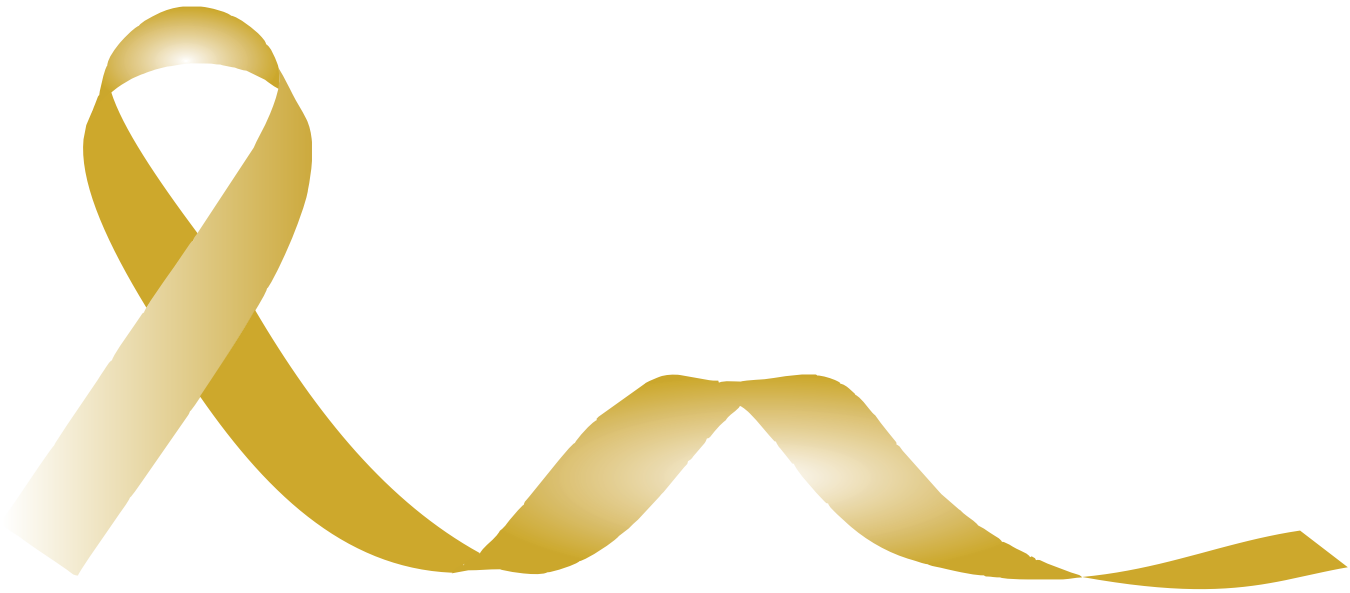
Republic of Zambia
Ministry of Health

CONSOLIDATED GUIDELINES FOR CHILDHOOD CANCER CARE IN ZAMBIA



FIRST EDITION 2025

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ACRONYMS AND ABBREVIATIONS

ADC	Apparent Diffusion Coefficient
ALARA	As Low As Reasonably Achievable
ALL	Acute Lymphoblastic Leukaemia
AML	Acute Myeloid Leukaemia
ANC	Absolute Neutrophil Count
APTT	Activated Partial Thromboplastin Time
B-ALL	B-cell Acute Lymphoblastic Leukaemia
BCL	B-cell Lymphoma markers
BL	Burkitt Lymphoma
BLM	Bloom
BM	Bone Marrow
BMA	Bone Marrow Aspiration
CCI	Childhood Cancer International
CHAI	Clinton Health Access Initiative
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
CNS	Central Nervous System
COG	Children's Oncology Group
CR	Complete Response
CRP	C - reactive protein
CRT	Cranial Radiation Therapy
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CXR	Chest X-Ray
DC	Differential Count
DIC	Disseminated Intravascular Coagulation
DWI	Diffusion Weighted Imaging
EBER	Epstein-Barr Virus-Encoded Small RNA
EBV	Epstein-Barr Virus
ECOG	Eastern Cooperative Oncology Group
ECHO	Echocardiography
EMA	Epithelial Membrane Antigen
ER	Early Recognition
ESR	Erythrocyte Sedimentation Rate
FBC	Full Blood Count
FDG-PET	Fluorodeoxy-glucose-Positron Emission Tomography
FISH	Fluorescent In Situ Hybridization
FLAIR	Fluid Attenuation Inversion Recovery
FNAC	Fine Needle Aspiration Cytology
GFAP	Glial Fibrillary Acidic Protein
Gy	Gray (radiation dose unit)
HCLGG	Hypothalamic/Chiasmatic Low Grade Glioma

HHV8	Human Herpesvirus 8
HICs	High-Income Countries
HL	Hodgkin Lymphoma
HPCZ	Health Professions Council of Zambia
HSCT	Haematopoietic Stem Cell Transplantation
IHC	Immunohistochemistry
IGF2	Insulin-Like Growth Factor 2
IM	Intramuscular
IMNCI	Integrated Management of Neonatal and Childhood Illnesses
IMP	Improvement (response criteria)
IMRT	Intensity-Modulated Radiotherapy
IT	Intrathecal
IV	Intravenous
IVC	Inferior Vena Cava
KFTs	Kidney Function Tests
LDH	Lactate Dehydrogenase
LFTs	Liver Function Tests
LGG	Low Grade Glioma
LIMCs	Low and Middle Income Countries
LP	Lumbar Puncture
LTFU	Long Term Follow-Up
MCH	Maternal and Child Health
MESNA	Sodium 2-mercaptoethane sulfonate
MOH-HQ	Ministry of Health Headquarters
MRI	Magnetic Resonance Imaging
NCCSP	National Cancer Control Strategic Plan
NF1	Neurofibromatosis Type 1
NHIMA	National Health Insurance Management Authority
NHL	Non-Hodgkin Lymphoma
NLPHL	Nodular Lymphocyte Predominant Hodgkin Lymphoma
NRC	National Registration Card
OPG	Optic Pathway Glioma
PATHAZ	Pathologists' Association of Zambia
PD	Progressive Disease
PET	Positron Emission Tomography
PPC	Paediatric Palliative Care
PR	Partial Response
PT	Prothrombin Time
QA	Quality Assurance
RB	Retinoblastoma
RECIST	Response Evaluation Criteria In Solid Tumours
RT	Radiotherapy
RT-PCR	Reverse Transcription-Polymerase Chain Reaction

SIOP	International Society of Paediatric Oncology
SOPs	Standard Operating Procedures
SPGR	Spoiled Gradient Recalled (MRI sequence)
STIR	Short Tau Inversion Recovery
SWOT	Strengths, Weaknesses, Opportunities, Threats
T-ALL	T-cell Acute Lymphoblastic Leukaemia
TAT	Turn-Around Time
TLS	Tumour Lysis Syndrome
TNM	Tumour-Nodal-Metastases
TP53	Tumour Protein 53
TPLGG	Tectal Plate Low Grade Glioma
UHC	Universal Health Coverage
UICC	Union for International Cancer Control
US	Ultrasound
UTHs-AH	University Teaching Hospitals-Adult Hospital
UTHs-CDH	University Teaching Hospitals-Cancer Diseases Hospital
UTHs-CH	University Teaching Hospitals - Children's Hospital
UTHs- EH	University Teaching Hospitals-Eye Hospital
VAD	Vincristine, Adriamycin, Dexamethasone
WAGR	Wilms Tumour, Aniridia, Genitourinary anomalies, and Developmental Delays
WHO	World Health Organization
WT	Wilms Tumour
ZPA	Zambia Paediatric Association

EXECUTIVE SUMMARY

The consolidated national guidelines for childhood cancer management in Zambia consists of six guidelines that include early diagnosis, early referral, Pathology and Imaging, Treatment, chemotherapy safe handling and supportive care. The process for developing the guideline included drafting by thematic area experts, review and editing coupled with reviewing the evidence for the included recommendations for case assessment, diagnosis and treatment. At least five such meetings were held over a period of three years. The draft and review teams consisted of the following: Paediatric oncologists, Paediatricians, Paediatric surgeons, Neurosurgeons, Radiation oncologists, Pathologists, Radiologists, Ophthalmologists, Pharmacists, Oncology nurses, Paediatric nurses, public health experts, cancer prevention officers, social workers and monitoring and evaluation experts as well as civil society organization representatives. Validation was undertaken with a group of experts not involved in the development of the guidelines. These experts reviewed the guidelines with a focus on the content's appropriateness for the levels of care as well as the evidence based for the recommendations and gave feedback to the writers. Thereafter, edits were done in accordance with the reviewers recommendations.

These guidelines are to be used as reference material in childhood cancer management for centers managing children with suspected or confirmed cancer across Zambia. The early diagnosis and referral guideline aim to have the entire health care team, starting at the first level of care, work to offer the child with cancer the best chances possible for timely treatment and therefore survival and proposes mitigating measures against bureaucracy, red tape, or the health team's lack of knowledge that contribute to delay in referral and diagnosis of the child with cancer.

The pathology guideline proposes to improve accurate histological diagnosis of childhood cancer by enhancing biopsy specimen handling and referral for second opinion, routine reporting of histological diagnoses by at least two independent pathologists at the tertiary level and standardizing the diagnosis reporting templates for six index cancers with a view to up-scale to other childhood cancers in the long term. It is envisioned that focused training of a general pathologist in the diagnosis of paediatric neoplasms, implementation of a basic IHC panel in a histopathology laboratory, and inclusion of the pathologist in a multidisciplinary team will improve the diagnostic precision of childhood cancers. The imaging guideline has provided standard techniques for optimally imaging childhood cancer cases for all the imaging professionals across the different levels of the health care continuum. The treatment guideline outlines the recommended treatment options for the six index childhood cancers, specifying the recommended diagnostic tests, disease directed therapy based on an individual patient's clinical parameters. The chemotherapy safe handling guideline provides guidance on safe prescribing, reconstitution, dispensing, and administration of chemotherapy and related agents used in the treatment of cancer. In addition, instructions on how to safely dispose of chemotherapy drug waste to protect healthcare workers from exposure are included. The supportive care guideline focuses on managing the health-related signs and

symptoms associated with the cancer itself and side-effects of cancer treatment, with a focus on improving the quality of life of the patient throughout their cancer journey.

The roll out of these guidelines should lead to improved early detection, timely referral and management of childhood cancer. This will ultimately achieve the global goal of improved childhood cancer survival of at least 60% by the year 2030. But for these guidelines to contribute to increased childhood survival in a Universal Health Coverage (UHC) manner, increased funding to this programme will be needed through the National Health Insurance, government funding and cooperating partners' funding support.

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ACKNOWLEDGMENTS

The development of the consolidated national guidelines for childhood cancer bears a significant landmark in the efforts to standardise and improve childhood cancer management. It is a step towards assuring early recognition, timely referral and effective treatment for children with cancer in Zambia.

Special gratitude goes to all who contributed towards the realisation of these guidelines in ensuring that they are evidence based and clinically relevant for children with cancer in Zambia. I would like to thank the experts for their dedication and commitment to ensure that these guidelines address the need for improving clinical outcomes of childhood cancer. Further, I especially want to appreciate the World Health Organisation, Clinton Health Access Initiative and other partners for partnering with the Ministry of Health, Zambia, in the formulation and publication of these guidelines.

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CHAPTER 1. INTRODUCTION

Of an estimated 400, 000 cases of childhood cancer diagnosed globally, 80% are from Low- and middle-income countries (LIMCs). There were approximately 438 new childhood cancer cases annually in Zambia for the 0 – 14-year olds (Globocan data estimates, 2022). The national referral hospital for cancer treatment, the Cancer Diseases Hospital (CDH) sees 180 – 250 new cases of childhood cancer aged 0 – 14 years old annually, which represents 42 – 58% of the national estimate. There are six WHO-designated index cancers, for use as a model to improve overall survival, that include acute lymphoblastic leukaemia, Burkitt lymphoma, Hodgkin lymphoma, Nephroblastoma, retinoblastoma and low-grade gliomas. These cancers constitute 50 – 70% of the ten most common new childhood cancers diagnosed at CDH annually as in other institutions in LMICs.

Childhood cancer treatment utilises a multimodality approach that includes surgery, chemotherapy and radiation therapy. When all these modalities are used in concert appropriately survival of the children with cancer improves. In Zambia less than 30% of these children survive. The World Health Organisation (WHO) has recommended that countries must include childhood cancer interventions in the national priorities in order to improve child cancer survival to more than 60% by 2030.

Childhood cancer differs from adult cancers in that there is no clearly known prevention as well as established screening strategies for early diagnosis to improve survival. They also progress very quickly but are highly responsive to chemotherapy and radiotherapy. The role of surgery in the management of childhood cancers is first to obtain the specimen (biopsy) to confirm the cancer diagnosis and then to provide the necessary cancer surgery required for treatment.

In this regard and given the complexity of current therapies, children with cancer should be referred as early as possible to facilities that have specialized human and technical resources, where they can be treated by health care providers trained in the different pediatric oncology specialties. Childhood cancers may have a good overall prognosis if appropriate and effective treatment is instituted in early stages.

The factors that contribute to poor outcomes of childhood cancer in Zambia include lack of pediatric cancer awareness, treatment abandonment, lack of supportive care for pediatric cancer patients and their families, limited finances, stigmatization of cancer diagnosis, and health system gaps (Walubita M, 2018). These challenges lead to the low annual case load seen at CDH as compared to the overall national estimate. Further, there is limited investment in pediatric cancer control programmes because of lack of information and awareness regarding the impact of cancer.

Radiotherapy and chemotherapy services for childhood cancer treatment are centralised and therefore not easily accessible to every child with cancer. Cancer surgery is practiced by paediatric surgeons and other surgical subspecialties such as orthopaedics and maxillofacial surgery. Currently there are few paediatric surgeons and these only receive

limited paediatric surgical oncology training and are found at the tertiary level of health care. Radiotherapy is only offered at CDH, whereas chemotherapy is offered at CDH and other tertiary and general hospitals where capacity exists.

A review of the national cancer control strategic plan (NCCSP) 2016 to 2021 found only 14 (12%) out of 116 districts offer retinoblastoma services and only 19 (16%) out of 116 have staff trained in examination for children aged 0-5 years for features of retinoblastoma. A complete list of Strengths, Weakness, Opportunities and Threats (SWOT) analysis for childhood cancers can be found in the NCCSP 2022 - 2026. In order to effectively implement these guidelines, they will be anchored at the Ministry of Health Headquarters in the Cancer Control Unit and the Directorate of Clinical Care and Diagnostics Services and coordinated through provincial focal point paediatricians and district Maternal and Child Health (MCH) coordinators.

There are childhood cancer treatment protocols available from High Income Countries (HICs) with proven efficacy that have contributed to increased childhood survival in those places to at least 80%. These protocols have been adapted as outlined in these guidelines to suite the Zambian Childhood cancer care context and should result in improved survival when fully implemented.

The systematic use of the said protocols in HICs is the factor that has made the biggest difference in improving childhood cancer cure rates. Therefore, it is expected that with achievement of these high cure rates in the coming years, globally, one out of every thousand young people will be a survivor of childhood cancer. For this reason, the current treatment focus for pediatric cancer is aimed at curing, but with as fewest treatment-related adverse effects as possible. Therefore, Zambia has developed the Consolidated Guidelines for Childhood Cancer management which include;

1. Early diagnosis guideline
2. Referral guideline
3. Pathology and Imaging Services guideline
4. Treatment guidelines for the six priority childhood cancers
5. Rational use of antibiotics and safe use of anti-cancer medicines guideline
6. Supportive Care guideline

Purpose of the Consolidated Guidelines for Childhood Cancer Management

The purpose of the consolidated guidelines is to help Health care providers across the paediatric care continuum identify children with cancer. This will enable timely referral and give children with cancer a chance for a cure. These guidelines will help improve the index of suspicion in front-line health care providers on childhood cancer symptoms and signs to enhance detection at early stages. This will further aid in early recognition of children suspected to have cancer and accord them an early referral and linkage to confirmatory diagnosis and appropriate effective treatment services. The guidelines will

also aid personnel at lower levels to manage children with cancer in a limited manner and after appropriate training for certain cancer types as close to the child's family as possible. This will in turn play a role in the decentralisation of childhood cancer treatment.

Scope

The guidelines apply to health care personnel at all levels of care in the paediatric care continuum, including:

- Primary care level
- Secondary care level
- Tertiary care level

For purposes of this guideline document and for patient access to childhood cancer medicines donated through the global platform for access to childhood cancer medicines, paediatric patients refer to those aged 0 – 19 years old.

Risk factors for developing childhood cancer

Although the cause of childhood cancer is not clearly known there are several risk factors that are associated with childhood cancer

Table 1. Risk factors associated with childhood cancer

RISK FACTOR	EXAMPLE OF CANCER TYPE
1. BIOLOGICAL FACTORS ➢ Epstein Barr virus ➢ Hepatitis B & C ➢ HIV ➢ HHV8	➢ Hodgkin lymphoma, nasopharyngeal carcinoma, Burkitt lymphoma. ➢ Hepatocellular carcinoma ➢ Non-Hodgkin lymphoma, leiomyosarcoma ➢ Kaposi sarcoma
2. CHEMICALS AND MEDICINES ➢ Pesticides ➢ Benzene ➢ N-nitroso compounds and tobacco. ➢ Alcohol and some diuretics	➢ Leukaemia, non-Hodgkin's lymphoma, and neuroblastoma. ➢ Leukaemia ➢ Central nervous system (CNS) tumours ➢ Neuroblastoma and Nephroblastoma
3. X-RAYS	➢ Leukaemias
4. GENETIC AND FAMILIAL FACTORS	➢ Retinoblastoma ➢ Bilateral Nephroblastoma ➢ Other Embryonal tumours
5. GENETIC DISORDERS ➢ Down syndrome ➢ Klinefelter syndrome	➢ Leukaemia ➢ Germ cell tumours of the mediastinum
6. AGE ➢ Infants ➢ Pre-school or school-age children	➢ Neuroblastoma, retinoblastoma, Leukaemia ➢ Nephroblastoma, gem cell tumours, retinoblastoma, brain tumours

CHAPTER 2. EARLY RECOGNITION & CLINICAL DIAGNOSIS GUIDELINE

Definition

Early recognition & diagnosis of cancer focuses on detecting symptomatic patients as early as possible so they have the best chance for successful treatment.

Systematic review of evidence for recognition and early diagnosis

This section of the consolidated childhood cancer management guideline will focus on childhood cancer early recognition and diagnosis. This guideline emphasises the six priority childhood cancers in Zambia: **- Acute Lymphoblastic Leukaemia (ALL), Hodgkin Lymphoma (HL), Burkitt Lymphoma (BL), Retinoblastoma (RB), Nephroblastoma, Low Grade Glioma (LGG).** It will cover the identification of symptoms that could be caused by any one of these cancers in children. It outlines appropriate investigations in primary health care facilities and the selection of children who need referral for further investigations and treatment. In Zambia, there is a delay in the referral of these children as well as high treatment abandonment rate. The delay may occur because of parental, societal and health care system associated factors. This can mean the difference between life and death of the child. It is the responsibility of all stakeholders involved in the care of children to ensure that the delay does not occur in health institutions in Zambia. This is our commitment to the children in developing the consolidated guidelines.

In order to shorten the time from appearance of symptoms and referral to a centre to confirm diagnosis and treatment initiation, a lot of training needs to be done among primary health care workers. This will be achieved through the inclusion of these components in the Integrated Management of Childhood Illnesses (IMCI) training. When a child is examined and vague signs and symptoms are elicited that might be associated with malignancy, cancer must be suspected and action taken accordingly to prevent late diagnosis.

Early diagnosis consists of three components:

- Awareness of symptoms by families and primary care providers
- Accurate and timely clinical evaluation, diagnosis, and staging (determining the extent to which a cancer has spread)
- Access to prompt treatment

Early diagnosis is relevant in all settings and improves survival for many cancers. Childhood cancer is associated with a range of warning symptoms that can be detected by families and by trained primary health-care providers.

The early recognition and clinical diagnostic features of the six priority childhood cancers guideline components are as follows:

2.1. LEUKAEMIA

This is a group of malignant diseases that cause an uncontrolled increase of mostly immature and poorly differentiated or undifferentiated blood cells in the bone marrow. Childhood Leukaemia usually presents with a combination of symptoms and signs resulting from bone marrow failure and/or manifestations of disease outside the bone marrow. It is the most common cancer in children and can be cured 90% of the time in those with low risk disease.

Leukaemia has a characteristic triad of fever, anaemia and bleeding.

The signs and symptoms are summarised below:

- Unexplained fever lasting days or months (most frequent)
- Recurrent/persistent infections
- Persistent and worsening fatigue
- Pallor
- Unexplained bleeding (Petechiae rash, Spontaneous bruising)
- Persistent and unexplained joint & bone pain and/or limp that may be the only symptom
- Loss of appetite
- Enlargement of the liver, spleen, kidney, testis
- Convulsions, headache, cranial nerve palsy (indicative of CNS Leukaemia)

- ***An unwell child with symptoms consistent with leukaemia needs immediate (same day) referral to an appropriate next level hospital where a bone marrow test can be done.***
- ***Well children with a single sign/symptom of leukaemia described above should be offered a very urgent Full Blood Count/Differential Count and results reviewed within 48 hours.***
- ***Definitive diagnosis is made by bone marrow aspiration done in a specialized center (Third Level).***

2.2. LYMPHOMAS

This is a group of diseases of the lymphatic system and associated cells of the blood (lymphocytes) found in the system. They are fast growing and are called solid haematological tumours to differentiate them from leukaemias. Symptoms include a mass of lymph nodes or extra-lymph node masses which, depending on location, may cause local mass effect. Other non-specific symptoms include fatigue, loss of appetite, fever, drenching night sweats and weight loss.

The two index lymphomas are Hodgkin lymphoma (HL) and Burkitt lymphoma (BL).

I. **HL mainly affects the lymphatic system. Its usual clinical presentation is** cervical, supraclavicular or axillary lymphadenopathy which is often painless, displaying progressive growth, firm in consistency and fixed to deeper layers. Progressive enlargement of lymph nodes, often occurs over many weeks or even months;

The signs and symptoms are summarised below:

- Drenching night sweats
- Unexplained weight loss
- Breathlessness (suggestive of airway obstruction for tumours in the chest)
- Pruritus (Itchy skin)
- Fever

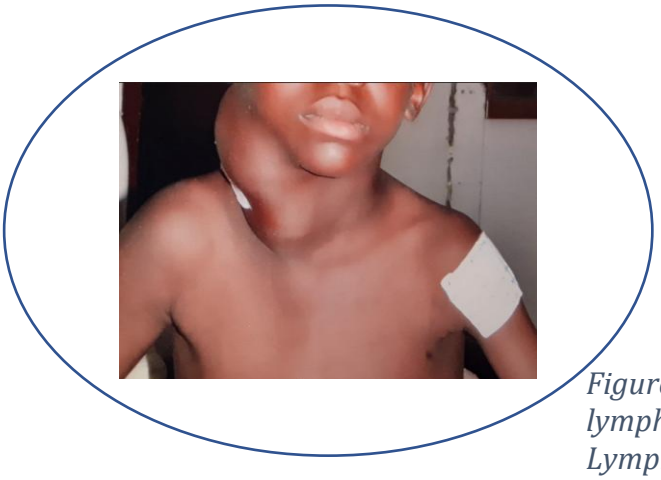


Figure 2. Child with cervical lymphadenopathy in Hodgkin Lymphoma

- **An unwell child with symptoms consistent with Hodgkin lymphoma needs immediate (same day) referral to the *hospital for further evaluation.***

ii. **BL** classically presents with a jaw mass (Figure 2.1 below). Other signs and symptoms:

- Jaw tumour or distortion of facial bones
- Painless swelling of the lymph nodes in the neck, chest, abdomen, under arm, or groin
- Abdominal swelling ± intestinal obstruction
- Thoracic lymphomas present as mediastinal masses with or without pleural effusion, may be accompanied by difficult breathing and superior vena cava compression

- Abdominal lymphomas present with abdominal distention, pain, and masses, usually in the lower right quadrant
- Lymphoma can also present in the skin, central nervous system, bones, and other organs as a lump in the affected area.
- Fever
- Night sweats
- Chills
- Itchy skin
- Weight loss
- Coughing or trouble breathing
- Tiring easily

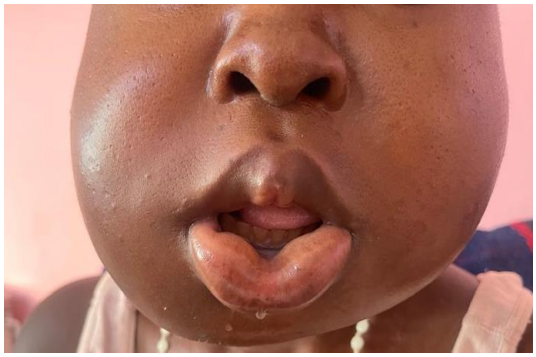


Figure 2.1. Child with bilateral lower jaw masses in Burkitt Lymphoma

- ***An unwell child with symptoms consistent with Burkitt lymphoma needs immediate (same day) referral to the hospital for further evaluation.***

2.3. LOW GRADE GLIOMAS (LGG)

These are solid tumours of the brain; they are more frequent in early childhood, appearing primarily from 5 to 10 years of age and declining after puberty. Symptoms range from non-specific to focal neurological symptoms, depending on the tumour's location in the brain. The most frequent symptom is headache, which at first is generalized and intermittent, increasing in intensity and frequency over time. Headache is usually accompanied by nausea, vomiting, and visual or auditory disturbances. The classic triad of symptoms that indicate intracranial hypertension is:

- Headache
- Nausea
- Vomiting

The headache wakens the child at night and is more intense in the morning, improving during the day with vertical position. Projectile vomiting sometimes occurs, not preceded by nausea. Other age-specific signs and symptoms include:

Infants and Children <5 years

- Persistent or recurrent vomiting
- Balance, coordination or walking problems
- Abnormal eye movements or suspected loss of vision
- Behaviour change
- Lethargy
- Afebrile seizures (Seizures not associated with fever)
- Head tilt
- Increasing head circumference crossing centiles

Children 5-11 years

- Persistent or recurrent headache
- Balance, coordination or walking problems
- Persistent or recurrent vomiting
- Abnormal eye movements
- Blurred vision or loss of vision
- New onset squint
- Behaviour change
- Seizures
- Head tilt

Teenagers 12-18 years

- Persistent or recurrent vomiting
- Persistent or recurrent headache
- Abnormal eye movements
- Blurred vision or loss of vision
- New onset squint
- Balance, coordination or walking problems
- Behaviour change
- Seizures
- Delayed or arrested puberty

Additional symptoms to consider at any age

- Reduced consciousness
- Nausea
- Polydipsia (excessive thirst)
- Polyuria (increased frequency of micturition)
- Failure to thrive or abnormal growth
- A new squint which does not correct with correction of refraction, and any paralytic squint, is a strong indicator of a brain tumour and the patient must be referred immediately

An unwell child with symptoms consistent with a brain tumour needs immediate (same day) referral to an appropriate hospital.

2.4. NEPHROBLASTOMA

This is an embryonal malignant neoplasm of the kidney cells, which commonly affects one of the two kidneys in over 90% of cases, although it can also be bilateral. It is the most common kidney cancer in young children, with greatest frequency among 2 and 3-year-olds. Nephroblastoma may be associated with underlying genetic conditions, particularly overgrowth syndromes and hemi-hypertrophy discussed further below in the treatment guideline. The typical clinical manifestations are:

- A palpable asymptomatic abdominal mass
- Abdominal pain
- Haematuria (blood in urine)
- Hypertension

Other less frequent signs include

- Anaemia
- Fever
- Constipation

Refer a child with an abdominal mass suggestive of nephroblastoma to the next appropriate hospital for further evaluation.

2.5. RETINOBLASTOMA

This malignant neoplasm originates in the primitive cells of the retina. It ranks 5th to 9th among child cancers, with its greatest incidence in children under 3 years of age. It may be frequent in developing countries, suggesting that it is due to exposure to infectious agents, particularly adenovirus and human papillomavirus. Other factors such as lack of vitamin A and folate in the diet have also been implicated.

Symptoms and signs include:

- White colour in the centre of the eye when light is shown or when a flash photograph of the child's eye is taken (Leukocoria)
- Strabismus (Squint)
- Red Inflamed eye
- Eye Swelling (bulphthalmos)
- Poor vision
- Nystagmus

Figure 2.2. Left eye leukocoria in a child with retinoblastoma

- ***Leukocoria in children under the age of 5 years should be considered synonymous with retinoblastoma and needs urgent referral to a hospital with an ophthalmologist for confirmation.***

In general, the early symptoms and warning signs of childhood cancer can be consolidated with the acronym **CHILDCANCER**:

- **C**ontinued, unexplained weight loss
- **H**eadaches, often with early morning vomiting
- **I**ncreased swelling or persistent pain in the bones, joints, back, or legs
- **L**ump or mass, especially in the abdomen, neck, chest, pelvis, or armpits
- **D**evelopment of excessive bruising, bleeding, or rash
- **C**onstant, frequent, or persistent infections
- **A** whitish colour behind the pupil
- **N**ausea that persists or vomiting without nausea
- **C**onstant tiredness or noticeable paleness
- **E**ye or vision changes that occur suddenly and persist
- **R**ecurring or persistent fevers of unknown origin

- ***Whenever these symptoms and signs persist even after treatment for more common non-cancer conditions, cancer must be suspected and the child referred appropriately.***

Assessment and classification of the possibility of childhood cancer

This section deals with the strategy for assessment of the possibility of cancer in a child. In every case, you must ask the mother/guardian about the child's problem, check for general danger signs in the child, and ask whether the child has cough or difficult breathing, diarrhoea, fever, ear and throat problems. In every case, you must assess the child's vaccination status, nutritional status, developmental milestones and possibility of anaemia.

Then determine whether the child could have cancer using a clinical criterion as follows:

1. **Check for and identify** suspected cancer signs through observation, questions related to the clinical history, and a complete physical examination as in table 2. below:

Table 2. Key components of the clinical history and physical examination

ASK

- Has the child had fever for more than 7 days and/or drenching night sweats?
- Has the child recently had a headache that has been:
  - Increasing in intensity?
  - Waking the child at night?
  - Is there associated vomiting?
- Has the child had bone pain in the last month that:
  - Is increasing in intensity?
  - Affects the child's activities?

  Does the child have poor appetite, weight loss, or overtiredness in the last 3 months?

OBSERVE, FEEL, IDENTIFY

- Any bleeding:
  - Petechiae
  - Bruising
  - Epistaxis
  - Haematuria
  - Black stools (Melaena=altered or digested blood)/ Frank blood in stool (haematochezia)
- Any eye abnormality:
  - Leukocoria (white pupillary reflex)
  - New strabismus (new squint)
  - Aniridia (lack of iris)
  - Heterochromia (different coloured eyes)
  - Hyphaema (visible blood in the eye)
  - Proptosis (bulging eye)
- Any disturbances in the vision? (double or blurred vision, blindness)
- Enlarged lymph nodes lasting for ≥ 4 weeks
- Any central nervous system signs and symptoms with sudden and/ or progressive onset:
  - Change in mental status or behaviour or speech
  - Unexplained convulsions
  - Asymmetry or weakness of a limb or one part of the body
  - Loss of balance when walking or unable to sit unassisted
- Palpable mass in the abdomen or a mass on any part of the body
- Liver or spleen enlargement (Hepatomegaly or splenomegaly)

2. **Classify**, through colour coding, the child's health status, and note the required actions as shown in table 2.1. below:

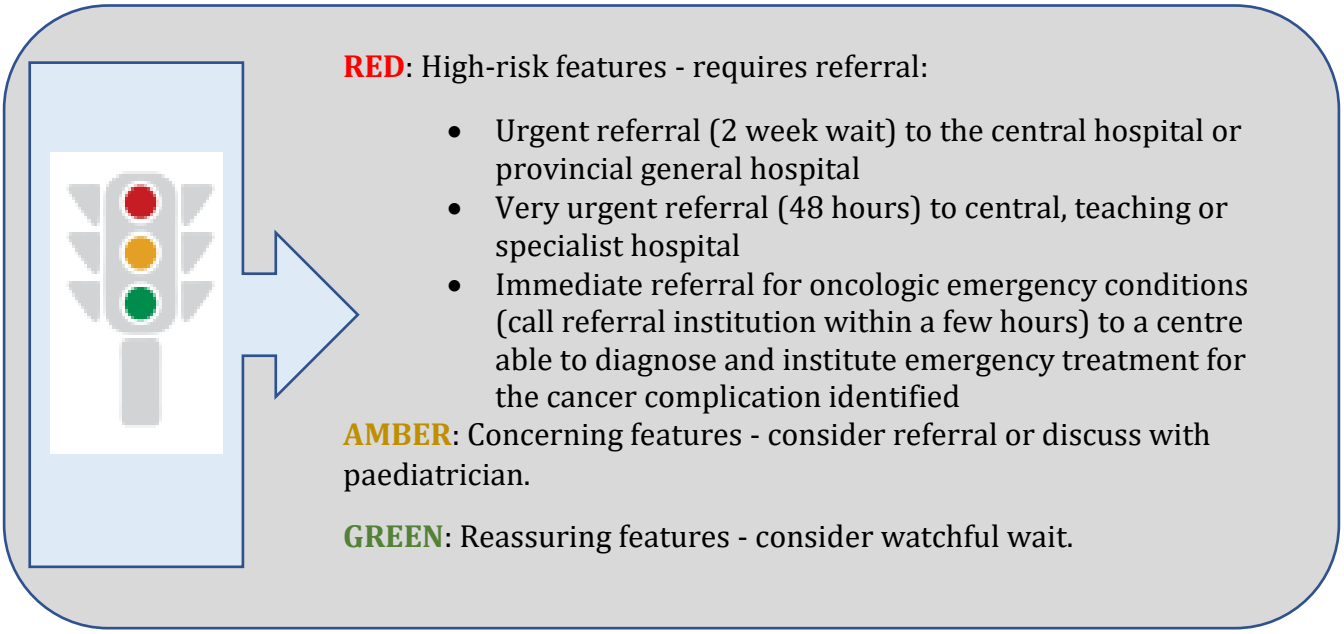
Table 2.1. Colour-coded health status classification and appropriate action

ASSESS	CLASSIFY	TREAT
One of the following • Fever for over 7 days with no apparent cause • Headache: Persistent and progressive, and primarily nocturnal, that awakens the child or appears when rising in the morning and may be accompanied by vomiting • Bone pain that has increased progressively in the last month and disrupts the child's activities • Petechiae, bruises, and/or bleeding • Severe palmar or conjunctival pallor • Leukocoria (White-eye) • Strabismus (squint) that has newly appeared • Aniridia (lack of iris) • Heterochromia (different coloured eyes) • Hyphaemia (Blood in the eye) • Proptosis (bulging eye) • Visual disturbances (blurred, double, sudden blinding) • Nodes >2.5 cm in diameter, hard, painless, lasting ≥4 weeks • Acute and/or progressive focal neurological signs and symptoms: i. Convulsion without fever or underlying neurological disease ii. Unilateral weakness (of one limb or one side of the body) iii. Physical facial asymmetry iv. Changes in consciousness or mental status (Behaviour change, confusion) v. Loss of balance when walking vi. Limping from pain vii. Difficulty speaking • Palpable abdominal mass • Hepatomegaly and/or splenomegaly • Mass in some region of the body with no signs of inflammation	**POSSIBLE CANCER OR VERY SEVERE DISEASE**	• Refer urgently to the nearest hospital's department of Paediatrics for stabilization • If necessary begin intravenous fluids, oxygen and pain management as below in table 2.3 • If a brain tumour is suspected and there is neurological deterioration give one dose of injection dexamethasone 16mg iv Stat • Speak with parents and explain the need and importance of the referral and its urgency • Resolve all administrative problems that occur that may cause delay • Communicate with the referral facility

One of the following • Loss of appetite in the last 3 months • Weight loss in the last 3 months • Tiredness or fatigue in the last 3 months • Significant night sweets, with no apparent causes • Mild palmar or conjunctival pallor • Painful lymphadenopathy or lasting <4 weeks or<=2.5 cm in diameter, or not hard in consistency	**SOME RISK OF CANCER OR SEVERE DISEASE**	• Do a complete physical examination to look for a cause for the signs found • Review the child's diet and correct any problem found • If there is weight loss, loss of appetite or fatigue, refer for paediatric consultation to investigate for possible causes • If there is isolated mild pallor, start haematinics and follow up at 2 weeks. If there is no improvement at the 2 weeks follow up visit, do a full blood count, differential white cell count, and peripheral smear to look for the cause of anaemia and to treat or refer for paediatric consultation • Treat the cause of the lymphadenopathy with antibiotics if necessary and follow up in 7 days. If there is no improvement, refer for paediatric consultation • Treat with antibiotics any inflammatory process that produces a painful swelling in any part of the body and follow up in 7 days. If there is no improvement, refer
Does not meet criteria to be classified in either of the above classifications	**DOES NOT HAVE CANCER**	• Ensure immunization and growth and development monitoring • Recommend a tobacco-free environment • Recommend a healthy diet and regular physical activity

3. **Treat the child.** After classifying the child's condition, if urgent referral is needed, administer essential treatment before referring. If the child needs treatment but can go home, prepare an integrated treatment plan and administer the first dose of treatment in the clinic.

Table 2.2. Colour codes according to the urgency of referral of a case



REFERRAL GUIDELINE

This section aims to prevent delays, due to various reasons, in diagnosing and treating children with cancer. Prompt referral of a suspected childhood cancer patient to the appropriate facility is essential. The goal for the entire healthcare team, beginning at the primary level of care, is to collaborate in giving the child the best possible chance for survival.

Introduction to Referral Systems Guideline

Effective referral systems are crucial in ensuring timely diagnosis and treatment for children with cancer in Zambia. Delays caused by inadequate coordination, lack of knowledge, or systemic inefficiencies can negatively affect survival outcomes. The guideline outlines the process for early referral of suspected childhood cancer cases to specialized healthcare facilities. A strengthened referral process will provide children with the best possible care, reduce barriers to timely treatment and improve survival rates.

General Objective

To ensure that all children with suspected cancer receive timely and appropriate referrals to specialized healthcare facilities in order to minimize delays in diagnosis and treatment.

How to Handle the Child Classified With "Possible Cancer or Very Severe Disease"

Once we have a child with a probable diagnosis of cancer, based on a proper clinical history, a complete physical exam, and the identification of suspicious signs or symptoms, the final diagnosis is anatomicopathological, carried out in a referral facility. Hence, the importance of understanding that, when there is a suspected possibility of cancer, the child should be referred to a center that specialises in cancer diagnosis. Although it is necessary to refer the child immediately, it is important to do so under appropriate conditions. Some children will definitely need to be stabilised before being sent to the next level or a specialised center, as described below:

a. **Oxygen -** Every child classified with severe or very severe disease, with danger signs, with respiratory problems, or symptoms of shock, and all those who required any resuscitation procedure, should be referred with supplementary oxygen. Nasal cannulae, prongs (delivery at rates of 1-4L/min) or mask (5-10L/min) can be used.

b. **Hemodynamic stability -** A child with signs of severe dehydration, or hypovolaemia of another aetiology, or shock should be stabilized before referral. Lack of a paediatric blood pressure monitor should not deter you from doing a good assessment of volume status. In this regard, it is necessary to know that some clinical signs are good predictors of hypovolemia (low volume) and low perfusion and of the need to improve volume. These are the signs that indicate hypo-perfusion:

   - Capillary refill time >2 seconds
   - Pale or mottled skin
   - Heart rate: tachycardia (refer to table 6. for age appropriate heart rates)
   - Altered state of consciousness

   Initial treatment in these cases consists of rapid fluid loading, usually with lactated Ringer's or 0.9% normal saline solution at a volume of 20 to 30 mL/kg in 30 minutes or less if necessary. It is important to remember, however, that some children with cancer can have severe anaemia, which means that a rapid load of fluids can produce pulmonary oedema in them. In these cases, as a result, fluids should be administered at 20mL/Kg preferably until the patient is transfused as required.

c. **Administration of fluids -** In the newborn, 10% dextrose should be administered without electrolytes at 80mL/kg/day, via umbilical catheter or, if possible, by peripheral vein. From the second day of life, use half-strength normal saline. Add 5mL potassium chloride to 500mL half-strength normal saline from the second day of life,

if there is no risk of tumour lysis syndrome. Infants older than 2 months and older children referred should receive, if there is no dehydration or shock, 5% dextrose-saline in volumes calculated as follows (Holliday-Segar method, based on water and calorie requirements):

1. <10kg body weight: 100ml/kg/day
2. 10-20kg body weight: 1000ml + (50ml/kg per each kg >10kg) per day
3. >20kg body weight: 1500ml + (20ml/kg per each kg >20kg) per day

Example of fluid calculation:
Child weighing 25kg: 1500ml + (20 x 5kg) 5kg are the kg above 20kg for a child weighing 25kg. 1500ml + 100 = 1600ml in 24 hours 1600ml/24 hours = 66.6 ml/hour. This means that a child weighing 25kg needs an intravenous solution of 5% dextrose with electrolytes at 66ml/hour. It is always necessary to add electrolytes to 5% dextrose solution to contribute to daily physiological requirements. Ideally, 3 to 5mmol/kg/day of sodium and 2 to 3mmol/kg/day of potassium should be provided.

- ***However, avoid addition of electrolytes if the child has suspected or confirmed tumour lysis syndrome***

d. Pain management - If the child is in pain, treat as follows before referring:
- **Mild pain**: Paracetamol 10-20mg/kg/dose every 4-6 hours
- **Moderate pain**: any one of Ibuprofen: 5-10mg/kg/dose every 6 hours, Diclofenac: 1-1.5mg/kg/dose every 8-12 hours, Naproxen: 5-7.5mg/kg/dose every 8-12 hours,
- **Severe pain**: Oral morphine 0.3mg/Kg every 4 hours in addition to the above agents for mild to moderate pain, with lactulose 5 – 15mL three times/day for prevention of constipation.

e. Management of intracranial hypertension - If a patient with a suspected brain tumour is exhibiting neurological deterioration, you must begin management of intracranial hypertension *(check for signs and symptoms of intracranial hypertension under section on LGG in the early recognition guideline above)* before referring, according to these steps:
- Bed rest with head of bed elevated to 45°
- Administration of high doses of steroids: intramuscular or intravenous dexamethasone at a rate of 0.15 to 0.25mg/kg/dose
- In case of convulsions, diazepam should be administered at a dose of 0.3mg/kg/IV or 0.5mg/kg/per rectal with a maximum dose of 10mg and a maximum of two doses at least 5 minutes apart; infusion should not exceed 1mg/min. Diazepam should not be administered IM. Following administration of diazepam, phenytoin should be administered at a dose of 10-15mg/kg/IV. If phenytoin is unavailable, administer phenobarbital 15-20mg/kg over 20 minutes

Urgent implementation of these measures makes it possible to transfer the patient to the third level of care.

f. **Recommendations in case of bleeding and severe anaemia -** If the child has a very low haematocrit and haemodynamic disturbances, packed red blood cells should be transfused at 10ml/kg; however, whenever possible, transfusion should be avoided until the child is studied and the transfusion done in the referral facility. *Transfuse only if the child's life is in danger*. If there is thrombocytopenia with a blood platelet count <20 X 10^9/L (20, 000/mm^3) with serious haemorrhagic manifestations, platelets should be transfused; however, if there are no severe hemorrhagic manifestations, do not transfuse and wait for the specialized center to decide when to transfuse. Keep the child at rest to prevent bleeding.

g. **Recording and monitoring -** All children with serious classifications must be monitored to ensure detection of new problems, signs, or symptoms and to keep them stable. Monitoring does not necessarily require expensive equipment, which tends not to be available in many of the health facilities. The best monitoring is that done by health workers, when they make sure to observe the signs of children with serious classifications, such as **heart rate, respiration rate, capillary refill time, difficult breathing, dehydration, and presence and quantity of diuresis (urine output)**, every 15 minutes or as appropriate based on clinical status until the child arrives at the destination hospital. This means that the health worker must accompany the child in the ambulance on the way to the hospital to monitor him throughout the trip.

h. **Informing parents -** It is crucial to keep the parents informed: remember that they are very worried because their child has a serious problem. Listen to all their fears and try to clear up their doubts:
   - Explain to the parents the need for referring the child to the hospital and obtain their consent.
   - Calm the parents and reassure them that the hospital where you are referring the child has the specialized medical team and will do everything necessary to properly diagnose and treat their child.
   - Explain to them what will happen in the hospital and how that will help their child.
   - Ask questions and make suggestions about who could help at home while they are with their other child at the hospital.
   - You may not be able to help the parents solve all their problems, but it is important to do everything you can to help so they feel supported.
   - Remember that if you do not refer the child immediately, his/her chances of survival can decrease and the prognosis could change completely.

i. **Parents** to give to the facility where the child will be transferred. Tell them to give it to the health workers in the hospital. This referral form should include:

   - The name and age of the child
   - The date and time of referral
   - Description of the child's problems and duration
   - The reason for referral (symptoms and signs leading to severe classification)
   - Treatment that you have given, including time and dosage of medicines

- Any other information that the hospital needs to know in order to care for the child, such as earlier treatment of the illness.
- Your name and the name of your clinic or facility.
- Contact details of the referring personnel (phone number/email)

How to Handle the Child Classified With "Some Risk of Cancer"

Children with this classification have clinical signs shared by many diseases, among them cancer, although without being strictly suggestive. Moreover, since cancer produces these signs at a lower percentage than other diseases, children should be treated based on the most frequent aetiology (cause). The most important thing is to follow up on the child. Following up will make it possible to observe the course of the illness and response to treatment and will also help to know precisely when other possible pathologies should be investigated.

Weight loss, loss of appetite, fatigue and tiredness of recent onset can be caused by many diseases, among them infections such as tuberculosis, malaria and HIV, nutritional or gastrointestinal system problems, and rheumatologic diseases. Tumours can also be associated with these symptoms, but usually the acute presentation of many of them means that they are not classical symptoms, as in many of the tumours of adults. However, every child with these symptoms should be assessed and if no improvement is seen at the follow-up appointment and they persist, or if they are associated with any of the symptoms described in the "possible cancer" classification, the child should be referred immediately.

Anaemia is often produced by many diseases, although the most frequent is iron deficiency due to inadequate diet. Even though it is one of the cardinal symptoms of the leukaemia triad, anaemia alone, without other symptoms such as purpura, should be considered to have another aetiology and should primarily be treated with iron. Nevertheless, if at the one-month follow-up, there is no clinical improvement, a haemogram and peripheral blood smear should be done to study the cause of anaemia and the absence of response to treatment with iron. Fortunately, cancer will be the cause in a minority of children, and this will be evident from the haemogram, and the patient will be referred to complete the study and begin management.

Lymphadenopathy with enlargement that has infectious inflammatory characteristics and does not meet the criteria to be considered malignant should be treated with an antibiotic (Amoxicillin 50 mg/kg/day in 3 doses for 5 -10 days). If no improvement is seen at the follow-up visit, or if lymphadenopathy persists after treatment for infection, the child should be referred to study the cause (with a biopsy)—which could be a neoplasm.

- ***These children should be scheduled for follow-up visits every 14 days until there is improvement in the signs or until a cause is found that better explains the symptoms and the corresponding management is begun.***

Parents should be taught danger signs requiring the child to return immediately and should continue with growth and development monitoring, immunization, and home care. The child with enlargement from an inflammatory or infectious etiology in any part of the body should be treated as appropriate and followed-up. If the enlargement persists after a month —or immediately, if it worsens—the child should be referred to a specialized center.

- ***In this group, proper counseling of the parents is of utmost importance, so they can detect danger signs and know when to return immediately.***

How to Handle the Child Classified As "Does Not Have Cancer"

Fortunately, at the time of the visit, these children do not have any sign or symptom that justifies classifying them with "possible cancer" or "risk of cancer." Even so, with these patients, the usual assessment, management, and recommended procedure should be done, along with providing preventive recommendations and promoting healthy lifestyles. Therefore, it is important to ensure that the child's immunizations are complete, and if not, bring them up to date, along with growth and development monitoring.

Table 2.3. Referral of a Child with suspected Cancer by level of care

NO.	LEVEL OF CARE	Intervention/Action/remarks
1	**Community level**	For a child identified with suspected signs and symptoms of childhood cancer do the following: a) Briefly counsel the parent/guardian on the need to refer the child to the nearby health facility. Highlight the following: I. Explain that the child's condition needs health workers' assessment and management at a health facility as soon as possible II. Tell the parent/guardian to carry their or the child's National Registration Card (NRC), National Health Insurance Management Authority (NHIMA) card if they have, under 5 card or Maternal & Child Health (MCH) booklet. III. Quickly respond and assist to address any of their fears and concerns b) If trained to use a community referral form, fill it up and give it to the parent/guardian. c) If possible, notify the receiving facility regarding the child being referred. d) If the family has no means of transport arrange the community aid referral transport
2	**Mini hospitals**, **Rural and urban health centres/ health post**	For the child identified with suspected signs and symptoms of childhood cancer do the following: a) Assess the child and check for any emergency signs and determine the initial classification (severe or very severe disease) b) If the child has a severe or very severe disease, give pre-referral treatment as in the 'how to handle a child with Possible Cancer or Very Severe Disease' section above: i. Child with respiratory problem or shock give oxygen (*where available*) ii. Child with signs of severe dehydration, or hypovolemia of another aetiology, or shock, give rapid intravenous fluid loading iii. If the child has severe anaemia, administer fluids more cautiously at two-thirds of the required as you refer the child iv. Pain Management - If the child is in pain, treat according to severity before referring. **Refer to pain management above**.

NO.	LEVEL OF CARE	Intervention/Action/remarks
		c) Briefly counsel the caregiver on the need to refer the child for specialised care. Explain the following: i. The child's condition needs further assessment and management at specialised higher-level facilities ii. Carry with you the NRC, NHIMA card, under 5 card or MCH booklet if available. d) Fill in the standard referral form or write the referral note and attach the findings. e) Notify the receiving facility. f) If the family has challenges of getting to the referral facility, facilitate referral of the child
3	**First referral Hospitals**	For the child identified with suspected signs and symptoms of childhood cancer do the following: a) Re-assess the child and check for any emergency signs and determine and confirm classification (severe or very severe disease) b) Check Airway, Breathing, 3Cs (Circulation, Coma, Convulsions), Dehydration c) Check the vital signs and document d) If the child has a severe or very severe disease, give pre-referral treatment as follows and urgently refer the child: i. Child with respiratory problem or shock give oxygen. ii. Child with signs of severe dehydration, or hypovolemia of another aetiology, or shock, give rapid fluid loading of Ringers lactate or 0.9% normal saline solution at a volume of 20 to 30 mL/kg in 30 minutes or less if necessary e) Note that some children with cancer can have severe anaemia, in such a case a rapid load of fluids can produce pulmonary oedema f) If the child has severe anaemia, administer fluids more slowly i.e. at two thirds of the required, as you refer the child g) Give maintenance intravenous fluid based on the Holliday-Segar method above under **'Administration of fluids'** h) In case of bleeding and severe anaemia endangering the child's life, give packed red blood cells at 10 ml/kg. Otherwise transfusion should be avoided until the child is investigated. i) Pain Management - If the child is in pain treat according to severity before referring. **Refer to the pain management above.** j) If patient has a suspected brain tumour with intracranial hypertension exhibiting neurological deterioration, you must

NO.	LEVEL OF CARE	Intervention/Action/remarks
		begin management of intracranial hypertension before referring, according to the steps above under '**Management of intracranial hypertension'** section k) Carry out investigation to confirm diagnosis l) Briefly counsel the caregiver on the need to refer the child for specialised care. Explain and do the following: i. The child's condition needs further assessment and management at specialised higher-level facilities ii. Carry with you the NRC, NHIMA card, under 5 card or MCH booklet. iii. Fill in the standard referral form or write the referral note and attach the findings including all tests done. m) Notify the receiving facility. n) If the family has challenges of getting to the referral facility facilitate transportation
4	**Second and Third Level Hospitals**	For the child identified with suspected signs and symptoms of childhood cancer do the following: a) Re-assess the child and check for any emergency signs and determine or confirm classification (severe or very severe disease) b) Check Airway, Breathing, 3Cs (Circulation, Coma, Convulsions), Dehydration c) Check the vital signs and document d) If the child has a severe or very severe disease, give pre-referral treatment and urgently refer the child as follows: i. Child with respiratory problem or shock give oxygen. ii. Child with signs of severe dehydration, or hypovolemia of another aetiology, or shock, give rapid fluid loading of Ringers lactate or 0.9% normal saline solution at a volume of 20 to 30 mL/kg in 30 minutes or less if necessary iii. Some children with cancer can have severe anaemia, in such a case a rapid load of fluids can produce pulmonary edema iv. If the child has severe anaemia, administer fluids more slowly i.e. at two-thirds of the required, as you refer the child. e) Give maintenance intravenous fluid based on the Holliday-Segar method above under **'Administration of fluids'** f) In case of bleeding and severe anaemia:

NO.	LEVEL OF CARE	Intervention/Action/remarks
		i. If the child has very low haematocrit and haemodynamic disturbances endangering his/her life, give packed red blood cells at 10 ml/kg. ii. If there is thrombocytopenia with a blood platelet count <20,000/mm^3 with serious haemorrhagic manifestations, platelets should be transfused at 10mL/Kg iii. Transfusion should be avoided if a full blood count is not done in a child who is haemodynamically stable but clinically anaemic. g) Pain Management If the child is in pain, treat before referring as in the **pain management** section above. h) If the patient has a suspected brain tumour with neurological deterioration treat them following the steps outlined in the **Management of intracranial hypertension** section above. i) Carry out investigation to confirm diagnosis j) briefly counsel the caregiver on the need to refer the child for specialised care as indicated below: i. Explain that the child's condition needs further assessment and management at specialised higher-level facilities ii. Remind the caregiver to carry the NRC, NHIMA card, under 5 card or MCH booklet. k) Fill in the standard referral form or write the referral note and attach the findings including results for investigative tests l) Notify the receiving facility m) If the family has challenges of getting to the referral facility facilitate transportation. n) All children with serious classifications must be accompanied and monitored to ensure detection of new problems, signs, or symptoms and to keep them stable.

Referral pathways

Referral pathways are essential to outline clear steps to follow in ensuring timely access to appropriate levels of care. Below is a structured approach to develop effective referral pathway;

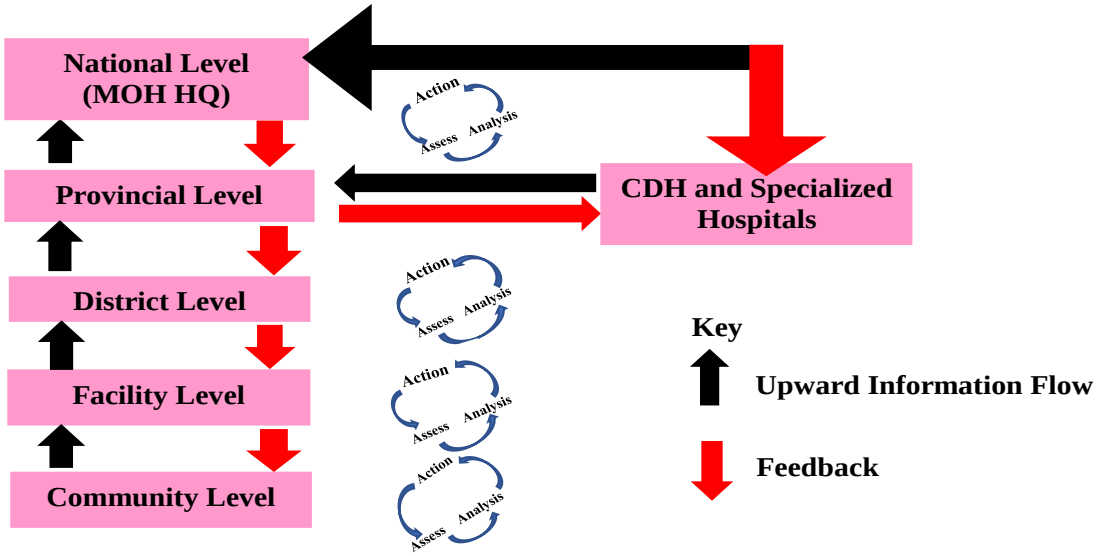


Figure 2.3. Referral pathway illustration

At each level of care ensure efficient and effective communication is done to the receiving facilities using standard referral documentation. Monitoring and evaluation of the entire referral system should be done at all levels.

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CHAPTER 3. PATHOLOGY SERVICES GUIDELINE

Accurate and precise histological diagnosis is crucial for appropriate treatment and prevention of disease progression in childhood cancers (Knowles D. et al, 2001). Survival rate of children with malignancies remains low in resource-constrained countries like Zambia due to inadequate resources, limited training in diagnosis and limited access to treatment. (Carter N.H. et al, 2018).

In order to improve histological diagnosis of childhood malignancies in Zambia, key quality parameters in diagnostic pathology need to be employed. These include timeliness, accuracy, completeness, conformance with current agreed standards, consistency and clarity in communication across disciplines and health facilities. These key quality parameters are useful if standardized histology report systems of childhood cancers are developed, adopted and utilised.

These pathology services guidelines will include templates for reporting the WHO six index cancers: Lymphomas (Burkitt & Hodgkin), ALL, RB, Nephroblastoma and LGG. The templates will serve as a model for scale up to include templates for other childhood malignancies in future editions. The current guidelines will apply to all levels of care where pathology specimens from children with suspected or confirmed cancer are collected and processed.

A. Childhood lymphomas templates

These templates include lymph node biopsy templates and bone marrow aspiration templates. Lymph node biopsy template includes details such as; demographic details, specimen type, surgical procedure, microscopic examination, ancillary tests, diagnosis and WHO classification. Bone marrow (BM) aspiration/ biopsy template details include; demographic, specimen type, surgical procedure, clinical history, ancillary tests, diagnosis and WHO classification.

B. Retinoblastoma Template.

Details include; demographics, specimen laterality, surgical procedure, tumour site, tumour size, Number of tumour foci, tumour involvement of other structures, growth pattern, microscopic examination, optic nerve invasion, Tumour-Nodal-Metastases (TNM) pathological staging (UICC 8th edition), additional findings, diagnosis and WHO classification.

C. Nephroblastoma template

Details include; demographics, pre-operative cytology, specimen type, specimen laterality, specimen weight, surgical procedure, tumour focality, tumour site, tumour size, histologic type, histologic grade, tumour extent, histologic features, tumour necrosis, lymphovascular invasion, margins, Staging for up-front nephrectomy [(children's oncology group staging system (COG)/Staging for pre surgical chemotherapy nephrectomy (international society for paediatric oncology (SIOP)], additional findings, diagnosis and WHO classification.

D. Low grade gliomas Template

Details include; demographics, specimen laterality, surgical procedure details, tumour site, ancillary studies (if applicable), additional findings, diagnosis and WHO classification.

Adoption of these templates in Zambian histopathology laboratories is likely to result in more complete reporting of essential parameters, improved standardization of diagnostic criteria and terminology, as well as easier retrieval of information.

3.1. STANDARDIZED HISTOLOGY REPORT SYSTEM OF WHO INDEX CHILDHOOD CANCERS

MICROSCOPIC EXAMINATION OF CHILDHOOD LYMPHOMAS

Table 3. Lymph node biopsy

	DETAILS (always needed)		**COMMENT**
A	**DEMOGRAPHIC DETAILS**		Age is important for predicting certain tumour behaviours
	Name:	Age: Sex:	
B	**CLINICAL DETAILS**		Clinical details are critical in enabling diagnosticians to assemble a complete differential diagnosis list. Name and facility of clinician is important for tracing specimens
	Name of Facility:		
	Clinicians Name: Clinicians contact number:		
	Date of collection:	Time of collection:	
	Neoadjuvant treatment given: Yes No Type of treatment given:		
	Clinical Details:		
C	**SPECIMEN TYPE**		Specifies where the biopsy was taken
	Lymph node(s)	Not specified:	
D	**PROCEDURE DETAILS**		Reliability of prognostic information vary depending on how the specimen was obtained
	Biopsy or Resection	Tumour Site	
E	**MICROSCOPIC EXAMINATION**		Tumour histology, grade, immunophenotyping, cytogenetic and molecular studies are strong predictors of clinical behaviour
	Histologic Type: Pathologic Extent of Tumour Additional Pathologic Findings	Immunohistochemistry (IHC) /Cytogenetic Studies Molecular Genetic Studies Clinical Prognostic Factors	
F	**CONCLUSION**		Summary which includes diagnosis provides strong predictors of clinical behaviours
	Diagnosis WHO classification (if relevant)		

Table 3.1. Bone marrow biopsies/aspirates with lymphoma

	DETAILS			COMMENT
A	**DEMOGRAPHIC DETAILS**			Age is important for predicting certain tumour behaviours
	Name:	Sex:	Age:	
B	**CLINICAL DETAILS**			May give important information required to make histological diagnosis
	Name of Facility:			
	Clinicians Name: Clinicians contact number**:**			
	Date of collection:	Time of collection:		
	Clinical History/ diagnosis: Full Blood count results:	Differential count results: Peripheral smear results:		
C	**PROCEDURE DETAILS**			Reliability of prognostic information vary depending on how the specimen was obtained
	Date of procedure: Indication of BM exam: Type of procedure:	Anatomical site of aspirate & biopsy: Ease/difficulty of aspiration		
D	**MICROSCOPIC EXAMINATION**			Tumour histology is a strong predictor of clinical behaviour.
	Blood count Cellularity of particles & cell trails Nucleated differential cell count Total number of cells counted Myeloid:Erythroid ratio Erythropoiesis	Myelopoiesis Megakaryocytes Lymphocytes Plasma cells Haemopoietic cells Abnormal cells		
E	**CONCLUSION**			Summary which includes diagnosis provides strong predictors of clinical behaviours
	Diagnosis WHO classification (if relevant)			

Table 3.2. Microscopic examination of retinoblastoma

	DETAILS		COMMENT
A	**DEMOGRAPHIC DETAILS**		Age is important for predicting certain tumour behaviour
	Name:	Sex: Age:	
B	**CLINICAL DETAILS**		Clinical details are critical in enabling diagnosticians to assemble a complete differential diagnosis list. Name and facility of clinician is important for tracing specimens
	Name of Facility:		
	Clinicians Name: Clinicians contact number:		
	Date of collection:	Time of collection:	
	Neoadjuvant treatment given: Yes No Type of treatment given:		
	Clinical Details:		
C	**SPECIMEN LATERALITY**		Specifies which side was affected
	Right / Left / Not specified		
D	**PROCEDURE DETAILS**		Reliability of prognostic information vary depending on how the specimen was obtained
	Enucleation Length of optic nerve	Partial exenteration or Complete exenteration	
E	**TUMOUR SITE BEFORE SECTIONING**		Site of neoplasm may correlate with tumour type, prognosis and predicting tumour behaviour
	Superotemporal quadrant of globe Superonasal quadrant of globe Inferonasal quadrant of globe	Inferotemporal quadrant of globe Anterior chamber	
F	**TUMOUR SITE AFTER SECTIONING**		Sectioning may reveal other sites involved by the tumour
	Superonasal Inferonasal	Superotemporal Inferotemporal	
G	**Tumour Size**		Tumour size is a strong predictor of clinical behaviour.
	Cannot be determined Greatest basal diameter	Greatest thickness	
H	**Tumour Involvement of Other Ocular Structures**		Involvement of other ocular structures may correlate with tumour type, prognosis and predicting tumour
	Cornea / Iris Anterior chamber Angle /Lens	Ciliary body Vitreous/ Choroid Sclera	
I	**Growth Pattern**		Endophytic tumours growth pattern are from the inner retinal while exophytic tumours are from outer surface of the retina
	Endophytic Exophytic	Combined endophytic/exophytic Diffuse	
J	**MICROSCOPY**		Tumour histology and grade are strong predictors of clinical behaviour.
	Histologic type Histologic Grade Anaplastic Grade Amplification	Margins Regional Lymph Nodes Cytologic Features Suggesting MYCN amplification	

K	**PATHOLOGIC STAGE CLASSIFICATION**		This staging system is used to describe the extent of tumour spread
	TNM Descriptors: m (multiple)/ r(recurrent)/y (post-treatment)	Primary Tumour (pT)Regional Lymph Nodes (pN) Distant Metastasis (pM)	
L	**ADDITIONAL PATHOLOGIC FINDINGS**		Additional findings may affect prognosis or therapeutic response
	Calcifications/Mitosis Apoptosis/Necrosis Inflammatory cells	Haemorrhage /Neovascularization Retinal detachment Basophilic vascular deposits	
M	**CONCLUSION**		Summary including diagnosis and grade provides strong predictors of clinical behaviour
	Diagnosis WHO classification (if relevant)		

Table 3.3. Microscopic examination of nephroblastoma

	DETAILS		**COMMENT**
A	**DEMOGRAPHIC DETAILS**		Age is important for predicting certain tumour behaviours
	Name:	Sex: Age:	
B	**CLINICAL DETAILS**		Clinical details are critical in enabling diagnosticians to assemble a complete differential diagnosis list. Name and facility of clinician is important for tracing specimens
	Name of Facility:		
	Clinicians Name: Clinicians contact number:		
	Date of collection:	Time of collection:	
	Neoadjuvant treatment given: Yes No Type of treatment given:		
	Clinical Details:		
C	**SPECIMEN LATERALITY & TUMOUR WEIGHT**		Specifies which side was affected
	Right	Left	
	Weight:	Weight:	
D	**PROCEDURE DETAILS**		Reliability of prognostic information vary depending on how the specimen was obtained
	Biopsy: Core/ Incisional /or Excisional	Resection: Partial / or radical	
E	**TUMOUR DIMENSIONS**		Dimensions of tumour may be important for predicting tumour behaviour
	Greatest dimension:	Additional dimensions:	
F	**TUMOUR FOCALITY**		Focality of neoplasm may correlate with tumour type, prognosis and predicting tumour behaviour
	Unifocal	Multifocal	
G	**TUMOUR EXTENT**		Anatomical extent of a neoplasm may correlate with tumour type, prognosis and predicting tumour behaviour
	Gerota's Fascia Renal Vein / Sinus	Renal Capsule Adjacent Organ	

<table>
<tr><td rowspan="2">H</td><td colspan="2">MICROSCOPY</td><td rowspan="2">Tumour histology and grade are strong predictors of clinical behaviour.

Post-therapy Histopathological Classification gives information on how the tumour responded to therapy</td></tr>
<tr><td>Histologic Type
Nephrogenic Rests
Pre/Post-therapy histopathological classification</td><td>Regional Lymph Nodes
Distant Metastasis</td></tr>
<tr><td rowspan="2">I</td><td>Staging for up-front nephrectomy</td><td>Staging for pre surgical chemotherapy nephrectomy</td><td rowspan="2">This staging system is used to describe the extent of spread of Nephroblastoma. It was developed by the National Nephroblastoma Study Group (NWTSG) and updated by the Children’s Oncology Group (COG) for pre-chemotherapy nephrectomy specimens and International society for paediatric oncology (SIOP) for post-chemotherapy nephrectomy specimens. (Vujanic.G.M. et al, 2002)</td></tr>
<tr><td>Not applicable (nephrogenic rests only)
Local Stage I: Tumour limited to kidney and completely resected
Local Stage II: Tumour extends beyond kidney completely resected,
Local Stage III: Residual tumour is suspected
Stage IV: Metastatic disease
Stage V: Bilateral renal involvement at diagnosis.</td><td>Stage I: Tumour limited to kidney with fibrous (pseudo) capsule if outside the contours of the kidney.
Stage II: Viable tumour extends beyond the kidney and/or fibrous (pseudo) capsule; completely resected.
Stage III: Residual viable/non-viable tumour beyond resection margins.
Stage IV: Haematological/Lymph node metastases outside the abdominal-pelvic region.
Stage V: Bilateral renal involvement at diagnosis (each side sub-staged accordingly).</td></tr>
<tr><td rowspan="2">J</td><td colspan="2">ADDITIONAL PATHOLOGIC FINDINGS</td><td rowspan="2">Additional findings may affect prognosis or therapeutic response</td></tr>
<tr><td colspan="2">Specify</td></tr>
<tr><td rowspan="2">K</td><td colspan="2">CONCLUSION</td><td rowspan="2">Summary which includes diagnosis and grade provides strong predictors of clinical behaviour</td></tr>
<tr><td colspan="2">Diagnosis
WHO classification (if relevant)
Tumour staging</td></tr>
</table>

Table 3.4. Microscopic examination of low-grade gliomas

	DETAILS				COMMENT
A	**DEMOGRAPHIC DETAILS**				Age is important for predicting certain tumour behaviour
	Name:		Sex:	Age:	
B	**CLINICAL DETAILS**				Clinical details are critical in enabling diagnosticians to assemble a complete differential diagnosis list. Name and facility of clinician is important for tracing specimens
	Name of Facility:				
	Clinicians Name: Clinician contact number:				
	Date of collection:		Time of collection:		
	Neoadjuvant treatment given: Yes No Type of treatment given:				
	Clinical Details:				
C	**SPECIMEN LOCALITY**				Anatomic site of a neoplasm may correlate with tumour type and prognosis
	Right	Left	Midline	Bilateral	
D	**PROCEDURE DETAILS**				Reliability of prognostic information vary depending on how the specimen was obtained
	Open biopsy Resection		Stereotactic biopsy		
E	**TUMOUR SITE**				Anatomic site of a neoplasm may correlate with tumour type and prognosis
	Skull Dura Leptomeninges Brain Cerebral lobes Basal ganglia		Thalamus Hypothalamus Pineal Cerebellum Cerebellopontine angle		
F	**MICROSCOPY**				Tumour histology and grade are strong predictors of clinical behaviour. Resection margins provide no prognostic information
	Histologic Type (WHO) Histologic grade (WHO)		Specimen Size Margins		
G	**ANCILLARY STUDIES, IF APPLICABLE**				They assist with diagnosis, prognosis, or to predict therapeutic response
	Special Stains Immunohistochemistry Electron Microscopy Molecular Genetic Studies				
H	**ADDITIONAL PATHOLOGIC FINDINGS**				Additional findings may affect prognosis or therapeutic response
	Specify				
I	**CONCLUSION**				Summary which includes diagnosis and grade provides strong predictors of clinical behaviour
	Diagnosis WHO classification WHO grade				

3.2. IMMUNOPHENOTYPING

This can be performed by either flow cytometry or immunohistochemistry.

a. Flow Cytometry

Immunophenotyping by flow cytometry is a test that detects the presence or absence of white blood cell (WBC) markers called antigens. These antigens are protein structures found on or within WBCs. Specific groupings of these antigens are normally present and are unique to specific cell types and stages of cell maturation. These patterns of antigens are also present on abnormal cells seen in leukaemias and lymphomas. Flow cytometry immunophenotyping may be useful in helping to diagnose, classify, treat and determine prognosis of these blood cell cancers. (Knowles D. et al, 2001)

b. Immunohistochemistry

This laboratory method uses antibodies to check for certain antigens (markers) in a sample of tissue. The antibodies are usually linked to an enzyme or a fluorescent dye. After the antibodies bind to the antigen in the tissue sample, the enzyme or dye is activated, and the antigen can then be seen under a microscope. Immunohistochemistry is therefore used to help diagnose cancer in tissues and may also help to classify cancers. (Knowles D. et al, 2001)

Flow cytometry and Immunohistochemistry both have their own advantages and disadvantages:

Table 3.5. Flow cytometry and Immunohistochemistry

SN	Immunophenotyping method	Advantages	Disadvantages
1	**Flow cytometry**	• It is a quantitative test • It is a rapid test • Multiple antigens can be evaluated • It is very accurate • It produces detailed data	• Antigen positivity cannot be correlated with architecture or cytologic features • It is relatively more expensive
2	**Immunohistochemistry**	• It allows correlation of antigen expression with architecture and cytology. • It can be used on fresh or frozen tissue. • The cost of IHC is relatively low.	• It requires long hours/days to perform. • Quantitation is subjective. • IHC is subject to human error. Well-trained personnel are paramount.

3.3. ESSENTIAL IN-VITRO DIAGNOSTICS FOR THE SIX INDEX CHILDHOOD CANCERS

Table 3.6. Immunohistochemistry

SN	MALIGNANCY	POSITIVE STAINS	NEGATIVE STAINS
1	**Acute Lymphoblastic Leukaemia/Lymphoblastic Lymphoma (ALL/LBL)**	**B-ALL**: CD19, CD79a, CD22, CD24, TdT, CD34, HLA-DR, CD10 & PAX5	Myeloperoxidase and lysozyme **B-ALL/LBL:** surface **immunoglobulin** is usually absent
		T-ALL / LBL: TdT, CD34, CD99, CD1a CD7 & cCD3	
2	**Burkitt Lymphoma**	CD 45	T cell markers: CD2, CD3, CD5, CD7
		Pan B cell markers: CD19, CD20, CD22, CD79a, PAX5	
		Germinal centre markers: CD10, BCL6	BCL2 and TdT
		Ki67 is approximately 100%	
		MYC protein expression in most cells	
3	**Hodgkin Lymphoma**	CD30	ALK
		CD15	TIA 1
		EBV	CD3, CD20
			CD45
			J-Chain, CD138
4	**Retinoblastoma**	SOX 2	Negative lymphocyte markers (CD45, CD3, CD20)
		MAP2	CD99
		Neuron specific enolase (NSE). Synaptophysin	GFAP
		Retinoblastoma associated protein (pRb).	
5	**Nephroblastoma**	WT 1	AMACR and CK7.
		<u>Blastema:</u> Diffuse expression of WT1, PAX8, vimentin Variable CD56, CD57, pancytokeratin, EMA, desmin	**Melanocytic markers**: (MelanA, HMB45)
		<u>Epithelium</u>: Cytokeratin, EMA, CD56	BRAF V600E, TFE3, TFEB, BCOR, FLI1
		<u>Stroma:</u> Vimentin, Bcl2, CD34	
6	**Low-Grade Glioma**	GFAP, Olig 2	Keratin
			CD45, CD20
			MelanA

Table 3.7. Molecular /cytogenetics of the six index childhood cancers

SN	Malignancy	Molecular /cytogenetics descriptions	
1	**Acute Lymphoblastic Leukaemia/ Lymphoblastic Lymphoma (ALL/LBL)**	Most B-ALL show clonal IgH	
		t(12;21) TEL-AML: very favourable prognosis; most common rearrangement in childhood B-ALL / LBL (25%), with cures of > 90%	
		Hyperdiploidy: favourable prognosis; trisomies 4, 10 and 17 have the best prognosis	
		t(9;22) BCR-ABL1 (Philadelphia chromosome): very poor prognosis; incidence increases with age, 3% of childhood cases and 25% of adult	
		t(v;11q23) MLL gene rearrangement: poor prognosis	
		Hypodiploidy: poor prognosis	
		BCR-ABL1-like IGH-CRLF2 translocation (and less commonly EPOR):	
2	**Burkitt Lymphoma**	c-MYC reciprocal translocation is characteristic but non-specific	
		Partner genes:	t(8;14) (q24;q32) c-MYC-IGH (~ 80%)
			t(8;22) (q24;q11) c-MYC-IGK (~ 15%)
			t(2;8) (p11;q24) c-MYC-IGL (~ 5%)
		In situ hybridization	EBER+ in EBV positive Burkitt lymphoma
			FISH for c-MYC translocation
3	**Hodgkin Lymphoma**	Hodgkin Reed-Sternberg (HRS) cell is aneuploid but has no consistent cytogenetic abnormalities; TNF receptor associated factors 1 & 2 are characteristic in HRS	
		Clonal Ig gene rearrangements (> 98% of cases) or clonal TCR gene rearrangements (rare), detectable only in isolated HRS DNA and not in whole tissue DNA	
		High load of somatic hypermutations in the variable region of Ig heavy chain genes (IGHV@) – supports derivation from germinal centre B cells	
		NFκB constitutively activated in HRS cells; also, blockage of the negative feedback loop of the JAK / STAT5 pathway	
		EBV: highest frequency (75%) - mixed cellularity, lowest (10 - 40%) - nodular sclerosing subtype; almost 100% in resource poor regions and HIV patients	
4	**Retinoblastoma**	Isochromosome 6p (45%): E2F3 and DEK genes	
		Gain of regions of chromosome 1q (44%): zsKIF14 and MDM4 genes	
		Monosomy 16 (18%): CDH11 gene	
		Gain of 1p (13%)	
5	**Nephroblastoma**	WT1 (11p13), prevalence 10 - 20%, early event: -stromal histology	
		CTNNB1 (3p22), prevalence ~15%, late event: -nephrogenic rests	
		IGF2 (11p15), prevalence ~70%, early event: -Blastemal histology	
		TP53 (17p13), prevalence ~70%, associated with anaplasia & overall survival	
		MYCN (2p24), prevalence ~15%, associated with anaplasia & overall survival	
		1q gain, prevalence ~30 - 40%, associated with overall survival	
6	**Low-Grade Glioma**	Over-expression of oncogenes, such as rat sarcoma (RAS), (PIK3CA), (CDK4), (MDM2) and epidermal growth factor receptor (EGFR).	

3.4. TURN-AROUND TIME (TAT)

Turn-around Time is broadly defined as the time between specimen receipt by the laboratory and the issuing of the final Pathologist's report. TAT for large or complex surgical pathology specimens is an indicator of efficiency in anatomical pathology and may affect coordination of patient care.

Assessment of TAT should account for variable fixation and processing duration. The following are minimum accepted TATs for different specimens:

Table 3.8. TAT for types of pathology specimens

SN	TYPE OF SPECIMEN	TURN AROUND TIME
1	Fine Needle Aspiration Cytology (FNAC)	2 days
2	Needle core biopsy	7 days
3	Incisional biopsy	7 days
4	Excisional biopsy	7 days
5	Large specimen	14 days

Specimen collection, fixation, preservation, transportation

Types of specimens taken at surgery of childhood cancers include FNAC, needle core biopsies, incisional biopsies, excisional biopsies (comprising of part of or the entire tumour) and large specimens (comprising part of or the entire organ involved by the tumour). Collection and transport of these specimens for histopathological examination involves a series of essential steps from the time it is taken from the patient at surgery up to its reception in the laboratory.

Table 3.9. Essential steps involved from collection to transportation of specimens

SN	ESSENTIAL STEPS	COMMENT
1	Putting the specimen in an appropriate container	The container should be large enough to easily accommodate the specimen so as to ensure proper specimen fixation (ideally 10x the volume of the sample).
2	Immersed in an appropriate type and amount of fixative	In order to achieve proper specimen fixation, the recommended tissue to formalin ratio is 1:10; (for small and very large specimens) of 10% Neutral Buffered Formalin.
3	Accurate identification and labelling of the specimen container with corresponding patient details on the request form.	Proper identification of specimen is mandatory to avoid mixing of specimens.
4	Completeness of information in the request form including relevant clinical details.	The laboratory request form is a communication link between the clinicians and the laboratory staff. Incomplete filling of the request forms may cause errors which can impact the quality of patient care.

HANDLING AND TRANSPORT OF HISTOPATHOLOGY SPECIMENS

These are instructions for collection and transport of histopathology specimens of different sizes to ensure optimal tissue fixation as well as accurate documentation, and inclusion of clinical information in the request form that may be needed to aid histopathological diagnosis.

The Pathology Request Form:

The use of a standardised request form for all tissue specimens is strongly recommended. The information on the request form should be precise and provided by the surgeon or other clinician as relevant to the specimen type. It is strongly recommended that the surgeon who performs the procedure should fill in the requisition form.
Each specimen container should be clearly labelled with the name of the patient and the nature, site and side of the specimen.

The pathology request should include at least the following items of information (Table 3.1.1. below):

Table 3.1.1. Vital Information to include on the pathology requisition form

SN	VITAL INFORMATION	COMMENT
1	Name of patient	Helps identify the specimen. This should also be accompanied by age, sex and patient's file number to avoid mixing of specimens in case of patients having similar names
2	Age and Sex	
3	Date and time of surgery or specimen collection.	Gives an idea to laboratory staff on how long the specimen was fixed. If no fixative was added, it will assist laboratory staff to determine if the specimen is viable for processing or not
4	Number of specimen containers submitted.	Assists in determining how many specimens were in the container to avoid misplacement of specimen
5	History and clinical findings	Assists laboratory staff to determine how the specimen will be processed and also assists in determining the final diagnosis
6	Radiology studies if indicated	Assists laboratory staff in determining the final diagnosis
7	Description or diagram of orienting sutures or clips	Helps laboratory staff to properly orient the specimen during grossing
8	Each specimen container should be clearly labelled	Helps identify the specimen for easy matching with the laboratory request form

Specimen Collection:

Specimen collection methods may include FNAC, incisional biopsy, excisional biopsy, bone marrow aspirate and/or biopsy and whole organ resections depending on the type of cancer and extent of disease:

Table 3.1.2. Specimen collection methods

SN	TYPE OF SPECIMEN COLLECTION	PROCEDURE	COMMENT
1	**FNAC**	FNAC involves the removal of tissue, fluid, or very small pieces from a tumour using a thin needle. Local anaesthetic is sometimes used to numb the area, but the test rarely causes much discomfort and leaves no scar.	It is a well-accepted minimally invasive diagnostic technique. The ease of FNAC along with its high diagnostic accuracy makes it a desirable method for diagnosing lesions in children.
2	**Incisional biopsy**	A cut is made to remove a sample of abnormal tissue or part of a lump or part of suspicious area. The tissue is then checked under a microscope for signs of disease.	A pathologist views the tissue under a microscope to look for cancer cells. An incisional biopsy is recommended when the lesion is on a hazardous location and suspicion for malignancy is high
3	**Excisional biopsy**	Involves surgical removal of a tumour and some normal tissue around it. The amount of normal tissue taken (also called the clinical margin) depends on the thickness of the tumour.	A pathologist views the tissue under a microscope to look for cancer cells. An excisional biopsy is more invasive as margins are also resected. It is recommended for very small lesions where complete excision is indicated.
4	**Bone marrow aspirate and/or biopsy**	Involves the removal of bone marrow aspirate (liquid), blood, and a small cylindrical piece of bone where the bone marrow is found, by inserting a needle into the hipbone or breastbone. The skin is cleansed and a local or general anaesthetic is given for pain control. A long, rigid needle is inserted or trephined into the bone marrow compartment, and cells are aspirated or trephine biopsy collected for study	Indications include diagnosis, staging, and therapeutic monitoring for childhood lymphoproliferative disorders (such as ALL), Hodgkin and non-Hodgkin lymphoma (such as BL) and solid tumours with propensity for spreading to the marrow such as retinoblastoma & neuroblastoma
5	**Whole organ resections**	A resection means surgically removing an entire organ, a whole section of an organ (like an entire lung lobe), or removing a body part such as amputation of the lower limb above the knee joint	Recommended where there is risk of spread to involve the whole organ. For example, enucleation or exenteration in retinoblastoma and Kidney resection (nephrectomy) in Nephroblastoma

- For small specimens, the specimen should be collected into a wide-mouthed container with a well-fitting lid containing an adequate amount of 10% neutral buffered formalin (completely submerge the specimen)

- For large specimens, the specimen should also be placed in a wide-mouthed container with a well-fitting lid, containing an adequate amount of 10% neutral buffered formalin. The container should be larger than the specimen, preferably a bucket.

- ***Do not squeeze the specimen into the container.***
- ***The recommended ratio of 10% buffered formalin to specimen volume is typically 10:1 - meaning for every 10 parts 10% buffered formalin to ensure proper fixation.***

- Orientation sutures should be placed and clearly identified in the request form.
- Slicing the specimen is not recommended in general. This is because the sliced specimen distorts on fixation, and accurate measurement of distance of the lesion to excision margins is distorted.
- If multiple biopsies are sent from the same patient, each specimen should be sent in a separate container indicating the site(s) of biopsy.
- Each of the containers should be accurately labelled with the patient's name, age, sex, ward and patient medical record or hospital number. (Lott R. et al, 2015).

Transportation of Specimens

Specimens should be transported to the laboratory as soon as possible for proper fixation procedures to be carried out.

For transport of all pathology specimens and associated materials by air or surface transport methods, the packaging must consist of three components:

- Primary receptacle
- Secondary packaging
- Outer packaging

This is also known as triple packaging.

Steps to Better Specimen Collection and Transport

Steps to Better Specimen Collection and Transport are shown in the table below:

Table 3.1.3. Steps to better specimen collection and transportation

STEP	DESCRIPTION	COMMENT
STEP 1	Avoid Mechanical Trauma	Ensure tissue is removed gently to avoid trauma to the specimen caused by crushing or tearing. This applies both during surgery and during any further dissection that may be required of a fresh specimen. Do not allow specimen to be damaged before fixation by crushing or tearing during removal.
STEP 2	Prevent Specimen Drying	Ensure that the specimen is not allowed to dry out prior to fixation. If immediate fixation is not practicable, gauze moistened with saline can be used to prevent this. Do not allow specimen to be left on absorbent surface for some time prior to fixation.
STEP 3	Avoid Heat Damage	Ensure that you avoid local heat damage to specimens (some damage by cautery may be unavoidable). Do not allow any unnecessary local heat applied to tissue to cause damage. Fresh tissue is particularly susceptible.
STEP 4	Avoid Chemical Damage	Ensure that you avoid contaminating fresh specimens with foreign chemicals or substances such as disinfectants. Do not allow the surface of unfixed tissue to be penetrated and damaged by foreign reagents or substances.
STEP 5	Label Specimens Properly	Ensure each specimen is properly identified and all details recorded as soon as possible. Do not allow delays in recording of specimen details.
STEP 6	Ensure Prompt Fixation	Ensure fixation is always carried out promptly. If it is necessary that a specimen remains unfixed for a short period of time, it should be refrigerated at 4 °C. Do not allow delays in fixation (degeneration of tissue elements commences as soon as the specimen is deprived of a blood supply).
STEP 7	Use Sufficient Fixative and a Suitable Container	Ensure an adequate volume of fixative (ratio of at least 10:1) is used in a container of an appropriate size. This avoids distortion of the fresh specimen and ensures good quality fixation. Do not allow specimens to be squashed into a small container with insufficient fixative to cover the specimen surface.
STEP 8	Check Fixative pH	Ensure the fixative is of high quality and at the optimal pH. Do not allow a fixative of poor quality and unknown pH. If formalin is used at acid pH it rapidly produces “formalin pigment” by reaction with haemoglobin. Near neutral solutions will still produce the pigment but much more slowly. In good histological preparations formalin pigment should be removed prior to staining.

ROLE OF SECOND OPINION

Second opinions are an integral part of pathology services. It is highly recommended to send cases for review and evaluation by an expert pathologist. A second opinion means your sample will be reviewed by another expert medical professional to give their opinion, either to back up the initial diagnosis or to provide another viewpoint.
It is advised that every new diagnosis of childhood malignancy be reviewed by a second local pathologist at the same institution before authorizing a histology report. Second opinions can also uncover a potential misdiagnosis or reveal that the proposed diagnosis may not follow current best evidence or is controversial.
Most histopathology laboratories, however, are run by a single general pathologist in the Zambian setting.

It is therefore advised that pathologists commit their services and allocate time to diagnose childhood cancers. They should not fail to participate as members of the paediatric oncology multidisciplinary team which, at the least, comprise of paediatric oncologists, radiologists and surgeons. It is expected that centres with such pathologists working closely with a paediatric oncology multidisciplinary team will demonstrate a lower rate of major disagreements in histological diagnosis compared with sites that do not have.

Anyone requesting a second opinion will provide information of the first report, the name and contact information of the reporting doctor (Pathologist) and the receiving doctor to be notified.

A second opinion will only be accepted if it is reported by a qualified medical doctor specialized in histopathology, surgical pathology, anatomic pathology or equivalent and is recognised and registered:

- On the histopathology specialist register of the Health Professions Council of Zambia (HPCZ).
- As a histopathology specialist by the Pathologists' Association of Zambia (PATHAZ).

- ***To ensure consistency in the implementation of second opinion for childhood cancer histological diagnosis, Pathology laboratories manned by single pathologists reporting on childhood malignancies should send slides or tissue specimens at the same time the child from whom the specimen was collected is referred to the Cancer Hospital.***
- ***The Pathology team at the Cancer Hospital will give the second opinion.***

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CHAPTER 4. DIAGNOSTIC IMAGING FOR CHILDHOOD CANCERS GUIDELINE

This section of the text provides information about the diagnostic imaging modalities and techniques for imaging in the course of management of the outlined childhood index cancers.

It is essential that imaging of the paediatric patient follows standardised guidelines to ensure reproducibility, reduce need for repeat imaging and provide comparable studies for follow-up. Special consideration should be taken when imaging the paediatric patient with regard to use of ionising radiation. As low as reasonably achievable (ALARA) principle must be applied in all cases and remember to "image gently". This is because of the potential risk of radiation exposure and possibility of developing secondary malignancies. Whenever possible consider the use of imaging modalities that do not use ionising radiation. The decision to use a particular imaging modality should be arrived at not only because of availability but also for optimally answering the clinical question at hand.

Some imaging modalities available country-wide include:

- Plain Radiography - This modality uses X-rays (ionizing radiation) to image different body parts.
- Ultrasound (US) - This modality is real-time imaging that uses sound waves (non-ionizing) to image different body parts.
- Echocardiography (ECHO) – Refers to use of sound waves to assess the structure and function of the heart.
- Computed Tomography (CT) - uses X-rays (ionizing radiation) and computer software to generate cross sectional imaging reconstructed in various planes of the imaged body part. This modality uses higher levels of ionizing radiation as compared to plain radiography. CT may be performed without or with administration of contrast media.
- Magnetic Resonance Imaging (MRI) - uses magnetic fields, radiofrequency pulses and computer software to generate cross sectional imaging with different sequences reconstructed in various planes without use of ionizing radiation. This may be performed without or with administration of contrast media.
- Nuclear medicine – Positron Emission Tomography (PET) is functional imaging which may be combined with either CT i.e. PET/CT or MRI i.e. PET/MRI. PET/CT and PET/MRI are important imaging modalities in the management of various cancers and are briefly mentioned in this guideline. However, both are currently not available in Zambia at the time of writing this guideline.

As children are particularly susceptible to the detrimental effects of ionising radiation (X-rays and CT imaging), with a primary concern being increased cancer risk. Even though most diagnostic CT and PET studies are associated with a very favourable risk–benefit ratio, there is a strong argument to be made that radiation exposure should be as low as reasonably achievable. (Weiser DA et al, 2013)

One way to reduce exposure to ionizing radiation is to consider MRI or ultrasound in place of CT scans and PET studies when feasible.
Suggested strategies for minimizing exposure to ionising radiation for paediatric imaging studies include but are not limited to the following;

- Check if CT is the optimal imaging modality for the clinical indication.
- Optimize equipment for paediatric patients.
- Adjust the exposure settings based on child size and organ(s) being imaged.
- Scan the smallest necessary area.
- Question if higher quality/resolution images are necessary to make a diagnosis.
- Follow ALARA principles at all times.
- Review educational materials and quality assurance initiatives.

Imaging request forms should be adequately completed for the purpose of adequate and efficient imaging protocol selection, appropriate image acquisition and image interpretation:

- A detailed clinical history and available appropriate laboratory results should be clearly documented.
- Renal function tests i.e. serum creatinine results performed <72 hours prior to imaging that requires IV contrast media, should be clearly indicated on the request form and the laboratory copy of the result attached.
- The weight of the patient should be clearly indicated to ensure adequate dosing of both contrast media and medication for sedation when required:
    - For CT - Water soluble iodine-based contrast media dose = 1 - 2 ml/kg body weight depending on the region to be imaged.
    - For MRI – Gadolinium-based contrast media as per manufacturer's recommendation based on body weight.

- For a female paediatric patient of child bearing age, a pregnancy test should be done and must be negative before imaging with an ionising radiation modality such as Plain radiography, CT or PET/CT.
- Consult an Anaesthesiologist for pre-evaluation and protocol for sedation prior to imaging in paediatric patients requiring sedation for best image quality.

Radiological request form

Patient File #:				**Radiological Exam #:**				
Tick Where Applicable	**CT ❑**	**X-RAY❑**	**DEXA❑**	**FLUORO❑**	**U/S ❑**	**MAMMO ❑**	**ANGIO ❑**	**NM ❑**

Patient Information

Requesting Date: ……..

Patient's Name: ……..

Gender: ……. **Age:** …… **Race:** ……..

Patient's Phone No: ……

Clinical Details:

……

……

……

Examination Required:(State organ/ Region):

……

Referring Department

1. **ER** ❑ ……..
2. **Inpatient** ❑ ……
3. **Clinics/OPD** ❑ ……..
4. **Private Hospital** ❑ ……

Physician Information

Senior Doctor Name (PRINT): ……

……

Signature: ……..

Contact Number: ……

Ward/ Clinic: ……

UNIT/ FIRM: ……..

Patient Information

Weight (kg): ……

Allergies (Specify if any): ……..

……

Creatinine results: ……

GCS (Where applicable): ……

Pregnant: Yes ❑ No❑ Diabetic: Yes ❑ No❑

NHIMA #: ……

NRC or Passport #: ……

OTHER SCHEME #: ……

Appointment Information (Radiology Department Use Only)

Appointment Date: …… **Appointment Time:** ……

❑ **Nothing by mouth 5-6 hours before the exam. Arrive 15 minutes before the Appointment Time**
❑ **Oral contrast Yes ❑ No ❑**
❑ **IV Contrast Yes ❑ No ❑**
Patient Preparation: ……..

Radiographer/ Radiography Technologist Name:……..

Signature: …… **Date**: ……

NB: Urgent requests to be discussed with radiologist.
Incomplete, illegible and unsigned request form will not be accepted.

4.1. RADIOLOGICAL EVALUATION FOR THE SIX INDEX CANCERS

Acute Lymphoblastic Leukaemia (ALL)

Imaging is not as useful for initial management of Leukemias in comparison to other cancers because it does not always form tumours. Imaging may be used to determine the extent of disease when it is thought to extend to other solid organs, or to look for complications such as infections.

- ***Imaging is not required to make a diagnosis of acute lymphoblastic leukemia.***
- ***Imaging should be guided by clinical dictate and in consultation with a Radiologist.***

Initial evaluation of ALL

Plain Radiography:

- Chest
  - Technique: PA or AP and Lateral CXR views
  - Comment: Evaluate for mediastinal Masses/Lymphadenopathy, Pleural effusion and Enlarged cardiac shadow (pericardial effusion)

- Musculoskeletal
  - Technique: Orthogonal views as per national Standard Operating Procedures
  - Comment: Evaluate for the presence of generalized osteopenia/osteoporosis, radiolucent Sub-metaphyseal bands i.e. leukemic lines, periosteal response, osteolytic lesions/ permeative lesions and pathological fractures including compression fractures and vertebral plana among other findings.

Ultrasound:

- Abdomen/Pelvis
  - Technique: Curvilinear probe (2-7 MHz)
  - Comment: Organomegaly (Hepatosplenomegaly, Nephromegaly), abdominal lymphadenopathy, and ascites. Wall thickening of the cecum and ascending colon +/- pericolic fat stranding and fluid collection in case of neutropenic colitis/typhlitis.

- Enlarged Peripheral nodes (cervical, axillary and inguinal) +/- Biopsy
  - Technique: Linear probe (7.5 - 15 MHz)
  - Comment: Size – Cortical thickness > 3mm, Loss of normal fatty Hilum and Loss of normal ovoid shape

- Testis
  - Technique: Linear probe (7.5 - 15 MHz)
  - Comment: Enlarged hypervascular testis on Doppler with homogeneous echogenicity or diffuse/focal hypoechoic lesions

ECHO

- Heart
  - Technique: Cardiac probe - 2D transthoracic ECHO, M-mode and Doppler
  - Comment: Assess pericardial effusion and cardiac function

Computed Tomography

- Head
  - Technique: CT head without and with contrast
  - Comment: Single or multiple intra and extra-axial lesions (Iso/hyperdense to cerebral parenchyma on CT with contrast), cerebral Hemorrhage, oedema/mass effect may be present, dural sinus thrombosis, leukaemic meningitis, orbital mass with adjacent bone erosion and enlarged optic nerves (Normal range 3 to 6mm, varying with age)

- Musculoskeletal e.g. limbs/spine
  - Technique: as per national standard operating procedure. Usually done without contrast.
  - Comment: As seen above on plain film

- Chest/abdomen/Pelvis
  - Technique: Without and with contrast
  - Comment: Mediastinal mass, lymphadenopathy, pleural effusion or pleural reactive changes, pericardial effusion, ascites and organomegaly (Hepatosplenomegaly, Nephromegaly)

MRI

- Brain
  - Technique: Protocol according to age and may include T1 - coronal and sagittal planes, T1 with contrast - in three planes, T2 -axial plane, Fluid Attenuation Inversion Recovery (FLAIR) - coronal plane and Diffusion Weighted Imaging/Apparent Diffusion Coefficient map (DWI/ADC) - in three planes. Gradient Echo (GRE) sequence in axial plane may be useful for blood products. Diffusion Tensor Imaging (DTI), perfusion studies or spectroscopy are additional sequences that can be considered but are currently not available in Zambia. Thin slices - 3mm.

  - Comment: Special considerations include:
    - For children below 2 years old T2 images can be replaced with dual -echo axial Short tau inversion recovery (STIR).
    - For children <2 - 3 months consider imaging without sedation, but with “feed and sleep method” if possible.

        - For children older than 7 years old, attempt to get the child acquainted with the machine and comfortable, providing distractions when possible, to minimize need for sedation.
        - Single or multiple intra- or extra-axial masses (T1 – Iso/hypointense, T2-heterogeneous Iso/hyperintense and have diffuse enhancement with gadolinium contrast administration. Optic nerve enlargement and enhancement with contrast enhancement and orbital mass with or without associated proptosis

- Spine
    - Technique: T1 and T2 - sagittal and axial planes in region of interest. Optional images include STIR sequences and Contrast enhanced T1 images. If patient has scoliosis coronal images may be included.
    - Comment: Bone marrow infiltrates replacing the normal fatty marrow (Diffusely T1 hypointense and T2/STIR hyperintense). Pathological fractures including compression fractures and vertebral plana.

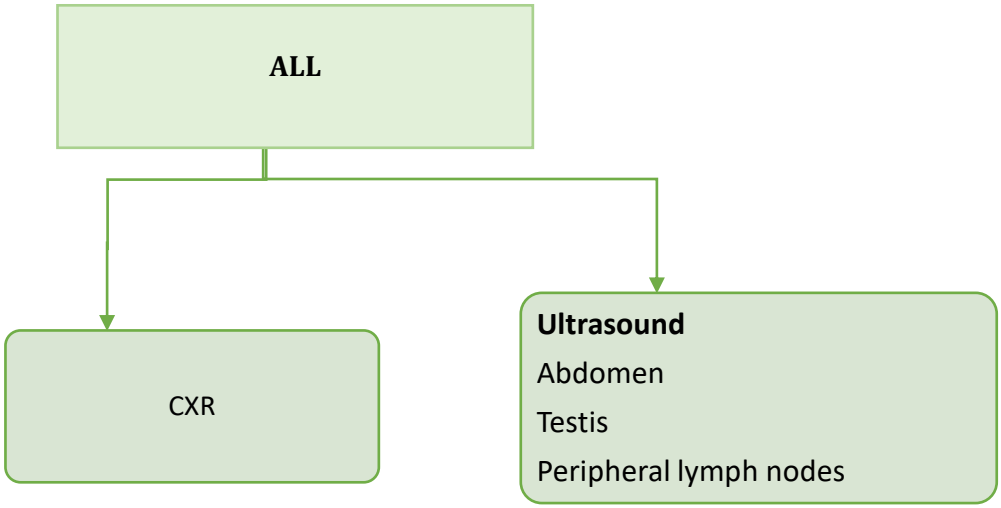

Figure 4. Initial Imaging for ALL

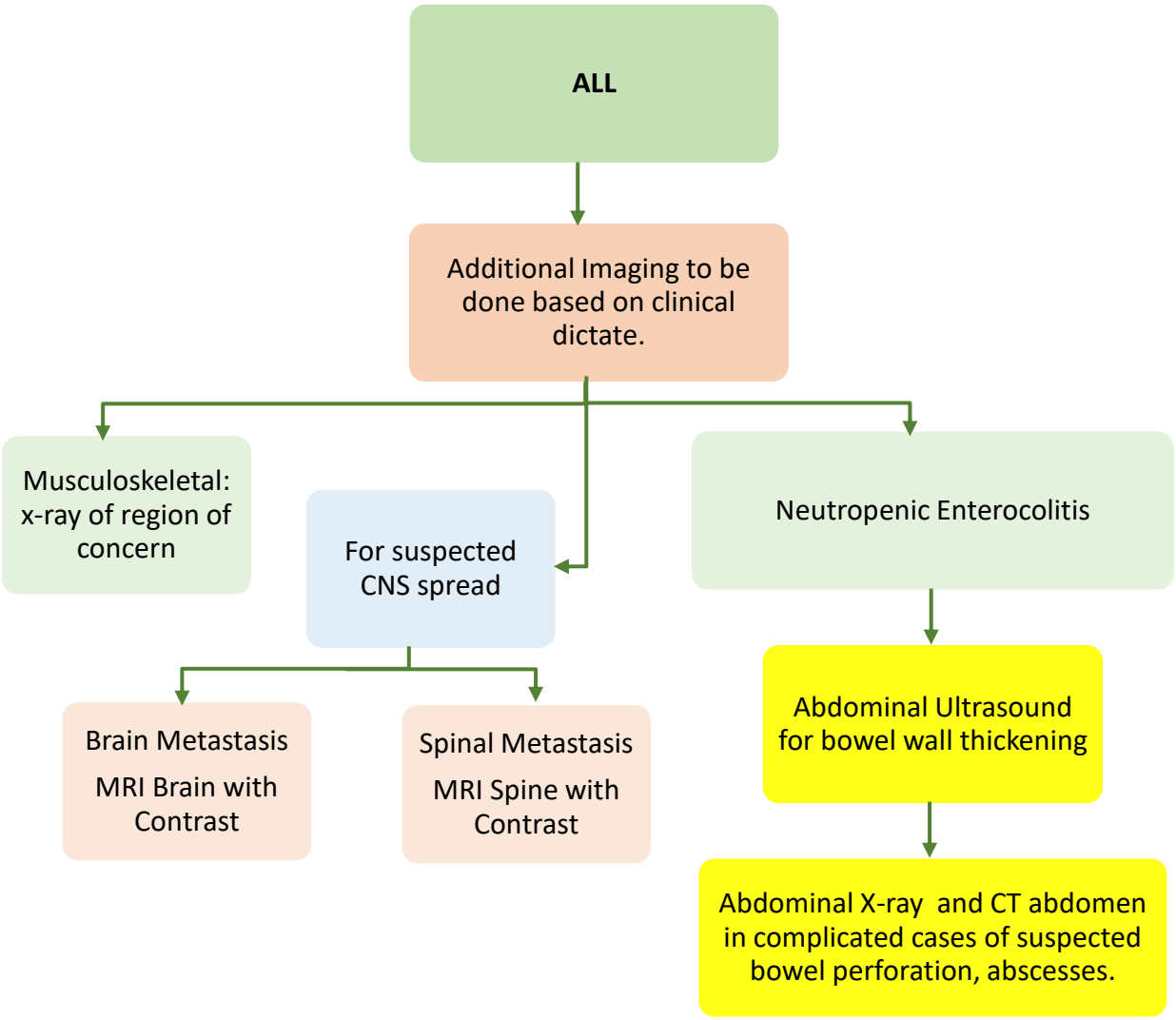

Figure 4.1. Further Imaging for ALL

4.2. LYMPHOMA (HL AND BL)

The imaging guide will here consider the two lymphomas together. Concerning foci of involvement, Hodgkin lymphoma (HL) is a nodal disease with spleen also being considered nodal but it can affect lung, bone, bone marrow and rarely liver. Whereas Non-Hodgkin lymphomas (NHL) including Burkitt Lymphoma (BL) is a more disseminated disease which can involve nodes but more commonly involves organs and can be seen in Central Nervous System and Gastrointestinal Tract.
Imaging findings tend to overlap for HL and NHL, however CNS and bone involvement are more common in NHL, because of this; head to toe imaging with PET/CT and/or PET/MRI is recommended for initial evaluation and treatment follow up where available. Due to similarities in imaging the gold standard differentiating between the two is histopathology.

- HL - Imaging is the major component of staging (determining nodal or extranodal disease, presence on one or both sides of the diaphragm), contributes to risk assessment and guides therapy regimen.
- BL - This commonly presents as a disseminated disease with multi-organ involvement. Imaging is therefore useful in assessing the extent of disease throughout the body, including but not limited to, evaluation of the CNS, bones and nodes.
- Imaging also plays a role in evaluation of treatment response and surveillance for relapse.

Imaging at Diagnosis and Initial staging of lymphoma

Plain Radiography - Primarily for initial evaluation

- Chest
  - Technique: PA or AP and Lateral CXR views
  - Comment: Findings may include:
    - HL - Mediastinal masses/lymphadenopathy without or with Airway compression, Pleural effusions or pleural reactive changes, Alveolar or interstitial infiltrates, Peri-bronchial/peri-vascular thickening without or with atelectasis, Masses or mass-like consolidations.
    - BL - Mediastinal and hilar lymphadenopathy, Pleural effusions and Pleural reactive changes, (Parenchymal disease is very rare)

- Musculoskeletal
  - Technique: Orthogonal views of areas of interest as per national standard operating procedures
  - Comment: Findings may include:
    - HL - Majority of the early bone lesions are lytic and blastic. Long bones, pelvis and ribs show osteolytic lesions. Spine is most commonly involved and variable with - erosion of anterior or anterolateral aspect of the vertebral

bodies, whereas sclerosing HL will demonstrate increased density including Ivory vertebra. However, intervertebral disc spaces are usually spared.
    - BL - Permeative bone lesions without local expansion or soft tissue masses may involve long bones, cranial vault and mandible

Ultrasound

- Neck
    - Technique: Linear Probe (7.5 - 15 MHz)
    - Comment: Findings may include:
        - HL and BL - Cervical lymphadenopathy without or with Necrosis may be present.
        - Lymph node size – Cortical thickness > 3mm, Loss of normal fatty Hilum and Loss of normal ovoid shape

- Abdomen/Pelvis
    - Technique: curvilinear Probe (2 - 7MHz)
    - Comment: Findings may include:
        - HL and BL - Renal enlargement with decreased parenchymal echoes and loss of renal sinus echoes or renal masses. Hepatosplenomegaly +/- focal hypoechoic lesions.
        - In addition, BL may have Solid hypoechoic abdominal mass lesions, or abdominal lymphadenopathy, ascites, asymmetric bowel wall thickening or Intussusception may occur

CT scan

- Neck/Chest/Abdomen/Pelvis
    - Technique: Without and with IV contrast multi-planar reformat images including coronal and Sagittal. For BL negative oral contrast can be used on suspected GIT involvement after discussion with Radiologist.
    - Comment: Findings may include:
        - HL - Radiographic features vary widely depending on organs involved. Lung masses or mass-like consolidations and alveolar/interstitial thickening more frequently seen in HL than in BL. Ensure to assess for bone lesions finding as noted on radiography
        - BL - Radiographic features vary widely depending on organs involved. Lung Parenchymal lesions are rare. GIT involvement may be seen. Ensure to assess for bone lesions finding as noted on radiography

MRI

MRI can be used as a problem-solving tool in consultation with the Radiologists, where other imaging modalities do not optimally demonstrate the pathology. It can be used for organs such as bone, spleen and CNS. Protocol is according to region of interest. Whole body MRI has been used in limited series but is not widely used.

- ***For treatment response evaluation, comparable imaging to the initial should be done, i.e. (CT scan without and with IV contrast), using the Response Evaluation Criteria in Solid Tumours (RECIST) response evaluation system.***

- ***For disease staging systems and patient follow-up imaging plans refer to treatment guidelines in the next section.***

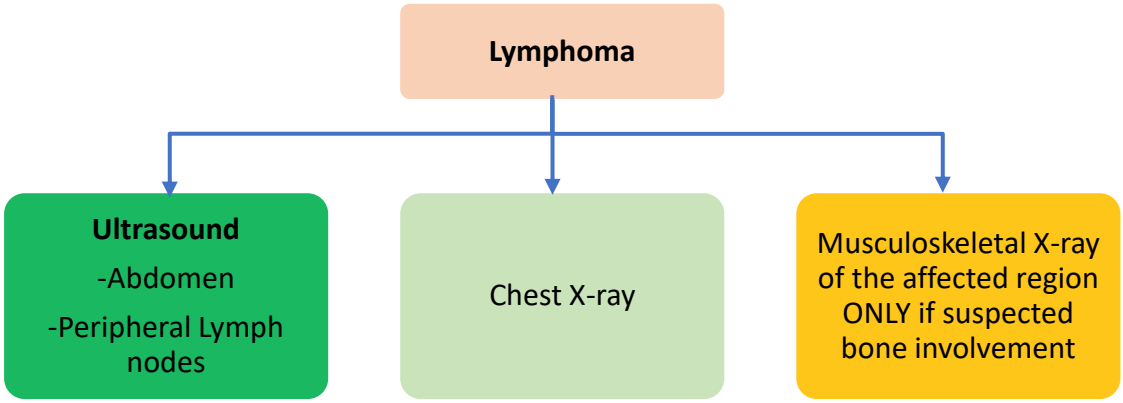

Figure 4.2. Initial Imaging for Lymphomas

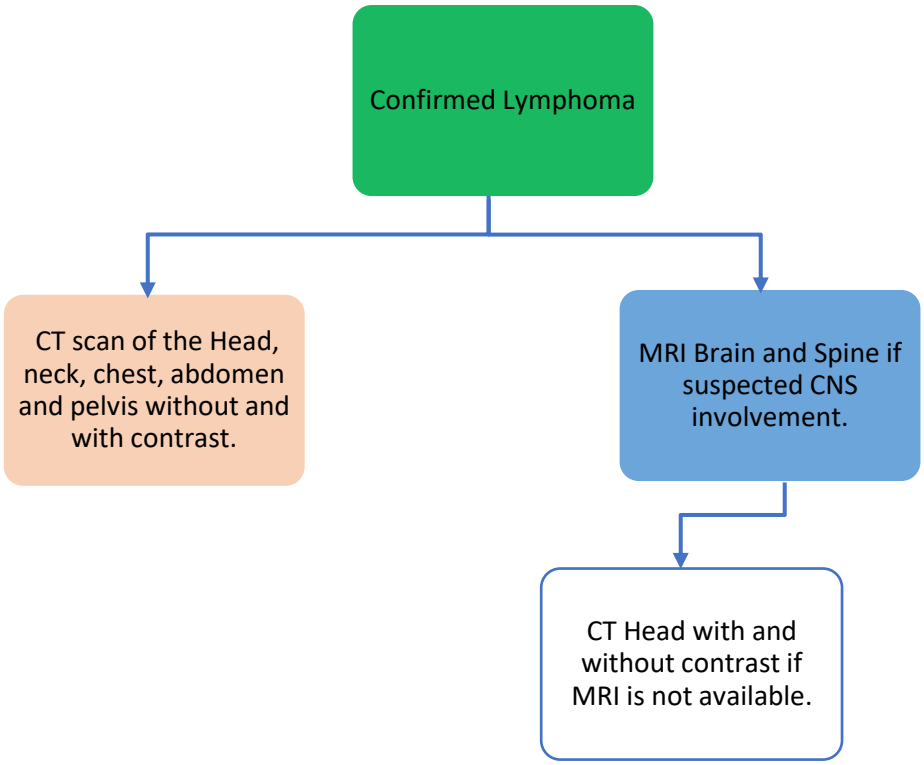

Figure 4.3. Staging Imaging for Lymphomas

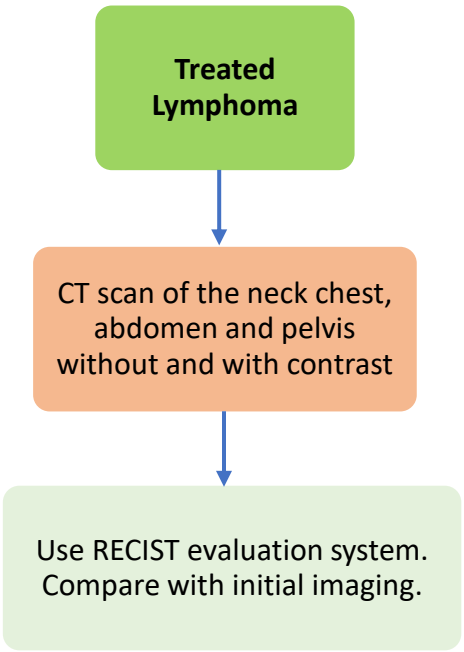

Figure 4.4. Treatment Response Imaging for Lymphomas

4.3. RETINOBLASTOMA (RB)

Imaging studies:

The primary role of imaging is to establish eye tumour presence and determine tumour spread locally and distantly. Imaging also plays an important role in the follow up of disease processes including but not limited to treatment response, disease progression and recurrence.

MRI is the modality of choice for evaluating RB both for initial assessment and follow-up. A 1.5 Tesla to 3 Tesla scanner should be used for optimal image acquisition. However, other modalities including Ultrasound and CT are also useful, particularly in resource limited environments where MRI is not readily available. Ultrasound is advantageous due to widespread availability and because it does not use Ionising radiation. It can therefore be used repeatedly, in addition, it does not require sedation, whereas sedation is often necessary with MRI particularly in the pediatric population due to the long image acquisition times. The disadvantage of ultrasound is that it is operator dependent. There is controversy in the use of CT for imaging of children with RB due to the theoretical risk of development of secondary tumours after ionising radiation exposure. This risk may be less in the setting of sporadic compared to hereditary RB.

- ***Other imaging modalities that are useful for evaluation of bone metastasis include scintigraphy and Positron Emission Tomography (PET); these are not discussed further in this guideline.***

Listed below are details of most common imaging features demonstrated on the various imaging modalities, this list is not exhaustive but will provide a guide in decision making.

Ultrasound:

- Ocular
  - Technique: Ocular probe (10 -20 MHz)
    - B-scan ultrasound: provides a two-dimensional cross-sectional image of the eye
    - Doppler ultrasound: used to assess blood flow within the tumor
  - Comment: Soft tissue intraocular mass which may have cystic component due to necrosis- Heterogeneously hyperechoic (caused by necrosis and haemorrhage). Calcifications, retinal detachment and/or choroidal thickening are also frequently seen. The detached retina will appear as an echogenic curvilinear membrane floating within the vitreous. Vitreous debris may represent vitreous seeding, necrotic debris or haemorrhage. Increased vascularity on doppler examination may be demonstrated.
- Head and Neck
  - Technique: Linear probe (7.5 - 15 MHz)

- Comment: Pre-auricular or cervical lymphadenopathy may be demonstrated.

- Abdomen/Pelvis
  - Technique: Curvilinear probe (2 - 7 MHz)
  - Comment: Hepatic metastasis in cases of advanced disease

CT scan

- Head/Neck
  - Technique: Without and with IV contrast, thin slices - 1 mm.
  - Comment: Solid smoothly marginated lobulated retrolental heterogeneous hyperdense mass with moderate contrast enhancement. Calcifications are better evaluated on CT as it is superior to other modalities for evaluation of calcification. Extraocular extension from the globe with optic nerve enlargement or abnormal soft tissue mass in the orbit seen in advanced disease. Intracranial extension - along optic nerve into the anterior cranial fossa, subarachnoid space, leptomeninges and bone. Changes in globe size such as macro-ophthalmia or in late-stage phthisis bulbi (small shrunken globe). Metastasis to Meninges and Metastasis to Pre-auricular/Cervical Lymph nodes can be demonstrated on CT.

- Chest/Abdomen/Pelvis
  - Technique: Without and with IV contrast
  - Comment: Pulmonary, Hepatic and Lymph node metastases may be demonstrated.

MRI

- Brain and Orbits
  - Technique: Protocol according to age and may include T1 - coronal and sagittal planes, T1 contrast enhanced - in three planes, T2 -axial plane, FLAIR - coronal plane and DWI/ADC - in three planes. GRE sequence in axial plane may be useful for blood products. DTI, perfusion studies or spectroscopy are additional sequences that can be considered. Thin slices - 3mm.
  - Comment: Special considerations for imaging of pediatric patients as documented above (refer to MRI imaging of ALL). Findings may include;
    - Intraocular mass;
      - T1- intermediate or hyperintense compared to vitreous
      - T2 - Hypointense compared to vitreous
      - T1 contrast enhanced - Variable enhancement (homogeneous when smaller, Heterogeneous when large)
      - DWI/ADC - Restricted diffusion on DWI on high *b* values and Low ADC values in contrast to high values of the vitreous.

    - Retinal detachment - Demonstrated as a T2 hypointense line focally around the tumour or V-shaped appearance for total detachment
    - Vitreous seeding - small foci of T2 hypointensity on background of

hyperintense vitreous
    - Choroid invasion - T1 post contrast Fat saturated images may demonstrate thickened and discontinuous choroid in contrast to normal curvilinear enhancement.
    - Optic Nerve invasion with heterogeneous enhancement on T1 post-contrast Fat Saturated.
    - Scleral and extra-scleral invasion demonstrated by tumour enhancement beyond the choroid with breech of the sclera and periocular soft tissue thickening/mass, enhancement and stranding
    - Intracranial extension - along optic nerve into the anterior cranial fossa, subarachnoid space, leptomeninges and bone
    - CNS midline embryonic tumours may be seen in heritable Retinoblastoma. (Pineal or sella/suprasella). Features will be similar to those of the ocular lesion
- Spine
    - Technique: T1 - sagittal planes and axial planes in region of interest, T2 - sagittal planes and axial planes in region of interest. As well as Contrast enhanced T1 images. Optional images include STIR sequences and coronal images if patient has scoliosis.
    - Comment: Leptomeningeal enhancement on T1 contrast enhanced occasionally appearing as plaque-like lesions in drop metastasis.

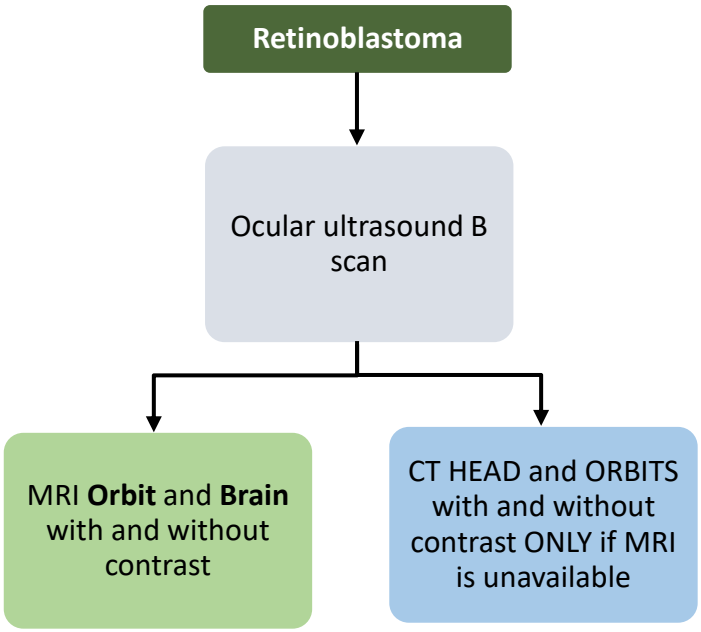

Figure 4.5. Initial Imaging for Retinoblastoma

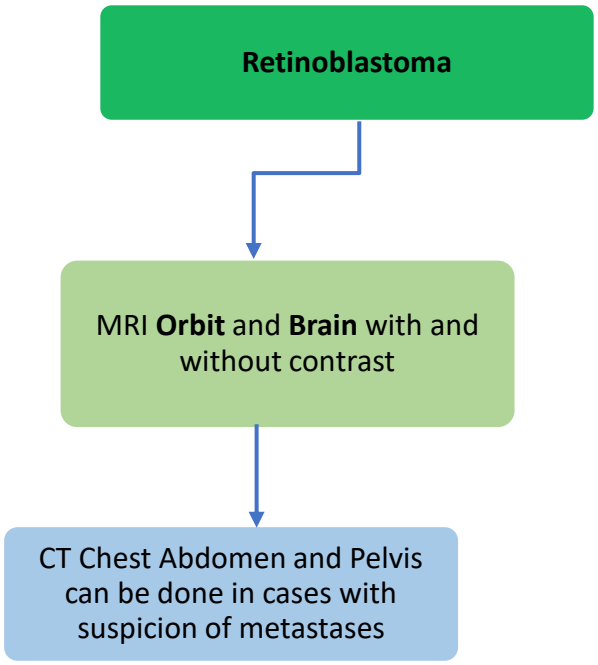

Figure 4.6. Staging Imaging for Retinoblastoma

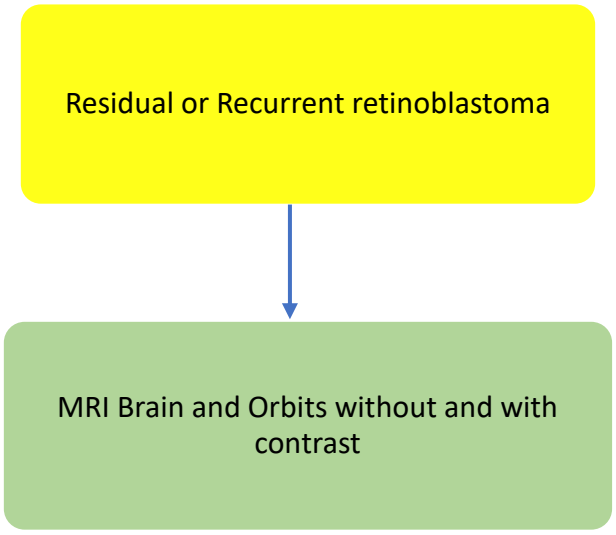

Figure 4.7. Initial Imaging for recurrent or progressive retinoblastoma

4.4. NEPHROBLASTOMA

Imaging plays an important role in diagnosis, staging, post-treatment evaluation and follow up surveillance in Nephroblastoma.

Various imaging modalities are available for imaging in Nephroblastoma, but use is determined by the purpose of the intended imaging and availability among others.

As in all paediatric imaging it is important to image cautiously, minimising use of ionising radiation. When ionising radiation cannot be avoided it is recommended to ensure dose minimising measures. Ultrasound and CT scan will be used particularly in these guidelines as they are more likely to be readily available compared to MRI especially for initial pre-surgery evaluation. MRI is recommended whenever possible. Plain radiography is generally not recommended, except for chest imaging, but may provide useful information as outlined below:

Plain Radiography

- Chest
  - Technique: PA/AP and Lateral CXR views
  - Comment: Findings may include lung metastasis presenting as nodules/masses

Ultrasound - This is the initial or baseline imaging modality for a suspected renal mass

- Abdomen

Technique: Curvilinear 2 - 7 MHz both greyscale and colour doppler. Image both kidneys to evaluate for synchronous contralateral lesions

  - Comment: Findings may include: Unilateral or bilateral solid heterogeneous mass with anechoic areas due to central necrosis, haemorrhage or cystic formation. Distortion of normal renal parenchyma with claw sign. Movement of the mass together with the kidney with breathing can help differentiate it from other retroperitoneal masses. Calcifications and hydronephrosis may be present. Liver and cul de sac should be evaluated for hepatic metastasis and peritoneal spill. Doppler may demonstrate tumour invasion into renal vein, Inferior Vena Cava (IVC) and Right atrium (on Echocardiography)

- ***Large retroperitoneal masses may be challenging to determine organ of origin***
- ***In cases where CT/MRI has already been performed ultrasound for vascular extension should be reserved for cases where CT/MRI is equivocal regarding vascular extension of tumour***.

CT scan - After confirmation of renal mass, further evaluation with CT is essential for staging

- Chest
  - Technique: CT chest without and with IV contrast
  - Comment: Findings may include: Lung parenchymal metastasis, Hilar/mediastinal lymphadenopathy (less common), Pleural effusions/pleural reactive changes that can be bilateral or unilateral and Intravascular thrombus

- Abdomen/Pelvis
  - Technique: Abdomen/Pelvis CT without/with IV contrast. No oral contrast. Portal venous phase is sufficient for delineation and delayed phase for evaluation of small lesions where nephron-sparing surgery could be amenable.
  - Comment: Mildly enhancing heterogeneous well-circumscribed soft tissue density mass which may demonstrate cystic components, focal haemorrhage, necrosis or calcifications (in <5%) and claw sign. Look for synchronous lesions on the contralateral kidney. Tumour thrombus in renal vein, IVC or right atrium should be evaluated. Hepatic metastasis and abdominal lymphadenopathy are also a feature of advanced disease.

- ***The use of CT vs MRI for staging of Nephroblastoma should be at the discretion of the treating institution as CT and MRI have been shown to have equivalent diagnostic value for loco-regional staging*** (Servaes s et al, 2015)

If the decision to perform an MRI is made evaluation of the chest should be done prior to the MRI, to avoid obscuring of lung bases by atelectasis especially in young children that require sedation.

MRI - Technique and features are outlined in the table below:

Table 4. MRI Nephroblastoma features

Region	Technique	Features
Abdomen and Pelvis	Single shot fast spin echo coronal and axial planes 4mm slice thickness	For Anatomy Overview
Abdomen	Steady - state balanced gradient Coronal and axial planes 4mm slice thickness	Bright blood for venous anatomy
	T2 FSE with Fat Sat - Axial plane 4mm slice thickness	Renal and liver anatomy
Abdomen	T1 gradient echo in/out of phase Axial plane 3-4mm slice thickness	
Abdomen and Pelvis	DWI/ADC b values: 0-50, 400-500 and 800-1000 Axial plane 5mm slice thickness	Useful for multifocal/synchronous tumours, lymph nodes and metastasis
Abdomen and Pelvis	3-D dynamic T1-W SPGR with fat saturation pre- and post-contrast Axial plane 3-4 mm slice thickness	
Abdomen and Pelvis	3-D T1-W SPGR with fat saturation post contrast Coronal and sagittal 3-4mm slice thickness	
MRI is the preferred imaging modality of children with bilateral Nephroblastoma or known bilateral tumour predisposition. It is essential to obtain high spatial resolution of the renal parenchyma in the nephrogenic phase as this aids in the detection of small lesions and nephrogenic rests.		

Post-treatment (post-neoadjuvant chemotherapy) imaging for treatment response assessment:

- Ensure that initial pre-treatment evaluation of the chest was done with CT, as post-treatment atelectasis could mimic pathology.
- Ensure that imaging is standardised, comparable and protocol as per initial imaging, focusing on the area of interest.
- Response assessment may be guided using RECIST

- ***For disease staging systems and patient follow-up imaging plans refer to treatment guidelines below.***

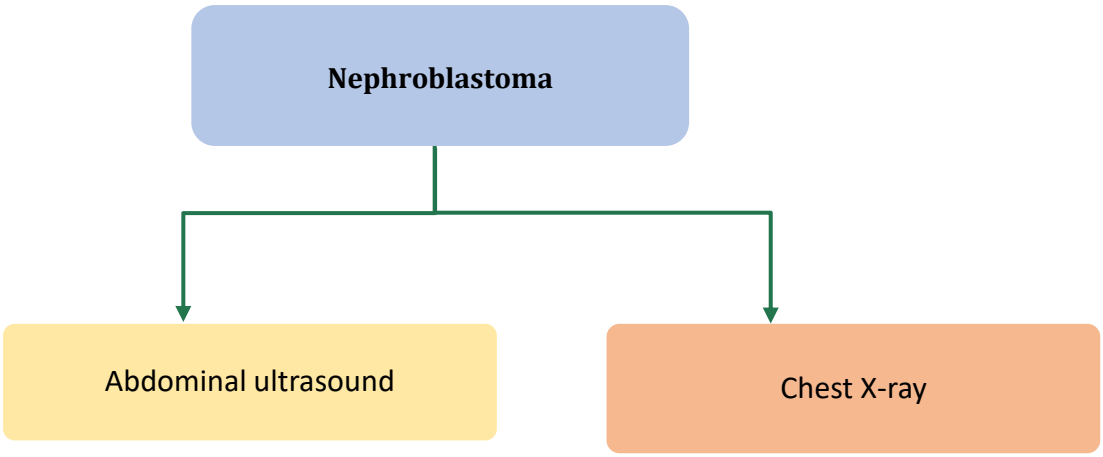

Figure 4.8. Initial Imaging for Nephroblastoma

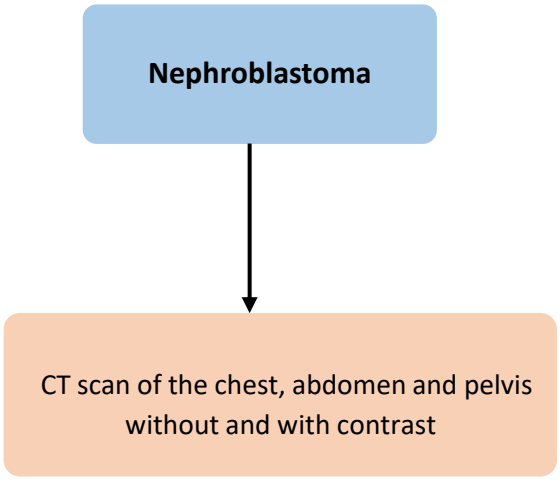

Figure 4.9. Staging for Nephroblastoma

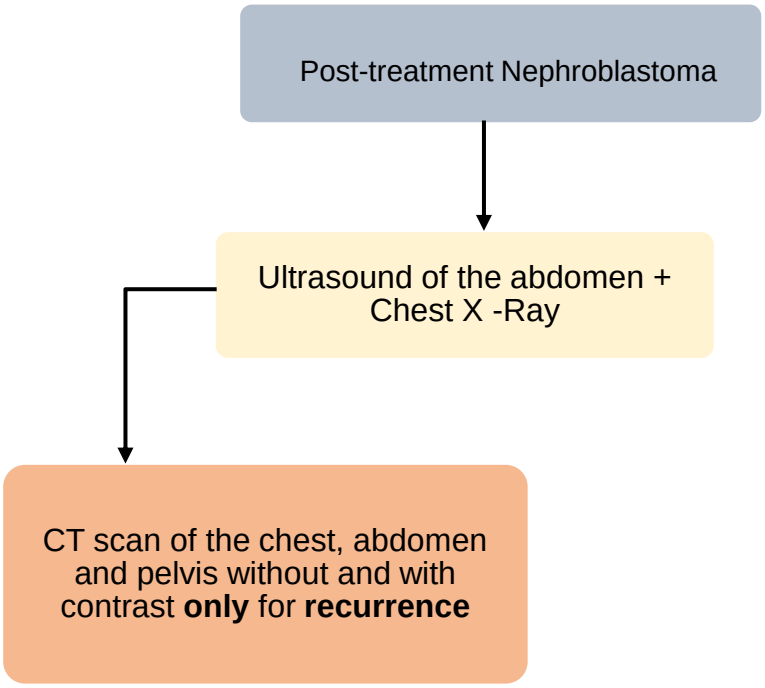

Figure 4.1.1. Follow up imaging for Nephroblastoma

4.5. LOW GRADE GLIOMA (LGG)

The age, location, clinical presentation and imaging finding can help distinguish the specific types of paediatric LGGs.
MRI is the imaging modality of choice. Standards for neuroimaging of these tumours have been established based on a consensus for a mandatory set of sequences as minimal requirements for brain and spine imaging (Ellingson B et al, 2015). The pre-, post- and follow-up examinations should be comparable and thus standardisation has to be assured. A minimum of a 1.5 Tesla to 3 Tesla MRI should be used for image acquisition.

Special consideration includes the following:

- Imaging the spine - 1.5 Tesla MRI is recommended and fat suppression is not necessary for delineation of meningeal disease and thus should not be routinely used.
- Additional MRI sequences may be used; however, this may result in prolonged image acquisition time and need for sedation.
- CT can be used for assessment of tissue density or calcification, whilst ensuring dose limiting measures.

Initial assessment

Using CT or MRI techniques and features outlined below:

CT scan

- Head
  - Technique: CT head without and with IV contrast, thin slices 1mm.
  - Comment: Findings may include: Iso/hypodense intra-axial mass with indistinct margin. Useful for assessing cell density and calcification. Haemorrhage which may present as hyperdense foci within the mass, variable enhancement with some aggressive necrotic/cystic lesions with ring enhancement, hydrocephalus

MRI – features will include those indicated in the table below:

Table 4.1. MRI features in LGG

Region	Technique	Features
Brain	T1 - Hypointense T2 - Hyperintense T1 C+ (Gd) - Subtle enhancement FLAIR - Hyperintense DWI/ADC - Restricted diffusion <4mm slice thickness, Axial, Coronal and Sagittal planes	Intra-axial mass
For Neurosurgical planning, slice thickness of 1mm is recommended. Consider T1W 3D GE and DTI. For differential diagnosis include MR perfusion and MR spectroscopy Additional sequences to consider are as outlined in MRI brain for ALL above.		
Spine for disseminated brain tumour	T1 T1 C+ (Gd) T2 <3mm slice thickness, Sagittal whole spine with axial images in area of interest	Findings similar to primary lesion
Spine for spinal primary tumour	T1 T2 T1 C+ (Gd) <3mm slice thickness Sagittal whole spine and axial in region of interest	

Tumour volume calculations should be obtained using maximum dimensions in the standard planes. For multiple lesions, obtain the volume of each lesion. Comparison to subsequent imaging measurements should be as accurate as possible and saved as annotated images.

- ***Early Post-operative imaging – should be obtained in the first 48 to 72 hours following surgery to assess for residual disease.***

Post-treatment evaluation and follow-up imaging should be comparable with initial imaging assessment, preoperative MRI images and surgical report should be available. Non-specific subdural/intradural enhancement and blood products may mimic

dissemination and may require repeat imaging after 2 weeks for clarification. In case of suspected residual tumour where imaging is unclear or inadequate or surgical cavity is difficult to assess, repeat imaging at 2 - 4 weeks with additional sequences, additional planes and better resolution.

Radiological criteria for non-surgical treatment of LGGs:

The decision for non-surgical management of unresectable of LGGs must be made in a multidisciplinary tumour board after careful consideration of the clinical history context.

Table 4.2. Decision making in management based on imaging findings

Radiological criteria in decision making for treatment
Increase of tumour volume of > 25% and the increase of the diameter of the optic nerve should be indicated separately.
Involvement of new areas or new lesions
Increase in the size or number of metastases

Follow-up MRI after treatment > 4 weeks after clinical criteria for response has been met:

- Comparability of follow-up MRI has to be assured. The criteria in the table below may be used for neuroradiological response evaluation.
- Confirm true progression by histology or Imaging, however imaging in the initial 12 weeks after treatment may mimic progression due to the effect of Radiotherapy and chemotherapy which lead to treatment-induced tissue reaction, (i.e. pseudo-progression). Repeat MRI after an additional 4-6 weeks from the end of the initial 12 weeks to confirm progression on imaging.

Table 4.3. Post-treatment response evaluation criteria in LGGs

Complete Response (CR)	No evidence of residual tumour, recurrence or dissemination.
Partial Response (PR)	Reduction of tumour volume of > 50% compared to reference MRI. (Partial response of meningeal disease is subjective and can only be estimated)
Improvement (IMP)	Reduction of tumour volume between 25% to 50%
Stable Disease	There is < 25% increase or decrease in size compared to reference MRI and/or no significant change in meningeal dissemination
Progressive Disease (PD)	Increase of tumour volume > 25% or new lesions or increase in size or number of metastatic foci. Growth of cysts only should not be considered as progressive disease and warrant follow-up

Follow-up surveillance imaging to be done 3-6 monthly with comparable imaging, ensuring prior imaging is available - *refer to treatment guideline below*.

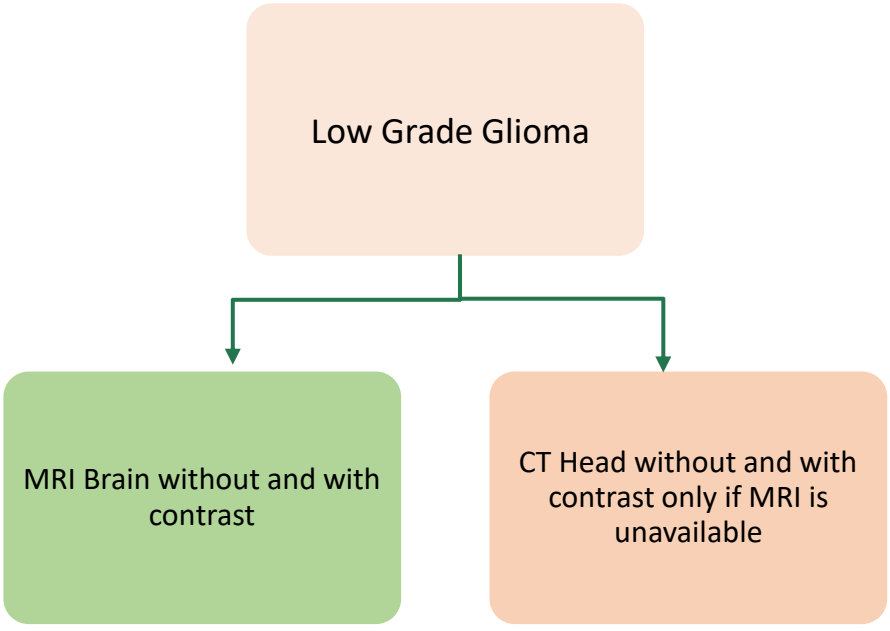

Figure 4.1.2. Initial Imaging for LGG

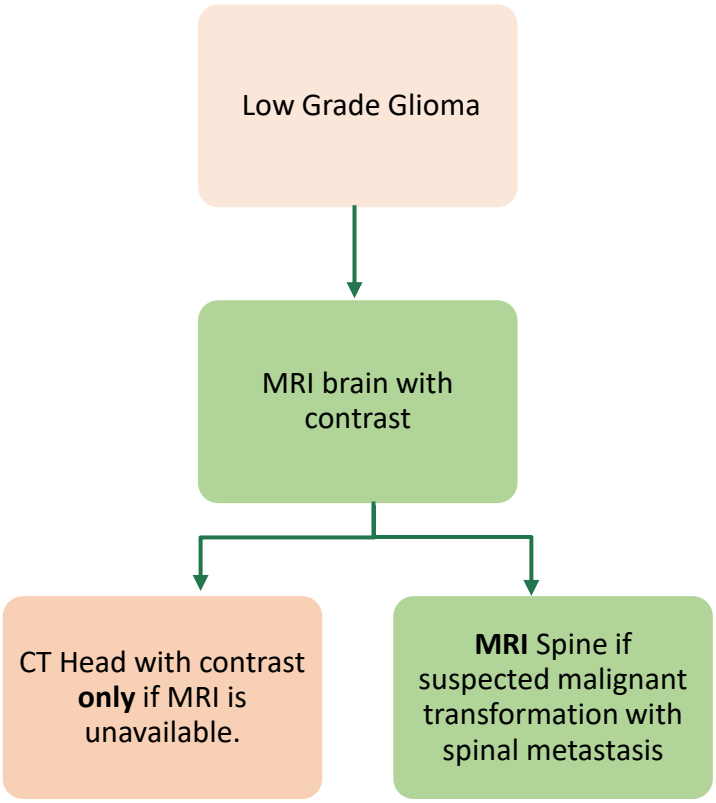

Figure 4.1.3. Staging for LGG

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CHAPTER 5. TREATMENT GUIDELINE

This section of the guidelines applies to the professionals and/or the multidisciplinary teams at the first, second and third level hospitals, and provides brief key clinical aspects for each of the six index cancers on

- Definition and epidemiological factors
- Symptoms and signs
- Diagnostic tests
- Staging systems
- Multi-modality treatment
- Follow-up care after treatment

Diagnosis and treatment will be offered at designated childhood cancer units as defined by the other complementary guidelines.

5.1. ACUTE LYMPHOBLASTIC LEUKAEMIA (ALL)

Definition: a clonal proliferation of immature lymphoid cells or lymphoblasts, underpinned by genetic abnormalities that lead to arrest in precursor cell differentiation and abnormal proliferation.

- Globally, ALL is the most common malignancy in children between ages 0-14 accounting for 25% of all childhood cancers.
- Of the childhood leukaemia ALL is the most prevalent at over 70%.

There are two main types of ALL with a slight male predominance overall:

- B-ALL 75%-80% of cases (peak incidence 2-5 years)
- T-ALL in 15% to 20% of cases (peak incidence in adolescence).

This disease is biologically similar to lymphoblastic lymphoma, which is usually distinguished from leukaemia by evidence of extramedullary disease and less than 25% bone marrow lymphoblasts. Classification systems focus on the immunophenotypic and molecular genetic/cytogenetic features of the disease for sub-classification.

Risk factors for ALL include:

a) Genetic/ inherited conditions including:
   - Down's syndrome (trisomy 21)
   - Fanconi anaemia
   - Ataxia telangiectasia
   - Bloom syndrome
   - Neurofibromatosis type 1
   - Li-Fraumeni Syndrome
b) High energy (ionizing) radiation exposure

The following diagnostic workup should be undertaken:

a) Thorough medical history and physical examination, including testicular exam for masses in boys.
b) Full Blood Count with Differential Count (FBC/DC)
c) Blood grouping and cross matching if any blood product is required for transfusion
d) Peripheral blood may be substituted for bone marrow in diagnosing ALL provided there is a significant amount of circulating lymphoblasts of ≥1,000 per microliter or ≥20% lymphoblasts. (Brown P, 2020)
e) Bone marrow aspirate and trephine biopsy from one appropriate site demonstrating ≥20% lymphoblasts on hematopathology
f) Review required to make a diagnosis.
g) Kidney function test (KFTs) to include serum creatinine, urea and creatinine clearance

h) Liver function tests (LFTs) to include Total and direct serum bilirubin, serum albumin, and markers of hepatocyte injury = Alanine aminotransferase (ALT) and Aspartate Aminotransferase (AST)
i) Disseminated intravascular coagulation (DIC) panel: d-dimers, fibrinogen level, fibrinogen degradation products, prothrombin time (PT) and Activated Partial Thromboplastin Time (APTT)
j) Tumour lysis syndrome panel: serum Lactate Dehydrogenase (LDH), uric acid, potassium (K^+), calcium (Ca^{2+}), phosphorus ($P0_4^{3-}$), sodium (Na^+), Chloride (Cl^-)
k) Test for Hepatitis B & C, HIV and sickle cell disease
l) Do CT scans (with contrast) of the neck, chest, abdomen, and pelvis as indicated for those with lymphadenopathy, features of central nervous system (CNS) infiltration and mediastinal mass as appropriate. (see radiology guideline above
m) Do Chest x-ray prior to sedation for diagnostic procedures: look for mediastinal widening which is common with T cell ALL
n) Do baseline Echocardiogram and electrocardiogram (ECG)
o) Do ultrasonographic testicular imaging ± biopsy for boys with testicular masses (see radiology guideline above for imaging)
p) Do Lumbar puncture (LP) once the platelet count is at least 100 X 10^9/L and the white cell count has normalized for those with high initial counts – *LP should be performed at the time of initial scheduled intrathecal therapy.*
q) Order and do further ancillary tests essential for the proper diagnosis, risk stratification, treatment planning and prognosis. These may include:
    - Flow cytometry for immunophenotyping of the leukaemia as in the pathology guideline section
    - Cytogenetic and Molecular Studies as in the pathology guideline above.

Table 5. ALL Subtypes (Alaggio R, et al 2022)

B-ALL/Lymphoblastic Lymphoma(LBL)
Not otherwise specified (NOS)
B-lymphoblastic leukaemia/lymphoma with: • **BCR::ABL1 fusion** • **KMT2A-rearranged** (MLL rearrangements) • **High Hyperdiploid** (≥55 chromosomes) • **Hypodiploid** (≤44 chromosomes) • **ETV6::RUNX1** • **IGH::IL3** • **TCF3::PBX1** • **iAMP21** (intrachromosomal amplification of chromomsome 21) • **TCF3::HLF fusion** • **BCR::ABL1-like** (Ph-like) • **ETV6::RUNX1-like features** • **Other defined genetic abnormalities**
T-ALL/LBL
T-lymphoblastic leukaemia / lymphoma, NOS
Early T-precursor lymphoblastic leukaemia / lymphoma

Table 5.1. Diagnostic testing for the level of available resources per health facility level and appropriate risk group-determining parameters

Level of resource availability	**Recommendations for diagnostic tests**	**Recommendations for risk assignment parameters based on resource availability**
Basic *(first and second levels)*	FBC, Microscopic cyto-morphology ± cytochemistry, CXR – mediastinal mass	Age, Initial leukocyte count
Limited *(second and tertiary levels)*	FBC, microscopic cyto-morphology and cytochemistry, Immunophenotyping	Age, Initial leukocyte count, immunophenotype (T-cell vs. B-cell); Prednisone response on day 8 and/or day 15 peripheral blood or bone marrow response, and end of induction bone marrow response; If available, BCR-ABL1, MLL-AFF1, ETV6-RUNX1
Enhanced *(Tertiary level)*	Same as for limited + DNA index, **RT-PCR** for BCR-ABL1, MLL-AFF1, ETV6-RUNX	Same as for limited ± DNA index, **RT-PCR** for BCR-ABL1, MLL-AFF1, ETV6-RUNX1, TCF3-PBX1, Cytogenetics for hyperdiploid and hypodiploid status **FISH** for chromosome 4, 10, 17 trisomies and BCR-ABL1

Maximal *(Tertiary level)*	Cyto-morphology, Immunophenotyping, DNA index **RT-PCR** for BCR-ABL1, MLL-AFF1, ETV6-RUNX1, TCF3-PBX1, Cytogenetics for hyperdiploid or hypodiploid, **FISH** for chromosome 4, 10,17 trisomies and BCR-ABL1,	Same as enhanced, Minimal residual disease measurements by IgH/TCR rearrangements, flow cytometry or deep sequencing, Genome-wide analysis to identify lesions responsive to ABL tyrosine kinase inhibitors, Pharmacogenetics

Clinical Risk Groupings for Acute Lymphoblastic Leukaemia

ALL risk groups refer to patient groupings based on estimates of disease response to treatment and overall patient survival when certain variables are present. This risk categorization facilitates risk-based therapeutic interventions by augmenting therapy in patients with a poor prognosis while helping to avoid overtreatment in those with a good prognosis.
Variables that determine risk stratification and are predictive of outcome differ in B-ALL and T-ALL. Age and presenting white blood cell count (WBC), are not independently prognostic in T-ALL.

Prognostic and risk classification variables

- Clinical parameters:
  - Age at diagnosis
  - Initial total white cell count (on full blood count) on first Full Blood Count (FBC) result with abnormalities consistent with the definitive diagnosis of ALL
  - Presence or absence of central nervous system (CNS) or testicular leukaemia

- Biological characteristics:
  - Presence or absence of specific genetic lesions:
    - Good risk: ETV6–RUNX1 fusion or Hyperdiploidy with favorable chromosome trisomies;
    - Poor risk: MLL-rearrangements (MLL-R), Hypodiploidy, intrachromosomal amplification of chromosome 21 (iAMP21), Philadelphia chromosome positive (Ph+ ALL)
- Risk stratification of T-ALL has been challenging, because, other than minimal residual disease (MRD) measurements, the clinical variables used to classify risk in B-ALL, including age and white blood cell counts, are not independently prognostic.

Hence T-ALL is categorized as high risk

- Response to therapy:
  - Early treatment response to prednisolone prophase by peripheral blood blast cell count
  - Treatment response evaluation of bone marrow at specific time points:
    - End of induction

- End of consolidation
- Before start of maintenance therapy

BMA Status at response assessment*: M1, <5% blasts; M2, 5–25% blasts; and M3, >25% blasts.*

CNS Status*: CNS1: no detectable blasts in CSF; CNS2: <5 WBCs/µL and blasts present in CSF; CNS3: ≥5 WBCs/µL and blasts present in CSF, or signs of CNS leukaemia (i.e. facial nerve palsy, hypothalamic syndrome, or brain/eye involvement)*

The risk assignment will mainly be in categories of standard, average, high risk and very high risk based on the parameters given in the tables 5.2. and 5.4. below.

For further parameter assessments according to the level of care for use in risk group assignment refer to table 5.1. above.

Table 5.2. Risk Categories for B-ALL

Parameter	**Variables**	**Standard risk**			**High risk**	**Very High risk**
		Low Standard Risk	**Average Standard Risk**	**High Standard Risk**		
Clinical factors	Age	1-9 yrs.	1-9 yrs.	1-9 yrs.	≥10yrs.	≥ 10yrs.
	Initial WBC	<50 X 10^9 cells/L	<50 X 10^9 cells/L	<50 X 10^9 cells/L	≥ 50 X 10^9 cells/L	≥ 50 X 10^9 cells/L
	Testicular involvement	None	None	Yes	No	Yes
	CNS Leukaemia status	No CNS2 or CNS3	No CNS2 or CNS3	CNS 3	No involvement	Yes, Involved
Response to Therapy	Steroid pre-treatment	None	None	Yes	None	Yes
	Peripheral blood blast count on Day 8 of induction	< 1000 cells	< 1000 cells	< 1000 cells	< 1000 cells	≥ 1000 cells
	Induction Day 29 bone marrow morphology	M1	M1	M2/M3	M1	M1/M2
	Day 29 flow cytometry based MRD	< 0.1%	< 0.1%	≥ 0.1–1%	< 0.1%	≥ 0.1–1%
Biological characteristics	Cytogenetics	Triple trisomy OR t(12;21)(p12;q22) translocation	No triple trisomy OR t(12;21)(p12;q22) translocation	*KMT2A* translocation with a rapid early responder	t(9;22) (BCR-ABL), or t(4;11) (MLL-AF4) Hypodiploidy	*KMT2A* translocation with a Rapid Early Responder

Treatment

Ensure the following supportive care is given before initiating the patient on any leukaemia-directed treatment with cancer drugs, including prednisolone or dexamethasone:

a) Supportive care
   - Infection control:
     - Preventive measures: Clotrimazole tablet for oral prophylaxis (age adjusted doses twice a day on Saturdays and Sundays) given throughout treatment.
     - Oral mouth wash (non-alcohol based) 2-3 times a day and sitz baths once or twice daily for prevention of anal/peri-anal infection.

   - Treat febrile neutropenia (FN) aggressively, preferably with a third-generation cephalosporin and aminoglycoside. Refer to the FN guideline below.

   - Tumour lysis syndrome (TLS) prevention and treatment:
     - Start intravenous fluids at 3L/m^2/day with 5% dextrose-saline or 5% Dextrose in water
     - Allopurinol at 10-20mg/kg/day in 2-3 divided doses orally for TLS prevention and continue for at least 5 days or until normalization in the WBC count.

   - Monitor the patient for medicine - related toxicity during maintenance phase of treatment: do FBC and LFTs every 1 - 2 weeks ensuring the absolute neutrophil count (ANC) is maintained between 1.0 X 10^9/L and 2.0 X 10^9/L and platelet count >75 X 10^9/L.
     - If any concerns on the above FBC results are found during maintenance phase treatment, immediately contact the paediatric cancer treatment unit.
     - If the FBC machine report only gives differential count percentages, the ANC can be calculated as follows:
       - % neutrophil × Total leucocyte count (TLC)/100

   - Avoid Immunization during all treatment phases
   - Give Anti-emetics – Ondansetron 0.15mg/Kg 8 hrly orally or IV, do not include dexamethasone for anti-emesis if the patient is already on a corticosteroid as part of the cancer regimen.
   - Consult the nutrition team for patient nutritional support during treatment
   - For those needing treatment of pain follow the WHO pain management ladder
   - Give Intravenous fluids, blood and blood products transfusion as indicated.
     - Transfuse with red cell concentrate (or packed red cell) to maintain haemoglobin level at least 7.0gm/dL prior to initiation and during the whole period of treatment.

- Platelet transfusion: prophylactic for those with counts below 10 X 10^9/L and to raise to 100 X 10^9/L for those who are to undergo procedures such as intrathecal injections or surgery.

b) Disease-Specific Treatment

Specific disease risk assessment and stratification of risk-adapted therapy are used in the treatment strategies for Ph-positive and Ph-negative B-cell ALL, T-ALL and infant ALL.

- The main phases of treatment are as given in tables 5.3., 5.4. & 5.5. below. The first five phases shall mainly be administered from CDH or other paediatric cancer treatment facilities. The sixth (maintenance phase) can be administered from the lower level facility closest to the patient's home as long as the attending staff are appropriately trained. The goal of each treatment phase strategy is as follows:
  - **Prophase** - reduce tumour burden and reduce on chemotherapy-related complications
  - **Induction phase** - maximally eliminate malignant blasts from the bone marrow resulting in resolution of signs and symptoms
  - **Consolidation phase** - further eradication of Marrow & sanctuary site residual disease e.g. central nervous system & testes
  - **Maintenance phase** - to prevent disease relapse
  - **Extramedullary disease prophylaxis or treatment** - such as intrathecal (IT) injections to prevent central nervous system (CNS) relapse and clear leukaemic cells from sites which are not easily accessible by systemically administered chemotherapy due to the blood-brain barrier.

Table 5.3. Chemotherapy regimen for Standard Risk B-ALL according to risk group

Treatment phase	Low Standard Risk	Average Standard Risk	High Standard Risk
		CNS Negative	*CNS Positive*
Prophase	**Prednisolone 60mg/m² /d** X 7 days	**Prednisolone 60mg/m² /d** X 7 days	**Prednisolone 60mg/m²** /d X 7 days
Induction	**Prednisolone 40mg/m² /d** X 21 days **Vincristine 1.5mg/m²** IV push over 5-10min day 1, 8, 15, 22 **L-asparaginase 6,000iu/m²** deep IM inj, day 1, 3, 5, 8, 10, 12 **IT methotrexate** (age adjusted) day 8, 28) **BMA on day 29 for response assessment**	**Prednisolone 40mg/m² /d** X 21 days **Vincristine 1.5mg/m²** IV push over 5-10min day 1, 8, 15, 22 **Daunorubicin 25mg/m²** IV over 1hr, day 1, day 8 **L-asparaginase 6,000iu/m²** deep IM inj, day 1, 3, 5, 8, 10, 12 IT methotrexate (age adjusted) day1, 8, 29) **BMA** on day 29 for response assessment	**Prednisolone 40mg/m²** /d X 21 days **Vincristine 1.5mg/m²** IV push over 5-10min day 1, 8, 15, 22 **Daunorubicin 25mg/m²** IV over 1hr, day 1, day 8 **L-asparaginase 6,000iu/m²** deep IM inj, day 1, 3, 5, 8, 10, 12 IT methotrexate (age adjusted) day 1, 8, 15, 29) **BMA on day 29 for response assessment**
Consolidation	**Vincristine 1.5mg/m²** IV push over 5-10min day 1 only **6-mercaptopurine 75mg/m²** once daily orally day 1 to day 28 **IT methotrexate** (age adjusted) day 1, day 8, day 15	**Cyclophosphamide (cyclo) 1g/**m² IV infusion over 1hr (with MESNA at 20% of calculated cyclo. Dose, given at 0hr, 4hr, 8hr of cyclo. Infusion) **Vincristine 1.5mg/ m²** IV push over 5-10min day 15 and day 22 **Cytarabine 75mg/ m²** IV day 1-4 & day 8-11 **6-mercaptopurine 60mg/m²** once daily orally day 1 to day 14 **IT methotrexate** (age adjusted) day 1, day 8, day 15	**Cyclophosphamide 1g/m²** IV infusion over 1hr (with MESNA at 20% of calculated cyclo. Dose, given at 0hr, 4hr, 8hr of cyclo. Infusion) **Vincristine 1.5mg/m²** IV push over 5-10min day 15 and day 22 **Cytarabine 75mg/m²** IV day 1-4 & day 8-11 **6-mercaptopurine 60mg/m²** once daily orally day 1 to day 14 **IT methotrexate** (age adjusted) day 1, day 8, day 15
Interim maintenance	**Vincristine 1.5mg/**m² iv push over 5-10min	**Vincristine 1.5mg/m²** IV push	**Vincristine 1.5mg/m²** IV push over 5-10min day 1,

	day 1, day 11, day 21, day 32, day 42 **Methotrexate** iv push over 10minutes with escalation of doses as follows: **100mg/m²** on day 1**; 150mg/m²** iv push day 11**;** **200mg/m²** on day 21; **250mg/m²** on day 32; **300mg/m²** on day 42	over 5-10min day 1, day 11, day 21, day 32, day 42 **Methotrexate IV** push over 10min day with escalation of doses as follows: 100mg/ m² on day 1; 150mg/ m² IV push day 11; 200mg/m² on day 21; 250mg/m² on day 32; 300mg/m² on day 42	day 11, day 21, day 32, day 42 **Methotrexate IV** push over 10min day with escalation of doses as follows: 100mg/m² on day 1; 150mg/m² IV push day 11; 200mg/m² on day 21; 250mg/m² on day 32; 300mg/m² on day 42
	Two recovery weeks for the patient before next phase of treatment	***Two recovery weeks for the patient before next phase of treatment***	***Two recovery weeks for the patient before next phase of treatment***
Delayed intensification	**Dexamethasone 10mg/m²/d** orally day1 to day 7 & day 15 to day 21 **Vincristine 1.5mg/m²** iv push over 5-10min day 1, day 8, day 15, day 43, day 50 **Doxorubicin 25mg/m²** iv infusion over 1hr day 1, day 8(if well),day15 (if well) **Mercaptopurine 60mg/m²/day** from day 29 to day 42, **Prednisolone 60mg/m² /day,** from day 29- 42 **L-asparaginase 6000iu/m² IM** day 3, day 5, day7, day10, day12, day14 **Cytarabine 75mg/m² iv** day29-32 **Cyclophosphamide 1g/m²** with MESNA day 29	**Dexamethasone 10mg/m²/d** PO D1-D7 & day 15 to day 21 **Vincristine 1.5mg/m²** IV push over 5-10min D1, day 8, day 15, day 43, day 50 **Doxorubicin 25mg/m²** IV infusion over 1hr day 1, day 8(if well), day15 (if well) **Mercaptopurine 60mg/m²/day,** from day 29 to day 42, **Prednisolone 60mg/m² /day**, from day 29-42 **L-Asparaginase 6000iu/m² IM** day3, day5, day7, day10, day12, day14 **Cytarabine 75mg/m²** IV day 29-32 **Cyclophosphamide 1g/m²** with MESNA day 29	**Dexamethasone 10mg/m²/d** orally day1 to day 7 & day 15 to day 21 **Vincristine 1.5mg/m²** IV push over 5-10min day 1, day 8, day 15, day 43, day 50 **Doxorubicin 25mg/ m²** IV infusion over 1hr day 1, day 8(if well), day15 (if well) **Mercaptopurine 60mg/m²/day** from day 29 to day 42, **Prednisolone 60mg/m² /day**; day 29-42 **L-Asparaginase 6000iu/m² IM** day3, day5, day7, day10, day12, day14 **Cytarabine 75mg/m²** IV day 29-32, and day 36-39 **Cyclophosphamide 1g/m²** with MESNA day 29
Maintenance	**Mercaptopurine 75mg/m²/day** daily in week 1 to week 12 , rest	**Mercaptopurine 75mg/m²/day** daily in week 1 to week 12 ,	**Mercaptopurine 75mg/m²/day** daily in week 1 to week 12 , rest for

	for a week and repeat cycle x 8 cycles **Methotrexate 20mg/m²** once weekly week 1 to week 12 (except week when patient is receiving intrathecal methotrexate) **Dexamethasone 6mg/m²/day** from day 1 to day 5 of each cycle **Intrathecal methotrexate (it mtx) (age adjusted) day1 and day 29 for cycles 1 to cycle 4**	rest for a week and repeat cycle X 8 cycles **Methotrexate 20mg/m²** once weekly week 1 to week 12 (except week when patient is receiving intrathecal methotrexate) **Dexamethasone 6mg/m²/day** from day 1 to day 5 of each cycle **Intrathecal methotrexate** (age adjusted) day1 and day 29 for cycles 1 to cycle 4	a week and repeat cycle X 8 cycles **Methotrexate 20mg/m²** once weekly week 1 to week 12 (except week when patient is receiving intrathecal methotrexate) **Dexamethasone 6mg/m²/day** from day 1 to day 5 of each cycle **Intrathecal methotrexate** (age adjusted) day1 and day 29 During Cycle 1 only **Cranial Radiation Therapy** 18Gy total at 1.8Gy per Fraction x 10 days during

Table 5.4. Chemotherapy protocols for High Risk B-ALL and T-ALL

Treatment phase	High Risk	Very High Risk
Prophase	**Prednisolone 60mg/m² /d** X 7 days	**Prednisolone 60mg/m² /d** X 7 days
Induction	**Prednisolone 40mg/m² /d** X 21 days **Vincristine 1.5mg/m²** IV push over 5-10min days 1, 8, 15, 22 **Daunorubicin 25mg/m²** IV over 1hr, day 1, day 8 **L-asparaginase 6,000iu/m²** deep IM inj, day 1, 3, 5, 8, 10, 12 **IT methotrexate** (age adjusted) day1, 8, 29) BMA on day 29 for response assessment	Glucocorticoid therapy: • <10 years: dexamethasone 10mg/m²/day on days1- 14 • ≥ 10 years: Prednisolone 40mg/m² /d X 21 days, then taper **Vincristine 1.5mg/m²** IV push over 5-10min days 1, 8, 15, 22 **Daunorubicin 25mg/m²** IV over 1hr, days 1, 8, 15, 22 **L-asparaginase 6,000iu/m²** deep IM inj, days 1, 3, 5, 8, 10, 12 **IT methotrexate** (age adjusted) days 1, 8, 15, 29) CNS positive to receive triple IT therapy BMA on day 29 for response assessment
Consolidation	**Cyclophosphamide 1g/m²** IV infusion over 1hr days 1, 29 (with	**Cyclophosphamide 1g/m²** IV infusion over 1hr days 1, 29 (with

	MESNA at 20% of calculated cyclophosphamide dose, given at 0hr, 4hr, 8hr of cyclophosphamide Infusion) **Vincristine 1.5mg/ m²** IV push over 5-10min days 15, 22, 43, 50 **Cytarabine 75mg/ m²** IV days 1-4, 8-11, 29-32, 36-39 **6-mercaptopurine 60mg/m²** once daily orally day 1 to 14, 29 to 42 **L-asparaginase 6,000iu/m²** IM days 15, 17, 19, 22, 24, 26 **IT methotrexate** (age adjusted) days 1,8,15, 22	MESNA at 20% of calculated cyclophosphamide Dose, given at 0hr, 4hr, 8hr of cyclophosphamide Infusion) **Vincristine 1.5mg/m²** IV push over 5-10min day 15, 22, 43, 50 **Cytarabine 75mg/m²** IV days 1-4, 8-11, 29-32, 36-39 **6-mercaptopurine 60mg/m²** once daily orally day 1 to 14, 29 to 42 **L-asparaginase 6,000iu/m²** IM days 15, 17, 19, 22, 24, 26 **IT methotrexate** (age adjusted) days 1,8,15, 22
Interim maintenance	**Vincristine 1.5mg/m²** iv push over 5-10min day 1, 15, 29, 43 **Methotrexate 200mg/m²** iv over 30min **then 1800mg/m²** iv over 23hrs 30 min on days 1, 15, 29, 43 **(with calcium folinate 10mg/m² x 10 doses 12 hrs after methotrexate infusion)** **6-mercaptopurine 25mg/m²** po once per day on days 1 to 56 **Methotrexate IT days 1, 29** **NB: If T-ALL, give methotrexate at a dose of** 500mg/m² IV over 30min then 4500mg/m² IV over 23hrs	**Vincristine 1.5mg/m²** IV push over 5-10min day 1, 15, 29, 43 **Methotrexate 500mg/m² IV over 30min then 4500mg/m² IV over 23hrs 30 min on** days 1, 15, 29, 43 (with calcium folinate 10mg/m² x 10 doses 12 hrs after methotrexate infusion) **6-mercaptopurine 25mg/m²** PO once per day on days 1 to 56 Methotrexate IT days 1, 29
	Two recovery weeks for the patient before next phase of treatment	***Two recovery weeks for the patient before next phase of treatment***
Delayed intensification	**Dexamethasone 10mg/m²/d** po day1-7 & day 15-21 **Vincristine 1.5mg/m²** iv push over 5-10min d1,8,15,43,50 **Doxorubicin 25mg/m²** iv infusion over 1hr day1, 8(if well), day15 (if well) **Mecarptopurine 60mg/m²/day,** day 29-42, **Prednisolone 60mg/m² /day,** day 29-42	**Dexamethasone 10mg/m²/d** orally day1-7 & day 15-21 **Vincristine 1.5mg/m²** IV push over 5-10min day 1,8,15,43,50 **Doxorubicin 25mg/ m²** IV infusion over 1hr day 1, 8(if well), day15 (if well) **Mecarptopurine 60mg/m²/day** day 29-42, **Prednisolone 60mg/m² /day**; day 29-42

	L-asparaginase 6000iu/m² i.m. day 3, 5, 7,17, 19, 21 **Cytarabine 75mg/m² iv** day 29-32 and day 36-39 **Cyclophosphamide 1g/m²** with MESNA day 29 **Methotrexate it** (age adjusted dose) days 1, 29, 36	**L-Asparaginase 6000iu/m² I.M.** day 3, 5, 7,17, 19, 21 **Cytarabine 75mg/m²** IV day 29-32, and day 36-39 **Cyclophosphamide 1g/m²** with MESNA day 29 Methotrexate IT (age adjusted dose) days 1, 29, 36
Maintenance	**Mercaptopurine 75mg/m²/day** daily in week 1 to week 12, rest for a week and repeat for 8 cycles in total **Methotrexate 20mg/m²** once weekly weeks 1-12 (except week when patient is receiving intrathecal methotrexate) **Dexamethasone 6mg/m²/day** day 1 to day 5 of each cycle **CNS prophylaxis:** intrathecal methotrexate (age adjusted) day1, 29 for cycles 1 to cycle 4. Cycles 5 onwards, once on day 1. Total of 12-week cycles repeated until the total duration of therapy is 2 years for female patients and 3 years for male patients from the start of interim maintenance	**Mercaptopurine 75mg/m²/day** daily in week 1 to week 12, rest for a week and repeat for 8 cycles in total **Methotrexate 20mg/m²** once weekly weeks 1 –12 (except week when patient is receiving intrathecal methotrexate) **Dexamethasone 6mg/m²/day**:days 1-5 of each cycle **Cranial irradiation for CNS3: 18Gy in 10 fractions, during the first 4 weeks of maintenance therapy and should be completed by day 29** **CNS prophylaxis:** Methotrexate **IT** on day 1 and day 29 of cycles 1 to 4, for patients who did not receive CNS radiation Total of 12-week cycles repeated until the total duration of therapy is 2 years for female patients and 3 years for male patients from the start of interim maintenance

Note:

- For Philadelphia chromosome positive B-ALL, give concurrent chemotherapy with a Tyrosine kinase inhibitor (Imatinib 340mg/m²/day as first line therapy), daily, from the second week of induction until end of therapy.

Table 5.5. Chemotherapy protocol for Infantile ALL (Interfant 06)

Treatment Phase	Drugs
Prophase	Prednisolone 60mg/m^2/d in 3 divided doses orally days1-7.
Induction	Dexamethasone 6mg/m^2/d p.o or i.v day 8-28, then taper
	Vincristine 1.5mg/m^2 iv push day 8,15,22,29
	Cytarabine 75mg/m^2/d iv 30 minutes infusion day 8-11, day 15-18
	Daunorubicin 30mg/m^2 IV days 8, 9
	L-Asparaginase 10000iu/m^2 IM on days 15,18,22,25,29,33
	IT Methotrexate (age adjusted) day 1, 29. Also on Days 8 and 22 if CNS+. If CNS leukaemia is still present at day 29 then weekly intrathecal MTX until the CNS is free of leukaemia
	IT Cytarabine (age adjusted) day 15
Protocol IB Starts at day 36 (day counts follow induction)	Cyclophosphamide 1,000 mg/m2/dose, i.v. over 1 hour, day 1 and 29 with MESNA at 20% calculated cyclophosphamide dose at 0, 4, 8 hours of cyclophosphamide infusion
	6 Mercaptopurine 60 mg/m^2/day p.o., days 1-28
	Cytarabine 75 mg/m^2/dose i.v. push Days 3-6 , Days 10-13, Days 17-20, Days 24-27
	Methotrexate IT (age adjusted) day 24
	Cytarabine IT (age adjusted) day 10
MARMA	6-Mercaptopurine: 25 mg/m^2 daily in 1 dose orally day 1-14
	Methotrexate: 5000 mg/m^2 iv as 24 hour infusion on day 1 and 8 given as follows: 500 mg/m^2 in 30 minutes iv followed by 4500 mg/m^2 IV infusion over 23hrs 30min. To be given with calcium folinate rescue, (same dose of calcium folinate as above in table ALL-5).
	IT MTX: At the end of the 24 hr MTX infusion, i.e. at day 2 and 9
	Cytarabine 3000 mg/m^2 iv 3 hrs infusion twice daily with 12 hrs interval on day 15, 16, 22, 23
	PEG-Asparaginase: 2500iu/m^2 IV over 1 hour or IM on day 23
OCTADA(D) Part 1 (2 weeks after the end of MARMA)	
	Dexamethasone 6mg/m^2/d p.o day 1-14, then taper
	Thioguanine 60mg/m^2/d p.o. day 1-28, 36-49
	Vincristine 1.5mg/m^2 IV push day 1, 8, 15, 22
	Daunorubicin 30mg/m^2 IV 1 hour infusion day 1, 8, 15, 22
	Cytarabine 75mg/m^2/d IV days 2-5, 9-12, 16-19, 23-26, 37-40, 45-48
	PEG-Asparaginase: 2500iu/m^2 IV in 1 hr or IM on day 1
	IT Cytarabine (age adjusted) days 1,15
	Cyclophosphamide 500mg/m^2 IV 1hour infusion day 36,49
Maintenance until 104 weeks after diagnosis	Mercaptopurine 50mg/m^2 P.O daily
	Methotrexate 20mg/m^2 P.O weekly
	Intrathecal methotrexate in week 1 and 15
	Intrathecal cytarabine in week 8

The primary eligibility criteria for referral for haematopoietic stem cell transplantation (HSCT) in infantile ALL are:

- Age at diagnosis: < 6 months
- MLL germline rearrangement

- Initial WBC ≥ 300 x 10^9/L

Poor response to prednisolone prophase

Table 5.6. Age adjusted doses for intrathecal chemotherapy

Methotrexate	
Age (years)	**Dose**
<1year	6mg
1 - <2years	8mg
2 - <3 years	10 mg
3-9 years	12 mg
>9 years	15 mg
Cytarabine	
Age (months)	**Dose**
<13 months	20mg
13 - <25 months	30mg
25 - <36 months	50mg
>36 months	70mg

Table 5.7. Radiotherapy in Acute Lymphoblastic Leukaemia

INDICATIONS	1. CNS involvement (Cranial Irradiation) given in the first ten days of the first maintenance cycle as in treatment tables above. 2. Testicular involvement 3. Whole body irradiation is often an important part of treatment before stem cell transplantation 4. Rarely to help shrink a tumour if it is pressing on the critical structures though chemotherapy is often used instead, as it may work more quickly. 5. Radiation can also be used to reduce pain in an area of bone invaded by leukaemia if chemotherapy hasn't helped.
PROCEDURE/ FIELDS	• There are challenges of initiating radiotherapy treatment in children due to non-familiarisation with the machines and presence of strangers (staff). • Play therapy is used to help the children to get familiar with the environments in which the treatment will occur, it should be done several weeks before commencement date of treatment • The technique of Cranial Radiation Therapy (CRT): Must ensure coverage of the cranial meninges as well as other areas of potential access to CNS such as: o The cribriform plate o Posterior part of the retina and posterior globe of the eye o The exit regions of cranial nerves III, IV, V and VI o The inferior extent of the temporal meninges
DOSE	The Linear accelerator machine with energies of 4 to 6 MV is usually used. Intensity-Modulated Radiotherapy (IMRT) can help reduce dose to critical structures. The doses vary with age: 1. < 12 months no radiotherapy 2. 12 - 24 months receive a dose of 12 Gy

	3. >2 years is 18 Gy and the fractionation is 1.8 Gy per fraction **Cranial Radiation therapy (CRT) based on risk category:** 1. B-Cell ALL HR CNS3, dose is 18Gy (Hogan L.E, 2023) 2. T-cell ALL HR*, VHR* with CNS1 and CNS2 dose is 12Gy (Dunsmore K.P, 2020) 3. T-cell ALL HR, VHR with CNS3 the dose is 18Gy (Dunsmore K.P, 2020 and Teachey D.T, 2022) 4. CNS relapse dose is 18Gy (Hogan L.E, 2023 and Lew G, 2021) **Testicular radiation therapy (TRT)** 1. Residual testicular leukaemia after induction therapy dose is 24Gy (Salzer W.L, 2020 and Hogan L.E, 2023). **Conditioning regimen for haematopoetic stem cell transplant** 1. Total body irradiation dose is 12-13.2Gy (Hogan L.E, 2023) 2. Cranial boost in CNS3 dose is 4-6Gy (Hogan L.E, 2023) 3. 3. Testicular boost for residual testicular leukaemia, dose is 6Gy (Hogan L.E, 2023)	
SIDE EFFECTS	**ACUTE**	**LATE**
	Headache Vomiting Anorexia Skin reaction	Scoliosis Hypothyroidism Infertility

* *HR = High risk, VHR = very high risk*

Follow-up

After completion of therapy, the patient should be periodically assessed for disease status:

- Complete physical examination including testicular evaluation, FBC, DC, liver function tests →every 1-4 monthly in first year, 3-6 monthly in second year, and 6-12 monthly from the third year until fully grown.
- Monitoring for long-term side effects of chemotherapy including weight and height monitoring, echocardiography for cardiotoxicity, neuro-psychological function and reproductive health monitoring are recommended
- Refer to guidelines on long-term follow up as previously published by the COG in the COG Long Term Follow Up (LTFU) guidelines – *see in reference number 35 below*.

- ***A child evaluated at all low levels of care with suspected or confirmed ALL shall be discussed with the paediatric oncology unit, for plan on relevant further local health facility diagnostic evaluation and any initial therapy that may be commenced before referral.***
- ***Prophase initiation at various levels shall proceed only after performance of BMA***

5.2. HODGKIN LYMPHOMA (HL)

Definition: A malignant condition arising from germinal centre B-lymphocytes with characteristically few pathognomonic tumour-forming Hodgkin Reed-Sternberg (HRS) cells in an inflammatory cell-rich infiltrate background.

- Epidemiological studies demonstrate three distinct forms of HL:
  - Childhood form (14 years or younger)
  - Young adult form (15 to 34 years), and
  - Older adult form (55 to 74 years)
- HL represents 6% of childhood cancers
- Male predominance before age of ten and about equal in adolescents.

This guideline applies to the childhood and young adult forms.

The WHO classification recognizes two major subtypes of HL based on their histology and immunohistochemical staining pattern as in table 5.8. below:

- Classical HL (cHL) and
- Nodular lymphocyte predominant HL (NLPHL)

Table 5.8. Histological Classification of HL

Histologic Type	Sub-type	CD15	CD30	CD45	CD20	Prevalence in Children (%)
cHL	Nodular sclerosis	+	+	-	+ or -	40-70
	Mixed cellularity					30
	Lymphocyte-rich					<5
	Lymphocyte-depleted					<5
NLPHL		-	-	+	Always +	<5

Clinical Presentation

- **cHL**
  - Lymphadenopathy – mostly painless cervical or supraclavicular adenopathy, firmer than inflammatory nodes, feel rubbery, and rarely may be tender to palpation if they have grown rapidly.
  - Tends to affect contiguous lymphatic areas in a predictable way
  - A non-productive cough, orthopnoea, or other symptoms of tracheal or bronchial compression may occur if there is mediastinal involvement especially in the sclerosing histological subtype
  - Primary disease presenting in a sub-diaphragmatic site is rare and occurs in only approximately 3% of cases.(Pizzo et al., 2015)
  - Features of bone marrow involvement such as anaemia, thrombocytopaenia in advanced cases.
  - Generalised pruritus may occur following a warm bath
  - Is strongly associated with Epstein-Barr virus (EBV**)**

- **NLPHL**
  - Often localized , painless lymphadenopathy typically in the neck or axilla
  - Has a typical indolent (slow growing) course and most patients present with early stage disease
  - Histologically characterized by presence of a lymphocyte-predominant cell population described as “popcorn cells”
  - NLPHL may transform into aggressive B-cell non-Hodgkin Lymphoma
  - EBV is rarely detected

Diagnosis

A child with suspected HL should have an **excisional nodal biopsy** to provide adequate tissue for morphological & IHC tests indicated in table 5.8. above.
The following information and imaging tests (Table 5.9.) should be obtained:

Table 5.9. Diagnostic and staging work up

Diagnostic evaluation	Important element	Comments
Medical history	"B" symptoms	Unexplained fever > 38.0°C Unexplained weight loss ≥ 10% within 6 months preceding diagnosis, and drenching night sweats.
	Symptoms of a large mediastinal mass	**Superior Vena Cava syndrome:** Dyspnoea, facial swelling, cough, orthopnoea, and headache **Tracheal or bronchial compression:** Cough, dyspnoea, and orthopnoea
Physical examination	Lymph nodes	Location and size
	Tonsils	Symmetry, size and nodularity
	Lung auscultation	Stridor and wheezing
	Abdomen	Hepatomegaly and splenomegaly
Laboratory tests	Full blood count	Anaemia, Leucopoenia/ leucocytosis/ normal WBC, abnormalities in WBC differential, abnormalities of platelet count.
	Biochemistry profile KFT and LFTs	Elevated ALP
	ESR, C-reactive protein, serum ferritin LDH	Elevation of markers of inflammation at diagnosis can be used to monitor response to therapy.
Diagnostic imaging, anatomical	Chest radiograph	Check for increase in the mediastinal to thoracic ratio
	CT of neck, Chest, abdomen and pelvis	Location and size of lymph nodes, to evaluate pulmonary involvement
	CT or MRI of abdomen and pelvis	Location and size of lymph nodes and hepato-splenic involvement.
Diagnostic imaging, functional	FDG-PET	Metabolic activity of involved nodes and organs. High sensitivity but low specificity
	Gallium-67 scintigraphy	Metabolic activity of involved nodes and organs. Low sensitivity, mostly replaced by PET scan.
	Technetium-99 bone scintigraphy	Metabolic activity in bone lesions. Being replaced by PET scan.
Biopsy	Bone marrow	Limited to patients with B symptoms or advanced disease (Stages III and IV)
	Lymph node	Histologic confirmation + IHCs CD45(LCA), CD15(LeuM1) CD30(Ki-1), CD 20, EMA

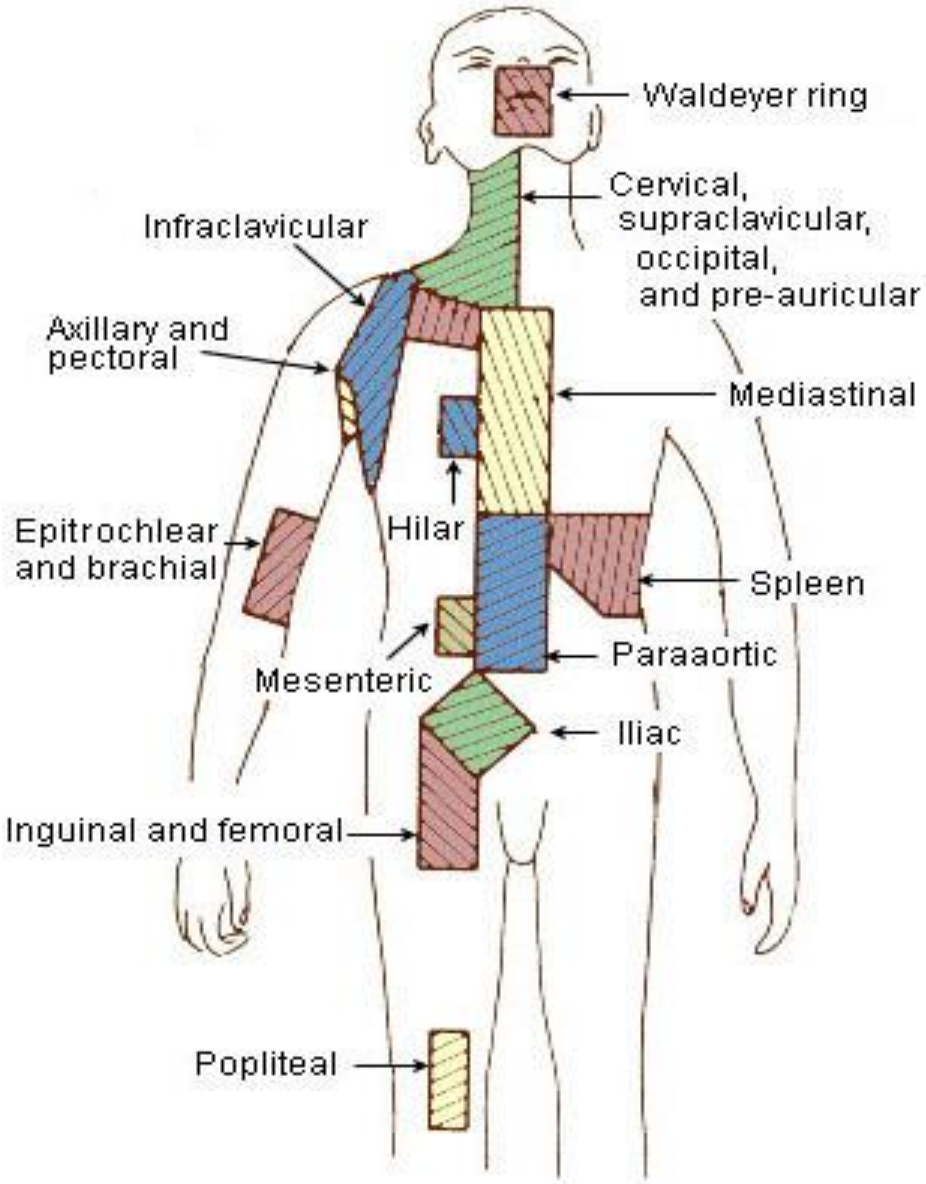


Figure 5. Anatomic definition of separate lymph node regions used for staging purposes. (Kaplan H. S. et al., 1966)

Table 5.1.1. Staging (Ann Arbor-derived Lugano classification with Cotswold modifications)

Stage	Definition
I	Involvement of a single lymph node region
II	Involvement of two or more lymph node regions on the same side of the diaphragm
III	Involvement of lymph node regions on both sides of the diaphragm
IV	Non-contiguous extra-lymphatic organ or site, regardless of lymphatic involvement (most commonly lung, liver, and bone or bone marrow)
suffix A	No detectable B symptoms
suffix B	B symptoms are present

***Note**:*

- The absence or presence of B symptoms (Table 5.9.) are to be denoted in all cases by the suffix letters A or B, respectively.

Risk Groups

Are essential for determining appropriate treatment strategies and predicting patient outcomes:

Key Risk Factors

- Mediastinal bulk = mediastinal lymphadenopathy measuring ≥ 33% of the maximum intrathoracic cavity diameter or ≥10cm on CT imaging. Often designated with an X as a suffix after the stage.
- Extranodal Disease: Denoted by Suffix letter E for limited extra-lymphatic involvement from contiguous nodal disease in stages I & II.
- Abdominal nodal mass ≥ 10cm while other nodal conglomerates ≥ 6cm

Based on the stage, extranodal site involvement, bulky disease and B-symptom presence the following will be the risk categories for cHL:

- Low risk = Stage IA or Stage IIA without bulky disease
- High risk = Stage IA or Stage IIA with bulky disease, Stages IB, IIB, IIIA/B or IVA/B

NLPHL has three groups based on stage of disease (Keller F. G., 2018):

- Early stage favourable,
- Early stage unfavourable
- Advanced stage

Treatment for classic Hodgkin Lymphoma:

a) **Supportive care pre-and post- chemotherapy**:
   Give at least 2 anti-emetics:
   i) **Dexamethasone 0.15mg/kg** PO or IV single dose /day 30minutes before chemotherapy.
      a. Omit dexamethasone for regimens that include a corticosteroid

ii) **Ondansetron 0.15mg/kg** 8 hourly PO or IV, starting 30minutes before receiving chemotherapy and continued for 2 -3 days after completion of chemotherapy administration.

b) **Chemotherapy**

ABVD Regimen: ABVD = Adriamycin, Bleomycin, Vinblastine, Dacarbazine respectively

- Doxorubicin (Adriamycin) 25 mg/m^2 IV days 1 and 15
- Bleomycin 10 IU/m^2 IV days 1 and 15
- Vinblastine 6mg/m^2 IV days 1 and 15
- Dacarbazine 375 mg/m^2 IV days 1 and 15

- Doxorubicin should be administered through the tubing of a rapidly infusing solution of 5% dextrose or 0.9% Saline and that it is infused into a large vein.
- Dacarbazine IV push or short infusion: Infuse the diluted solution over 15-60 minutes. Slow the infusion rate, as needed, to mitigate on the burning sensation during administration. Local pain, burning, and irritation may be relieved by application of hot packs. Protect medicine from light.

R-CHOP regimen: R-CHOP = Rituximab, Cyclophosphamide, Doxorubicin, Oncovin (Vincristine) and Prednisolone.

- Rituximab 375mg/m^2 Day 1
- Cyclophosphamide 750mg/m^2 Day 2
- Doxorubicin 50mg/m^2 Day 2
- Vincristine 1.5mg/m^2 Day 2
- Prednisolone 40mg/m^2 Days 1 – 5

CVinbP Regimen: CVinbP = Cyclophosphamide, Vinblastine, Prednisolone.

- Cyclophosphamide 500mg/m^2 Day 1
- Vinblastine 6mg/m^2 Days 1 and 8
- Prednisolone 40mg/m^2 Days 1-7

N.B. Rituximab can be added to make R-CVinbP at the same dose as in R-CHOP and should be given on Day 1

Table 5.1.2. Treatment regimens for each risk group:

Risk Group	Number of ABVD cycles
Low Risk	ABVD X 4 cycles every 4 weeks Patients will be evaluated with contrast-enhanced CT (CECT) scan for response 4 -6 weeks after completing all chemotherapy cycles ○ Patients who have a complete response (CR) will not receive radiotherapy (RT) after chemotherapy ○ Patents who do not have a CR receive RT ○ For patients who have widespread stage II disease it may be optimal to consider extended chemotherapy
High risk	ABVD X 6 cycles every 4 weeks Evaluate for response 4 -6 weeks after completing all chemotherapy cycles. ○ Patients who have a complete response (CR) will not receive RT after chemotherapy ○ Patents who do not have a CR receive RT

Table 5.1.3. Treatment for Nodular Lymphocyte Predominant Hodgkin Lymphoma

Stage	Treatment
Early-Stage IA, IIA (Favourable)	• Surgery alone for localized fully resectable stage IA disease Unresectable stage I & IIA disease in young children: three courses of **CVinbP** 2 to 3-weekly (Shankar et al, 2012) • Involved field radiotherapy (IFRT) for those with complete response – up to dose of 21Gy • For patients not suitable for IFRT treat as advanced stage disease below
Early stage with bulky disease or B symptoms (Unfavourable)	Chemotherapy (**R-CHOP** or **CVinbP** regimen) followed by involved site radiotherapy (ISRT) – (Thi An VU et al, 2024)
Advanced-Stage IIB, III, IV	Multi-agent chemotherapy + Rituximab (R**)- (**Eichenauer DA, et al, 2023)**:** • **R-CHOP or** • **R-ABVD** • **R-CVinbP**

Table 5.1.4. Radiation Therapy for Hodgkin Lymphoma

<table>
<tr><td>Indications</td><td colspan="2">1. Early-stage NLPHL
2. As part of combined modality in;
• Early-stage classical HL (after adequate systemic chemotherapy)
• Advanced stage disease (III and IV)
• For residual lymphoma after full chemotherapy
3. Radiotherapy is an integral part of some regimens for advanced stage disease (Abuzetun J.Y, 2008)</td></tr>
<tr><td>Procedure</td><td colspan="2">• Staging with PET/CT or just CECT, before treatment with chemotherapy or after chemotherapy depending on histology.
• There are challenges of initiating radiotherapy treatment in children due to non-familiarity with the RT machines and presence of strangers (staff).
○ Play therapy is used to help the children to get familiar with the environments in which the treatment will occur, it should be done several weeks before commencement of treatment.
• Immobilization is done in the mould room (this is important for treatment position reproducibility).
• CT simulation, acquired images are used for treatment planning.
• During radiotherapy planning/treatment measures like blocking and transposition of testes or ovaries is important.
• Verification of plan is done then treatment delivery.</td></tr>
<tr><td>Field</td><td>Supra-diaphragmatic fields involves nodes from skull base to 10th thoracic level:
• Mantle field
• Mini mantle
• Modified mantle
• Involved fields
• Waldeyer’s ring fields
• Involved Field Radiotherapy (IFRT) – smaller fields, treats regional nodal areas.</td><td>Sub-diaphragmatic fields:
• Inverted Y which targets para-aortic, pelvic, inguinal nodes and the spleen
• Modifications to the Inverted Y may include para-aortic or pelvic fields alone.
• Total nodal irradiation - involves both the supra- and sub-diaphragmatic fields, also has modifications like subtotal nodal irradiation</td></tr>
<tr><td>Dose</td><td colspan="2">Non-bulky disease: 20 – 30 Gy
Bulky disease: 30 – 36 Gy</td></tr>
<tr><td rowspan="2">Side effects</td><td>Acute</td><td>Late</td></tr>
<tr><td>Skin toxicity (erythema/ dermatitis)
Fatigue
Nausea
Vomiting
Anorexia
Hair loss
Haematological toxicity</td><td>Hypothyroidism
Infertility
Scoliosis
Height stunting
Secondary cancers
Lung fibrosis</td></tr>
</table>

Follow up

3-monthly (1st year), 6 monthly (next 2 years) with clinical examination, LDH, ESR, FBC and imaging as appropriate, then yearly thereafter until adulthood.

5.3. BURKITT LYMPHOMA (BL)

Definition: BL is a form of Non-Hodgkin Lymphoma (NHL) that arises from transformed germinal center B cells. BLs are high grade tumours with very high mitotic activity from uncontrolled proliferation giving rise to tumour masses that enlarge rapidly.

From an epidemiological stand point:

- BL accounts for up to 40% of NHL paediatric cases, with NHL as a group accounting for 60% of lymphomas in children less than 15 years old (Kliegman R. 2012).
- Tissue sections of biopsies will often show a "starry-sky" appearance that results from reactive macrophages scattered among the malignant lymphoid cells that are engulfing apoptotic debris from the rapidly dividing tumour cells.

BL is classified as:

- Endemic
- Sporadic (the type found in non-malarial areas)
- Immunodeficiency-related

Malaria is hypothesized to increase the risk of endemic BL by impairing T-cell-mediated control of EBV-infected B cells, leading to an increased chance of malignant transformation.

Endemic BL is observed along the equatorial malaria-belt for incompletely understood reasons. The immunodeficiency-associated variant is 1,000 times more frequent in HIV-infected than in uninfected children. Across all types boys are more frequently affected than girls (Pizzo et al, 2015).

Table 5.1.5. Clinical Presentation

Feature	Endemic	Sporadic	Immunodeficiency-related
Clinical Features	Peak: 4 – 7 yrs. Males > Females	Peak: 6 – 12yrs. Males > females	Peak: 3 – 12yrs. Male > females
Common Tumour Sites	Jaw, Abdomen, Cerebrospinal Fluid	Abdomen, Ovaries, Lymph nodes, bone marrow	Abdomen-ileocaecal and mesentery, CNS
Site-specific manifestations	• Includes painless, rapid lymph node enlargement • Cough, superior vena cava (SVC) syndrome, dyspnoea with thoracic involvement • Abdominal (massive and rapidly enlarging) mass, intestinal obstruction with intussusception-like symptoms, and ascites • Nasal stuffiness, tonsil enlargement, earache and hearing loss with Waldeyer ring involvement • Localized bone pain may indicate primary or metastatic disease site • CNS: confusion or decreased alertness, weakness, paralysis, or seizures depending on tumour location, hydrocephalus.		

Diagnosis:
The following diagnostic tests should be undertaken promptly when a diagnosis of BL is considered to facilitate early treatment initiation. If there's difficulty in obtaining a tissue biopsy, the child should be referred promptly to the next level of care with capabilities to take tissue biopsy. Paediatric surgeons and/or maxillofacial surgeons are key for obtaining biopsies in such cases.

Table 5.1.6. Key diagnostic tests

Diagnostic Test	Comment

Primary tumour biopsy specimen	Collected in the least non-invasive manner & processed to be sent to the local provincial hospital Pathology laboratory or Tertiary UTHs laboratories for:
	• Immunophenotyping/Immunohistochemistry for origin (T, B, or null). The level of expression can be used to distinguish Burkitt lymphoma from other high-grade B-cell lymphomas:
	  ○ Positive for CD19, CD20, CD79A, PAX5, CD10, and BCL6
	  ○ Usually negative for CD5, BCL2, and TdT.
	  ○ Strong BCL2 expression is uncommon.
	Additional tests may include:
	• Fluorescent in situ hybridization (FISH) or quantitative Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) for specific genetic translocations, molecular hallmark of Burkitt lymphoma is the t(8;14) translocation.
	  ○ *See tables under immunohistochemistry and molecular/cytogenetic studies under pathology guideline above*

Tests to determine extent of spread of tumour (metastatic workup)	• Bilateral bone marrow aspiration and biopsies • Lumbar puncture to obtain CSF for cytology, cell count and protein levels • Pleural/paracentesis fluid for cytology, cell count and protein levels • Chest x-ray prior to any sedation • Abdominal-pelvic Ultrasound • CECT scan head, neck, chest, abdominal, and pelvic (as indicated) • PET scan when available • Bone scan (optional) ○ *See imaging guideline above*
Blood & other tests	• Full blood count; ESR • Serum urea, creatinine, electrolytes (Na+, K+, Cl-, Ca^{2+}, Mg^{2+} PO_4^{3-}), uric acid. • Bilirubin, albumin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) • Lactate Dehydrogenase (LDH)

Table 5.1.7. BL Staging:

STAGE	DESCRIPTION
I	A single tumour (extranodal) or single anatomic area (nodal), with the exclusion of mediastinum or abdomen
II	A single tumour (extranodal) with regional node involvement
	Two or more nodal areas on the same side of the diaphragm
	Two single (extranodal) tumours with or without regional node involvement on the same side of the diaphragm
	A primary gastrointestinal tract tumour, usually in the ileocecal area, with or without involvement of associated mesenteric nodes only, which must be grossly (>90%) resected
III	Two single tumours (extranodal) on opposite sides of the diaphragm
	Two or more nodal areas above and below the diaphragm
	Any primary intrathoracic tumour (mediastinal, pleural, or thymic)
	Any extensive primary intra-abdominal disease All paraspinal or epidural tumours, regardless of other tumour site(s)
IV	Any of the above, with initial involvement of central nervous system or bone marrow at time of diagnosis

Treatment

Supportive care:

Give at least 2 anti -emetics:

i. Dexamethasone 0.15mg/kg single dose /day (but avoid if patient already on corticosteroid)
ii. Ondansetron 0.15mg/kg 8 hourly during and for 2 -3 days after chemotherapy administration completion.

Patients with BL are prone to tumour lysis syndrome (TLS) so ensure the following are done:

- Intravenous (IV) fluids with 5% Dextrose-Normal Saline (DNS) at 3L/m^2 daily for the first 5 – 7 days starting 24 hours before initiation of chemotherapy
- Monitor Urine output
- Monitor electrolytes including K^+, Na^+, Ca^{2+}, Mg^{2+}, PO_4^{3-}, 12 hourly for the first 5 days
- Give allopurinol at 10 – 20mg/kg in two divided doses starting 24 hours before initiation of chemotherapy and continue for 7 days
- Give MESNA 360mg/m^2 IV whenever administering doses of cyclophosphamide greater than 600mg/m^2; start MESNA doses with the cyclophosphamide infusion and then repeat MESNA doses at 4 & 8 hours later for a total of 3 doses.
- Give granulocyte colony-stimulating factor (Filgrastim) at 5 micrograms/kg subcutaneously once daily for at least one week starting at least 24 – 48hours after the last dose of the chemotherapy regimen, for regimens (B2, B3, CODOX-M/ IVAC) that cause severe neutropenia as a result of bone marrow suppression (myelosuppression).
- Give prephase therapy as appropriate.

Prephase treatment

This phase uses low dose cancer chemotherapy. It is important for prevention of early death upon initiation of chemotherapy, due to fulminant TLS. TLS can be fatal given the limitations for renal replacement therapy and rasburicase unavailability. This approach can "rescue" patients felt to be too sick for dose-dense cytotoxic treatment, and provides time for stabilization measures before bulky, proliferative tumours are subjected to intense or higher dose multi-agent chemotherapy.

Table 5.1.8. Assessment of performance status to decide when to start definitive BL treatment

Performance status	Treatment
Poor performance status: • Lansky performance status ≤50, or • Eastern Cooperative Oncology Group [ECOG] performance status ≥3)	Prednisolone x 5 to 7 days, followed by COP (cyclophosphamide, vincristine, and prednisolone) X 5-7 days. Definitive treatment started 5-7 days later
Good performance status: • Lansky performance status >50, or • Eastern Cooperative Oncology Group [ECOG] performance status ≤ 2	COP (cyclophosphamide, vincristine, and prednisolone) X 5-7 days. Definitive treatment started 5-7 days later

COP regimen (Gopal S. et al, 2018)
Cyclophosphamide 300-400mg/m^2 IV infusion over 30 -60 minutes on day 1
Vincristine (**O**ncovin) 1mg/m^2 IV push over at least 5 minutes on day 1
Prednisone 1.5mg/kg/day PO days 1-5 with gastric protection with Omeprazole 20 - 40mg once daily for the duration of prednisolone

Chemotherapy regimens for Burkitt lymphoma
There are three broad categories based on availability of resources and supportive care:

- Low-intensity regimens approach
- Higher-intensity regimens approach incorporating anthracyclines
- Higher-intensity regimen approach incorporating moderate to high-dose methotrexate (Moleti ML et al, 2007)

Table 5.1.9. Low-intensity Approach

Drugs	Comment
Cyclophosphamide 1200mg/m^2 IV day 1 (with MESNA as above) Vincristine 1.4mg/m^2 IV day 1 Methotrexate 75mg/m^2 IV day 1 Methotrexate IT (age adjusted) days 1 and 8 Cytarabine IT (age adjusted) day 4	• Next cycle starts on day15 if ANC ≥ 1.0 x 10^9/L, and platelets ≥ 75 x 10^9/L • Give 3-4 cycles for low risk (single extra-abdominal site < 10cm) & 6 cycles for high risk

Table 5.2.1. Higher-intensity approaches incorporating anthracyclines (CHOP regimen)

Drug	Comment
Cyclophosphamide 750mg/m^2 IV day 1 (with MESNA as above) Doxorubicin 40mg/m^2 IV day 1 Vincristine 1mg/m^2 IV day 1 Prednisone 1.5mg/kg/d PO days 1-5 Methotrexate IT (age adjusted) days 1	Cycles repeated on day 22 if ANC ≥ 1.0 x 10^9/L, and platelets ≥ 75 x 10^9/L X 6 cycles

Table 5.2.2. Higher-intensity approaches incorporating anthracyclines (B2 & B3 regimens)

Week	B2 Regimen	B3 Regimen
1	Vincristine 1.5mg/m2 (max 2.0mg) IV push Day 1 Cyclophosphamide 1200mg/m^2 (maximum 2.4g) IV infusion over 1 hour with MESNA as above Prednisolone 60mg/m^2 day 1 - 5 IT MTX day 1	Vincristine 1.5mg/m^2 (max 2.0mg) IV push Day 1 Cyclophosphamide 1200mg/m^2 (maximum 2.4g) IV infusion over 1 hour with MESNA as above. Prednisolone 60mg/m^2 day 1 - 5 IT MTX day 1
2	Vincristine 1.5mg/m^2 (max 2.0mg) IV push Day 1 Cyclophosphamide 1800mg/m^2 (maximum 2.4g) IV infusion over 1 hour with MESNA as above. IT MTX day 1	Vincristine 1.5mg/m^2 (max 2.0mg) IV push Day 1 Doxorubicin 60mg/m^2 IV infusion in 100 - 300mL 0.9% saline over 1 – 2 hours Cyclophosphamide 1800mg/m^2 Methotrexate IT
3	Vincristine 1.5mg/m^2 (max 2.0mg) IV push Day 1 Cyclophosphamide 1200mg/m^2(max 2.4g) IV infusion over 1 hour with MESNA as above Doxorubicin 60mg/m^2 day 1 IT MTX day 1	Vincristine 1.5mg/m^2 (max 2.0mg) IV push Day 1 Cyclophosphamide 1800mg/m^2(max 2.4g) IV infusion over 1 hour with MESNA as above IT MTX day 1
4	No chemotherapy	Vincristine 1.5mg/m^2 (max 2.0mg) IV push Day 1

		Cyclophosphamide 1800mg/m^2(max 2.4g) IV infusion over 1 hour with MESNA as above Etoposide 150mg IVI over 1 hr Days 1-2 IT MTX day 1
5	Vincristine 1.5mg/m^2 (max 2.0mg) IV push Day 1 Cyclophosphamide 1200mg/m^2(max 2.4g) IV infusion over 1 hour with MESNA as above Doxorubicin 60mg/m^2 day 1 IT MTX day 1	Vincristine 1.5mg/m^2 (max 2.0mg) IV push Day 1 Cyclophosphamide 1800mg/m^2(max 2.4g) IV infusion over 1 hour with MESNA as above Etoposide 150mg IVI over 1 hr Days 1-2 IT MTX day 1
6	No chemotherapy	Vincristine 1.5mg/m^2 (max 2.0mg) IV push Day 1

Table 5.2.3. Higher-intensity approaches incorporating moderate to high-dose methotrexate (CODOX-M/ IVAC Regimen) use

Risk Category	Parameters	Treatment
Low Risk	Non-bulky disease (< 10 cm) Early stage (I or II) disease, Good performance status Normal LDH level	Three CODOX-M cycles every 3 weeks
High Risk	Bulky disease (≥ 10 cm), Advanced stage (III or IV) disease, Poor performance status Elevated LDH level	Four cycles alternating between CODOX-M and IVAC regimens every three weeks.

Table 5.2.4. CODOX-M Regimen

Drug	Comment
Cyclophosphamide 800 mg/m^2 IV day 1 (with MESNA as above) and 200mg/m^2 day 2-5 Doxorubicin 40mg/m^2 IV day 1 Vincristine 1.5 mg/m^2 day 1,8 and (15*) Methotrexate 2g/m^2 IV (4hr infusion) day 10 Calcium folinate 15mg/m^2 IV 6hrly X 10 doses starting 12-18 hours after methotrexate infusion Cytarabine IT (age adjusted) day 1, 3 Methotrexate IT (age adjusted) day 15	*Third dose only in course 3 and only if no neuropathy. Patients with CNS disease at presentation receive additional intrathecal chemotherapy during the first two cycles. Give cycle when absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L, platelet count ≥ 100 x 10^9/L, Hb > 8g/dL. Alkaline hydration administered 2hrs before and 2hrs after methotrexate

Table 5.2.5. IVAC Regimen

Drugs	Comment
Ifosfamide 1.5g/m^2/d IV (with MESNA) day 1-5 Etoposide 60mg/m^2/d IV day 1-5 Cytarabine 2g/m^2 b.i.d IV day 1 and 2 Methotrexate IT (age adjusted) day 5	Give cycle when ANC ≥ 1.0 x 10^9/L, platelet count ≥ 100 x 10^9/L, Hb > 8g/dL

Table 5.2.6. Radiotherapy for Burkitt Lymphoma

Indications	1. Residual bulky disease. 2. CNS involvement (spinal cord compression or intracranial mass effect). 3. Palliative treatment (pain, bleeding, obstruction caused by tumour) 4. Localised bone involvement or impending bone fracture. 5. Refractory or relapsed disease.	
Procedure	• Imaging – MRI/CT Scan to delineate tumour sites • Play therapy is used to help the children to get familiar with the environments in which the treatment will occur, it should be done several weeks before commencement of treatment. • Immobilisation – body cast or mask used for reproducibility of treatment plan. • CT Simulation done in treatment position. • Multidisciplinary Planning- done in consultation with paediatric oncologist to ensure it compliments chemotherapy in order not to compromise overall treatment. • Treatment delivery- 3D conformal radiotherapy or IMRT.	
Field/dose	Field includes tumour bed with a margin to cover microscopic disease and any adjacent lymph nodes. Dose minimisation to surrounding critical structures is ensured. Curative dose 20-30 GY. Standard dose 24-30 Gy at 1.8-2 Gy per fraction. Palliative dose 10-20 Gy CNS involvement lower doses are used to reduce toxicity – 18-24 Gy.	
Side effects	**ACUTE**	**LATE**
	Fatigue Skin toxicity (erythema/dermatitis) Nausea Vomiting Diarrhoea Bone marrow suppression Mucositis	• Growth and developmental delays • Hypothyroidism • Cardiac and pulmonary toxicity (mediastinal RT) • Renal and hepatic toxicity (Abdominal RT) • Secondary malignancies • Neurocognitive effects (Brain RT)

Follow Up care:
3-monthly (1st year), 6 monthly (next 2 years) with clinical examination, LDH, ESR, FBC and imaging as appropriate, then yearly thereafter until adulthood.

- ***Every effort to initiate treatment early must be made as BL is a high grade malignancy with dramatic negative consequences on the patient (airway compromise & malnutrition) if there is delays in treatment initiation.***
- ***If in some treatment centers cytology or histopathology is not readily available, or the waiting time for the report is too long to help in the acute management, treatment should then be started based on the clinical diagnosis.***

5.4. LOW GRADE GLIOMAS (LGG)

Definition

Low grade gliomas (LGGs) are a heterogeneous spectrum of neoplasms comprising 40% of primary pediatric brain tumours (Rickert C. H., et al. 2001). The posterior fossa is the most common site of involvement (15-25%) followed by the cerebral hemispheres (10-15%) and the optic pathways (6%) (Pollack I.F., 2003; Angela J. et al, 2009). Majority arise sporadically, while some arise within cancer-predisposition syndromes, such as neurofibromatosis type 1 (pilocytic astrocytoma) and the Tuberous sclerosis complex (sub-ependymal giant cell astrocytoma). It is reported that 15–20% of NF1 patients (Angela J. et al, 2009) will develop hypothalamic/chiasmatic/optic pathway gliomas (HCLGG) as well as LGG in other sites, however these tumours often behave more indolently than sporadic LGG in non-NF1. Boys are affected more commonly than are girls in non-Optic Pathway Gliomas (non-OPGs), whereas boys and girls are equally affected in Optic pathway Gliomas (OPGs). The average age at diagnosis ranges from 6.5 to 9.0 years for non-OPGs, and first 5 years for OPGs. They are generally slow evolving, with relatively benign histological appearance. In general, high rates of long-term survival are characteristic, despite low but steady rates of disease progression even 10 years from diagnosis (Pizzo et al, 2015).

Table 5.2.7. Classification According to Histology and WHO Grading System

Type	Grade I	Grade II
Astrocytic Tumours	• Pilocytic astrocytoma • Subependymal giant cell astrocytoma	• Diffuse astrocytoma • Pilomyxoid astrocytoma • Pleomorphic xanthoastrocytoma
Oligodendroglial Tumours		Oligodendroglioma
Neuronal and mixed neuronal glial tumours (mixed oligo-astro neuronal features)	• Ganglioglioma • Gangliocytoma • Desmoplastic infantile ganglioglioma • Dysembroplastic neuroepithelial tumour	Oligoastrocytoma

Clinical Presentation

- Almost 50% of children will have had 6 months or longer symptom duration prior to the eventual diagnosis.
- The clinical presentation primarily reflects the site of tumour origin, the age and developmental level of the affected child, and, occasionally, the tumour type.
- Clinical prodromes may include features of increased Intracranial pressure (ICP), symptoms and signs of a localising nature, or symptoms and signs without a localisation (Pizzo et al, 2015):

a) **Generalizing symptoms and signs**: this is due to increased ICP from obstruction of the ventricles and include:
   I. headaches (particularly in the morning),
   II. nausea and vomiting
   III. lethargy
   IV. Older children also display abnormal pupillary reaction to accommodation, sixth cranial nerve palsies, and papilloedema.
   V. Infants and young children exhibit irritability, anorexia, failure to thrive, and developmental delay or regression, macrocephaly and separation of the cranial sutures, tense or bulging anterior fontanelle associated with a shrill, neurogenic cry, or setting-sun eye sign.
   VI. Fundoscopic examination may reveal only optic pallor but no evidence of papilloedema in infants.

b) **Specific symptoms and signs**: Localizing symptoms are dictated by tumour location and include:
   I. Focal neurological findings
   II. seizures
   III. Endocrinopathies

c) The presentation of tumours of the cerebral hemisphere depends upon which lobe is involved and includes:
   I. Seizures
   II. Hemiparesis
   III. Behaviour change

d) Optic pathway gliomas may arise anywhere along the visual pathway. Children can present with:
   I. Decreased visual acuity
   II. Optic nerve atrophy
   III. Proptosis
   IV. Strabismus
   V. Lower cranial nerve deficits (dysphagia, dysarthria, abnormal breathing)
   VI. Long tract signs (hemiparesis, spasticity, hyperreflexia, Babinski's sign)

Diagnosis

Radiological imaging is the cornerstone in the diagnosis of pediatric brain tumours – *refer to radiology guideline above.*

- CT scan should include both pre- and post-contrast views. If available, multi-planar reconstruction is particularly helpful in evaluating certain tumours (e.g. coronal plane for HCLGGs and sagittal plane for tectal plate low grade gliomas (TPLGG).
- Brain and spine MRI (without & with contrast). Spinal metastatic disease may be seen in up to 10% of children with LGG, if possible an initial spinal MRI should be performed.

- Biopsy should be considered for children with unresectable low-grade gliomas where there is a doubt with regard to diagnosis.
- Certain tumours such as HCLGG and tectal plate gliomas may be reliably diagnosed on imaging alone. Where diagnosis is uncertain, it is vital that a biopsy is taken and sent to a pathological service at the provincial hospital or UTHs main pathology laboratory to ensure accurate diagnosis.
- OPGs are generally low-grade glial neoplasms that are not routinely biopsied.
    - Visual assessment is vital both in terms of deciding when to treat and as a monitoring tool during treatment for optic pathway LGG (Avery R. A. et al, 2013). It should however be noted that visual deterioration may occur in children with neurofibromatosis type 1 (NF1) without any evidence of tumour growth and also that treating such a tumour may not result in arresting visual deterioration (Zeid J. et al, 2006).

Treatment

Children with suspected or confirmed LGG should be referred to a tertiary level centre with appropriate expertise as this may offer a survival and outcome advantage (Zaghloul M. S, 2016). The mainstay of treatment is surgical excision except for tumours in the deep midline supratentorial region, optic pathway/hypothalamus, and brain stem. Figure 5.1. below summarises the treatment decision process:

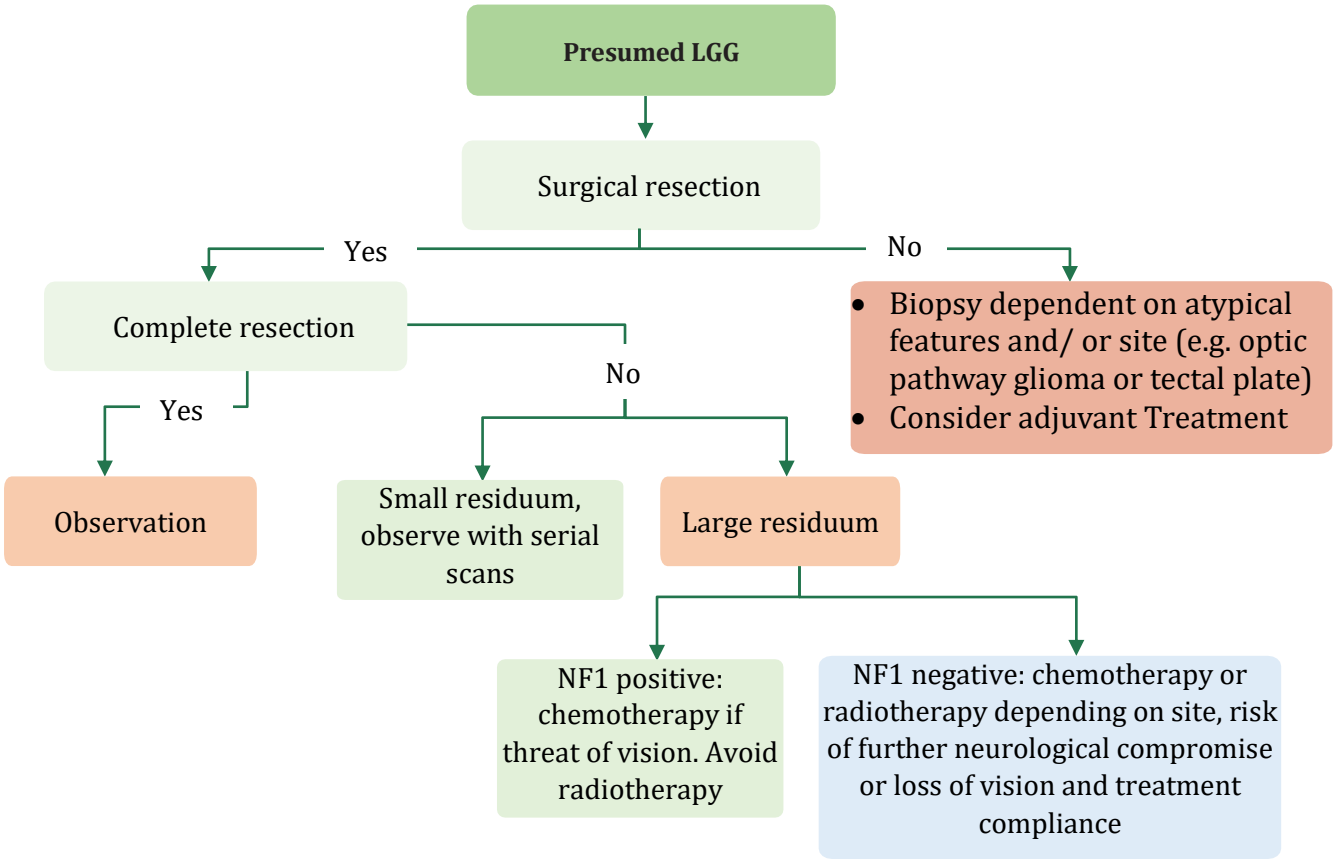


Figure 5.1. Treatment algorithm for low grade gliomas

For tumours located in areas where gross total resection is possible, surgery is the most effective treatment (Wisoff J. H, et al, 2011). If >95% tumour resection, monitor with scans every 4-month for 3 years. Review the treatment plan if the patient worsens or tumour size increases. If the lesion progresses review treatment options.
Treatment options for tumours that are not amenable to surgical resection are chemotherapy, radiotherapy (RT) or observation alone:

- Small tumours, especially for children with NF1, is close observation with MRI scans. (Benesch M. et al, 2006)
- Chemotherapy: indications include children younger than 3 years and children for whom delay of radiation therapy is desirable for avoidance of long-term neuropsychological and neuroendocrine problems, tumours in the deep locations or sensitive structures, and progressive disease after RT.
- RT is used for inoperable, recurrent or progressive tumours. It is also used in children older than 4-5 years with progressive or significant visual compromise (Freeman C. R., et al, 1998).
- RT is not recommended for OPG (vascular and neuroendocrine problems especially if patient has NF1).

CbV Chemotherapy regimen for paediatric LGG

Induction Phase

- Ten-week induction course consisting of:
  - **IV carboplatin 175 mg/m²** infused over 1 hour in 0.9% saline weekly X 8 doses in weeks 1-4 & 7-10
  - **Vincristine 1.5 mg/m²**, (maximum 2 mg per dose) weekly by IV push over 5 -10 minutes X 10 doses

Maintenance Phase

- If objective response to treatment, or stable disease (as defined in imaging guideline) maintenance for up to 8 cycles of the same two drugs above (begins 2 weeks after last cycle of induction) (Laila H. et al, 2018) should be given:
  - **IV carboplatin 175 mg/m²** infused over 1 hour in 0.9% saline weekly X 4 doses in weeks 1-4
  - **IV Vincristine 1.5 mg/m²**, (maximum 2 mg per dose) weekly by IV push over 5 -10 minutes X 3 doses in weeks 1-3

Table 5.2.8. Radiotherapy in Low Grade Glioma

<table>
<tr><td>Indications</td><td colspan="2">1. Incomplete surgical resection
2. Symptomatic tumours
3. Tumours located in critical areas (brainstem, optic pathway), where surgery cannot be done.
4. Recurrent disease</td></tr>
<tr><td>Procedure</td><td colspan="2">• Imaging done prior to treatment (MRI/CT scan) to determine tumour size.
• There are challenges of initiating radiotherapy treatment in children due to non-familiarity of the machines and presence of strangers (staff).
• Play therapy is used to help the children to get familiar with the environments in which the treatment will occur.
• Play therapy should be done weeks before commencement of treatment.
• Immobilisation in a custom-made mask (for reproducibility of treatment plan).
• CT Simulation
• Treatment Planning
• Treatment delivery</td></tr>
<tr><td>Field/dose</td><td colspan="2">The field includes the tumour, surrounding tissues or tumour bed in those post-surgery. The radiation field is planned to avoid or block off critical structures like eyes, optic nerve and brainstem where tumours are near those regions.
IMRT or proton therapy are recommended to spare critical organs
Dose given ranges from 45-54 Gy at 1.8Gy per fraction.</td></tr>
<tr><td>Side effects</td><td>Acute</td><td>Late</td></tr>
<tr><td></td><td>Fatigue
Hair loss
Skin toxicity (erythema, dermatitis)
Nausea
Vomiting
Anorexia
Headache</td><td>Neurocognitive decline (impact on memory, attention, learning abilities)
Hypothyroidism
Stunting growth
Hearing loss
Visual changes
Secondary malignancies.</td></tr>
</table>

- **Children with suspected or confirmed low grade glioma should be evaluated and treated in a tertiary centre that has both the facilities to diagnose and treat them.**

5.5. NEPHROBLASTOMA (WILMS TUMOUR)

- Globally, kidney tumours account for 7% of all childhood cancers (Pizzo et al, 2015).
- Nephroblastoma or Wilms tumour (WT), an embryonal tumour, accounts for up to 95% of these kidney tumours.
- Peak age group at presentation for Nephroblastoma is 2-5 years, with a slight female preponderance.
- Although it can occur in children older than 5 and up to 15 years the likelihood of other renal tumours is higher after the age of nine (Breslow N. et al, 1993)
- It is also known to be more prevalent in black than Asian populations.
- Nephroblastoma accounts for 14% of all childhood cancers seen at CDH annually. Survival is over 85% in high income countries and 11-50% in sub-Saharan Africa (Israels T. et al, 2013) and about 46.7% one year survival at University Teaching Hospitals-Cancer Disease Hospital (Muulu et al., 2024).

Clinical Presentation

- Majority of children present with asymptomatic abdominal mass incidentally found while bathing or dressing the child.
- Abdominal pain (40%)
- Fever
- Intermittent macroscopic (18%) and microscopic (24%) haematuria (Amar A. M. et al, 2001).
- Hypertension due to increased renin excretion in 25%

Features due to mass effect of abdominal mass may include

- Vomiting
- Early satiety
- Diaphragmatic splinting
- Prominent abdominal wall vessels
- Varicoceles with consequent spermatic vein thrombosis
- Bilateral lower limb oedema due to obstruction of the IVC
- Pulmonary embolus (rarely)
- Pulmonary congestion from tumour spread pulmonary metastases (most common metastatic site)

There is a need for careful assessment of the child for aniridia, urogenital anomalies (hypospadias, cryptorchidism), developmental delay, overgrowth syndromes and hemihypertrophy (see table 5.2.9. below). Approximately 5 -7% have bilateral kidney disease. Bilateral disease can be synchronous or metachronous, in the latter, affecting the remaining kidney within 4 years of the diagnosis of the initial contralateral tumour (Breslow N., et al, 1993)

Tumour Spread

- Tumour may extend locally and haematogenously.
- **Local spread:** the tumour may extend directly through the renal capsule and affect surrounding tissues and the regional lymph nodes. The tumour may also extend into the renal pelvis and grow into the ureter, or form a tumour thrombus that extends inferiorly and superiorly which may extend up into the right atrium.
- **Haematogenous spread:** affect the lung (80%), liver (15%) and rarely bone marrow and brain (Pizzo et al, 2015)

Table 5.2.9. Genetic Syndromes associated with Nephroblastoma

Up to 10% of children with Nephroblastoma have a known syndromic association as below:

Genetic Syndrome	Locus	Genetic Lesion	Phenotype	Estimated WT Risk
WAGR	11p13	Deletion of WT1 gene	Aniridia, genitourinary anomalies, delayed-onset renal failure, developmental delays	30%
Denys-Drash	11p13	Point mutation in zinc finger region of WT1 gene	Ambiguous genitalia, diffuse mesangial sclerosis	>90%
Beckwith-Wiedemann/ isolated Hemihypertrophy	11p15	Mutation or epigenetic dysregulation of IGF2	Organomegaly, large birth weight, macroglossia, omphalocoele, hemihypertrophy, ear pits & creases, neonatal hypoglycaemia	5%
Fanconi D1	13q12	BRCA2 mutations	Short stature, radial ray defects, bone marrow failure	20%
Li-Fraumeni	17p13	TP53 Mutations	Familial predisposition to cancer	Low, but several cases reported
Bloom	15q26	BLM Mutations	Short stature, photosensitivity, characteristic facial features	3%
Perlman	2q37	DIS3L2 mutations	Prenatal overgrowth, facial dysmorphism, developmental delay, cryptorchidism, renal dysplasia	33%

Diagnosis

Imaging is crucial in initially delineating the renal tumour with features that are consistent even before tissue biopsy. Surgical excision of the tumour, combination chemotherapy and radiotherapy, all play an important part in the treatment of Nephroblastoma though surgery is the cornerstone of treatment. In Zambia, multidisciplinary meetings, the basic chemotherapy, radiotherapy and other services necessary for the treatment of Nephroblastoma are available at the UTHs.

Table 5.3.1. Physical examination findings, Laboratory and Imaging diagnostic tests

Baseline investigations and evaluation	**Laboratory investigations and imaging:**
• Nutritional status • Side and size of the tumour • Size of the liver • Blood Pressure • Suspected lymph nodes or other masses • Congenital anomalies and syndromic features, if any	• FBC • Biochemistry: Liver and renal function tests • CECT scan of chest, abdomen and pelvis • Coagulation profile including von Willebrand factor
Chest Radiology should mention the following points: • Metastasis present/absent • Unilateral/Bilateral involvement - Number on each side: up to five or more than five ○ **CT scan of Chest is recommended for detection of pulmonary metastasis.** ○ **If Chest radiograph is showing a doubtful lesion, then a CT Chest would be desirable**	**Abdominal Radiology should mention the following points:** • Size of tumour in maximum dimension • Laterality with a comment on contralateral kidney • Presence of thrombus • Lymph node status • Liver nodules: Number, size, site • Relationship with aorta and inferior vena cava: pushed, engulfed, none • Origin of tumour: Upper pole, lower pole or hilum • Tumour relation to the diaphragm
Needle Biopsy is to be considered in following situations	**Needle Biopsy procedure**
• Inoperable renal mass with poor response neoadjuvant chemotherapy • Unusual clinical presentations: Age > 5–6 years • Urinary infection, Septicaemia, Psoas inflammation • Unusual findings by imaging: Calcification, Voluminous adenopathies, renal parenchyma not visible or almost totally extrarenal process	• Needle biopsy should be from a retroperitoneal approach without more than 2–3 attempts, and image guided when possible. • Biopsy is not recommended in bilateral tumours if radiological picture is consistent

Staging

The extent of the disease is defined by two surgical staging systems dependent on when nephrectomy is done: when tumour resection is done upfront and then when tumour resection is done after an imaging-based diagnosis is followed by a course of NeoAdjuvant ChemoTherapy (NACT). The table below shows details for the two staging systems. They are included because individual patients will be managed on a case by case basis in relation to when nephrectomy is done.

Table 5.3.2. Staging of Nephroblastoma

Stage	Staging with upfront Nephrectomy	Staging for cases that receive pre-surgery chemotherapy
I	Tumour is limited to the kidney and is completely resected. The renal capsule is intact. The tumour is not ruptured or biopsied before being removed. No involvement of renal sinus vessels. No evidence of the tumour at or beyond the margins of resection. All lymph nodes sampled are negative.	Tumour is limited to kidney or surrounded with fibrous pseudocapsule. If outside the normal contours of the kidney, the renal capsule or pseudocapsule may be infiltrated with the tumour, but it does not reach the outer surface, and is completely resected (resection margins "clear") The tumour may be protruding into the pelvic system and "dipping" into the ureter (but it is not infiltrating their walls) The vessels of the renal sinus are not involved Intrarenal vessel involvement may be present
II	The tumour is completely resected, and there is no evidence of tumour at or beyond the margins of resection. The tumour extends beyond the kidney as evidenced by any one of the following criteria: There is regional extension of the tumour (i.e., penetration of the renal capsule, or extensive invasion of the soft tissue of the renal sinus, as discussed below). Blood vessels in the nephrectomy specimen outside the renal parenchyma, including those of the renal sinus, contain tumour cells. Margins are clear.	The tumour extends beyond kidney or penetrates through the renal capsule and/or fibrous pseudocapsule into perirenal fat but is completely resected (resection margins "clear") The tumour infiltrates the renal sinus and/or invades blood and lymphatic vessels outside the renal parenchyma but is completely resected The tumour infiltrates adjacent organs or vena cava but is completely resected

	Vascular extension of tumour is considered stage II only if it is completely removed en bloc in the nephrectomy specimen. All lymph nodes sampled are negative.	
III	There is postsurgical residual non-haematogenous tumour that is confined to the abdomen. Any one of the following may occur: Lymph nodes in the abdomen or pelvis are involved by tumour. (Lymph node involvement in the thorax or other extra-abdominal sites is a criterion for stage IV.) The tumour has penetrated through the peritoneal surface. Tumour implants are found on the peritoneal surface. Gross or microscopic tumour remains postoperatively (e.g., tumour cells are found at the margin of surgical resection on microscopic examination). The tumour is not completely resectable because of local infiltration into vital structures. Tumour rupture before surgery or any spill during surgery is considered stage III. Any biopsy is performed, regardless of type ; Tru-cut biopsy, open biopsy, or fine needle aspiration, before the tumour is removed. The tumour is removed in more than one piece (e.g., tumour cells are found in a separately excised adrenal gland; a tumour thrombus in the renal vein is removed separately from the nephrectomy specimen). Extension of the primary tumour in the vena cava into the thoracic vena cava and heart is considered stage III, rather than stage IV, even though outside the abdomen—	Incomplete excision of the tumour, which extends beyond resection margins (gross or microscopic tumour remains postoperatively Any abdominal lymph nodes are involved Tumour rupture before or intra-operatively (irrespective of other criteria for staging) The tumour has penetrated through the peritoneal surface Tumour thrombi present at resection margins of vessels or ureter, transected or removed piecemeal by surgeon The tumour has been surgically biopsied (wedge biopsy) prior to preoperative chemotherapy or surgery

	and it can even be stage II if completely resected en bloc with the nephrectomy specimen. Lymph node involvement and microscopic residual disease are reported as highly predictive of outcome in patients with stage III favourable histology Nephroblastoma	
IV	One of the following is present: Haematogenous metastases (lung, liver, bone, brain). Lymph node metastases outside the abdominopelvic region	Haematogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdominopelvic region
V	Bilateral involvement by tumour is present at diagnosis	Bilateral renal tumours at diagnosis

Pathology and risk categorisation:

The risk stratification and prognostication are related to the tumour histology in addition to the stage of disease (R Carachi, 2008). For post-chemotherapy cases, risk categories are as described in table 5.3.3. and for primary nephrectomy specimen, risk categories are based on histology findings as in table 5.3.4. below. Histological features are broadly classified as Favorable and Unfavorable with prognostic implications. Anaplastic histology is considered the single most important histologic predictor of response and survival in patients with nephroblastoma. If further risk categorizing factors like loss of heterozygosity at chromosomes 1p and/or 16q are done, treatment will be as outlined in table 5.3.9 below.

Table 5.3.3. Risk categories based on post-chemotherapy histological findings

Low-risk	Mesoblastic nephroma, Cystic partially differentiated nephroblastoma, Completely necrotic nephroblastoma
Intermediate-risk	Nephroblastoma - epithelial type, Nephroblastoma - stromal type, Nephroblastoma - mixed type, Nephroblastoma - regressive type, Nephroblastoma - focal anaplasia
High-risk	Nephroblastoma - blastemal type, Nephroblastoma - diffuse anaplasia

Table 5.3.4. Risk categories based on upfront nephrectomy histological findings

Favourable histology (FA)	No anaplasia
Unfavourable Histology (UH)	Focal or diffuse anaplasia

Treatment

The treatment of nephroblastoma should be carried out by or under supervision of an experienced multidisciplinary team (MDT) consisting at the least the following: pediatric surgeon, pediatric or clinical radiation oncologist, pediatric oncologist, paediatrician, pathologist, radiologist and an Oncology-trained nurse.

In view of the likelihood of huge tumours at presentation, which may either be unresectable or risky to resect; pre-operative chemotherapy followed by delayed surgery will be the preferred approach in managing children with renal tumours suspected to be nephroblastoma.

If upfront nephrectomy is considered safe by the surgical team, then the child shall have an upfront nephrectomy followed by the adjuvant treatment that will be based on the disease stage and histological findings as in the Figure 6. below

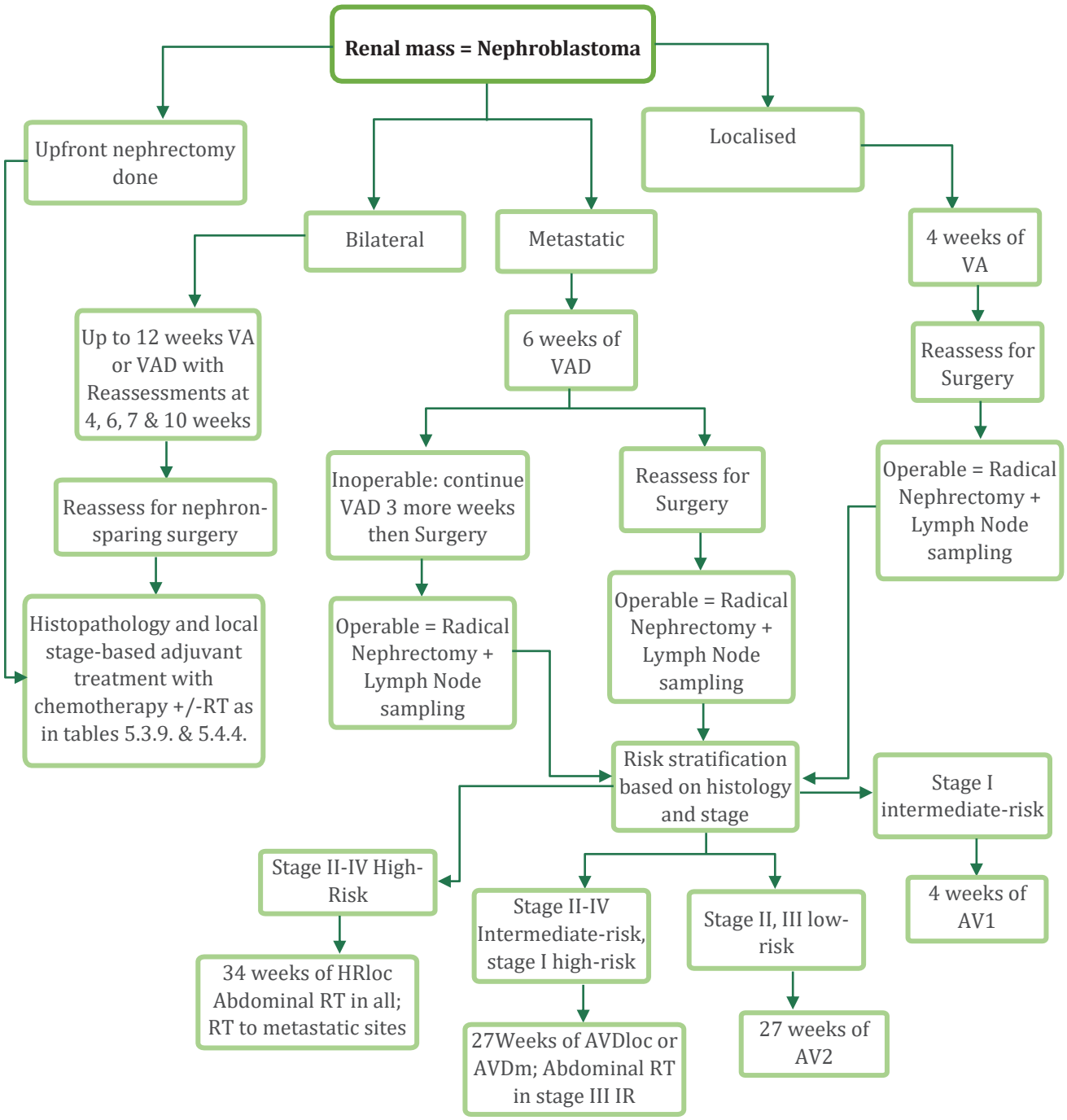


Figure 5.2. Treatment algorithm for Nephroblastoma

Pre-surgery chemotherapy for tumours where upfront surgery is not possible (inoperable tumours):

Table 5.3.5. Localised Disease: VA regimen

Drug	Week				
	1	**2**	3	4	
Vincristine 1.5mg/m2 IV push over 5min (0.05mg/kg if <10kg BWT or BSA <0.6m^2)	*	*	*	*	**Reassess radiologically and consult Surgery**
Actinomycin D 0.05mg/kg IV push over 5-10min (adjust dose for infants to 2-thirds)	*		*		

Table 5.3.6. Bilateral Disease: VA regimen

Drug	Week					Week				Week				
	1	2	3	4		5	6	7		8	9	10	11	12
Vincristine 1.5mg/m2 IV push over 5min (0.05mg/kg if <10kg BWT or BSA <0.6m^2)	*	*	*	*	**Stop and reassess. If good response, continue**	*	*	*	**If ongoing good response, may continue chemotherapy**				*	
Actinomycin D 0.05mg/kg IV push over 5-10min (adjust dose for infants to two-thirds)	*		*			*							*	

Table 5.3.7. Metastatic Disease/Bilateral Disease: VAD regimen

Drug	Week						Chest X Ray. If no metastases evident, consult paediatric surgeons for nephrectomy If metastases evident on chest X Ray, give 3 more cycles	Week			Consult Surgery
	1	2	3	4	5	6		7	8	9	
Vincristine 1.5mg/m^2 IV push over 5min (0.05mg/kg if <10kg BWT or BSA <0.6m^2)	*	*	*	*	*	*		*	*	*	
Actinomycin D 0.05mg/kg IV push over 5-10min (adjust dose for infants to two-thirds)	*		*		*			*		*	
Doxorubicin 50mg/m^2 in 0.9% saline IV over 1-2 hours	*				*					*	

Table 5.3.8. Adjuvant Treatment Regimens:

Drug	AV1	AV2	AVDloc	AVDm	HRloc
Vincristine (V) 1.5mg/m^2 Day 1 only	x 4 doses weekly	x 20 weekly doses in week 1-8, 11-12, 14-15, 17-18, 20-21, 23-24, 26-27	x 20 doses in week 1-8,11-12, 14-15,17-18,20-21, 23-24,26-27	Weekly doses in week 1-8,11-12, 14-15,19-20, 22-24, 26-27	
Actinomycin D (A) 0.05mg/kg Day 1 only	x 1 dose in week 2 only	x 9 doses in week 5,8,11,14,17,20, 23,26	x 9 doses week 2,5,8,11,14,17,20,23,26	x 8 doses in week 2,5,8,11, 14, 19,22-23, 26	
Doxorubicin (D) 45mg/m^2 Day 1 only			x 4 doses Wk 2, 8, 14, 20	X 5 doses in Week 2,8,14,22,26	
Doxorubicin (D*) 50mg/m^2 Day 1 only					In Week1,7,13,19,25,31,
Carboplatin (J) 200mg/m^2 Days 1-3					In Week 4,10,16,22, 28,34
Etoposide (E) 150mg/m^2 day 1-3					In Week 4,10,16,22, 28,34
Cyclophosphamide (C) 400mg/m^2 Day 1-3					In Week1,7,13,19,25,31

The following regimens will apply when tumour resection is done upfront:

- Regimen UH-1 and UH-2 for high-risk tumors such as anaplastic nephroblastoma
- Regimen DD4A or Regimen M for stage IV favorable-histology nephroblastoma

- For patients with stage I and II favorable-histology nephroblastoma with LOH of 1p and 16q, doxorubicin has been added to vincristine and dactinomycin (ActinomycinD) while those without LOH of 1p and 16q will get regimen EE4A

Table 5.3.9. Treatment options for nephroblastoma following up-front nephrectomy

Stage	Histology + Cytogenetic studies + Other parameters	Treatment
I	FH, > 2yrs of age	Nephrectomy + Lymph node sampling followed by Regimen EE-4A
	FH + LOH 1p/16q	Nephrectomy + Lymph node sampling followed by Regimen DD-4A
	FA or DA	Nephrectomy + Lymph node sampling followed by Regimen DD-4A + RT
II	FH	Nephrectomy + Lymph node sampling followed by Regimen EE-4A
	FH + LOH 1p/16q	Nephrectomy + Lymph node sampling followed by Regimen DD-4A
	FA or DA	Nephrectomy + Lymph node sampling followed by Regimen DD-4A + RT
III	FH with or without positive lymph nodes	Nephrectomy + Lymph node sampling followed by RT + Regimen DD-4A
	FH with LOH 1p or 16q	Nephrectomy + Lymph node sampling followed by RT + Regimen M
	FA	Nephrectomy + Lymph node sampling followed by RT + Regimen DD-4A
	DA	Nephrectomy + Lymph node sampling followed by abdominal RT + Regimen UH1
IV	FH + Isolated lung nodules	Nephrectomy + lymph node sampling followed by abdominal RT +/- bilateral lung RT + Regimen DD-4A or Regimen M
	FH + LOH 1p & 16q	Nephrectomy + lymph node sampling followed by abdominal RT + RT to metastatic sites + Regimen M
	FA	Nephrectomy + lymph node sampling followed by abdominal RT +/- bilateral lung RT + other metastatic sites Regimen DD-4A
	DA	Nephrectomy + lymph node sampling followed by abdominal RT +/- bilateral lung RT + other metastatic sites + Regimen UH2 or Regimen I

LOH = loss of heterozygosity, FA = focal anaplasia, DA = diffuse anaplasia, FH = favourable histology

Table 5.4.1. Treatment regimens for nephroblastoma following up-front nephrectomy

Regimen Name	Regimen Description	Doses
Regimen EE-4A	Vincristine, dactinomycin × 18 weeks post nephrectomy ***(13 doses of vincristine and 7 doses of dactinomycin)***	**Vincristine 1.5mg/m²** given weekly in Weeks 1 -10,12, 15, 22 **Dactinomycin 0.05mg/Kg** given in weeks 0, 3, 6, 9, 12, 15, 18
Regimen DD-4A	Vincristine, dactinomycin, doxorubicin × 24 weeks; baseline nephrectomy or biopsy with subsequent nephrectomy ***(15 doses of vincristine, 5 doses of dactinomycin, and 4 doses of doxorubicin)***	**Vincristine 1.5mg/m²** given in weeks 1-10, 12, 15, 18, 21, 24 **Dactinomycin 0.05mg/Kg** given in weeks 0, 6, 12, 18, 24 **Doxorubicin 45mg/m²** given in Weeks 3, 9 & 30mg/m² in weeks 15, 21
Regimen I	Vincristine, doxorubicin, cyclophosphamide, etoposide × 24 weeks post nephrectomy ***(9 doses of vincristine, 4 doses of doxorubicin, 7 cycles of 3 or 5 daily doses of cyclophosphamide and 3 cycles of 5 daily doses of etoposide)***	**Vincristine 1.5mg/m²** 1, 2, 4,5, 6,7,8, 10, 11 **Doxorubicin 45mg/m²** (1.5mg/Kg for patients <33Kg body weight) in weeks 0, 6, 18, 24 **Cyclophosphamide 440mg/m²** (14.7mg/Kg if weight<30Kg) Day 1-3 in weeks 3, 9, 15, 21 & Day 1-5 in weeks 6, 12, 24 **Etoposide 100mg/m²** (3.3mg/Kg if weight<30Kg) Day 1-5 in weeks 9, 15, 21
Regimen M	Vincristine, dactinomycin, doxorubicin, cyclophosphamide, and etoposide x 24 weeks with subsequent radiation therapy	9 doses **of Vincristine 1.5mg/m²**, 5 doses of **dactinomycin 0.05mg/Kg**, 5 doses of **doxorubicin 30mg/m²**, 4 cycles of 5 daily doses of **Cyclophosphamide 440mg/m²**, and 4 cycles of 5 daily doses of **Etoposide 100mg/m²** Dactinomycin and doxorubicin are given together, and cyclophosphamide and etoposide are given together
Regimen UH1	Vincristine, doxorubicin, cyclophosphamide, carboplatin, and etoposide × 30 weeks	15 doses of Vincristine, 5 doses of cyclophosphamide, 5 single doses of cyclophosphamide, 5 cycles of 4 doses of cyclophosphamide, 5 doses of carboplatin, and 5 cycles of 4 doses of etoposide for stage IV with focal anaplasia
Regimen UH2	Vincristine, doxorubicin, cyclophosphamide, carboplatin, etoposide, vincristine, and irinotecan × 36 weeks	19 doses of vincristine, 5 doses of doxorubicin, 5 doses of cyclophosphamide, 5 cycles of 4 daily doses of cyclophosphamide, 5 doses of carboplatin, 5 cycles of 4 daily doses of etoposide, and 2 cycles of 5 daily doses of irinotecan for stage II–IV with diffuse anaplasia

SURGICAL TREATMENT OF NEPHROBLASTOMA

Goals of the surgery

- To perform safe surgery
- Remove the kidney without intraoperative spill
- Sample lymph nodes: Lymph node pathology is an essential component of proper staging of Nephroblastoma. When the lymph node status is unknown with favorable tumours that otherwise may not need aggressive chemotherapy or radiation therapy will be over treated.
- Document all findings such as preoperative or intraoperative tumour rupture, extension into other structures and presence of peritoneal metastases.

The Role of Imaging in Surgery

Prior to surgical options radiological imaging is crucial. Imaging preoperatively has been known to reduce complications during surgery such as haemorrhage that could be up to 50mL/Kg.

Radiological imaging helps to assess: (See radiological guidelines above)

i. The presence of two functioning kidneys
ii. Contralateral tumour
iii. Evidence of intravascular tumour extension
iv. The organ of origin of the tumour
v. The presence or absence of metastases (such as lung).

Steps of the surgical procedure (Radical Nephroureterectomy)

Complete radical nephroureterectomy without capsular violation and adequate lymph node sampling is the objective for local control in nephroblastoma.

The renal tumour is resected via an adequate subcostal or thoracoabdominal incision. A flank or paramedian incisions are not be used because they are associated with higher complications and offer limited exposure.

Inspection of the abdomen should include looking for intraperitoneal spread and liver metastases. The vena cava, should also be palpated to assess for intravascular tumour extension. Bloody peritoneal fluid is considered a marker for tumour rupture. Prior to actual nephrectomy it should be confirmed that the tumour can be removed without the radical resection of adjacent organs, otherwise neoadjuvant chemotherapy should be considered before Nephrectomy (This applies especially when upfront nephrectomy is being considered). Because of improved imaging, routine exploration of the contralateral kidney is no longer needed

The colon is mobilized medially off the renal bed to expose the kidney and renal hilum (kockerization). Renal biopsy can be done if decision is to abandon the operation due to inoperability though this upstages the tumour due to tumour spillage.

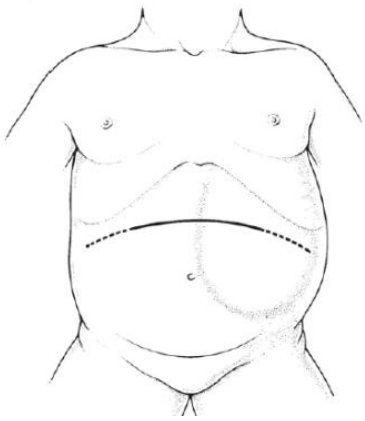
Lymph node sampling in the renal hilum and along the vena cava or aorta is critical for adequate staging. Even in children with stage IV disease, local staging is critical as it will determine whether or not abdominal radiotherapy is utilized in treating the patient. Lymph node clearance is not known to improve local tumour control.

The ureter is divided close to the bladder to avoid creating a "diverticulum "on the bladder which might produce recurrent urinary tract infection. If the tumour involves the upper pole, the adrenal gland may be resected with tumour. The adrenal gland may be preserved in lower pole lesions.

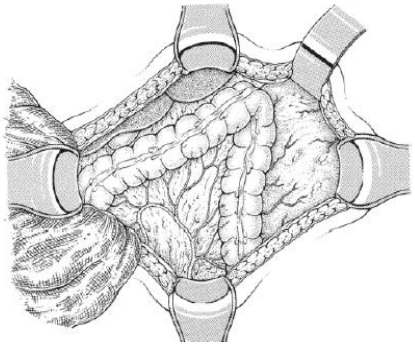
In the event of large tumours where the hilum is not visualised even after neoadjuvant chemotherapy, the dissection can be started from the lower pole then proceeding to identifying the ureter. Thereafter follow the ureter proximally to the renal pelvis to identify the hilum. Adhesions to the diaphragm and spleen may have to be released prior to dissection at the hilum. In this instance of the large tumour that's adherent to the diaphragm, the ipsilateral adrenal gland may need to be taken out with the tumour.

Nephron Sparing Surgery (NSS) of one or both sides are advocated in bilateral Nephroblastoma (Carachi R, 1994).

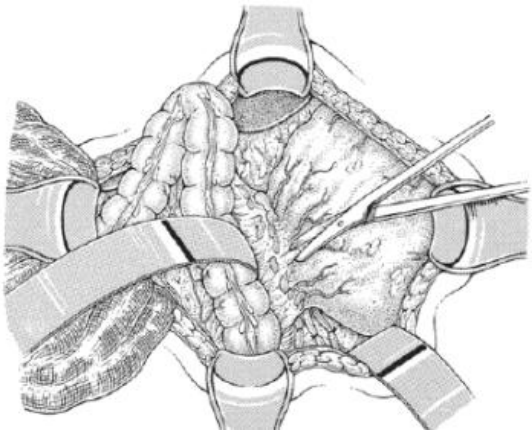
For Nephroblastoma in Horse shoe kidney, Intrahepatic and suprahepatic inferior vena cava (IVC) involvement after neoadjuvant chemotherapy surgery should be done at centers that have substantial experience in this peculiar nephroblastoma presentation. Paediatric Surgical unit at UTH have a good experience with complicated cases of nephroblastoma of such presentations and any clinician having such unique case should refer to UTH or have an in-depth discussion with the surgeons at the institution.



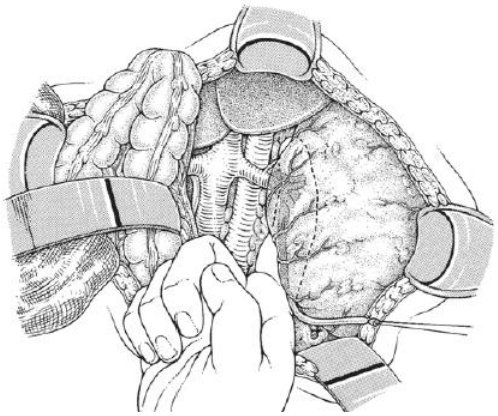
A generous transverse upper abdominal incision on the side of the tumor, extending across the contralateral rectus muscle, allows complete exposure of the kidney and access to its pedicle in particular the side of the tumour.



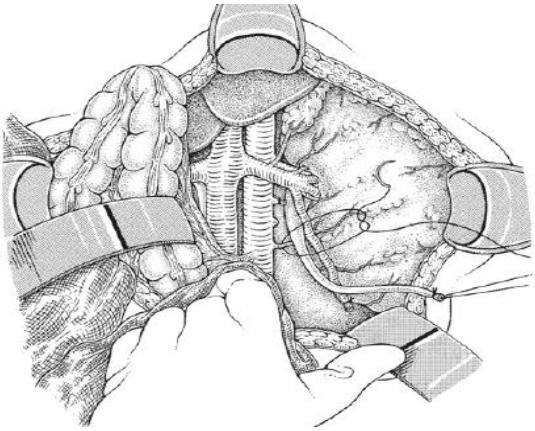
The abdominal contents are carefully examined for liver and peritoneal secondaries.

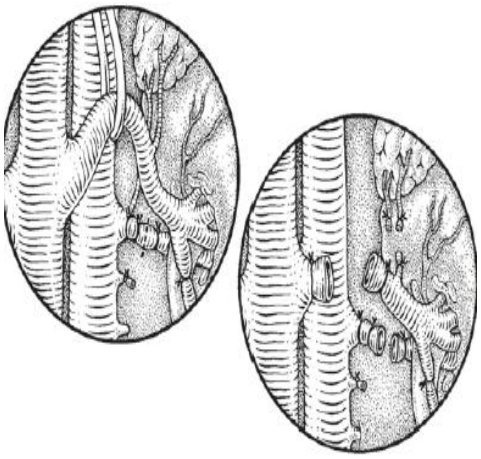


The colon with its mesentery is dissected carefully from the anterior surface of the tumour after first dividing the lateral peritoneal attachment

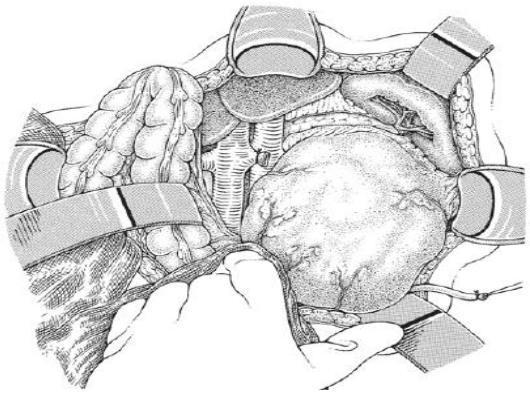


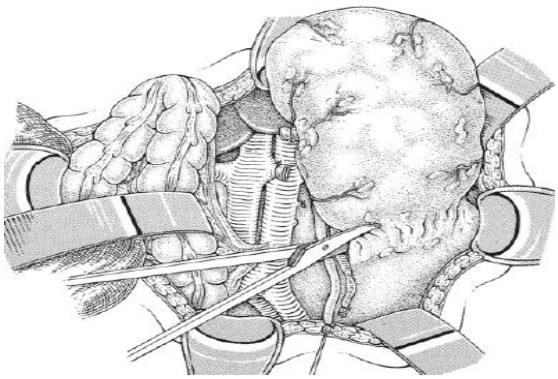
The ureter and gonadal vessels are ligated well below the kidney and may now be transected. The renal vessels cross in front of the ureter and renal pelvis, so this is used as a guide to find them as dissection continues cranially.





The renal vein is gently mobilized and elevated with a vascular sling to expose the renal artery, which is typically situated behind the upper border of the renal vein. It is preferable to ligate and divide the renal artery first so as to prevent swelling of the kidney with arterial blood. Due to the size of the tumour, this sequence of ligation is not always possible.





The superior dissection is done on the left side, care is taken not to damage the spleen and tail of the pancreas. On the right side, the tumour may be stuck to the undersurface of the liver, therefore Care is taken during separating capsule. The adrenal gland is removed only if the tumor is in the upper pole of the kidney

The kidney within Gerota's fascia is lifted out of the abdomen and the posterior dissection is completed under direct vision. The renal bed is inspected following removal of the kidney. Remaining lymph nodes on the great vessels are sampled and separately labelled for histology, Titanium clip to renal bed may be needed for further radiotherapy if available

(Spitz and Coran, 2013)

Table 5.4.2. Pertinent helpful operative documentation for post-operative oncological treatment:

Clearly document the following in the referral notes or attach surgical notes detailing the following:

S/N	Parameter
i.	Evidence of tumour rupture
ii.	Evidence of tumour spill
iii.	Lymph nodes sampled or not, If sampled number of lymph nodes should be stated
iv.	Presence of vascular invasion
v.	Presence of metastases
vi.	Complete tumour excision or not
vii.	Unilateral or bilateral disease
NB: 1. The above components should always be stated in the operative notes 2. When referring the patient to the oncologist always attach operative notes	

Table 5.4.3. Radiotherapy in Nephroblastoma

<table>
<tr><td>Indications</td><td colspan="2">1 Based on Histology:
a. All patients with unfavourable histology receive radiotherapy to the flank despite the stage.
b. Patients with Favourable histology who are post-operative with high-risk features for local recurrence include;
i. Incomplete resection
ii. Positive margins
iii. Nodal involvement
iv. Residual thrombus in the IVC, renal vein and ureter
v. Tumour rupture (Rupture is also considered in tumour positive ascitic fluid/bloody peritoneal fluid and traumatic rupture of the tumour preoperatively with the result that tumour cells are disseminated throughout the peritoneal or retroperitoneal space)
vi. Tumour Spill at operation (Spill is also considered to have occurred if the renal vein or ureter are transected where they contain tumour)
2 Based on Stage:
a. Patients with stage I and II favourable histology do not need radiotherapy.
b. Patients with stage III and IV require radiotherapy to flank and/or abdomen</td></tr>
<tr><td>Procedure</td><td colspan="2">• There are challenges of initiating radiotherapy treatment in children due to non-familiarity with machines and presence of strangers (staff).
• Play therapy is used to help the children to get familiar with the environments in which the treatment will occur, it should be done several weeks before commencement of treatment.
• Patient is simulated and treated in a supine position
• Body mask is used for immobilization.
• CT simulation is used to acquire images, which are used to make a treatment plan.
• Plan verification is done and treatment is commenced.</td></tr>
<tr><td>Fields</td><td colspan="2">Field size is individualised as follows;
• Whole abdomen RT (extensive tumour spillage or peritoneal metastases)
• Flank or abdominal RT (localized tumours, tumour bed post-surgery)
• Lung irradiation (Lung metastases)
• Boost radiation (tumour bed for residual disease post-surgery)</td></tr>
<tr><td>Doses</td><td colspan="2">Doses range from 10-20Gy, depending on stage, response to treatment and area being irradiated. (Details in the table 5.4.4. below)</td></tr>
<tr><td>Side effects</td><td>ACUTE</td><td>LATE</td></tr>
<tr><td></td><td>Fatigue
Nausea
Vomiting
Anorexia
Skin toxicity (erythema, dermatitis)
Abdominal pain or cramping
Haematological toxicity</td><td>Growth asymmetry
Height stunting
Organ underdevelopment (kidney, liver)
Renal dysfunction
Liver dysfunction
Secondary malignancies
Lung fibrosis
Cardiovascular effects
Infertility</td></tr>
</table>

Table 5.4.4. Recommendations for Radiation therapy for patients with upfront nephrectomy

Local/Locoregional Disease				
	Stage I	Stage II	Stage III	Stage III (diffuse spill, peritoneal metastasis, preoperative rupture)
Favorable histology	No RT	No RT	10.8 Gy	10.5 Gy
Focal anaplasia	10.8 Gy	10.8 Gy	10.8 Gy	10.5 Gy
Local/Locoregional Disease				
Diffuse anaplasia	10.8 Gy	10.8 Gy	19.8 Gy	10.5 Gy + 9 Gy boost
Metastatic Disease				
	Stage IV Lung	Stage IV Liver	Stage IV Brain	Stage IV Bone
Favorable histology	10.5 Gy for age <12 months; 12 Gy for age >12 months	19.8 Gy +/- 5.4 to 10.8 Gy boosted	21.6 Gy + 10.8 Gy boost for age <16 years; 30.6 Gy for age >16 years	25.2 Gy for age <16 years; 30.6 Gy for age >16 years
Focal or diffuse anaplasia	10.5 Gy for age <12 months; 12 Gy for age >12 months	19.8 Gy +/- 5.4 to 10.8 Gy boosted	21.6 Gy + 10.8 Gy boost for age <16 years; 30.6 Gy for age >16 years	25.2 Gy for age <16 years; 30.6 Gy for age >16 years

RT = radiation therapy.

Requires whole-abdominal RT in 1.5 Gy daily fractions. Patients with diffuse unresectable peritoneal implants receive 21 Gy.

Whole-lung irradiation is given in 1.5 Gy daily fractions.

Not all patients receive radiation therapy.

A boost is given for macroscopic disease.

Table 5.4.5. Post-treatment follow-up recommendations

Recommendations on Follow-up after treatment:

	Investigation	**Frequency**	**Duration after stopping therapy**
In all patients	Clinical examination	Every 3 months	1st year
		Every 6months	2nd & 3rd year
	CXR	Every 3 months	1st year
	Ultrasound Abdomen	Every 6months	2nd & 3rd year
	Serum creatinine	Every 6months	
	Blood pressure	Every visit	
In patients who have received anthracycline (Doxorubicin)	Echocardiography	Every 2 years	
Patients with Metastatic unilateral nephroblastoma	CXR	Every 3 months	
	Ultrasound Abdomen	Every 3 months	
	Serum creatinine	Every 6months	
	Blood pressure	Every 6months	
Irradiated patients	X-ray bony structures, yearly to full growth, Spine+/- pelvis	Yearly to full growth Every 5 years thereafter	
Bilateral tumours	CXR	Every 2-3months	1st & 2nd year
	Ultrasound Abdomen	Every 6months Every year	3rd & 4th year Until 10 yrs post Treatment
	Proteinuria	Every 6months	
Partial Nephrectomy	Ultrasound Abdomen	Every 3 months	1st & 2nd year
		Every 6months	3rd & 4th year
		Every year	Until 9-10 yrs post Treatment
Patients with underlying syndromes who have completed therapy for nephroblastoma	Ultrasound Abdomen	Every 3 months	Until 5 years for *WT1*-related syndromes & 8 years for Beckwith-Wiedemann syndrome
Patients with nephrogenic rests	Ultrasound Abdomen		Until at least 5 years old

- ***A child with an abdominal mass must be subjected to investigations at the local facility that include abdominal colour doppler ultrasound, chest x-ray, urinalysis, Blood pressure check, full blood count, kidney and liver function tests.***

- ***If CT scan is available a contrast enhanced CT of the chest, abdomen and pelvis should be done.***

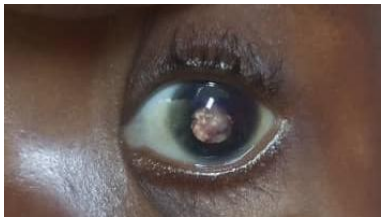
- ***If imaging is suggestive of nephroblastoma the child should be referred to a designated childhood cancer treatment unit for further investigation and treatment.***

5.6. RETINOBLASTOMA (RB)

Definition - an ocular malignancy where the tumour arises from primitive retinoblasts of the developing retina, with loss of function of the Rb tumour suppressor gene (13q14).
It is the most common primary ocular malignancy of childhood (Pizzo et al, 2015).
Retinoblastoma can either be hereditary (25-30%) or sporadic (70-75%).
Lifetime incidence is 1 in 15–20,000, and there is no gender or racial predilection.
Globally the median age at presentation is under 12 months in heritable cases, and closer to 24 months in sporadic cases. In Zambia, the reported average age at presentation was 31.1 months (Nyaywa et al, 2016).
Presentation after the age of 6 years is rare.

Clinical Presentation

- Commonly presents with **leukocoria** (white pupillary reflex) followed by strabismus.



Leukocoria in the left eye

Child with strabismus (esotropia or squint)

- Other symptoms and signs include proptosis, spontaneous hyphema glaucoma, orbital mass and features associated with distant disease dissemination (commonly in the bones, bone marrow and liver).
- Trilateral retinoblastoma presents with brain tumour in the pineal region with unilateral or bilateral ocular disease.

Diagnosis

A child presenting with signs and symptoms suggestive of retinoblastoma, should promptly be referred to an ophthalmologist for evaluation.
Evaluation should include history, clinical examination and examination under anaesthesia.
Examination under anaesthesia is crucial for staging the disease

- Careful scleral depression to evaluate the entire retina is necessary to confirm the diagnosis of retinoblastoma as well as to determine the exact location and extent of the tumour(s) and the tumour staging.
- Photographic documentation for future comparison is recommended. The wide-angle digital camera, RetCam can capture high resolution images of the posterior and peripheral retina for comparison of tumour progression and regression over time.
- Complete retinal examination of both eyes is necessary to rule out bilateral disease.

Investigations:

1. Investigations for Staging of Retinoblastoma

a. The intraocular extent of disease
   - Bi-dimensional ocular ultrasonography (B-scan and A-scan) of the globe can show the characteristic calcifications of RB

b. mThe orbital extent of disease
   - MRI scan of the head and orbits to confirm intraocular tumour, evaluate optic nerve involvement and brain involvement in cases of trilateral RB (CT scan can be done where MRI is not available)

2. Metastatic evaluation
   - Lumbar puncture: CSF for cytology
   - Full blood count
   - Liver function tests, ferritin and neuron-specific enolase
   - Bilateral bone marrow aspiration and biopsy
   - Abdominal US (liver/spleen)
   - CT scan of brain, head and abdomen
   - Bone scan
   - Biopsy of extraocular masses
   - Globe and optic nerve stump histopathology (if enucleation is done)

3. Genetic testing
   - Genetic testing for *RB1* mutation in the proband and family members using genetic sequencing
   - FISH
   - Methylation studies for epigenetic changes and multiplex ligation-dependent probe amplification (MLPA)

Table 5.4.6. Intraocular Classification of Retinoblastoma (ICRB) – ***Key for Vision Prognosis***

Group A (very low risk)	Retinoblastoma ≤ 3 mm (in basal dimension or thickness)
Group B (low risk)	Retinoblastoma > 3 mm (in basal dimension or thickness) or • Macular location (≤3 mm to foveola) • Juxtapapillary location (≤1.5 mm to disc) • Additional subretinal fluid (≤3 mm from margin)
Group C (moderate risk)	Retinoblastoma with: • Subretinal seeds ≤ 3 mm from tumour • Vitreous seeds ≤ 3 mm from tumour • Both subretinal and vitreous seeds ≤ 3 mm from tumour
Group D (high risk)	Retinoblastoma with: • Subretinal seeds > 3 mm from tumour • Vitreous seeds > 3 mm from tumour • Both subretinal and vitreous seeds > 3 mm from retinoblastoma
Group E (very high risk)	Extensive retinoblastoma occupying >50% globe or with • Neovascular glaucoma • Opaque media from haemorrhage in anterior chamber, vitreous or subretinal space • Invasion of postlaminar optic nerve, • choroid (>2 mm), sclera, orbit, anterior chamber

Table 5.4.7. Retinoblastoma overall staging system – ***Key for Child's overall Prognosis***

Stage	Description
0	Patient treated conservatively
1	Eye enucleated, completely resected on histopathological examination
2	Eye enucleated, microscopic residue disease
3	Regional extension a) Overt orbital disease b) Pre-auricular or cervical lymphadenopathy
4	Metastatic disease a) Hematologic metastasis (without CNS disease) 1. Single lesion 2. Multiple lesions b) CNS extension (with/ without any other site of regional/ metastatic disease Central nervous system extension (with or without any other site of regional or metastatic disease) 1. Pre-chiasmatic lesion 2. Central nervous system mass 3. Leptomeningeal and cerebrospinal fluid disease

*This staging is for the overall prognosis of the child and ICRB defines ocular or vision prognosis**

Treatment

Requires a MDT approach (ophthalmologists, paediatricians, paediatric oncologists, radiologists, radiation oncologists, pharmacists, nutritionists, social workers, counsellors, pathologists, nurses etc.)

Current treatment options include:

- Focal or local-regional therapies: laser photocoagulation, cryotherapy, thermotherapy, External Beam RT, plaque RT, sub-conjunctival chemo-reduction, intra-arterial chemotherapy, enucleation, orbital exenteration (Pizzo et al, 2015)
- Systemic therapy with chemotherapy
- Genetic counselling of both the patient and family members

Table 5.4.8. Treatment Approach based on Laterality of Disease

Extent of Disease	Feature and characteristics	Recommend treatments
Unilateral retinoblastoma	Group A, B, C Group D, E (Ocular Stage) without buphthalmos	**Eye-conserving therapy** (done in institutions performing sequential chemotherapy combined with laser, cryotherapy, and/or RT) **Non-eye conserving therapy** (upfront enucleation+/-chemo or RT based on histopathology findings as below)
	Pathologic finding of post laminar invasion, or invasion of the surgical margins of the optic nerve, or extension through the sclera into the orbital tissues	Theses pathological features require treatment with 6 x VJE in adjuvant setting
	When Buphthalmos present	NACT X 2 cycles of VJE followed by enucleation then 4 cycles of adjuvant chemotherapy (ACT)
	Orbital retinoblastoma only with MRI or CT findings of optic nerve or extrascleral invasion	NACT X 2-3 cycles of VJE followed by enucleation then 5-6 cycles of VJE (Total of 8 cycles)+ RT
	Overt Orbital-Metastatic retinoblastoma -Stage III-IV	Palliative treatment: Standard dose chemotherapy VJE, at discretion of treating physician or metronomic therapy with intention of life prolongation. Consider palliative RT

Bilateral retinoblastoma	Group A, B, C Group D, E (Ocular Stage) without buphthalmos	**Eye-conserving therapy** (done in institutions performing sequential chemotherapy combined with laser, cryotherapy, and/or RT) **Non-eye conserving therapy (**upfront enucleation+/-chemo or RT based on histopathology findings as below)
	Intraocular retinoblastoma with one or both eyes with buphthalmos	Preoperative chemotherapy 2 cycles VJE combined with sequential laser/cryotherapy to the eye on conservative treatment delivered with every cycle of chemotherapy Adjuvant chemotherapy 4 cycles VJE combined with sequential laser/cryotherapy to the eye on conservative treatment delivered with every cycle of chemotherapy. Complete a total of 6 cycles of chemotherapy ± RT based on histopathology findings
	One or both eyes with extraocular/orbital retinoblastoma only with MRI or CT findings of optic nerve or extrascleral invasion	Neo-adjuvant chemotherapy 2-3 cycles VJE - Bilateral enucleation after cycle 2 or 3 of VJE Adjuvant chemotherapy 5-6 cycles VJE to complete a total of 8 cycles) ± RT based on histopathology findings
	Overt orbital-metastatic retinoblastoma - Stage III-IV	Palliative treatment, either standard dose chemotherapy or metronomic therapy with intention of life prolongation. Consider palliative RT
Trilateral retinoblastoma	Unilateral or bilateral with suprasellar tumour or pineal gland tumour	Therapies include radiation, combination of systemic chemotherapy (platinum-based regimens), intrathecal chemotherapy, and surgical resection/craniotomy in combination with radiation and/or chemotherapy.

Table 5.4.9. Treatment Regimen

Medicine Name	**Administer every 3-4wks for 6-12 cycles depending on the stage of disease Medicine doses**	
	≥3yrs/>10kg body weight	<3yrs/<10kg body weight
Vincristine **(V)**	1.5mg/m^2 IV push over 5 min day 1	0.05mg /kg IV push over 5 -10min day1
Etoposide **(E)**	100mg/m^2 IV infusion over 1 hr day1,2,3	5mg /kg IV infusion over 1hr day1, day2
Carboplatin **(J)**	600mg/m^2 IV infusion over 1hr day1	18.6mg/kg IV infusion over 1 hour day 1

Table 5.5.1. Radiotherapy in Retinoblastoma

Indications	• In early disease all patients receive brachytherapy as the primary treatment of choice • Residual disease after chemotherapy and local therapy • Diffuse vitreous seeds • Recurrence after chemotherapy • High risk features post enucleation (sclera involvement, extraocular extension and optic nerve involvement) • CNS metastatic disease • Recurrent disease if patient did not receive RT in the initial treatment.	
Procedure	• There are challenges of initiating radiotherapy treatment in children due to non-familiarity with machines and presence of strangers (staff). • Play therapy is used to help the children to get familiar with the environments in which the treatment will occur, it should be done several weeks before commencement of treatment. • Patient is simulated and treated in a supine position • Face mask is use for immobilization. • CT simulation is used to acquire images, which are used to make a treatment plan. • Plan verification is done and treatment is commenced.	
Fields	Radiotherapy is given to the affected side of the head (orbit) It is associated with a lot of side effects in these children. The side effects are more common with the use of 2D treatment techniques. Advanced treatment techniques like IMRT/Image-Guided RT (IGRT) have better outcomes with fewer side effects.	
Doses	Traditional EBRT doses of 40 to 50 Gy The use of doses less or equal to 36Gy have been reported with better tumour control (Kim J. Y, 2015)	
Side effects	**ACUTE**	**LATE**
	Fatigue Loss of eye lashes and eye brows Glaucoma Skin toxicity	Cataracts Retinal detachment Dry eyes Facial asymmetry Secondary malignancies Optic nerve damage (sight loss)

Recommended Follow-up of Retinoblastoma Patients:

- Every 4 weeks during treatment
- Every 2 to 3 months during the first year after treatment
- Every 3 to 6 months until the age of 6 to 7 years
- Every year after that until young adulthood

During follow up visits:

1. A full eye examination including dilated fundoscopy should be done and younger children may need examination under anesthesia.
2. Examination should include eye socket examination if the child's eye was removed.
3. Visual rehabilitation and support should be offered to the child.
4. MRI brain may be done every six months or earlier if indicated to look for tumours of the pineal gland (trilateral retinoblastoma) in children who have had tumours in both eyes (bilateral retinoblastoma).
5. Monitor for complications of chemotherapy and radiotherapy
6. Monitor for secondary tumours as these patients are at high risk for tumours such as osteosarcoma.
7. Siblings to affected child should also have a dilated eye examination as soon as possible in the first month of life until the age of 7 years.

- ***A child presenting with any feature suggestive of retinoblastoma like leukocoria, should promptly be referred to an ophthalmologist for fundoscopic examination under anaesthesia and ocular ultrasound for clinical diagnosis, followed by a MDT-derived plan of treatment***
- ***The primary goal of RB treatment is to save the child's life. Vision and eye globe salvage are secondary goals and should not be allowed to undermine the primary goal.***

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CHAPTER 6. SUPPORTIVE CARE GUIDELINE

Febrile Neutropenia

Febrile neutropenia (FN) is a life-threatening complication of cancer therapy. FN is a medical emergency that requires thorough patient evaluation and prompt initiation of broad-spectrum empiric antibiotics.

- For this guideline,
  - Fever is defined as an axillary temperature of 37.8°C measured once or axillary temperature of ≥ 37.5°C measured twice at time points an hour apart (Esther M, 2024, unpublished).
  - Clinically significant neutropenia in the context of FN is defined as an absolute neutrophil count (ANC) of <0.5 x 10^9/L (500 cells/$mm^{3)}$ or an ANC expected to fall below 0.5 x 10^9/L (500 cells/mm^3) within 48 hours. Profound neutropenia is defined as ANC < 0.1x 10^9/L, while prolonged neutropenia is defined as neutropenia lasting >7 days (Freifeld et al. 2011).

- Critical assessment of the child with FN begins by obtaining a complete medical history and performing a thorough physical examination. The initial assessment should be thorough as it will direct diagnostic evaluations.
- Initial work up includes a complete blood count, a comprehensive metabolic panel and blood cultures from both a central venous catheter, if present, and peripheral blood sample.

Risk Assessment Criteria

Patient is considered High Risk if **ANY ONE** of the following is present:

- Signs and symptoms of sepsis
- ANC < 0.1 X 10^9/L
- Focal infection: Mucositis, Abdominal pain; Perianal tenderness
- Patient receiving therapeutic Dexamethasone or Prednisolone
- Infant ALL and AML
- Induction or Intensification chemotherapy

Discharge Criteria

- Afebrile for 24 hours
- Negative blood culture for 48 hours
- No signs of localized or documented infection
- Performance status back to baseline
- ANC 0.2 x 10^9/L and rising steadily
- 24- hour caregiver who:
  - Is able to take patient's temperature
  - Lives within 1 hour of accessible medical care
  - Has phone access
  - Has transportation at any time

Risk Factors for Invasive Fungal Infection (IFI)

Patient is considered High Risk if any of the following is present:

- Signs/symptoms of sepsis with neutropenic fever
- Persistent fever >4 days
- Prolonged fever and ANC <0.1 x 10^9/L
- Mucositis
- Steroid or high-dose cytarabine therapy
- ALL (Induction, DI), AML, severe aplastic anaemia
- Allogeneic HSCT patient< 100 days from transplant
- Prolonged use of total parenteral nutrition/lipids
- Prolonged use of broad-spectrum antibiotics
- Previous IFI history
- Active Graft-Versus-Host Disease (GVHD)/prolonged immunosuppressive therapy

Signs and Symptoms of Sepsis

- Chills
- Abnormal vitals- *see table 6. below for age-appropriate readings*

Table 6. Vital Sign Ranges According to Patient Age

Age	Heart Rate	Systolic BP
1 week to 1 month	> 180 and < 100	80
1 month to 1 year	> 180 and < 90	80
1 year to 5 years	> 140	75
5 years to 12 years	> 130	80
12 to 18 years	> 110	90

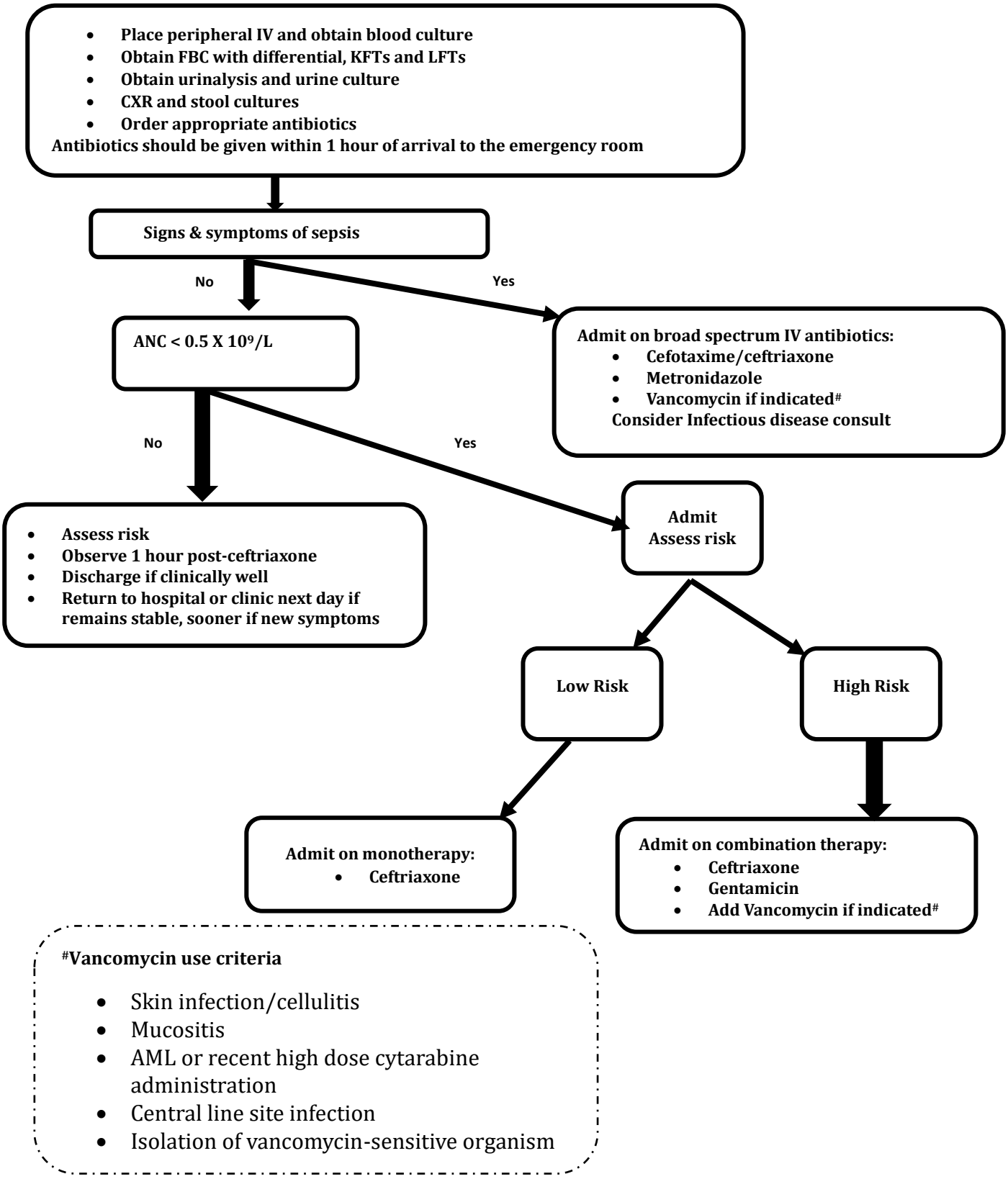

Figure 6. Fever and Neutropenia in Children Receiving Cancer Treatment

6.1. RATIONAL USE OF ANTIBIOTICS

Antibiotics are essential in prevention and treatment of infections, but irrational use of these agents may lead to resistance. Rational use of Antibiotics constitutes a constant pre-occupation in the clinical area. Prescribers must ensure that the prescription of antibiotics is aligned with the WHO Access, Watch & Reserve (AWaRe) standard and guideline.

The AWaRe classification is intended to be used as a tool to better support antibiotic monitoring and stewardship activities. This classification is included on the WHO model lists of Essential Medicines List. The AWaRe system classifies antibiotics in three groups: Access, Watch and Reserve, depending on the level of clinical importance and the risk of promoting resistance.

- ACCESS: these are essential first and second choice treatments for empirical treatments options against a wide range of commonly encountered susceptible pathogens
- WATCH: This class, which includes most of the highest priority agents, has higher resistance potential. These antibiotics essential for first and second choice treatment options for a limited number of specific infectious syndromes, are considered key targets of stewardship programs and monitoring.
- RESERVE: These antibiotics should be reserved for treatment of confirmed or suspected infections due to multidrug resistant organisms. This class is the 'last resort' option.

It is advisable during the prescription and use of the antibiotics to make use of:

- The culture and sensitivity tests
- The local antibiogram

Therefore, prescribers should indicate for each patient:

- That culture has been ordered or not
- That the antibiotic used at a particular time is for empirical treatment or not.
- The duration of treatment for each antibiotic.

Antibiotic use during cancer chemotherapy treatments is critical to treat infections and for prophylactic use owing to the higher risk of infectious complications. It must be noted that using antibiotics when not needed could affect the efficacy of these therapies.

6.2. SAFE HANDLING OF CHEMOTHERAPY

Background

The purpose of this section is to provide guidance on the safe prescribing, reconstitution, dispensing, and administration of chemotherapy and related agents used in the treatment of cancer. Medication errors can occur for a number of reasons including procedural, technical and behavioural reasons.

The aim is to prevent and minimize medication errors and thereby achieve the following:

- Protection of the patient
- Protection of health personnel and family caregivers
- Protection of the environment by safe handling and disposal of chemotherapy waste

Prescribing, dispensing and administration errors relating to chemotherapy that result in patient harm are well documented in literature as well as effects on the caregivers and the environment.

Competency and Skills

All clinical staff required to prescribe, reconstitute and administer chemotherapy and related therapy should receive appropriate training and should demonstrate competency.

Safe prescribing of chemotherapy

The Prescriber is responsible for:

- Making treatment decisions and ensuring that each treatment is appropriate for the patient according to diagnosis, laboratory parameters, performance status and organ function.
- Monitoring the effects of the treatment and ensuring appropriate medical review of patients during and after treatment.
- Ensuring that all professional and legal responsibilities are met with respect to prescribing.
- Prescribers and clinicians must ensure that the prescription for chemotherapy has the following:
    1. Patient name and two other unique identifiers (e.g. hospital number, or national identity card number)
    2. Diagnosis
    3. The date treatment is intended to be commenced.
    4. Name of the chemotherapy protocol to be given
    5. Intended duration of treatment and the number of cycles for treatment
    6. Response assessment tests to be performed after specified number of cycles
    7. Therapeutic goal of treatment (e.g. curative, palliative)
    8. Any treatment variations such as dose reductions
        - If dose reduction occurs, then the reduction factor should be clearly documented along with the reason for the reduction.
    9. The name and contact details of the physician completing the treatment plan

6.3. QUALITY ASSURANCE (QA)

These are a set of processes that are undertaken to ensure that standards are met and maintained.

Table 6.1. Standard operating procedures (SOPs) for safe chemotherapy handling

Type	Standard Operating Procedure
Cytotoxic Medicine	• Ensure that all medicines have been prescribed according to protocol and that there are no omissions with respect to the requirements of the protocols including chemotherapy, targeted therapy, pre-medication and supportive therapy. • Check that supportive adjuvant medication has been prescribed as per protocol. • Verify that the administration route for each medicine is correct and is specified. • Verify that the duration of infusion and diluent requirements are specified all the time. • Verify that the frequency and sequencing of administration is correct. • Ensure that the patient has no documented allergies/ hypersensitivity reactions to any of the medication prescribed.
Doses	• Verify that all doses are correct according to protocol, patient weight, BSA, creatinine clearance. • Verify maximum and cumulative doses are not exceeded for the dose or the course. • Verify dose reductions are correct according to the protocol, patient parameters. • Medicines should be systematically withdrawn from vials and diluted with fluids one at a time to avoid errors
Scheduling	• The date and time of the chemotherapy administration should be indicated. • Verify that the length of the treatment course and time interval between each cycle is appropriate for the protocol and tumour type. • Verify that the appropriate time period has passed between last cycle and current cycle. • It is important to maintain an up-to-date treatment history relating to all chemotherapy medicines, doses and treatment dates
Laboratory parameters	• Verify that the absolute neutrophil count and platelet count are appropriate for administration of the chemotherapy. • Verify that the renal and liver function is appropriate for the dose of the medicine to be administered. • Where appropriate, obtain results of other tests specific to certain medicine toxicities such as lung function prior to bleomycin, methotrexate levels, urine pH level for methotrexate, and ejection fraction for anthracyclines e.t.c.
Protocol variations	• Verify that variations from the original protocol are valid for the patient and protocol. • Ensure they are authorized by the prescriber and documented.

Medicine related interactions	• A medication history should be taken by the pharmacist at the initial and subsequent cycles to include prescribed medication, over the counter and herbal medication and must take into account any changes in medication during treatment. The pharmacist must investigate and advise on any potential medicine interactions.
Adverse Medicine reactions	• Details of previous and current adverse medicine reactions should be verified with the patient and documented. • Adverse medicine reactions may occur with chemotherapy agents, targeted therapies and supportive therapy during treatment and appropriate recording and reporting must be ensured. • Documentation of re-challenges and subsequent reactions is also essential

Labelling of chemotherapy

Labelling of chemotherapy is important to avoid errors. Labelling should be done in a systematic manner to ensure all important aspects are included.

Table 6.2. SOPs for chemotherapy labeling

Labelling	Standard Operating Procedure
Reconstituted medicine	• The name of the medicine should appear in generic form. • If the trade name is required, this should not form the main part of the medicine name • Abbreviations and chemical names are not acceptable
Strength of the medicine	• Where the medicine is in parenteral form, the total dose should be expressed as a total concentration e.g. 25mg in 52ml and the form of medicine and the medicine diluent where appropriate for infusion chemotherapy • Intended route of administration for parenteral therapy • Distinctive warning labels are to be placed on vinca-alkaloids, **"FOR INTRAVENOUS USE ONLY. FATAL IF ADMINISTERED BY ANY OTHER ROUTE"**
Beyond use date	• Indicate appropriately for reconstituted infusion chemotherapy
Cytotoxic warning label	• Chemotherapy must be labelled with a cytotoxic warning sticker in accordance with National Institute for Occupational Safety & Health (NIOSH) guidelines. • Suggested labelling is a permanent, adhesive purple cytotoxic warning label with the distinctive warning; "**Cytotoxic, Handle with Care**". • Cautionary and advisory labels must be added to the container as required.

6.4. CHEMOTHERAPY CALCULATIONS

Chemotherapy dose calculations are important and should be undertaken carefully to avoid errors.

- Calculations performed manually should be independently checked by the pharmacist.
- Computerized systems should be validated and implemented to ensure accuracy of automated calculations.
- In verifying the prescription, the pharmacist must have access to the following information:
  - The treatment protocols
  - The relevant laboratory results
  - The weight and height of the patient
  - The Patient's Body Surface Area (BSA) - must be recorded on the chemotherapy order and an independent check carried out [the BSA should be manually calculated using the Mosteller equation = [√height (cm) X weight (Kg)/3600]
  - In case of renal insufficiency – use appropriate formulas (Area under curve –AUC)

SAFE HANDLING OF CHEMOTHERAPY RECONSTITUTION

Table 6.3. Procedure for reconstituted chemotherapy handling

Category	Procedure
All Personnel handling antineoplastic (cytotoxic) medicines	• All that handle antineoplastic medicines must receive appropriate orientation, training and certification prior to assignment to the reconstitution unit.
	• Personnel in the reproductive age should indicate in writing that they understand the risks involved in handling antineoplastic agents
	• Baseline parameters for personnel should be recorded, including full blood count, Kidney and liver function, Cardiac function tests and Blood pressure
The pharmacist	• Ensure clinical verification of the medicine order including chemotherapy, targeted therapy and supportive medications are prescribed according to the medicine protocol, patient's treatment plan and patient parameters • Ensure clarification and resolution of any identified discrepancies with the prescriber are undertaken. • Ensure preparation of chemotherapy is done in accordance with the set standards. • All reconstitution processes should be carried out in a Class II B_2 or higher class Biosafety Cabinet (Class 3 or Isolator) • **NO** personal phones and jewellery (**ear, finger, nose tongue rings**), long and artificial nails should be worn in the reconstitution room. • The institutional phones designated for the compounding room should not be removed from the room except for maintenance purposes. • Prior to accessing the compounding room Donning of PPE, including Masks, ChemoPlus gowns, gloves, shoes and head covers must be done in the Anteroom before the red line. • NIOSH Certified N95 Masks shall be donned during the reconstitution

	process • Every volume of medicine withdrawn from the vial must be confirmed, written down by a colleague, and signed for by both personnel before transfer to the intravenous fluid bag. • Ampoules should not be admissible in the reconstitution room to eliminate the risk of cytotoxic medicine exposure to the staff. The pharmacist and Nurses should confirm the patient identifiers before chemotherapy is collected through the pass (hatch) for administration.

Administration of chemotherapy

Introduction:

- Current diagnosis, medical and medication history of relevance including treatment history.
- Details of any medicine allergies
- A patient treatment plan and an original or legible copy of the prescription. These should be completed with the detail specified in the prescribing section of this document
- Patient parameters (height, weight, BSA) and relevant laboratory values including blood counts, urea and electrolytes, liver function tests.
    - Nursing staff should confirm performance of required tests and results and contact the medical officer where results fall outside acceptable parameters
- Policies, procedures and equipment required for safe administration and handling of cytotoxic medicines and related waste including emergency procedure protocols, medications and the management of extravasation should be at hand.

Table 6.4. Chemotherapy administration procedure

Category	Standard Operating Procedures
Routes of administration	• Oral (PO) • Topical • IntraThecal (IT) • Intravenous (IV) bolus and infusion • Intramuscular (IM) • Subcutaneous (SC) and intradermal • Intraperitoneal
Procedures for administration	**1. Administration via the Oral route** Oral therapy carries the same risks in terms of toxicity and risk of medication errors as therapy administered by parenteral routes • Ensure that the patient can swallow the medication and that there are no risk factors for aspiration, if patient cannot swallow tablets/capsules consider alternative preparation e.g. solution • If an anti-emetic is required administer 30 to 90 minutes before administration of oral cytotoxic therapy unless instructed otherwise in the protocol. • Oral chemotherapy should be administered using the "**no touch technique'** when placing medication is in a disposable pill container. If the patient vomits within 30 minutes after ingestion, a further dose

	must not be administered again. ○ Inform the treating medical officer of the episode for further guidance. • Ensure appropriate education and precautions have been provided on how to take the medication prevent exposure for patients receiving therapy at home. **2. Topical chemotherapy** • Used in treating non-melanoma skin cancer and other skin conditions. • Medication may be in the form of an ointment, solution or suspension. The formulation should be applied in a thin layer to the affected area with an applicator at the frequency ordered by the prescriber (usually once or twice a day). • Care should be taken to avoid contact with the unaffected skin; the skin should be observed for hypersensitivity reactions. • The patient should be advised that the skin may be temporarily unsightly in appearance and local discomfort may be experienced during the application of the product but they need to report any "burning" pain. **3. Administration via the Intrathecal route** • Formal training and regular competency assessment for all staff involved in the administration of Intrathecal medicines should be instituted. • Staff administering intrathecal medicines must use checking procedures that includes a 'time out' involving at least two health professionals. • 'Time Out' is a final patient safety check undertaken immediately before commencing the treatment. It should be carried out in a quiet place without interruption. **4. Administration via the Intravenous route** • Intravenous therapy may be administered through a central or peripheral vein as a bolus, intermittent infusion or continuous infusion. For all prolonged infusions and vesicant medications, a Central Venous Access Device (CVAD) is the preferred route of administration. • Ensure a well - stocked emergency tray is available • Programming for infusion pumps should be independently checked by a second competent nurse to include calculation of infusion rates. Care must be taken to ensure the rate is correctly set according to the time span i.e. mL/hour • Intravenous lines must not be primed with chemotherapy, instead the infusion fluid should be used as the priming liquid. **5.** The nurse should be aware of the risk of extravasation and be able to identify which medications are vesicants or irritants. • Staff must be able to manage an extravasation according to local

	procedure. **6. Administration via the Intramuscular and Subcutaneous route** • Checking and cautionary points that apply to intravenous administration apply to the Intramuscular (IM) and Subcutaneous (SC) routes • IM injections may be administered into the deltoid, dorsogluteal, rectus femoris, vastus lateralis and ventrogluteal muscle groups • SC injections are administered through the epidermal and dermal layers into the subcutaneous tissue. **7. Intraperitoneal administration** • Requires surgical procedures such as laparoscopy and laparotomy for administration and are not discussed further here
Emergency Tray	• Ensure all relevant essential medicine and medical supplies are readily available
Adverse reactions procedures	• The nurse should be aware of the risk of hypersensitivity reactions, be able to identify which medications have potential for these reactions and be able to manage them according to local procedure as well as other side effects associated with the therapy during and after administration (e.g. extravasation, nausea, vomiting, pruritus and rashes). • Ensure all standard operating procedures are clearly displayed in case of any adverse reactions. • The infusion must be stopped immediately and medical doctor notified if the patient shows any sign of an anaphylactic reaction or a medicine extravasation. The SLAP (Stop infusion, leave cannula in-situ, Aspirate and Plan the next steps) procedure should be adhered to. • After administration the intravenous line must be flushed with a sufficient volume of compatible fluid to ensure the medication is cleared from the line
Premedication	• Ensure the following steps are done during premedication: o Clean Cannulation to avoid extravasation o Flush cannula with water for injection to check for patency o Evaluate hydration of child and give premedication accordingly o Run prescribed fluid (e.g. 100 – 200ml of DNS) o Give the anti-emetics (e.g. ondansetron) and Steroids (dexamethasone) at least 30 min – 60min before administration of chemotherapy o Pre-medication required to be taken at home has been taken by the patient as instructed e.g. Steroids required to be commenced 24 hours prior to docetaxel
Administration	• Before the actual infusion: o Two nurses should validate the prescription o Determine the drop rate per minute vis-à-vis the infusion time. o Monitor the patient throughout the infusion

HANDLING SPILLAGES IN CHEMOTHERAPY

Chemotherapy spills are common during reconstitution and administration. Such accidents require a speedy and accurate SOP to avoid exposure.

Table 6.5. Spill Kit contents

Category	Procedure / Contents
Training	• All personnel who handle spills must be given prior training/orientation on how to use a spill kit
Availability	• All units that handle chemotherapy must have a spill kit readily accessible at all times. These include the reconstitution unit, administration area, wards, pharmacy and storage area, and on the transportation carts.
Spill kit contents	• American Society Testing for Materials (ASTM) disposable gloves (x 2 pairs) • Disinfectant • N95 Face mask (NIOSH Certified) • ChemoPlus Gown • 2 shoe covers • 2 Head covers • Goggles • Yellow waste bag (for empty IV bags, empty syringes, gloves, pads, gowns) • Bio-wipe bag • Absorbent pad • Scooper • towels • Chemo spill sign • (Hazard) report card
Procedure for Spillage *(see the flow in figure 6.2. below for sequential steps)*	• Restrict the spillage area immediately • Open the spillage kit away from the contaminated area • Do not touch the contaminated area until the protective clothing supplied in the spillage kit are donned. • Document the incidence (date, time, location, the medicine involved, if any people were contaminated, who the incidence was reported to) • Replace the spill kit.

Source: NIOSH handbook on safe chemotherapy handling

Figure 6.1. Pictures showing contents of the spill kit

The standard operating procedure when there is a hazardous spill is as follows:

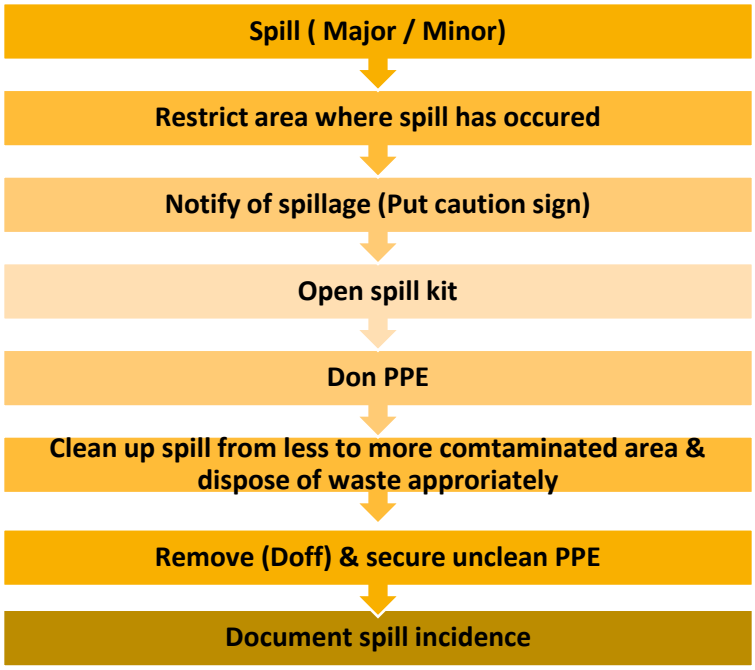

Figure 6.2. Standard operating procedure when there is a hazardous spill

CHAPTER 7. PALLIATIVE CARE

Paediatric palliative care (PPC) is a holistic approach to care for children with life-limiting conditions, such as cancer. It begins at diagnosis and continues throughout the child's illness, regardless of whether they receive treatment aimed at curing the disease (National cancer Institute, 2025). This care focuses on enhancing the quality of life for both the child and their family by addressing physical, emotional, social, and spiritual needs. It involves managing distressing symptoms, providing support for the family, and ensuring the child's comfort and dignity (WHO, 2013). Paediatric palliative care can be provided in various settings, including hospitals, community health centers, and even at home, making it accessible and adaptable to the needs of each child and their family (Olver I et al, 2018).

Table 7. Aims, Principles and incorrect beliefs in PPC

Aims of PPC
• Relieve suffering • Improve quality of life, • Facilitate informed decision-making • Assist in care coordination between clinicians and across levels of care.
Principles of PPC
• Holistic care of the child (body, mind and spirit) • Provides relief from total suffering (pain and other distressing symptoms) • Integrates the psychological and spiritual aspects of care • Offers support alongside cure-focused treatment. • Offers a support system to help patients live with the cancer as actively as possible • Offers a support system to help patients' families cope from diagnosis, during the patient's illness and in bereavement • Uses Multidisciplinary Team approach. • Palliative care neither hastens nor postpones death but affirms life and regards dying as a normal process. • Mobilisation of existing community resources.
Common incorrect beliefs in PPC
• Children do not need palliative care. • Children's palliative care is the same as adult palliative care. • Palliative care is only needed at the end-of-life. • Palliative care means giving up hope and stopping treatment. • Palliative care can only be provided in tertiary facilities or a hospice. • Palliative care aims at shortening life or hastening death to avoid unnecessary suffering

7.1. PALLIATIVE CARE ASSESSMENT

A Multidisciplinary Team (MDT) will carry out a comprehensive assessment of the patient and family. This will form the basis for the development of an individualized patient and family palliative care plan. The initial assessment will be conducted in person by one or more MDT members.

The team will perform the initial and subsequent assessments at regular defined intervals.

Table 7.1. Initial assessment in PPC

Initial Assessment in PPC
• Ensuring that patient and family understand the diagnosis, the seriousness of the illness, prognosis, goals of care, treatment preferences, and capacity to meet patient needs • Ascertain the developmental status and decision-making authority of the child and/or adolescent • Review the medical history, identify co-morbid medical, cognitive, and psychosocial conditions present in order to institute recommended treatments • Establish the social determinants of health that pertain to the patient and family including financial vulnerability, housing, nutrition, safety, cultural factors, caregiving support and caregiver willingness • Inquire on patient and family emotional and spiritual concerns, including previous exposure to trauma, assessment of family risk for prolonged grief disorder • Ensure patient and family needs related to anticipatory grief, loss, and bereavement, including a review of signed advance directives, if available.

7.2. THE CONCEPT OF TOTAL PAIN

The concept of total pain acknowledges that pain does not only involve the physical dimension, but also the spiritual, psychological, as well as the social dimension. For example, a child with cancer may eventually suffer deterioration of health which they have to endure up to death. This can cause other types of pain such as psychological pain to set in arising from the depreciation of the body.

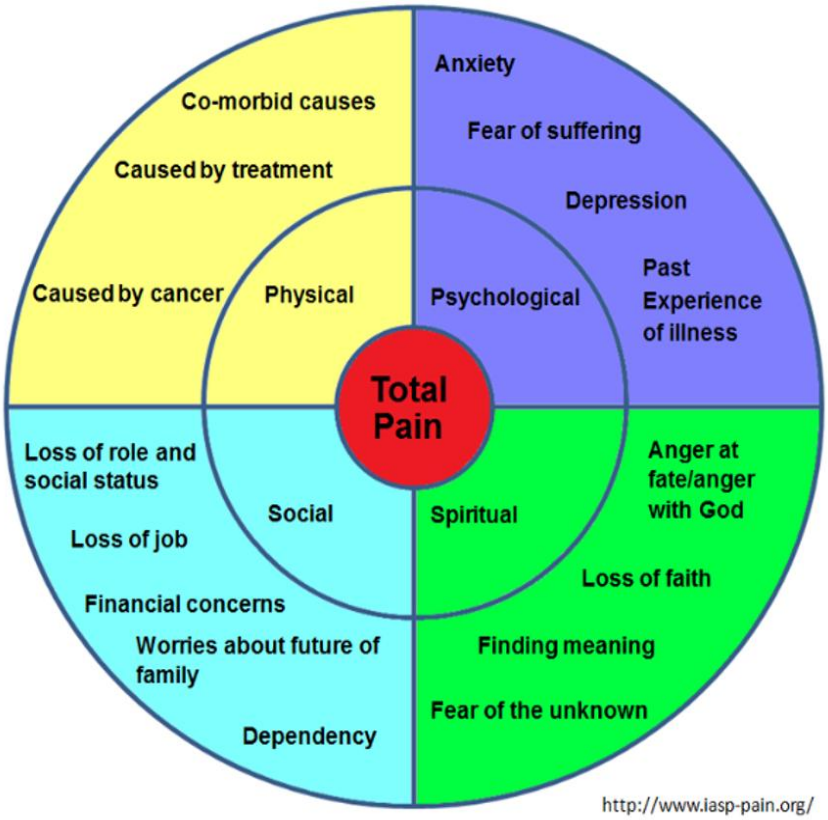

Figure 7. Concept of total pain (IASP, 2009).

Source:https://iaspfiles.s3.amazonaws.com/GlobalYearFactSheets/TotalCancerPain_Final.pdf

Physical pain does not usually occur alone. Therefore, when assessing a child's pain in palliative care, it is essential to incorporate the concept of total pain thereby ensuring that a holistic assessment is undertaken.

7.3. PAIN MANAGEMENT

Pain is a complex and subjective experience that can significantly impact a child's physical, emotional, and psychological well-being. The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage (https://pmc.ncbi.nlm.nih.gov/articles/PMC7680716/).

Effective pain management is crucial for children with acute and chronic conditions, including cancer, post-surgical pain, and other medical conditions. Proper pain assessment ensures that healthcare providers can understand the child's experience, identify underlying causes, and implement appropriate treatment strategies. Addressing pain adequately can enhance comfort, improve recovery outcomes, and reduce the long-term psychological impact of untreated pain (https://www.iasp-pain.org/resources/topics/pain-assessment-and-measurements/).

Pain Assessment

Pain assessment in children presents unique challenges due to their varying cognitive and communicative abilities. Various tools are available to assess pain based on a child's age, cognitive function, and ability to articulate discomfort.

Pain Assessment Tools

- **Numeric Pain Rating Scale**: Used for children who can understand and verbally express their pain intensity on a scale of 0 to 10.
- **Wong-Baker FACES Pain Rating Scale**: Uses facial expressions to help children describe their pain, suitable for young children and those with communication difficulties.
- **FLACC Pain Scale (Face, Legs, Activity, Cry, Consolability)**: A behavioural scale used for infants and non-verbal children, assessing five categories of pain-related behavior.

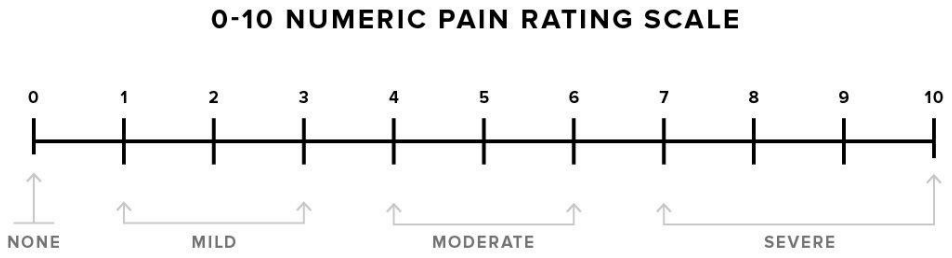

Figure 7.1. Numeric pain rating scale

Figure 7.2. Wong-Baker FACES pain rating scales

Source: Wong-Baker FACES Foundation (https://wongbakerfaces.org/wp-content/uploads/2016/05/FACES_English_Blue_w-instructions.pdf)

The **F**ace, **L**egs, **A**ctivity, **C**ry and **C**onsolability (FLACC) Pain Scale (Merkel S. et al; 1997)

Sometimes it is difficult to assess pain in children who are non-verbal. The FLACC Pain scale is a system that can help parents and health care workers assess pain levels in such children who have limited or no expressive communication. The Table below shows the categories for scoring: 0, 1 or 2 points which are given to each of the five behaviour categories: **F**ace, **L**egs, **A**ctivity, **C**ry and **C**onsolability.

Interpreting the behaviour score: Each category is scored on the 0-2 scale with the resulting total score 0 – 10 as below:

0	Relaxed and comfortable	4-6	Moderate pain
1-2	Mild Discomfort	1-10	Severe discomfort &/or Pain

Table 7.2. The FLACC pain scale

Category	Score 0	Score 1	Score 2
Face **F**	No Particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Legs **L**	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity **A**	Lying quietly, normal position moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry **C**	No crying (Awake or asleep)	Mourns or whimpers, occasional complaint	Crying steadily, scrams or sobs, frequent complaints
Consolability **C**	Content, relaxed	Reassured by occasional touch, hugging or being talked to, distractable	Difficult to console or comfort
N.B. If a child is showing these behaviours, it does not necessarily mean that they are in pain as some of the behaviours measured by the FLACC scale can happen for other reasons. However, parents should be advised to present these to a health care worker if observed.			

WHO Pain Ladder

The WHO developed a stepwise approach for pain management in pediatric patients. The Ladder provides a framework for appropriate analgesic selection based on pain severity:

1. **Mild Pain (Score 1 - 3)**: Non-opioid analgesics (e.g., paracetamol, ibuprofen) and non-pharmacological interventions.
2. **Moderate Pain (Score 4 - 6)**: Non-opioid analgesics as in the referral guideline above.
3. **Severe Pain (Score 7 - 10)**: Strong opioids (e.g., morphine, fentanyl) along with adjunctive therapies.

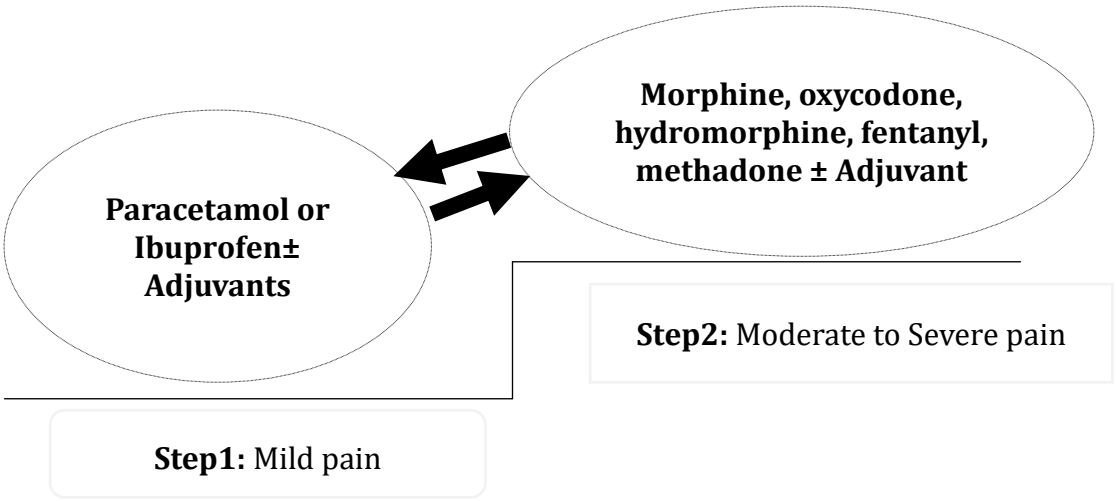

Figure 7.3. WHO Two-step Analgesic Ladder Adapted from the WHO Pain Relief Ladder

Pharmacological Management

- **Non-Opioid Analgesics**: Paracetamol and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) for mild to moderate pain.
- **Opioid Analgesics**: Used for severe pain but require careful dosing and monitoring.
- **Adjunctive Medications**: Antidepressants, anticonvulsants, and corticosteroids for neuropathic pain.

Table 7.4. Pharmacologic Pain Management

Step	Analgesics	Comments	Adjuvant
Step 1 (non-opioid)	**Infants from 1 to 3 months** • Paracetamol 10mg/kg every 4-6 hrs (max 4 doses/day) **Children from 3 months to 12 years** • Paracetamol 10-15mg/kg every 4-6 hrs (max 4 doses/day, max 1g at a time). • Ibuprofen 5-10mg/kg every 6-8 hours (max dose 40mg/kg/day)	• Aspirin is rarely used in children	• Amitriptyline (used for neuropathic pain) - children from 2-12 years, 0.2-0.5mg/kg (max 25mg) at night – increase if needed to max 1mg/kg bd • Diazepam (used for anxiety or skeletal muscle spasm) o 1-6 years: 1mg/day in 2-3 divided doses o 6-14 years: 2-10mg/day in 2-3 divided doses • Hyoscine Butylbromide (used for smooth muscle spasm or excessive bronchial secretions) o 1month – 2 years: 0.5mg/kg 8hrly o 2-5 years: 5mg 8hrly o 6-12 years: 10mg 8hrly • Dexamethasone (used for inflammation and pressure symptoms) 1-2mg/kg daily
Step 2 (Opioid)	**Infants from 1 month to 1 year** • Oral morphine: 80 – 200 **mcg**/kg every 4 hrs **Children from 1 to 2 years** • Oral morphine: 0.2 – 0.4mg/kg every 4 hrs **Children from 2 to 12 years** • Oral morphine: 0.2 – 0.5mg/kg every 4hrs	• **Titration:** After a starting dose, the dosage should be adjusted to the level that is effective with a maximum dosage increase of 50% per 24 hours.	

Source: Adapted from Mulago Palliative Care Unit, Kampala, Uganda

NON-PHARMACOLOGICAL MANAGEMENT

- **Cognitive-Behavioral Therapy (CBT)**: Helps children develop coping mechanisms.
- **Distraction Techniques**: Music, storytelling, or interactive play to shift focus from pain.
- **Physical Interventions**: Massage, heat/cold therapy, and physical therapy.
- **Parental Involvement**: Educating parents on pain management strategies and providing emotional support to children.

Effective pain management in pediatric patients requires a multimodal approach that combines pharmacological and non-pharmacological strategies. Proper assessment tools, individualized treatment plans, and a holistic approach to care can significantly improve a child's comfort and overall well-being. Ongoing research and education are essential to enhance pediatric pain management and ensure that children receive the best possible care.

COMMUNICATION IN PAEDIATRIC PALLIATIVE CARE

Effective communication between health care providers and the patient or their family plays a great role in the achievement of treatment plans and overall health goals set.

COMMUNICATION SKILLS

Communication skills are abilities you use when giving and receiving different kinds of information. These skills are important because they allow you to understand and to be understood by others. Communication skills involve listening, speaking, observing and empathising.

In palliative care, listening must go beyond hearing the words spoken, and must involve paying particular attention to what is being spoken and responding appropriately. This is active listening. Listen to how the family interacts, listen to what they are saying and

listen for what is not being said. Every patient and family have a story to tell. You need to let them tell you their story or they will not be able to hear you. Doctors, nurses and other health professionals on the palliative care team should be trained in communication. Since communication plays a very important role in the management and caring of a child who needs palliative care, health care professionals must be empathetic and also use simple language.

BREAKING SIGNIFICANT NEWS

Significant news is considered any information that negatively changes the patient's view of the future, is inevitable and occurs at suspicion and confirmation of cancer. Breaking significant news involves informing the child with cancer and their family about the disease. The news may concern a new chronic disease or information that a chronic disease has worsened.

Breaking significant news in paediatric palliative care using the `SPIKES` protocol, the recommended framework is summarized in the table below:

Table 7.5. SPIKES protocol

STEPS	Item	Description
STEP 1	Setting	Choose an appropriate setting for the conversation. Plan ahead for privacy, comfort and involve significant others (if the patient wants that).
STEP 2	Perception	Assess the patient's and family's understanding. Ask open-ended questions to find out how patient parent/guardian perceives the medical situation.
STEP 3	Invitation	Find out how much detailed information the patient wants regarding diagnosis and prognosis.
STEP 4	Knowledge	Provide information in small amounts, use short sentences, and check periodically for understanding.
STEP 5	Emotions	Identify the patient's primary emotion and express that you recognize that what the patient is feeling is a result of the information received.
STEP 6	Strategy and summary	Present treatment or palliative care options, being sure to align your information with what you ascertained (during the assessment of the patient's perceptions) to be the patient's knowledge, expectations, and hopes. Providing a clear strategy will lessen the patient's anxiety and uncertainty.
Consideration 1	Cultural sensitivity	• Recognize cultural, religious, and linguistic factors. • Inquire about cultural preferences and beliefs. • Use professional interpreters if needed.
Consideration 2	Team approach	• Involve social workers, chaplains, and other supportive staff. • Coordinate messaging and emotional support
Consideration 3	Emotional support	• Show empathy and allow families to express emotions. • Offer resources for grief counseling

Table 7.6. Characteristics for breaking significant news outline:

Important Characteristics for health workers in breaking significant news
1. Be knowledgeable about the disease 2. Be honest. Do not divert from the truth in order to please the patient. 3. Be prepared to answer their questions. However, in your answering you must instill hope bearing in mind that although you cannot add days to their life, you can still add life to their days. 4. Respect their ability to cope with the news, and their right to hear it. 5. Provide reassurance without giving false promises. 6. Model good self-care. 7. Seek help for the child and family where necessary.

STEPS OF BREAKING SIGNIFICANT NEWS

Buckman and Kason (1992) identify a six-step protocol for breaking significant news as discussed below.

Table 7.7. Six steps in breaking significant news

Discussion	Activity
Getting started	• Use an ideal environment for breaking significant news. Where should it be done from, and who should be there when significant news is being delivered to the patient?
Finding out how much the patient knows	• Find out how much the patient knows about their medical condition
Finding out how much the patient wants to know:	• Do not be in a hurry to break significant news without establishing how much the patient wants to know. • Ask questions which may help you to establish the willingness of the patient to know more about their health condition, such as "would you like me to tell you more about your health condition?" • Do not push more information to them beyond what they want to hear at a particular time.
Sharing the information	• Make sure that you have enough information about the patient's condition. • Start from the patient's starting point • Begin to break the news from what the patient knows • Provide the necessary education by giving information in small chunks • Check if the patient is able to understand what you are explaining. • Provide information in the simplest manner possible without using technical jargon.

Responding to the patient's feelings.	• Respond to the patient's feelings. • Be prepared for a broad range of reactions that may arise such as outburst of strong emotions. • Give time to patient, parent or guardian to react. • Listen quietly, attentively and encourage descriptions of feelings. During this process, use non-verbal communication as well.
Planning and follow-through.	• Include additional information, tests to be done, treat symptoms, referrals as needed. • Include discussion of potential sources of support, next appointment, and practical other actions relevant to the wellbeing of the patient.

COUNSELLING

Counselling in palliative care is defined as skilled consultation between a professional and patient in which each draws on the expertise and knowledge of the other in order to assist the patient with any physical, psychosocial or spiritual issues he would like to explore (Nieuwmeyer and Hosking, 2006).

COUNSELLING CHILDREN

The following structure would help when counseling children (Amery, 2009):

Table 7.8. Steps in Counseling Children

Steps to consider when counselling Children
• Find a quiet, child friendly place with toys, crayons and everyday objects that he or she can use in acting out or telling his/her story. • Assess what the child already knows. • Assist the child in deciding whether or not he/she would like to discuss the issues more fully. • Establish ground rules of safety, trust and confidentiality. • Help the child identify what he or she does to cope with stress and reinforce and encourage those as strengths. • Try and get the child to begin to tell you his/her story, either verbally or through play or stories. *Don't rush*. • Begin to draw up a list of the main problems and issues that might be underpinning their distress. • Start discussing these, offering plenty of encouragement and congratulations, for each try to help the child come up with coping strategies that work for him/her. Don't be too directive. Use the child's own inner resources and the resources of the family and community to build strategies. • Don't make empty promises. • Keep following up the child until he/she has worked through the issues. • If the child is at risk, take steps to involve the necessary agencies. Do not keep it to yourself.

7.4. FAMILY CONFERENCE (FC)

Communication between members of the health care team and the family is important when a family member is in the hospital. It can be hard to match schedules in the fast-paced hospital setting. Connecting with the many people on your child's medical team can be a challenge. One way to bring everyone together is to set up a family care conference (FC). This is a meeting of the patient and family with the health care team. (Powazki and Walsh, 2014) observe that the operational concept of a FC is that of a formal scheduled meeting and its major components are 3-fold:

The 3-fold component of Family Conference outlined below;

Table 7.9. Family Conference outline

1. Preparation; team communication and data collection.
2. The conference; a medical and psychosocial agenda.
3. Follow-up; contingency plans and feedback.
A family care conference can help when: • The hospital stay is long. • There are complex issues. • Something has changed unexpectedly
The goals of conferences include: • Discussing the family's concerns and decisions that need to be made. • Outlining a plan for your child's care. NOTE: This is sometimes described as "getting everyone on the same page." Families and the care team will talk about what to expect and how to prepare for the future.

Conferences are needed to help with these things:

- Talk about an extended hospital stay.
- Talk about different goals or viewpoints.
- Talk about a serious change in a patient's condition.
- Make changing goals of care clear.
- Get ready for discharge (going home or to the hospice).
- Improve communication by having the family speak with more than one health care provider at the same time.
- Find more ways to support a patient and family.

These team members are usually included in the care conference:

- Attending doctor
- Consulting specialists
- Bedside nurse
- Social worker
- Care coordinator

Other members of your child's health care team who have experience working with similar situations may also be included, such as:

- Therapists
- Chaplain
- Home care provider(s)

END OF LIFE CARE

End-of-life care is the support and care that is provided to the child and family when a child's clinical condition has reached a stage where the child is dying or is likely to die soon. It may begin hours, days or even weeks before their death.

End of life care is essential in paediatric palliative care as the patient who nears end of life requires more care than those whose conditions have not advanced. Paediatric end of life care aims to improve the planning and management of care for infants, children and adolescents with cancer aged 0-17 years (NICE Guidelines, 2016).

Children who are dying need care in four areas—physical comfort, mental and emotional needs, spiritual issues, and practical tasks.

Below is a table showing the four areas of care for dying children

Table 7.1.1. Care for Dying Children

Area	Description
Physical Comfort	• Patient presenting with terminal Restlessness treated with Midazolam, Haloperidol or Levomepromazine to be given as a continuous infusion. • Counsel in addition to medication. • Manage patients' pain (pharmacological/non-pharmacological)
Mental and Emotional	• Manage Psychological distress. • Manage Emotional distress. • Facilitate for Psychotherapy part of improving the quality of life in palliative care patients. It reduces mental health symptoms (Abramson, 2022). • Assess for various mental health challenges that affect paediatric patients such as mood disorder, depression, anxiety, insomnia as well as suicidal ideation. • Assess adolescents for anticipatory grief and changes in peer relationships which can affect their quality of life (Aldelstein and Kavalieratos, 2015).
Spiritual Issues	• Addresses emotional, social, and existential needs. Respect the beliefs of the patient, parent or guardian, and providing comfort. • Actively listen to patients and families. Understand their fears, hopes, and questions. • Show empathy—acknowledge their emotions and validate their experiences. • Discuss the importance of understanding cultural, religious, and personal beliefs. • Encourage open-ended questions: "What gives you strength?" or "How do you find meaning during difficult times?" • Collaborate with colleagues to address spiritual needs comprehensively.

	• Be present matters, sit quietly with patients and families, offering comfort • Explore rituals: prayer, meditation, or simple ceremonies based on the family's preferences • Respect patients' and families' boundaries • Encourage honesty tempered with compassion • After a patient's passing, continue supporting the family through grief and bereavement
Practical Tasks	• Establish trust with the child and family, listen actively and empathetically to their concerns. • Provide honest information about the child's condition and prognosis • Assess and manage the child's pain and other symptoms (e.g., nausea, fatigue). • Collaborate with the interdisciplinary team to optimize comfort. • Offer Psychosocial and emotional support to both the child and family by addressing anxiety, fear, and grief. • Connect them with counselling services if needed. • Coordinate appointments, medications, and therapies. • Ensure seamless transitions between hospital, home, and other care settings • Teach parents and caregivers how to manage symptoms at home. • Educate them about the child's condition and treatment options. • Discuss Advance Care Planning which include goals of care with the family. • Document preferences for end-of-life care • Respect the family's beliefs and rituals • Encourage Respite Care by arranging for short breaks for caregivers. • Provide respite services to prevent burnout • Prepare the family for the possibility of loss. • Offer grief counselling and follow-up after the child's passing. • Creating Meaningful Moments: • Facilitate special experiences for the child and family (e.g., art, music, and storytelling). • Celebrate milestones and create positive memories

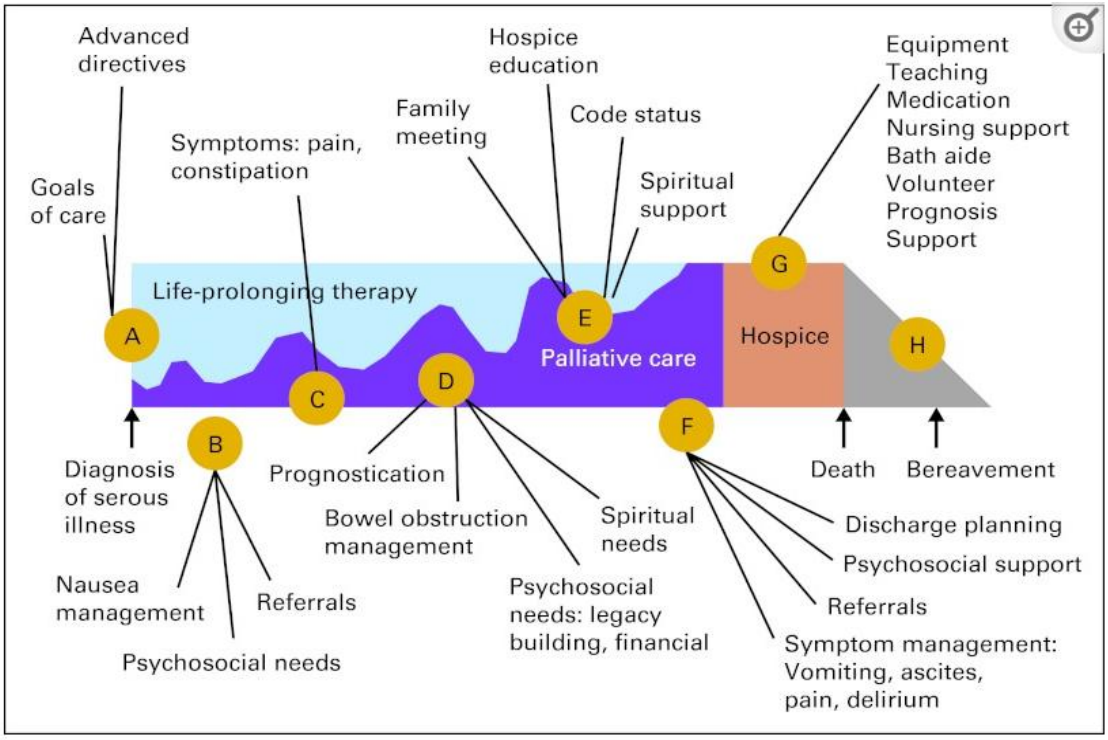

Figure 7.4. Palliative intervention examples

John et al, 2013, observed that depending on their condition, a patient may be quite independent, or may need help with just a few things, or they may need a greater level of help with lots of daily tasks. The ability of a patient to perform practical tasks is likely to change over time. Because there is no one who likes to lose their independence, helping the person to maintain their independence as long as they can is best. Eating healthy foods, physical activity, and maintaining good personal hygiene daily will help the patient to feel more positive and have more self-confidence, and will lower the chances of getting any new illnesses or complications. However, as earlier mentioned, disease progression will determine the extent to which these tasks can be performed.

Practical tasks may involve helping with taking medications. Medication should always be taken as prescribed. However, sometimes this may not be so easy due to certain circumstances such as having nausea which can cause the patient not to take their pain medicine by mouth. In such a case, the nurse or doctor may need to give an injection to stop the nausea and to treat the pain. Where a patient is required to take strong pain medicines, such as morphine, the doctor, pharmacist or palliative care team can explain to the patient and family why, how and when it should be taken.

Practical tasks may also involve helping a child to eat or drink. This is important because people with life-limiting illness can lose their appetite or not feel like eating at various times of their illness, and this might be due to the side effects of their treatment, or may also just be feeling sick, tired or constipated. According to John et al, 2013, where possible and depending on the person's illness, it is important to eat foods that are enjoyable, even if they are not the healthiest foods. The argument is that enjoying food to improve the

quality of life is important as a person nears the end of their life. Further, a patient may need help to maintain hygiene. For example, moving in and out of bed or to the bathroom.

TRANSITIONING TO HOME CARE OR NEAREST LOCAL FACILITY

Home care is a well-accepted option for children with chronic illnesses, such as cancer patients. Successful home care includes assessment of the readiness of the child and family, development of a comprehensive care plan, education of care givers, and continuously evaluating the care plan. Nurses play a major role in the discharge planning for home care. They are actively involved the education of care givers, by providing opportunities for care givers to demonstrate competence before assuming total responsibility. The aim of this process is to normalize home care for the child and the care giver. It is vital to establish sound parent-professional partnerships, thus providing family support that empowers family members to assume the responsibilities of caring for their child (Wong, 1991). However, other members of the palliative care team such as social workers, counselors, nutritionists, and others are needed as well in the process of referral of the patient for Home Based Care (HBC) or hospice care.

WHO SHOULD BE INVOLVED IN THE PROVISION OF END OF LIFE CARE?

Palliative care at the end of life is very important as the patient would need more care at this time. All relevant stakeholders should be involved in the provision of end of life care according to their skill, expertise and need. The following are the major categories of people who should be involved:

- Pastors/chaplains
- Families
- Friends
- Health care professionals
- Community

It is important that patients who need end of life care receive adequate support in the last few days of life. This can be done through:

- Being seen by a doctor regularly and if the condition is deteriorating, health care providers must explain this to the patient/family.
- The staff involved in the care of the patient should talk sensitively and honestly to the patient / family.
- The patient / family should be involved in making decisions about how they are treated and cared for.
- The needs of the patient/ family should be met as far as possible.
- The care plan for the patient should be implemented with compassion.

Table 7.1.2. Guide for palliative and supportive care according to health facility level

Symptom	Palliative and supportive care			
	Home	**First level Care**	**Second level care**	**Third level care**
Pain	Non-pharmacological: Massage, turning, fanning, diversion therapy e.g. music Pharmacological: Analgesia according to WHO analgesic ladder. Opioids including morphine can be safely used in the home.	Appropriate analgesia including opioids if indicated	Appropriate analgesia including opioids if indicated	Appropriate analgesia including opioids if indicated
Nausea/ Vomiting/ Diarrhoea	Control pain, suppress intractable cough, give anti-emetics regularly and as needed, for diarrhoea use loperamide if non-infective. Refer to hospital if intractable or suspicion of infection.	Anti-emetics regularly and AS NEEDED (in severe cases give parenterally). For diarrhoea loperamide after each loose stool, treat infection, codeine can be used alone or in combination with loperamide	Anti-emetics regularly and AS NEEDED (In severe cases give parenterally) For diarrhoea loperamide after each loose stool, treat infection, codeine can be used alone or in combination with loperamide	Anti-emetics regularly and AS NEEDED (in severe cases give parenterally. For diarrhoea loperamide after each loose stool, treat infection, codeine can be used alone or in combination with loperamide
Constipation	Encourage regular bowel regimen, Laxative if cause is opioid use, hydration	Hydration, manual evacuation for mild faecal impaction, laxatives	Hydration, manual evacuation, surgical management of manual obstruction, correct electrolyte imbalance	Hydrate parenterally, Relieve manual obstruction surgically where possible, address electrolyte imbalanced

Anxiety/agitation	Discuss the anxiety, invite a counsellor, support groups, day hospice care, distract the patient, use relaxation techniques, asses how family is coping, exercise	Discuss the anxiety, counselling, asses how family is coping	Psychological services, Benzodiazepines, Selective serotonin reuptake inhibitors	Psychological or psychiatric services, Cognitive Behavioural Therapy, Benzodiazepines, Selective Serotonin Reuptake Inhibitors (SSRIs)
Dyspnea	Position patient to aid in breathing, reassurance, distraction, home physiotherapy, open windows to allow air circulation, take to hospital is infection suspected or worsening breathlessness despite other measures.	Treat pneumonia, asthma exacerbation, refer to higher level if condition cannot be managed at the institution.	Treat underlying cause (i.e. heart failure, asthma, Chronic Obstructive Pulmonary Disease (COPD) exacerbation, pulmonary embolism), chest physiotherapy. Oral morphine may be used where indicated (anxiety and pain). Corticosteroids for inflammatory oedema or in Superior Vena cava obstruction.	Treat underlying cause (i.e. heart failure, asthma, COPD exacerbation, pulmonary embolism), chest physiotherapy. Oral morphine may be used where indicated (anxiety and pain). Corticosteroids for inflammatory oedema or in Superior Vena cava obstruction, spinal cord compression.
Bleeding	Have anticipatory discussion with primary health care provider, take to hospital when patient bleeds	Refer if haemorrhage is catastrophic	Have anticipatory discussion with family and care giver, have a proposed management plan if patient bleeds, intervene where it is appropriate, don't leave patient alone, give anxiolytic if	Have anticipatory discussion with family and care giver, have a proposed management plan if patient bleeds, intervene where it is appropriate, don't leave

			patient distressed, debrief the family and offer support.	patient alone, give anxiolytic if patient distressed, debrief the family and offer support
Seizures	Check glucose if glucometer available. Send to hospital.	Treat hypoglycaemia, Give midazolam. Refer to next level hospital	Look for, and manage reversible causes i.e. hypoglycaemia. Status epilepticus protocol. Use Levetiracetam if patient was already on it. Refer to specialist	Look for, and manage reversible causes i.e. hypoglycaemia. Status epilepticus protocol. Use Levetiracetam if patient was already on it. Refer to specialist.
Insomnia	Have fixed times for going to bed and waking up, Try to avoid napping during daytime, provide comfortable sleeping environment, Avoid caffeine, avoid heavy meals at night,	Benzodiazepines	Benzodiazepines	Benzodiazepines
Physical disability	Home physiotherapy, assist patient with practical tasks (I.e. bathing, feeding), use of a wheel chair	Physiotherapy, aid with practical tasks	Physiotherapy, aid with practical tasks	Physiotherapy, aid with practical tasks

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