



MALIGNANT DISEASES IN CHILDHOOD

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"In its beginning the malady is easier to cure but difficult to detect, later it becomes easy to detect but difficult to cure"

Machiavelli, 1469

Although cancer is relatively rare in childhood under 15 (110–130 per million children per year in Europe and North America) it kills more children than any other disease and is second only to accidents as the commonest cause of death between 4 and 15 years of age. Overall about 1:600 children will develop a malignant disease before the age of 15 years. Its lethal nature, insidious onset, emotional impact and the increasing prospects of cure make it one of the most challenging aspects of paediatric practice. The steady improvement in the overall survival rate of children with cancer has done much to dispel pessimism and has given rise to a new era of cautious optimism. This has been achieved through clinical trials evaluating the most effective combinations of multi-agent chemotherapy, radiotherapy and surgery. Leukaemia and brain tumours are the most common malignancies. The solid tumours are comprised mainly of embryonal malignancies (e.g. neuroblastoma, neuroblastoma) and sarcomas, rather than carcinoma. The cancers of children generally are responsive to one or several of the treatment interventions available today.

MALIGNANT DISEASE IN THE WESTERN CAPE

Annual incidence of all malignant tumours in the Western Cape is about 75/1 000 000 children <15 yrs of age. This is partly under ascertainment (other parts of the country report even lower incidence rates) but may also represent a real difference in

epidemiology. The outcomes cited here are those documented by the Haematology/Oncology Unit at the Red Cross Children's War Memorial Hospital.

The spectrum of cancer in children differs strikingly from that in adults. The common cancers of adult life (ie. lung, breast, gastro-intestinal, skin) are of epithelial origin and present with manifestations that make them candidates for screening. Tumours in children are usually deep seated and often diagnosed at advanced stage with metastases. Screening is not effective or practical. In general terms 70% are curable with good response to surgery, radiotherapy and chemotherapy usually in combination. A 5 year tumour free period is usually indicative of cure. Prognostic factors include age at diagnosis, histological grade and stage of disease.

Many paediatric tumours have their peak incidence in children less than 5 years of age.

Early clinical awareness and diagnosis are critical and with the advances in paediatric surgical techniques, radiotherapy and effective chemotherapy, the prognosis of most malignant tumours in children has improved considerably during the last few decades. Neuroblastoma remains regrettably a tumour with poor prognosis (<30% overall survival).

Sidney Farber (1969) said that "every solid, semi-solid-cystic mass in an infant or child should be regarded as a malignant tumour until its exact nature is determined by histological examination of the removed tumour." This generalization is still used, for the words not only indicate the most reliable means of earlier recognition of

a malignant tumour, but also imply the ideal management.

Aetiology

The aetiology of cancer is complex, usually multifactorial and at the present time not fully understood. Some children are at increased risk of developing malignancy.

Genetic Predisposing factors

- Hereditary cutaneous syndromes (albinism with squamous cell carcinoma)
- Hereditary neurocutaneous syndromes (neurofibromatosis: rhabdomyosarcoma, pheochromocytoma or medullary thyroid cancer)
- Chromosomal abnormalities (Down Syndrome has 15 times higher incidence of leukaemia)
- Cancer Family pattern (SBLA syndrome: Sarcoma, breast, brain, leukaemia, lung, adrenal carcinoma aggregate in autosomal dominant pattern)
- Gastro-intestinal syndromes (hereditary bowel disease: polyposis coli and adenocarcinoma, Ulcerative colitis and carcinoma)
- Hemi-hypertrophy and Beckwith-Weidemann syndrome (eg. Wilms tumour, hepatic tumours and adreno-cortex carcinoma). As many as 25% of children have an associated neoplasm.

Viruses

A virus that can cause cancer is called an oncovirus. These include human papillomavirus (cervical carcinoma), Epstein-Barr virus (B-cell lymphoma, Kaposi's sarcoma) herpes virus, hepatitis B and hepatitis C viruses (hepatocellular carcinoma), and Human T-cell leukemia virus-1 (T-cell leukemias).

Immunodeficiency syndromes

- HIV (lymphoma, Kaposi sarcoma)

- Transplant patients on immunosuppression have 100 times greater incidence in a lifetime

Prior malignant disease

Survivors of childhood malignancy. The 20 years cumulative probability of developing a second malignancy is 12%, peaking at 15-19 years after initial diagnosis. There is therefore a great need to continue follow-up on all survivors of childhood cancer.

Pathogenesis

The chief characteristic of a malignant tumour is the ability of its cells to grow and multiply at a rapid uncontrollable rate. When the tumour reaches a cell size of 1×10^9 it becomes clinically manifest. The clinical picture will depend on the anatomical localisation and size of the tumour, its secretory function and complications. The malignant cell therefore, after undergoing malignant transformation, becomes a real life threatening entity. Sooner or later clumps of cells leave the parent organ and metastasise by direct spread or via blood vessels or lymphatic channels to establish secondary deposits elsewhere. The time period between malignant transformation, clinical detection and institution of therapy, is a critical factor affecting prognosis.

Presentation

A complete personal and family history and physical examination is mandatory in every child suspected of having a malignant tumour.

Cancer in children presents in one of three ways:

Constitutional symptoms

Non-specific symptoms related to the tumour. Malignant malaise is a convenient general term for this ill-defined but typical clinical picture so important in childhood malignancies.

Special attention should be paid to the mother stating "my child is sick". Para-neoplastic syndromes include pallor, pyrexia of unknown origin, weight loss, lassitude, lethargy, tiredness, irritability, loss of appetite, hypertension, diarrhoea, and aches and pains in the limbs, which may be transient and recurrent.

Local findings

These are determined either by the anatomical presence and size of the tumour or by complications. These include gastro-intestinal haemorrhage, neurological signs, resulting from brain and spinal cord lesions, hematuria from a Wilms tumour or bladder rhabdomyosarcoma, or endocrine symptoms resulting from hormone production by the tumour. Many solid tumours in children are situated in the flank area on abdominal examination.

The "**dictum of sixes**" emphasizing the relationship between age and pathology is of great practical importance. It is taught that between 0 and 6 months, a lumbar mass in a child is usually benign and sited anatomically in the retroperitoneal space, the organ involved is usually the kidney, the abnormality, a congenital anomaly causing hydronephrosis or a related cystic form of renal dysplasia. Between the ages of 6 months and 6 years, malignant abdominal tumours are more common, and for this reason, any abdominal mass is assumed to be malignant until it is proved otherwise in this age group. During the period 6 years and older, a broader differential diagnosis is considered including inflammatory, benign and malignant conditions. A mass lesion therefore should alert one to the possibility of malignancy, since there are only a few mass lesions, which can be considered benign on a basis of location or physical appearance alone.

Metastases

The sudden and spontaneous appearance of metastases may be the

first indication of an underlying malignant process, e.g. neuroblastoma metastases to the orbit with ecchymosis, a pathological fracture, subcutaneous nodules, dyspnoea, haemoptysis.

Warning signs

- Pallor plus bleeding such as purpura, unexplained bruises or persistent oozing from the nose or mouth
- Fever, apathy or weight loss that is persistent or unexplained after excluding TB or HIV infection
- Bone pain, often poorly localized that may wake the child at night. It may present as a limp in the older child or refusal to walk in a toddler
- Persistent backache is sinister and may denote a spinal tumour. Backache is always abnormal in children and should be fully investigated
- Localized lymphadenopathy that is persistent and unexplained. Discreet non tender nodes >2cm in diameter that do not respond in 2 weeks to antibiotic therapy and all supraclavicular nodes should be biopsied
- Unexplained mass (abdomen, testis, head and neck, limbs) An abdominal mass in children under 6 is likely to be a malignancy
- Unexplained neurological signs like longstanding or early morning headaches (>2 weeks) early morning vomiting, ataxia or cranial nerve palsies
- Eye signs: Leucocoria (white spot in the eye or white light reflex) recent onset squint or proptosis and loss of vision

Investigations for malignant disease

Laboratory Assays

Careful, thorough, appropriate investigations may help to establish diagnosis. Consider urinalysis, FBC, ESR, LFTs and tumour markers:

Wilms tumour and Rhabdomyosarcoma – LDH

Neuroblastoma – LDH and Ferritin

Non-Hodgkin lymphoma – LDH and uric acid

Germ Cell tumour – α FP and β HCG

Hepatoblastoma – α FP

Radiography

Chest x-ray and tomography, skeletal survey, sonography, computed tomography, MRI and radioisotope scanning.

Biopsy

Appropriate biopsies are important for the diagnosis and staging of malignancies. This may include FNAB, needle core (Tru-cut), open wedge biopsy or partial or complete resection of the tumour

Principles of Treatment

Early diagnosis of all malignancies improves

outcome. In addition children have a survival advantage if managed at a paediatric cancer centre and should be referred to paediatric oncologists for definitive care. Standardized treatment protocols using multimodal therapeutic approach have led to dramatic improvements in the outcome of childhood malignancies over the last 20 years. Better understandings of the pathophysiological basis of tumours and host immune responses, together with advances in surgical, anaesthetic and intensive care have contributed to this improvement.

Prognostic factors include the age of the patient, site and size of the tumour, extension to local tissues and lymph nodes, the presence of metastases and the histological grading and genetics of the tumour.

All children with a suspected malignancy must be discussed promptly with a paediatric oncologist. Avoid unnecessary investigations that may delay diagnosis and referral. A few basic investigations are helpful

and include a chest X-ray, HIV test, full blood count with a differential count, coagulation screen, ESR, urea, creatinine and electrolytes, LDH [a non-specific marker of cell turnover and lysis] and serum urate. For suspected germ cell tumours or hepatoblastoma α -fetoprotein and/or serum s-chorionic gonadotrophin (sHCG) levels are helpful as tumour markers and are used in follow-up for the early detection of recurrence.

Management

The ultimate aim is the restoration of health, free of disease.

Management depends on a proven diagnosis of malignancy since no treatment should be given until the risks can be justified. Optimal treatment demands a multi-disciplinary approach is necessary in a centre specialized and equipped to treat childhood cancer.

The obligation of the primary physician is to maintain a high index of suspicion concerning childhood malignancy, to diagnose it early, to confirm the diagnosis and to participate as a member of a multidisciplinary team in the treatment of that patient.

- Evaluate general clinical status of the child. Will the child be able to tolerate various procedures?
- A careful systematic assessment of the extent of the disease
- A plan of approach - time, site of biopsy or surgery
- Confirmation of diagnosis: histology favourable / unfavourable and the stage of the disease
- Treatment is instituted in the sequence and intensity determined by the management team
- Careful follow up

Treatment Modalities

Surgery

- Surgery can determine the histology, extent of the disease and resectability
- Biopsy and staging procedures. The biopsy material must be representative of the area most involved with the disease
- Tumours can either be excised primarily or by delayed primary excision after chemotherapy or radiotherapy. These modalities often reduce tumour bulk and vascularity making surgery safer. The histologic assessment of tumours after chemotherapy may indicate the degree of response to drugs used (e.g. Burkitt lymphoma, osteogenic sarcoma, rhabdomyosarcoma).
- Second look surgery after chemotherapy may be important to resect previous unresectable tumours, to re-evaluate the extent of residual disease and response to treatment.
- Palliative treatment in children with no reasonable chance of cure. Surgical procedures may make the terminal stages of the illness more comfortable (e.g. gastrostomy, colostomy, and tracheostomy).
- Surgery of metastatic disease - lung, bone, solid organs (biopsy or excision). Resection of single metastases may be curative
- Surgery of complications e.g. bowel obstruction.
- Long term venous access in the form of ports and tunnelled lines

Radiotherapy

Irradiation is still often used in the therapy of paediatric neoplasms. However because of long-term effects on bone and soft tissue growth its use is restricted.

Chemotherapy

Most effective at the time of cell division and when the tumour burden is small

Supportive Therapy

Blood, platelets, nutritional, psychiatric

Potent treatment modalities are used in the treatment of childhood cancer resulting in a growing population of patients who are apparently cured of their disease. Detailed follow up allows for the prevention and treatment of complications and timeous identification and management of recurrence and second malignancies.

THE EFFECTS OF CANCER THERAPY

Acute problems include

- the tumour lysis syndrome with rapid breakdown of tumour and release of intracellular components – hyperkalaemia, hyper-uricaemia, hyperphosphataemia and hypocalcaemia
- spinal cord compression
- superior vena-cava syndrome
- anaemia and haemorrhage
- neutropaenia with opportunistic infections.

Long-term sequelae include the following

- Second Malignancy. These children have a much higher incidence of developing a second tumour.
- Skeletal: Osteopaenia and osteoporosis can occur and osteogenic sarcoma can develop.
- Chest: Cardiac toxicity (adriamycin) and lung fibrosis (RT, bleomycin).
- GIT: The bowel may develop radiation or chemotherapy induced enteritis and fibrosis.
- Urinary tract: Renal toxicity, progressive renal insufficiency, cystitis and proctitis.
- Endocrine: Stunted growth and thyroid cancer are less frequently seen with modern treatment modalities.
- Reproductive function: Infertility.

Significant long-term psycho-social abnormalities can occur

MALIGNANT TUMOURS OF CHILDHOOD

Solid tumours

Wilms Tumour (Nephroblastoma)
Neuroblastoma
Rhabdomyosarcoma
Teratomas
Soft Tissue Sarcomas
Hepatoblastoma
Testicular Tumours

Other Tumours

Brain Tumours
Bone Tumours (Osteogenic Sarcoma, Ewing's Sarcoma)
Retinoblastoma

Haematological malignancies

Leukaemia
Lymphoma (Hodgkin, Non-Hodgkin including Burkitt)

COMMON SOLID TUMOURS IN INFANCY AND CHILDHOOD

NEUROBLASTOMA

This is a common intra-abdominal tumour of neural crest origin – usually in the adrenal medulla or sympathetic chain. Most children present before the age of two years

Sites

It can occur anywhere along the sympathetic nervous system from the neck to the pelvis, and in the cerebral medulla. Histologically vary from a primitive highly malignant neuroblastoma to a more benign ganglioneuroma. Maturation of the tumour can occur either spontaneously or after chemotherapy.

Diagnosis

More than 50% present with an abdominal mass. Associated symptoms include pain, fever, anaemia, weight loss, FTT, flushing,

sweating or irritability. 25% have hypertension at diagnosis. More advanced tumours may present with paraplegia due to compression of the cord, proptosis or CNS signs. The majority of children have advanced or disseminated disease at presentation. Neuroblastomas secrete catecholamines which are best measured by spot urine HVAs. Needle (Tru-cut) biopsy is preferred to fine needle aspiration biopsy (FNAB) where neuroblastoma is suspected.

Investigations

These include AXR (calcification) US, CT and or MRI to assess the mass and a metastatic workup including nuclear medicine bone isotope scans looking for bone metastases and bone marrow biopsy.

Neuroblastoma Staging

Stage I: Tumour confined to the organ or structure of origin

Stage II: Tumours extending in continuity beyond the organ or structure of origin but not crossing the midline; regional lymph nodes on the ipsilateral side may be involved

Stage III: Tumours extending in continuity involved bilaterally

Stage IV: Remote disease involving skeleton, organs, soft tissue, or distant lymph node groups

Stage IVS: Patients who would otherwise be Stage I or II, but who have remote disease confined only to one or more of the following sites: liver, skin, or bone marrow (without radiographic evidence of bone metastases on complete skeletal survey).

Therapy

Children with Stage I + II disease have a \pm 90% survival rate if the tumour is removed completely.

Stage III has a 60% survival rate. They require chemotherapy, surgical excision of the primary and radiotherapy (RT) to areas of known residual tumour. Stage IV disease carries an ominous prognosis with only 15% surviving. Stage VI-S is unusual. They often occur in children less than 1 year of age, have a much better prognosis than Stage IV and may even undergo spontaneous regression.

Outcome

Age >15months at diagnosis, advanced stage, extent, site of the tumour [adrenal primary] and the histological characteristics [anaplasia] including N Myc amplification and ploidy [diploid vs hyperploidy DNA] are all indicators of a poorer outcome

**WILMS TUMOUR
(NEPHROBLASTOMA)**

Nephroblastoma is the most common renal tumour of childhood. The peak incidence is around 3 years of age and males and females are equally affected. It is often associated with a number of congenital abnormalities (hemihypertrophy, Beckwith Wiedemann syndrome, aniridia, and the WAGR sequence) many of which are related to the WT1 and WT2 genes. Wilms tumour is linked to a pre-malignant anomaly of renal tissue in infants called nephrogenic rests or nephroblastomatosis.

Diagnosis

Usually presents with an abdominal mass, often found after minor abdominal trauma. Other features are haematuria (20%), hypertension (25%) and weight loss. Diagnosis is usually made with US or CT scanning. It is important to assess the opposite kidney for function and bilateral involvement (Stage V disease).

Investigations

To investigate the mass and the extent, as well as rule out other differential diagnoses, imaging may include ultrasound, abdominal and chest X-ray, CT chest and MRI abdomen. HVAs should be done if neuroblastoma is a consideration. FNAB is adequate for histology

Staging according to the US Children's Oncology Group

Stage I Tumour limited to the kidney and completely resected.

Stage II Tumour extends beyond kidney but is completely resected.

Stage III Residual non hematogenous tumour confined to the abdomen, including tumour rupture (or biopsy) peritoneal implants and lymph node involvement.

Stage IV Haematogenous metastases (lung/liver)

Stage V Bilateral renal involvement

*It is important to differentiate between favourable and unfavourable histology.

Therapy

European oncologists treat all patients with neoadjuvant chemotherapy prior to surgery, whereas North American teams prefer primary surgery where this is feasible. This has been the source of much debate but the results are comparable (except in situations where surgical expertise is limited and primary surgery results in excessive tumour rupture and spillage, increase morbidity and compromises results).

Our institution performs resection initially, and follows with chemotherapy. In selected cases, irresectable tumours are first treated with chemotherapy. Resection is then carried out later after tumour shrinkage. Chemotherapy is given to virtually all patients and radiotherapy for residual tumour after surgical resection or if there are unfavourable histologic findings. RT is also given to pulmonary metastases.

Outcome

Stage I/II 95% 5 year survival
 Stage III 85% 5 year survival
 Stage IV 55% 5 year survival
 Unfavourable histology: 50% 5 year survival

RHABDOMYOSARCOMA

Rhabdomyosarcoma constitutes about 10 to 15% of childhood malignancy and has a bimodal age distribution with 1 peak between 2 to 5 years and the next between 15 and 19 years of age. This is a highly malignant soft tissue tumour and arises from primitive mesenchymal cells. Primary tumours occur in the head and neck (35%), genitourinary system (26%) (prostate, bladder, and vagina), trunk and extremities (19%), biliary tract, and retroperitoneal areas. Prognosis depends on site, histology and stage. Significant improvement in survival has been achieved using multimodal therapy which includes surgery, radiotherapy and combination chemotherapy.

Diagnosis

There are no tumour markers and the diagnosis is made on biopsy of the tumour mass. Embryonal Rhabdomyosarcoma has a good prognosis and alveolar a poor prognosis. Two further sub-types are seen namely undifferentiated and pleomorphic

Staging using surgical groups

Stage I: Localized disease completely resected no lymph node involvement.

Stage II: Localized or regional disease with total gross resection

Stage III: Incomplete resection or biopsy, with residual unresected disease

Group IV: Distant metastatic disease present at diagnosis

Treatment

Surgical excision as for other soft tissue malignancies followed by chemotherapy. If microscopic residual disease remains or if lymph nodes are involved, local irradiation is added. If

the disease is initially unresectable, chemotherapy and RT are given followed by excision of the tumour bed and resection of any residual disease.

Head and neck tumours can be managed without surgical ablation.

Teratoma

These may arise at any age and may be benign or malignant. Common sites include sacrococcygeus, ovary, testis and retroperitoneum, but all other sites may be involved.

Sacrococcygeal teratomas present at birth as a mass in the pre-sacral area and are premalignant if not resected early. They vary in size. 75% occur in girls. They may have presacral extension or may present with an abdominal mass so imaging is important to delineate the extent. Serum alfa-feto protein is a good marker of the tumour in most cases. Treatment is complete excision along with the coccyx.

HEPATOBLASTOMA

This represents 2/3 hepatic malignancies in childhood with 60% occurring under the age of 2. Risk factors include Beckwith Wiedemann and hemi hypertrophy and the FAP gene. Chemotherapy is used to reduce the size of the tumour prior to surgical excision which is required to cure the child. If all sectors of the liver are involved and the tumour is chemosensitive transplantation is indicated.

BRAIN TUMOURS

There are four common tumours

Medulloblastoma

Cerebellar astrocytoma

Brainstem glioma

Ependymoma.

Unlike in adults 60% are found below the tentorium cerebri.

Clinical presentation

They usually present in one of two ways: [1] raised intracranial pressure with headaches, vomiting, seizures and papilloedema and [2] localising signs with ataxia, inco-ordination of limb movements and 6th cranial nerve palsy. Symptoms are often present for 6 months before the diagnosis is established.

LYMPHADENOPATHY

Enlarged lymph glands are commonly found in children. In most instances they represent transient responses to benign, local or generalized infections. Lymph glands are **abnormal** if they are in

- In neonates
- Supraclavicular or mediastinal in position.
- Firm and non-tender.
- Matted together
- Fixed to skin and underlying tissue
- Enlarging
- More than 2.5 cm in diameter
- Not responding to antibiotics

Excisional biopsy should be done as soon as possible if there is uncertainty about a gland due to its size, localization or character. Burkitt lymphoma has a doubling time of 24 hours, so any rapidly expanding mass, needs urgent biopsy.

LYMPHOMA

Lymphoma accounts for 10% of childhood cancer.

Non-Hodgkin lymphomas (which include Burkitt lymphoma, Lymphoblastic lymphoma and Anaplastic large cell lymphoma) typically occur between 5 and 15 years and childhood Hodgkin lymphoma peaks in late childhood and early adolescence. Lymphomas may present with localised disease or dissemination to the bone marrow and the central nervous system (CNS). Those with a bone marrow blast count < 25% are referred to as stage IV lymphomas; those with a blast count >

25% are considered to have leukaemia.

With the advent of chemotherapy survival rates for NHL in the US rose from about 30% in the 1960s to over 80% in the new millennium, and survival rates over 90% have been achieved for HL. Despite the fact that lymphoma is no longer a surgical disease, there is a need for primary surgery in some cases (e.g. Burkitt lymphoma presenting with intussusception) and paediatric surgeons play a vital role in biopsying abdominal disease in children where the bone marrow is uninvolved.

NEONATAL TUMOURS

Solid masses are not uncommon in the neonatal period. Most are benign but malignant neonatal tumours still comprise 2% of childhood malignancies.

Pathology:

- Teratomas and mixed Germ cell tumours >80%.
- Soft tissue sarcomas
 - Fibrosarcoma
 - Rhabdosarcoma
- Neuroblastoma
- Renal tumours
- Hepatoblastoma

Surgery is the mainstay of treatment. Radiation therapy is avoided if possible (bone growth, carcinogenesis). Chemotherapy may be indicated but doses are usually reduced to avoid severe toxic side effects.



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