucosae or submucosa<ul style="list-style-type: none"><li>- T1a tumours have invaded the lamina propria or muscularis mucosae</li><li>- T1b tumours have invaded the submucosa</li></ul></li><li>▪ T2 tumours have invaded the muscularis propria</li><li>▪ T3 tumours have invaded the adventitia</li><li>▪ T4 tumours have invaded adjacent structures<ul style="list-style-type: none"><li>▪ T4a tumours have invaded adjacent structures e.g. the outer lining of the lungs (pleura), heart (pericardium), abdomen (peritoneum) or the diaphragm and can be treated by surgery</li><li>▪ T4b tumours have invaded other adjacent structures such as the aorta, vertebral body or trachea</li></ul></li></ul> |

## Treatment

Treatment approaches include:

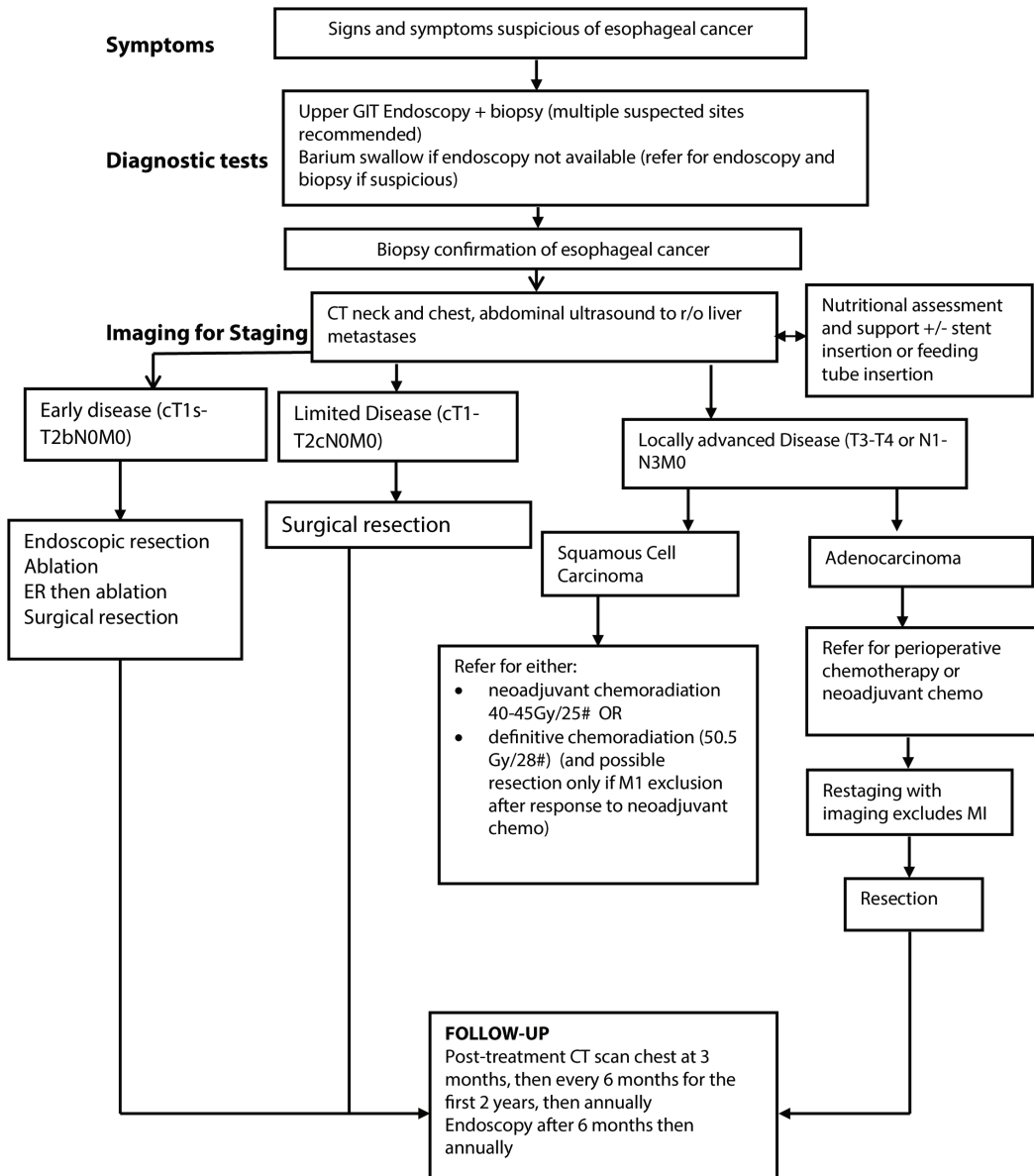
- Endoscopic resection (ER) with/without ablation: is used for very early disease and superficial disease ER with/without ablation for lesions <2cm and ablation or esophagectomy for lesions >2cm.
- Surgery can be used alone for early stage lesions; or in combination with chemoradiation for locally advanced lesions;
- Radiation -definitive chemoradiation for locally advanced lesions. For patients who are potentially curative consider chemoradiation prior to stenting.
- Chemotherapy-in combination with radiotherapy for locally advanced lesions; or as monotherapy in stage 4 disease;
- Palliative care for poor performance status, recurrent or metastatic disease.

Locally advanced SCC disease can be potentially resectable or unresectable.

Pathways for care would thus be:

- Neoadjuvant chemoradiation then restage to assess operability;
- Endoscopic stenting as a palliative procedure if unresectable; this is then followed by palliative chemotherapy or radiotherapy 30Gy in 10# or both with palliative care;
- Esophageal surgery should be carried out in experienced (high volume) centres only;
- For patients not willing to undergo esophageal surgery or who are medically unfit for major surgery, palliative chemoradiation or feeding tube insertion should be preferred.

## Algorithm for Management of Esophageal Cancer



## Chemotherapy Protocols

1. Adenocarcinoma
  - ECX/ECF/EOX: Epirubicin/Cisplatin/Xeloda/Oxaliplatin or 5-Fluorouracil
  - LOFT regimen : Leucovorin/Oxaliplatin/5-FU/Docetaxel
2. Squamous cell carcinoma
  - Cisplatin/5-Fluorouracil regimen

## Supportive Care

- If endoscopic stenting is not possible in patients with unresectable tumor, PEG tubes or feeding gastrostomy or jejunostomy tubes may be required in patients who are obstructed for nutritional support.
- Psychosocial support, counselling and pain management important.

## Follow Up

Follow-up visits should be concentrated on symptoms management, nutrition and psychosocial support. In the case of complete response to chemoradiation and no operation, a 3-month follow-up based on endoscopy, biopsies and CT scan may be recommended to detect early recurrence leading to a discussion about salvage surgery.

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## 4.2 Gastric Cancer

### Introduction

Gastric cancer is the 6th commonest malignancy in Kenya with approximately 2,127 new cases and 2,068 deaths annually (GLOBOCAN, 2018). It is the 3rd most common gastrointestinal malignancy after esophageal and colorectal cancers. Most (90%) of gastric cancers are adenocarcinomas.

### Risk Factors

- Male gender (incidence twice as high)
- Infection with *Helicobacter pylori*
- Lifestyle risk factors: Tobacco use, alcohol use, high-salt diet, processed meat and low fruit and vegetable intake.
- Atrophic gastritis
- Partial gastrectomy
- Pernicious anaemia
- Cardia tumors are associated with obesity, while gastroesophageal junction tumors are associated with reflux and Barrett's esophagus.
- Familial aggregation in ~10% of cases and an inherited genetic predisposition is found in ~1–3%.

### Signs and Symptoms

When symptomatic, Gastric Cancer tends to be advanced. Common symptoms include:

- Abdominal pain
- Weight loss
- Dysphagia
- Dyspepsia
- Vomiting
- Early satiety
- Anaemia (usually an iron deficiency anaemia)

Take a complete history including lifestyle risk assessment, family history and past medical history among others. Perform a thorough physical examination.

### Initial Assessment

1. Endoscopy: Esophagogastroduodenoscopy and biopsy to obtain tissue for diagnosis for suspicious lesions.  
Immunohistochemistry may be considered to determine Her-2 receptor expression especially in advanced/metastatic cancer.
2. FBC, renal function tests and liver function tests.



### Imaging for Staging

- Contrast enhanced CT chest, abdomen and pelvis.
- Pelvic ultrasound in female patients if clinically indicated.
- Ideally: Endoscopic ultrasound (where available) for accurate assessment of T and N stage to distinguish between T2/T3 tumors.

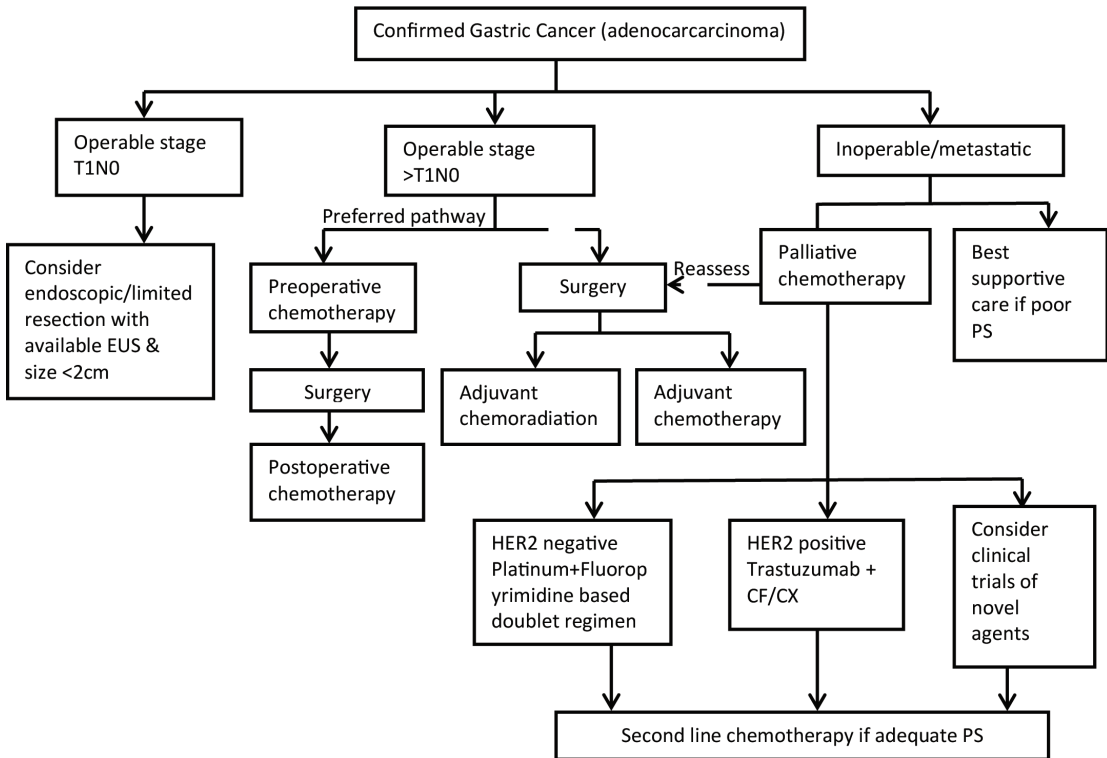
### TNM Staging of Gastric Cancer as per AJCC, 7th edition

| Primary Tumour (T)  | Regional lymph nodes (N)                          | Distant metastasis (M)                                |
|---|---|---|
| TX Primary tumour cannot be assessed  | NX Regional lymph nodes cannot be assessed        | M0 No distant metastasis                              |
| T0 No evidence of primary tumour  | N0 No regional lymph node metastasis              | M1 Distant metastasis or positive peritoneal cytology |
| Tis Carcinoma in situ: intraepithelial tumour without invasion of the lamina propria  | N1 Metastasis in 1–2 regional lymph nodes         |   |
| T1a Tumour invades the lamina propria or the muscularis mucosae   | N2 Metastasis in 3–6 regional lymph nodes         |   |
| T1b Tumour invades the submucosa  | N3 Metastasis in 7 or more regional lymph nodes   |   |
| T2 Tumour invades the muscularis propria  | N3a Metastasis in 7–15 regional lymph nodes       |   |
| T3 Tumour penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures  | N3b Metastasis in 16 or more regional lymph nodes |   |
| T4 Tumour invades the serosa (visceral peritoneum) or adjacent structures<br>T4a Tumour invades the serosa (visceral peritoneum) T4b Tumour invades adjacent structures |   |   |



## Treatment

### Algorithm for Treatment of Gastric Cancer



**Figure 4. 1: Gastric Cancer Treatment Algorithm (Adapted from ESMO clinical practice guidelines)**

### Locoregional Disease

- CTis/cT1a: Endoscopic resection is appropriate for selected medically fit patients.
- Stage IB–III non-metastatic gastric cancer, radical gastrectomy is indicated in medically fit patients with operable tumors with peri-operative chemotherapy.
- Medically fit patients should undergo D2 resections.

### Perioperative Treatment

- Perioperative (pre- and postoperative) chemotherapy with EOX, ECF, ECX, FOLFOX is recommended for patients with  $\geq$  Stage IB resectable gastric and gastroesophageal junction cancers.
- Peri-operative (pre- and postoperative) chemotherapy with a platinum/fluoropyrimidine combination may be considered in patients with  $\geq$  Stage IB resectable gastric cancer.
- Recommended treatment duration is 2–3 months.

### Advanced and Metastatic Disease

- Patients with inoperable advanced and/or metastatic (stage IV) disease should be considered for systemic treatment (chemotherapy) if they are fit for treatment. This has shown improved survival and quality of life compared with best supportive care alone. Co-morbidities, organ function and performance status must always be taken into consideration.
- In general, resection of the primary tumor is NOT recommended in the palliative setting; however, a small number of patients with initially unresectable locally advanced disease may be deemed operable following a good response to systemic therapy upon restaging with contrast-enhanced CT chest/abdomen/pelvis.
- Palliative patients may also benefit from bypass procedure in the setting of gastric outlet obstruction.
- Palliative radiotherapy for patients with uncontrollable tumor bleeding and pain.
- Doublet combinations of platinum, and fluoro-pyrimidines; for example oxaliplatin/capecitabine, cisplatin/paclitaxel, carboplatin/paclitaxel/docetaxel are generally used.

### Targeted Therapy

Trastuzumab is recommended in conjunction with platinum and fluoropyrimidine-based chemotherapy for patients with HER2-positive advanced gastric cancer.

### Follow Up/Survival

This should be tailored to the individual patient and the stage of the disease. Follow up is indicated 3-6 monthly for 3 years then annually. At initial follow-up, restaging is preferred.

- Monitor Vitamin B12 levels and mineral deficiencies in surgically resected patients and provide dietary support as indicated.
- In the advanced disease setting, identification of patients for second-line chemotherapy and clinical trials requires regular follow-up to detect symptoms of disease progression before significant clinical deterioration.
- If relapse/disease progression is suspected, then a clinical history, physical examination and directed blood tests should be carried out.
- Radiological investigations should be carried out in patients who are candidates for further chemotherapy or radiotherapy.

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## 4.3 Colorectal Cancer

### Introduction

Globally, it is the 3rd most common type of cancer with 1,849,518 new cases and 880 792 deaths annually. In Kenya it is the 5th most common cancer with an estimated 2,203 new cases and 1,395 deaths annually (GLOBOCAN, 2018). Majority of colorectal cancers arise from benign polyps and most are adenocarcinomas.

### Risk Factors

#### Non- modifiable

- Older age - > 45 years old
- Inflammatory bowel disease - Crohn's disease or ulcerative colitis
- Family history of colorectal cancer or polyps in a blood relative
- Personal history of colorectal cancer or polyps
- Presence of genetic syndromes, such as familial adenomatous polyposis (FAP) or hereditary non-polyposis colorectal cancer (Lynch syndrome).

#### Modifiable /Lifestyle Associated

- Intake of red and processed meats
- Physical inactivity
- Low fruit and vegetable intake
- A low-fiber and high-fat diet
- Obesity
- Alcohol intake
- Tobacco use

## Clinical Evaluation

### History taking

Signs and symptoms depend on the location of the tumor in the bowel and the presence of metastasis.

#### Signs and symptoms of colon cancer:

- Altered bowel habits (commonly constipation, diarrhea)
- Blood in stool
- Anemia or fatigue
- Anorexia
- Weight loss
- Nausea/Vomiting
- Abdominal pain
- Intestinal obstruction

#### Signs and symptoms of rectal cancer:

- Haematochezia
- Altered bowel habits
- Feeling of incomplete bowel emptying
- Cramping or Abdominal pain
- Weight loss
- Intestinal Obstruction
- Narrow stool
- Anaemia or fatigue

About 50% of patients are asymptomatic. Inquire and document any risk factors including past medical history, family history and lifestyle risk factors among others.

### Physical examination

Perform a thorough physical examination including abdominal and digital rectal examination (DRE). Vaginal examination should be done in women with rectal cancer.

### Investigations

1. Complete colonoscopy with endoscopic biopsy (for histological diagnosis) is the investigation of choice.

*High risk histological features include lymphatic or venous invasion, poorly differentiated (grade 3) tumor, level 4 invasion (invades the submucosa of the bowel wall), , serosal involvement, perforated tumours, extramural vascular invasion, less than 12 lymph nodes examined and involved margins of excision, close, indeterminate or positive resection margins (CRM).*

2. Other laboratory tests include Complete Blood Count, Urea Creatinine, Liver function tests, Carcinoembryonic antigen

**NOTE: Diagnosis of rectal cancer is based on a DRE and endoscopy with biopsy**

### Imaging (for staging after diagnosis)

1. CT chest, abdomen and pelvis.

2. MRI pelvis is crucial for local staging of rectal disease to identify circumferential resection margin (CRM) involvement which would influence pre-operative treatment.

## TNM Staging

| TNM Stage | Definition   |
|-----------|--|
| T1        | Tumour invades submucosa   |
| T2        | Tumour invades muscularis propria  |
| T3        | Tumour invades through muscularis propria into subserosa or into non-peritonealised pericolic or perirectal tissue |
| T4        | Tumour directly invades other organs/structures and/or perforates visceral peritoneum                              |
| N1        | 1-3 regional lymph nodes involved  |
| N2        | 4 or more regional lymph nodes involved ( <b>NOTE: at least 12 should be submitted for proper nodal staging</b> )  |
| M1        | Presence of metastases   |

## Treatment of Colorectal Cancers

Surgery is the mainstay of treatment for colon cancer which removes the lesion with wide margins and loco-regional nodes. Early colorectal cancer is potentially curable if treated appropriately.

### Treatment of Early/Non-Metastatic Colon Cancer

| Stage   | Type of Surgery  | Chemotherapy   |
|---|--|--|
| Malignant Polyp, no risk of invasion              | Polypectomy  | No benefit   |
| Malignant polyp, with risk of invasion            | Resection and lymph node excision  | No benefit   |
| Stage 0 (TisN0 M0, T1 N0 M0) & Stage I (T2 N0 M0) | Local excision OR Segmental resection/ Wide colectomy and lymph node dissection with >12 nodes | No benefit<br>(Patients with intestinal obstruction should be considered for defunctioning colostomy/stenting and definitive removal of the tumour).<br>Assess for high risk features. |
| Stage II (T3 N0 M0, T4 N0 M0)                     | Colectomy and lymph node dissection  | No benefit.<br><i>(ONLY indicated if high risk features present OR in those with MSI-low/MMR abundant on IHC- Capecitabine/Oxaliplatin preferred)</i>                                  |
| Stage III (any T, N1 M0, any T, N2 M0)            | Colectomy with LN dissection   | Adjuvant chemotherapy indicated (start within 2-4 weeks of surgery)<br>(Oxaliplatin/Capecitabine or FOLFOX)  |

## Treatment of Early/Non-Metastatic Rectal Cancer

### Stage I

1. Total mesorectal excision (TME) with abdominal-perineal resection (APR – for low lesions) or low anterior resection (LAR- for mid-upper lesions).
2. No adjuvant treatment if pathologically T1-2N0. Adjuvant chemotherapy and chemoradiation if T3N0 and high risk with RO resection.

### Stage II & III (Locoregional disease)

1. Neoadjuvant long course (for involved mesorectum, node-positive disease) or short course (for T3N0, limited T4aN0, elderly or frail patients) chemo-radiation with radiotherapy and oral Capecitabine then;
2. Surgical resection (LAR/APR) if possible followed by adjuvant 5-FU based chemotherapy.

*Restaging is recommended prior to surgery. Surgery is recommended within 6-8 weeks of treatment.*

### Adjuvant treatment for Early Colorectal Cancer

- Chemotherapy is indicated for patients with positive nodes post-operatively and recommended protocols include:
  1. Oral Capecitabine monotherapy every 3 weeks.
  2. XELOX/CAPOX regimen: Capecitabine plus Oxaliplatin every 3 weeks.
  3. FOLFOX and
  4. FOLFIRI (in exceptional cases where Oxaliplatin cannot be administered).
- Radiotherapy is recommended for all rectal cancer patients who did not undergo neoadjuvant therapy.

*If obstructed – need for diverting colostomy or stenting prior to definitive treatment. Stenting is useful in colonic and high rectal tumors; avoid in mid-low rectal tumors due to risk of stent migration.*

### Metastatic Colon & Rectal Cancers

Available treatment options depend on the patient's predominant symptoms, disease burden, performance status, wishes and prior therapy. For management of metastatic rectal cancers, patients are divided into three groups:

1. Resectable: Surgery of the primary disease + metastatectomy recommended for carefully selected colorectal cancer patients with resectable liver metastasis.
  2. Potentially resectable: Surgery for the primary disease with metastatectomy is recommended after neoadjuvant therapy or as a staged procedure.
  3. Unresectable: Palliative options such as surgery in cases of obstruction (colostomy), palliative chemotherapy, radiotherapy, with supportive care, pain management and stenting for obstruction.
- Palliative radiotherapy is useful in rectal tumors and fixed caecal tumors for symptoms of bleeding, discharge and local pain.
  - Palliative transanal debulking of symptomatic tumors has been shown to improve quality of life.

- Multiple palliative chemotherapy exist, usually given for 16-18 weeks or to disease progression such as:
  - Single agent 5-Fluorouracil or Capecitabine OR
  - Combination of 5-Fluorouracil/Capecitabine with Irinotecan or Oxaliplatin – improves overall survival but associated with increased toxicities.

### Targeted agents

- Bevacizumab can be used in combination with FOLFIRI, XELOX or FOLFOX.
- Cetuximab & Panitumumab can be used for All RAS wild type with 5-Fluorouracil/Capecitabine plus Irinotecan or Oxaliplatin or as monotherapy
- Pembrolizumab
- Aflibercept –with FOLFIRI
- Regorafenib – is used last when all other modalities have been used and have failed.

### Supportive Care

- Psychosocial support
- Stoma care
- Pain management
- Nutrition

### Follow Up

- Clinical assessment plus CEA every 3 months for the first 2 years.
- If high risk of recurrence, consider Abdominopelvic CT scan every 4-6 months.
- Colonoscopy in year 1 then every 2 years if negative.

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## 4.4 Pancreatic Cancer

### Introduction

Approximately 95% of pancreatic cancers occur within the exocrine portion. The most common type is ductal adenocarcinoma which accounts for about 80% of all pancreatic cancers. In Kenya, there are approximately 735 new cases and 719 deaths annually



(GLOBOCAN, 2018). Approximately 60-70% of pancreatic cancer arises in the head of the pancreas, 20-25% in the body and tail, and the remaining 10-20% diffusely involves the pancreas. The vast majority (>80%) of pancreatic carcinomas are due to sporadically occurring mutations.

### Risk Factors

- Age > 65 years
- Cigarette smoking
- Alcohol consumption
- Obesity
- Dietary factors-high consumption of processed food, saturated fat, butter
- Familial pancreatic cancers (at least two first-degree relatives with pancreatic cancer) account for 5-10% of all cases, mutation in BRCA2 is common.
- Other familial/genetic conditions including hereditary pancreatitis.

### Signs and Symptoms

Patients typically report the gradual onset of non-specific signs and symptoms. Pancreatic head tumors present with painless jaundice. Abdominal pain (upper abdominal, mid-epigastric or back), back pain or weight loss are usually signs of late-stage disease. Other symptoms include anorexia, malaise, nausea, fatigue, dark urine, diarrhea and steatorrhea (fatty stools).

*Pancreatic tumors may present with newly diagnosed diabetes.*

### Imaging

- Contrast enhanced CT scan (pancreatic protocol) is the investigation of choice.
- MRI abdomen and pelvis
- Magnetic Resonance Cholangiopancreatography (MRCP) for staging
- Endoscopic Retrograde Cholangiopancreatography (ERCP).

### Laboratory investigations

- Total blood count
- Coagulation profile, PTI/INR
- Biochemistry: U/E/C, LFTs, Blood sugar
- Tumor markers – CA 19-9 and Carcinoembryonic antigen (CEA) can be used **with other tests to aid diagnosis, measure disease burden and to monitor treatment.**
- Consider serum IgG4.
- Biopsies can be done in various ways:
  - Percutaneous biopsy(CT or Ultrasound guided)
  - Endoscopic biopsy
  - Surgical biopsy

*A histological proof of malignancy is mandatory for unresectable cases before chemotherapy.*



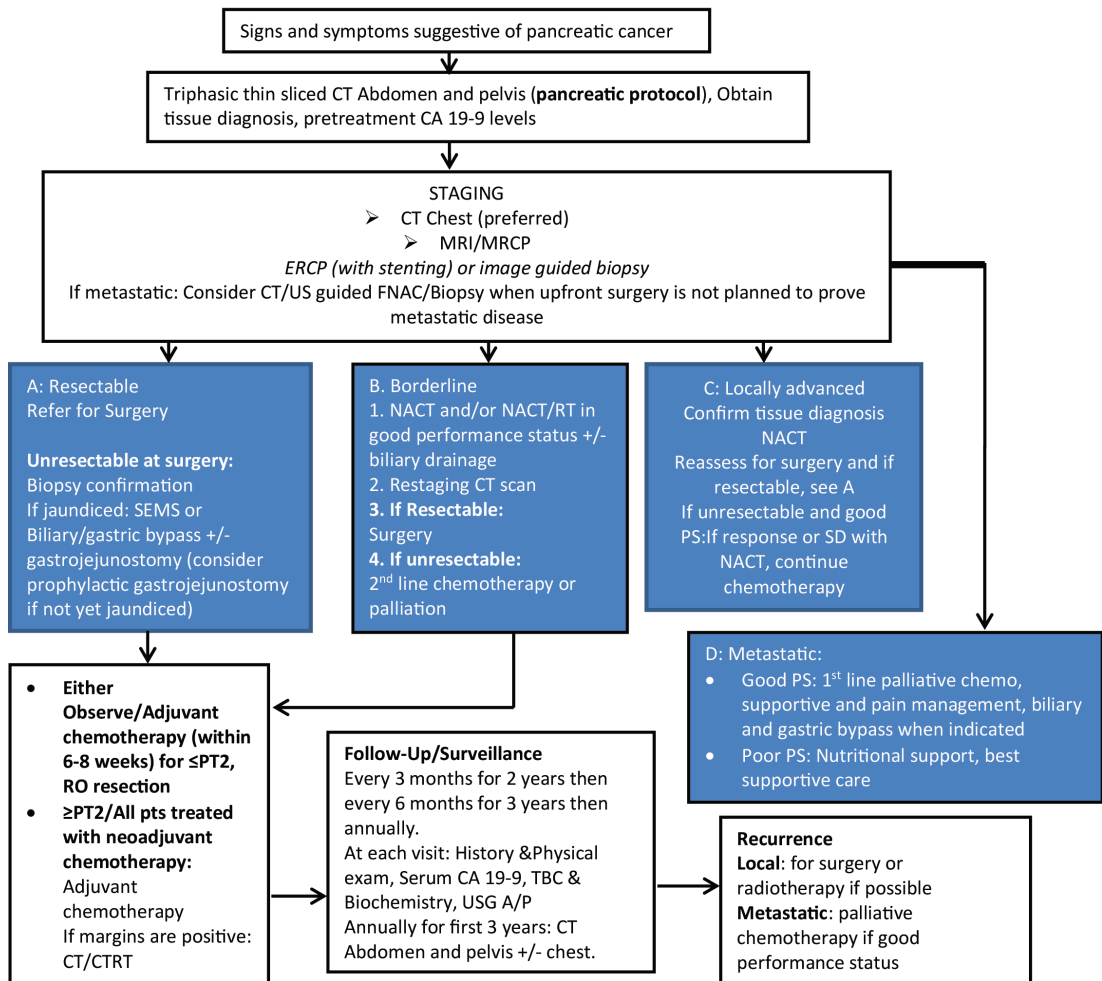
## Staging

Stage the tumour and categorize as resectable, borderline resectable, locally advanced or metastatic disease.

## Treatment

Defining the treatment strategy for patients suffering from pancreatic carcinoma requires a specialized multidisciplinary team. Surgical resection is the only potentially curative treatment of pancreatic adenocarcinoma.

### Treatment Algorithm for Pancreatic cancer



## Chemotherapy Protocols

### First-line regimens

1. FOLFIRINOX: 5-FU, Leucovorin, Irinotecan, Oxaliplatin every 2 weeks for 6 to 12 cycles.
2. FOLFIRI; Irinotecan, infusional 5-Fluorouracil/ Leucovorin every 2 weeks.

### Other regimens

1. Gemcitabine
2. Cisplatin and albumin-bound Paclitaxel

### Follow Up Care

Follow up visits should focus on symptoms management, nutrition and psycho-social support.

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## 4.5 Hepatocellular Carcinoma

### Introduction

Hepatocellular carcinoma (HCC) is a primary tumour of the liver that usually develops in the setting of chronic liver disease. It is the 5th most prevalent cancer globally and the 2nd most frequent cause of cancer-related deaths. It is more common in males in the ratio 2:1. Over 80% of the cases are diagnosed in developing countries. Highest incidence is in SE Asia followed by Sub-Saharan Africa where the annual mortality is 87,890 deaths with 80% of HCC due to HBV infection. GLOBOCAN 2018 data estimates show liver cancer as the 10th most common cancer in Kenya with an estimated 1,346 new cases and 1,331 deaths annually.

### Risk Factors

- Chronic hepatitis B infection
- Cirrhosis
- Alcohol intake
- Chronic hepatitis C
- Aflatoxin B1 (mycotoxin)
- Iron overload
- Metabolic syndrome (obesity, diabetes & dyslipidemia leading to fatty liver)
- Non-alcoholic steatohepatitis
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Fibro-lamellar HCC

### Clinical Evaluation

#### History Taking

- Assess for risk factors: including drug use and alcohol intake, history of diabetes, obesity and arterial hypertension.
- Common signs and symptoms include: jaundice, ascites, encephalopathy, bleeding, and splenomegaly.

#### Physical Evaluation

Assess for above signs among others, performance and nutritional status.

#### Investigations

1. The three key diagnostic tests will include:
  - HBV panel and HCV testing
  - Alpha fetoprotein levels
  - Multiphase multidetector CT scan abdomen, chest and pelvis:  
Diagnosis should be made based on the identification of the typical vascular hallmark of HCC; hyper vascular in the arterial phase with washout in the portal venous or delayed phases.

2. Other lab tests: Liver function tests (prothrombin time, albumin and bilirubin), Haemogram.
3. Other imaging studies:
  - MRI scan if CT scan not available
  - Consider a contrast-enhanced abdominal ultrasound (CEUS) if CT scan or MRI not possible
4. Liver biopsy- not mandatory for treatment initiation. The decision for the biopsy of a focal liver lesion should only be discussed by a multidisciplinary team, which should include a hepatobiliary surgeon and an interventional radiologist. Additional immunohistochemical staining may also be helpful in diagnosis.

### Staging

Staging is important in determining the outcome, planning for therapy and includes assessment of tumour extent, liver function, portal pressure and clinical performance status.

Tumour extent (TNM) should be assessed using various imaging modalities. This is to assess for tumour extent, number and size of nodules, vascular invasion and extrahepatic spread. These include contrast-enhanced MRI or helical CT scan; a chest CT scan and a bone scan especially in advanced disease.

Liver function should be assessed by the Child-Pugh scoring system which entails bilirubin, albumin, ascites, prothrombin time and hepatic encephalopathy. Portal hypertension should also be an important factor in staging.

Several staging systems exist: The TNM staging system is relevant to stratify patients for studies on adjuvant treatments.

The Barcelona Clinic Liver Cancer (BCLC) staging system is a widely acceptable system that links staging of HCC in cirrhosis with treatment modalities

**Table 4. 1: Barcelona clinic liver cancer (BCLC) staging**

| Stage                                     | Description  |
|---|--|
| Very early (stage 0)                      | PS 0, Child-Pugh A, single HCC < 2 cm  |
| Early (stage A)                           | PS 0, Child-Pugh A-B, single HCC or 3 nodules < 3 cm                               |
| Intermediate (stage B)                    | PS 0, Child-Pugh A-B, multinodular HCC   |
| Advanced (stage C)                        | PS 1-2, Child-Pugh A-B, portal vein invasion, nodal metastases, distant metastases |
| Terminal (stage D)                        | PS >2, Child-Pugh C  |
| Abbreviation: PS, ECOG performance status |  |



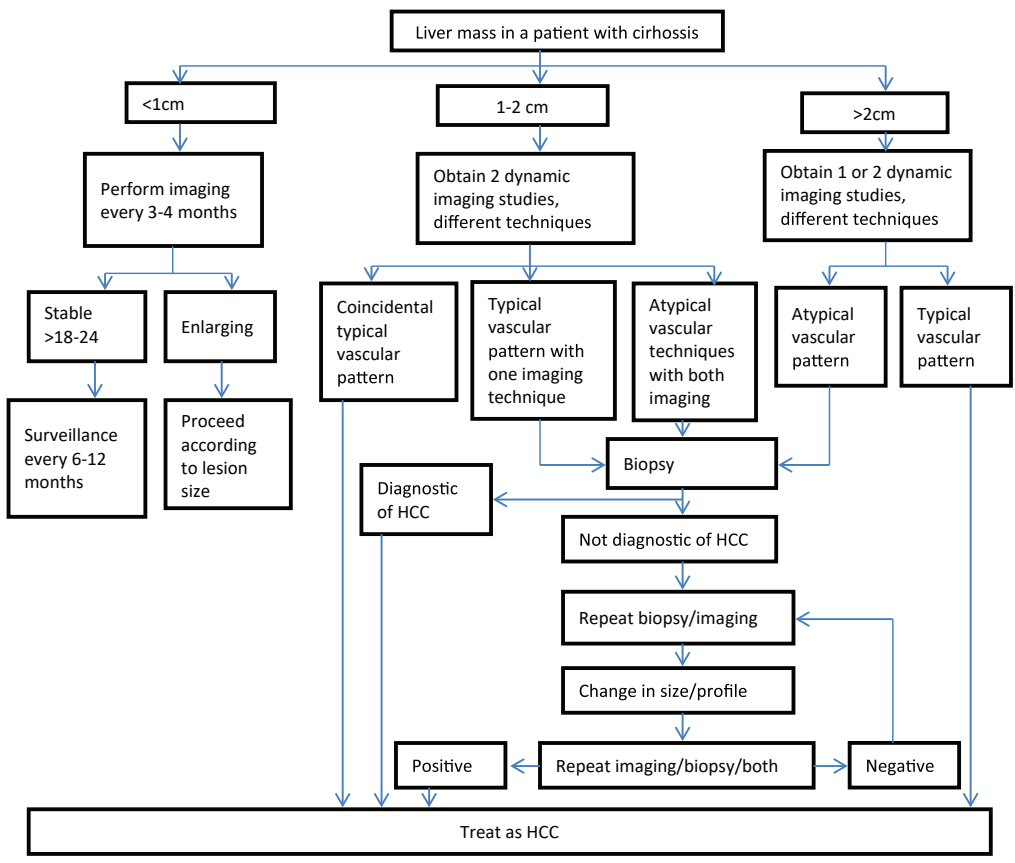
**Table 4. 2: Child Pugh-Turcotte Score**

| Measure                | 1 point | 2 points                                   | 3 points                     | units   |
|------------------------|---------|--|------------------------------|---------|
| Bilirubin (total)      | <22     | -3   | >3                           | mg/dL   |
| Serum albumin          | >35     | 28-35                                      | <28                          | mg/L    |
| INR                    | <1.7    | 1.71-2.20                                  | >2.20                        | no unit |
| Ascites                | None    | Suppressed with medication                 | Refractory                   | no unit |
| Hepatic encephalopathy | None    | Grade I-II (or suppressed with medication) | Grade III-IV (or refractory) | no unit |

**Interpretation**

The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement. Chronic liver disease is classified into Child- Pugh Turcotte class A(5-6), B(7-9) and C (10-15),S employing the added score from above.

**Diagnostic Workup Algorithm for Work-Up for a Patient with Liver Mass and Cirrhosis**



**Table 4. 3: Treatment Options for Hepatocellular Carcinoma**

| BCLC stage | Diagnostic description   | Treatment (standard of care)   | Alternative Treatment   |
|------------|--|--|---|
| 0-A        | Single tumor of any size or up to 3 nodules ≤3 cm, preserved liver function<br>ECOG PS 0 | Resection<br>Transplantation<br>Thermal ablation<br>Trans-arterial chemo-embolization (TACE) |   |
| B          | Multinodular<br>Preserved liver function<br>ECOG PS 0                                    | Trans-arterial chemo-embolization (TACE)   | Transplantation<br>Resection<br>Systemic therapy (after TACE failure /refractoriness) |
| C          | Portal invasion  | Sorafenib (first line)   | Nivolumab (second line)<br>Lenvatinib   |
|            | Extra-hepatic spread<br>Preserved liver function<br>ECOG PS 1-2                          | Regorafenib (second line)  | Pembrolizumab (second line)<br>Cabozantinib<br>Ramucirumab                            |
| D          | End-stage liver function   | Best supportive care   |   |

### Evaluation of the response to treatment and follow-up

Assessment of response should be based on dynamic CT or MRI studies, and the modified Response Evaluation Criteria in Solid Tumours (mRECIST) criteria. Viable tumour should be defined as uptake of contrast agent in the arterial phase on imaging. The mRECIST criteria is based on the measurement of the diameter of the viable tumour component or target lesions. It also includes guidelines regarding evaluation of vascular invasion, lymph nodes, effusions and new lesions.

### Follow Up & Supportive Care

Serum tumour markers especially AFP levels may be helpful particularly in the case of disease that is not easily measurable. They should not, however be used as the only determinants for treatment decisions.

Patients who underwent radical treatments (resection or RFA) should undergo clinical evaluation for liver decompensation and dynamic CT or MRI studies every 3 months for the first 2 years to detect any recurrences and every 6 months thereafter. Patients with disease recurrence after radical therapies may still be candidates for curative therapies. Patients treated with TACE or systemic agents e.g. sorafenib should be evaluated clinically for signs of liver decompensation and for tumour progression by dynamic CT or MRI every 3 months to guide therapy decisions.

## Prevention and Surveillance

90% of HBV chronicity results from perinatal infection, 20- 50% chronicity from infection before 5 years and only 5% from infection in adulthood. 15-40% of HBV infection leads to cirrhosis, liver failure and eventually HCC. Preventive strategies include:

- HBV vaccination and preventive programs to stop transmission of hepatitis B and C.
- Early antiviral (HBV with Tenofovir & HCV with direct acting antivirals (DAAs) such as sofosbuvir and Ledipasvir/Sofosbuvir for infection eradication.
- Surveillance programs for persons at risk of HCC (patients with cirrhosis, non-cirrhotic HBV carriers with a high viral load, patients with chronic HCV with advanced cirrhosis).
- An abdominal ultrasound, done every 6 months is the imaging of choice for surveillance of persons at risk of HCC.

### Key Recommendations

- Screen all the antenatal mothers for HbsAg
- Treat all HbsAg positive mothers with Tenofovir during the 3rd trimester
- Every child should receive a birth dose of hep B vaccine
- For children born of HbsAg positive mothers, they should receive HB-immunoglobulin
- Hep B vaccination for all children as per immunization schedule
- Patient with chronic hepatitis irrespective of the aetiology should be screened for HCC with liver ultrasound and alfa fetoproteins every 6 months
- Those found with liver tumors should be referred to the national referral hospitals for further management.

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## 4.6 Anal Carcinoma

### Introduction

Globally, there are an estimated 27,000 new cases every year. Approximately 88% of cases are associated with human papillomavirus (HPV) infection worldwide. In Kenya, there are approximately 113 new cases and 71 deaths annually (GLOBOCAN, 2018). They are predominantly squamous cell carcinomas (95%); the rest are adenocarcinomas, basaloid and cloacogenic among others.

### Risk Factors

- Human papillomavirus (HPV) infection
- Human immunodeficiency virus (HIV) infection
- Anal sex
- Older age >50 years
- Multiple sexual partners
- Tobacco use
- History of cervical, vulvar or vaginal cancer
- Immunosuppressive drugs (for example after organ transplantation) or conditions

### Signs and Symptoms

- Anal bleeding
- Perianal itching
- Anal discharge
- Fecal incontinence and fistula
- Perianal or low abdominal pain
- Non-healing ulcer
- Anal mass
- Altered bowel habits
- Weight loss
- Vomiting of feeds

### Physical examination

Conduct a complete physical examination including a digital rectal examination. Biopsy is indicated if any visible anal growth or masses are noted. Vaginal examination is mandatory in females.

### Investigations

- FBC, UEC, LFTs, HIV testing and if HIV positive, do CD4 counts.
- Rigid proctoscopy with biopsies (direct examination under anesthesia).
- FNA of any palpable inguinal nodes.

### Imaging for Staging (after biopsy confirmation)

- CT chest and abdomen
- Pelvic MRI for staging



## Treatment

All patients who are newly diagnosed HIV positive should be started on ARVs. Diverting colostomy should be considered for all patients before starting the definitive treatment.

**Table 4. 4: Factors to consider in treatment decision-making for Anal Cancer**

| Disease-related factors  | Patient-related factors                                   | Other                                |
|--|---|--------------------------------------|
| Clinical and radiological TNM stage  | Patient preferences                                       | Local expertise (brachytherapy etc.) |
| Site of tumour (margin, canal, rectal)   | Biological age/renal function                             |                                      |
| Extent of tumour, i.e. involvement of vagina (risk of fistulation) in addition to size | Co-morbidities/current medications and performance status |                                      |
| Response to treatment (early and at 26 weeks)  | Socioeconomic and psychological factors/social support    |                                      |
| Need for symptom control   | Severity of initial symptoms                              | Specialist palliative care           |

## Treatment Protocols

### Role of Surgery

- Anal canal: Surgery (radical or local excision) is generally contra-indicated as primary treatment option.
- Anal margin: For stage I, well differentiated lesions, local excision (re-excision or chemo-radiation if involved/close margins on histopathological evaluation).

### Limited/Localized Disease (Any T, Any N, M0)

- First line: 5-Fluorouracil + Mitomycin + concurrent radiotherapy
- Alternatives: Capecitabine + Mitomycin + concurrent radiotherapy

### Metastatic Anal Cancer (Any T, Any N, Any M)

- 5-FU + Cisplatin
- Carboplatin/Taxane
- Cetuximab/Irinotecan may be considered, as appropriate, for anal canal tumors. Repeat cycle every 4 weeks for 6 cycles.

## Follow Up

Re-evaluate patients starting 8-12weeks after chemo-radiation using pelvic MRI.

### i. Complete Remission

- DRE and inguinal node examination every 3-6 months for 5 years

- Proctoscopy 6 monthly for 3 years
- CT chest, abdomen and pelvis annually for 3 years

**ii. Persistent disease**

Re-evaluate after 4 weeks:

- If tumor regresses, or no progression, then continue observation every 3 months
- If tumor progresses, re-biopsy and re-stage and consider for AP resection and groin dissection

**iii. Progressive disease**

Re-biopsy, re-stage and consider for A-P resection and groin dissection

**iv. Metastatic disease**

Palliative treatment

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**Roles of Health Care Facilities for Gastrointestinal Cancers**

| Level           | Roles  |
|-----------------|--|
| Level I, II,III | Detection of symptoms, signs and risk factors for gastrointestinal cancers.<br>Early and appropriate referral of patients.   |
| Level IV,V      | Detection of symptoms, signs and risk factors for gastrointestinal cancers.<br>Early and appropriate referral of patients for further evaluation, staging and further management.<br>Targeted investigations for diagnosis to include a total blood count, and liver function tests.<br>Key diagnostic imaging tests including X-rays, Barium swallow, Abdominal ultrasound, CT- Scan  |
| Level VI        | Detection of symptoms, signs and risk factors for gastrointestinal cancers.<br>Full range of diagnostic laboratory investigations<br>Full range of key diagnostic Imaging tests including a CT- Scan chest/abdomen/ MRI abdomen for diagnosis/ and staging, endoscopy and colonoscopy and FED-PET where applicable.<br>A bone scans for advanced disease and liver/ pancreatic biopsy for diagnosis.<br>Appropriate TNM and BCLC stage allocation.<br>Appropriate multidisciplinary team management of these patients.<br>Develop treatment protocols for various disease stages to include those for liver transplant.<br>Be able to offer surveillance and follow-up.<br>Offer best supportive and palliative therapy for advanced disease based on evidence.<br>Conduct research and training to better improve patient management. |

# 5

## **CHAPTER FIVE**

### Gynaecological Cancer Treatment Protocols

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# GYNAECOLOGICAL CANCER TREATMENT PROTOCOLS

## List of abbreviations

|        |                                     |
|--------|-------------------------------------|
| AFP    | Alpha Fetoprotein                   |
| BSO    | Bilateral salpingo-oophorectomy     |
| CA-125 | Cancer Antigen 125                  |
| EBRT   | External Beam Radiation Therapy     |
| EUA    | Examination under Anaesthesia       |
| GTD    | Gestational Trophoblastic Disease   |
| GTN    | Gestational Trophoblastic Neoplasia |
| HCG    | Human Chorionic Gonadotrophin       |
| HIV    | Human Immunodeficiency Virus        |
| HPV    | Human Papillomavirus                |
| LDH    | Lactate Dehydrogenase               |
| PLND   | Pelvic lymph node dissection        |
| RMI    | Risk Malignancy Index               |
| TAH    | Total Abdominal Hysterectomy        |
| TVS    | Trans Vaginal Ultrasound            |

## 5.1 Ovarian Cancer

### Introduction

Ovarian cancer is the 7th most common cancer in women globally both in incidence and mortality with an age-standardized incidence and mortality rate of 6.1/100,000 and 3.4/100,000 respectively. In Kenya, it is the 5th leading cause of cancer deaths among women after cervical, breast, esophageal and stomach cancers (GLOBOCAN, 2018). There are three main types of ovarian cancer: epithelial, germ cell and sex cord/stromal. Epithelial ovarian cancer accounts for 90% of all cases of malignant tumors of the ovaries. Fallopian tube cancer and primary peritoneal cancer are much rarer, but share histologic, prognostic, and treatment response features with epithelial ovarian cancer.

### Risk factors

- Older age (40-69 years);
- Family history or previous personal history of ovarian, breast or endometrial cancer;
- Hormonal: Early menarche and late menopause, nulliparity or first birth after age 35 years;
- Obesity.

### Signs and Symptoms

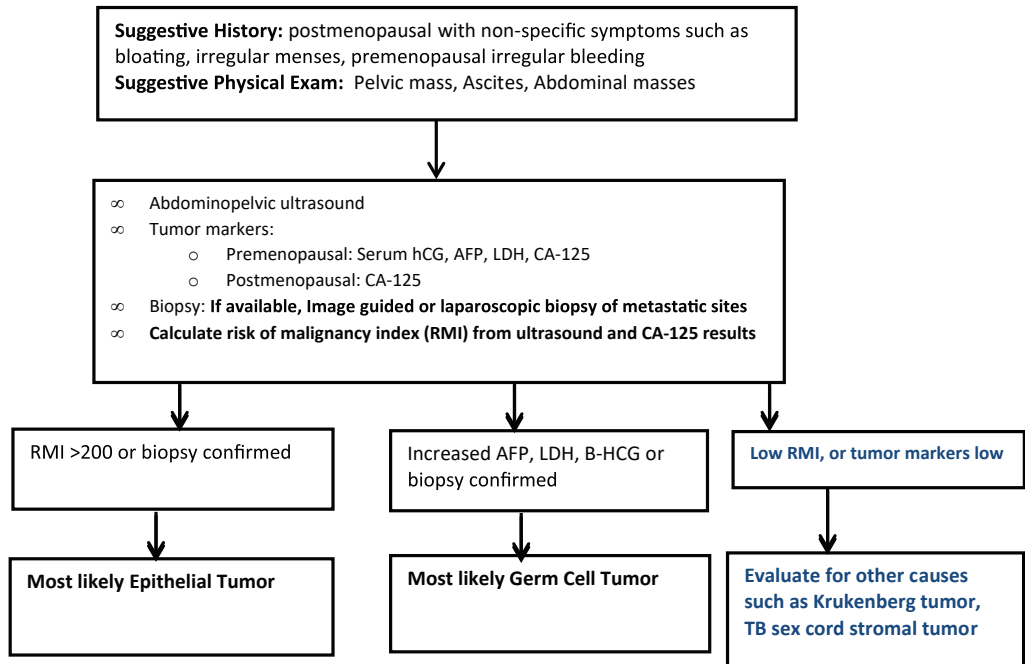
The disease is often easily missed since it presents with non-specific persistent gastrointestinal signs and symptoms (such as early satiety, indigestion, bloating, mild abdominal or pelvic pain), leading to late diagnosis when the patient has already developed an abdominal mass or ascites.

Other symptoms include vague abdominal discomfort, constipation, poor appetite, nausea, vomiting, frequent micturition, pelvic pressure, abdominal distension, irregular vaginal bleeding, low back pain, fatigue, dyspareunia and weight loss.

### Clinical 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 with/without an upper abdominal mass and/or ascites is highly suggestive of ovarian malignancy.

## Diagnostic Algorithm for Ovarian Cancer



### Diagnosis

- Abdominopelvic ultrasound, with transvaginal ultrasound (TVS) for further evaluation of the adnexa may be needed.
- Tumor markers
- Biopsy

Risk of Malignancy Index (RMI) is used to predict whether an adnexal mass is likely to be malignant, since CA-125 is raised in benign conditions like endometriosis, pelvic inflammatory disease and other abdominal conditions. It combines three pre-surgical features: serum CA-125 (CA-125), menopausal status (M) and ultrasound score (U). The RMI is a product of the ultrasound scan score, the menopausal status and the serum CA-125 level (IU/ml).

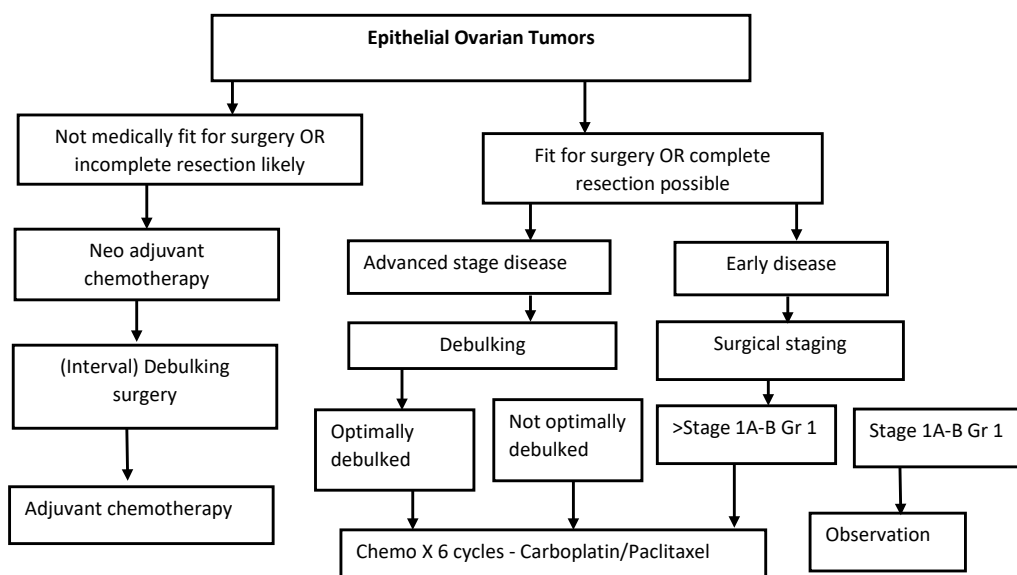
$$\text{RMI} = \text{U} \times \text{M} \times \text{CA-125}$$

- The ultrasound result is scored 1 point for each of the following characteristics: multilocular cysts, solid areas, metastases, ascites and bilateral lesions. U = 0 (for an ultrasound score of 0), U = 1 (for an ultrasound score of 1), U = 3 (for an ultrasound score of 2–5).
- The menopausal status is scored as 1 = pre-menopausal and 3 = post-menopausal
- The classification of 'post-menopausal' is a woman who has had no period for more than 1 year or a woman over 50 who has had a hysterectomy.
- Serum CA125 is measured in IU/ml and can vary between 0 and hundreds or even thousands of units

### FIGO Classification for Ovarian Cancer for Staging

| <b>STAGE I: Tumor confined to ovaries</b>   |   |
|---|---|
| IA  | Tumor limited to 1 ovary, capsule intact, no tumor on surface, negative washings  |
| IB  | Tumor involves both ovaries otherwise like IA.  |
| IC - Tumor limited to 1 or both ovaries   | IC1 Surgical spill  |
|   | IC2 Capsule rupture before surgery or tumor on ovarian surface.   |
|   | IC3 Malignant cells in the ascites or peritoneal washings   |
| <b>STAGE II: Tumor involves 1 or both ovaries with pelvic extension (below the pelvic brim)</b> |   |
| IIA   | Extension and/or implant on uterus and/or Fallopian tubes   |
| IIB   | Extension to other pelvic intraperitoneal tissues   |
| <b>STAGE III: Tumor involves 1 or both ovaries with cytologically or histologically</b>         |   |
| IIIA  | (Positive retroperitoneal lymph nodes and /or microscopic metastasis beyond the pelvis)   |
| IIIB  | Macroscopic, extrapelvic, peritoneal metastasis $\leq 2$ cm $\pm$ positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen               |
| IIIC  | Macroscopic, extrapelvic, peritoneal metastasis $> 2$ cm $\pm$ positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.                 |
| <b>STAGE IV: Distant metastasis excluding peritoneal metastasis</b>                             |   |
| IVA   | Pleural effusion with positive cytology   |
| IVB   | Hepatic and/or splenic parenchymal metastasis, metastasis to extraabdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity) |

## Treatment Algorithm for Epithelial Ovarian Cancers



### Chemotherapy regimens

First line:

- Carboplatin and paclitaxel – preferred due to a better side effect profile
  - Cisplatin and cyclophosphamide – acceptable alternative and more affordable
- Standard frequency for both is 3 weekly x 6 cycles. Other methods of administration (such as dose-dense regimens) exist and may be used based on clinical judgement & expertise of the oncologist.

### Recurrent/Metastatic disease

Platinum-resistant disease: recurs within 6 months of administration of the chemotherapy. Pegylated doxorubicin is preferred as a second line in this case.

Platinum-sensitive disease: recurs after more than 6 months of chemotherapy. The same regimen can be repeated.

Bevacizumab in combination with chemotherapy is indicated in metastatic disease.

### Follow up & Surveillance

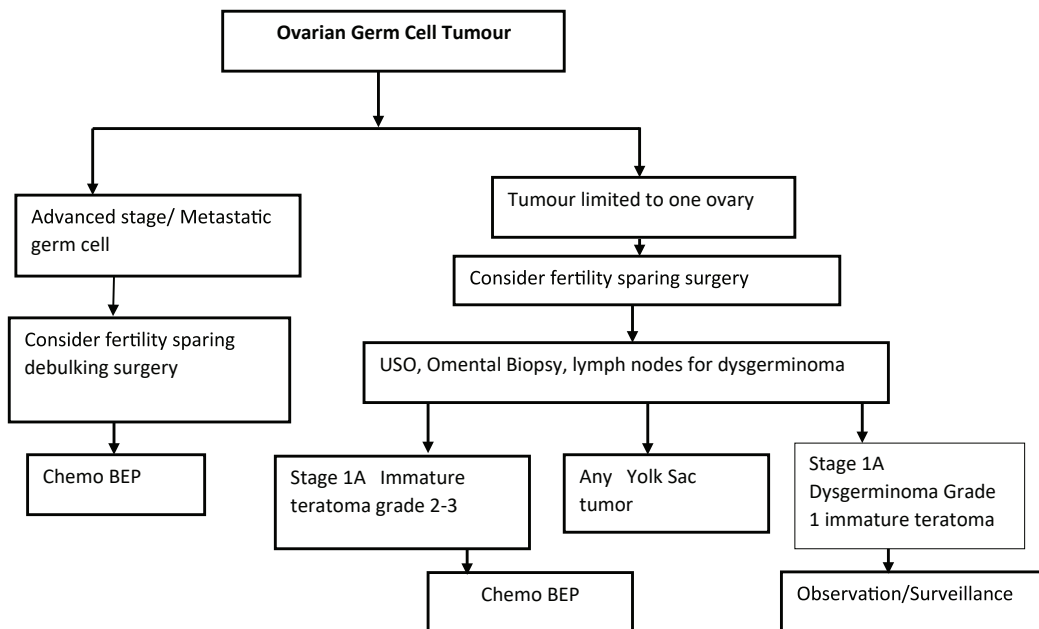
Three monthly reviews for 2 years, then 6 monthly for 3 years is recommended.

At follow-up: Take history, conduct physical examination and tests should be done if the patient is symptomatic, including CA-125, CT scan and PET scan. PET CT scan may be useful for assessing recurrence.

### Treatment Algorithm for Ovarian Germ Cell Tumors

Germ cell tumors typically respond well to chemotherapy. Most patients are young and therefore extensive surgery is rarely indicated. Fertility-sparing surgery is acceptable even in advanced disease.





### Chemotherapy regimens

- BEP (Bleomycin/ Etoposide /Cisplatin) regimen;
- EP (Etoposide /Cisplatin) regimen is also acceptable.

### Follow up & Surveillance

- 3 monthly for two years then 6 monthly for 3 years. At follow-up, take history, perform a physical examination and repeat tumor markers (using the marker that was initially elevated at diagnosis).
- Imaging is necessary if recurrence is suspected ;
- The role of CA-125 in follow-up is not fully established.

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## 5.2 Cervical Cancer

### Introduction

Globally, cervical cancer is the second most common cancer overall, contributing to over half a million new cases and over 300,000 deaths annually. Most of these cases occur in Africa and other low-and middle-income countries (LMICs). In Kenya, it is the second leading cause of cancer deaths contributing to 10% of all cancer deaths. It accounts for 5,250 (12.9%) of the new cancer cases and 3,286 (11.84%) of all cancer deaths annually. Among women, it ranks as the second cancer in incidence after breast cancer, but ranks top in cancer deaths (GLOBOCAN, 2018).

### Risk factors

- HPV infection
- HIV infection
- Sexually transmitted infections
- Tobacco use
- Sexual history: Having multiple sexual partners, early onset of sexual activity.
- Multiparity
- Immunosuppression

### Clinical Evaluation

#### Signs and Symptoms

##### 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
- Severe back pain
- Weight loss
- Oliguria (due to ureteric obstruction or renal failure)
- Urinary/ fecal incontinence
- Edema of lower limbs

Any woman presenting with any of the above symptoms should have a pelvic and bimanual examination and speculum examination to visualize the cervix, and any visible lesions should be biopsied.

During pelvic exam and bimanual exam, 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. Examination under 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.

### Investigations

- Complete Blood Count;
- HIV test;
- Biochemistry: Liver function tests and Renal function tests;
- Cervical biopsy and pathology review.

### Imaging for Staging (After biopsy confirmation)

- Abdominal and ultrasound scan with focus on urinary system;
- Plain chest radiograph (CXR);
- MRI/CT scans if available, are particularly useful for measurement of size of lesion and/or parametrial involvement for early stage and identification of pelvic/para-aortic nodal involvement in later stages.

### Staging for Cervical Cancer (FIGO Staging 2018)

#### Stage I:

The carcinoma is strictly confined to the cervix uteri (extension to the corpus should be disregarded)

- **IA** Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm
  - **IA1** Measured stromal invasion <3 mm in depth
  - **IA2** Measured stromal invasion  $\geq$ 3 mm and <5 mm in depth
- **IB** Invasive carcinoma with measured deepest invasion  $\geq$ 5 mm (greater than stage IA), lesion limited to the cervix uteri
  - **IB1** Invasive carcinoma  $\geq$ 5 mm depth of stromal invasion and <2 cm in greatest dimension
  - **IB2** Invasive carcinoma  $\geq$ 2 cm and <4 cm in greatest dimension
  - **IB3** Invasive carcinoma  $\geq$ 4 cm in greatest dimension

#### Stage II:

The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall

- **IIA** Involvement limited to the upper two-thirds of the vagina without parametrial involvement
  - **IIA1** Invasive carcinoma <4 cm in greatest dimension
  - **IIA2** Invasive carcinoma  $\geq$ 4 cm in greatest dimension
- **IIB** With parametrial involvement but not up to the pelvic wall

### Stage III:

The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or paraaortic lymph nodes

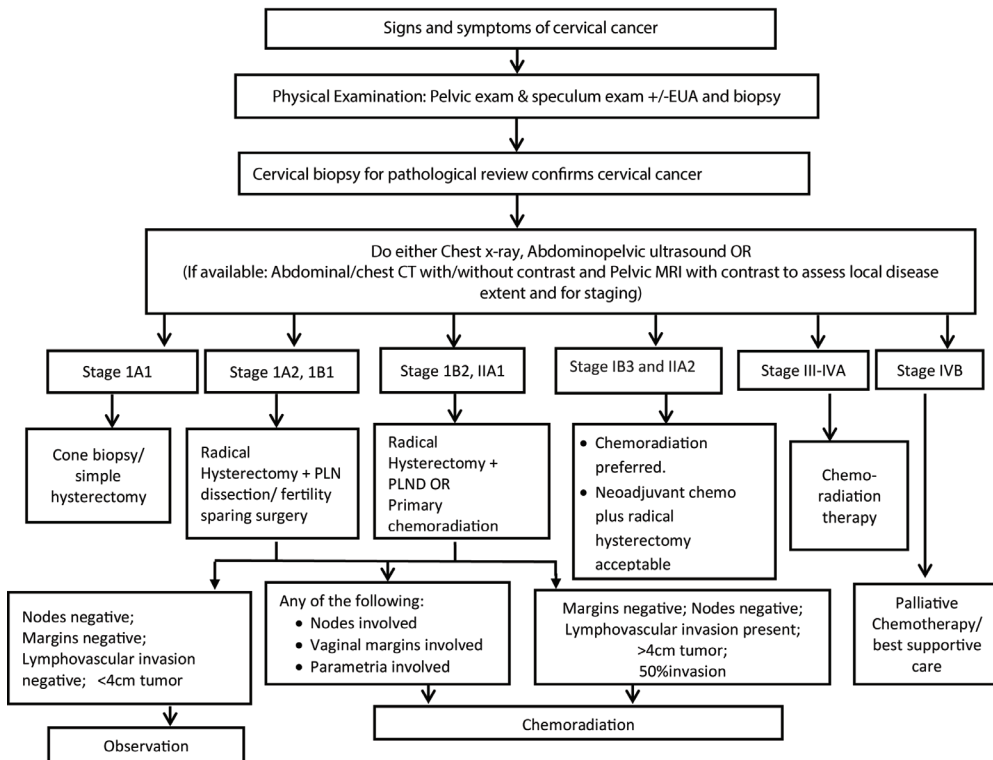
- **IIIA** Carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
- **IIIB** Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)
- **IIIC** Involvement of pelvic and/or paraaortic lymph nodes, irrespective of tumor size and extent (with r and p notations)
  - **IIIC1** Pelvic lymph node metastasis only
  - **IIIC2** Para-aortic lymph node metastasis

### Stage IV:

The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV

- **IVA** Spread of the growth to adjacent organs
- **IVB** Spread to distant organ

## Cervical Cancer Management Algorithm



## Chemotherapy regimens

| Indication                | Chemotherapy agent  |
|---------------------------|---|
| Concurrent chemoradiation | 1. Single agent Cisplatin/Carboplatin<br>2. Weekly carboplatin/paclitaxel |
| Neoadjuvant setting       | 3. Cisplatin + Paclitaxel Day 1 every 21 days x 3 cycles                  |
| Metastatic disease        | 4. Paclitaxel + Cisplatin   |
|                           | 5. Carboplatin + Taxane (Paclitaxel/ Docetaxel)                           |
|                           | 6. Bevacizumab (until disease progression)                                |

## Follow up and Surveillance

Patients who have been treated with curative intent should undergo complete history and physical exam with the following evaluation every 3 months for the first 3 years and every 6 months for the next 2 years.

Colposcopy and either pelvic ultrasound scan (or Pelvic CT scan if available) can be done at follow-up if recurrence is suspected.

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National Comprehensive Cancer Network (NCCN). Cervical Cancer Guidelines

## 5.3 Vulvar Cancer

### Introduction

Vulva cancer accounts for 4% of all gynecological cancers worldwide, with an estimated 6000 new cases and 1200 deaths in 2018 (SEER, 2018). In Kenya it comprises less than 1% of all cancer cases, with 119 new cases and 32 deaths annually (GLOBOCAN, 2018). It is among cancers related to human papillomavirus (HPV) infection and can be detected early through screening. About 90% are squamous cell carcinomas.

### Risk Factors

- HPV infection
- Immunodeficiency including HIV
- Tobacco use
- Increasing age
- Inflammatory conditions of the vulva, among others.

### Signs and symptoms

Some are asymptomatic. Elderly women could present with vulvar pain, burning, pruritus and soreness. They could also present with vulvar lump or mass, groin mass, vulva bleeding or discharge.

Any vulvar symptom should prompt an examination of the genital tract.

### Physical examination

Physical exam requires careful inspection in good light. One may observe signs of vulvar pruritus which occurs several years before actual cancer. Colposcopy may be useful after application of 2% acetic acid if no lesion is visible grossly. Warts are uncommon in elderly women and should be regarded with suspicion. Vulvar lesion may be raised, fleshy, ulcerated, leukoplakic or warty mostly on labia major but also on labia minora, clitoris. The lesion may be multifocal. There may also be change in colour of the skin to brown or black, change in surface from smooth to scaly or ulcerated among others.

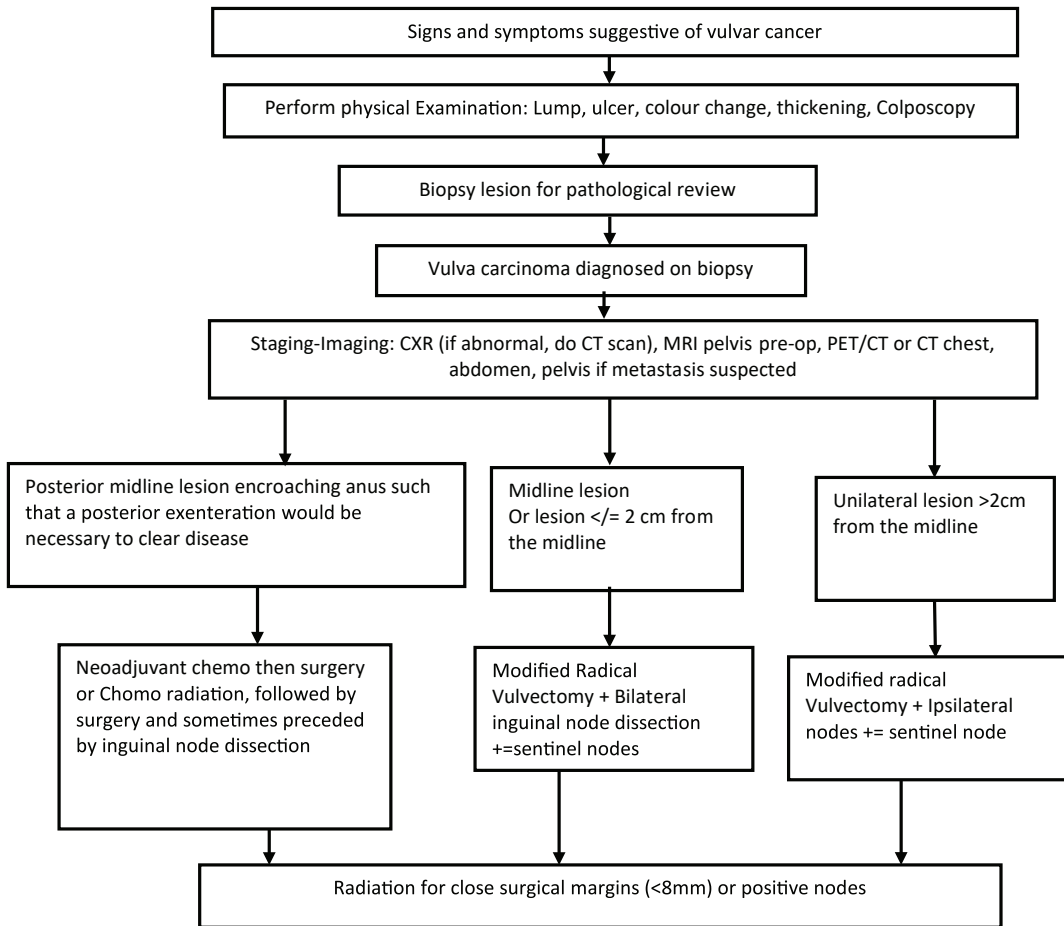
### Investigations

- Tissue biopsy is the preferred method for diagnosis. Include underlying dermis and connective tissue for evaluation of depth & nature of stromal invasion. Preferably leave primary lesion in situ to allow the treating surgeon to fashion adequate surgical margins.
- 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 to assess pelvic node involvement.
- Laboratory work up should include full blood counts, renal function tests, liver function tests, VDRL, HIV test and random blood sugar.

## Staging for Vulval Cancer

|      |  |
|------|--|
| I    | Tumor confined to the vulva  |
| IA   | Lesions $\leq 2$ cm in size, confined to the vulva or perineum and with stromal invasion $\leq 1.0$ mm, no nodal metastasis  |
| IB   | Lesions $> 2$ cm in size or with stromal invasion $> 1.0$ mm, confined to the vulva or perineum, with negative nodes   |
| II   | Tumor of any size with extension to adjacent perineal structures (lower third of urethra, lower third of vagina, anus) with negative nodes   |
| III  | Tumor of any size with or without extension to adjacent perineal structures (lower third of urethra, lower third of vagina, anus) with positive inguinofemoral nodes   |
| IIIA | <ol style="list-style-type: none"><li>1. With 1 lymph node metastasis (<math>\geq 5</math> mm), or</li><li>2. With 1–2 lymph node metastasis(es) (<math>&lt; 5</math> mm)</li></ol>  |
| IIIB | <ol style="list-style-type: none"><li>1. With 2 or more lymph node metastases (<math>\geq 5</math> mm), or</li><li>2. With 3 or more lymph node metastases (<math>&lt; 5</math> mm)</li></ol>  |
| IIIC | With positive nodes with extracapsular spread  |
| IV   | Tumor invades other regional (upper 2/3 urethra, upper 2/3 vagina), or distant structures  |
| IVA  | Tumor invades any of the following: <ol style="list-style-type: none"><li>1. upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or</li><li>2. fixed or ulcerated inguinofemoral lymph nodes</li></ol> |
| IVB  | Any distant metastasis including pelvic lymph nodes  |

## Treatment Algorithm for Vulvar Cancer



### Follow up and Surveillance

A three monthly follow-up with, history and physical exam and imaging if recurrence is suspected is recommended.

### References

GLOBOCAN, 2018: Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin [Internet]. 2019 Feb 22 [cited 2019 Feb 22]; Available from: <http://doi.wiley.com/10.3322/caac.21492>

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## 5.4 Gestational Trophoblastic Disease (GTDs)

### Introduction

These are rare but highly curable diseases arising from the products of conception in the uterus. They result from abnormal fertilization where abnormal trophoblast cells grow inside the uterus after conception. GTDs include non-cancerous lesions (such as hydatidiform moles and partial moles), and cancerous conditions (such as Choriocarcinoma, Placental site tumor, Epithelial trophoblastic tumor and Invasive mole).

### Risk factors

- Maternal age (younger than 20 or older than 35; higher in >45 years);
- Previous history of hydatidiform mole;
- They can also complicate normal or ectopic pregnancies, and spontaneous or induced abortions.

### Clinical Presentation

Abnormal and excessive vaginal bleeding is the commonest mode of presentation and may or may not follow a period of amenorrhea. Women with GTD may present with pelvic pain or sensation of pressure, anemia, hyperemesis gravidarum, hyperthyroidism, and preeclampsia in early pregnancy.

Gestational Trophoblastic Neoplasias should also be suspected in any woman presenting with per vaginal bleeding after any gestation term pregnancy, abortion or ectopic. In addition to the above symptoms, GTN may present symptoms and signs depending on the site of metastasis e.g. lungs, liver and brain.

### Physical examination

Examination includes speculum pelvic examination which may show vaginal deposits.

### Investigations

1. Pregnancy Detection Test: A positive pregnancy test should prompt further diagnostic workup.
2.  $\beta$ -hCG in blood,
3. Imaging (usually for evaluation of metastatic disease): Pelvic ultrasound and Chest X-ray. Brain CT scan is done if metastases are found in the chest.

### Staging and Risk stratification

Each patient with a gestational trophoblastic neoplasia is assigned both a FIGO stage and a WHO prognostic score. The patients diagnosis is assigned to a FIGO stage represented by a Roman number I, II, III, IV separated by a colon and the WHO risk score. For example, II: 7 to mean stage II with a WHO score of 7.

**Table 5. 1: FIGO Anatomical Staging for Gestational Trophoblastic Neoplasms**

|           |  |
|-----------|--|
| Stage I   | Tumour confined to the uterus.   |
| Stage II  | Tumour extending to the adnexa or vagina but limited to the genital structures (adnexa, vagina, broad ligament). |
| Stage III | Tumour extending to the lungs, with or without known genital tract involvement.                                  |
| Stage IV  | All other metastatic sites.  |

**Table 5. 2: WHO Prognostic Scoring**

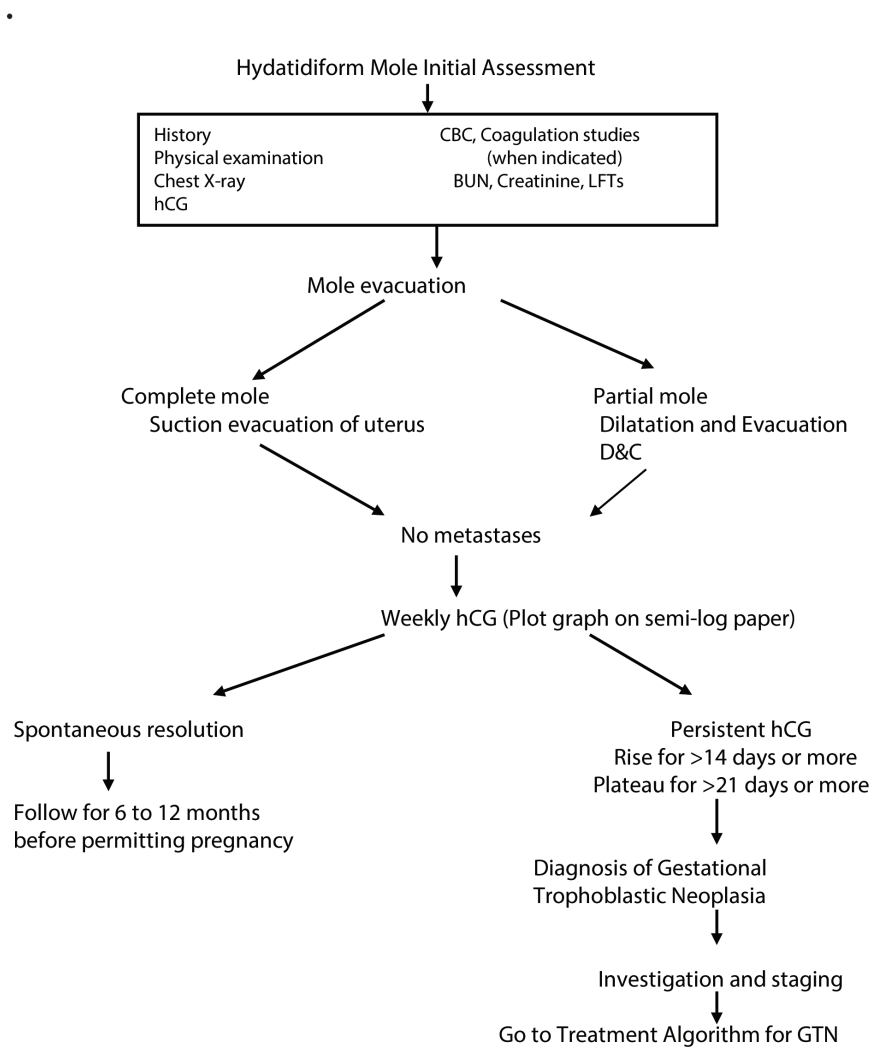
| SCORE                                 | 0                | 1                                | 2                                | 4                |
|---------------------------------------|------------------|----------------------------------|----------------------------------|------------------|
| Age (years)                           | <40              | ≥40                              | –                                | –                |
| Antecedent pregnancy                  | Mole             | Abortion                         | Term pregnancy                   | –                |
| Interval months from index Pregnancy  | <4               | 4–6                              | 7–12                             | >12              |
| Pretreatment serum hCG (iu/l)         | <10 <sup>3</sup> | 10 <sup>3</sup> –10 <sup>4</sup> | 10 <sup>4</sup> –10 <sup>5</sup> | >10 <sup>5</sup> |
| Largest tumor size (including uterus) | <3               | 3–4 cm                           | ≥5 cm                            | –                |
| Site of metastases                    | Lung             | spleen, kidney                   | gastrointestinal                 | liver, brain     |
| Number of metastases                  | –                | 1–4                              | 5–8                              | >8               |
| Previous failed chemotherapy          | –                | –                                | single drug                      | ≥2 drugs         |

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.

## Management of Gestational Trophoblastic Neoplasms

### 1. Hydatidiform mole

- Suction curettage is the standard treatment.
- Administer anti-D after uterine evacuation if indicated
- Provide combined oral contraceptive pill for at least one year after treatment.
- Monitor by serum -hCG levels weekly until three negative values then monthly for one year. Any rise or plateau will be considered malignant and is staged and scored appropriately.
- Hysterectomy is an alternative to evacuation in women who have achieved desired family size.



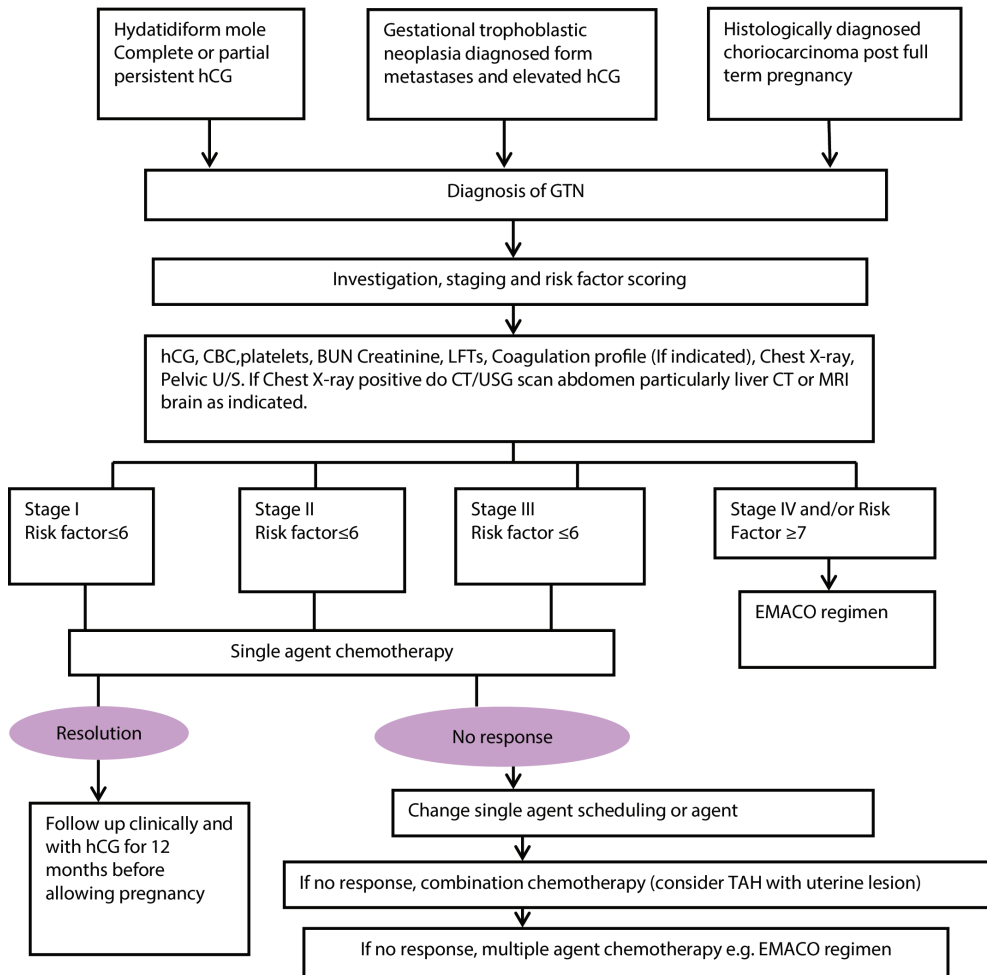
**NOTE:** Gestational Trophoblastic Disease (GTD) includes all aspects of this entity. The term Gestational Trophoblastic Neoplasia is reserved for entities that require chemotherapy and replaces invasive mole, malignant GTD and other such term. Choriocarcinoma is a pathologic term. PSST is classified separately.

## 2. Gestational Trophoblastic Neoplasia

These include and any hydatidiform mole with persistent HCG, metastasis with high HCG levels or histologically confirmed choriocarcinoma

For stage I, II, and III disease with low risk score (0-6) single agent chemotherapy is indicated. For high risk disease (FIGO II, III, IV with score  $\geq 7$ ), combination chemotherapy regimen is preferred.

## Treatment Algorithm For Gestational Trophoblastic Neoplasia (GTN)



*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.*

### Treatment regimens

a) Single agent chemotherapy regimens for low- risk gestational trophoblastic neoplasia include.

- MTX-FA (methotrexate with folinic acid) 8-day regimen (50 mg MTX IM on days 1,3,5,7 with folinic acid 15 mg orally 24 hours after MTX on days 2,4,6,8); repeat every 2 weeks.
- MTX 0.4 mg/kg (max. 25 mg) intravenously or intramuscularly for 5 days every 2 weeks.
- Actinomycin D pulse 1.25 mg/m<sup>2</sup> intravenously every 2 weeks.
- Actinomycin D 0.5 mg intravenously for 5 days every 2 weeks
- Others: MTX 30–50 mg/m<sup>2</sup> intramuscularly weekly, MTX 300 mg/m<sup>2</sup> infusion every 2 weeks

b) Combination chemotherapy (EMACO REGIMEN); 2 day EMA (Etoposide, Methotrexate, Actinomycin D) then Day 8 CO (Vincristine and Cyclophosphamide).

- Etoposide 100mg/m<sup>2</sup>/day IV on days 1 and 2

- Actinomycin 0.5mg IV push on days 1 and 2
- Methotrexate 300mg/m<sup>2</sup> IV infusion over 12 hours on day 1
- Leucovorin 15mg PO or IM every b12 hours for 4 doses starting 24 hours after start of methotrexate
- Cyclophosphamide 600mg/m<sup>2</sup> IV on day 8
- Vincristine 1mg/m<sup>2</sup> (Maximum 2mg) IV over 5 – 10 minutes on day 8  
(Repeat every 2 weeks until hCG normalizes, then continue for 2 more cycles).

### Follow up & surveillance

Monitor serum  $\beta$ -HCG levels monthly. In low-risk disease, this is carried on for a year. In high-risk patients, this should be performed for a period of 2 years. During this period of monitoring, it is important to prescribe effective contraception e.g. combined oral contraceptive pill to avoid pregnancy.

Prognosis is good even with metastatic disease especially when only lungs are involved.

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## 5.5 Endometrial Cancer

### Introduction

Endometrial cancer is a heterogenous group of diseases. Globally, it is the sixth most commonly occurring cancer in women with 380,000 new cases in 2018. It most commonly occurs in post-menopausal women, with post-menopausal bleeding being the most common presenting symptom.

### Risk factors

- 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

*Breastfeeding reduces the risk of endometrial cancer.*

## Clinical Presentation

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.

## Physical examination

Initial evaluation should include full physical examination, including a pelvic examination noting the size, position and contour of the uterus.

## Diagnosis

Diagnosis requires histopathological evaluation of endometrial tissue. Devices for use in the office such as novaks curette allow endometrial sampling and accurate diagnosis. Hysteroscopic evaluation and biopsy may be performed where facilities are available. Pelvic ultrasonography may be suggestive of disease. Endometrial thickening above 5 mm in a postmenopausal woman should make the clinician be suspicious.

## 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 and nodal assessment.

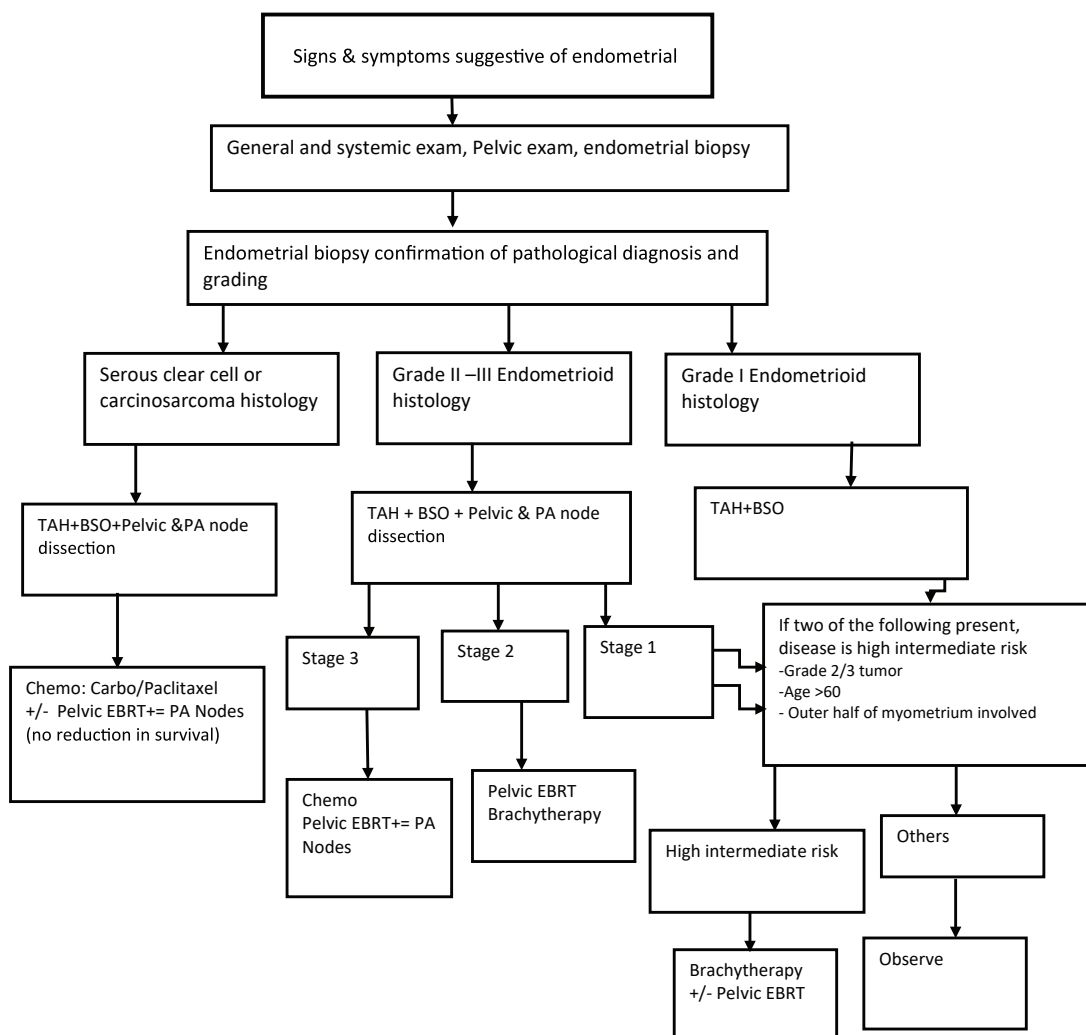
## FIGO Staging for Endometrial Carcinoma

|        |   |
|--------|---|
| Ia     | Tumor confined to the corpus uteri  |
| IAa    | No or less than half myometrial invasion  |
| IBa    | Invasion equal to or more than half of the myometrium                           |
| IIa    | Tumor invades cervical stroma, but does not extend beyond the uterus            |
| IIIa   | Local and/or regional spread of the tumor                                       |
| IIIAa  | Tumor invades the serosa of the corpus uteri and/or adnexae                     |
| IIIBa  | Vaginal involvement and/or parametrial involvement                              |
| IIICa  | Metastases to pelvic and/or para-aortic lymph nodes                             |
| IIIC1a | Positive pelvic nodes   |
| IIIC2a | Positive para-aortic nodes with or without positive pelvic lymph nodes          |
| IVa    | Tumor invades bladder and/or bowel mucosa, and/or distant metastases            |
| IVAa   | Tumor invasion of bladder and/or bowel mucosa                                   |
| IVBa   | Distant metastasis, including intra-abdominal metastases and/or inguinal nodes) |

## Management

Surgery followed by adjuvant chemotherapy and or radiotherapy are the main stay of treatment. Complete surgery involves total abdominal hysterectomy (TAH), bilateral salpingoophorectomy (BSO), infracolic omentectomy, pelvic and para-aortic node dissection. Adjuvant treatment is given based on a risk assessment for possibility of recurrence and treatment is tailored to this.

### Treatment algorithm for Endometrial Cancer





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International Journal of Obstetrics and Gynecology Volume 143, Issue S2, Special Issue: FIGO Cancer Report 2018

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## 5.6 Anticipated Services for Gynecological Cancers per Level of Care

| Level of Care     | Anticipated Services   |
|-------------------|--|
| Level 1           | Awareness creation/education on gynaecological cancer signs and symptoms, referral of suspected cases, palliative care   |
| Level 2 and 3     | Awareness creation/education on gynaecological cancer signs and symptoms, Triage and referral of suspected cases, Palliative care  |
| Level 4 and 5     | All above and in addition;<br>Diagnosis and workup-imaging, laboratory<br>Diagnostic biopsies, endometrial sample,<br>Dilatation & Curettage, Simple hysterectomy<br>Palliative care<br>Referral for services not available<br><b>Level 5 facilities with requisite HR and personnel</b> can do radical surgeries, lymph node dissection, chemotherapy, radiotherapy, ureteric stents and nephrostomy tube insertion incase of urinary tract obstruction, dialysis in patients with renal failure among others in addition to the above. |
| Level 6 hospitals | As above plus;<br>Specialised investigations such as PET scans<br>Referral downward<br>Conduct research and training; clinical trials  |



# 6

## **CHAPTER SIX**

### Head and Neck Cancers Treatment Protocols

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# HEAD AND NECK CANCERS TREATMENT PROTOCOLS

## List of Abbreviations

|      |   |
|------|---|
| Ab   | Antibody                                  |
| CD4  | Cluster of differentiation 4 type T-cells |
| CT   | Computed tomography scan                  |
| CXR  | Chest X-Ray                               |
| EBRT | External Beam radiotherapy                |
| EBV  | Epstein Barr Virus                        |
| ENT  | Ear nose and throat                       |
| FNA  | Fine needle aspirate                      |
| HIV  | Human Immunodeficiency virus              |
| HPV  | Human papilloma virus                     |
| IMRT | Intensity modulated radiotherapy          |
| LFT  | Liver function tests                      |
| MDT  | Multidisciplinary team                    |
| MRI  | Magnetic resonance imaging                |
| PET  | Positron emission tomography              |
| PNS  | Post nasal space                          |
| RFT  | Renal function test                       |
| SCC  | Squamous cell carcinoma                   |
| SLT  | Speech and language therapist             |
| TBC  | Tuberculin test                           |
| TFT  | Thyroid function test                     |
| TNM  | Tumour node metastasis                    |
| WCC  | White cell count                          |
| WHO  | World Health Organization                 |

## 6.1 Introduction

These are tumors affecting the upper aerodigestive tract above the level of the clavicle (excluding those of the central nervous system and skin). They constitute about 5.7% of the cancer burden in Kenya. Anatomically, these include oral cavity; oropharynx; hypopharynx; larynx; nasopharynx; sinonasal regions; thyroid and salivary glands tumors. Majority are squamous cell carcinomas.

## 6.2 Risk Factors

A high index of suspicion is recommended for patients who are:

- Heavy smokers or other forms of tobacco use and/or chewing betel (areca nut)
- History of harmful use of alcohol
- Aged over 45 years
- Male sex.

Other risk factors include: exposure to carcinogenic human papilloma virus (HPV) strains, environmental/occupational inhalants (textile, glue, leather, wood dust).

## 6.3 Signs & Symptoms

### *Urgent referral Considerations*

#### 1. Head & Neck Cancers

- Hoarseness persisting for > 2weeks
- Ulceration of oral mucosa persisting for > 2weeks
- Oral or facial swellings persisting for > 2 weeks
- All red or red and white patches of the oral mucosa
- Dysphagia and odynophagia persisting for > 2 weeks
- Unilateral nasal obstruction, particularly when associated with purulent discharge
- Unexplained tooth mobility not associated with periodontal disease
- Unresolving neck masses persisting for > 2 weeks
- Cranial neuropathies
- Orbital masses, strabismus, proptosis (unilateral or bilateral) and visual impairment.
- Ear pain without evidence of local ear abnormalities
- Unilateral middle ear effusion or hearing loss especially in adults.

#### 2. Thyroid cancer

Patients with thyroid lump/swelling/enlargement AND:

- Age > 65 years
- Previous radiotherapy
- Positive family history of thyroid cancer
- Stridor
- Cervical lymphadenopathy
- Voice change

## 6.4 Clinical Evaluation

All patients with the above symptoms should be referred IMMEDIATELY to the ENT/maxillofacial clinic in Level 5 & 6 referral hospitals for further management.

History and Physical examination

- Take a detailed history
- Perform a complete physical examination
- Refer patient for visual examination by ENT specialist (i.e. indirect laryngoscopy/ direct laryngoscopy and hypopharyngoscopy during examination under anesthesia/ Rigid nasal endoscopy under local or general anesthesia).

### **Imaging**

- \*CT; \*\*MRI; ultrasound and chest x-ray (CXR) are used for assessment of the primary and staging (Appendix 1).
- PET scan if available can be used to detect the occult primary with neck disease and the detection of distant metastases.

\*Features of mastoiditis on CT should prompt evaluation of the PNS.

\*\*MRI is used where CT was inconclusive and also for imaging of oral cavity tumours.

### **Pathology**

- Tissue biopsy\* – for all patients for histological diagnosis & staging (See Appendix).
- Immunohistochemistry - an important adjunct for confirmation of diagnosis.
- Fine needle aspirate (FNA) cytology of suspected metastatic neck nodes should also be done. FNAC is also essential in diagnostic work-up of thyroid carcinoma.

*Open biopsy of metastatic neck disease is not recommended.*

*\*Patients with metastatic neck disease and occult primary should have tissue biopsy obtained from the nasopharynx, oropharynx, hypopharynx and tonsillar region during examination under anaesthesia.*

### **Laboratory tests**

Total Blood Count, Liver Function Tests, Renal Function Tests, HIV test + CD4 levels, Epstein Barr Virus Antibody titers, Thyroid Function Tests, Parathyroid hormone and Bone Marrow Aspirate.

### **Hearing evaluation**

Audiometry should be done prior to treatment.

### **Dental evaluation**

Should be done for those receiving irradiation of the oral cavity.

### **Nutritional evaluation**

For possible feeding gastrostomy or PEG tube insertion before start of any radiotherapy to head/neck.

### **Airway evaluation**

For possible tracheostomy insertion before treatment to prevent airway obstruction as an emergency.

## 6.5 Staging

**Table 6. 2: Stage Grouping of Head and Neck Cancers**

| PRIMARY TUMOUR (T)       |   |
|--------------------------|---|
| TX P                     | Primary tumour cannot be assessed                                 |
| TO N                     | o evidence of primary tumour                                      |
| Tis                      | Carcinoma in situ   |
| T1 T                     | tumour < 2 cm in greatest dimension                               |
| T2 T                     | tumour < 2 cm but < 4 cm  |
| T3 T                     | tumour < 4 cm   |
| T4                       | Tumour invades adjacent structures (defined under specific site)  |
| T4a                      | Tumour invades adjacent structures, but is potentially resectable |
| T4b                      | Tumour invades adjacent structures, but is unresectable           |
| Regional Lymph nodes (N) |   |
| Nx R                     | Regional lymph nodes cannot be assessed                           |
| NO N                     | o regional node metastasis  |
| N1 M                     | Metastasis in a single ipsilateral lymph node, < 3 cm             |
| N2a                      | Metastasis in single ipsilateral lymph < 3 cm but < 6 cm          |
| N2b                      | Metastasis in multiple ipsilateral lymph nodes, none > 6 cm       |
| N2c                      | Metastasis in bilateral or contralateral lymph nodes/ none > 6 cm |
| N3 M                     | Metastasis in a lymph node > 6 cm in greatest dimension           |
| Distance Metastasis (M)  |   |
| Mx                       | Distant metastasis cannot be assessed                             |
| M0 No D                  | istant metastasis   |
| M1 D                     | istant metastasis   |

**Table 6. 2: Stage Grouping of Head and Neck Cancers**

|     |      |      |    |   |
|-----|------|------|----|---|
| 0   | Tis  | N0   | M0 |   |
| I   | T1   | N0   | M0 |   |
| II  | T2   | N0   | M0 |   |
| III | T1-3 | N1   | M0 | T3 N0 M0                                    |
| IVA | T4   | N0-2 | M0 | T1-3 N2 M0 (advanced, resectable disease)   |
| IVB | AnyT | N3   | M0 | T4 AnyN M0 (Advanced disease, unresectable) |
| IVC | AnyT | AnyN | M1 | (advanced distant, metastatic disease)      |

*Above staging excludes nasopharyngeal carcinoma*

*T staging of hypopharyngeal and salivary gland carcinomas is similar to others in tumour size but also depends on local tumour extension.*

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

*Adapted from AJCC 8th Edition 2018*



**Table 6. 3: Nodal Assessment of Thyroid Cancers**

|     |  |
|-----|--|
| Nx  | Nodal disease cannot be assessed   |
| N0  | One or more cytological or histologically confirmed benign node  |
| N1a | Metastases to level VI and VII nodes (pre-tracheal, para-tracheal, pre-laryngeal/Delphian or upper mediastinal)        |
| N1b | Metastases to unilateral, bilateral or contralateral lateral neck nodes (level I,II,III,IV,V) or retropharyngeal nodes |

*Adopted from AJCC 8th edition 2018*

## 6.6 Management

Challenges in the management of head and neck cancers include the preservation of functional integrity of the upper aerodigestive tract, minimizing the adverse effects of the different treatment modalities, and aesthetics. The core multidisciplinary team (MDT) needed for their management includes a surgeon, pathologist, radiologist, radiation oncologist, nutritionist, oncology nurse, physiotherapist and counsellor.

### Head and Neck Cancers

Surgery and radiotherapy are the key modalities in the treatment of head and neck cancer.

#### Surgery

- Surgery is the mainstay of treatment and is guided by clinical staging and performance status.
- Early tumors of the larynx/pharynx will be assessed for open or laser excision or radical radiotherapy.
- Tumors that are not of mucosal origin are also surgically treated where amenable. Histological grade may also determine the need for post-operative radiation with or without chemotherapy.

#### Radiotherapy

Radical radiotherapy requires 1-2 weeks for planning and 6-7 weeks to complete the actual treatment. These timelines need to be well communicated to the patient.

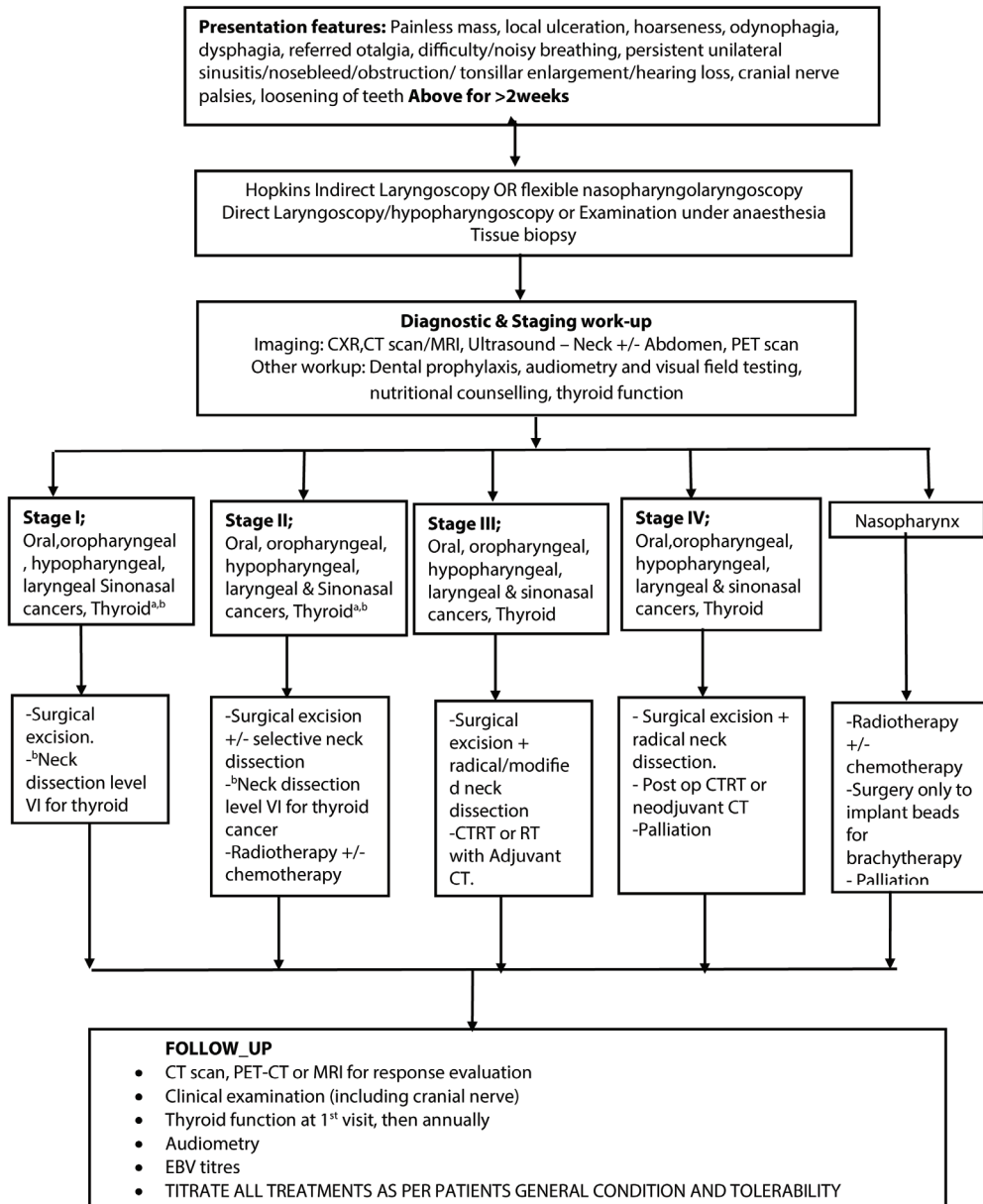
Indications for post-operative radiotherapy include:

- Incompletely excised lesions (margins <5mm)
- Perineural invasion
- T3/T4 tumors
- 2 or more positive lymph nodes
- Extra-capsular extension of nodes
- Vascular invasion
- High-grade thyroid tumors
- Metastatic disease sites like fractures, painful nodes/nodules among others.

**Note that:**

- Concurrent chemo radiation or brachytherapy (with or without External Beam Radiotherapy) is an option in selected stage T3 and T4 cancers.
- Nasopharyngeal tumors are treated with radiotherapy with or without chemo therapy, depending on stage.
- Where the primary lesion is occult, treat the neck disease appropriately as the search to identify the primary continues.

**Management Algorithm for Head & Neck SCC and Thyroid Cancers**



## Thyroid Carcinomas

Include differentiated subtypes (follicular, Hurtle cell, medullary and papillary) and undifferentiated subtypes (anaplastic).

**Surgery** remains the mainstay treatment modality for thyroid cancers amenable to surgery.

**Iodine<sup>131</sup> ablation** should be carried out at designated centers for: tumor diameter > 1 cm; tumor with gross extra-thyroid extension and distant metastases. A post-ablation scan is indicated 3–10 days after the procedure.

## Palliative Treatment

Patients with the below features must be booked with the multidisciplinary team for a decision on the appropriate modality of treatment:

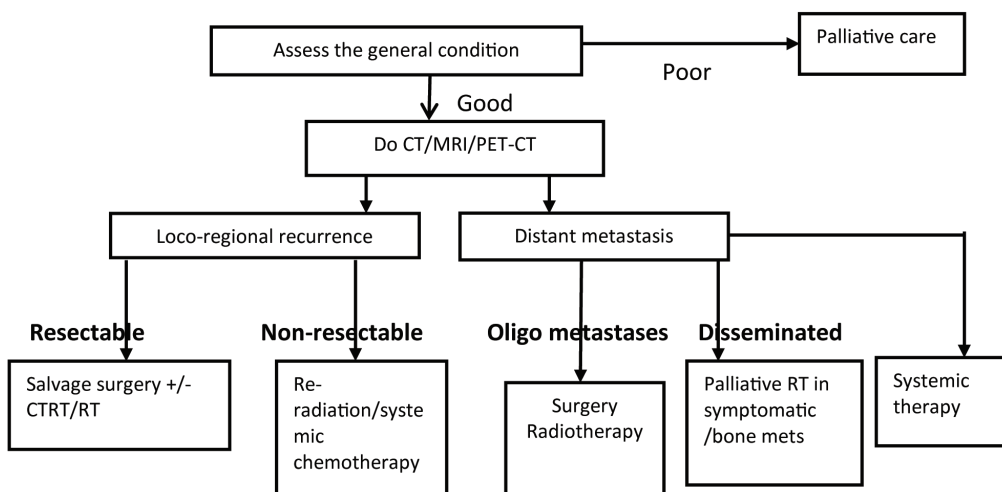
- Extensive primary/ nodes that is inoperable
- Distant metastases
- Recurrent or persistent disease not amenable to surgery
- Performance status >2
- Requiring radiotherapy for symptom control

Patients can also be palliated with weekly Methotrexate with Leucovorin rescue 15mg orally 24h later and reviewed every 3 weeks. Alternatively, give oral Methotrexate 8mg hourly for 3 consecutive days per week and Leucovorin 15mg on Day 4 (repeat weekly). Patients are reviewed every 3 weeks.

### Note:

Renal function should be monitored initially and a full blood count performed weekly. In patients with renal compromise, reduce Methotrexate dose or discontinue. Do not give if the patient has pleural effusion or ascites, because of the 'reservoir effect'. Mild stomatitis signals low white cell count; wait until WCC recovers before commencing.

## Management Algorithm for Recurrent/Metastatic Head & Neck Cancers





## 6.7 Supportive Management for Head and Neck Cancer

| Symptom/sign  | Referrals/assessments/interventions to be considered  |
|---|---|
| <b>Shoulder/accessory nerve Problem</b><br><br><b>Problems with speech</b><br><br><b>Dysphagia</b>  | Referral to physiotherapy<br>Referral to specialist shoulder unit<br>Referral back to MDT<br>Referral to speech and language therapist (SLT)<br>Laryngectomy patients should maintain lifelong links with local head and neck SLT services<br>Referral to SLT/referral to dietitian<br>Assessment by SLT<br>Assess weight loss<br>Dietary modification and dietary advice<br>Referral back to MDT   |
| <b>Trismus</b><br><b>Dental problems/ORN</b><br><b>Dry mouth</b><br><br><b>Excessive fatigue</b><br><br><b>Weight changes</b><br><br><b>Raised blood sugars</b> | Referral to SLT, Dietary advice, Referral Back to MDT<br>Referral back to specialist MDT<br>Artificial saliva<br>Carry water bottle<br>Referral to occupational therapy/physiotherapy for fatigue--management strategies<br>Support for family and care givers<br>Training in management strategies<br>Consider if steroid related and reduce/increase dose if clinically indicated<br>Referral to dietitian<br>If weight loss related to nausea and vomiting, consider anti-emetics<br>If weight gain, consider reducing dietary intake<br>Referral to diabetic nurse specialist/GP<br>Start medication if appropriate<br>Monitor blood sugars regularly<br>Encourage low sugar diet<br>Referral to dietitian for dietary advice |
| <b>Constipation</b>   | Regular laxatives, ENCOURAGE ORAL fluid intake, referral to dietitian   |
| <b>Tobacco use</b>  | Cessation services  |
| <b>Anxiety/depression</b>   | Non-pharmacological techniques: counselling, cognitive behaviour therapy, psychologist<br>Antidepressant<br>Consider psychiatric referral if depression unresponsive to treatment or if suicide risk identified   |



## Chemotherapy Protocols

| Regime   | Indications   |
|--|---|
| Cisplatin single agent   | For definitive concurrent/chemoradiotherapy<br>Post-operative concurrent /chemoradiotherapy for fit patients with high risk features.<br>Palliative chemotherapy for unfit or unresected recurrence |
| Carboplatin AUC 5 single agent   | As above, where cisplatin is not tolerated or is contraindicated.   |
| Cetuximab<br>Single agent  | Concurrent/Chemoradiation for definitive and postoperative therapy.<br>Palliative therapy   |
| Single agent:<br>Methotrexate, Docetaxel,<br>Ifosfamide,<br>Bleomycin OR 5FU | Metastatic or unresectable recurrent with unfit or poor performance status  |
| Cisplatin and 5FU doublet<br>Or Carboplatin and 5FU doublet                  | Induction chemotherapy<br>Metastatic or unresected recurrent very fit/ performance status 1-2   |
| Cisplatin, 5FU and Docetaxel   | Induction chemotherapy  |
| Cisplatin/<br>carboplatin<br>and Taxane OR<br>Cisplatin/<br>cetuximab        | Metastatic fit patients<br>Unresectable recurrent and fit.  |

## 6.8 Patient Follow-Up

Any patients with a new primary or a suspected recurrence after radical treatment should be referred back to the ENT/ maxillofacial clinic for re-assessment and further treatment. Recommended post-treatment follow-up intervals (Should be at Level 5 or 6 hospitals by the relevant specialists):

- o Monthly for the initial 3 months, then 3-monthly for 1 year
- o 6-monthly in the second year
- o Annually until the fifth year

## 6.9 Anticipated Care at Different Levels of Health System

A high index of suspicion and a clear referral structure from the primary to the tertiary health care levels will reduce delays in diagnosis and ensure timely access to treatment.

| Level of Care | Activity   |
|---------------|--|
| Level 1       | Awareness creation on signs and symptoms & risk factors<br>Urgent referral   |
| Level 2 – 4   | Clinical evaluation – including visual examination<br>Clinical suspicion of malignancy<br>Urgent referral  |
| Level 5-6     | Clinical evaluation<br>Diagnosis<br>Management by MDT team to include ENT/ maxillofacial specialist, medical and radiation oncologist, radiologist, pathologist and palliative care team among others. |

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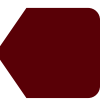
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# 7

## **CHAPTER SEVEN**

# Adult Haematological Cancers Treatment Protocols

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# Adult Haematological Cancer Treatment Protocols

## List of abbreviations

|            |  |
|------------|--|
| ALP        | Alkaline Phosphatase   |
| LDH        | Lactate Dehydrogenase  |
| FISH       | Fluorescence in situ Hybridization                                   |
| HLA        | Human Leukocyte Typing   |
| APML       | Acute Promyelocytic Leukaemia  |
| FLAG-Ida   | Fludarabine, Cytarabine, GCSF and Idarubicin                         |
| HiDAC      | High dose Cytarabine   |
| PCR        | Polymerase Chain reaction  |
| TKI        | Tyrosine Kinase Inhibitor  |
| FDG-PET CT | Fluorodeoxyglucose Positron Emission Tomography- Computed Tomography |
| IFRT       | Involved Field Radiotherapy  |
| ISRT       | Involved Site Radiotherapy   |
| MGUS       | Monoclonal Gammopathy of Undetermined Significance                   |
| SPEP       | Serum Protein Electrophoresis  |
| UPEP       | Urine Protein Electrophoresis  |
| SFLC       | Serum Free Light Chain   |

## 7.1 Acute Leukaemias

### Introduction

Acute leukaemia is characterized by the presence in the bone marrow and/or peripheral blood circulation of immature cells (blasts) with lymphoblasts in acute lymphoblastic leukaemia (ALL) and myeloblasts in acute myeloid leukaemia (AML). Both have a slight male preponderance with an aggressive biological behavior and rapid progression to fatality if not properly treated. They are the 8th most prevalent cancers in Kenya with about 1699 new cases annually.

#### History: Symptoms include-

- Persistent or recurrent infections
- Persistent fatigue,
- Generalized body weakness, shortness of breath, dyspnea on exertion
- Bleeding or easy bruisability, epistaxis, gum bleeding, menorrhagia,
- Unexplained weight loss
- Drenching night sweats
- Persistent fever
- Bone pains

#### Examine for:

- Pallor (anaemia)
- Petechiae
- Bruising (purpura)
- Gum hypertrophy
- Splenomegaly
- Hepatomegaly
- Lymphadenopathy –assess all groups of lymph nodes
- Skin infiltration (leukaemic cutis)
- Myeloid sarcoma
- Features of hyperleukostasis in high count leukaemias

### Diagnostic Workup

#### Laboratory Evaluation

1. Hemogram, with differential count (cytopenias or leukocytosis) and peripheral blood film examination (blasts).  
*Consider a very urgent full blood count in patients with above unexplained symptoms and refer adults, children and young people with a blood count or blood film reported as acute leukaemia immediately.*
2. Bone Marrow examination and trephine biopsy is mandatory {>20% blasts is diagnostic}
3. Immunophenotyping by trephine immunohistochemistry or flow cytometry on peripheral blood or bone marrow aspirate

#### Staging and Risk Assessment

- Liver and renal function tests, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), uric acid, 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.
- Others depending on clinical presentation: septic screen.

*\*Both stained and unstained slides should be prepared at site and sent with the whole blood to the pathology laboratory for review, if not initially reported by a specialist pathologist.*

Ancillary tests are **recommended** and include: cytogenetics and FISH or molecular studies for establishing subtype, risk stratification and prognostication.

For all patients requiring allogeneic stem cell transplantation, HLA typing of siblings must be done at or soon after diagnosis of ALL/AML.

## Treatment

*Urgently refer all patients suspected to have acute leukemia for specialist oncologist review and management in tertiary facilities with adequate supportive care services.*

Definitive treatment includes induction, consolidation and maintenance therapy along with CNS prophylaxis (in ALL) and should be initiated by an oncologist at specialist centers with adequate supportive services. Supportive care should be instituted early enough in the treatment. There are various protocols available and the regimen used is determined primarily by the Philadelphia chromosome status and the age of the patient.

## Supportive care

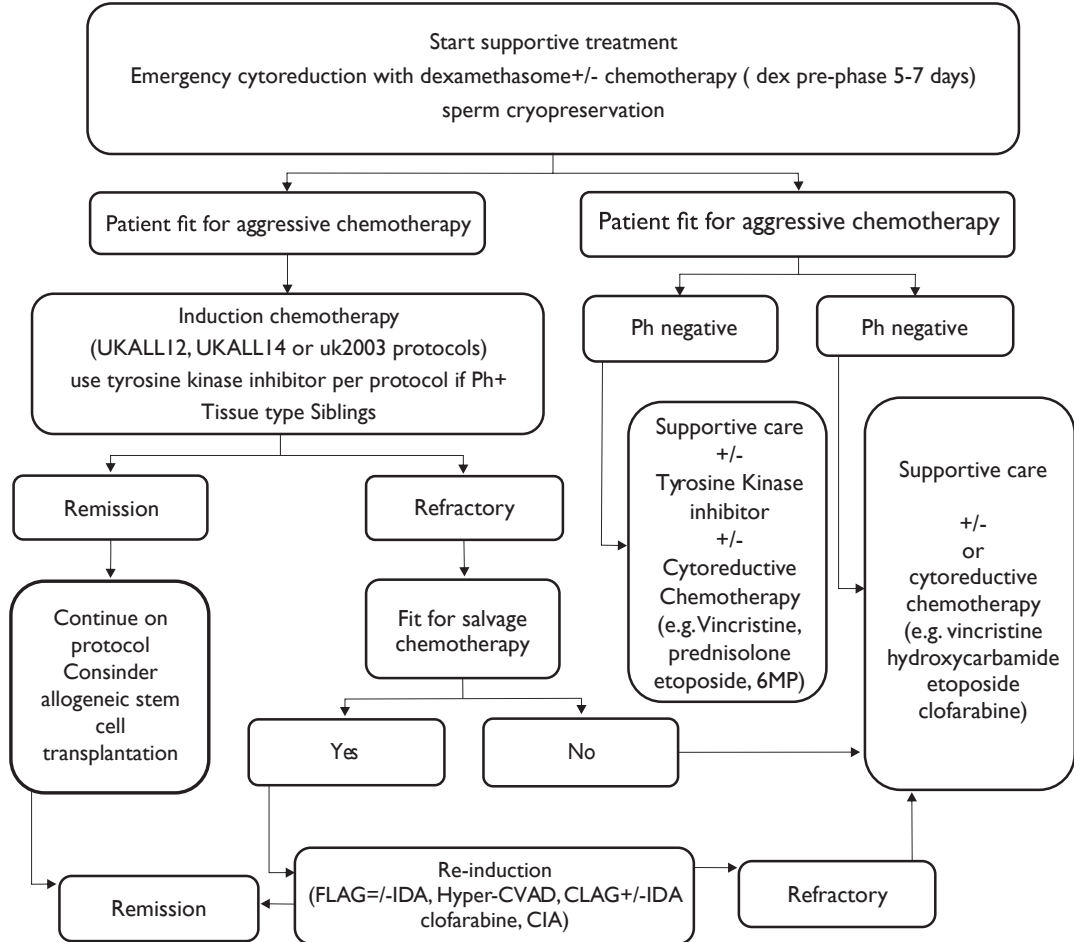
- *Transfusion* of blood components (packed cells and platelet concentrates) as needed.
- *Leukapheresis*: risk factors for leukostasis include a markedly elevated WBC count, especially  $> 100,000/\text{mm}^3$ . Symptoms include dyspnea due to pulmonary infiltration and altered mental status due to CNS effects. Patients should receive emergency leukapheresis to rapidly reduce the WBC count.
- *Prophylaxis and treatment of tumor lysis syndrome*: risk factors include elevated WBC count, especially  $> 50,000/\text{mm}^3$ ; marked elevation of LDH, especially  $> 1000 \text{ U/L}$ ; baseline hyperuricemia; and baseline renal dysfunction. Patients should receive aggressive hydration @  $3\text{L}/\text{m}^2$  and allopurinol; high-risk patients should also receive uricolytic agents such as rasburicase.
- *Prevention and treatment of infections*: Most patients are neutropenic and immunocompromised therefore barrier nursing and isolation should be emphasized.

Afebrile patients usually receive prophylactic antibiotics, such as ciprofloxacin (or **levofloxacin**) and acyclovir (or **valacyclovir**), and an azole antifungal (**posaconazole, voriconazole, itraconazole**, or fluconazole) during induction therapy. Febrile neutropenic patients require prompt initiation of broad-spectrum antibiotics regimens which include a third- or fourth-generation cephalosporin or carbapenem with or without vancomycin.



## 7.1.1 Acute Lymphoblastic Leukaemia

### Treatment Algorithm for ALL



The entire treatment course will run over 2½ years with the first 6 months requiring admission for intravenous chemotherapy from time to time. Other treatment regimens commonly used for acute lymphoblastic leukemia include:

- CALGB 8811 REGIMEN
- HYPER-CVAD/METHOTREXATE-CYTARABINE
- LINKER 4 REGIMEN.
- Pediatric-style intensive multi-agent chemotherapy regimens include; GRAALL-2003, COG AALL-0434, CCG-1961, CALGB 10403 and DFCI regimen.

## CNS Prophylaxis

Patients with ALL have an increased chance of CNS involvement; therefore, intrathecal methotrexate and cranial irradiation 2400cGy is recommended for CNS prophylaxis either after consolidation or during maintenance.

## Role of stem cell transplantation

- If HLA-matched sibling available: consider Allogeneic Transplantation after the 6 month induction chemotherapy.
- If no HLA-matched sibling available: consider Autologous Stem Cell Transplant.
- Patient is not able/ not willing to undergo a stem cell transplant: proceed with oral maintenance with weekly **Methotrexate** and oral **6-Mercaptopurine** daily.
- Stem cell transplantation is the most intensive post remission therapy and potentially increases a patient's chance for cure.

**NOTE:** Autologous stem cell transplantation has lower treatment-related mortality than allogeneic transplantation but the relapse rate is higher. Allogeneic stem cell transplantation patients frequently develop graft versus host disease that can affect long-term survival as well as quality of life.

## Treatment of Relapse

Though the prognosis after relapse is generally poor, the best outcome is obtained if patients achieve a second remission and then proceed to allogeneic stem cell transplantation. Most of the earlier regimens used for first line therapy may be used for salvage though other drugs for consideration may include: **Clofarabine** (for patients up to 21years), **Nelarabine**, **Vincristine liposomal** and **Blinatumomab**.

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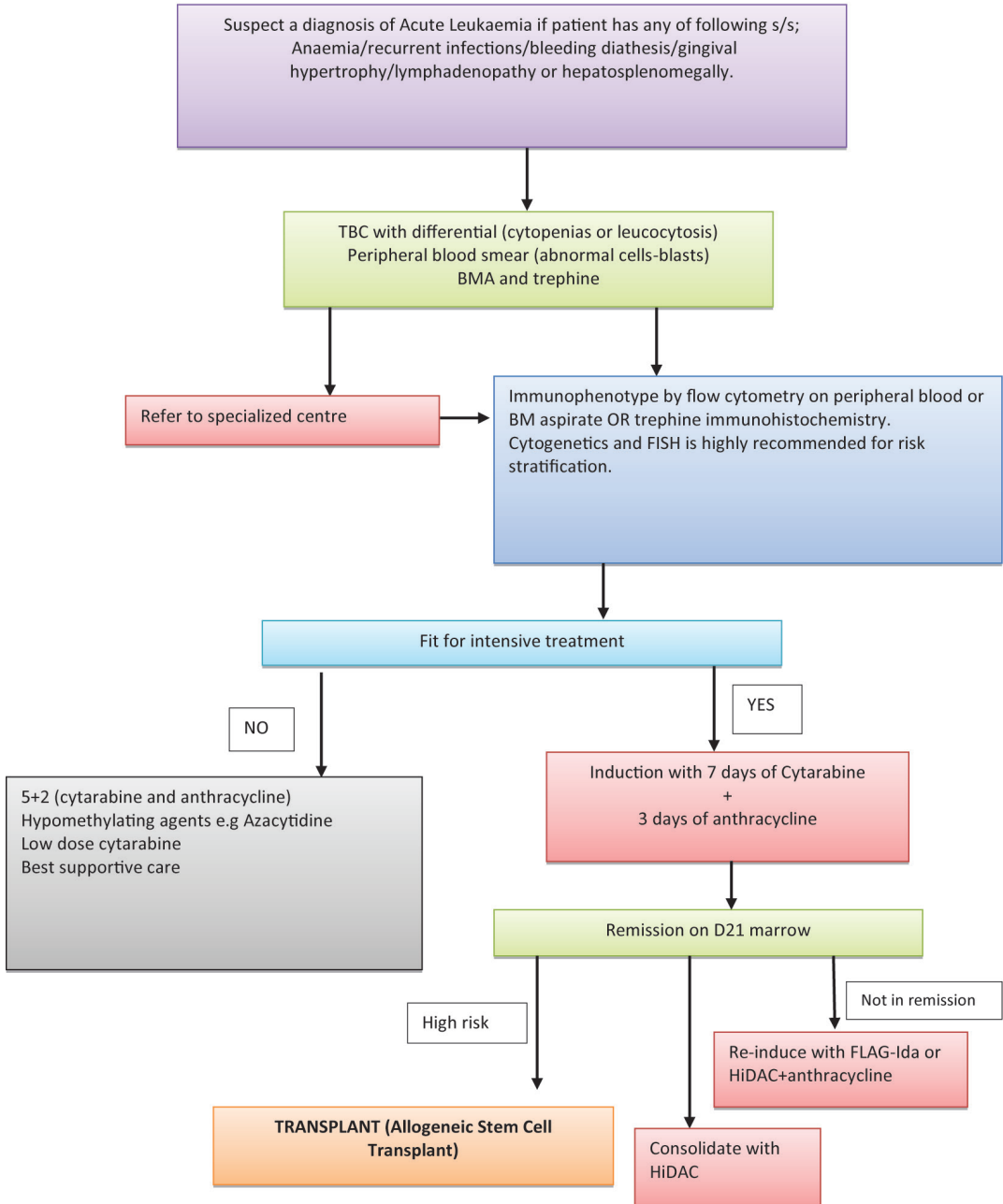
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### **7.1.2 Acute Myeloid Leukaemia**

This is a heterogeneous group of diseases which, though infrequent, are highly malignant yet curable in a sizeable proportion of cases. AML shows 2 peaks in occurrence, one in early childhood with the majority occurring later in adulthood. The 2016 WHO classification categorizes AML as:

- AML with recurrent genetic abnormalities e.g. APML with t(15,17)
- AML with myelodysplasia related changes
- Therapy related AML
- AML, not otherwise specified.
- Myeloid sarcoma
- Myeloid proliferation of Down Syndrome.

## Acute Myeloid Leukemia Treatment Algorithm





Risk stratification has a bearing on management of the patient and time of referral for transplant. Low risk patients can be managed with chemotherapy unless they do not achieve remission in first induction. High risk patients are preferentially referred for transplant on achieving remission post first induction (CR1).

**Treatment recommendations for patients < 60y OR select patients ≤ 75y (good performance status, minimal/no co-morbidities);**

Induction therapy: with a combination of cytarabine and anthracycline. Do a bone marrow aspirate reassessment at Day 21.

Consolidation: Assess the risk stratification and remission status to decide on management:

|                               |   |
|-------------------------------|---|
| Good risk patient             | High-dose cytarabine IV on days 1, 3, and 5 for 2-3 cycles.   |
| Standard or intermediate risk | High-dose cytarabine IV on days 1, 3, and 5 for 4 cycles OR allogeneic stem cell transplantation  |
| Adverse risk                  | Allogeneic stem cell transplantation OR Clinical trial OR High-dose cytarabine IV every 12h on days 1, 3, and 5; if clinical trial or transplant not available. |

*\*\* Patients receiving HiDAC have a high risk for cerebellar toxicity. Stop if you notice any of these signs: nystagmus, slurred speech.*

*\*\* Saline or steroid eye drops should be administered to both eyes four times daily until 24hours after cytarabine.*

**Treatment recommendations for patients ≥ 60yrs: There is no standard therapy for this patient population; a clinical trial is preferred, recommended**

|   |
|---|
| Azacytidine Iv/sc For 7d Every 4-5wk OR Decitabine IV over 1 hr daily 5-10days every 4 wks.   |
| Low-dose cytarabine for 10d every 4weeks  |
| In patients with a high WBC count (especially > 30,000) who are unlikely to respond to low-intensity therapy, consider therapies as in younger patients (i.e.5 days of Cytarabine and 2 days of anthracycline (5+2); however, tolerance and response may be poor. |
| Best supportive care with transfusion and infection management.   |

*It is important to note that despite these being low intensity treatments, best supportive care is still crucial.*

### Treatment recommendations for relapsed or refractory disease;

- Response rates depend on duration of first remission
- Patients in complete remission (CR) longer than 2y have a 60% chance of responding to front-line regimens
- Patients in CR 1-2y have a 40% chance of responding to front-line regimens; clinical trials are preferred
- Patients in CR less than 1y are unlikely to respond to front-line regimens and should be referred for clinical trials
- The prognosis for patients beyond first salvage is very poor.

Discuss with family about need for transplant.

HLA typing to identify donor should be discussed and process started.

FLAG-IDA (fludarabine, cytarabine, idarubicin, and filgrastim)

HiDAC with anthracycline

REFER FOR TRANSPLANT once patient goes into remission.

### Role of Radiotherapy

Patients who present with isolated extramedullary disease (myeloid sarcoma) should be treated with systemic therapy and radiation therapy used for residual disease. In a small group of patients where the extramedullary disease is causing nerve compression, a small dose of radiotherapy may be considered to reduce the disease burden.

#### 7.1.2.1 Acute Pro-myelocytic Leukaemia

**Acute Pro-Myelocytic Leukemia (APML)** is relatively rare and comprises about 7% to 8% of adult AML. It represents a medical emergency with a high rate of early mortality, often due to hemorrhage from a characteristic coagulopathy. Clinician needs to have a high index of suspicion. It is treated differently from AML with induction using a combination of all trans retinoic acid (ATRA) and anthracyclines (such as daunorubicin). Arsenic trioxide is shown to have superior outcomes for low to intermediate disease. Maintenance therapy is part of standard of care and may go up to 24 months.

## Treatment Protocols for Acute Promyelocytic Leukaemia

| TREATMENT regimen  | INDUCTION   | CONSOLIDATION   |
|--|---|---|
| <b>North American Intergroup Study C9710 regimen</b><br><br><b>OR</b><br><br><b>European APL regimen</b>   | ATRA and Arsenic Trioxide starting on Day 1 and/or Daunorubicin and /or Cytarabine                                | <u>First cycle:</u> Daunorubicin plus Cytarabine<br><br><u>Second cycle:</u> Daunorubicin plus Cytarabine plus IT chemotherapy<br><br>ATRA administered concurrently with cycles above (especially for intermediate- and high-risk patients)                        |
| <b>PETHEMA regimen</b>   | ATRA (started on day 1)<br><br><i>plus</i> Idarubicin   | <u>First cycle:</u> Idarubicin on days 1-4<br><br><u>Second cycle:</u> Mitoxantrone on days 1-3<br><br><u>Third cycle:</u> Idarubicin bolus (1 dose)<br><br>ATRA administered concurrently with cycles above. (especially for intermediate- and high-risk patients) |
| <b>APML .....</b><br><br><b>*Low-intermediate risk</b><br><br><b>*Good ECOG</b><br><br><b>*Frail and elderly</b><br><br><b>*If patient unsuitable for anthracycline.</b> | ATRA upto CR or until 60 days.<br><br><i>plus</i><br><br>Arsenic trioxide first 5 doses then weekly in weeks 2-8. | Arsenic trioxide for 5days every other month for 4 cycles<br><br><i>plus</i><br><br>ATRA PO in 2 divided doses for 2weeks per month for 7 cycles  |

\*Consolidation regimen is dependent on risk with high risk patients having Cytarabine as part of their regimen.

\*Monitor coagulation parameters daily until coagulopathy is corrected by administration of prophylactic fresh frozen plasma and platelets.

\*Arsenic trioxide: monitor electrolytes (maintain  $K > 4.0 \text{ mmol/l}$  and  $Mg > 1.8 \text{ mmol/l}$ ) and monitor for QTc prolongation.

\*Patient should have re-assessment marrow at 30days which should include molecular testing.



## Response criteria for Leukemias

- Complete remission (CR): bone marrow blasts < 5% in aspirate with spicules, no evidence of extramedullary disease, transfusion independence, PCR negative, absolute neutrophil count (ANC) > 1000/ $\mu$ L with platelet count > 100,000/ $\mu$ L
- CR with incomplete blood count recovery (CRi) or incomplete platelet count recovery (CRp): CR plus persistence of cytopenia (eg, underlying myelodysplastic syndrome [MDS] in the elderly)
- Partial remission (PR) or treatment failure: 5-25% blasts in bone marrow or 50% decrease in blasts and normalization of blood counts.

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## 7.2 Chronic Leukaemias

### 7.2.1 Chronic Lymphocytic Leukemia (CLL) /Small Lymphocytic Lymphoma (SLL)

#### Introduction

A monoclonal disorder characterized by a progressive accumulation of functionally incompetent lymphocytes. CLL is the most common leukemia globally especially 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.

#### Symptoms to look out for:

- Recurrent infections
- Bleeding or easy bruisability
- Unexplained weight loss
- Drenching night sweats
- Persistent fever
- Waxing and waning lymph node

#### Clinical signs to look out for in a full clinical examination:

- Pallor (anaemia)
- Lymphadenopathy
- Splenomegaly
- Hepatomegaly
- Bruising (purpura)

#### Laboratory Evaluation

1. Full blood count (FBC), with differential count and peripheral blood film examination  
*The diagnosis of CLL is established by the presence in the peripheral blood of >5000 monoclonal lymphocytes/l for the duration of at least 3 months.*  
Patients with cytopenias i.e. haemoglobin < 11g%, platelets <100,000 and progressive splenomegaly have more aggressive disease and will require urgent referral for treatment.
2. Bone Marrow Aspirate (mandatory)
3. Trepine biopsy(recommended)
4. Immunophenotyping recommended on trephine (immunohistochemistry) or blood (flow cytometry- to confirm clonality of circulating B lymphocytes and distinguish it from other lymphoid proliferations that can present with leukemic phase such as mantle lymphoma)
5. Ancillary tests: Cytogenetics and FISH where available for risk stratification.
6. Pre-treatment investigations: LFTS, U/E/Cr, Uric acid, LDH, ALP, HBV, HCV, HIV.

## Imaging

Ideally a CT scan of chest and Abdomen is recommended but if not available then do a Chest XR and Abdominopelvic ultrasound especially in SLL.

## Treatment

This differs based on stage, age and cytogenetics and should be provided ONLY by oncologists in tertiary facilities with good supportive care services and resuscitation facilities. Start prophylaxis for tumor lysis syndrome in patients with high tumor burden, infectious disease prophylaxis and blood transfusions as necessary. Treatment is only indicated in advanced and symptomatic disease. The only curative treatment is allogeneic stem cell transplant.

**Table 7. 1: Modified Rai Staging & Classification**

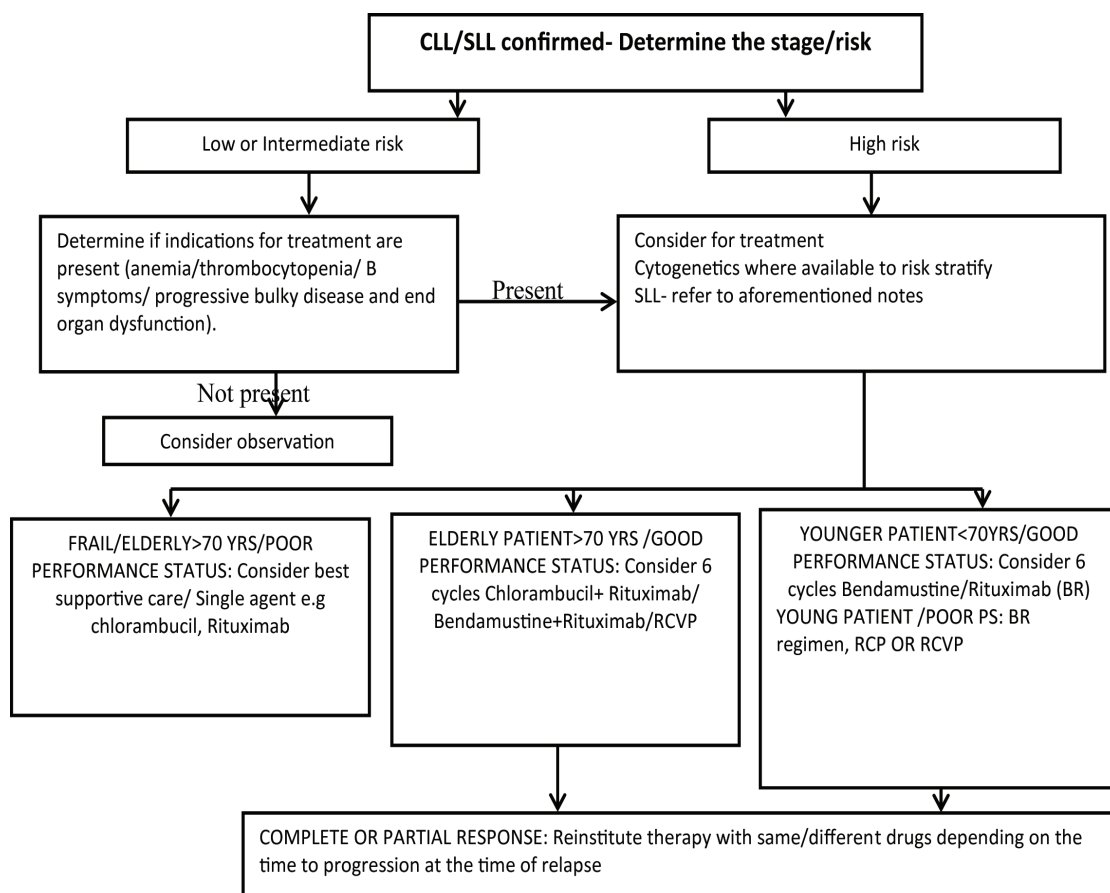
| Risk Classification | Rai Stage | Features   | Consideration   |
|---------------------|-----------|--|---|
| Low risk            | 0         | Peripheral blood lymphocyte count $> 5.0 \times 10^9$ /L. Bone marrow, if done, contains $> 30\%$ lymphocytes* | Observe   |
| Intermediate risk   | 1         | Stage 0 + lymphadenopathy  | Observe if no indications, start treatment if there are indications             |
|                     | 2         | Stage 0 + hepatomegaly and splenomegaly  |   |
| High risk           | 3         | Stage 0 + anemia (Hgb $< 110$ g/L)   | Therapies started based on the individual patient's age and performance status. |
|                     | 4         | Stage 0 + thrombocytopenia (Platelets $< 100 \times 10^9$ /L).   |   |

The other staging criteria is the Binet system.

### **Special Considerations for Treatment**

- For relapse of disease that occurs more than 3 years after initial treatment, re-treat with first-line therapy.
- Loco regional radiation therapy is appropriate for patients with Ann Arbor stage I small lymphocytic lymphoma; i.e. CLL largely limited to lymph nodes.

## Treatment Algorithm for CLL/SLL



### Examples of chemotherapy regimens include:

1. Bendamustine-based therapy: BR regimen (bendamustine and rituximab). The regimen is given every 28 d for 6 cycles.
2. Fludarabine-based therapy: FCR (fludarabine, cyclophosphamide, and rituximab) and FR (fludarabine and rituximab). Both regimens are given every 28 d, along with infectious disease (ID) prophylaxis.
3. Chlorambucil with or without prednisone.
4. Cyclophosphamide and prednisone, with or without rituximab.
5. Reduced-dose FCR or Alemtuzumab: three times weekly on alternate days, for a maximum of 12 weeks.
6. The PCR regimen (Cyclophosphamide, Pentostatin and Rituximab) is given every 21 d, with growth factor support and antibiotic prophylaxis, for six cycles.

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## 7.2.2 Chronic Myeloid Leukemia (CML)

### Introduction

A myeloproliferative neoplasm arising from a primitive hematopoietic stem cell in the bone marrow that involves all three myeloid lineages: granulocytes, erythroid cells, and megakaryocytes. It is defined by the presence of the BCR/ABL1 fusion gene, which results from the reciprocal translocation t (9; 22) (q34; q11.2). The Philadelphia chromosome refers to the abnormally short chromosome 22 in CML.

CML occurs in three phases: Chronic/Stable phase (most patients are first diagnosed here), accelerated phase and blast transformation/crisis (acute myeloid or lymphoid leukemia).

CML has an annual global incidence of 1:1.5 per 100000 and comprises 10-15% of all the leukemias with most cases occurring sporadically. The M: F ratio is 1.4:1 and median age of occurrence is about 50years. In Kenya, Abinya et al found an M: F ratio of 1.26:1 with median age of 44years.

### Clinical Evaluation

The most common presenting symptoms include:

- Fatigue (usually related to mild to moderate anemia)
- Weight loss
- Left upper quadrant fullness/pain
- Early satiety from splenomegaly.

### Other presentations that are less common include:

- Priapism caused by marked leukocytosis +/- thrombocytosis
- Gouty arthritis due to increased uric acid levels
- Bleeding caused by platelet dysfunction or low platelets
- Deafness
- Upper git ulceration and bleeding due to histamine release associated with basophilia.
- Hyperviscosity symptoms can occur due to sludging of cells in pulmonary or cerebral vessels resulting in confusion, drowsiness or dyspnea.
- In accelerated phase, constitutional symptoms of fever, sweat and weight loss are present.
- Bleeding can occur especially in accelerated and blast phase.

### Physical examination

1. Pallor.
2. Splenomegaly: record spleen size by palpation (cm below costal margin).
3. Hepatomegaly.
4. Lymphadenopathy and skin infiltration are rare.

## Laboratory Evaluation

1. Full blood count with differential count.
2. Peripheral blood smear: demonstrate full maturation spectrum of myeloid series.
3. Bone marrow aspirate for characterization of phase of CML.
4. Molecular genetic test: Quantitative reverse transcriptase –PCR for BCR-ABL1 or FISH to detect translocation t (9, 22).
5. UEC and LFTs.
6. Uric acid level.

*\*Other investigations based on clinical presentation or co-morbidities.*

## Treatment

- Imatinib Mesylate is the treatment of choice, in all newly diagnosed patients.
- Switch to second line TKI if suboptimal molecular response.

Use second line TKI based on existing co-morbidities (pre-existing vascular disease-avoid Nilotinib; lung disease/pleural effusion-avoid Dasatinib) and mutational analysis. If positive for T315I mutation switch to ponatinib. If negative, options are dasatinib, nilotinib or bosutinib.

*NB: There may be mutations that affect the other drugs therefore where possible a full mutation panel is recommended however this is more expensive.*

*Blood counts need to be monitored during treatment to avoid cytopenias and loss of hematological response.*

Regular molecular monitoring once a year is acceptable or earlier in cases of loss of hematological or clinical response.

**Role of hydroxyurea:** has no effect in treating the underlying molecular abnormality in CML but is useful in controlling high white cell counts and most patients are indicated on this and allopurinol as they await transition to a Tyrosine Kinase Inhibitor.

**Table 7. 2: Assessment of response criteria**

| Definition                          | Response criteria   |
|-------------------------------------|---|
| Complete Hematologic Response (CHR) | Complete normalization of peripheral blood white count ( $< 10 \times 10^9$ ), and platelet count ( $< 450 \times 10^9$ ) sustained for at least 4 weeks  |
| Major Cytogenetic Response (MCR)    | $< 35\%$ Philadelphia positive bone marrow metaphases by conventional cytogenetic analysis.<br>This is equivalent to a 1 log reduction in BCR/ABL transcripts from baseline as measured by quantitative PCR ( $<10\%$ ) |
| Complete Cytogenetic Response (CCR) | No Philadelphia positive bone marrow metaphases by conventional cytogenetic analysis.<br>This is equivalent to a 2 log reduction in BCR/ABL transcripts from baseline as measured by quantitative PCR (1%)              |
| Major Molecular Response (MMR)      | Greater than or equal to a 3 log reduction in BCR/ABL fusion transcripts compared to baseline by PCR analysis (0.1%)  |
| Deep Molecular Response (CMR)       | 4 log reduction in BCR-ABL ( $<0.01\%$ )  |



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## 7.3 Lymphomas

These are cancers of lymphocytes that represent clonal proliferation derived from various lymphocytic cell-lines, mainly B cells and also T-cells or NK cells at different stages of differentiation and/or activation. They are broadly classified as Hodgkin's Lymphoma (HL) and Non-Hodgkin's Lymphoma (NHL) with the latter occurring more commonly. Both are more common in males.

### Clinical Evaluation

History: Symptoms to look out for:

- Painless progressive lymph node enlargement
- B- symptoms:
  - Unexplained Weight loss >10% in 6 months
  - Drenching night sweats
  - Persistent fever >38°C
- Others: HL- pruritus, alcohol-induced pain on involved nodes

Examination: Clinical signs to assess for in a full physical examination:

- Pallor (anaemia)
- Lymphadenopathy (Map all groups of lymph nodes including the Waldeyers ring), size
- Hepatosplenomegaly
- Ascites
- Extranodal sites- testis, CNS

*Consider urgent referral in adults presenting with unexplained lymphadenopathy or Splenomegaly or associated symptoms particularly; Fever, Night sweats, Shortness of breath, Pruritus, Weight loss or Alcohol-induced lymph node pain.*



## Diagnosis

1. Biopsy: a lymph node excisional biopsy preferred.  
*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, and referred immediately for histopathological evaluation in order to reduce diagnostic delay.*  
Fine needle aspirations (FNA) are inappropriate for a reliable diagnosis and may only be done as a screening test.  
Core biopsies should be performed in case of deep-seated nodes e.g. retroperitoneal or intra-abdominal sites.
2. Immunohistochemistry to subtype the lymphoma.
3. Molecular Studies: are optional but may be helpful where morphology and immunohistochemistry are inconclusive.

## Staging and Risk Assessment

### Tests for Evaluation of Organ Function/Staging

1. Full blood count
2. Erythrocyte sedimentation rate (ESR) for Hodgkin's lymphoma.
3. Bone marrow aspirate and trephine is strongly recommended for staging.
4. Biochemistry: LFTs, RFTs, LDH, urate, ALP and liver enzymes.
5. Thyroid-stimulating hormone (TSH) recommended for patients with Hodgkin's lymphoma.
6. Viral serology for HIV (mandatory), Hepatitis B and Hepatitis C (strongly recommended).
7. Serum Protein Electrophoresis should be considered.
8. 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.
9. Fertility team review, counselling and preservation measures.

## Imaging

1. CT-Scan of chest, abdomen and pelvis is strongly recommended.
2. If CT-scan is unavailable, then CXR and abdomino-pelvic ultrasound should be done.
3. MRI is the investigation of choice for suspected CNS disease.
4. PET-CT scan where available for the high grade lymphomas.



### 7.3.1 Hodgkins Lymphoma

#### Introduction

It comprises about 1.7% of all cancers in Kenya with about 420 new cases and approximately 200 deaths. It has a worldwide bi-modal age distribution with peak 15-30 and 50-70 years. However, in Kenya a single peak at about 17 years has been observed. The male to female ratio is 4:3 worldwide although in Kenya, it is about 3:1.

#### Risk factors

There are no clear risk factors for HL, but several associations have been observed such as:

- EBV infection associated mainly with mixed cellularity type (30%)
- HIV infection
- Woodworking, farming
- Chemical exposure mostly from agricultural chemicals
- Ionizing radiation
- Genetic predisposition: First degree relatives have 5-fold increased risk for HL
- High socio-economic status
- Men are affected more than women
- Whites affected more than blacks and Asians

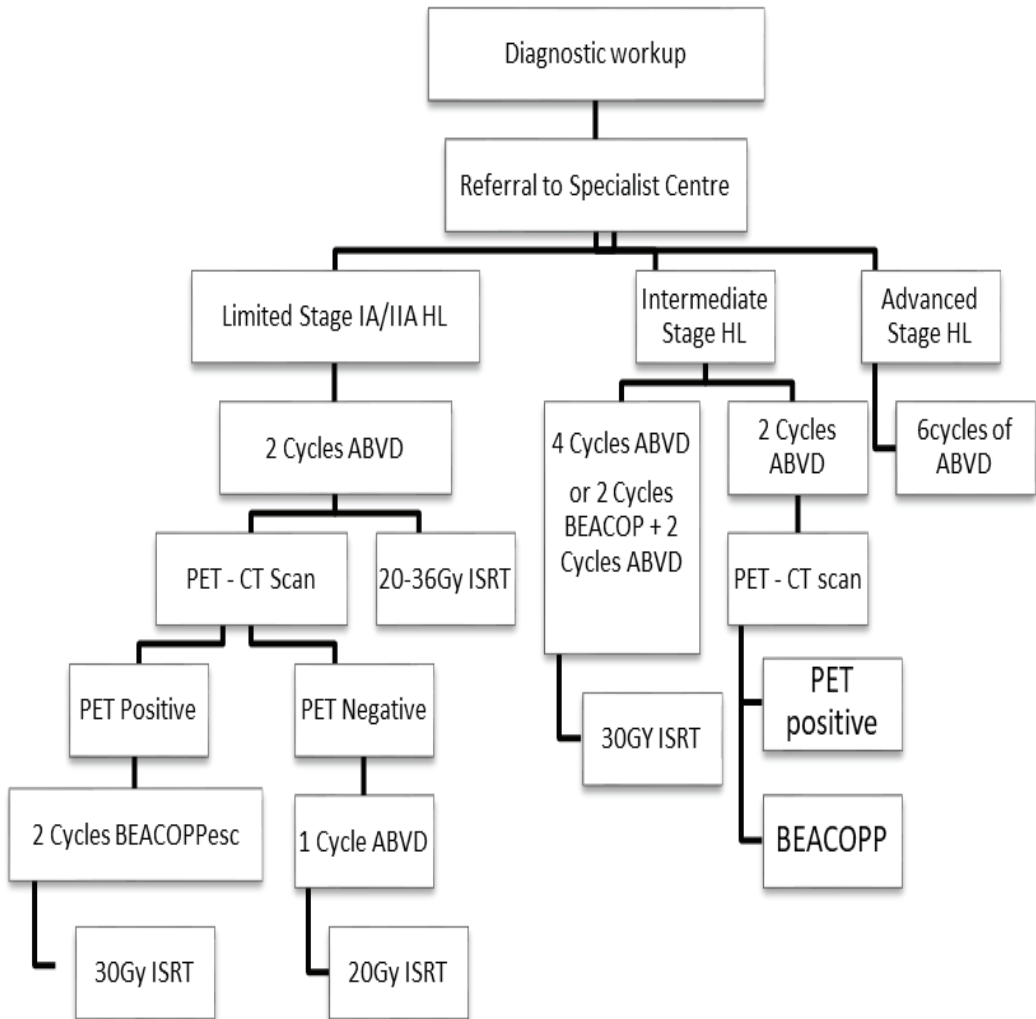
**Table 7. 3: Diagnosis and Work-up**

|                                 |   |
|---------------------------------|---|
| Diagnosis                       | Confirmatory workup: excisional biopsy/core biopsy of the lymph node. Diagnosis rests on identification of RS cell or its variants with IHC demonstrating positivity for CD15,30 and possibly EBV markers for classical HL and CD20, CD45, EMA for nodular lymphocyte predominant HL    |
| Staging and risk stratification | Medical history and physical examination<br>X-ray of the chest<br><b>Contrast-enhanced CT scan of the neck, chest abdomen and pelvis</b><br>Whole body FDG PET CT scan<br>TBC, blood chemistry, ESR, LDH, <b>BMA &amp; Trepine not necessary with PET</b><br>HBV, HCV and HIV screening |
| Pre-treatment examinations      | ECG, Echocardiography<br>Pulmonary function test, Reproductive counselling (in patients of reproductive age)<br>Serum pregnancy test (female of reproductive age)   |

**Table 7. 4: Ann Arbor Staging for Hodgkin’s Lymphoma**

| Ann Arbor Staging (1971)  |  |
|---|--|
| STAGE   | DESCRIPTION  |
| I   | Involvement of a single lymph node region or a single extralymphatic organ or site (IE)  |
| II  | Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site (IIE)                             |
| III   | Involvement of lymph node regions on both sides of the diaphragm (III) or localized involvement of an extralymphatic organ or site (IIIE) or spleen (IIIS) or both (IIISE)         |
| IV  | Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement. Bone marrow and liver involvement are always stage IV. |
| ☒ Identification of the presence or absence of symptoms should be noted with each stage designation: A, asymptomatic; B, fever, sweats, weight loss more than 10% of body weight. |  |

## Treatment Algorithm for Hodgkins Lymphoma



*Metabolic response reflected by FDG-PET has emerged as one of the most important prognostic factors for survival, and it forms the rationale for response-adapted therapy as shown in the treatment algorithm.*



### Early Stage Hodgkins Lymphoma (Stage 1A/11A)

Treatment regimens that combine chemotherapy and involved site radiation therapy (ISRT) are recommended.

- ABVD regimen (Adriamycin, bleomycin, vinblastine, and dacarbazine). Patients with fewer than two disease sites can be safely treated with two cycles of ABVD followed by ISRT. Alternative is the Stanford V regimen-doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone given in a 28-day cycle;
- PET positive: Escalated BEACOPP (Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) given in a 21-day cycle followed by ISRT.

*Poor prognostic factors for early stage Hodgkin's Lymphoma include: Age >50, large mediastinal mass/bulky, ESR  $\geq$ 50 without B symptoms, ESR  $\geq$ 30 with B symptoms and  $\geq$ 4 nodal sites involved.*

### Stages III-IV Hodgkins Lymphoma

Systemic chemotherapy with six cycles of ABVD (first line) or escalated BEACOPP regimen.

Consider ISRT following any of the above chemotherapy regimens for patients with bulky disease or those exhibiting a slow response to therapy by functional imaging (PET scan).

### Relapsed/refractory Hodgkins Lymphoma

The treatment approach is influenced by the time to relapse and the nature of the initial treatment, but generally consists of a multistep process of salvage chemotherapy, hematopoietic stem cell mobilization, high-dose chemotherapy with autologous stem cell rescue (HDC-ASCT). This can result into cure for approximately 50% of patients.

The best timing for HDC-ASCT is after the first relapse.

Regimens for patients eligible for HDC-ASCT (treatment goal = cure):

- The goal of salvage regimens is to achieve maximum tumor burden cytoreduction in preparation for HDC-ASCT
  - o ICE regimen (ifosfamide, carboplatin, and etoposide)
  - o DHAP regimen (high-dose cytarabine [Ara-C], cisplatin, and dexamethasone)
  - o ESHAP regimen (etoposide, methylprednisolone, Ara-C, and cisplatin)
- Regimens for patients who are not eligible for HDC-ASCT or patients who have elapsed/refractory disease after HDC-ASCT:
  - o Brentuximab Vedotin
  - o C-MOPP (cyclophosphamide, vincristine, procarbazine, prednisone):
  - o ESHAP regimen (etoposide, methylprednisolone, Ara-C, and cisplatin)
  - o GCD (Gemcitabine, carboplatin, dexamethasone):
  - o GVD (gemcitabine, vinorelbine, liposomal doxorubicin):
  - o IGEV (ifosfamide, gemcitabine, vinorelbine)
  - o Mini-BEAM (carmustine, cytarabine, etoposide, melphalan)
  - o MINE (etoposide, ifosfamide, mesna, mitoxantrone)

## Treatment of Nodular Lymphocyte Predominant Hodgkin's Lymphoma

**Early-stage disease:** either radiation alone or abbreviated chemotherapy plus radiation. Patients with stage IA disease with full excision may be observed. The choice of chemotherapy is controversial; most groups recommend ABVD for two to four cycles plus radiation, but retrospective data suggest that alkylating agents are more effective, and CHOP or CVP can be used. Survival for early-stage disease is excellent and approximates 90% with at least 10 years of follow-up.

**Advanced-stage disease:** six cycles of ABVD, CHOP, or CVP and since NLPHL expresses CD20, the addition of rituximab to management strategies has been evaluated with a response rate of 94 to 100%. The major risk in NLPHL survivors appears to be transformation to DLBCL (or T-cell rich diffuse large B-cell lymphoma, [TCR-DLBCL]), which should be treated as any transformed aggressive B-cell lymphomas.

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## **7.3.2 NON- HODGKIN'S LYMPHOMA**

### **7.3.2.1 High Grade B cell Lymphomas**

#### **i. Diffuse Large B Cell Lymphoma**

Diffuse large B-cell lymphoma (DLBCL) constitutes 30%–60% of lymphoma series worldwide including Kenya. Significant risk factors for the development of the disease include underlying immune deficiency, such as HIV-related or in the post-solid organ transplant setting.

#### **Clinical features**

- Rapidly enlarging tumor mass at single or multiple nodal or extranodal sites.
- Roughly 30–40% patients present with Stage I or Stage II disease.
- Constitutional symptoms which are often dictated by the organ or anatomical site involvement.

#### **Investigations and diagnosis**

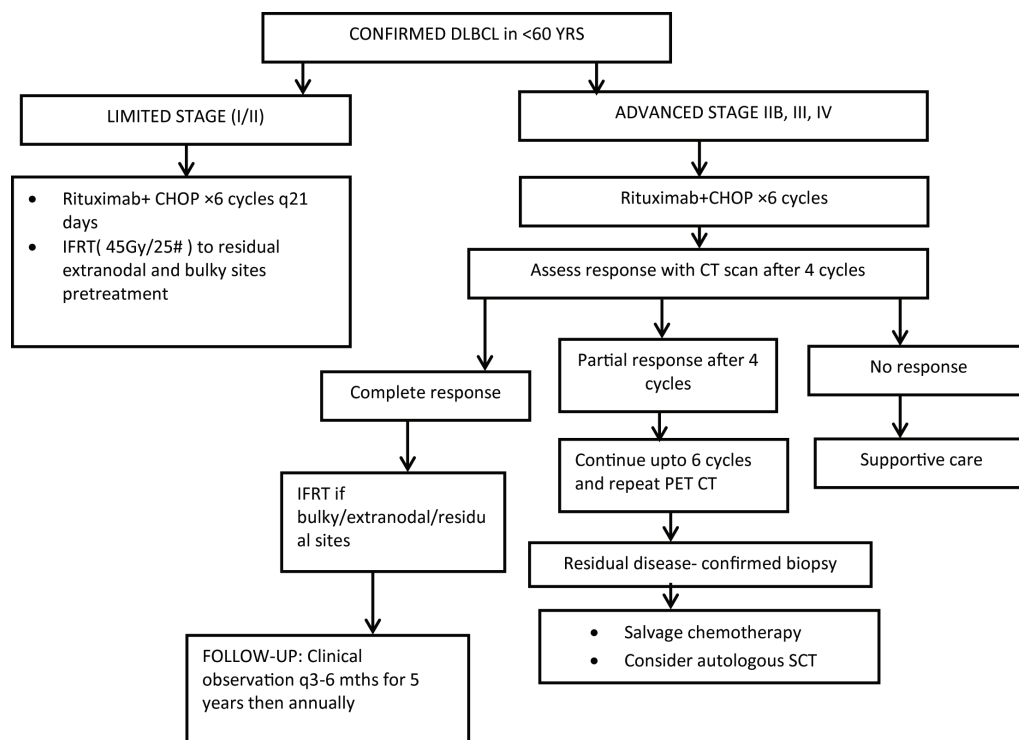
- The use of PET/CT is more accurate than CT alone in staging DLBCL;
- MRI or CT scan of the brain, spine, orbits and sinuses should be performed if central nervous system (CNS) or craniofacial disease is present or suspected.

**Staging is done according to the Ann Arbor Staging system.**

#### **Treatment**

- The standard therapy is Rituximab plus CHOP 6-8 cycles.
- There is a role for radiotherapy in DLBCL, in early stage disease (used alone) or if there bulky disease (radiotherapy is adjuvant to standard chemotherapy).
- CNS disease is best treated with high doses of chemotherapy.

## Treatment Algorithm for DLBCL



*There is emerging evidence that an interim PET does not alter outcome and that PET should only be done at the end of treatment.*

### Treatment considerations in specific cases:

- In elderly or frail where no overt co-morbid illness exists consideration of dose attenuated R-CHOP (mini R-CHOP) should be considered.
- ISRT should be considered at the end of chemotherapy to sites of initial bulk ( $\geq 7.5$ cm).
- Primary G-CSF prophylaxis is recommended for patients aged  $>65$  years, frail patients and those with significant co-morbidities.

### Relapsed disease

The prognosis of patients with relapsed disease after R-CHOP chemo-immunotherapy is poor, especially relapses observed within 1 year of treatment. The aim of treatment should be to: induce objective clinical response ( $>50\%$  reduction in disease bulk and ideally achievement of CMR, associated with superior outcome post-autoSCT) with salvage chemo-immunotherapy regimens, and in responding patients proceed to consolidation with high-dose chemotherapy and autologous stem cell transplant.



For eligible patients, salvage platinum-based chemotherapy followed by high-dose chemotherapy and autologous stem cell transplant.

Salvage regimens include:

- **R-GDP:** Rituximab, Gemcitabine, Dexamethasone, Cisplatin
- **R-DHAP:** Rituximab, Dexamethasone, Cytarabine, Cisplatin
- **R-ESHAP:** Rituximab, Etoposide, Cytarabine, Cisplatin, Methylprednisolone
- **R-ICE:** Rituximab, Ifosfamide, Epirubicin, Etoposide
- **R-IVE:** Rituximab, Ifosfamide, Epirubicin, Etoposide
- **R-GemP:** Rituximab, Gemcitabine, Cisplatin, Methylprednisolone
- **R-Gem-Ox:** Rituximab, Gemcitabine, Oxaliplatin
- **Elderly patients:** consider Bendamustine plus Rituximab.

## ii. Primary CNS Lymphoma

The usual histology of PCNSL is DLBCL (90% of cases). The treatment of primary DLBCL of the CNS includes remission induction with regimens that contain high-dose methotrexate every 2–3 weeks. The addition of cytarabine and thiopeta improve remission rate and outcome.

Chemotherapy treatment should be given in conjunction with rituximab as the combination has been shown to further improve response rates and survival.

### 7.3.2.2 Low Grade B cell Lymphomas

#### i. Follicular lymphoma

Follicular lymphoma (FL) is the most common form of indolent lymphoma in the Western World and second most common form of Non-Hodgkin's lymphoma presenting in 5/100,000 population/year with a median age of onset of around 60 years.

#### Diagnosis

A diagnosis can typically be made through histological examination of adequate tissue samples stained with haematoxylin and eosin (H&E) supported by immuno-staining for: CD20+, CD10+, Bcl-2+, CD5-, CD3- (+/- Bcl-6, cyclin D1, CD43,  $\kappa$  and  $\lambda$  light chains).

Staging should be performed with a CT scan of neck, chest, abdomen and pelvis. PET/CT is a valid alternative to CT in staging of FL.

#### Follicular lymphoma, grades 1, 2 and 3a

##### First line management


##### a) Limited stage disease (Stage 1A +/- 2A non-bulky)

- FL is highly radiosensitive. Limited stage 1 or 2 disease and no adverse factors may be considered for local radiotherapy utilizing 24Gy over 12 fractions with curative potential.
- A lower radiation dose of 4Gy split over 2 fractions may be appropriate in cases where a palliative approach is pursued or radiation toxicity requires particular consideration.

##### b) Advanced stage disease

There is no overall survival benefit to initiation of anti-lymphoma therapy in advanced





stage disease based solely on the presence of FL in the absence of other adverse factors. Therefore one must determine whether treatment is indicated where indications for treatment include:

- rapidly progressive disease
- B symptoms
- pruritus
- vital organ compression/compromise
- significant bone marrow infiltration/haematopoietic suppression
- bone lesions
- renal infiltration
- ascites
- pleural effusion
- splenomegaly
- bulky disease including multiple (>3LNs each >3cm in diameter or single sites >7cm in diameter).

Be aware that patients with bulky disease are likely to have a short duration to progression.

### **Systemic treatment regimens**

Combination immuno-chemotherapy (rituximab + chemotherapy).

#### **Front-line therapy:**

- R-CHOP regimen should be considered for FL that demonstrates clinically aggressive behaviour
- Rituximab, cyclophosphamide, vincristine, prednisolone (R-CVP) in non-aggressive disease
- Bendamustine + Rituximab
- Rituximab-Chlorambucil for frail patients

#### **Consolidation of response**

Maintenance: Rituximab given once every 3 months for 2 years is recommended if a complete or partial response is received following first-line systemic therapy.

#### **Second (and subsequent) line management**

At progression or relapse, biopsy of index lesions is strongly recommended particularly to assess the possibility of disease transformation. The patient's preference, initial response duration, evidence of aggressive disease transformation, previous treatment regimens, toxicities, patient fitness and co-morbidities and the stage of disease helps guide management.

- Less fit patients with limited stage disease can have a palliative approach to treatment with local radiotherapy as 4Gy split in 2 fractions.
- In advanced disease, particularly if low bulk and in absence of other indications for treatment, selected patients may again be appropriate for watch and wait with close disease monitoring.



- If systemic treatment is indicated at relapse/progression following initial management consider whether a patient is a candidate for consolidation of response to second line treatment by either high-dose chemotherapy with autologous haematopoietic stem cell transplantation (HDT + Auto-HSCT) or allogeneic haematopoietic stem cell transplantation (Allo-HSCT).
- Fit patients who demonstrate a sufficient response to second line therapy should be considered for auto-HSCT
- Rarely, particularly in young, otherwise fit patients with rapidly progressive/early refractory disease then allo-HSCT should be considered.

### **Systemic second-line treatment regimens**

- An alternative regimen to the initial one used should be considered, especially if remission duration was less than 12-24 months.
- Re-treatment with a previous regimen may be appropriate in selected cases who experienced good response duration and lack of significant toxicity with appropriate consideration of fitness, co-morbidities and patient preference.
- In addition to R-CHOP, R-CVP and R-Bendamustine mentioned above, options include: Fludarabine, Cyclophosphamide, Rituximab (FCR), mitoxantrone with Rituximab(R-FM), and cyclophosphamide + mitoxantrone (R-FCM). However, these may have significant toxicity and full courses are not recommended.
- Rituximab monotherapy or rituximab + chlorambucil may be appropriate in less fit cases.

### **Consolidation of response**

Maintenance rituximab given once every 3 months for 2 years if a complete or partial response is received following second-line systemic therapy.

### **Follicular Lymphoma, Grade 3b**

This should be managed as per diffuse large B cell lymphoma (DLBCL) guidelines.

### **Transformation**

FL has a risk of undergoing histological high-grade disease transformation to aggressive lymphoma (typically DLBCL) at a rate of around 3% of cases per year. If transformation is suspected, biopsy is recommended. Clinical indicators suggestive of possible transformation include:

- Sudden rise in LDH to  $\geq$ twice upper limit of normal
- Rapid discordant localised nodal growth (detected clinically or by imaging)
- New involvement of unusual extra-nodal sites (e.g. liver, bone, muscle, brain)
- New B symptoms
- New hypercalcaemia.

Transformation to DLBCL should be managed as per de novo DLBCL with the anthracycline containing R-CHOP regimen and consideration of consolidation of response by HDT + Auto-HSCT in patients fit enough for this approach.

Alternative regimens to R-CHOP (such as rituximab, dexamethasone, high-dose cytarabine, cisplatin; R-DHAP) can be considered in patients fit enough for this approach.

### 7.3.2.3 Peripheral T-Cell Lymphomas and Leukaemias

Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of rare malignancies accounting for approximately 10–12% of all lymphoid neoplasms. Most have an aggressive clinical behaviour and, apart from anaplastic large cell lymphoma (ALCL), a poor response to conventional chemotherapy with only 30% survival at 3 years.

#### Clinical presentation

- Palpable lymphadenopathy
- Systemic symptoms - fever, weight loss, night sweats, body weakness among others
- Presentation at extranodal sites is common

#### Investigation

- A tissue biopsy supplemented by detailed immunohistochemistry, flow cytometry, cytogenetics and molecular genetics, where available is essential for diagnosis.
- In addition, PTCL patients should have EBV PCR and Strongyloides testing where ATLL is suspected.
- Staging is according to the modified Ann Arbor staging, after a CT chest, neck, abdomen pelvis or PET CT is performed.

#### Treatment

Patients often have very aggressive disease and treatment delays should be avoided (use of GCSF may be indicated). Infection risk is high because of immunosuppression. Urgently refer all suspected cases to specialist centres for further work-up and treatment.

## 7.4 Multiple Myeloma

#### Introduction

A plasma cell malignancy characterized by abnormal proliferation of clonal plasma cells. It can either be secretory (majority, secretes an abnormal serum or urine immunoglobulin referred to as M protein or paraprotein in majority of cases) or non-secretory (2-5%, fails to produce abnormal immunoglobulin). Patients can also present with solitary or multiple masses (plasmacytomas).

#### Epidemiology

It occurs almost exclusively in the middle-aged to elderly population all over the world with a male preponderance. Local studies have shown a lower median age of 53 to 59 years with a slight male predominance.

#### Clinical Presentation

Multiple myeloma is often manifested by complications of enhanced bone loss associated with diffuse osteopenia or lytic bone lesions, renal failure, hypercalcemia, immunosuppression or anemia.

## Signs and Symptoms

- Fatigue and generalized body weakness
- Bone pains or back pain
- Recurrent infections
- Weight loss
- Pathological fracture
- Paraplegia due to cord compression.
- Paraesthesias.
- Mass (more commonly in head)

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

- Pallor (anemia)
- Bone tenderness
- Vertebral collapse or spinal cord compression

## Diagnostic Workup

1. Total blood count with differential and peripheral blood smear.
2. Bone marrow aspirate (mandatory) and trephine (recommended) OR tissue biopsy for histology and immunohistochemistry in case of suspected plasmacytoma.
3. Serum protein electrophoresis (SPEP) and urine protein electrophoresis to establish clonality. Serum Immunofixation to identify immunoglobulin sub- type (IgG, A, D, M). Serum free light chains (SFLC) and SFLC ratio.
4. Investigations to look for end organ disease or for prognostication include: UECs, Total protein, Alkaline phosphatase, Serum calcium and albumin, B2 microglobulin and serum LDH, Albumin and the Myeloma FISH panel.
5. Viral serology for HIV is mandatory, hepatitis B and hepatitis C is strongly recommended.

## Imaging

- a) Whole body MRI
- b) Whole body low dose CT imaging without contrast.
- c) Skeletal survey (has a low sensitivity and misses early bone disease can be performed if above are not available). Chest Radiograph, anteroposterior and lateral views of cervical spine and thoraco-lumbar spine, pelvis and skull. Radiographs of other bones depending on clinical presentation.
- d) Localized imaging depending on clinical presentation (e.g MRI spine in case of suspected cord compression).
- e) Whole body PET CT scan (where available).

*\*\*If skeletal survey is negative, Whole body MRI or PET CT scan should be done to differentiate active from smouldering disease. Recommendations are MRI with contrast*

**Table 7. 4: Diagnostic Criteria as Defined by the International Myeloma Working Group (2014)**

| Monoclonal Gammopathy of undetermined significance   | Smouldering Myeloma   | Multiple Myeloma   |
|--|---|--|
| <p>Serum paraprotein &lt;30g/l</p> <p>BMA plasmacytosis of &lt;10%</p> <p>No myeloma defining events</p> <p>No evidence of B cell lymphoproliferative disease or other plasma cell dyscrasias.</p> | <p>Serum paraprotein &gt;30g/l</p> <p>Urine monoclonal protein &gt;500mg in 24hours</p> <p>BMA plasmacytosis 10-60%</p> <p>No myeloma defining events *</p> <p>No amyloidosis</p> | <p>BMA plasmacytosis &gt;10% or extramedullary plasmacytoma</p> <p>And</p> <p>Myeloma Defining Events*</p> <p>or</p> <p>Biomarkers of malignancy**</p> |

\*Myeloma defining events: hypercalcemia (corrected serum calcium >2.75mmol/l, renal insufficiency (serum creatinine >177umol/l, anemia Hb<10gm/dl, lytic bone lesions

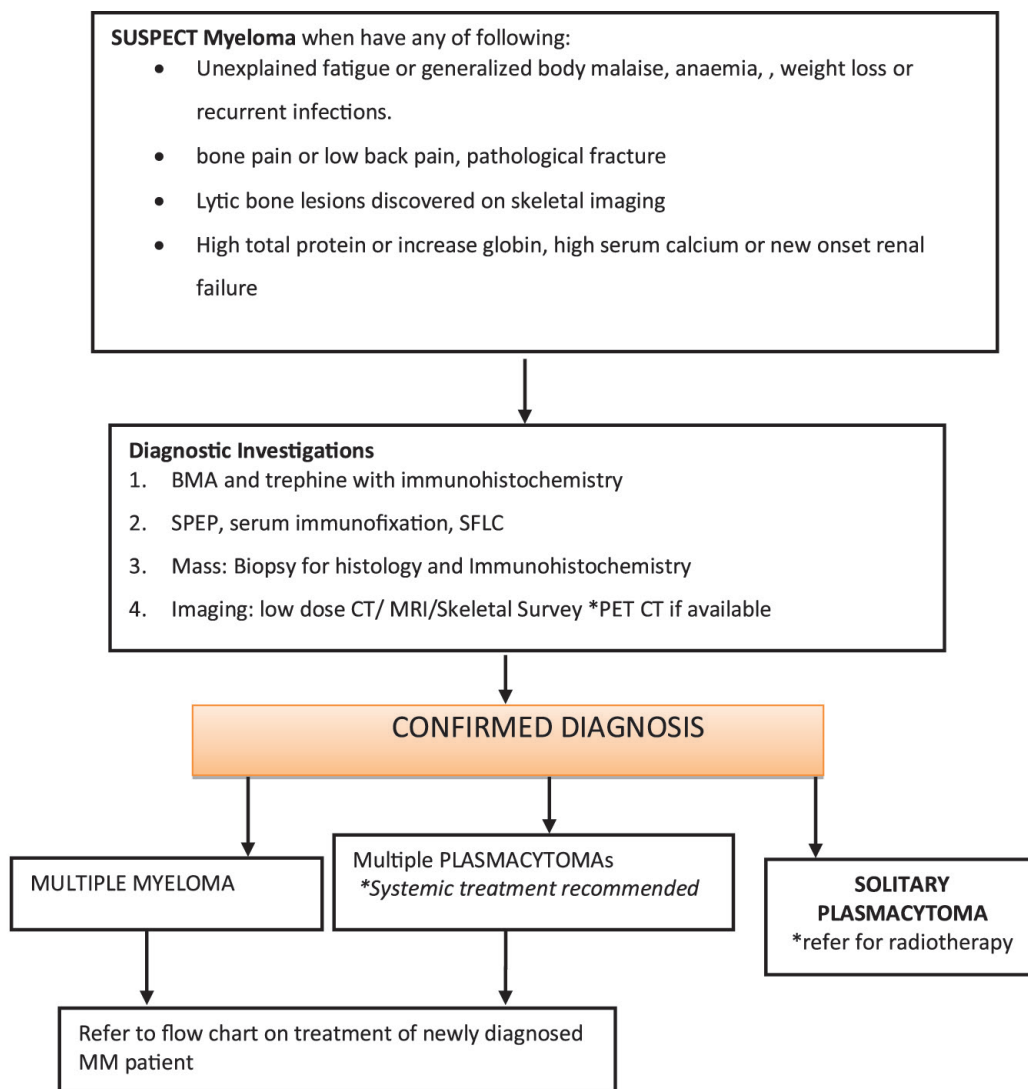
\*\*Biomarkers of malignancy: clonal BMA plasmacytosis >60%, involved to uninvolved serum free light chain ratio >100 and >1 focal lesion on MRI (>5mm).

**Table 7. 5: International Staging System Risk Stratification Model**

| B   | 2 microglobulin   | Albumin       |
|-----|---|---------------|
| I   | <3.5mg/dl   | >35g/l        |
| II  | Not I or III<br>*B2M <3.5 and low albumin <35g/l<br>*B2M 3.5- 5.5 irrespective of albumin |               |
| III | >5.5mg/dl   | Normal or low |

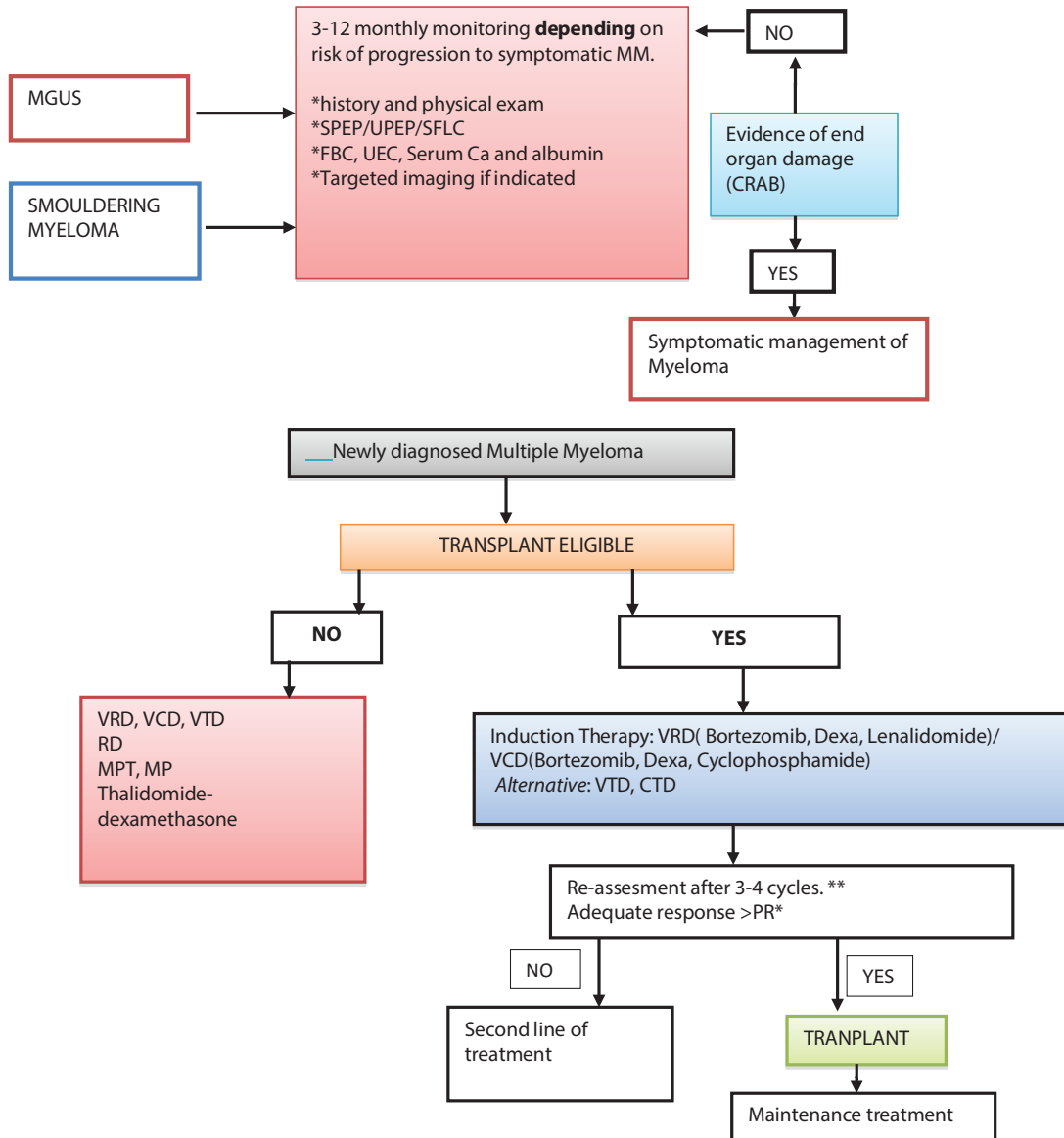
\*Revised ISS risk stratification model incorporates serum lactate dehydrogenase and chromosomal abnormalities detected by interphase Fluorescent in-Situ Hybridization (FISH) or conventional cytogenetics.<sup>7</sup>

## Diagnostic Algorithm for Multiple Myeloma



*Urgently refer all patients suspected to have myeloma or with confirmed diagnosis for specialist management.*

## Treatment Protocols for Multiple Myeloma



*\*\*Assessment needs to be individualized to the patient based on the baseline measurable disease.*



|   |
|---|
| <p><b>Transplant Eligible Regimens</b></p> <p><b>Preferred therapy regimens:</b></p> <p>Bortezomib/Lenalidomide/Dexamethasone</p> <p>Bortezomib/Cyclophosphamide/Dexamethasone</p> <p><b>Other regimens:</b></p> <p>Bortezomib/Thalidomide/Dexamethasone</p> <p>Cyclophosphamide/Thalidomide/Dexamethasone</p> <p>Bortezomib/Dexamethasone in some circumstances.</p> |
|---|

|  |
|--|
| <p><b>Transplant Ineligible</b></p> <p>Bortezomib/Lenalidomide/Dexamethasone</p> <p>Bortezomib/Cyclophosphamide/Dexamethasone</p> <p>Bortezomib/Thalidomide/Dexamethasone</p> <p>Bortezomib/Melphalan/Prednisone</p> <p>Lenalidomide/Dexamethasone</p> <p>Thalidomide-Dexamethasone</p> <p><b>Maintenance Therapy</b></p> <p>Lenalidomide</p> <p>Thalidomide</p> |
| <p><b>Relapse/ Refractory Myeloma</b></p> <p><i>Consider previous treatment and duration of response.</i></p> <p><i>&gt;6months consider primary treatment.</i></p>  |

Radiotherapy may be indicated for plasmacytomas, fractures, pain control and spinal cord compression.

**Staging**

**Table 7. 5: International Myeloma Working Group Response Criteria**

| <b>Criteria</b>     | <b>Definition</b>  |
|---------------------|--|
| CR                  | Disappearance of any soft tissue plasmacytomas and <5% plasmacytosis in BMA. |
| VGPR                | >90% reduction in measurable disease   |
| PR                  | 50% reduction in measurable disease  |
| Progressive disease | Increase in 20% from lowest confirmed response                               |



## Supportive Treatment

Concerns in the treatment of patients with multiple myeloma include renal impairment, thrombosis, infection, and skeletal events.

1. Renal impairment: Avoid use of nephrotoxic agents such as NSAIDs and IV contrast agents. The preferred regimen is Bortezomib and high-dose dexamethasone.
2. Biphosphonates, as appropriate, to decrease occurrence of skeletal-related events such as monthly Zoledronic acid or Pamidronate, provided renal function is adequate. A monthly injection for 2 years is recommended followed by reassessment.
3. Thromboprophylaxis especially for patients receiving either thalidomide or lenalidomide regimens with dexamethasone.
4. Infection prevention: vaccination for pneumococcal infections, antiviral prophylaxis for herpes infections for patients on Bortezomib (low dose Acyclovir), anti-parasitic (*Pneumocystis jiroveci* pneumonia [PCP]) and antifungal prophylaxis for patients on high-dose steroid treatment.
5. Spinal cord compression is a common complication of multiple myeloma, occurring in as many as 20% of patients at some point during the course of their illness; a high index of suspicion is the key to early diagnosis. An MRI would be needed to confirm and define extent of involvement.

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# 8

## CHAPTER EIGHT

### Kaposi's Sarcoma Treatment Protocol

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# KAPOSI'S SARCOMA TREATMENT PROTOCOL

## List of abbreviations

|      |   |
|------|---|
| cART | Combined antiretroviral therapy             |
| CXR  | Chest X-ray                                 |
| ECG  | Electrocardiography                         |
| GIT  | Gastrointestinal tract                      |
| HHV8 | Human Herpes Virus-8                        |
| KS   | Kaposi's Sarcoma                            |
| KSHV | Kaposi's Sarcoma Herpes Virus               |
| MCD  | Multicentric Castleman's Disease            |
| MTCT | Maternal To Child Transmission              |
| OI   | Opportunistic infections                    |
| PJP  | Pneumocystic Jiroveci Pneumonia(PJP), (MCD) |

## Introduction

Kaposi's Sarcoma (KS) originates from the vascular endothelium with simultaneous eruptions in several parts of the body, more commonly on the skin and oral cavity. It is the most common opportunistic malignancy associated with HIV infection. All types of KS are associated with Human Herpes Virus-8 (Kaposi's sarcoma Herpes Virus, KSHV). Epidemiological forms of KS include classic KS, endemic KS, immunosuppression-associated KS and epidemic KS. Epidemic KS occurs in advanced HIV disease, is more aggressive and affects muco-cutaneous and visceral sites.



It has a global incidence of 41,799 with a mortality of 19,902 deaths annually. In Kenya, it ranked as the 8th most common cancer with an estimated 1,782 cases and the 10th most common cause of death with 930 deaths (2.8% of all cancer deaths) annually. A study conducted at Kenyatta National Hospital, reported a decreasing male to female ratio among patients with muco-cutaneous Kaposi's sarcoma.

KS has been reported to affect young patients with a median age of 34 years. Transmission of KSHV is postulated to occur through sexual intercourse, saliva, mother to child transmission (MTCT), transfusion of contaminated blood and consumption of infected breast milk.

## Clinical Evaluation

### History Taking

Inquire about:

1. Constitutional symptoms: Fever, night sweats, weight loss
2. KS specific signs and symptoms- onset of lesions, location, appearance, distribution; Melena stools or oral lesions (GIT involvement); cough, chest pain, haemoptysis (Pulmonary involvement)
3. Comprehensive HIV and opportunistic infection (OI) history, excluding other OIs such as tuberculosis, Pneumocystic Jiroveci Pneumonia(PJP), multicentric Castleman's disease (MCD) and lymphoma.
4. Medication history: If HIV positive ask for first line medication, second line medication, dates started, dates changed and reasons for change.

## Physical Examination

- Conduct a comprehensive skin, oral & systemic examination and document type of lesion, site, size, number, morphology, and limb circumference.
- Photography of oral, conjunctival, and cutaneous lesions should be done for documentation of extent of disease.
- Look out for the signs and symptoms tabulated below:

| Site   | Clinical presentation   |
|--|---|
| Mucocutaneous                                  | Skin lesions in the limbs, trunk, groin, face, eyes, and external genitalia increase as disease progresses. They are often raised, violaceous/black, brown, plaques, macules, papules & nodules along tension lines of the skin |
| Extremities, groin, face, peri-orbital tissues | Lymphoedema occurs due to vascular obstruction by tumor or effect of cytokines released by KSHV.  |
| Oral cavity                                    | Bleeding painful lesions in the hard palate, gingiva, tongue, uvula, tonsils, pharynx, trachea  |
| Cervical and inguinal areas                    | Lymphadenopathy- moderate or massive painful nodes  |
| Pulmonary                                      | Lesions in the pulmonary parenchyma, pleura, airways, and intrathoracic nodes. Pleural effusions are common and may be hemorrhagic.   |
| Gastro-Intestinal system                       | Lesions may involve the entire GIT resulting in bleeding, ulceration and intestinal obstruction   |

## Diagnosis

### Laboratory Tests

- Human immunodeficiency virus test.
- HIV viral load and CD4 to evaluate viral control and immune function.
- If chemotherapy or radiotherapy is planned: Do tests to evaluate organ function such as Total blood count and biochemistry (Liver Function Tests, Renal Function Tests) and Pregnancy test (for women in child bearing age). These tests should be done for everyone at diagnosis of KS.

### Diagnostic Pathology

- Tissue biopsy (punch biopsy preferred or if not, excisional biopsy).
- Immunohistochemistry for HHV8 where the microscopy is not clear. Silver Stains to exclude Bacillary Angiomatosis where the diagnosis is not clear-cut on morphology and immunohistochemistry.
- Biopsy of other sites if co-existing disorders suspected (such as multicentric Castleman's Disease, lymphoma).



### Imaging & other procedures

- CT Abdomen/ Pelvis or Abdominal ultrasound (if CT not available).
- CT Chest or Chest X-ray (if CT not available).
- Endoscopy/bronchoscopy if pulmonary and gastrointestinal sites symptomatic by history and physical examinations.

*Differential diagnoses include: Purpura, hematomas, angiomas, dermatofibromas, nevi, bacillary angiomatosis, extrapulmonary PCP, disseminated cryptococcosis, lymphedema, keratoacanthoma, pyogenic granuloma and fibrosarcoma.*

### Staging and Prognostication of Kaposi's Sarcoma

The AIDS Clinical Trial Group (ACTG) staging classifies patients with KS into good-risk or poor-risk groups based on:

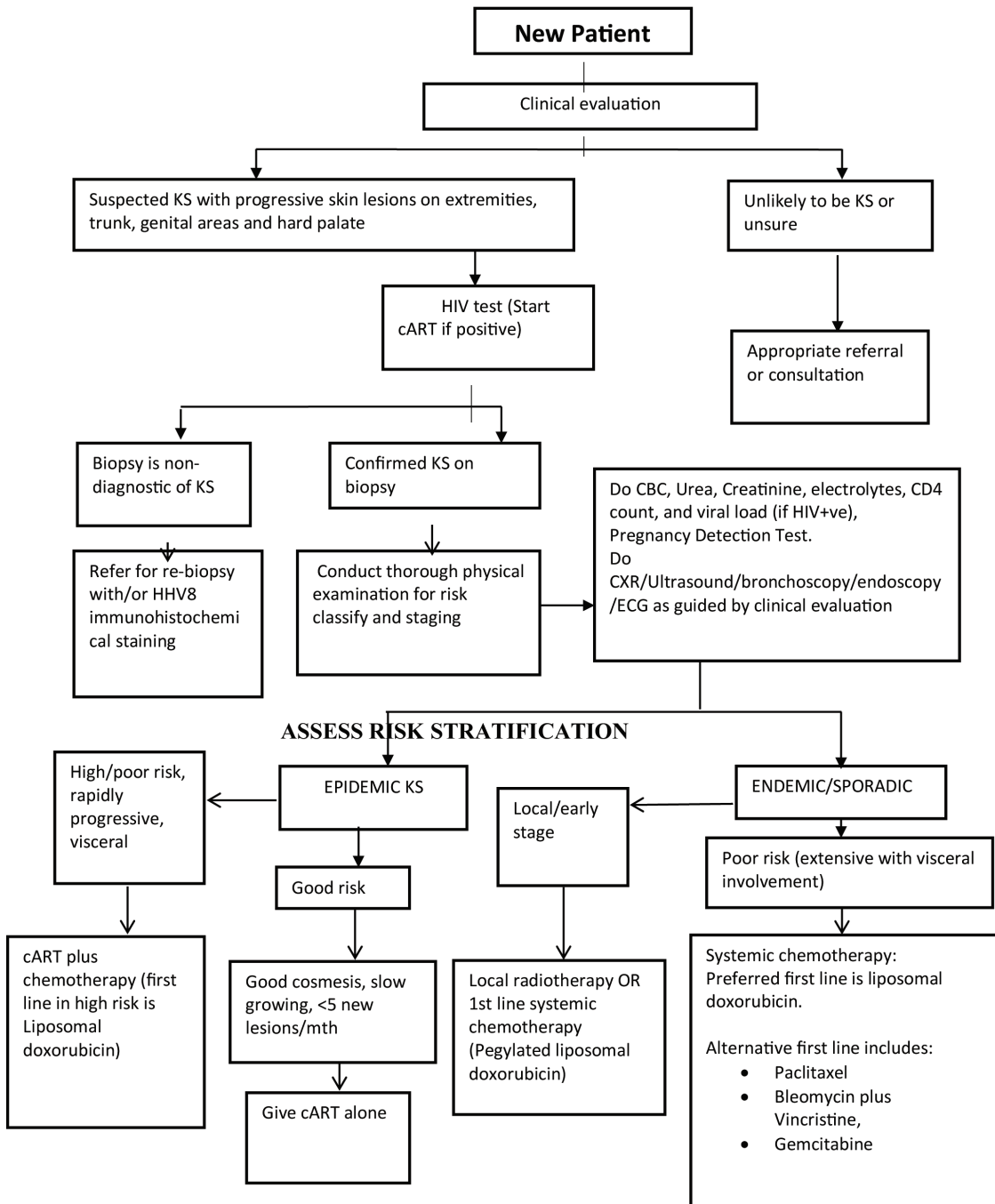
- Tumor extent (T)
- Immune profile status (I) as measured by CD4 cell count
- Evidence of HIV-associated systemic illness (S)

**Table 8. 1: Revised AIDS Clinical Trial Group (ACTG) staging classification for KS**

|                             | <b>Good Risk (0)<br/>(all of the following)</b>                                      | <b>Poor Risk(1)<br/>(any of the following)</b>   |
|-----------------------------|--|--|
| <b>Tumor (T)</b>            | Confined to skin and/or lymph nodes and/or minimal oral disease                      | Tumor associated edema or ulceration. Extensive oral KS or KS in other non-nodal viscera. Mucous lesion located on the conjunctiva |
| <b>Immune system (I)</b>    | CD4 cells >200/ $\mu$ L  | CD4 cells < 200/ $\mu$ L   |
| <b>Systemic illness (S)</b> | No history of OI or thrush<br>No 'B' symptoms<br>Kantorfsky performance status > 70% | History of OI and/or thrush<br>'B' symptoms present<br>Performance status < 70%  |

The ACTG staging predicts the prognosis of Kaposi's sarcoma; survival is significantly shorter in the poor risk category.

## Treatment Algorithm for Kaposi's sarcoma



**Table 8.2: Systemic Chemotherapeutic Agents for KS**

| Treatment   | Drugs  |
|-------------|--|
| First line  | <p><b>Preferred:</b> Pegylated liposomal doxorubicin or liposomal daunorubicin (anthracyclines)- every 3 weeks</p> <p><b>Alternate:</b> Paclitaxel – every two weeks</p> <p><b>Alternate:</b><br/>Bleomycin/Vincristine with sequential addition of Adriamycin in patients with poor response by cycle 3<br/>Adriamycin/Bleomycin/Vincristine - may be considered as first line in early stage endemic/sporadic KS</p> |
| Second line | <p>Gemcitabine</p> <p>Pomalidomide</p> <p>Thalidomide</p> <p>Lenalidomide</p>  |

### Radiotherapy

- Patients with epidemic KS are managed with radiotherapy for ulcerated lesions, head and neck mucocutaneous disease, or residual disease post chemotherapy.
- Radiotherapy schedule is based on site and volume of disease with fractionation ranging from 30Gy in 10 fractions to 20Gy in 5 fractions and single shot of 8Gy.
- In Endemic KS radiotherapy doses will range from 30-45 Gy given in 1.8Gy-3Gy fractions.

### Treatment Response

**Table 8.3 : Evaluation of Treatment Response used in ACTG (Aids Clinical Trial Group)**

| Response               | Definition   |
|------------------------|--|
| Complete Response (CR) | Absence of detectable lesion, including tumour associated oedema, for more than 4 consecutive weeks  |
| Partial Response (PR)  | Diminution of 50% of the total number and/or the size of previously existing lesions (skin, oral, measurable visceral disease) for more than 4 consecutive weeks and/or flattening of 50% of the nodular lesions without occurrence of new muco-cutaneous lesions (oral or skin or new visceral sites)<br>Complete response but with persistence of residual lymphoedema |
| Stable disease (S)     | Any response not meeting the criteria for progression or PR  |
| Progression            | -≥ 25% increase in the number and/or size of previously existing lesions<br>-Appearance of new muco-cutaneous lesions (nodules, plaque, macula, edema, ulceration or infiltration) or new localizations  |



### Supportive Care

This includes psycho-social support, pain management, spirituality counselling and sexuality counselling. Systemic involvement with KS, particularly visceral and lymph node involvement can carry a poor prognosis. Supportive care may be required for patient’s nutritional, mobility, social, and psychological wellbeing, to control pain, and to monitor and treat disease complications if and when they occur.

### Anticipated Services per Level of Care

| Level of Care | Activities  |
|---------------|---|
| Level 1       | Awareness creation, appropriate referral  |
| Level 2 & 3   | Awareness creation, history taking and examination, appropriate referral, palliative care   |
| Level 4       | History taking and examination, laboratory & histologic diagnosis, appropriate referral, palliative care                              |
| Level 5 & 6   | History taking and examination, laboratory & histologic diagnosis, endoscopy, staging, advanced diagnosis, treatment, palliative care |

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# 9

## **CHAPTER NINE**

### Lung Cancer Treatment Protocol

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# LUNG CANCER TREATMENT PROTOCOL

## List of abbreviations

|       |   |
|-------|---|
| ALK   | Anaplastic Lymphoma Kinase                      |
| CNS   | Central Nervous System                          |
| COPD  | Chronic Obstructive Pulmonary Disease           |
| CRT   | Chemo-radiotherapy                              |
| CT    | Computerized Tomography                         |
| ECHO  | Echocardiogram                                  |
| EGFR  | Epidermal Growth Factor Receptor                |
| FEV   | Forced Expiratory Volume                        |
| FVC   | Forced Vital Capacity                           |
| KRAS  | Kirsten Rat Sarcoma viral oncogene              |
| MRI   | Magnetic Resonance Imaging                      |
| NSCLC | Non-Small Cell Lung Cancer                      |
| PET   | Positron Emission Tomography                    |
| PCI   | Prophylactic Cranial Irradiation                |
| ROS1  | A type of receptor tyrosine kinase              |
| SIADH | Syndrome of Inappropriate Anti-Diuretic Hormone |
| SCLC  | Small Cell Lung Cancer                          |
| SQLC  | Squamous cell lung cancer                       |
| SVC   | Superior Vena Cava                              |
| TB    | Tuberculosis                                    |

## Introduction

Lung cancer is the most common cancer and leading cause of deaths globally. Incidence in Africa however, remains generally low. In Kenya there are an estimated 670 new cases with 659 deaths annually. There are two main types of lung cancer:

- Non-Small Cell Lung Cancer (NSCLC) constitutes 80-85% of cases. The most common subtypes are adenocarcinoma (60% of lung cancers), and Squamous cell lung carcinoma (SQCLC).
- Small Cell Lung Cancer (SCLC) constitutes 15% of all lung cancers, is associated with smoking. Majority (70%) have advanced disease at diagnosis.

## Risk factors

- Tobacco smoking, both active and passive (associated with 85% of all cases),
- Environmental exposure (asbestos exposure, radon exposure, air pollution, and occupational exposure),
- Family history of lung cancer
- Chronic lung diseases such as COPD and TB
- Prior history of lung cancer.
- Age 55-74 years

*Patients aged 55-74 years with  $\geq 30$  pack years of smoking are at the highest risk of developing lung cancer.*

## Clinical Evaluation

### History Taking

*Suspect lung cancer in patients with persistent pulmonary symptoms getting TB treatment.*

- Inquire about onset and duration of:
  - **Constitutional symptoms** such as anorexia, unexplained weight loss, and sweating;
  - **Symptoms of primary lung lesion** such as cough, dyspnea, chest pain, hemoptysis, wheezing;
  - **Symptoms of regional invasion** such as dysphagia, superior vena cava (SVC) obstruction, Horner's syndrome and brachial obstruction.
- In metastatic stage, patients may present with bone pain and tenderness, CNS symptoms such as headache, seizures, motor sensory deficits, and symptoms of liver metastasis such as abdominal pain and hepatomegaly. Paraneoplastic symptoms are also common in lung cancer, especially in SCLC and include Syndrome of Inappropriate ADH secretion (SIADH), Cushing's syndrome, ectopic parathyroid hormone secretion, hypercalcemia and Eaton-Lambert syndrome.
- Assess for risk factors especially smoking history, family history, and occupational exposure.
- Document the past medical history including history of chronic lung diseases, medication history among others.

## Physical examination

Conduct a thorough physical examination and assess for pleural effusion and lung mass among others.

## Diagnosis

### *Initial Imaging*

- Chest X-ray
- CT Scan chest and upper abdomen (to include liver and adrenal glands): further defines abnormalities seen on Chest X-ray, detects very small nodules in the lung and is useful for staging.

**Urgently refer for Lung Cancer or Mesothelioma management in patients with chest x-ray or CT chest findings that suggest Lung Cancer or Mesothelioma**

### *Further Imaging (After Biopsy)*

This is usually guided by CT chest and upper abdomen findings when a confirmed lung cancer diagnosis on tissue biopsy is available. This is usually for metastatic workup.

- PET CT scan: only if CT scan findings indicate early, localized disease (T1-3, N0-2) and especially in NSCLC.
- MRI brain: in SCLC whether symptomatic or asymptomatic; in NSCLC only in symptomatic patients.
- Radionuclide bone scan should be done for all SCLC at diagnosis or during follow-up if bone symptoms develop.

## Pathology

- Biopsy the most accessible site using minimal invasive techniques first for example cervical/ supraclavicular/axillary lymph nodes.
- Flexible bronchoscopy or CT-guided biopsy for tissue diagnosis and assessing local extent of disease.
- If biopsy is inconclusive consider Immunohistochemistry where available. For -adenocarcinoma (TTF1+ and Napsin+), SQCLC (p64+ and p40+) and SCLC (TTF1+, CD56+, chromogranin+, synaptophysin+).
- Metastatic disease: EGFR, ALK/ROS & Kras mutation tests where appropriate by specialists

## Laboratory tests

- UECs, CBC, LFTs, HIV test
- Pulmonary & cardiac function tests such as ECHO, FEV, FVC will determine eligibility for surgery for those with early stage NSCLC only.

## Staging

Stage the patient using the TNM staging.

## Treatment

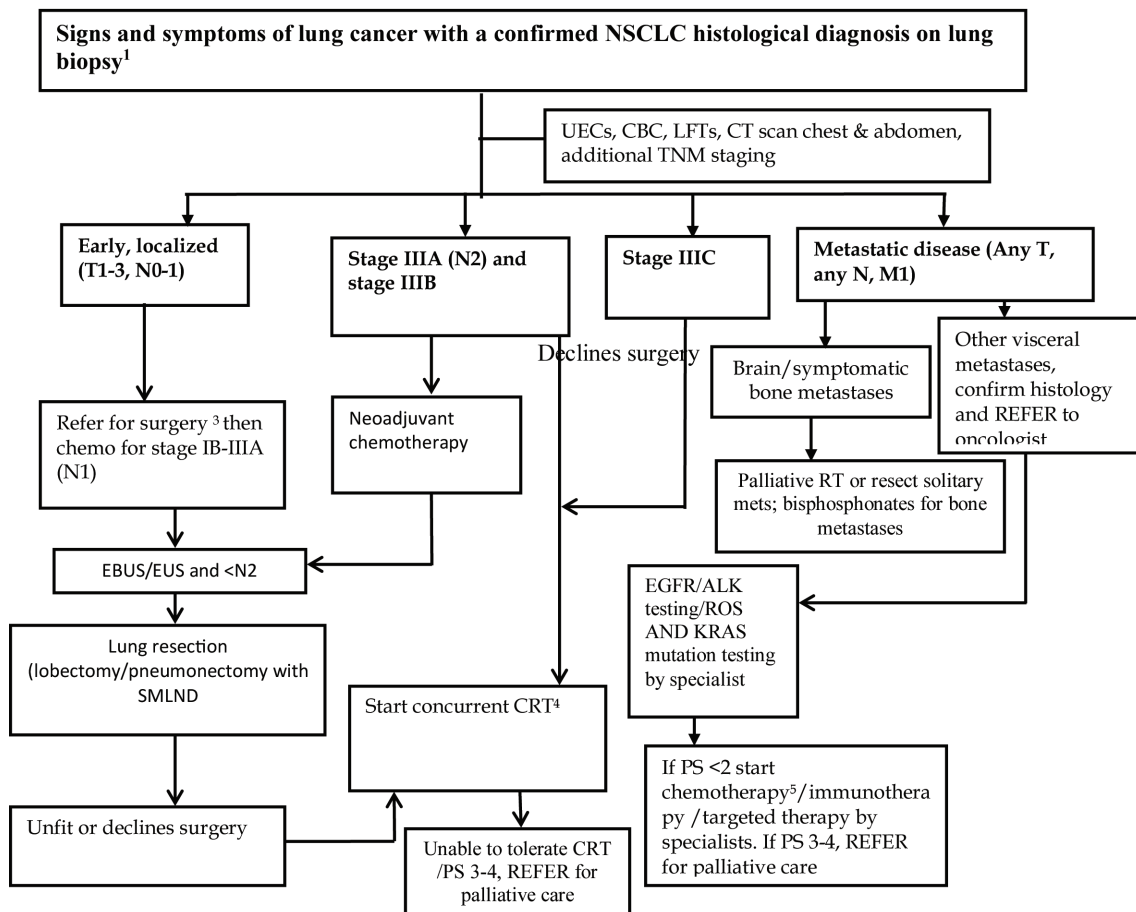
Treatment must be discussed in a multidisciplinary team whose core team includes a thoracic surgeon, radio-oncologist, medical oncologist and palliative care specialist, among others. Prognosis should be explained to the patients, relatives and medical caretakers. Ideally, surgery should be done by thoracic surgeons who have the requisite skills and experience.

The management of lung cancer is complex and requires a centre that specialises for this care.

**Table 9.1: Treatment Summary for Lung Cancer**

| Stage           |  | Treatment summary   |
|-----------------|--|---|
| Stage I         | T1 – 2N0   | Surgery followed by adjuvant chemo except for stage IA  |
| Stage IIA       | T2N0   | OR  |
| Stage IIB       | T1 -2N1 or T3N0  | Stereotactic RT   |
| Stage IIIA (N1) | or T3N1 or T4N0-1  | OR<br>Concurrent chemo-radiotherapy (CCRT) if inoperable                                      |
| Stage IIIA (N2) | T1 – 2N2   | Neoadjuvant chemo then resection and radiotherapy   |
| Stage IIIB      | T1-2N3 or T3-4N2   | OR<br>Concurrent chemo-radiotherapy (CCRT) if unresectable                                    |
| Stage IIIC      | T3-4N3   | Concurrent chemo-radiotherapy (CCRT)  |
| Stage IV        | Contralateral lung nodule, pleural or pericardial effusion (M1a), single extrathoracic metastasis (M1b), multiple extrathoracic metastasis (M1c) | Systemic chemotherapy or targeted therapy<br>WBRT if indicated<br>Bisphosphonate if indicated |

## Algorithm for Non-Small Cell Lung Cancer



1. In some cases, surgery may precede histological diagnosis. Adjuvant chemotherapy is not recommended for stage IA, maybe considered for stage IB, should be given to stage IIA-III A. Re-resect tumor if margins positive.
2. PET/CT should be considered for suspected stage I/II disease ONLY; other diagnostic procedures include bronchoscopy and biopsy; transbronchial needle aspiration, transthoracic needle aspiration, video assisted thoracoscopy, endoscopic bronchial ultrasound and thoracentesis, brain MRI for asymptomatic stage IIIA/B and T4.
3. Resectability should be determined by cardiothoracic surgeons. Pulmonary and cardiac reserves should be determined prior to surgery. Anatomic resections are preferred.
4. Concurrent chemoradiation (CRT) is preferred, at doses of at least 60Gy, but sequential may be given to unfit patients. CCRT may be given pre-operatively for resectable stage Pancoast tumors
5. Targeted therapy are 1st line for eligible stage IV patients in developed countries. Avoid chemotherapy in Performance score 3-4.



### Small Cell Lung Cancer (SCLC) Staging and Prognosis

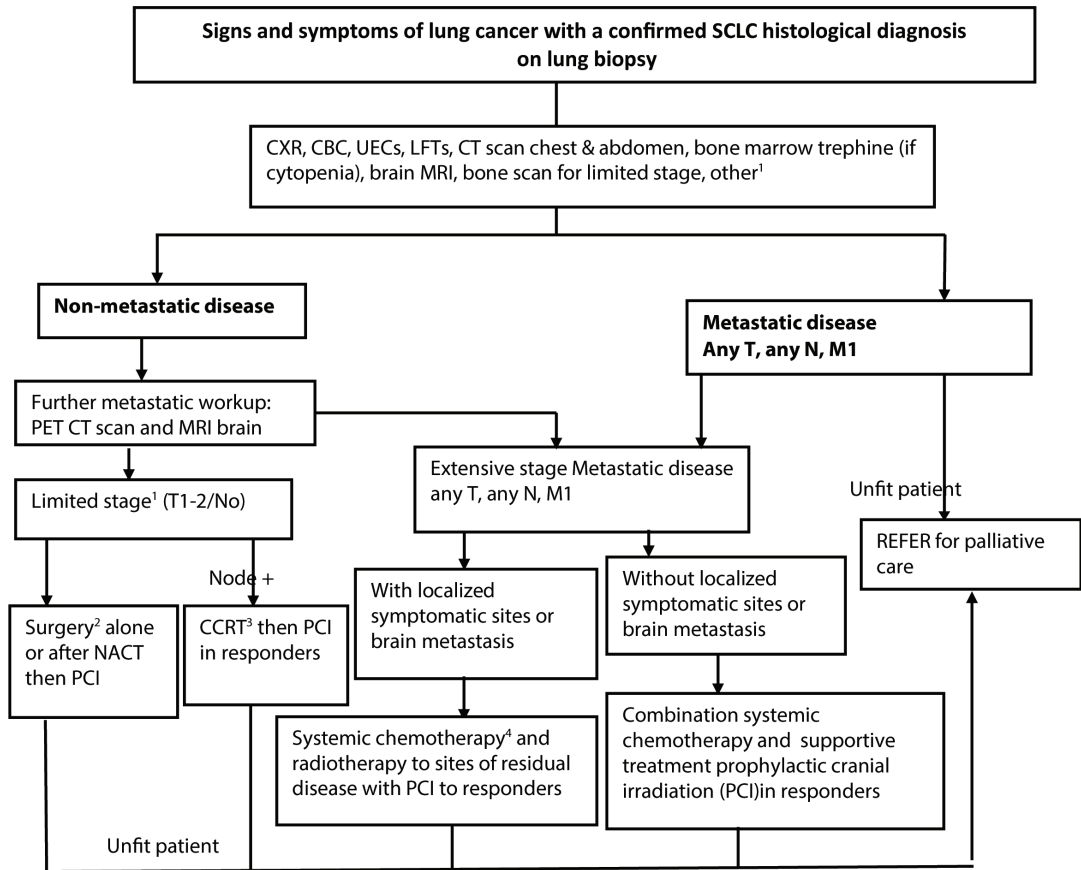
Use both TNM system and the Veterans Administration Lung Study Group (VALSG) system as below to classify the tumor stage.

**Table 9.2 The Veterans Administration Lung Study Group System**

| Stage  | Treatment summary  |
|--|--|
| Limited disease<br>(to ipsilateral hemithorax) | Surgery<br>Or<br>Neoadjuvant chemoradiotherapy (NACT) then surgery<br>Or<br>Concurrent chemoradiotherapy if node positive<br>Palliative care |
| Extensive disease                              | Systemic chemotherapy (thoracic radiotherapy for residual disease)<br>Or<br>Concurrent chemoradiotherapy<br>Palliative care                  |

*\*In SCLC, Prophylactic Cranial Irradiation (PCI) is recommended for both limited and extensive disease.*

## Algorithm for Small Cell Lung Cancer



1. Mediastinoscopy or other staging should be done to rule out nodal disease
2. Pulmonary function tests to evaluate for surgery. Patients in excess of T1-2N0 do not benefit from surgery.
3. Concurrent chemoradiation preferred to sequential typically 45Gy in 3 weeks twice daily. Concurrent chemoradiation should be used only in patients with a suitable performance status. Otherwise, give sequential as tolerated.

**Table 9.3: Systemic Chemotherapy Protocols**

|   | <b>Adenocarcinoma</b>   | <b>Squamous cell lung cancer</b> | <b>Small cell lung cancer</b>   |
|---|---|----------------------------------|---|
| 1 <sup>st</sup> line neoadjuvant, adjuvant & palliative chemo | 4-6 cycles of<br>Pemetrexed/platinum<br>Paclitaxel /carbo/bevacizumab<br>Paclitaxel/platinum<br>Docetaxel/ platinum<br>Gemcitabine/platinum | Gemcitabine/<br>Cisplatin        | Carboplatin/<br>etoposide<br>Cisplatin / etoposide  |
| Maintenance chemo   | Pemetrexed  |                                  |   |
| Chemotherapy used concurrently with RT                        | Paclitaxel /platinum<br>Docetaxel/ platinum<br>Etoposide/cisplatin<br>Pemetrexed/cisplatin  |                                  | Cisplatin /Etoposide<br>Carboplatin/Etoposide   |
| 2 <sup>nd</sup> line chemo                                    | Docetaxel<br>Gemcitabine/<br>Vinorelbine  |                                  | Topotecan<br>Irinotecan<br>Paclitaxel<br>Docetaxel<br>Temozolomide<br>Vinorelbine<br>Etoposide<br>Gemcitabine |
| First line Immunotherapy PDL1 ≥50%                            | Pembrolizumab   |                                  |   |
| Metastatic adenoCa with EGFR mutational antibodies            | Tyrosine kinase inhibitors (where available)<br>Gefitinib<br>Afatinib<br>Erlotinib  |                                  |   |
| ALK /ROS1 mutation present                                    | ALK inhibitors (where available)<br>Crizotinib  |                                  |   |

### **Palliative and Supportive Care**

- Support groups with smoking cessation services.
- Psycho-social support and spirituality support in advanced cases.
- Counselling on healthy lifestyle and sexuality should be available.
- **Palliative Radiotherapy** can alleviate symptoms in 41–95% of cases. Indications of palliative radiotherapy include: Brachytherapy (in case of disturbance of ventilation in the course of airway narrowing or in airway obstruction), pain and hemoptysis, symptomatic metastases to the central nervous system or bone.
- **Palliative Chemotherapy** can relieve pain, cough and other ailments. If there is shortness of breath following the toxic effects of chemotherapy on pulmonary parenchyma, discontinuation of administration of cytotoxic drugs and incorporation of steroids is necessary. When chemotherapy starts to increase side effects then it should be discontinued.
- **Symptom management** e.g. dyspnea, cough, hemoptysis, pleural effusion, pain management, superior vena cava syndrome and fatigue among others.

## Follow Up

### Stage I and II lung cancer

- 3 to 6 months after initial treatment.
- Then every 6 months for 5 years.

During follow-up visits: Clinical evaluation includes history of chest symptoms, and for smokers, whether they have stopped, examination for effusion or mass in chest or abdomen, CT scan chest, ALP for liver and bone metastasis.

### Stage IIIA

- Surveillance every 6 months for 2 years with history, physical examination and contrast-enhanced chest CT at least at 12 and 24 months, thereafter every 12 months is recommended.

### Stage IIIB

- 6-monthly CT chest scans for 3 years is recommended for patients who are suitable for salvage treatment.

**Table 9.4: Anticipated lung cancer services per level of health care**

| Level of Health Care  | Anticipated Cancer Services   |
|---|---|
| Community Health Care Level   | <p><b>Awareness creation</b></p> <p><b>Patient identification</b></p> <p>Intergrate Lung cancer assessment in TB and cough assesment</p> <p>Signs and symptoms of lung cancer</p> <p><b>Referral to level 4</b></p> <p><b>Palliative care</b></p>   |
| Primary Health Care Level (Dispensary and Health centres)                   | <p><b>As above</b></p> <p>Intergrate Lung cancer assessment into TB and cough clinics</p>   |
| Secondary Health Care Level (County Referral Hospitals)- previously level 5 | <p><b>As above plus;</b></p> <p>Intergrate Lung cancer assessment into TB and cough clinics</p> <p><b>CXR, CT scan chest and upper abdomen</b></p> <p><b>Bronchoscopy, mediastinoscopy, CT guided biopsy, thoracentesis</b></p> <p><b>Lung biopsy and review by specialist</b></p> <p><b>Metastatic work-up:</b></p> <p>(i) Refer for PET/CT scan ONLY in early disease.</p> <p>(ii) Brain MRI may be utilized</p> <p>Pulmonary &amp; cardiac function tests e.g. ECHO, FEV, FVC</p> <p><b>Therapy:</b></p> <p>i. Surgical management by thoracic surgeons</p> <p>ii. Can manage patients with metastatic disease with chemotherapy under guidance of specialist/oncologists</p> <p>iii. Palliative care</p> <p>iv. Supportive services</p> <p>v. Patient follow-up</p> |
| Tertiary Hospitals (previously level 6)                                     | <p><b>All above plus:</b></p> <ul style="list-style-type: none"> <li>• <b>Immunohistochemistry &amp;targeted therapy</b></li> <li>• PET CT scan</li> <li>• <b>Radiotherapy</b></li> </ul>   |

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# 10

## CHAPTER TEN

### Urological Cancer Treatment Protocols

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# UROLOGICAL CANCER TREATMENT PROTOCOLS

## List of abbreviations

|        |   |
|--------|---|
| ALP    | Alkaline Phosphatase                          |
| ADT    | Androgen Deprivation Therapy                  |
| CT     | Computer Tomography Scan                      |
| BCG    | Bacille Calmette Guerin                       |
| CXR    | Chest X ray                                   |
| DRE    | Digital rectal examination                    |
| ECOG   | Eastern Cooperative Oncology Group            |
| EBRT   | External Beam Radiotherapy                    |
| HPC1   | Hereditary Prostate Cancer 1                  |
| HIV    | Human immunodeficiency virus                  |
| IB     | Interstitial Brachytherapy                    |
| ISUP   | International Society of Urological Pathology |
| KUB    | Kidney Ureters & Bladder ultrasound           |
| MRI    | Magnetic Resonance Imaging                    |
| PO BID | Per oral twice a day                          |
| PCA3   | Prostate Cancer Antigen 3 gene                |
| PSA    | Prostate-Specific Antigen                     |
| RP     | Radical Prostatectomy                         |
| RT     | Radiotherapy                                  |
| SC     | Subcutaneous                                  |
| TRUS   | Transrectal ultrasound                        |
| TURBT  | Transurethral resection of bladder tumor      |

## 10.1 Prostate Cancer Treatment Protocols

### Introduction

Globally, prostate cancer is second in incidence and fifth in mortality in males. In Kenya, it is the most common cancer and the second leading cause of cancer mortality in males annually, with 2864 cases (14.9%) and 1663 deaths (11.7%) respectively (GLOBOCAN 2018).

The specific mechanisms that lead to the development of prostate cancer are still unknown, but several risk factors have been identified such as:

- Increasing age: prostate cancer seldom develops before the age of 40; two out of three cases occur in men over the age of 65.
- Family history: men whose first degree relatives develop prostate cancer are more likely to develop the disease. A gene known as hereditary prostate cancer 1 (HPC1) appears to significantly predispose men to prostate cancer when inherited in a mutated form.
- Race: Africans suffer the disease more than other races. The mortality is also higher.
- Environmental factors, such as workplace exposures to cadmium, have also been associated with an increased risk of prostate cancer.

### Clinical Evaluation

#### History taking

Prostate cancer usually progresses slowly and produces no symptoms in its initial stages. In advanced stages, symptoms will include:

- Lower urinary tract symptoms such as:
  - Difficult or painful urination;
  - Hesitancy (delay in starting) and dribbling at the end of urine flow;
  - Frequent urination, especially at night;
  - Urgency in urinating;
  - A sense of incomplete emptying of the bladder;
  - Loss of bladder control;
  - Decreased flow of urine stream; and
  - Blood in the urine (hematuria) or semen.

*These symptoms, however, may have other causes, such as infection or benign prostate enlargement.*

- Pain in the lower back, pelvis, or upper thighs may signal spread to the ribs, pelvis, and other bones.

Other important aspects of history will include:

- Risk factor assessment : age, first degree family history, environmental factors
- Past medical history.
- Co-morbidities such as diabetes, hypertension and HIV infection
- Erectile dysfunction
- Modifiable lifestyle risk factors such as unhealthy diet, alcohol and tobacco use



## Physical exam

Conduct a complete physical examination including:

- Digital rectal exam – size, shape, firmness, tenderness of the prostate and mobility of the rectal mucosa should be reported.
- Determine the patient's performance status as per ECOG score or Karnofsky performance score.

## Diagnosis

### Laboratory

- Prostate-specific antigen (PSA) test – raised PSA level does not necessarily indicate the presence of cancer. Urgently refer men whose PSA level is above the age-specific reference range.
- Prostatic core biopsy- Confirmatory diagnosis.  
*The urologist should consider factors that lead to an increased PSA including prostate volume, patient's age, and inflammation, ratio of total to free PSA, PSA velocity and PSA doubling time, rather than using an absolute level to determine the need for a prostate biopsy.*
- Other lab tests may include: Full blood count, renal function test, Liver function test, Lactate dehydrogenase test, Serum calcium and alkaline phosphatase (ALP).

### Imaging

- Increasingly, a multi-parametric MRI is necessary before any biopsy is obtained.
- Trans-rectal ultrasound (TRUS) and multi-parametric MRI are useful in guiding the biopsy process. TRUS is useful in obtaining core biopsy where clinical suspicion occurs. Acquisition of 10-12 cores is considered as minimum standard for TRUS-guided biopsy (to be done by an experienced urologist or radiologist).
- The indication for multi-parametric MRI is TRUS negative biopsy despite a high suspicion of prostate cancer for example in cases with abnormal DRE/ high PSA and/or increasing PSA velocity.

### The Indications for Prostate Biopsy

- PSA > 10ng/mL - generally should lead to a biopsy.
- PSA 4 - 10ng/mL - requires further interrogation with adjunctive studies like multi-parametric MRI of the prostate. In addition, DRE, PSA derivatives (PSA density and age specific reference ranges) and PSA kinetics (velocity and doubling time), PSA molecular forms (percent free PSA and pro-PSA), newer urinary markers (PCA3), and prostate imaging should be considered secondary tests (not primary screening tests) that can help to guide on the justification for a prostate biopsy.

## Staging

Multi-parametric MRI is the best imaging modality for local disease staging.

### Metastatic disease workup

- For suspected skeletal metastases:
    - o Bone scan: Indications include PSA above 10, T3-T4 disease, Gleason 8-10/ISUP Group 4, bone pain, raised alkaline phosphatase.
- A bone scan should be done for all patients before any definitive curative treatment.
- o MRI
  - o CT scan
  - o Plain radiography.
- For suspected visceral metastases -Abdominal pelvic CT scan or MRI.

## Treatment

The treatment of prostate cancer generally depends on the stage of the cancer, risk stratification and the life expectancy of the patient. Treatment modalities include:

1. Active surveillance (actively monitoring the course of the disease with the expectation to intervene with potentially curative therapy if the cancer progresses);
2. Watchful waiting (monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam of PSA that suggest symptoms are imminent);
3. Surgery;
4. Radiation therapy
5. Systemic chemotherapy and targeted therapy
5. Hormonal therapy.

## Clinically Localized Prostate Cancer

Patients with localized prostate cancer should be categorized according to their risk based on PSA levels, Gleason Score and clinical staging. The risk stratification below is based on ESMO guidelines 2015 thus for;

1. Low risk disease (PSA  $\leq$ 10ng/ml and Gleason Score 6 and T1-T2a)
  - If the expected survival is < ten years: watchful waiting.
  - If the life expectancy is > ten years then treatment options include:
    - (i) active surveillance,
    - (ii) definitive external beam radiotherapy,
    - (iii) interstitial brachytherapy, and
    - (iv) Radical prostatectomy with a lymph node dissection.
2. Intermediate (moderate) risk disease (PSA 10-20 ng/ml or Gleason Score 7 or T2b /T2c )
  - If the expected survival is < ten years: watchful waiting.
  - If the life expectancy is > ten years then treatment options include:
    - (i) active surveillance,
    - (ii) radical prostatectomy,
    - (iii) definitive RT\* + short term hormonal therapy 4-6 months, or
    - (iv) Adjuvant RT after RP (if +ve Surgical margins or Lymph nodes).

3. High risk disease (PSA >20ng/ml or Gleason Score 8-10 or T2c-T3). Neoadjuvant Androgen Deprivation Therapy (ADT) followed by Radical Radiotherapy (RT) and Long-term ADT 2-3 years. Radical prostatectomy can be offered to a select group of patients but with the understanding that there is a 50% chance of requiring an additional therapy.

## Metastatic disease

### 1. Castration sensitive metastatic disease

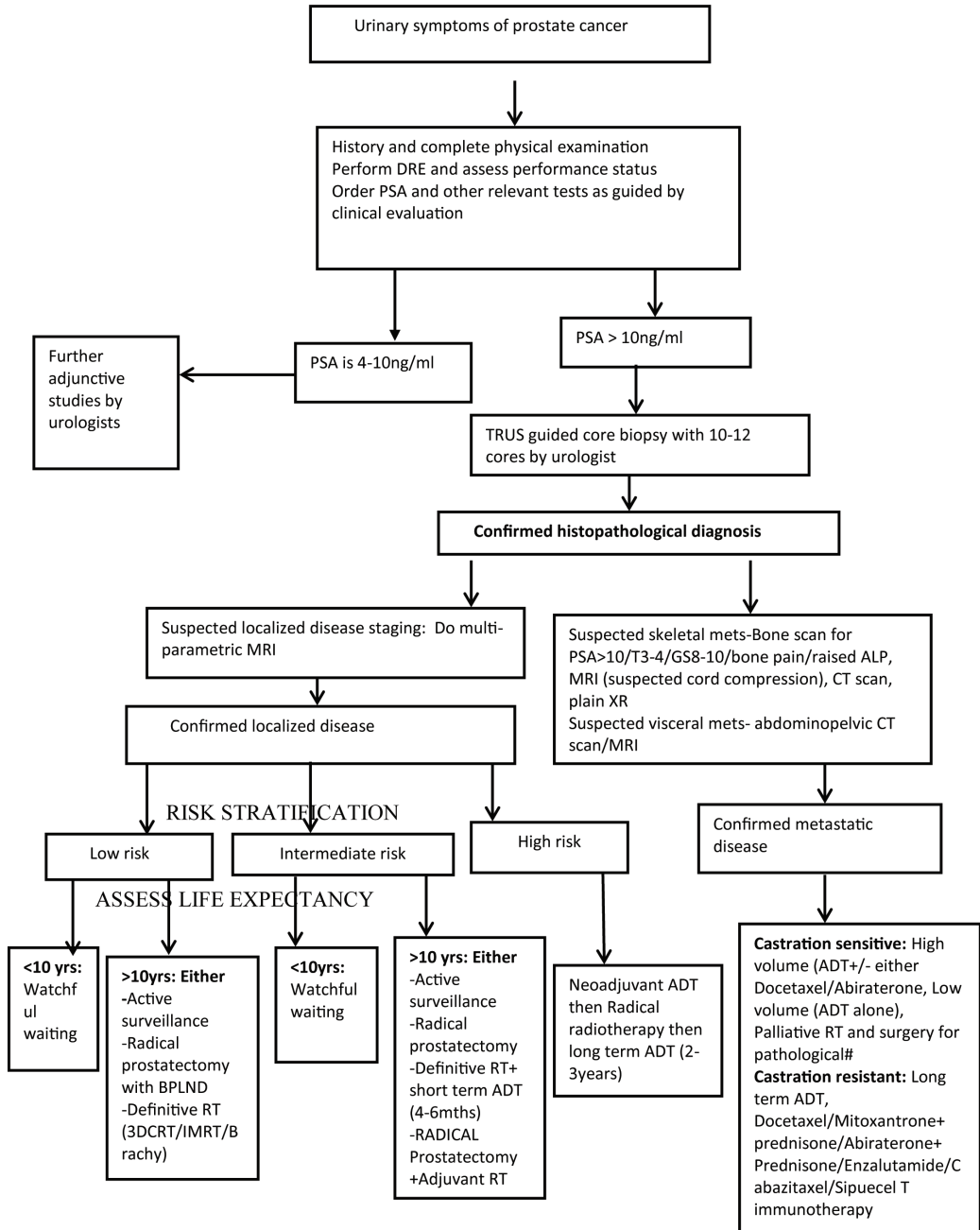
- i. High risk/High Volume: either ADT plus Docetaxel up to 6 cycles OR ADT plus Abiraterone OR ADT alone
- ii. Low risk/Low volume metastatic disease: ADT alone.
- iii. Palliative radiotherapy ± chemotherapy: radiation may be used for palliation in patients with painful bone metastases or impending spinal cord compression.
- iv. Surgical intervention may be necessary for weight-bearing bones involved in pathologic fracture.

### 2. Castrate-resistant metastatic disease

- Maintain Androgen Deprivation Therapy to keep the testosterone below castrate levels (less than 50ng/dl).
- Docetaxel; repeat cycle every 21 days for up to a total of 10 cycles.
- Abiraterone 1000 mg PO daily plus prednisone 5 mg PO BID until disease progression.
- Enzalutamide 160mg PO daily until progression.
- Cabazitaxel with prednisone can be used for patients who have hormone-refractory metastatic prostate cancer that was previously treated with a docetaxel-containing treatment regimen;
- Symptomatic men who are not candidates for docetaxel-based regimens may be candidates for Mitoxantrone IV on day 1 plus prednisone 5 mg PO BID daily; repeat cycle every 21 days.
- Sipuecel T immunotherapy is useful in low risk, low-burden disease.



## Treatment Algorithm for Prostate Cancer



### **Castration-Resistant Prostate Cancer and Bone Metastases**

Bisphosphonates are recommended for all men with hormone-refractory prostate cancer and symptomatic bone metastases as appropriate. They reduce skeletal-related events.

- (i) Zoledronic acid 4 mg IV 3 monthly over no less than 15 min (check renal functions and adjust accordingly) or
- (ii) Denosumab 120 mg SC every 4 week.

The radiopharmaceutical radium-223 dichloride (XoFIGO) is approved for men with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease:

### **Biochemical Failure**

- Approximately 20-30% of patients treated with intent for cure will have biochemical recurrence, which most commonly manifests as a rising PSA level (within 2-3 years of radical treatment).
- Biopsy of the prostatic bed is usually not recommended unless the patient is a candidate for salvage therapy.
- Monitor PSA, alkaline phosphatase, and calcium every 3 months and determine whether the doubling time is less than 1 year.

### **Post-Radical Prostatectomy Recurrence**

- Defined as a detectable PSA that increases on two subsequent measurements or a PSA that fails to fall to undetectable levels.
- Best PSA threshold unknown but probably between 0.2 and 0.4 ng/ml.
- PSA that fails to fall to undetectable levels after prostatectomy may indicate residual prostate cancer or prostate cancer recurrence.
- Treatment options include salvage radiation therapy, androgen deprivation, and surveillance.
- Adjuvant radiation therapy may be more beneficial than salvage radiation therapy in men with poor pathologic features [2, 3]

### **Post-Radiation Therapy Recurrence**

There are two recognized definitions of recurrence after radiotherapy

i. The 1996 ASTRO definition of PSA failure following EBRT is three consecutive PSA rises, with the time of failure backdated to the midpoint between the PSA nadir and the first rising PSA, or any rise great enough to provoke initiation of salvage therapy; a minimum follow-up of 2 years was recommended for presentation or publication of data.

ii. The "Phoenix Definition" (current ASTRO/RTOG definition) of PSA failure after EBRT, with or without short-term HT

- Defined as a rise in PSA of 2 ng/ml or more above the nadir (defined as the lowest PSA achieved after radiotherapy).
- PSA can bounce up and down after radiation.

Treatment options include salvage prostatectomy, ADT, surveillance, high-intensity focused ultrasound (clinical trials), cryotherapy.



## Follow-Up

After initial definitive therapy, perform PSA every 6 to 12 months for 5 years and then annually.

DRE every year but may be omitted if PSA is undetectable.

For metastatic disease –physical exam and PSA every 3 to 6 months or earlier if clinically indicated; bone imaging for symptoms and as often as every 6-12 months.

## Supportive Care for Prostate Cancer

- Incontinence management
- Pain and symptom management
- Sexuality counseling and management
- Rehabilitative therapy
- Anticipatory approach to symptom management
- Oncologic emergencies e.g. bone pain, spinal cord compression

## Planned Scope of Cancer Service Provision per Levels of Health Care

| Level of Health Care  | Anticipated Cancer Services  |
|---|--|
| Community Health Care Level   | <p><b>Awareness creation</b></p> <p><b>Patient identification</b></p> <p>Urinary symptoms of prostate cancer</p> <p>Advanced prostate cancer signs &amp; symptoms</p> <p><b>Referral to level 4</b></p> <p><b>Palliative care</b></p>  |
| Primary Health Care Level<br>(Dispensary and Health centres)                      | <p><b>Patient identification</b></p> <p>Urinary symptoms of prostate cancer</p> <p>Advanced prostate cancer signs &amp; symptoms</p> <p><b>Referral to level 4</b></p> <p><b>Palliative care</b></p>   |
| Secondary Health Care Level<br>(County Referral Hospitals)-<br>previously level 5 | <p><b>Patient identification</b></p> <ul style="list-style-type: none"> <li>• Urinary symptoms of prostate cancer</li> <li>• Advanced prostate cancer signs &amp; symptoms</li> </ul> <p><b>Prostatic biopsy and review by specialist</b></p> <p><b>Metastatic work-up:</b></p> <ul style="list-style-type: none"> <li>(i) Refer for bone scan (if symptomatic or PSA &gt;10 ng/ml)</li> <li>(ii) Plain CT scan pelvis, and MRI may be utilized</li> </ul> <p><b>Therapy:</b></p> <ul style="list-style-type: none"> <li>i. Radical prostatectomy</li> <li>ii. Can manage patients with metastatic disease with androgen deprivation therapy, anti-androgens and docetaxel under supervision of oncologist or urologist</li> </ul> |
| Tertiary Health Care Level (National Referral Hospitals)                          | <p>All work up and therapy as in level 5 including bone scan</p> <p>Therapy:</p> <ul style="list-style-type: none"> <li>i) External beam radiotherapy (ERBT)</li> <li>ii) Interstitial brachytherapy (IB)</li> <li>iii) Radical prostatectomy (RP).</li> <li>iv) Chemotherapy and ADT</li> </ul> <p>Referrals back to nearest health facility and follow up care</p>   |

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## 10.2 Bladder cancer

### Introduction

Cancer of the urinary bladder is the 20th most common cancer in Kenya with an estimated 568 cases and 335 deaths in 2018 (GLOBOCAN 2018). It occurs more in males than females and more in Caucasians than Africans. The most common histology is transitional cell carcinoma. Other variants include primary squamous cell carcinoma, adenocarcinoma and carcinosarcomas.

### Risk Factors

- Tobacco use;
- Age >65 years;
- Exposure to chemicals used in rubber, dye, textile and print industries, aromatic hydrocarbons and arsenic compounds;
- Exposure to radiation and chemotherapy agents such as cyclophosphamide;
- Chronic bladder problems such as bladder stones, long term catheterisation and chronic cystitis such as infection with Schistosomiasis.

### Signs and symptoms

- Blood or blood clots in the urine – 80% of patients present with painless hematuria.
- Pain or burning sensation during urination
- Frequent urination
- Feeling the need to urinate many times but not being able to pass urine
- Lower abdominal pain
- Loss of appetite and weight loss
- Fatigue
- Swelling of the feet
- Bone pain

*Urgently refer patients aged 45 and over with unexplained visible haematuria without urinary tract infection.*

### Diagnosis

Pathological confirmation is done from biopsy on specimen collected during cystoscopic examination of the bladder. The grading of the tumor is very important in guiding therapy. Open bladder biopsy or excision is contraindicated.

### Staging

Use the TNM Staging (AJCC version 8).



### Imaging

- Bladder ultrasound – if negative, further imaging and cystoscopy still needed/KUB.
- CT scan of the chest, abdomen and pelvis.
- MRI of the pelvis (if available).
- Cystoscopy and transurethral resection of bladder tumor (TURBT) – for local staging of disease.
- Consider bone scan (if symptomatic or elevated alkaline phosphatase).

### Other tests

- Urinalysis with cytology.
- FBC, liver function tests and renal function tests.

### Treatment

| Stage                     | Therapy   |
|---------------------------|---|
| Superficial (low risk) Ta | TURBT alone<br>Consideration for intravesical chemotherapy  |
| Superficial (high risk)   | TURBT alone<br>If incomplete resection or no muscle in specimen, repeat TURBT<br>+ intravesical BCG or bleomycin weekly for 6 weeks<br>For patients with very high risk superficial disease (multifocal grade 3 T1 tumors with Tis, or increased depth of invasion) – consider cystectomy     |
| Muscle invasive disease   | Partial cystectomy if only dome of bladder is involved<br>Radical cystectomy with extended lymphadenectomy plus/minus external beam radiotherapy OR<br>Bladder preservation with maximal TURBT followed by concurrent chemoradiotherapy OR<br>Neoadjuvant chemotherapy followed by cystectomy |
| Metastatic disease        | Palliative chemotherapy<br>Palliative radiotherapy  |

### Treatment regimens

These regimens can be used in the neoadjuvant, adjuvant and metastatic setting.

- Gemcitabine and cisplatin
- Dose dense methotrexate, vinblastine, doxorubicin and cisplatin (DDMVAC)
- Gemcitabine and carboplatin
- Single agent gemcitabine
- Gemcitabine plus paclitaxel
- Ifosfamide and doxorubicin and gemcitabine
- Atezolizumab
- Pembrolizumab

## Follow Up & Surveillance

| <b>Risk</b>                           | <b>Cystoscopy</b>  | <b>Upper tract imaging</b>   | <b>Abdominal/ pelvic imaging</b>          | <b>Blood tests</b>  | <b>Urine tests</b>  |
|---------------------------------------|--|--|---|---|---|
| Low risk non muscle invasive disease  | 3 and 12 months then annually for 5 years                                      | Baseline and then as clinically indicated  | Baseline and then as clinically indicated | Not applicable  | Not applicable  |
| High risk non muscle invasive disease | Every 3 months for the first 2 years<br>Every 6-12 months for the next 3 years | Baseline and every 1-2 years for 10 years  | Baseline and then as clinically indicated | Not applicable  | Urine cytology every 3 months for 1 year and every 6-12 months for 5 years                    |
| Muscle invasive disease               | (post cystectomy therefore not indicated)                                      | Every 3-6 months for first 2 years (include CXR or CT chest)<br>Then annually for the next 4 years | As per upper tract imaging                | UEC, LFTs, CBC every 3 to 6 months for the 1 <sup>st</sup> year and then annually for 4 years | Urine cytology every 6-12 months for the 1 <sup>st</sup> 2 years then as clinically indicated |

## Planned scope of cancer service provision per levels of health care

| Level of Health Care  | Anticipated Cancer Services  |
|---|--|
| Level I and II (Community and dispensary)                         | Patient identification from signs and symptoms<br>Referral to level 3-4<br>Palliative care   |
| Level III and IV(Health centres and Sub-county Hospital)          | Patient identification signs & symptoms<br>Referral to level 5 -6<br>Palliative care   |
| Level 5(County Referral Hospital)                                 | Patient identification<br>Review by specialist<br>Cystoscopy examination<br>Metastatic work-up<br>Therapy: <ol style="list-style-type: none"> <li>i. Radical cystectomy and extended lymphadenectomy if expertise is available</li> <li>ii. Can manage patients who require chemotherapy either in the neoadjuvant/adjuvant or metastatic setting under supervision of oncologist</li> </ol> |
| Level 6 (Tertiary Health Care Level, National Referral Hospitals) | All work up and therapy as in level 5<br>Metastatic workup<br>Therapy<br>External beam radiotherapy (ERBT)<br>Chemotherapy<br>Radical cystectomy<br>Hospital- based cancer registry<br>*Referrals back to nearest health facility and follow up care.  |

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AJCC TNM staging Version 8

NCCN Clinical Practice Guidelines in Oncology – Bladder Cancer Version 1.2019 [www.nccn.org](http://www.nccn.org)

# 11

## CHAPTER ELEVEN

### Childhood Cancer Treatment Protocols

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# CHILDHOOD CANCER TREATMENT PROTOCOLS

## List of Abbreviations

|          |  |
|----------|--|
| ALL      | Acute Lymphoblastic Leukaemia          |
| AML      | Acute Myeloid Leukaemia                |
| ATRA     | All Trans-retinoic acid                |
| BEP      | Bleomycin Etoposide Cisplatin          |
| BMA      | Bone Marrow Aspirate                   |
| BMI      | Body Mass Index                        |
| CCNU     | Lomustine                              |
| CNS      | Central Nervous System                 |
| CRT      | Chemoradiation                         |
| CSI      | Cerebrospinal Irradiation              |
| CXR      | Chest X-ray                            |
| DNA      | Deoxy ribonucleic acid                 |
| EBV      | Ebstein Burr Virus                     |
| EUA      | Examination Under Anaesthesia          |
| FAB      | French-American-British classification |
| GCT      | Germ Cell Tumors                       |
| IQ       | Intelligence Quotient                  |
| LDH      | Lactate Dehydrogenase                  |
| LFTs     | Liver Function Tests                   |
| MDS      | Myelodysplastic Syndrome               |
| MSR      | Maximal Safe Resection                 |
| PNET     | Primitive neuroectodermal tumors       |
| RB       | Retinoblastoma                         |
| RMS      | Rhabdomyosarcoma                       |
| UECr     | Urea Electrolyte Creatinine            |
| VP Shunt | Ventriculoperitoneal Shunt             |
| WBC      | White Blood Cell                       |
| WBRT     | Whole Brain Radiotherapy               |

## Introduction

Childhood cancer is among the leading causes of death among children and adolescents with approximately 3,272 new cancer cases diagnosed in 2018. The leading cancers include lymphomas, leukaemias, brain tumors and retinoblastomas. In Kenya, survival rates are at an average of about 19 to 30% in contrast to high income countries where survival rates are about 80%.

## 11.1 Leukaemias

### 1. Acute Lymphoblastic Leukaemia (ALL)

#### Introduction

In East Africa, it is the 2nd most common cancer in children, after non-Hodgkin lymphoma, with peak age at diagnosis at 2 to 5 years, and 85% of patients diagnosed between ages 2 and 10 years.

#### Risk factors

- Exposure to ionizing radiation
- Genetic conditions:
  - Identical twins (20% increased risk in 2nd twin if the first twin develops leukemia in the first 5 years of life)
  - Chromosomal abnormalities such as Trisomy 21 (Down syndrome)
  - Genetic conditions such as ataxia telangiectasia, Li-Fraumeni syndrome, neurofibromatosis, diamond-Blackfan anemia, Bloom syndrome

Most cases of leukemia are associated with somatic genetic alterations and not inherited genetic predisposition.

#### Signs and Symptoms

- Fever (61%)
- Recurrent infections
- Arthralgia
- Anemia and lethargy (50%)
- Bleeding tendencies (petechiae, purpura, ecchymoses) (48%)

Clinical features of extramedullary involvement include:

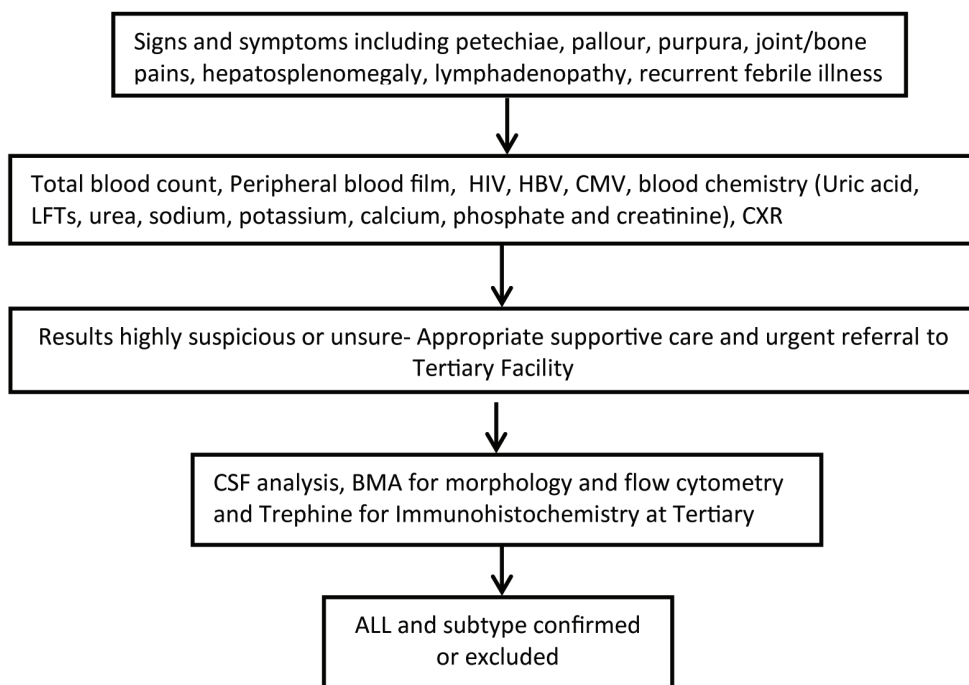
- Bone (and joint pains) (23%)
- Lymphadenopathy (50%)
- Splenomegaly (63%)
- Hepatosplenomegaly (68%)
- Central Nervous System: headache, cranial nerve palsies, convulsions, vomiting and hyperphagia
- Testicular and ovarian involvement: painless enlargement of the testis
- Renal involvement: occasionally hematuria and hypertension.

## Laboratory tests and features

1. Total Blood Count: combinations of anemia (usually normocytic normochromic), thrombocytopenia and leucopaenia or leucocytosis. Some patients may present with a pancytopenia.
2. Peripheral blood smear: Lymphoblasts are often present, may be absent especially in leucopaenia
3. Bone marrow exam: Confirmatory test by identification of >25% blast cells.
4. Special studies:
  - Immunophenotyping by DNA flow cytometry is important in differentiation of precursor B-cell ALL from, T-cell ALL or AML
  - Cytogenetics to identify high risk genetic translocations
  - Karyotyping
5. Cerebrospinal fluid: Diagnosis of CNS leukemia when there are >5WBC/microlitre and a positive cytospin and/or presence of CNS signs and symptoms.
6. Blood chemistry: Uric acid, LFTs, blood urea, electrolytes, creatinine, calcium, phosphorus prior to starting chemotherapy.
7. Infectious disease profile: Hepatitis B & C, cytomegalovirus and HIV screening.

Chest X-ray may show a mediastinal mass especially in T-cell ALL and/or compression of the trachea by lymphadenopathy.

### **Diagnostic Algorithm for ALL**





## Treatment

Urgently refer all suspected cases of ALL to level 6 (tertiary) facilities for treatment. Selection of intensity of treatment protocol to use depends on the supportive care available as well as prognostic features present at diagnosis.

**Table 11.1: Risk stratification**

| Factor                         | Favourable (Standard risk)                         | Less favourable (High risk)                           |
|--------------------------------|--|---|
| Age in years                   | 1-9  | <1 or >9  |
| WBC count(x10 <sup>9</sup> /L) | <50  | >50   |
| CNS involvement                | absent   | present   |
| Immunophenotype                | B-precursor cell                                   | T-cell  |
| Genetics                       | Hyperdiploidy >50 chromosomes<br>or DNA index>1.16 | Hypodiploidy <44<br>chromosomes or DNA index<br><0.81 |
|                                | Trisomy 4,10 and 17                                | MLL rearrangement                                     |
|                                | t(12;21)/ ETV6-RUNX1                               | Philadelphia chromosome =<br>t(9;22)/ BCR-ABL1 iAMP21 |

*The most important prognostic factor is response to treatment and minimal residual disease at the end of induction. Patients who are not in remission at the end of induction therapy and those who relapse early in maintenance phase have a poor prognosis and together with other High risk group should be fast tracked for bone marrow transplant when feasible.*

The phases of treatment of Acute Lymphoblastic Leukemia include:

**Remission induction:** This includes a steroid prophase from Day 1 to 7. Do a peripheral blood blast count on Day 8. Patients with standard risk disease receive a 3 drug induction that includes Prednisone, Vincristine and L-asparaginase while patients with high risk disease will have Doxorubicin added to standard therapy.

**Central Nervous System directed treatment:** is administered from induction to maintenance phase

- CNS negative disease at diagnosis: intrathecal methotrexate from induction to maintenance phase. These do not require craniospinal irradiation.
- CNS positive disease at diagnosis: weekly intrathecal 3-drug (Methotrexate, Cytosar, Hydrocortisone) until first two negative CSFs then continue with protocol. These may be considered for craniospinal irradiation.
- CNS relapse during treatment : Give weekly triple intrathecal drugs until first two negative CSFs and continue with protocols and give craniospinal irradiation.



**Consolidation:** This phase has the intensity increased with different drugs to eradicate disease in the sanctuary sites (brain, testes or ovaries) and obtain more cure with continued CNS prophylaxis / treatment.

**Interim Maintenance phase:** This is usually with oral methotrexate and 6-mercaptopurine for 6 weeks meant to allow bone marrow recovery pending re-intensification.

**Delayed intensification/Reinduction:** This phase aims to intensify therapy before maintenance phase. It is one phase that has been shown to improve survival in the treatment of acute lymphoblastic leukemia.

**Maintenance.** The optimal duration has been shown to be 2 years (from start of treatment) with regimens with duration below 18 months associated with higher risk of relapse.

**Table 11.2: Acute Lymphocytic Leukemia Chemotherapy Protocols**

| Phase                          | Drugs  | Supportive management   |
|--------------------------------|--|---|
| <b>Induction</b>               | Prednisone, Vincristine, L-asparaginase, Doxorubicin, Intrathecal Methotrexate   | Tumor lysis prevention, nutritional support, infection control, blood support with Folinic acid |
| <b>Consolidation</b>           | Cyclophosphamide, oral 6-mercaptopurine, cytarabine, vincristine, L-asparaginase, Intrathecal methotrexate                             | Infection prevention with Folinic acid  |
| <b>Interim maintenance</b>     | Methotrexate, Vincristine, intrathecal methotrexate  | Infection prevention with Folinic acid  |
| <b>Delayed intensification</b> | Dexamethasone, Vincristine, doxorubicin, L-asparaginase, cyclophosphamide, oral 6-mercaptopurine, cytarabine, intrathecal methotrexate | Infection prevention with Folinic acid  |
| <b>Maintenance</b>             | Oral 6-mercaptopurine, methotrexate, intrathecal methotrexate  | Infection prevention with Folinic acid  |

*Daunorubicin is preferable to Doxorubicin especially in high risk disease.*

### Follow up

Monthly follow up with clinical examination, blood count and peripheral blood film for the first year, every 2 months in the second year and every 3 months in third year then twice yearly till 5 years.

Booster vaccinations are recommended after 6 months of treatment completion.

A comprehensive multidisciplinary follow-up is recommended.

### References

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## 2. Acute Myeloid Leukaemia (AML)

### Introduction

AML constitutes 15-20% of all childhood acute leukemia cases. Survival rates have increased over the past few decades to about 70% for low risk AML in industrialized countries, due to improved supportive care, optimized risk stratification and intensified chemotherapy. In most children, AML presents as a de novo entity, but in a minority, it is a secondary malignancy.

### Risk factors

- Genetic factors include Trisomy 21, Fanconi Anaemia, Bloom Syndrome, Diamond-Blackfan anaemia, and Noonans syndrome
- Environmental factors include treatment with alkylating agents, radiation exposure.

## Clinical features

The common presenting features include fever, anemia, unusual bleeding and bruising, petechiae, ecchymoses, gingival hypertrophy, chloromas, frequent or persistent infections and other symptoms depending on systems affected by infiltrating disease.

## Investigations

- Complete blood count with differential white cell counts: can have leukocytosis/leucopenia, Neutropenia, anemia, thrombocytopenia
- Peripheral blood smear: blasts may be identified.
- Bone Marrow Aspirate and Cytology or Trepine biopsy: Blast count of >20% is diagnostic of AML. Patients with myelodysplastic syndrome may require a trephine biopsy if there is a dry tap.
- Serum chemistry: UECs, LFTs
- Grouping and crossmatch
- Screen for and treat any infections.

## Prognostic Factors

The prognostic factors are both patient and disease-related characteristics:

### - Patient characteristics

- Patients with Down's syndrome have a better prognosis
- BMI of >95 percentile confers a poor prognosis

### - Clinical characteristics

- WBC count: a high count confers a poorer prognosis
- Response to therapy: Early response which is usually assessed after the first course confers a good prognosis
- Cytogenetic/Molecular characteristics: Favourable; t(8:21), inv(16), t(15:17) (the latter only if ATRA and/or ATO is used), Unfavourable (Monosomy 5, 7, MLL gene rearrangements among others).

## Treatment

Treatment consists of a combination of intensive anthracycline and cytarabine-containing chemotherapy and stem cell transplantation in selected genetic high-risk cases or poor responders. In general, phases in the treatment of AML include:

**1. Induction:** The induction phase consists of one or two cycles of chemotherapy. Intrathecal chemotherapy is also administered if there is CNS disease. Remission assessment is done using immunophenotypic flow cytometry or by Polymerase Chain Reaction (PCR) and/or fluorescent in situ hybridization (FISH).

**2. Intensification or consolidation:** is continued treatment to eliminate residual leukemia cells after induction. Patients in remission are given an additional 3 to 4 cycles of high dose Cytarabine with/without Mitoxantrone. Those not in remission are referred for palliative chemotherapy or Hematopoietic Stem Cell Transplant (HSCT). Meticulous supportive care which includes infection control, timely availability of blood components is required for these patients.

**Table 11.3: Chemotherapy Protocols for AML**

| Phase of Treatment   |   | Supportive Management   |
|--|---|---|
| <b>AML: Induction phase(1 or 2 cycles)</b>   | <b>Consolidation phase(2-3 cycles)</b>              |   |
| <b>1. <u>7+3 protocol:</u></b><br>Cytarabine D1-D7<br>Daunorubicin D1-D3<br>Triple therapy IT for intermediate and high risk AML: IT Methotrexate, IT Cytarabine and IT Hydrocortisone | High dose Cytarabine+/- Mitoxantrone<br><br>Or HSCT | Tumor lysis, treat infection, oral care, blood support, nutritional support, infection prevention |
| <b>2. <u>ADE protocol:</u></b><br>Cytarabine D1-D7<br>Daunorubicin D1- D3<br>Etoposide D1-3  | High dose Cytarabine+/- Mitoxantrone<br><br>Or HSCT | Tumor lysis, treat infection, oral care, blood support, nutritional support, infection prevention |

**Table 11.4 Treatment Protocols for Acute Promyelocytic Leukaemia**

| TREATMENT regimen  | INDUCTION   | CONSOLIDATION   |
|--|---|---|
| <p>North American Intergroup Study C9710 regimen</p> <p>OR</p> <p>European APL regimen</p>                   | <p>ATRA and Arsenic Trioxide starting on Day 1 and/or Daunorubicin and /or Cytarabine</p>                         | <p><u>First cycle</u>: Daunorubicin plus cytarabine</p> <p><u>Second cycle</u>: Daunorubicin plus Cytarabine plus IT chemotherapy</p> <p>ATRA administered concurrently with cycles above (especially for intermediate and high risk patients)</p>                          |
| PETHEMA regimen  | <p>ATRA (started on day 1)</p> <p>plus Idarubicin</p>   | <p><u>First cycle</u>: Idarubicin on days 1-4</p> <p><u>Second cycle</u>: Mitoxantrone on days 1-3</p> <p><u>Third cycle</u>: Idarubicin bolus for 1 dose</p> <p>ATRA administered concurrently with cycles above. (especially for intermediate and high risk patients)</p> |
| <p>APML .....</p> <p>*low-intermediate risk</p> <p>*good ECOG</p> <p>*if not suitable for anthracycline.</p> | <p>ATRA upto CR or until 60 days.</p> <p>plus</p> <p>Arsenic trioxide first 5 doses then weekly in weeks 2-8.</p> | <p>Arsenic trioxide for 5 days every other month for 4 cycles</p> <p>plus</p> <p>ATRA PO in 2 divided doses for 2 weeks per month for 7 cycles</p>  |

### Follow-up care

Monthly follow up with haemogram including peripheral blood film and clinical exam for the first year, every 2 months for the second year and every 3 months in third year then twice yearly until 5 years.

Booster vaccination after 6 months of treatment completion. At each visit evaluate for late effects of chemotherapy.

### References

Jasmijn D. E. de Rooij, C. Michel Zwaan, and Marry van den Heuvel-Eibrink Pediatric AML: From Biology to Clinical Management: *J Clin Med.* 2015 Jan; 4(1): 127–149  
*Blood* 2012 120:3187-3205; doi: <https://doi.org/10.1182/blood-2012-03-36>; Diagnosis and management of acute myeloid leukemia in children and adolescents: recommendations from an international expert panel.

## 11.2 Burkitts Lymphoma

### Introduction

It is classified as either:

- Endemic Burkitts lymphoma (eBL) - It is most common in children in the East African region, peaks between the age of 2-7 years old, median onset age is 6 years and is more common in males than females (ratio 4:1).
- Sporadic Burkitts lymphoma
- HIV-related Burkitts lymphoma

### Risk factors

- Infectious agents: HIV infection, coinfections with Epstein–Barr virus (EBV) and *Plasmodium falciparum* malaria early in life
- Congenital immunodeficiency disorders such as severe combined immunodeficiency, hypogammaglobulinaemia, common variable immunodeficiency, Wiskott-Aldrich syndrome, and ataxia-telangiectasia.
- Environmental exposures

### Clinical Evaluation

Burkitts lymphoma often presents as a rapidly-growing painless mass at extra nodal sites commonly on the jaw but can also occur as a progressive abdominal swelling, on the chest and to a lesser extent in the bone. CNS involvement is often present, with cranial nerve palsies or paraplegia. It is a fast-growing tumor and the tumor size can double within a 48-hour period. It thus requires urgent diagnostic and treatment intervention.

**Table 11.4: The St. Jude's Staging System**

|                  |   |
|------------------|---|
| <b>Stage I</b>   | A single tumor (extranodal) or single anatomical area (nodal), not mediastinum or abdomen.  |
| <b>Stage II</b>  | Single tumor (extranodal) with regional node involvement,<br>Two or more nodal areas on the same side of the diaphragm,<br>A primary GIT tumor with or without involvement of mesenteric nodes, |
| <b>Stage III</b> | Two single tumors or nodal areas on opposite sides of the diaphragm, Primary intrathoracic tumors, extensive intra-abdominal disease, and all paraspinal or epidural tumors.                    |
| <b>Stage IV</b>  | Any of the above with initial CNS and/or bone marrow involvement.   |

It should be handled as an oncological emergency with prompt confirmation of diagnosis and staging before start of treatment since it is a fast growing tumor. Evidence shows no advantage in performing extensive surgery or debulking, since tumor re-growth is fast and surgery delays and may complicate chemotherapy.

Prognostic factors include the stage, LDH level, bone marrow involvement and CNS involvement.

### Investigations

- 1. Diagnosis:** Histology preferred (biopsy of lymph node/mass)/ cytology (fine needle aspiration).
- 2. Staging:** CXR, abdominal ultrasound, CT of neck, chest, abdomen and pelvis, CSF cytology, bone marrow aspiration or trephine biopsy for evaluation of marrow involvement,
- 3. Laboratory:** HIV status, CBC/ESR/PBF, LDH, LFTs, uric acid, UECs.

### Treatment

Definitive treatment involves 6-8 cycles of Cyclophosphamide, Vincristine, Prednisone, high dose Methotrexate with folinic acid rescue and high dose Cytarabine. CNS directed therapy is also essential with IT Methotrexate and Hydrocortisone (add IT Cytarabine in confirmed CNS disease).

### Supportive care

Supportive care is important in the management of Burkitts lymphoma prior and during treatment.

- Tumor lysis syndrome prevention:
  - o Start allopurinol 10 mg/kg/dose TDS upon diagnosis, at least 1 day before starting chemotherapy.
  - o Start hyper hydration 12-24 hours before chemotherapy with 3000 ml/m<sup>2</sup>/day (normal saline alternate with 5% Dextrose ) till 48 hours after chemotherapy and then continue hydration at maintenance level. Initial aim is adequate urine output of >3ml/kg/hr which must be achieved before start of chemotherapy.



- o Check daily weight; and creatinine and electrolytes at 24 and 48 hrs after commencement of chemotherapy.
- Spinal cord compression occurs frequently in Burkitts lymphoma. Presenting features include: back pain, incontinence, urinary retention, paraplegia and other neurological deficits.
- Increased intracranial pressure may occur due to pleocytosis and lumbar puncture should be performed with caution.

### **Second line chemotherapy**

This will be determined on a case-by-case basis by the oncologist

### **Follow up**

Relapses occur early within the first year after diagnosis. Upon completion of the last course of treatment, evaluate the patient clinically and including by imaging of initial site of disease.

After chemotherapy, follow up will be done: Monthly for 3 months; then every 3 months for a year; then every 6 months for 2 years then annually thereafter. At follow-up conduct a clinical examination and other appropriate investigations.

A multidisciplinary follow up plan should be instituted.

## **11.3 Nephroblastoma (Wilms' Tumour)**

### **Introduction**

It is one of the most common abdominal childhood malignancy with an incidence of about 208 cases per year, accounting for 6 - 7% of all childhood malignancies in Kenya. Peak incidence is between 2 and 6 years and it occurs with an equal frequency in both sexes. Ninety percent of cases occur before 3 years of age and about 5% present with bilateral disease. Wilms tumour may be associated with hereditary cancer syndromes such as Beckwith-Weiderman syndrome, WAGR syndrome (Wilms tumour, aniridia, malformations of the urinary genital system and mental retardation) Denys-Drash syndrome and neurofibromatosis type 1. The major differential diagnosis for nephroblastoma is neuroblastoma affecting the same age group. Benign and quasi-malignant renal conditions like polycystic kidney, perinephric abscess, nodular renal blastema, mesoblastic nephroma, neuroblastomatosis and ganglioneuroma should be excluded.

### **Clinical Evaluation**

Signs and symptoms:

- Abdominal mass (80%)
- Abdominal pain/ haematuria (25%)

- Hypertension, gross haematuria and fever (5-30%)
- Urinary tract infections and varicocele (less common)
- Anaemia and fever: incase of bleeding
- Respiratory symptoms in patients with lung metastases

Conduct a complete physical evaluation including a gentle abdominal examination. Always examine for stigmata of other conditions that may be associated with Wilms tumor such as hemihypertrophy, genital abnormalities and aniridia.

### Imaging for Diagnosis

Treatment is usually commenced on the basis of findings of an intrarenal mass on CT scan of the abdomen. *CT scan should be reviewed together by the radiologist, surgeon and oncologist at the time of initial patient presentation.*

### Staging

*Surgical staging is useful in management of Wilm's Tumor therefore adequate documentation at surgery including lymph node sampling is crucial.*

- CT abdomen and chest: evaluate the origin and extent of the tumour, presence of a renal vein or inferior vena cava thrombus, presence of enlarged lymph nodes, invasion of the ureters and metastatic disease within the abdomen.
- Abdominal ultrasound (where CT is not available).
- A chest X-ray (where CT is not available) is mandatory at initial diagnosis to evaluate for metastatic disease.

### Laboratory investigations

Complete Blood Count, Liver Function Tests, U/E/Cr, Calcium, Urinalysis, Coagulation profile and Urinary catecholamines (to exclude neuroblastoma).

### Staging

The National Wilms Tumor (NWT) study staging system:

|           |  |
|-----------|--|
| Stage I   | Tumor within renal capsule - completely resected   |
| Stage II  | Tumor extends beyond the kidney but is completely resected   |
| Stage III | Gross or microscopic residual tumor remains post-operatively, spillage of tumor preoperatively or intraoperatively, regional lymph node metastasis |
| Stage IV  | Haematogenous metastasis or lymph node metastasis outside the abdomen (often to lungs and liver)   |
| Stage V   | Bilateral tumors   |

## Treatment

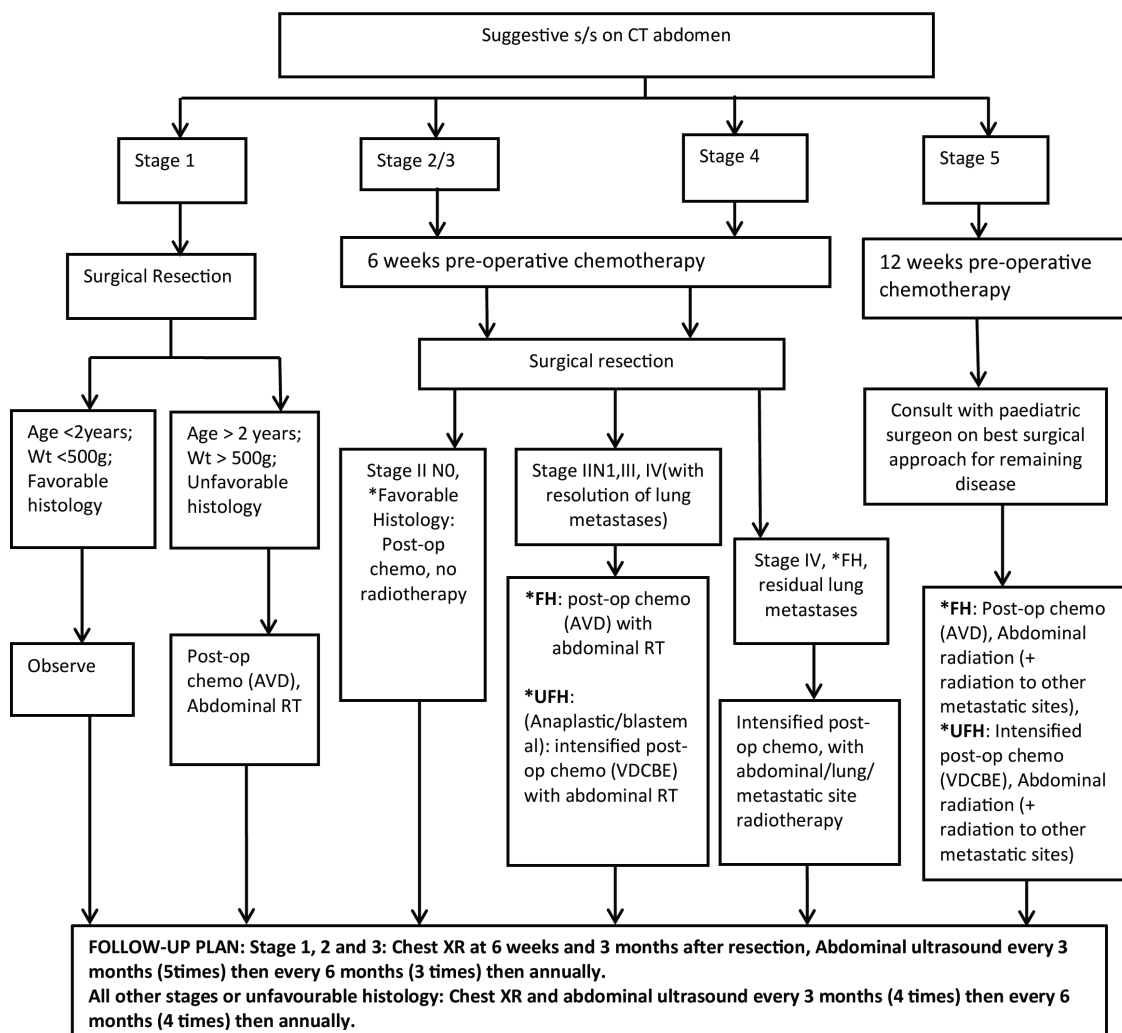
A multidisciplinary stage and risk adapted approach is recommended which combines surgery, chemotherapy and radiotherapy. In an effort to provide comprehensive and timely patient care without unnecessary delays, early and frequent communication between senior physicians is crucial.

Pathologic staging of disease (after surgical resection, post-neoadjuvant chemotherapy)

| Low-risk     | Intermediate-risk | High-risk                                 |
|--------------|-------------------|---|
| No anaplasia | Focal anaplasia   | Diffusely anaplastic or blastemal-type WT |

The histologic staging of the disease is useful for determining whether to augment therapy. Surgery is the mainstay of treatment. Pre-operative and postoperative chemotherapy is given with radiotherapy to tumor bed after chemotherapy. Where there is unfavorable histology post-operatively, the treatment is augmented with further drugs (see Post-op treatment plan below).

## Treatment Algorithm for Wilms Tumor



*FH: Favourable Histology*

*UFH: Unfavorable Histology (anaplastic or blastemal histology)*

*AV: (Dactinomycin Vincristine); AVD:( Dactinomycin, Vincristine, Doxorubicin) ;VDCBE (Vincristine, Doxorubicin/Cyclophosphamide/Carboplatin/Etoposide)*

## Initial treatment plan

| Stage                                    | Clinical status           | Therapy  |
|--|---------------------------|--|
| I (all vessels visualized)<br>AND        | Performance $\geq$<br>70% | Resection  |
| I (without vessels visualized)<br>AND/OR | Performance $\leq$ 60%    | Vincristine + Dactinomycin x 6 weeks, then resection   |
| II-IV                                    | Any                       | Vincristine, Dactinomycin, Doxorubicin x 6 weeks, then resection   |
| V  | Any                       | Vincristine, Dactinomycin, Doxorubicin x 12 weeks, then resection after discussion with paediatric surgeon |

## Post-operative treatment plan

| Stage             | Histology                           | Treatment   |
|-------------------|-------------------------------------|---|
| I                 | Any                                 | <b>Child &lt;2 and tumour &lt;550 g:</b> Observation<br><br><b>Others:</b> Vincristine + Dactinomycin   |
| II N <sup>o</sup> | Favorable                           | Vincristine, Dactinomycin, Doxorubicin  |
| II N <sup>1</sup> | Favorable                           | Vincristine, Dactinomycin, Doxorubicin, Abdominal radiation   |
| II                | Anaplastic or Blastemal-predominant | Vincristine, Doxorubicin, Cyclophosphamide, Etoposide, Carboplatin, Abdominal radiation   |
| III               | Favorable                           | Vincristine, Dactinomycin, Doxorubicin, Abdominal radiation   |
| III               | Anaplastic or Blastemal-predominant | Vincristine, Doxorubicin, Cyclophosphamide, Etoposide, Carboplatin, Abdominal radiation   |
| IV                | Favorable                           | <b>Lung mets resolved and no other mets at presentation:</b> Vincristine, Dactinomycin, Doxorubicin, Abdominal radiation<br><br><b>Persistent lung mets, other mets at diagnosis:</b> Vincristine, Dactinomycin, Doxorubicin, Etoposide, Cyclophosphamide, Abdominal and whole lung radiation |
| IV                | Anaplastic or Blastemal-predominant | Vincristine, Doxorubicin, Cyclophosphamide, Etoposide, Carboplatin, Abdominal and whole lung radiation (+ radiation to other metastatic sites)  |
| V                 | Favorable                           | Vincristine, Dactinomycin, Doxorubicin, Abdominal radiation (+ radiation to other metastatic sites)   |
| V                 | Anaplastic or Blastemal-predominant | Vincristine, Doxorubicin, Cyclophosphamide, Etoposide, Carboplatin, Abdominal radiation (+ radiation to other metastatic sites)   |



## References

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Kenyan Wilms Tumor Consortium. A collaborative group from Kenyatta National Hospital, Moi Teaching and Referral Hospital, University of Nairobi and other collaborators who met and discussed a proposed treatment schedule for Wilm's tumour in 2015.

Jeffrey S. Dome, Norbert Graf, James I. Geller, Conrad V. Fernandez, Elizabeth A. Mullen, Filippo Spreafico, Marry Van den Heuvel-Eibrink, and Kathy Pritchard-Jones (2015) Advances in Wilms Tumor Treatment and Biology: Progress Through International Collaboration . J Clin Oncol 33:2999-3007.

Paintsil V, David H, Kambugu J, et al: The Collaborative Wilms Tumour Africa Project; base-line evaluation of Wilms tumour treatment and outcome in eight institutes in sub-Saharan Africa. Eur J Cancer 51:84-91, 2015

## 11.4 Brain and Central Nervous System Tumours

### Introduction

CNS tumours are the 4th most common type of childhood tumours with approximately 154 cases annually (8% of all childhood tumours). Most childhood brain tumours occur in the infratentorial region.

### Clinical Evaluation

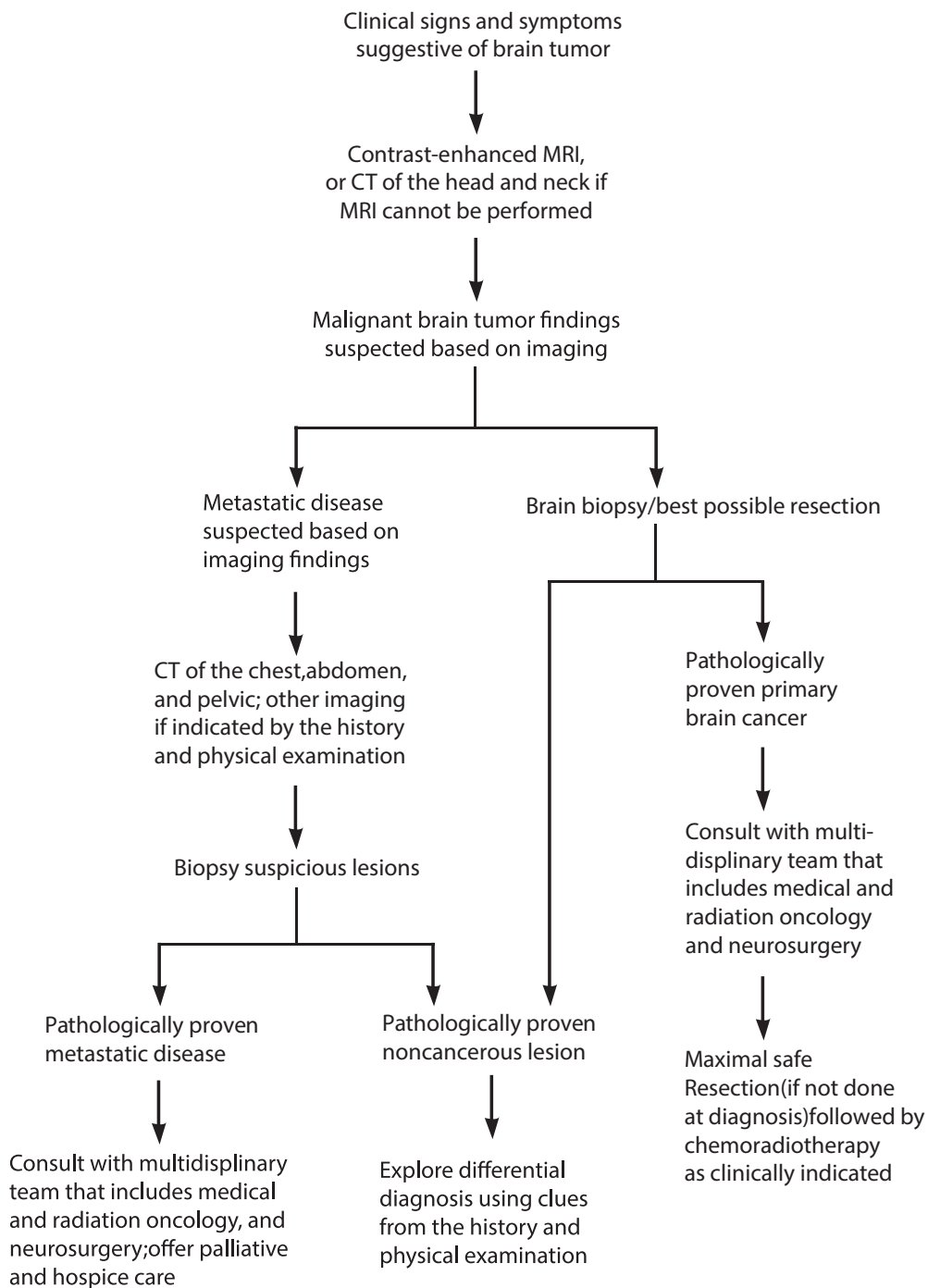
Common signs and symptoms occur due to increased intracranial pressure or depending on location and extent of the tumour and include:

- **Intracranial pressure/Obstruction:** headache, vomiting, hydrocephalus -papilledema, sun setting eyes, Cushing's Triad, increased head/fontanelle size.
- **Focal neurological deficits:** Frontal lobe (personality changes, seizures, headache), Temporal lobe (seizures, speech problems), suprasellar (endocrinopathies, visual problems), thalamus (motor sensory deficits), cerebellar (nystagmus, ataxia, hydrocephalus, resting tremor, incoordination), brainstem (cranial neuropathies, gait, swallowing, incoordination, drooling, breathing dysfunction), posterior fossa (nausea, vomiting).
- **Brain dysfunction:** mental function deterioration, personality changes, seizures. Take a complete history and conduct a thorough physical examination including the central nervous system examination.

### Diagnosis

- Contrast-Enhanced MRI
- CT scan head and neck (If MRI not available or condition does not allow)

*Urgently refer all suspected cases for review to level 5 or 6 facilities with a multidisciplinary team consisting of a paediatrician, paediatric neurologist, paediatric neurosurgeon, paediatric oncologist, ophthalmologist, radiologist, medical and radiation oncologist among others.*





## Treatment Protocols

| DIAGNOSIS                     | Grade/Risk category                   | SURGERY                        | CHEMOTHERAPY  | RADIOTHERAPY  | IMAGING                                  |
|-------------------------------|---------------------------------------|--------------------------------|---|---|--|
| Cerebellar Astrocytoma        | JPA                                   | Maximal safe resection(MSR)    | Nil   | 50.4Gy/28#  | MRI Brain                                |
| Medulloblastoma               | Average risk                          | VP shunt +/- MSR               | Adjuvant Vincristine/Cisplatin/ CCNU OR Carboplatin/Vincristine/Etoposide | CSI 23.4Gy/13#, Boost 32.4Gy/18#  | MR Brain and whole spine, CSF assessment |
|                               | High Risk                             | VP shunt +/- MSR               | CCRT with Vincristine then adjuvant 6-8 cycles as above                   | CSI 36Gy/20#, Boost 19.8Gy/11#  | MR Brain and whole spine, CSF assessment |
| Ependymoma                    | WHO Grade 1-3, Ependymoblastoma(PNET) | MSR                            | No benefit  | 54Gy/30# local disease, CSI in disseminated disease   | MR Brain and whole spine, CSF assessment |
| Brainstem Glioma              | Diffuse/intrinsic, Low/high grade     | Nil                            | Nil   | 56Gy/28# on 2D, Consider 54Gy/30# with 3DCRT  | Diagnosis on imaging                     |
| Intracranial Germ Cell Tumors | Germinoma                             | Biopsy                         | CE with extended local RT   | WBRT 45Gy/25# or Chemo and 25.2Gy/14#   |  |
|                               | Non-Germinomatous                     | For residual masses post chemo | BEP/ CE   | Focal RT or CSI( metastatic disease) 30.4Gy/19#, Boost 19.8Gy/11# Post Chemo CSI 24Gy/15#, Boost 30.6Gy/17# |  |
| Hemispheric glioma            | -                                     | MSR                            | No Gold standard Adjuvant Vinc,CCNU,Prednisolone to be considered         | 45Gy/25# Large Volume, Boost 14.4Gy/8# (Adjust boost for OAR as needed)                                     | Prognosis depends on resection           |
| Visual pathway glioma(OPG)    | JPA/Fibrillary                        | Nil (protect visual pathway)   | Emerging evidence for Vincristine/Carboplatin)                            | 45Gy/30#  | Observation in NF1 patients              |
| Craniopharyngioma             | Adamantinomatous                      | MSR                            | Intra Omayo Bleomycin/ interferon alpha                                   | 54Gy/30#  | Follow up in combined paediatric clinic  |



### Sequelae of therapy & Follow up

1. Neurocognitive effects - patients need to be followed up in a combined clinic set up with access to a developmental specialist as they experience a decline in IQ with problems in organization, attention learning and executive functions. Memory impairment and a wide range of fine and visual motor skills can be affected.
2. Neuroendocrine effects- Truncal growth failure should be monitored at every clinic visit (sitting and standing height), hypothyroidism, delayed or precocious puberty and adrenocortical dysfunction should be monitored.
3. Secondary malignancies - mostly occur in the radiotherapy field being meningiomas and high grade gliomas. Acute lymphocytic leukaemia can occur due to use of alkylating agents.
4. Hearing impairment- occurs due to chemotherapy and radiotherapy given. Should be monitored on follow up.
5. Psychological sequelae – usually relate to post therapy changes including but no /limited to short stature, deafness, abnormal gait and learning or coping difficulties. A clinical psychologist needs to be part of the multidisciplinary team looking after these children.
6. Management of intracranial hypertension and spinal cord compression.

## 11.5 Osteogenic Sarcoma

### Introduction

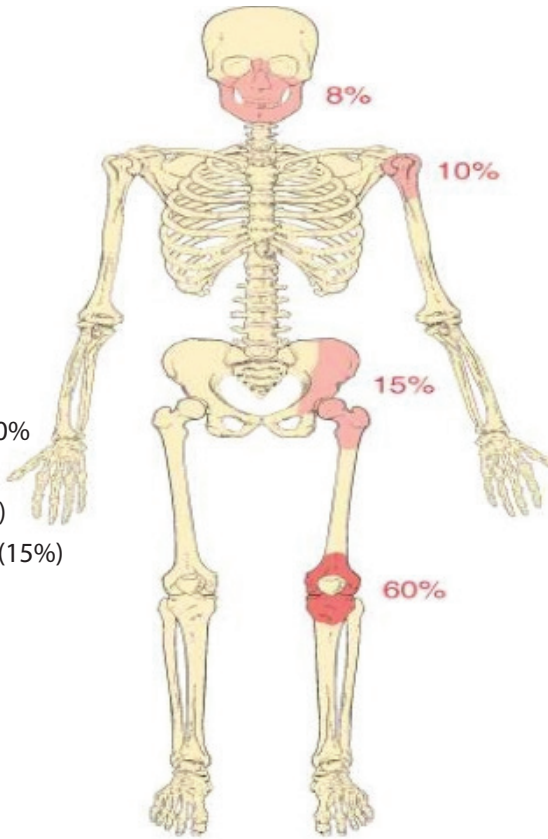
Bone tumours constitute 3-5% of all childhood cancers. Osteosarcoma is a primary malignant mesenchymal bone tumour. It is the most commonly diagnosed primary malignant bone tumour, with incidence peak during the pubescent growth spurt, with an age peak of 12 years in girls and 16 years in boys. While its aetiology is unknown, some factors that correlate with occurrence include: bone growth, genetic factors, human predisposition syndromes and environmental factors.

### Clinical Evaluation

Symptoms are usually present for several months before diagnosis, with an average duration of 3months. The commonest symptoms are:

- Pain at tumour site (90%)
- Local swelling (50%)
- Decreased range of motion (45%)
- Pathologic fracture (8%)

- **Sites:**
  - Metaphysis: 90%
  - Diaphysis: 8-10%
  - Epiphysis: 1%
- **Occurrence:**
  - Long Bones: 70%-80%
  - Distal FEmur (40%)
  - Proximal Tibia (20%)
  - Proximal Humerus (15%)
  - Axial Skeleton
  - Pelvis
  - Jaw



**Figure 11.1 : Common sites of involvement of osteosarcoma in children**

Approximately 10-20% have evidence of metastatic disease at diagnosis, with commonest sites being lungs and bone.

## Diagnosis

### Initial Imaging

- Plain X-ray of affected limb: characteristic radiological features are sun-burst appearance, periosteal lifting with formation of Codman's triangle, new bone formation in the soft tissues along with permeative pattern of destruction of bone and other features for specific types of osteosarcoma.
- Chest X-ray: to detect metastasis in form of cannon ball appearance or nodules in the lung.

### Imaging after biopsy(for staging)

- Chest CT Scan: early detection of small sub-centimal nodules in the lung. It delineates the bony anatomy like cortical integrity more clearly and picks up pathological fracture and is helpful in assessing ossification and calcification more accurately.
- MRI: most accurate tool for determining the limits of tumour within and outside the bone. Include the whole of the involved bone with one joint above and below so that skip lesions are not missed in the same bone and across the joint. MRI accurately and precisely delineates (1) extent of the tumour into the soft tissues and the medullary canal, (2) involvement of joint, (3) crossing of the lesion through and/or around the growth plate, (4) any skip lesion in the same bone and across the joint in other bone, (5) proximity/encasement of the neurovascular bundle by the tumour.

## Laboratory

### Biochemical tests includes:

- Serum alkaline phosphatase (ALP): elevated in osteosarcoma due to increased osteoblastic activity. Higher levels are associated with heavy tumour burden and poor prognosis.
- Lactate dehydrogenases (LDH).  
The response of therapy can be monitored with the levels of these enzymes. High levels after treatment may persist with residual disease or recurrence and in the presence of metastasis.
- Other tests include: Blood count, Urinalysis, BUN, Creatinine, LFT, Total Bilirubin.

### Pathology:

Biopsy using percutaneous core needle is a better, safe and accurate method for diagnosing bone tumours.

Other tests will include a baseline audiogram and echocardiogram prior to chemotherapy

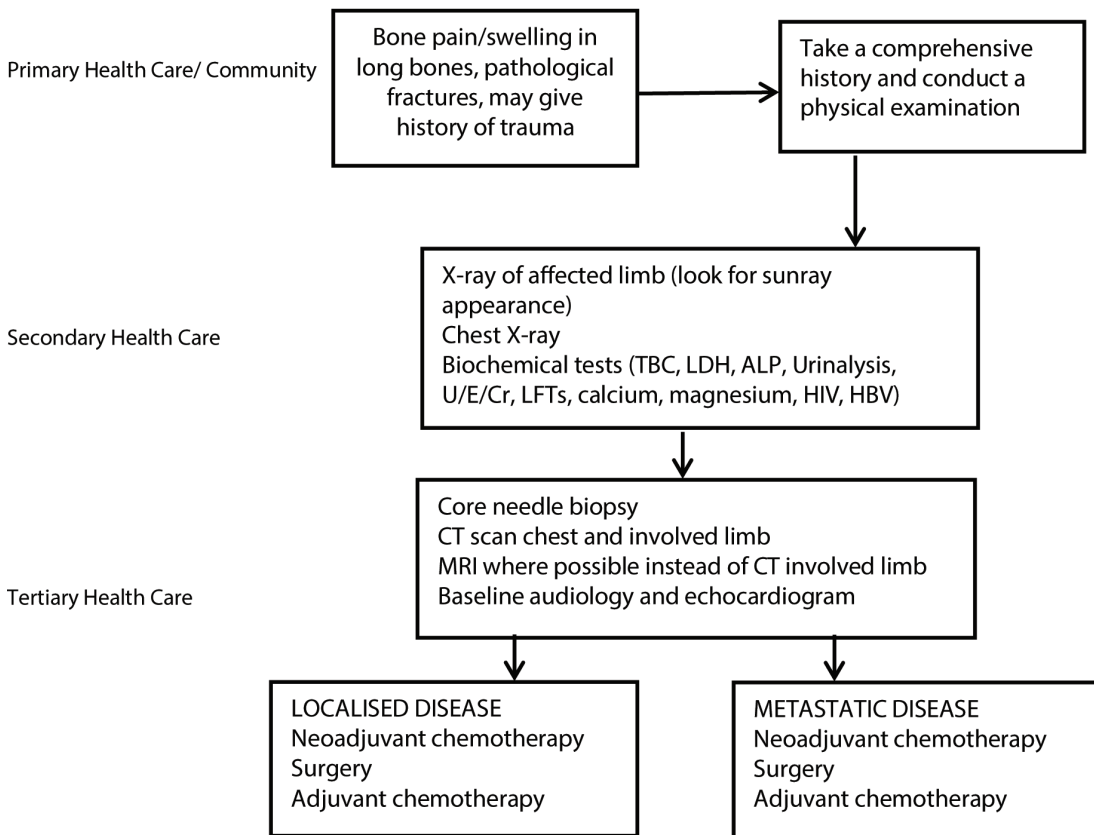
## American Joint Committee Cancer System for Staging Bone Sarcomas

| Stage | Grade | Size  | Metastasis              |
|-------|-------|-------|-------------------------|
| I-A   | Low   | <8 cm | None                    |
| I-B   | Low   | >8 cm | None                    |
| II-A  | High  | <8 cm | None                    |
| II-B  | High  | >8 cm | None                    |
| III   | Any   | Any   | Skip metastasis         |
| IV-A  | Any   | Any   | Pulmonary metastasis    |
| IV-B  | Any   | Any   | Nonpulmonary metastasis |

### Management

High-dose methotrexate, doxorubicin, and cisplatin (MAP): Give 2 cycles of neoadjuvant chemotherapy then perform surgical resection on all sites of disease if possible including an amputation/limb salvage procedures.

### Algorithm for Management of Osteogenic Sarcoma



## Chemotherapy Protocols

High dose methotrexate- based regimens with folinic acid rescue are recommended.

## 11.6 Rhabdomyosarcoma

### Introduction

It is the most common soft tissue sarcoma in children with various histological subtypes such as embryonal, alveolar, sarcoma botryoides and pleomorphic. It is more common in boys than girls, affecting patients between 8 years and 15 years, with median age at diagnosis of 7 years.

### Clinical Evaluation

Head and neck region: signs and symptoms include;

- Orbital- proptosis,
- Mastoid- bloody aural discharge, cranial nerve paralysis and eventually a polypoid mass in the middle ear,
- Nasopharyngeal tumours- airway obstruction, difficulty in mastication and trismus
- Neck tumours- invasion of cervical or brachial plexus with peripheral neurological deficits.

Pelvic region: signs and symptoms include;

- Prostate or bladder area -urinary obstruction
- Scrotum and spermatic cord- scrotal masses.
- In females it commonly presents as the classic sarcoma botryoides (cluster of grapes) of the margins of vagina and uterus.

Other sites include gluteal or perianal region, paravertebral and flank muscles, hands, thighs, arms and legs. Metastasis can be seen in the regional nodes, lungs, bone marrow and other bones resulting in pulmonary insufficiency, cachexia, pancytopenia and pneumonia.

### Intergroup Rhabdomyosarcoma Study Group Staging System

| STAGE | SITE OF PRIMARY TUMOR   | TUMOR SIZE | LYMPH NODES | DISTANT METASTASES |
|-------|---|------------|-------------|--------------------|
| 1     | Orbit, non-PM head/neck; GU non-bladder/prostate; biliary tract | Any size   | N0, N1      | M0                 |
| 2     | All other sites   | ≤5cm       | N0          | M0                 |
| 3     | All other sites   | ≤ 5cm      | N1          | M0                 |
|       |   | >5cm       | N0 or N1    | M0                 |
| 4.    | Any site  | Any size   | N0 or N1    | M1                 |

## Clinical Group

The clinical group is based on the extent of the disease and how completely it is removed during initial surgery. The groups are defined as follows:

### Group I

This group includes children with localized RMS (the cancer has not spread to nearby lymph nodes or to distant sites in the body) that is removed completely by surgery.

### Group II

This group includes children with localized RMS, but in whom cancer cells have been found at the edges (margins) of the removed specimen (meaning that there may have been a small amount of cancer left behind).

It also includes children with RMS that has spread to the nearby lymph nodes.

### Group III

These children have tumours that could not be removed completely. Some tumour was left behind that could be seen with the naked eye. The cancer may have spread to nearby lymph nodes, but there is no sign that it has spread to distant organs.

### Group IV

At the time of diagnosis, these children have evidence of distant cancer spread to places such as the lungs, liver, bones, bone marrow, or to distant muscles or lymph nodes.

## Risk Groups

Using the IRSG stage, the clinical group, and the PAX/FOXO1 fusion gene status, patients are divided into 3 risk groups which helps decide how treatment will be administered.

## Treatment

The goal should be cure despite the cytological or histological prognostic features.

- o Surgery: role varies with the anatomic location, size and extent of the primary tumour but remains the most effective treatment modality in a localised rhabdomyosarcoma.
- o Chemotherapy: combination chemotherapy often dependent on the patient's risk group.

Low-risk group:

- VA: vincristine and dactinomycin (also known as actinomycin-D)
- VAC: vincristine, dactinomycin, and cyclophosphamide

Intermediate-risk group:

- VAC: vincristine, dactinomycin, and cyclophosphamide
- VAC/VI: vincristine, dactinomycin, and cyclophosphamide, alternating with vincristine and irinotecan. Temsirolimus, a targeted therapy, is under study for addition to this regimen.

High-risk group and those with metastatic disease:

- VAC regimen
- Intensive chemotherapy that includes doxorubicin, ifosfamide, and etoposide.
- Consider higher doses, sometimes followed by a stem cell transplant though the advantage over standard chemotherapy is not clear and can cause more side effects.

o Radiotherapy is used when some of the main tumour is still left after surgery (clinical group II or III), or if removing the tumour completely would mean loss of an important organ, like the eye or bladder, or would be disfiguring. It is not usually needed for children with embryonal rhabdomyosarcoma that can be removed completely by surgery (clinical group I). It is given to any area of remaining disease after 6 to 12 weeks of chemotherapy. The exception is when a tumour near the meninges has grown into the skull bones/brain/spinal cord when radiation therapy is given upfront along with chemotherapy.

Stage I: Resection of primary tumour then adjuvant chemotherapy VA.

Stage II: Resection of primary tumour then radiotherapy 4000 to 4500 cGy is given to all patients.

Stage III: Neoadjuvant VAC is used to shrink tumour and to treat occult metastatic foci for 6 weeks, then radiotherapy dose varying from 4000 to 5500cGy (age and amount of residual tumour put into consideration).

Stage IV: VAC is used to shrink tumour and to treat occult metastatic foci for 6 weeks. Tumour is then radiated, dose varying from 4000 to 5500 cGy (age and amount of residual, tumour put into consideration).

Relapse: Any recurrence whether local, regional or distant augurs a poor prognosis. The approach to treatment however still remains cure.

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Last Medical Review: July 16, 2018 Last Revised: July 16, 2018

## 11.7 Retinoblastoma

### Introduction

Retinoblastoma (RB) is a hereditary childhood cancer that arises in the immature cells of the retina. It is the most common primary malignant intraocular cancer in children, and it is almost exclusively found in young children less than 5 years. It is curable if detected and treated early and therapeutic approaches need to consider not only the cure of the disease but also the need to preserve vision with minimal long-term side effects.

While in the developed world, most children (over 90%) treated for retinoblastoma survive, in Africa most of them die from advanced disease. RB is associated with the retinoblastoma gene (a tumor suppressor gene), a mutation in the long arm of chromosome 13. When both homologous loci of the suppressor gene become non-functional by either deletion error or by mutation, retinoblastoma develops.

Retinoblastoma presents in two distinct clinical forms:

1. A bilateral or multifocal, heritable form (25% of all cases), characterized by the presence of germ-line mutations of the RB1 gene; and
2. A unilateral or unifocal form (75% of all cases), 90% of which are non-hereditary.

### Epidemiology

In Kenya, it accounts for 4.8% of all childhood cancers, mostly under the age of 5 years, with an incidence of 1:15,000-20,000 live births. There appears to be no racial predilection for RB and it affects male and female children equally. Bilateral disease is diagnosed at an average age of 13 months, while unilateral disease is diagnosed at an average age of 24 months. About 5-10% of patients who develop this disease have a positive family history although about 30% are hereditary.

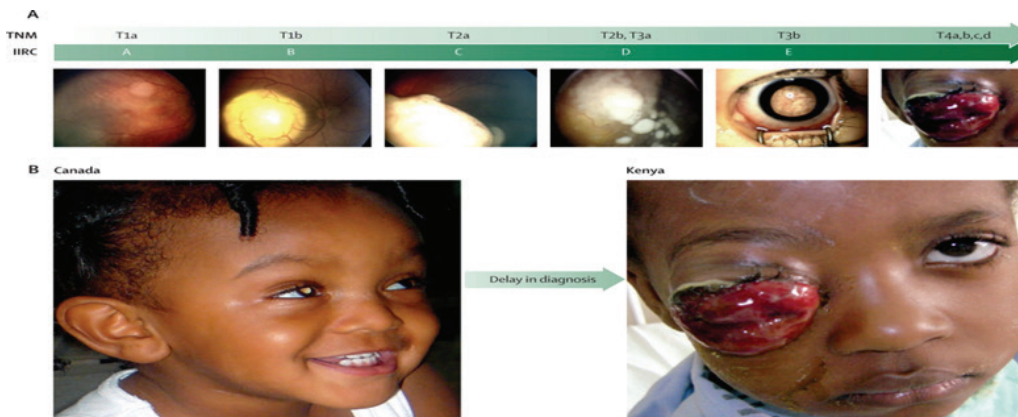
### Clinical Evaluation

**History taking:** Take a comprehensive history and inquire about onset of signs and symptoms, duration and family history. Common presentations include:

- white pupil (leukocoria),
- squint (strabismus),
- proptosis,
- absence of red reflex (light shone into child's eyes in a dimly lit room)
- Others: red painful eye with glaucoma, orbital cellulitis

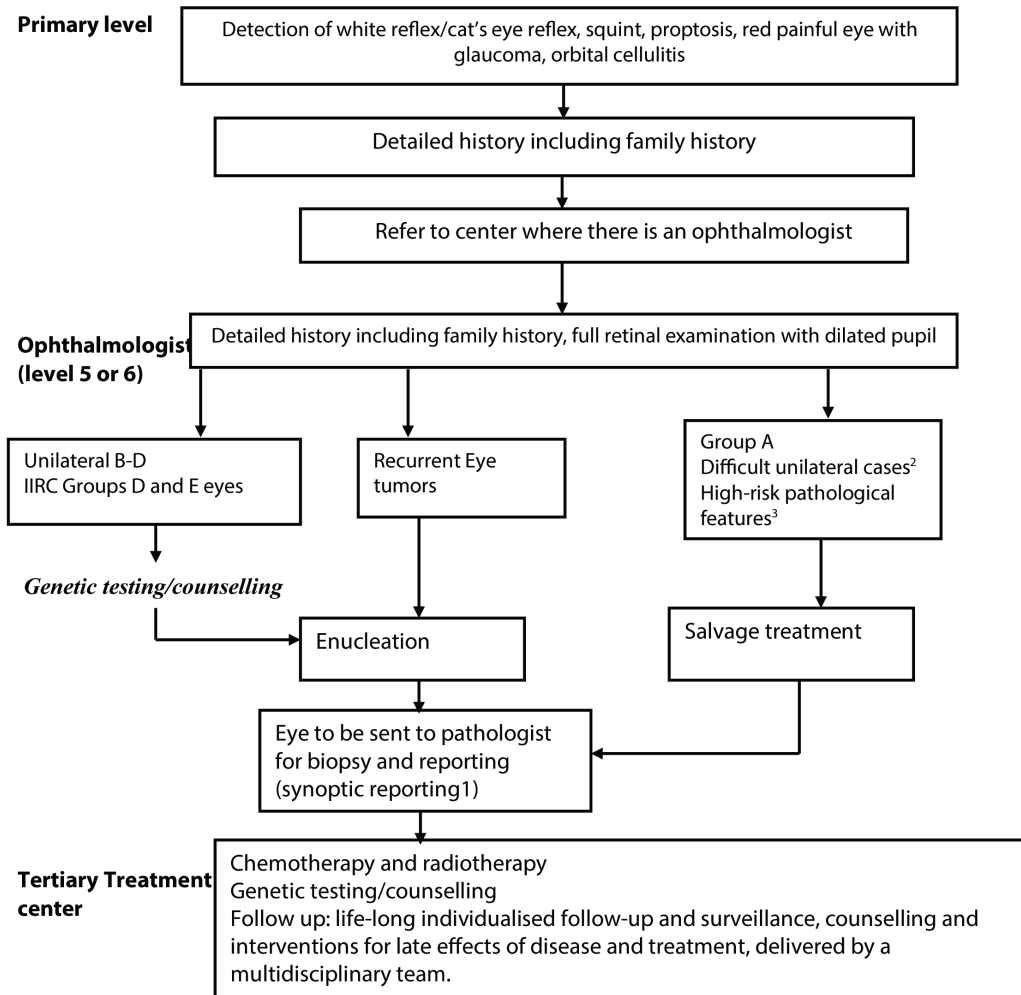
Patients with a family history of retinoblastoma should undergo an ophthalmology review from birth.

**Physical examination:** Conduct a thorough physical examination and examine for white reflex.





## Management Algorithm



1. Pathologist experienced in ocular pathology
2. Very young child; potential to save the eye; unilateral multifocal and/or germline RB1 mutation), positive family history, or risk for extraocular disease and bilateral cases

Imaging after biopsy – MRI of the head and orbits should be done upon diagnosis to check for evidence of intracranial cancer and extent of the disease.

### Treatment

Early stage management involves surgery whereas advanced/late stage involves palliative surgery, chemotherapy and radiotherapy. Couples should undergo genetic counselling.

## Ocular treatments

1. Enucleation to be performed for:
  - a. IIRC Groups D and E eyes when the other eye is normal or Group A
  - b. Unilaterally affected eyes (unless Group A)
  - c. When optimal salvage treatment and follow-up are not possible
  - d. Recurrent tumours when all other treatment modalities (including EBR) have failed,
2. Cryotherapy to be performed for:
  - a. Treatment of small peripheral tumors in group A,B and C eyes
  - b. Posterior Rb refractory to laser focal therapy
  - c. Pre-chemotherapy cryotherapy 24-72 hours prior to increase drug penetration into the eye, particularly for vitreous seeding (except in presence of retinal detachment)
3. Laser therapy to be performed for:
  - a. Posterior tumors in group A, B & C bilateral eyes
4. Systemic chemotherapy for:
  - a. Reduction for tumours in group B, C and D eyes in bilateral disease
  - b. For recurrences after other therapy prior to focal therapy
  - c. In combination with focal therapy for the primary treatment of bilateral IIRC Group B, C or D eyes, but not Group A. If the better eye is group A, B or C, enucleation of group D eyes should be performed. If both eyes are group D then chemoreduction and focal therapy for both eyes in an attempt to save vision as much as possible.
5. Intravitreal chemotherapy for eyes that have vitreous seeds refractory to systemic chemotherapy

## Radiotherapy

Ocular radiotherapy is used only as salvage therapy for the only remaining eye after chemotherapy and focal therapy have failed to control the tumour.

## Extraocular disease

For the purpose of decision making for treatment: Patients are categorised into two groups-

## Summary of Treatment Modalities

| Presentation                 | Treatment Modality                       |
|------------------------------|--|
| All E eyes                   | Enucleate                                |
| Unilateral RB Group B-D      | Enucleate                                |
| Bilateral RB Group A-D       | Salvage                                  |
| Group A                      | Focal Laser or Cryotherapy               |
| Group B-D                    | Chemoreduction + focal treatment         |
| Pathology pT2a               | No Chemotherapy                          |
| Pathology pT2b-PT3a          | 4 courses of chemotherapy                |
| Pathology pT3b and worse     | 6 courses of Chemotherapy + Radiotherapy |
| Proptosis without metastasis | Chemotherapy before enucleation          |
| Metastasis                   | Palliative chemotherapy/radiotherapy     |

### Follow-Up

#### Ophthalmology follow-up

1. EUAs for children at risk of developing new Rb tumours every 3 weeks, or at longer intervals as tumour activity decreases, until risk of new tumours and recurrences is low, and the child is able to cooperate in clinic. The frequency of examinations will be highest when the child has a proven RB1 germline mutation, family history of disease and/or bilateral Rb.
2. EUA or clinic visits for retinal exam continue every 6 months to age 5 and thereafter annually for life.
3. Children shown to not carry the RB1 mutant allele of their family through a blood test do not require EUA or intense surveillance.
4. Examination of an enucleated socket for infection, fit of prosthesis and implant exposure or extrusion at every EUA and clinic visit. Prescribing and monitoring the use of protective eyewear for children who are functionally unioocular.
5. School age with significantly reduced visual fields or visual acuity less than 6/12 undergo visual assessment and referral to a low vision centre for additional assistance.

#### Oncology follow-up

RB survivors treated with chemotherapy or external beam radiotherapy, undergo oncology clinic follow up monthly for 3 months, then every 3 months for 1 year then 6 monthly for one year then yearly or earlier as necessary. Follow up should be comprehensive and multidisciplinary include psychological, endocrinological and counselling for life.



## References

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# 12

## **CHAPTER TWELVE**

### Common Oncologic Emergencies Treatment Protocol

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# COMMON ONCOLOGIC EMERGENCIES

An acute life-threatening condition that occurs due to the cancer itself, or its treatment leading to morbidity or mortality. Most common oncologic emergencies can be categorized as either:

- Metabolic- Tumor lysis syndrome, hypercalcemia of malignancy, syndrome of inappropriate ADH secretion
- Hematologic- hemorrhage, hemoptysis, hemorrhagic cystitis, thrombosis, hyper viscosity syndrome, hyper leukocytosis,
- Structural- superior vena cava syndrome, spinal cord compression, urinary tract obstruction, pathological fractures
- Treatment related- tumor lysis syndrome, febrile neutropenia and sepsis, hemorrhagic cystitis, anemia.

## 12.1 Febrile Neutropenia And Sepsis

**Neutropenia:** Absolute neutrophil count = ANC (% neutrophils x total WBC)

Mild: ANC < 1000/mcL

Severe: ANC < 500/mcL

**Fever:** Single axillary temperature > 38.50 C OR temperature of >38.00 C in 2 readings 1 hour apart.

### Evaluation of Febrile Neutropenia

#### History

Age  
Time since last chemotherapy  
Recent antibiotic therapy / prophylaxis  
HIV status  
Other co-morbidities  
Exposure to sick persons  
Exposure to animal excreta/ live plants/ flowers

#### Laboratory

Bloodslide for malaria parasites  
CBC including differentials  
CXR if respiratory symptoms  
Blood culture  
Urine culture if symptoms or catheter  
Or if severe neutropenia  
Stool culture if diarrhea

#### Examination

Site of bruise  
Skin  
Lungs  
Alimentary canal (mouth, pharynx)  
Perivaginal / perirectal

### Initial Therapy for Fever and Neutropenia

- Haematopoietic growth factors such as filgrastim can be initiated prophylactically post-chemotherapy in patients at high risk for severe neutropenia.
- Re-emphasize infection prevention measures.
- Choice of antibiotics should be tailored to findings on history and physical exam.

#### High risk patient:

IV antibiotics should be used, covering gram +ve and gram -ve organisms

Monotherapy: Cefepime, Ceftazidime or Meropenem are the best.

Use reliable ceftriaxone or combination drugs: Aminoglycoside + antipseudomonal penicillin + beta lactamase inhibitor

If in 48 h no response: Add AB covering anaerobes (IV Metronidazole)

If in 72 h no response: Add antifungal (Amphotericin-B, Fluconazole if ampho-B is unavailable)

#### Low risk patient (and outpatient Rx):

Oral antibiotic allowed: Ciprofloxacin or Amoxicillin/Clavulanic acid

Mouth care with antiseptic

Close observation, and review by a clinician within 72 hours

**NOTE:** Assess for Systemic Inflammation Response Syndrome (SIRS) criteria, symptoms or signs, in an afebrile patient currently receiving chemotherapy (some patients cannot mount fever for example in long term use of corticosteroids). If hypotensive, tachycardic, unstable, and neutropenic, institute febrile neutropenia procedures. Systemic Inflammation Response Syndrome (SIRS) is recognized by:

- Temperature  $> 38^{\circ}\text{C}$  or  $< 36^{\circ}\text{C}$
- Heart rate  $> 90$  beats/minute (tachycardia)
- Respiratory rate  $> 20$  breaths/minute (tachypnea)
- Systolic blood pressure  $\leq 90$  mm Hg (hypotension)
- Abnormally high or low white blood cells

SIRS criteria (1 or more) predict serious infection and sepsis in a chemotherapy patient at time of presentation / triage even in the absence of fever.

## Infection Prevention during Chemotherapy

|                 |  |
|-----------------|--|
| <b>Ward</b>     | <p>Patient should be in isolation area (away from acute infections)</p> <p>Only one patient per bed</p> <p>In severe neutropenia one patient per cubicle</p> <p>Strict asepsis for invasive devices</p> <p>Change nebulizers, humidifiers, water in jugs daily</p> <p>Strict hand washing / hand sanitizer in between patients</p> |
| <b>Staff</b>    | <p>In severe neutropenia handling of the patients should be as little as possible fresh linen should be provided daily</p> <p>Live flowers and plants should be out of patients room</p>   |
| <b>Food</b>     | <p>Only use safe foods (no salads, raw eggs, left over foods)</p>  |
| <b>Visitors</b> | <p>Allow only limited visitation, without respiratory infections</p> <p>Visitors should wash hands before entering patients room</p>   |
| <b>Personal</b> | <p>Prevention of infection, Regular hand washing</p> <p>Oral hygiene: Cleaning of mouth with water after every meal (with assistance if needed) Use of soft tooth brush twice daily</p> <p>Betadine mouth wash in severe neutropenia</p>   |
| <b>Drugs</b>    | <p>For paediatrics, Pneumocystis carinii prophylaxis in all patients on chemotherapy:</p> <ul style="list-style-type: none"> <li>• Use Cotrimoxazole 15+3 mg/kg OD</li> <li>• Continue till end of maintenance</li> </ul>  |

## 12.2 Superior Vena Cava Syndrome

This refers to impaired blood flow from the SVC to the right atrium due to obstruction which may either be: internal (for example, thrombus) or external (malignant/non-malignant). Malignancies associated with superior vena cava syndrome include: Lung Cancer – SCLC, NSCLC, Non-Hodgkins Lymphoma, Thymoma, Germ cell tumors of mediastinum and Metastatic tumors.

### Clinical Presentation

Early symptoms – Dyspnea and non-productive cough, headache, dysphagia, hoarseness, chest pain, facial puffiness.

Late symptoms -Visual disturbances, dizziness, syncope, lethargy, irritability and mental status changes.

Physical examination often reveals engorgement of veins and collaterals in the upper extremities.

### Management

Bed rest with head elevation, Oxygen administration prn, corticosteroids, and diuretics, restrict intravenous fluids, no IV line in upper limbs.

Other specific management depends on the cause; such as local lytic therapy or anticoagulation (for catheter induced thrombosis), chemotherapy, radiotherapy, and stents insertion.



## 12.3 Spinal Cord Compression

2.5–5.0% of patients have spinal cord compression (SCC) within the last 2 years of their illness.

-Prostate, breast cancer, lung cancer most common each ~15–20%

-NHL, multiple myeloma, and renal cancer ~5–10% of patients

Thoracic spine affected in 60–80% of cases though 50% may present with disease in multiple spinal areas.

### Signs and Symptoms

Presents with new onset back pain (initially localized, typically increasing in intensity, worsens when the patient is lying down, pain with percussion of vertebral bodies), weakness (60–85% of patients present with weakness), about 2/3 are non-ambulatory at presentation. Late neurologic signs are associated with permanent deficits such as paraplegia, urinary retention and loss of sensory function.

Often leads to permanent neurologic dysfunction though 80–90% of patients ambulatory at treatment retain function. Ambulatory status is therefore the most important prognostic feature.

### Imaging

- Non-contrast MRI of whole spine is recommended
- If MRI not available, can use Myelography/CT
- Biopsy if: metastatic disease not proven/documented, or no previous diagnosis of cancer.

### Management

Strict bed rest, start on steroids immediately to reduce edema and further cord compression.

WITH FRACTURE AND UNSTABLE BONE FRAGMENTS: Surgical decompression and stabilization.

WITH FRACTURE, STABLE FRAGMENTS: Radiation therapy

CORD COMPRESSION WITH NO FRACTURE: Radiation Therapy or Chemotherapy.

## 12.4 Hypercalcaemia of Malignancy

It occurs in 10 % of cancer patients. Malignancies associated with hypercalcemia include: Multiple myeloma, breast cancer, lung cancer, lymphomas, renal cell carcinoma and esophageal cancer.

Can be humoral or local osteolytic hypercalcemia. Management: Intravenous saline infusion, steroids and osteoclast activation blockade using bisphosphonates, RANKL block by denosumab.



## 12.5 Syndrome of Inappropriate ADH Secretion

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. 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.

## 12.6 Haematological Emergencies

**Hyperviscosity Syndrome:** Serum viscosity >4.0 Ostwald units. Treatment; intravenous fluids followed by diuresis, plasma exchange, chemotherapy

**Hyperleukocytosis:** WBC count in the peripheral blood higher than 100,000/uL. Management: involves lowering the WBC count, which can be accomplished with leukapheresis or chemotherapy.

**Thrombosis:** Both deep venous thrombosis and pulmonary thromboembolism. Management: anticoagulation and appropriate mechanical approaches as appropriate.

**Bleeding:** Prolonged bleeding both internally and externally. Management: Treat the primary cause and give blood components.

## 12.7 Genitourinary Emergencies

**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.

**Urinary Tract Obstruction:** Involve ureters, or urethra Management: Relieve obstruction by catheterization and stenting as appropriate.

**Acute Renal Failure (ARF):** This is characterized by sudden decrease in glomerular filtration rate, leading to an acute rise in blood urea nitrogen (BUN) and serum creatinine (Cr) levels. It is a serious complication of many malignancies, which causes important morbidity and mortality.

**Presentation-** Symptoms related to ARF will differ based on the underlying cause (Pre, intra and post renal causes) and mechanism.

The diagnosis is based on laboratory results, with a decrease in glomerular filtration rate, and a rise in BUN and serum Cr levels. Treatment is established according to the underlying cause.

## 12.8 Respiratory Emergencies

**Airway Obstruction:** Common in lung cancer, head and neck tumors, lymphomas, thymomas and thyroid malignancies. Symptoms include cough, dyspnea, stridor.

Management: Surgical intervention (Intubation and tracheostomy) with or without appropriate medication (steroids, bronchodilators, chemo/radiotherapy) Oxygen prn. Definitive Treatment: Chemoradiotherapy, radiotherapy

**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. Options include bronchial artery embolization or tumor resection, external beam radiation therapy (EBRT), local epinephrine injection, laser treatment, electrocautery, photocoagulation, balloon tamponade, or iced-saline lavage.

**Toxic Lung Injury:** Presents as acute respiratory distress syndrome. Management: Support as appropriate.

## 12.9 Chemotherapy-Induced Extravasations

Some chemotherapy drugs are vesicants, hence higher potential to cause local damage after extravasation, leading to ulcers, and tissue necrosis or nerve damage of the area. These drugs include Vincristine, Vinblastine, Vinorelbine, Actinomycin D, Adriamycin, Epirubicin, Mitomycin C and Paclitaxel.

1. **Risk factors for extravasation include:** Patient related factors-consider preventative measures/insertion of a central venous access device if cannulation is difficult for example veins (Small, fragile, hard/sclerosed, prominent but mobile), obesity, sensory deficits
2. **Procedure-related factors:** untrained/inexperienced staff, multiple cannulation attempts, unfavorable sites such as antecubital fossa/over joints/ inner wrist/lower extremities, prolonged infusions, bolus injections,
3. **Management:** Stop and disconnect infusion, prompt expulsion of the extravasated agent and remove cannula.
4. **Anthracyclines/Antibiotics/Alkylating agents:** Cooling with ice packs for 20 minutes 4 times daily for 24-48 hours,
5. **Vinca alkaloids/Taxanes/Platinum:** Dry warm compressions for 20 minutes 4times daily for 24-48hours, injections of hyaluronidase (Vinca alkaloids and Taxanes).
6. **For non-vesicant drugs:** local dry cold compresses.

Limb elevation and urgent consultation of plastic surgeons for early debridement.

Put information down in records about extravasation so that appropriate follow-up is arranged.

### References

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<https://repositorio-aberto.up.pt/bitstream/10216/112860/2/273345.pdf>

Ministry of Health Cancer Management guidelines (2013)

A

APPENDICES

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## APPENDIX 1: PATIENT PERFORMANCE STATUS FOR CHILDREN

Based on the Lansky performance measure for childhood cancer patients.(12)

- 100 – fully active, normal
- 90 – minor restrictions in strenuous physical activity
- 80 – active, but gets tired more quickly
- 70 – greater restriction of play and less time spent in play activity
- 60 – up and around, but active play minimal; keeps busy by being involved in quieter activities
- 50 – lying around much of the day, but gets dressed; no active playing  
participates in all quiet play and activities
- 40 – mainly in bed; participates in quiet activities
- 30 – bedbound; needing assistance even for quiet play
- 20 – sleeping often; play entirely limited to very passive activities
- 10 – doesn't play; does not get out of bed
- 0 – unresponsive

## APPENDIX 2: PERFORMANCE SCALES: KARNOFSKY AND EASTERN CO-OPERATIVE ONCOLOGY GROUP (ECOG) SCORES

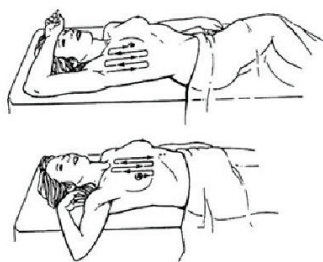
| Karnofsky Status  | Karnofsky Grade | ECOG Grade | ECOG Status   |
|---|-----------------|------------|---|
| Normal, no complaints   | 100             | 0          | Fully active, able to carry on all pre-disease performance without restriction  |
| Able to carry on normal activities. Minor signs or symptoms of disease      | 90              | 1          | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| Normal activity with effort   | 80              | 1          | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| Care for self. Unable to carry on normal activity or to do active work      | 70              | 2          | Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours                            |
| Requires occasional assistance, but able to care for most of his needs      | 60              | 2          | Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours                            |
| Requires considerable assistance and frequent medical care                  | 50              | 3          | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours  |
| Disabled. Requires special care and assistance                              | 40              | 3          | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours  |
| Severely disabled. Hospitalisation indicated though death nonimminent       | 30              | 4          | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair   |
| Very sick. Hospitalisation necessary. Active supportive treatment necessary | 20              | 4          | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair   |
| Moribund  | 10              | 4          | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair   |
| Dead  | 0               | 5          | Dead  |

As published in Am J Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair. Adapted from ESMO Guidelines.

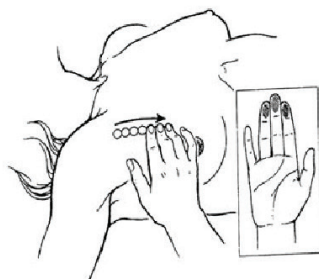
## APPENDIX 3: CLINICAL BREAST EXAMINATION

### Evaluation: Physical Exam

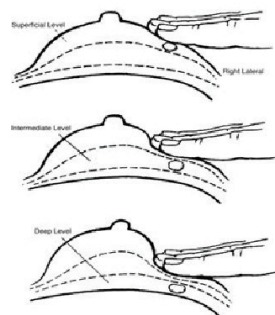
#### ■ Clinical Breast Exam:



Position the patient in the direction of palpation for the CBE.



Use pads of the index, third, and fourth fingers (*inset*) make small circular motions



Make three circles with the finger pads, increasing the level of pressure (subcutaneous, mid-level, and down to the chest wall) with each circle

Sanslow, D, et. al. Clinical breast examination” practical recommendations for optimizing performance and reporting. CA Cancer J Clin. 2004 Nov-Dec; 54(6): 327-44

## APPENDIX 4: COTSWOLDS\_ MODIFIED ANN ARBOR STAGING OF HODGKINS LYMPHOMA

|                  |  |
|------------------|--|
| <b>Stage I</b>   | Involvement of a single lymph node region or lymphoid structure (e.g. spleen, thymus)  |
| <b>Stage II</b>  | Involvement of two or more lymph node regions on the same side of the diaphragm  |
| <b>Stage III</b> | Involvement of lymph node regions on both sides of the diaphragm   |
| <b>Stage IV</b>  | Involvement of extranodal site(s)  |
| <b>A</b>         | No constitutional symptoms   |
| <b>B</b>         | Constitutional symptoms: Unexplained fever ( $>38.5^{\circ}\text{C}$ ), weight loss ( $\geq 10\%$ total body weight in six months), drenching night sweats |
| <b>X</b>         | Bulky disease: $>1/3$ the width of the mediastinum; $>10\text{cm}$ maximal diameter of nodal mass  |



## APPENDIX 5: SAMPLE MEDICAL REFERRAL FORM

Use this form to refer patients to a cancer treatment facility. Fill in all the areas as completely and accurately as possible.

|  |  |  |  |  |  |   |  |                    |             |  |                    |  |
|--|--|--|--|--|--|---|--|--------------------|-------------|--|--------------------|--|
| <b>Name (last)</b>   |  |  |  | <b>(first)</b>   |  |   |  | <b>(middle)</b>    |             |  |                    |  |
| <b>Hospital name</b>   |  |  |  |  |  | <b>Hospital No. /Ward</b>                                     |  |                    | <b>Ward</b> |  |                    |  |
| <b>Residence Address</b>   |  |  |  |  |  | <b>Contact information</b>                                    |  |                    |             |  |                    |  |
| <b>Date of birth</b>   |  |  |  | <b>Gender (Tick )</b>  |  |   |  | <b>Height (cm)</b> |             |  | <b>Weight (Kg)</b> |  |
|  |  |  |  | <b>Male</b> <input type="checkbox"/><br><b>Female</b> <input type="checkbox"/> |  |   |  |                    |             |  |                    |  |
| <b>Referral Type</b>   |  |  |  |  |  |   |  |                    |             |  |                    |  |
| <input type="checkbox"/> Immediate referral (to be seen within 24hrs of referral)<br><input type="checkbox"/> Urgent referral (to be seen within 2 weeks of the referral)<br><input type="checkbox"/> Non-urgent referral (can be seen after 2 weeks at referral facility) |  |  |  |  |  |   |  |                    |             |  |                    |  |
| <b>Presenting clinical features</b> <i>(include duration of symptoms, physical examination findings)</i>   |  |  |  |  |  |   |  |                    |             |  |                    |  |
| <b>Family and social history</b>   |  |  |  |  |  |   |  |                    |             |  |                    |  |
| <b>Immunization status( for children):</b> <i>Include the dates when given</i>   |  |  |  |  |  |   |  |                    |             |  |                    |  |
| <b>Vaccine</b>   |  |  |  |  |  | <b>Date</b> <i>(month and year if actual dates not known)</i> |  |                    |             |  |                    |  |
|  |  |  |  |  |  |   |  |                    |             |  |                    |  |



|  |                       |                 |    |
|--|-----------------------|-----------------|----|
| <b>Investigation results</b> <i>(include dates where known)</i>              |                       |                 |    |
| <b>Probable diagnosis/differentials</b>                                      |                       |                 |    |
| <table border="1"><tr><td>OR</td></tr></table>                               |                       |                 | OR |
| OR   |                       |                 |    |
| <b>Diagnosis and stage</b> <i>(if known)</i>                                 |                       |                 |    |
| <b>Comorbidities</b> <i>(include treatments for this)</i>                    |                       |                 |    |
| <b>Treatments given</b> <i>(all anticancer treatments must be indicated)</i> |                       |                 |    |
| <b>Date</b>  | <b>Dose and route</b> | <b>duration</b> |    |
|  |                       |                 |    |
| <b>Discharge medications</b> <i>(list all)</i>                               |                       |                 |    |
| <b>Date</b>  | <b>Dose and route</b> | <b>duration</b> |    |
|  |                       |                 |    |
| <b>Reason for referral</b>   |                       |                 |    |
| <b>Person referring</b> (name)   |                       | <b>Date</b>     |    |

## APPENDIX 6: IMAGING PROTOCOLS

### BREAST IMAGING PROTOCOLS

#### Bilateral Mammography

The optimal mammogram images will include:

1. Bilateral MLO and CC views
  - a. MLO views: Pectoralis muscle well demonstrated with caudal level in line with the nipple convex outwards with inframammary fold and nipple in profile. No skin folds
  - b. CC views: Pectoralis muscle demonstrated posteriorly in both breasts. Nipple in profile with inframammary folds. No skin folds.
2. Supplementary views as recommended by the radiologist

*All mammograms should be read by a radiologist with experience in mammography reading.*

#### Breast MRI

An ideal MRI should have:

1. High field (Bo) magnet (>1.5T) that is bilateral with complete breast and axillary coverage.
2. Breast dedicated only surface coils (High SNR)
3. Dynamic Contrast Imaging
4. Multiphasic T1
5. Minimum two post contrast T1W1 – the 1st within 4 minutes of contrast injections
6. DWI

### HEAD & NECK CANCER IMAGING PROTOCOLS

#### CT SCAN NECK

This is the imaging modality of choice for most head and neck (except for Thyroid tumors where ultrasound is the first line imaging modality).

#### Protocol:

The field covered should extend from the middle cranial fossa to the thoracic inlet to show the arch of the aorta and the lung apices. This enables the demonstration of the brain stem which is home of the cranial nerve nuclei thus enabling demonstration of peri-neural spread if present.

This will also enable assessment of lymph node (i.e. levels I to VII) involvement by tumor at the same sitting for nodal staging. Pre and post I.V contrast scans should be acquired.

A radiologist's report should always be part of the examination.

#### ULTRASOUND

Ultrasound scan should be used as complementary to the CT scan for example:

- To characterize a neck mass as solid (lymph node) or cystic (cyst). But one should be cautious as a malignant necrotic lymph node may appear cystic.
- To guide FNA or Lymph node biopsy.

#### MRI (MAGNETIC RESONANCE IMAGING)

This imaging modality plays a problem solving role i.e.:

- To assess for perineural tumour spread
  - To plan for surgery where CT SCAN findings are equivocal
- It has even more limited role in imaging of the laryngeal lesions due to image degradation by breathing and swallowing movements.

## SUMMARY OF HEAD & NECK CANCER IMAGING

### 1. **Nasopharyngeal Cancer**

This is a commonly symptom poor region in early disease and is not easily accessible to the clinician. The disease can first present with enlarged neck lymph nodes and reduced hearing. Imaging thus plays an important role in early detection of the disease. So a patient who presents to the primary level of health with suspicious enlarged neck lymph nodes should expeditiously be offered CT Scan Neck by the managing clinician.

### 2. **Oropharyngeal/Hypopharyngeal Cancer.**

Commonly presents with pain or difficulty on swallowing. It is easily accessible to the clinician for assessment visually. The role of imaging is to assess for deep extent of the tumour and staging. Nodal involvement is common at time of presentation. CT scan is the imaging modality of choice.

### 3. **Oral Cavity Cancer**

This includes tumours of the anterior 2/3rds of the tongue, gingiva and buccal mucosa. It is easily visualized by the clinician on oral clinical inspection. MRI is the imaging modality of choice for tongue tumours because CT scan has poor soft tissue contrast. CT SCAN with puffed mouth protocol is sufficient for gingival and buccal tumours assessment.

### 4. **Laryngeal Cancer**

Early symptoms include change of voice e.g. hoarseness of voice. Tumour progression will cause air way obstruction which may need emergency tracheostomy. CT scan is the imaging modality of choice commonly done after laryngoscopy for tumour and nodal staging.

### 5. **Sinonasal Cancer**

This is a tumour involving the nasal cavity and paranasal sinuses. Imaging modality of choice is CT scan. Images should be printed in axial and coronal series.

### 6. **Thyroid Cancer**

May present with visible thyroid gland enlargement or hoarseness of voice. High resolution (linear Probe) can be used for the initial assessment. It is also useful for guiding tissue biopsy and lymph nodes involvement assessment.



### 7. **Tracheal Cancer.**




This is rare compared to the other head and neck cancers. It may present with difficulties in breathing due to airway obstruction. CT scan is the imaging modality of choice.

## CLINICAL INDICATIONS FOR PET CT SCAN

| CANCER         | PET CT INDICATIONS   |
|----------------|--|
| Breast         | <p><b>FDG PET CT</b></p> <ul style="list-style-type: none"> <li>• Assessment of multifocal disease or suspected recurrence where other imaging is negative</li> <li>• Characterization of indeterminate lesions on conventional imaging</li> <li>• Differentiation of treatment induced brachial plexopathy from tumor infiltration in symptomatic patients</li> </ul>   |
| Prostate       | <ul style="list-style-type: none"> <li>• Ga68-PSMA PET CT and F-Choline PET CT to assess for biochemical recurrence</li> </ul>   |
| Gynaecological | <p><b>FDG PET CT</b></p> <ul style="list-style-type: none"> <li>• Staging or restaging patients with uterine (cervical/endometrial) malignancies considered for radical chemo-radiotherapy or exenterative surgery</li> <li>• Suspected recurrence where conventional imaging is negative for ovarian cancer</li> </ul>  |
| Haematological | <p><b>FDG PET CT</b></p> <p><b>Lymphoma:</b></p> <ul style="list-style-type: none"> <li>• Staging,</li> <li>• Radiotherapy planning</li> <li>• Remission assessment</li> <li>• Suspected relapse</li> <li>• Suspected post-transplant lymphoproliferative disorder</li> </ul> <p><b>Myeloma:</b></p> <ul style="list-style-type: none"> <li>• Staging and follow up to assess treatment response</li> <li>• Identify patients with smouldering myeloma with high risk of progression to symptomatic disease requiring treatment</li> <li>• Assessment of patients with apparently solitary plasmacytoma to exclude other sites of disease</li> </ul> |
| GIT            | <p><b>FDG PET CT</b></p> <p><b>Oesophago-gastric cancers</b></p> <ul style="list-style-type: none"> <li>• Staging and assessment post neo-adjuvant therapy</li> </ul> <p><b>Hepato-pancreatic tumors</b></p> <ul style="list-style-type: none"> <li>• Staging of selected patients where conventional imaging is equivocal</li> </ul> <p><b>Colorectal cancer</b></p> <ul style="list-style-type: none"> <li>• Suspected recurrence, staging of patients with synchronous metastases at presentation</li> </ul>  |
| Head & Neck    | <p><b>FDG PET CT</b></p>   |

# APPENDIX 7: CANCER TREATMENT JOB AID

|  |   |
|--|---|
| <p><b>Assess</b></p>    | <ol style="list-style-type: none"> <li>1) Evaluate the information the patient currently has about their diagnosis. Ask about:             <ul style="list-style-type: none"> <li>• What has the patient been told?</li> <li>• Who spoke with the patient?</li> <li>• Who was there with the patient?</li> <li>• What written/other information was offered to support the patient to learn more about:                 <ul style="list-style-type: none"> <li>▪ The specific Cancer,</li> <li>▪ What to expect</li> <li>▪ Treatment pathway (Chemotherapy, Radiotherapy, Surgery, etc.)</li> <li>▪ Self-care</li> <li>▪ What follow-up is required</li> </ul> </li> </ul> </li> <li>2) Psychological status, financial implications and support structures             <ul style="list-style-type: none"> <li>• Assess the psychological and general financial implications to the patient and document the same in the patient file.</li> <li>• Assess the patient support system i.e. family? Friend(s)?</li> </ul> </li> <li>3) Specialist assessment and intervention summary             <ul style="list-style-type: none"> <li>• Explain the implications of the assessment and what it means for the patient</li> </ul> </li> <li>4) Treatment plan summary             <ul style="list-style-type: none"> <li>• Discuss the treatment plan with the patient</li> <li>• Address any concerns the patient and their family may have concerning the treatment <i>options</i></li> <li>• Explain to the patient and their family the intent of the treatment                 <ul style="list-style-type: none"> <li>Is the treatment curative? Why?</li> <li>Is the treatment palliative? Why?</li> </ul> </li> <li>• <i>Any amendments must be made in consultation with the patient</i></li> </ul> </li> </ol> |
| <p><b>Advise</b></p>  | <ol style="list-style-type: none"> <li>1) Next steps – when treatment will be started             <ul style="list-style-type: none"> <li>• Discuss the treatment schedule with the patient and their family</li> <li>• Address any concerns the patient and their family may have concerning the treatment <i>schedule</i></li> </ul> </li> <li>2) Summary of medications and alterations to medication             <ul style="list-style-type: none"> <li>• Discuss the summary of medication with the patient and their family</li> <li>• Outline what the patient should expect in the course of treatment</li> <li>• Highlight any potential side effects and how they will be managed</li> </ul> </li> </ol>   |

|  |   |
|--|---|
| <p>Agree</p>      | <ol style="list-style-type: none"> <li>1) Jointly set a treatment <i>start date</i> with the patient and their family</li> <li>2) Agree on critical lifestyle modifications for the patients to enhance their quality of life e.g. cessation of tobacco and alcohol use, nutrition, rest, exercise, etc.</li> <li>3) Agree on critical decisions in the treatment pathway namely / e.g. treatment, monitoring during survivorship, etc. This will help the patient to prepare for their recovery journey and enhance adherence to treatment</li> <li>4) Agree on other support mechanisms to enhance quality of life e.g. linkages to palliative care, psychosocial support groups; Counseling; health talks and build these into the patient treatment plan and schedule</li> </ol> <p><i>Note: The patient is the central focus of the multidisciplinary team and must be given full information in order to make informed choices about their treatment. Their agreement and participation in decisions about their treatment enhance adherence to plan and self-efficacy.</i></p> |
| <p>Assist</p>    | <ol style="list-style-type: none"> <li>1) Assist the patient and their family to plan for the treatment journey by: <ul style="list-style-type: none"> <li>• Providing them with a written summary of their treatment plan</li> <li>• Helping the patient and their family to schedule their next appointments</li> <li>• Giving clear and documented referrals to other entities that may / will support their treatment e.g. Laboratory, Nutrition, Counselling, Psychosocial support groups, insurance, etc.</li> <li>• Linking patients and their families to critical support entities <ul style="list-style-type: none"> <li>○ <i>NHIF</i>; For registration and/or further information about medical cover</li> <li>○ <i>Foundations and Philanthropic entities</i> that may assist with various aspects of treatment</li> <li>○ <i>Palliative care</i></li> </ul> </li> </ul> </li> <li>2) Skills and tools for self-management, adherence</li> </ol>   |
| <p>Arrange</p>  | <ol style="list-style-type: none"> <li>1) At every visit, arrange and record next appointment date, including family (as appropriate)</li> <li>2) Arrange and record care activities/support between visits</li> <li>3) Provide the patient and family the contact details of the clinic for further information/discussion</li> <li>4) Assure the patient that they can call at any time</li> <li>5) Survivorship care planning</li> </ol>   |

## APPENDIX 8: LIST OF INDIVIDUALS, ORGANISATIONS AND INSTITUTIONS THAT PARTICIPATED IN THE PROTOCOL DEVELOPMENT PROCESS

| Name                       | Organization  |
|----------------------------|---|
| David Makumi               | Kenya Network of Cancer Organizations (KENCO)       |
| Dr. Ahmed Kalebi           | Lancet Kenya  |
| Dr. Ahmed Komen            | Kenyatta National Hospital                          |
| Dr. Alfred Karagu          | National Cancer Institute-Kenya (NCI)               |
| Dr. Anne Mwirigi           | Aga Khan University Hospital                        |
| Dr. Allan Rajula           | Aga Khan University Hospital                        |
| Dr. Angela Mcligeyo        | University of Nairobi                               |
| Dr. Anne Ng'ang'a          | National Cancer Control Program                     |
| Dr. Anthony Ndiritu        | Kenyatta National Hospital                          |
| Dr. Beatrice Mugi          | Kenyatta National Hospital                          |
| Dr. Betty Musau            | Nairobi Hospital                                    |
| Dr. Caroline Kirigo        | Kenya Ear Nose and Throat Society (KENTS)           |
| Dr. Catherine Nyongesa     | Kenyatta National Hospital                          |
| Dr. Daniel Ojuka           | University of Nairobi                               |
| Dr. David Wata             | Kenyatta National Hospital                          |
| Dr. Doreen Mutua           | Gertrude's Hospital                                 |
| Dr. Edna Kamau             | University of Nairobi                               |
| Dr. Edward Sang            | MP Shah Hospital                                    |
| The late Dr. Eliud Njuguna | Kenyatta National Hospital                          |
| Dr. Elizabeth Dimba        | University of Nairobi                               |
| Dr. Eric Hungu             | Kenyatta National Hospital                          |
| Dr. Esther Munyoro         | Kenyatta National Hospital                          |
| Dr. Eunice Gathitu         | National Cancer Control Program                     |
| Dr. Ezzi Mohammed          | University of Nairobi                               |
| Dr. Germaine Makory        | Kenyatta National Hospital                          |
| Dr. Gladys Mwango          | University of Nairobi                               |
| Dr. Greg Ganda             | Jaramogi Oginga Odinga Teaching & Referral Hospital |
| Dr. Helena Musau           | Meru County   |
| Dr. Innocent Maranga       | Kenyatta National Hospital                          |
| Dr. Irene Weru             | Kenyatta National Hospital                          |
| Dr. Izaq Odongo            | Ministry of Health                                  |
| Dr. Jamila Rajab           | University of Nairobi                               |
| Dr. Jasper Muruka          | Kenyatta National Hospital                          |
| Dr. Joan Paula Bor         | National Cancer Control Program                     |
| Dr. Joel Okumu             | Ministry of Health                                  |
| Dr. John Weru              | Aga Khan University Hospital                        |
| Dr. Joseph Kibachio        | Ministry of Health                                  |
| Dr. Khadija Warfa          | Aga Khan University Hospital                        |
| Dr. Leonora Okubasu        | Independent Consultant                              |
| Dr. Lilian Kochola         | Ministry of Health                                  |
| Dr. Mary Nyangasi          | National Cancer Control Program                     |
| Dr. Matilda Ongondi        | Kenyatta National Hospital/University of Nairobi    |
| Dr. Michael Mwachiro       | Tenwek Hospital                                     |



|                        |   |
|------------------------|---|
| Dr. Miriam Mutebi      | Aga Khan University Hospital                                    |
| Dr. Naftali Busakhala  | Moi University  |
| Dr. Nancy Okinda       | Aga Khan University Hospital                                    |
| Dr. Njoki Njiraini     | Ministry of Health  |
| Dr. Peter Bird         | Kijabe Hospital   |
| Dr. Peter Kitunguu     | Kenyatta National Hospital                                      |
| Dr. Peter Oyiro        | Kenyatta National Hospital/University of Nairobi                |
| Dr. Primus Ochieng     | Ministry of Health  |
| Dr. Richard Njoroge    | Ministry of Health  |
| Dr. Sarah Muma         | Kijabe Hospital   |
| Prof. Shaheen Sayed    | Aga Khan University Hospital                                    |
| Dr. Sitna Mwanzi       | Aga Khan University Hospital                                    |
| Dr. Siwillis Mithe     | Murang'a County   |
| Dr. Timothy Mutala     | University of Nairobi   |
| Dr. Valerian Mwenda    | National Cancer Control Program                                 |
| Dr. Vijay Narayanan    |   |
| Dr. Wilson Miriti      | Kenyatta National Hospital                                      |
| Dr. Wycliffe Kaisha    | Kenyatta National Hospital                                      |
| Dr. Zipporah Ali       | Kenya Hospices & Palliative Care Association                    |
| Mishka Cira            | US National Cancer Institute                                    |
| Ms. Hannah Gitungo     | National Cancer Control Program                                 |
| Ms. Lydia Kirika       | National Cancer Control Program                                 |
| Patricia Njiri         | Clinton Health Access Initiative                                |
| Prof Jessie Githanga   | University of Nairobi   |
| Prof Lucy Muchiri      | University of Nairobi   |
| Prof. Muthoni Musibi   | University of Nairobi/Kenyatta National Hospital                |
| Prof. Fred Chite       | Academic Model for the Prevention and Treatment of HIV (AMPATH) |
| Prof. Godfrey Lule     | Nairobi Hospital  |
| Prof. Othieno Abinya   | University of Nairobi   |
| Prof. William Macharia | Aga Khan University Hospital                                    |
| Roselyne Okumu         | Kenyatta National Hospital                                      |
| Ruth Muia              | National Cancer Institute-Kenya                                 |
| Stellamaris Musomi     | Kenyatta National Hospital                                      |

## List of Reviewers

1. Breast Cancer- Prof. Fred Chite, Prof. Othieno Abinya
2. Brain and Central Nervous System- Prof. Nimrod Mwang'ombe
3. Gastrointestinal Tract- Prof. Godfrey Lule
4. Gynaecological Cancers- Dr. Elkanah Omenge
5. Head and Neck Cancers- Kenya ENT Society
6. Adult Haematological- Prof. Muthoni Musibi, Prof. Othieno Abinya
7. Kaposi's Sarcoma- Dr. Naftali Busakhala, Prof. Fred Chite
8. Lung Cancers- Prof. Fred Chite
9. Urological Cancers- Dr. David Kimani
10. Paediatric Cancers- Prof. William Macharia

